Assessing recovery of adrenal function in glucocorticoid-treated patients: Our strategy for screening and management

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\textbf{A B S T R A C T}

Background: Long-term glucocorticoid (GC) use is the most frequent cause of adrenal insufficiency through suppression of the hypothalamic-pituitary-adrenal axis. There are no guidelines for predicting adrenal insufficiency (AI) and minimizing its risk.

Methods: This is a prospective observational study carried out in the Endocrinology-Diabetology and Nutrition department between 2014 and 2021. All patients had received GC therapy for longer than 3 weeks before switching to hydrocortisone substitution, for various indications. These patients were admitted to our department for stimulation tests. We assessed the prevalence of AI, predicting factors, screening and management.

Results: In our study the GC-induced AI was found in 49% of patients. We found a strong correlation between the basal morning serum cortisol, body mass index and the peak cortisol level after stimulation tests, while no correlation was found between adrenal function and age, sex, indication of GC therapy, duration of corticosteroid therapy, cumulative dose and daily dose. Patients with GC induced AI took a mean of 12 \pm 12.18 months to recover. Adrenal function recovery rate was higher in patients tested by short Synacthen than in those tested by Insulin Hypoglycemia.

Conclusions: We demonstrated the positive correlation between serum cortisol peak levels after stimulation and body mass index. The study supports that basal cortisol level, the duration of corticoid cessation and the type of stimulation test can predict the response of cortisol to stimulation tests.

1. Introduction

Adrenal Insufficiency (AI) is defined as the inability of adrenal gland to produce an adequate level of cortisol. Long-term glucocorticoids (GCs) use (Daily use of an equivalent of 5 mg predison or more for longer than 3 weeks for inflammatory or immune-mediated conditions) is the most common cause of AI due to the suppression of the hypothalamic-pituitary-adrenal axis. The clinical manifestations of AI include non-specific symptoms, including nausea, fatigue, hypotension, and weight loss. Cortisol deficiency can lead to a life-threatening adrenal crisis in stressful situations \cite{1, 2}. Hence the importance of GC replacement therapy (hydrocortisone) in preventing adrenal crisis and giving time to the hypothalamic-pituitary-adrenal axis to recover its normal function. Glucocorticoids are secreted into the systemic circulation in an ultradian and circadian rhythm, with a peak of cortisol in the morning and a nadir at midnight. Normal cortisol production is between 5 mg and 10 mg per m2 of body surface daily, while the oral replacement dose is 15–25 mg of hydrocortisone per day for an adult considering incomplete intestinal absorption \cite{3}. There is no guidelines to predict the occurrence of adrenal insufficiency after discontinuation of long-term corticosteroid therapy according to parameters like: the type of glucocorticoid used, the way of administration (intravenous, oral, inhaled …), the duration of corticosteroid therapy, the cumulative dose, the daily dose … This may be explained by the considerable inter-individual variability. For this purpose, stimulation tests (Synacthen and insulin hypoglycemia) have been used \cite{4}.

The aim of our study was to investigate the epidemiological, clinical and biological parameters in patients with long-term corticosteroid therapy to predict adrenal insufficiency.

2. Methods

This is a prospective observational study carried out in the Endocrinology-Diabetology and Nutrition department at the Mohammed VI Hospital of Oujda, Morocco. Patients were referred from different departments (Hepato-Gastroenterology, Pneumology, Nephrology, Rheumatology, Dermatology and Neurosurgery departments) between December 2014 and August 2021.

We included all patients that had received GC therapy for longer than 3 weeks, for various indications and having switched to hydrocortisone...
substitution for at least 4 weeks.

We collected data on patient age, sex, BMI, diagnosis, date of GC introduction, highest dose of GC, the dose of corticosteroid when switching to hydrocortisone, duration of glucocorticoid use, total cumulative dose, hydrocortisone replacement duration and dose. These patients were admitted in our department for stimulating tests.

The short Synacthen stimulation test (SST) was performed between 08:00 and 08:30 after an overnight fast and a 24-h break from hydrocortisone. Cortisol levels were measured before and 60 min after a 250 µg bolus of intramuscular administered Synacthen. When using insulin Hypoglycemia, a dose of rapid insulin of 0.1–0.15 ui/kg was administered at T0 and venous blood glucose and cortisol samples were taken at T15, T30, T60, T120, T150. The test is valid if hypoglycemia is reached at 0.45 g/l or below, a second dose of 50% of the initial dose of insulin is added if hypoglycemia is not reached. Baseline and after stimulation cortisol levels are used as criteria to define adequate or inadequate adrenal cortisol reserve to decide whether to continue or stop hydrocortisone.

The ethical review committee at the Faculty of Medicine, Mohamed the First University of Oujda (CERBO), approved the study design and protocol. Our study has been reported following the STROCSS 2021 criteria [5].

3. Results

Ninety patients were included in the study. In a close collaboration between the different departments and our department, prednisolone treatment was interrupted (after progressive degression of doses) then switched to hydrocortisone (for at least 3 months) (all patients were on Hydrocortisone doses of 30 mg or less). Before stimulation tests, Glucocorticoid-induced adrenal insufficiency was found in 47% of patients with acute admissions of 5 patients for adrenal crises.

Forty-nine patients were tested. Out of the 41 patients who were not tested, 9 are currently awaiting testing, 6 patients had a relapse of the disease and a clinical indication to continue prednisolone, 6 patients were lost to follow-up, 9 had a very comfortable 8-h cortisol resulting in discontinuation of hydrocortisone without testing with a good clinical outcome and their tests are referred. Eleven patients had a very low 8-h cortisol (<3 µg/dl) and their testing was postponed (Fig. 1).

The characteristics of the 49 patients who were tested are presented in Table 1. Twenty-four patients recovered their adrenal function with a mean recovery time of 12 ± 12,18 months while 25 patients did not recover, after a mean duration of 22.9 ± 12,49 months of corticosteroid discontinuation. Out of the 24 responders, 12 patients responded during the first 13 months of corticosteroid discontinuation (hydrocortisone therapy), 6 patients responded during the first 24 months, and 5 patients recovered their adrenal function after 24 months of GC therapy discontinuation.

Twenty-four tests were done using short Synacthen and 25 were done using insulin hypoglycemia. Out of the 24 patients who recovered their adrenal function, 15 patients (62.5%) were tested by short Synacthen. Fifteen patients (65.2%) who did not recover responders were tested by HI.

Our study have shown a strong correlation between the basal morning serum cortisol and the peak cortisol level after stimulation tests (p = 0.01) while no correlation has been found between adrenal function and age, sex, disease, duration of corticosteroid therapy, cumulative dose and daily dose (see Table 2).

In our patients, we found a higher peak cortisol level after testing in patients with higher body mass index (BMI), concluding to a positive correlation between total serum cortisol levels and BMI (p = 0.012) (see Table 2).

4. Discussion

In our study, the GC-induced AI was found in nearly half of our patients (49%). This finding is consistent with the literature data. Rebecca M Joseph et al. [2] in their review that included 73 studies, that the AI prevalence mediane was 37%.

Our patients were receiving GCs for the most common indications without a significant correlation between AI and the disease. Our results

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**Table 1**

Patient characteristics (tested patients).

| Variables                          | Number of patients tested |
|-----------------------------------|--------------------------|
| Number of patients tested         | 49                       |
| Sex                               |                          |
| Men                               | 14                       |
| Women                             | 34                       |
| Mean age                          | 41.51±14.53 years        |
| body mass index (kg/m2)           |                          |
| less than 18                      | 0                        |
| 18.5–24.9                         | 18                      |
| 25–29.9                            | 19                      |
| ≥30                                | 10                       |
| Glucocorticoid indication (disease) |                        |
| Lupus                             | 8                        |
| Osteoarthritis and rheumatoid arthritis | 9                        |
| Sarcoidosis                       | 4                        |
| Inflammatory bowel disease        | 8                        |
| Glomerulonephritis                | 6                        |
| Hyperthyroidism                   | 5                        |
| others                            | 9                        |
| Mean daily dose of Prednisolone   | 51.27±14.38 mg           |
| Final dose of Prednisolone        | 7.5 mg                   |
| Mean Cumulative dose              | 16282                    |
| Mean duration of Prednisolone     | 19.51±30.76 months       |
| Mean duration of Hydrocortisone   | 16.35 months             |
| Adrenal function test             |                          |
| Short Synacthen                   | 24                       |
| Insulin hypoglycemia              | 25                       |
A study carried out on 100 unmedicated subjects tested by SST, that consisted in evaluating the impact of various clinical and biological factors on the test results, found a positive correlation between the body mass index and the variation of cortisol at 30 min for both sexes [9]. We had the same findings in our study, in fact 18 of the responders (78%) had a BMI > 25 kg/m², while 14 patients (56%) of the non-responders had a BMI < 25 kg/m², this confirms the positive correlation between serum total cortisol levels and BMI.

Multiple limitations have been encountered during our study. First of all, Synacthen was not marketed in our country; and the patients found this test too expensive. In this regard, another test could be performed before the discontinuation of a long-term corticosteroid therapy, such as the short Synacthen test (SST) [8]. Synacthen or tetracosactrin (polypeptide) has a similar action to natural corticotropin and which stimulates the adrenal cortex [4].

To evaluate adrenal function in glucocorticoid-treated patients, basal (unstimulated) morning cortisol measurement can be used as a first step, but for conclusive results one will need to resort to dynamic test, the most widely practiced method by endocrinologists to evaluate adrenal sufficiency is the short synacthen test (SST) [8]. Studies have shown better results with SST than with the insulin tolerance test (ITT) while assessing adrenal function. It should be noted that these studies have evaluated AI in patients at risk of having it and not established AI [4]. Studies of overtrained athletes have shown that they had baseline cortisol levels within the reference range. After stimulation with insulin-induced hypoglycemia, the peak of cortisol levels exceeded the lower limit to rule out adrenal insufficiency, but was not high enough to conclude to a normal adrenal function [10].

During the follow-up of all responders, none of them presented an acute adrenal insufficiency crisis (patients tested by SST and IIH). Whereas in the non-responders group, for those with biological AI we maintained the same dose of HC replacement therapy, and for those with altered cortisol without AI we decreased the dose of HC and re-tested them later, using the SST test or IIH.

In our study, pre-test basal cortisol was significantly higher in responders with a mean of 20.12 ± 29.14 μg/dl; whereas it was lower in non-responders. Patients who had basal cortisol over 21 μg/dl (6 patients) responded positively to stimulation test. In different studies basal cortisol is the best and simplest predictor of response to stimulation test [6,8].

A study carried out on 100 unmedicated subjects tested by SST, that consisted in evaluating the impact of various clinical and biological factors on the test results, found a positive correlation between the body mass index and the variation of cortisol at 30 min for both sexes [9]. We had the same findings in our study, in fact 18 of the responders (78%) had a BMI > 25 kg/m², while 14 patients (56%) of the non-responders had a BMI < 25 kg/m², this confirms the positive correlation between serum total cortisol levels and BMI.

Multiple limitations have been encountered during our study. First of all, Synacthen was not marketed in our country; and the patients found difficulties to bring it from Europe. Then, the necessity of a multidisciplinary approach to decide the switch from corticosteroids to hydrocortisone.

5. Conclusion

After the discontinuation of a long-term corticosteroid therapy, prediction of adrenal insufficiency occurrence based on age, sex, disease, type of glucocorticoid used, duration of corticosteroid therapy, cumulative dose or daily dose is irrelevant. On the other hand, based on the data collected in the literature and on the results of our studies, we can predict the results of these stimulation tests, based on clinical criteria such as BMI and biological criteria such as baseline cortisol, even the type of test can give us a hint on the response. Studies with larger numbers are required to give us more information about these different parameters.
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This research was not funded.

Ethical approval

The ethical review committee at the Faculty of Medicine, Mohamed the First University of Oujda, approved the study design and protocol. Data were anonymously registered in our database. Access to data was approved by the head of the department.

Consent

A written informed consent was obtained from patients for using their medical records. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Dr. Najat Draoui wrote the manuscript. Dr. Achwak Alla collected data, analysed and wrote the manuscript. Dr. Nada Derkaoui collected data, analysed and wrote the manuscript. Dr. Aymane Loukili helped in writing and literature review. Pr. Siham Rouf helped in writing, supervised the redaction and revised the manuscript. Pr. Hanane Latrech helped in writing, supervised the redaction, revised and approved the final draft for publication. All authors approved the final version of the manuscript.

Registration of research studies

1. Name of the registry: researchregistry7745
2. Unique Identifying number or registration ID: researchregistry7745
3. Hyperlink to your specific registration (must be publicly accessible and will be checked):

Guarantor

Pr. Hanane Latrech.

Declaration of competing interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.103710.

References

[1] Antje K. Blacha, Amir H. Rahvar, Jörg Flitsch, et al., Impaired attention in patients with adrenal insufficiency – Impact of unphysiological therapy, Steroids 167 (2021) 108788.
[2] Rebecca M. Joseph, Ann Louise Hunter, David W. Ray, et al., Systemic glucocorticoid therapy and adrenal insufficiency in adults: a systematic review, in: Seminars in Arthritis and Rheumatism, WB Saunders, 2016, pp. 133–141.
[3] Eystein S. Husebye, Pearce, H. Simon, Krone, P. Nils, et al., Adrenal Insufficiency, The Lancet, 2021.
[4] Mark Sherlock, et al. M. Paul, The short Synacthen test and its utility in assessing recovery of adrenal function in patients with central adrenal insufficiency, J. Clin. Endocrinol. Metabol. 104 (1) (2019) 17–20.
[5] G. Mathew, R. Agha, for the STROCSS Group, STROCSS 2021: strengthening the Reporting of cohort, cross-sectional and case-control studies in Surgery, Int. J. Surg. 96 (2021) 106165.
[6] KARANGIZI, H.K. Alvin, Al-Shaghana, L.O.G.A.N. May, Sarah, et al., Glucocorticoid induced adrenal insufficiency is common in steroid treated glomerular diseases–proposed strategy for screening and management, BMC Nephrol. 20 (1) (2019) 1–7.
[7] Irina Bancos, Stefanie Hahner, Jeremy Tomlinson, et al., Diagnosis and management of adrenal insufficiency, Lancet Diabetes Endocrinol. 3 (3) (2015) 216–226.
[8] Stina W. Borresen, Toke B. Thorgrimsen, Bente Jensen, et al., Adrenal insufficiency in prednisolone-treated patients with polymyalgia rheumatica or giant cell arteritis–prevalence and clinical approach, Rheumatology 59 (10) (2020) 2764–2773.
[9] Naomi Wintrob, Elliot Sprecher, , JOSEFSBERG, Zeev, et al., Standard and low-dose short adrenocorticotropin test compared with insulin-induced hypoglycemia for assessment of the hypothalamic-pituitary-adrenal axis in children with idiopathic multiple pituitary hormone deficiencies, J. Clin. Endocrinol. Metabol. 83 (1) (1998) 88–92.
[10] M. Guinot, M. Duclos, N. Idres, et al., Value of basal serum cortisol to detect corticosteroid-induced adrenal insufficiency in elite cyclists, Eur. J. Appl. Physiol. 99 (3) (2007) 205–216.