Cortisol During the Day in Patients with Systemic Lupus Erythematosus or Primary Sjögren's Syndrome

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ABSTRACT. ***Objective.*** To compare the level and change of cortisol during the day of patients with systemic lupus erythematosus (SLE) and primary Sjögren's syndrome (pSS) with low and high erythrocyte sedimentation rate (ESR).

Methods. Saliva was collected in the real-life environment of 21 women with SLE, 16 women with pSS, and 30 age-matched healthy women at 9 fixed timepoints during 2 consecutive days. Repeated measures ANOVA was performed to examine whether cortisol levels during the day were different for the patients with low ESR (≤ 20 mm/h) versus those with high ESR (> 20 mm/h).

Results. The groups with low and high ESR showed the characteristic change of cortisol during the day (time-of-day effect, $F = 124.9$, $p < 0.001$). The cortisol awakening level was lower for patients with high ESR than for patients with low ESR (group*time effect, $F = 3.1$, $p = 0.02$).

Conclusion. The cortisol awakening level differs for patients with low and high ESR, which indicates the usefulness of further studies of hypothalamic-pituitary-adrenal axis dynamics in patients with SLE and pSS. (First Release Dec 15 2010; J Rheumatol 2011;38:285–8; doi:10.3899/jrheum.100572)

Key Indexing Terms:
HYPOTHALAMIC-HYPOPHYSEAL SYSTEM
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Both animal models and research in patients with rheumatic diseases suggest that the hypothalamic-pituitary-adrenal (HPA) system is implicated in the modulation of rheumatic inflammation[1,2,3]. In rheumatic diseases, antiinflammatory counter-regulation of the HPA system is ineffective in alleviating inflammation. This relative hypoactivity may be a result of chronic inflammation or it may be a premorbid dysfunction that is important in the etiology of rheumatic diseases. In healthy subjects, the circadian (24-hour) rhythm of salivary cortisol is characterized by highest levels in the early morning hours and lowest levels around midnight[4]. On top of this circadian rhythm there is a pronounced release of cortisol in response to awakening in the morning: the cortisol awakening response. This circadian pattern of cortisol levels has been confirmed for patients with longstanding rheumatoid arthritis (RA)[5].

Our previous study in patients with recent-onset RA showed that dynamic cortisol responsiveness as reflected in the cortisol awakening response was not disturbed, but that afternoon cortisol levels were increased in patients with elevated erythrocyte sedimentation rate (ESR), which suggests that the HPA system was still responsive to inflammation[6]. In studies with small samples (n = 11 and n = 7) of patients with newly diagnosed untreated systemic lupus erythematosus (SLE), no indication of altered HPA axis activity was found[7,8]. In patients with established Sjögren's syndrome (SS), the late afternoon levels of both adrenocorticotropic hormone and cortisol were found to be significantly lower in patients compared to healthy controls, thus suggesting a hypofunctional HPA system[9,10].

To summarize, the few available data indicate that the HPA response to chronic inflammation is insufficient, although the response in early disease appears still to be present. ESR levels correlate with adrenal cortisol secre-

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tion[11,12]. ESR in patients with SLE may fluctuate with disease exacerbations. ESR in patients with primary Sjögren's syndrome (pSS) does not directly reflect disease activity, but it may indicate expression of the disease. Our hypothesis, based on little previous empirical support, was that the change of cortisol during the day in chronic SLE and pSS, as an indicator of HPA axis responsiveness, would be impaired. The aim of our study was to compare levels and change of cortisol during the day of patients with SLE or pSS with low and high ESR. Data of healthy participants were used as reference values.

MATERIALS AND METHODS

Research participants were all women: 21 patients with SLE, 16 patients with pSS, and 30 age-matched healthy women. The assessments in patients were taken before they participated in a study that compared effects of oral administration of 200 mg DHEA or placebo[13,14]. Patients were ≥ 18 years and fulfilled the European criteria for classification of pSS including a focus score ≥ 1 on minor salivary gland biopsy, or they fulfilled at least 4 of the SLE classification criteria of the American College of Rheumatology[15,16]. Both patients with pSS and patients with SLE who did not use prednisone currently or in the previous year were invited. Disease activity of patients with SLE had to be quiescent. Exclusion criteria were malignancy within the preceding 5 years and abnormal levels of thyroid-stimulating hormone or serum creatinine, or abnormal liver functions. The study had been approved by the local ethics committees and written consent was obtained.

ESR was determined according to standard procedures. Saliva for cortisol assessments was collected with cotton swabs (Salivette, Sarstedt AG & Co., Nümbrecht, Germany) in the real-life environment of the patients at 9 fixed timepoints during 2 consecutive days. The first 4 saliva samples were collected at awakening and at 15, 30, and 45 minutes after awakening to assess the cortisol awakening response. The other saliva samples were collected at 10:00 AM, 12:00 noon, 2:30 PM, 5:00 PM, and 7:30 PM. Salivary cortisol was analyzed with a time-resolved immunoassay with fluorescence detection (DELFIA; Pharmacia, Uppsala, Sweden) as described[17].

Analysis. The 0.8% of the cortisol measurements that was considered an outlier ($z > 3.29$) was assigned a score 1 unit larger than the next most extreme score of the score distribution[18]. Repeated measures ANOVA was used to examine whether the course of cortisol across the day was different for patients with low ESR (≤ 20 mm the first hour) versus high ESR (> 20 mm the first hour). The ESR cutoff of 20 mm the first hour was used previously and is considered to indicate the difference between normal (different levels for sex and age groups, but all below 20 mm the first hour) and increased ESR[3]. The cortisol levels of the 2 groups at each timepoint were tested for differences using independent samples t tests. The cortisol values of healthy participants were used as reference values to interpret the results. All analyses were done with SPSS 15.0. Two-sided significance levels were set at $p < 0.05$.

RESULTS

Of the patients with SLE, 48% had a low ESR (mean age 43 yrs; mean disease duration 14 yrs) and 52% had a high ESR (mean age 44 yrs; mean disease duration 11 yrs); the mean titer of anti-dsDNA antibodies was 32 IU/ml (range 2–116 IU/ml) and the SLE Disease Activity Index was ≤ 4 for most patients, with 2 patients having a score of 6. Of the patients with pSS, 38% had a low ESR (mean age 49 yrs; mean disease duration 2 yrs) and 62% had a high ESR (mean age 56 yrs; mean disease duration 4 yrs). Although none of the participants had used glucocorticoids in the 12 months before the assessments, past use of glucocorticoids was more frequent in patients with SLE than in patients with pSS (86% and 31%, respectively).

The characteristics of the participants are shown in Table 1. The mean ESR was 10 mm/h (range 5–20 mm/h) and 37 mm/h (range 23–94 mm/h) in the groups with low and high ESR, respectively. Sixty-two percent of the patients had used glucocorticoids in the past.

The low and high ESR groups as well as the controls showed the characteristic cortisol rhythm during the day as reflected by a significant time-of-day effect ($F = 124.9$, $p < 0.001$; Figure 1). The course of cortisol during the day was different for the patients with low versus those with high ESR as reflected in a significant group*time effect ($F = 3.1$, $p = 0.02$); patients with low ESR showed more pronounced cortisol awakening levels than patients with high ESR. Analysis with continuous ESR scores showed a similar result: the Pearson correlation between area under the curve of cortisol values for the first 3 measurements and ESR was –0.36 ($p = 0.03$), showing lower cortisol values with higher ESR values. With the small sample sizes, the cortisol patterns during the day of patients with low and high ESR were not significantly different, in the group of patients with SLE ($F = 1.7$, $p = 0.18$) or in the group of patients with pSS ($F = 1.8$, $p = 0.16$). However, in both disease groups the patients with low ESR had higher cortisol awakening levels than the patients with high ESR (data not shown). Comparing the levels at each timepoint during the day, the cortisol levels were significantly different for the low and high ESR groups at the time of awakening ($p = 0.01$) and 15 minutes later ($p = 0.049$). The cortisol levels after awakening of the controls were between the values of the low and high ESR groups and did not significantly differ from the levels of the patient groups ($F = 2.0$, $p = 0.06$).

DISCUSSION

In patients with SLE or pSS, the cortisol awakening level, as an indicator of dynamic cortisol responsiveness, was observed to be higher for patients with low ESR than for patients with high ESR. Repeated cortisol measurements over the day during followup of patients are needed to conclude whether this result reflects a more or less consistent difference between individuals (between-subject difference) or whether it reflects that HPA dynamics change in cases of increased inflammation or disease expression (within-subject difference).

Based on the characteristic cortisol rhythm, no clear dysfunction of the HPA axis was found in patients with SLE or pSS as compared to the controls, which suggests that the HPA system was still responsive. Our finding of diminished cortisol awakening levels in patients with high ESR, and the finding that in patients with established SS the stimulated

Table 1. Patient characteristics.

Characteristics	ESR ≤ 20, n = 16	ESR > 20, n = 21	Controls, n = 30
Patients with SLE	10	11	
Patients with pSS	6	10	
Age, yrs (mean ± SD)	45 ± 7	50 ± 16	50 ± 13
Postmenopausal (number, %)*	10 of 16 (63)	5 of 21 (24)	12 of 27 (44)
Disease duration, yrs (mean ± SD)	10 ± 8	8 ± 6	
Awakening time Day 1 (mean ± SD)	7:17 ± 0.36	7:35 ± 0.46	7:22 ± 0.53
Awakening time Day 2 (mean = SD)	7:26 ± 1.00	7:41 ± 0.47	7:25 ± 0.51
ESR, mm/h (mean ± SD)	10 ± 4	37 ± 18	
Glucocorticoid therapy in past, oral or intravenous, no. (%)	11 of 16 (69)	12 of 21 (57)	
Glucocorticoid therapy in past, 0.5–1 mg/kg, oral or intravenous, no. (%)	7 of 16 (44)	9 of 21 (43)	
Glucocorticoid-free period before study, months, mean (range)	61 (12–143)	56 (26–143)	

* Postmenopausal status was defined as amenorrhea for 1 year or more in women with a uterus *in situ* and by follicle-stimulating hormone (FSH) > 35 IU/l in hysterectomized women. Menopausal status was unknown for 3 controls in whom FSH was not determined. SLE: systemic lupus erythematosus; pSS: primary Sjögren's syndrome; ESR: erythrocyte sedimentation rate.

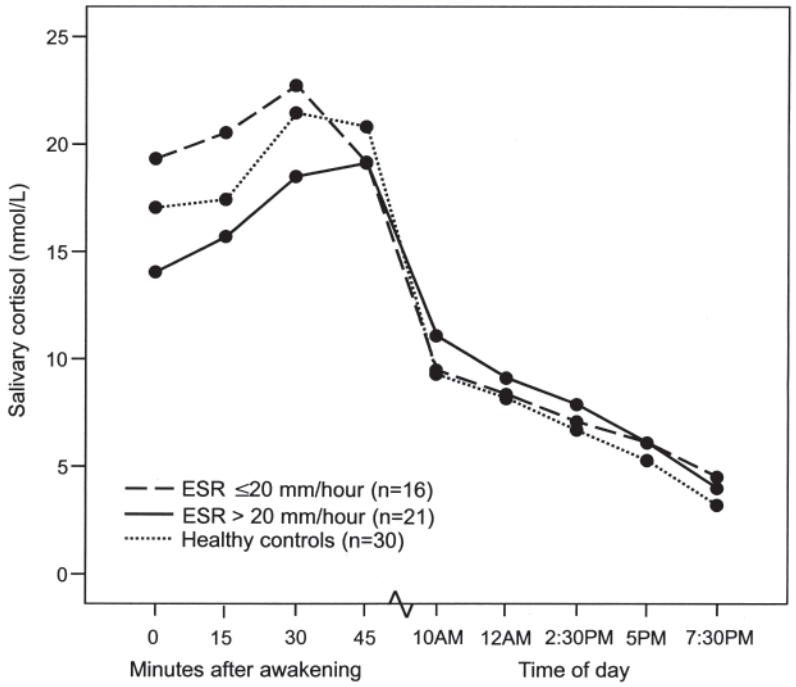

Figure 1. Salivary cortisol values after awakening and during the day in patients with low and high erythrocyte sedimentation rate (ESR) and in controls.

pituitary and adrenal response is blunted compared to controls[10], may reflect that in ongoing disease, the HPA axis is stimulated continuously (even during the night), causing a downregulation of dynamic HPA system responsiveness to momentary stressors such as awakening.

Our study is the first to describe cortisol levels during the day in patients with chronic SLE and pSS. The number of patients was limited, but the group was rather homogeneous. Only women were included. Although some studies indicate that the HPA axis is still responsive in early rheumatic disease[6,7,8], HPA axis functioning is relatively insufficient to reduce disease activity, while treatment with exogenous glucocorticoids often does reduce inflammation[19,20,21]. Because treatment with glucocorticoids affects HPA axis functioning and inflammation, we excluded patients who had used glucocorticoids in the preceding 12 months.

Future research should focus on clarifying the meaning of the suggested deviation in HPA axis dynamics in patients with chronic rheumatic diseases compared to controls. It could be that the attenuated cortisol responsiveness is due to the disease, but it is also possible that diminished HPA axis responsiveness is a characteristic of patients who are more at risk for a systemic autoimmune disease. Moreover, it should be investigated whether cortisol levels in patients with high ESR are elevated during the night, causing the attenuated cortisol awakening levels.

The cortisol awakening response differs between patients with low and high ESR, which indicates the usefulness of prospective studies of HPA axis dynamics during the night and day in patients with SLE and pSS.

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