Serum dehydroepiandrosterone sulphate levels and laboratory and clinical parameters indicating expression of disease are not associated with fatigue, well-being and functioning in patients with primary Sjögren’s syndrome

A. Hartkamp1,3, R. Geenen1,2, A.A. Kruize1, E.R Bossema2, G.L.R. Goeaert2, H. Bootsma2, J.W.J. Bijlsma1, R.H.W.M. Derksen1

1Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, Utrecht, The Netherlands; 2Department of Clinical and Health Psychology, University Medical Center Utrecht, The Netherlands; 3Department of Rheumatology, Jeroen Bosch Hospital, ’s-Hertogenbosch, The Netherlands; 4Department of Rheumatology and Clinical Immunology, Medical Center Groningen, Groningen, The Netherlands.

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Please address correspondence and reprint requests to: Dr Rinie Geenen, Department of Clinical and Health Psychology, P.O. Box 80140, 3508 TC Utrecht, The Netherlands. E-mail: r.geenen@uu.nl

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Competing interests: none declared.

ABSTRACT

Objective. The aim of this study was to compare serum dehydroepiandrosterone sulphate (DHEAS) levels and clinical and laboratory parameters reflecting expression of disease between female patients with primary Sjögren’s syndrome (pSS) and age-matched healthy women and to examine in pSS patients the correlation of these variables with fatigue, well-being, and functioning.

Methods. Comparisons were made between 60 female pSS patients and 60 age-matched healthy women. We assessed questionnaire scores of general fatigue, depressed mood, mental well-being, and physical functioning, tear production (Schirmer I test), tender point counts, serum DHEAS level, haemoglobin concentration, erythrocyte sedimentation rate, and serum immunoglobulin G.

Results. As compared to healthy participants, patients had more fatigue and depressed mood, reduced well-being and functioning, more dryness and pain, lower serum DHEAS levels, and more expression of disease as reflected by laboratory assessments (p≤0.001). In pSS patients, fatigue, well-being, and functioning correlated with tender point counts, but not with the extent of dryness and also not with laboratory assessments including serum DHEAS levels.

Conclusion. The high prevalence of fatigue and reduced functioning in pSS patients might suggest a mediating role of generalised autoimmune processes. In the present study, clinical observations and laboratory assessments are not correlated with persistent fatigue and reduced functioning. Our results suggest that treatment of fatigue, well-being, and functioning, should target other variables than those examined in this study, preferably psychological variables or perhaps specific immunologic parameters.

Introduction

The high prevalence of fatigue and reduced well-being and physical functioning in patients with primary Sjögren’s syndrome (pSS) suggests a correlation of these variables with generalised autoimmune disease. Three classes of laboratory and clinical variables are examined in this paper. Firstly, reduced levels of dehydroepiandrosterone (DHEA) and its sulphate ester DHEAS may affect fatigue and functioning (1). In small samples of women with pSS, reduced serum levels of DHEA (2) or DHEAS (3), and a positive correlation between circulating levels of DHEAS and mental well-being were suggested (3). Secondly, while validated disease activity criteria for pSS are lacking, we investigated three general indicators of expression of disease as possible predictors of fatigue and functioning: erythrocyte sedimentation rate (ESR), serum haemoglobin concentration, and serum immunoglobulin G (IgG) level. One previous study suggested that ESR and serum haemoglobin did not correlate with fatigue (4). Thirdly, dryness and pain may influence fatigue, well-being, and functioning (5).

The aim of our study was to compare serum DHEAS levels and clinical and laboratory indicators of expression of disease between female pSS patients and age-matched healthy control women and to correlate in pSS patients these variables with fatigue, well-being and physical functioning, eventually in order to search for guidance in developing more effective interventions.

Materials and methods

Participants

Research participants were 60 female patients with pSS and 60 age-matched healthy women. Patients from the departments of Rheumatology and Clinical Immunology of the University Medical Centres of Utrecht and Groningen (the Netherlands) participated in a study that compared effects of oral administration of 200 mg DHEA and placebo (6). The current study analysed the baseline assessments. The study was approved by ethical review boards. Participants provided written informed consent.

Patients fulfilled the European criteria for classification of pSS including a focus score ≥1 on minor salivary gland biopsy (7) and were ≥18 years. Exclusion criteria were specified (6).
Assessments
- Characteristics
Age, education level, and menopausal status were assessed.
- Fatigue, depressed mood, mental well-being, and physical functioning
Fatigue was assessed using the general fatigue scale of the Multidimensional Fatigue Inventory (MFI, range 4–20) (8). The Zung self-rating depression scale (range 20–80) assessed depressed mood (9). The RAND short form-36 (SF-36) health survey (10) measured physical functioning (PCS) and mental well-being (MCS) (11).
- Clinical observations
The Schirmer I test was used to measure the mean tear production of both eyes (7). Wetting of calibrated filter paper <5.5 mm in 5 minutes was regarded abnormal. As clinical observation of pain, tender point count was performed according to classification criteria for fibromyalgia (12).
- Laboratory assessments
Serum DHEAS levels were measured using an Advantage Chemiluminescence System (Nichols Institute Diagnostics, San Juan Capistrano, USA): lower detection limit 0.2 μmol/L, inter-assay variation <11%, normal values in our laboratory 0.5–9 μmol/L. Samples were stored at -80°C and analysed in single runs. Serum haemoglobin concentration, ESR, and serum IgG level were determined according to standard procedures.

Statistical analysis
Chi-square tests, Mann-Whitney tests, and independent sample t-tests examined differences between groups with respect to frequencies (education level, pre- or post menopausal status, having an abnormal Schirmer I test, fulfilling fibromyalgia criteria), continuous variables with a non-normal score distribution (tender point counts, Schirmer I scores, general fatigue), and continuous variables with a normal score distribution (all other variables). Pearson correlations and Spearman correlations were computed for variables with a normal and non-normal score distribution. Statistical analyses were performed using SPSS 15.0; 2-sided p-values <0.05 were considered statistically significant.

### Table I. Participant characteristics, clinical observations, laboratory variables, and fatigue, well-being, and physical functioning in 60 female patients with primary Sjögren’s syndrome and 60 age-matched female, healthy research participants.

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Healthy controls</th>
<th>p-value</th>
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<tbody>
<tr>
<td><strong>Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age in years, mean (SD)</td>
<td>53.3 (13.1) 19–76</td>
<td>52.5 (12.1) 19–75</td>
<td>0.72</td>
</tr>
<tr>
<td>Education level, n (%)</td>
<td>3 (5)</td>
<td>5 (8)</td>
<td></td>
</tr>
<tr>
<td>Tertiary</td>
<td>43 (72)</td>
<td>43 (72)</td>
<td></td>
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<tr>
<td>Postmenopausal, n (%)</td>
<td>37 of 60 (62)</td>
<td>28 of 52 (54)</td>
<td>0.40</td>
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<tr>
<td><strong>Laboratory assessments</strong></td>
<td></td>
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<tr>
<td>Haemoglobin in mmol/L, mean (SD) range</td>
<td>8.1 (0.7) 6.8–9.7</td>
<td>8.5 (0.6) 7.2–10.0</td>
<td>0.001</td>
</tr>
<tr>
<td>DHEAS in μmol/L, mean (SD) range</td>
<td>1.85 (1.08) 0.35–4.60</td>
<td>2.63 (1.33) 0.53–7.70</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Clinical observations</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Abnormal Schirmer I test, n (%)</td>
<td>31 of 60 (52)</td>
<td>1 of 59 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tender point count, median (25th and 75th percentile)</td>
<td>4 (2–11)</td>
<td>0 (0–1)</td>
<td>&lt;0.001</td>
</tr>
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Results
Three assessments were taken in patients with pSS only: disease duration (mean 7.0, SD=5.9, range 0.3–24.0, years), ESR (mean 32, SD=26, range 2–109, mm/h), and serum IgG level (mean 18.6, SD=8.1, range 8.8–47.2 g/L).

Group comparisons
- Characteristics
Patients and healthy participants did not differ with respect to age (t=0.36, p=0.72), education level (χ²=0.65, p=0.72), or menopausal status (χ²=0.70, p=0.40) (Table I).
- Clinical observations
An abnormal Schirmer I test was found in 52% of pSS patients and in one healthy participant (χ²=37.79, p<0.001). PSS patients had more tender points than healthy control participants (U=571, p=0.001); 23% (14/60) of pSS patients and none of the healthy participants met the fibromyalgia classification criteria.

Fig. 1. Dehydroepiandrosterone sulphate (DHEAS) levels in female patients with pSS and age-matched female healthy control (HC) participants. Data are shown as dots for every participant and boxplots. Each box represents the 25th to 75th percentiles. Bars outside the boxes represent the 10th to 90th percentile.
Laboratory assessments
Mean serum haemoglobin concentration was lower in pSS patients than in healthy participants \( (t = -3.44, p = 0.001) \).
As shown in Figure 1, DHEAS levels in pSS patients were low compared to levels in healthy participants \( (t = -3.54, p = 0.001) \). None of the DHEAS levels was below the detection limit of the assay or below normal age-related values. The correlations between lower DHEAS levels and a higher age \( r = -0.49 \) \( (p < 0.001) \) in pSS patients and \( r = -0.26 \) \( (p = 0.047) \) in healthy controls.

- Fatigue, well-being, and physical functioning
Compared to healthy participants, pSS patients reported more general fatigue \( (U = 236, p < 0.001) \), more depressed mood \( (r = 0.57, p < 0.001) \), reduced mental well-being \( (MCS, r = -0.07, p < 0.001) \), and reduced physical functioning \( (PCS, r = -13.51, p < 0.001) \). More than 75% of the patients rated their fatigue as more severe than the worst scoring 25% of healthy participants. The effect sizes of the difference between the two groups were large \( (d > 0.8) \) for depressed mood \( (d = 1.2) \) and physical functioning \( (d = 2.6) \), and moderate \( (d > 0.5) \) for mental well-being \( (d = 0.7) \).

Correlational analyses
- Dehydroepiandrosterone sulphate
The correlations between serum DHEAS and fatigue \( (rho = -0.01, p = 0.97) \), depressed mood \( (r = 0.02, p = 0.89) \), mental well-being \( (r = 0.00, p = 0.99) \), and physical functioning \( (r = -0.05, p = 0.73) \) were far from significant and remained non-significant after adjustment for age \( (p > 0.18) \).
- Patient characteristics, clinical observations, and laboratory variables
Significance was observed for only three of 36 correlations of fatigue, depressed mood, mental well-being, and physical functioning with the characteristics age, education level, menopausal status, and disease duration, the clinical observations Schirmer I test and fibromyalgia tender point count, and the laboratory assessments haemoglobin, ESR, and serum IgG level. A worse score on physical functioning was correlated with more tender points \( (rho = -0.39, p = 0.002) \) and a higher score on the Schirmer I test \( (rho = -0.44, p < 0.001) \). Also fatigue was correlated with a higher score on the Schirmer-I test \( (rho = 0.26, p = 0.049) \).

Discussion
Female pSS patients reported more fatigue and depressed mood, less well-being, and more impaired physical functioning than age-matched healthy female control participants, and they deviated on laboratory and clinical variables: lower serum DHEAS and haemoglobin levels, increased ESR and serum-IgG levels, and more dryness and pain. Fatigue, depressed mood, well-being, and physical functioning were not correlated with laboratory assessments or demographic variables. Worse physical functioning correlated with more tender points. Both worse physical functioning and fatigue correlated with less ocular dryness.

Our study confirms previous observations of reduced serum DHEAS levels (2-3), more fatigue, and reduced well-being and functioning in women with pSS (5, 13-14). In contrast with a previous observation comprising 21 patients \( (3), \) serum DHEAS levels were not associated with any of these variables in our study of 60 patients. Our results do not suggest a role of DHEA in fatigue, well-being, and physical functioning of women with pSS. Although, at onset of disease, perhaps autoimmune inflammation may play a role in initiating fatigue and reduced well-being and functioning, in our sample of patients with established pSS, ESR, serum IgG level, and serum haemoglobin as parameters of expression of disease were not correlated with fatigue and reduced well-being and functioning. Recent clinical trials with rituximab indicate that perhaps other pathophysiological factors such as B cell hyperactivity play a role in persistence of fatigue.

More tender points were associated with reduced physical functioning, as expected \( (12) \). A previous study found no associations of sicca features with well-being and functioning \( (15) \). Our observation that less instead of more dryness was associated with fatigue and reduced physical functioning is opposite to the hypothesis that the disease process reduces functioning. This may reflect that pSS is a heterogeneous disease including both patients with many features of autoimmune involvement and patients whose main feature is severe dryness as well as fatigue and reduced physical functioning.

Our study did not take account of extraglandular manifestations. The findings cannot be generalised beyond the studied sample and variables. Our study does not suggest a role of disease-related variables in fatigue and functioning of patients with pSS. When thinking of treating fatigue, well-being, and functioning in pSS patients, it is possible that in the future other – more specific immunologic – variables than those examined in this study could be targeted. At the moment, although fatigue and reduced well-being and physical functioning are indisputably adverse consequences of the disease, to target these variables behavioural means such as life-style adjustment and cognitive-behaviour, physical exercise, and sleep hygiene interventions should be considered.

References
Fatigue in Sjögren’s syndrome / A. Hartkamp et al


