Clinical and Experimental Rheumatology 2022; 40: 1789-1792.

Impaired adrenal cortex reserve in patients with rheumatic and musculoskeletal diseases who relapse upon tapering of low glucocorticoid dose

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Received on October 12, 2021; accepted in revised form on January 1, 2022.

Key words: adrenal insufficiency, arthritis, glucocorticoid tapering, tetracosactide stimulation, adrenal reserve, rheumatic and musculoskeletal diseases

Competing interests: none declared.

ABSTRACT

Objective. *To examine adrenal cortex reserve in patients with rheumatic and musculoskeletal diseases (RMD) who relapse upon tapering of low glucocorticoid dose, despite concomitant treatment with disease-modifying anti-rheumatic drugs (DMARDs).*

Methods. *A morning standard dose of 250 mcg tetracosactide (Synacthen test) was given in 25 consecutive patients (13 rheumatoid arthritis, 2 psoriatic arthritis, 5 systemic lupus erythematosus, 2 dermatomyositis, 1 systemic sclerosis, 2 temporal arteritis) at the time of relapse upon small reductions (1-2 mg daily) of low prednisolone dose (<7.5 mg daily), while being on stable concomitant treatment with methotrexate, leflunomide, hydroxychloroquine, azathioprine, mycophenolate, tofacitinib, belimumab, anti-TNF, anti-IL-6 or anti-IL-1 regimens (n=14; 3; 9; 1; 2; 1; 1; 5; 2; 1, respectively). Sex-matched apparently healthy individuals (n=45) served as controls.*

Results. *Baseline cortisol levels and time-integrated cortisol response to tetracosactide were lower in patients than controls (12.01±4.47 vs. 15.63±4.16 mcg/dl, p=0.001, and 1050±286 vs. 1284±182, p<0.001, respectively). No significant associations were observed between the cortisol response to tetracosactide and age, duration of disease or glucocorticoid treatment. An abnormal Synacthen test, indicative of adrenal insufficiency, presumably secondary to chronic glucocorticoid administration, was noted in 5/25 patients. The remaining 20 patients (80%) had normal Synacthen test demonstrating, however, lower cortisol response than controls, independently of age (β-coefficient=-0.373, p=0.033).*

Conclusion. *Patients with RMD in remission under DMARDs who relapse upon concomitant low glucocorticoid dose tapering should be tested for iatrogenic adrenal insufficiency. Whether a marginally normal Synacthen test should discourage further attempts to withdraw glucocorticoid treatment in these patients warrants further investigation.*

Introduction

Long-term remission in rheumatic and musculoskeletal diseases (RMD) is the ultimate treatment goal in the management of these patients. The advent of disease-modifying anti-rheumatic drugs (DMARDs), including targeted biological and synthetic agents, and their application in clinical practice have dramatically improved prognosis in RMD supporting the task of a sustained drug-free remission goal.

In a substantial proportion, patients with RMD require chronic administration of glucocorticoids to maintain disease remission. Despite their considerable clinical efficacy, glucocorticoids have multiple side effects over the long term. According to the updated European League Against Rheumatism (EULAR) guidelines, glucocorticoids should be tapered as rapidly as feasible (1). Also, for the majority of patients at long-term daily prednisone ≤5 mg the risk of complications still exists, when considering osteoporosis, hyperglycaemia/diabetes mellitus, cardiovascular disease and infections, highlighting the role of both drug-specific (dose, duration) and patient-specific (age, gender) parameters on the level of glucocorticoid harm (2). In clinical practice, however, tapering is often difficult due to the high rate of subsequent RMD flares.

A suboptimal response of hypothalamic-pituitary- adrenal (HPA) axis to stress and inflammation, termed "relative or functional" adrenal insufficiency has been described in some patients with RA even in the presence of an apparently intact HPA axis (3-6). In addition, apart from the tertiary iatrogenic adrenal insufficiency induced by long-term treatment with exogenous glucocorticoids, a compromised adrenal reserve without clinical and/or biochemical evidence of adrenal insufficiency has been considered [reviewed in (4)]. Herein, we tested the hypothesis that patients with RMD in remission who relapse upon tapering of low glucocorticoid dose, despite concomitant standard treatment with DMARDs, may have an impaired adrenal cortex reserve.

Patients and methods

Adult patients with RMD followed-up at the Rheumatology Unit of the first Department of Propaedeutic and Internal Medicine, National and Kapo-

Table I. Demographic, clinical characteristics and serum cortisol levels during the Synacthen test in RMD patients and controls.

Parameters	RMD patients (n=25)	Controls (n=45)	*p*-value
Age (years)	57.7 ± 15.4	27.8 ± 11.1	<0.001
Males, n (%)	3 (12.0%)	7 (15.6%)	0.684
Premenopausal females, n (%)	6 (25%)	42 (91%)	<0.001
Duration of RMD (years)	10 (2, 40)	-	NA
Duration of glucocorticoids use (years)	7.0 (1, 40)	-	NA
Incidence of adrenal insufficiency, n (%)	5 (20%)	0	0.002
Baseline cortisol levels (mcg/dl)	12.01 ± 4.47	15.63 ± 4.16	0.001
Serum cortisol levels (mcg/dl) at 30 min after stimulation with tetracosactide (Synacthen test)	18.57 ± 5.20	22.29 ± 3.11	<0.001
Serum cortisol levels (mcg/dl) at 60 min after stimulation with tetracosactide (Synacthen test)	20.82 ± 5.35	25.44 ± 3.69	<0.001
Total cortisol response to tetracosactide (AUC calculation)	1049.83 ± 285.77	1283.66 ± 181.66	<0.001

Data are presented as mean ± SD for normally distributed continuous variables or median (min, max) if otherwise distributed. Student's t-test for independent samples or the Mann-Whitney U-test for continuous variables was used for mean comparisons. Categorical variables are presented as n (%), two-tailed Fisher's exact test was used to compare categorical data.
RMD: rheumatic and musculoskeletal disease; AUC: area under the curve, NA: not applicable.

distrian University of Athens Medical School, between September 2019 and June 2021, being on long-term stable treatment (>1 year) with low glucocorticoids daily dose (<7.5mg of prednisolone or equivalent, daily) combined with DMARDs were considered eligible for the study. The enrolment criteria included the following: (i) RMD remission, based on standard clinical scales at the time of assessment, and (ii) subsequent RMD relapse, based on clinical and/or biochemical evidence, upon reductions of 1–2 mg of prednisolone (or equivalent). Exclusion criteria included the presence of chronic kidney disease stage 3b and above, liver failure, malignancy, uncontrolled thyroid disease and treatment with agents known to interfere with the HPA axis (*e.g.* oestrogens and selective estrogen modulators). Apparently healthy individuals who had never been treated with glucocorticoids and met the exclusion criteria were also recruited from the hospital's personnel at the same time-period and included in the analysis as controls. All participants signed an informed consent form and the procedures followed were in accordance with the 1975/83 Declaration of Helsinki.

Study protocol

A morning standard dose 250 mcg Synacthen (tetracosactide) test was performed in all participants after a 48-h withdrawal of glucocorticoids and an overnight fast. In brief, blood cortisol was measured before an intravenous injection of 250 mcg of tetracosactide, and 30, and 60 min thereafter, using Elecsys® Cortisol II assay (second generation) (Roche Diagnostics, GmbH, Mannheim, Germany). Laboratory assay-specific cut-off values for normal adrenal function were serum cortisol ≥18 mcg/dl at 30 min and/or 60 min (7). Coefficients of variation (CVs) for repeatability, intermediate precision, and reproducibility for serum samples are ≤2.6%, ≤5.8%, and ≤9.5%, respectively.

Statistics

Normality of distributions was tested by the Shapiro-Wilk test. Data are presented as mean ± standard deviation (SD) or median (min, max), as applicable. Time-integrated cortisol response to tetracosactide was calculated employing the integrated area under the curve (AUC) using the trapezoidal method, as previously described (8). Pearson's correlation coefficient or Spearman's rank correlation coefficient was used for associations between the calculated AUC and age, sex, duration of glucocorticoid treatment, and duration of RMD.All *p*-values are two-sided and a value of $p<0.05$ was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics for Windows, v. 26 (IBM SPSS Statistics for Windows, IBM Corporation, Armonk, NY, USA).

Results

Twenty-five consecutive patients (88% females, mean age 57.71±15.43years) who visited the outpatient clinic due to disease relapse between September 2019 and June 2021 and fulfilled the enrollment criteria were included in the analysis. RMDs included RA (n=13), psoriatic arthritis (n=2), systemic lupus erythematosus (n=5), dermatomyositis (n=2), temporal arteritis (n=2), as well as one woman 54 years old with 9 years history of systemic sclerosis and persisting arthritis. DMARDs treatment included methotrexate (n=14), leflunomide (n=3), hydroxychloroquine (n=9), azathioprine (n=1), mycophenolate mofetil (n=2), tofacitinib (n=1), belimumab (n=1), as well as anti-TNF (n=5), anti-IL-6 (n=2) or anti-IL-1 (n=1) agents. Forty-five sex-matched apparently healthy individuals who met the exclusion criteria served as controls. Demographic and clinical characteristics of the study population and serum cortisol measurements are depicted in Table I.

Baseline cortisol levels and time-integrated cortisol response to tetracosactide as determined by the AUC calculation were decreased in patients than controls (12.01±4.47mcg/dl *vs*. 15.63±4.16 mcg/dl, $p=0.001$, and 1050±286 *vs*. 1284±182, $p<0.001$, respectively) (Table I, Fig. 1a). Cortisol response to tetracosactide was not associated with age (r=-0.21, $p=0.299$), duration of the disease (rho= -0.21, $p=0.329$) or duration of treatment with glucocorticoids (rho= -0.04, $p=0.851$).

Five patients (20%) but no control subject, exhibited overt adrenal insufficiency based on the prespecified cut-off values of serum cortisol at baseline, 30, and 60 minutes after the tetracosactide in-

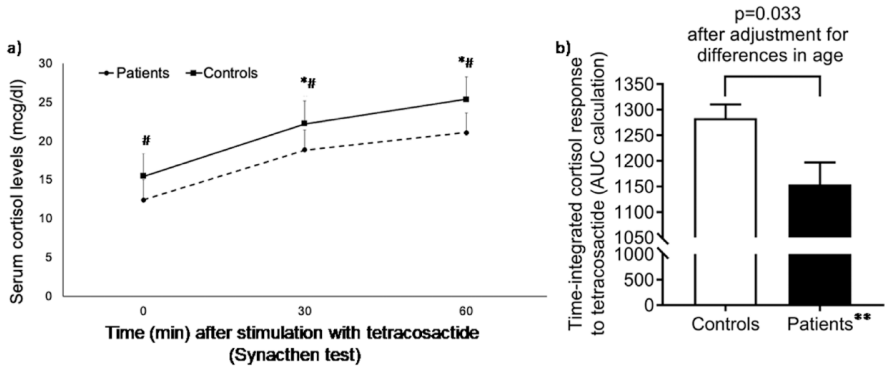

Fig. 1. Time integrated serum cortisol response to acute stimulation with tetracosactide (Synacthen test) in **a**) patients (whole group, n=25) *vs*. controls (n=45), **b**) patients with normal Synacthen test (n=20) *vs*. controls (n=45). Data are presented as mean ± SEM.
* $p<0.05$, Comparisons are performed with baseline values within each group, using One-way repeated measures ANOVA with Bonferroni *post-hoc* test.
# $p<0.05$, Comparisons are performed between groups at each time point.
** Only patients with normal Synacthen test are included (n=20).
Multivariate regression analysis was used to correct differences in age between the 2 groups (patients *vs*. controls) (β-coefficient = -0.373, 95% CI: -297.09, -12.92, $p=0.033$)

jection. Of them, 4 women aged 54, 70, 73 and 78 years had RA of 22, 3, 40 and 3 years duration, respectively, whereas a, 81-year-old male had temporal arteritis of 5 years duration. Age, duration of the disease or duration of treatment with glucocorticoids were comparable between those 5 RMD patients with adrenal insufficiency and the remaining patients in whom the response to Synacthen test was considered normal. Notably, the difference in the cortisol response to tetracosactide between RMD patients and controls remained significant when the five patients with overt adrenal insufficiency were excluded (AUC: 1154±193 *vs*. 1284±182, respectively, $p=0.011$). As shown in Figure 1b, multivariate analysis adjusting for differences in age confirmed the lower cortisol response to tetracosactide (β-coefficient=-0.373, 95%CI: -297.09, -12.92, $p=0.033$) in RMD patients with normal response to Synacthen test than controls.

Discussion

Adrenal insufficiency is an established adverse effect of chronic glucocorticoid treatment. Previous studies have shown that up to 48% of RA patients on long-term glucocorticoid treatment develop tertiary iatrogenic adrenal insufficiency (9-11). However, the proportion of patients without overt adrenal insufficiency who are unable to discontinue glucocorticoids due to arthritis relapse is reportedly higher (65%), implying subtle dysregulations of the HPA axis (4, 12). The preliminary data presented herein indeed suggest that, in addition to patients with iatrogenic adrenal insufficiency, an underlying impaired adrenal cortex reserve is present in those patients who are unable to taper or completely withdraw even low doses of glucocorticoids, although being in remission under concomitant standard DMARD therapy. Moreover, and in line with previous studies (9, 12, 13), we did not find significant associations between the reduced cortisol response to tetracosactide and the duration of the disease or the duration of treatment with glucocorticoids. Limitations of our study, besides its cross-sectional design and the rather small patient number, include the lack of stress-assessment in our patients, which could potentially contribute to the impaired function of the HPA axis.

Subtle differences in the HPA axis activity have been described in subpopulations with RMD without any prior risk for, or evidence of adrenal insufficiency; a concept coined as 'relative adrenal insufficiency' (3). Underlying potential pathophysiologic mechanisms include chronic stress-induced suppression of the HPA axis, dysfunctional glucocorticoid receptor expression, or HPA axis defectiveness due to genetic background, though current evidence is still inconclusive [reviewed in (4)]. Earlier studies in RA have shown an impaired functionality of the HPA axis, *i.e*. either a blunted or an exaggerated response of ACTH and cortisol secretion to increased endogenous IL-6, dependent on the disease activity and duration (4, 6). Experimental results in collagen-induced arthritis, a rat model resembling severe human arthritis, demonstrated that local inflammation of the adrenal glands may also play a role in the reduced corticosterone production (14).

Regardless of the underlying mechanisms, an intact and functional HPA axis has a significant role in the long-term management of RMDs, and glucocorticoids remain a critical component of the therapeutic regimen despite concomitant administration of effective DMARDs. The SEMIRA (Steroid EliMination In Rheumatoid Arthritis) study showed that RA patients on low disease activity with a combination treatment of 5mg prednisone/day and anti-interleukin-6 receptor antibody tocilizumab, maintained higher rates of disease remission than those in whom tapering of oral glucocorticoids was attempted (15). Increasing knowledge on the active pathways involved in RA, have provided novel and specific therapeutic targets at tissue level suitable for tailored therapeutic approaches. As such, a drug conjugate of anti-TNF antibody linked to a glucocorticoid receptor modulator or Janus kinase (JAK) inhibitors may render precision medicine approaches rather feasible, now more than ever (16).

To conclude, our data suggest that patients with RMD in remission under standard treatment with DMARDs who relapse upon concomitant low glucocorticoid-dose tapering should be tested for iatrogenic adrenal insufficiency. Whether a marginally normal Synacthen test should discourage further attempts to withdraw glucocorticoid treatment in these patients warrants further investigation. Identification of the characteristics of patients upon diagnosis of RMD who will not be able to successfully withdraw glucocorticoids from the backbone of their main treatment regimen (17)in due time remains an unmet and challenging need. Greater understanding of the complex

interaction between the HPA axis and the pathophysiology of chronic RMD will pave the way towards personalised medicine and more successful management of these patients.

Acknowledgement

This study is dedicated to the memory of our colleague Dr Evangelos Spanos, who passed away on April 18th, 2020, due to COVID-19-related complications, in Athens, Greece. The support he generously lent to this project was truly invaluable and most highly appreciated.

References

1. SMOLEN JS, LANDEWÉ RBM, BIJLSMA JWJ *et al*.: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis* 2020; 79: 685-99.
2. STREHL C, BIJLSMA JW, DE WIT M *et al*.: Defining conditions where long-term glucocorticoid treatment has an acceptably low level of harm to facilitate implementation of existing recommendations: viewpoints from a EULAR task force. *Ann Rheum Dis* 2016; 75: 952-7.
3. IMRICH R, VLCEK M, ALDAG JC *et al*.: An endocrinologist's view on relative adrenocortical insufficiency in rheumatoid arthritis. *Ann NY Acad Sci* 2010; 1193: 134-8.
4. FILIPPA MG, TEKTONIDOU MG, MANTZOU A *et al*.: Adrenocortical dysfunction in rheumatoid arthritis: Alpha narrative review and future directions. *Eur J Clin Invest* 2022; 52: e13635.
5. STERNBERG EM, HILL JM, CHROUSOS GP *et al*.: Inflammatory mediator-induced hypothalamic-pituitary-adrenal axis activation is defective in streptococcal cell wall arthritis-susceptible Lewis rats. *Proc Natl Acad Sci USA* 1989; 86: 2374-8.
6. CHROUSOS GP: The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. *N Engl J Med* 1995; 332: 1351-62.
7. BORNSTEIN SR, ALLOLIO B, ARLT W *et al*.: Diagnosis and treatment of primary adrenal insufficiency: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2016; 101: 364-89.
8. PRUESSNER JC, KIRSCHBAUM C, MEINLSCHMID G, HELLHAMMER DH: Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. *Psychoneuroendocrinology* 2003; 28: 916-31.
9. BORRESEN SW, KLOSE M, BASLUND B *et al*.: Adrenal insufficiency is seen in more than one-third of patients during ongoing low-dose prednisolone treatment for rheumatoid arthritis. *Eur J Endocrinol* 2017; 177: 287-95.
10. HICKLIN JA, WILLS MR: Plasma "cortisol" response to Synacthen in patients on long-term small-dose prednisone therapy. *Ann Rheum Dis* 1968; 27: 33-7.
11. KIRWAN JR, HICKEY SH, HALLGREN R *et al*.: The effect of therapeutic glucocorticoids on the adrenal response in a randomized controlled trial in patients with rheumatoid arthritis. *Arthritis Rheum* 2006; 54: 1415-21.
12. BACON PA, MYLES AB, BEARDWELL CG, DALY JR: Corticosteroid withdrawal in rheumatoid arthritis. *Lancet* 1966; 2: 935-7.
13. BROERSEN LH, PEREIRA AM, JORGENSEN JO, DEKKERS OM: Adrenal insufficiency in corticosteroids use: systematic review and meta-analysis. *J Clin Endocrinol Metab* 2015; 100: 2171-80.
14. STANGL H, KRAMMETSVOGL A, LESIAK M, WOLFF C, STRAUB RH: MHC/class-II-positive cells inhibit corticosterone of adrenal gland cells in experimental arthritis: a role for IL-1beta, IL-18, and the inflammasome. *Sci Rep* 2020; 10: 17071.
15. BURMESTER GR, BUTTGEREIT F, BERNASCONI C *et al*.: Continuing versus tapering glucocorticoids after achievement of low disease activity or remission in rheumatoid arthritis (SEMIRA): a double-blind, multicentre, randomised controlled trial. *Lancet* 2020; 396: 267-76.
16. SILVAGNI E, SAKELLARIOU G, BORTOLUZZI A *et al*.: One year in review 2021: novelties in the treatment of rheumatoid arthritis. *Clin Exp Rheumatol* 2021; 39: 705-20.
17. CUTOLO M, PAOLINO S, GOTELLI E: Glucocorticoids in rheumatoid arthritis still on first line: the reasons. *Expert Rev Clin Immunol* 2021; 17: 417-20.