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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. Hartkamp[1,3], R. Geenen[1,2], A.A. Kruize[1], E.R Bossema[2], G.L.R. Godaert[2], H. Bootsma[4], J.W.J. Bijlsma[1], R.H.W.M. Derksen[1]

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

André Hartkamp, MD
Rinie Geenen, PhD
Aike A. Kruize, MD, PhD
Ercolie R. Bossema, PhD
Guido L.R. Godaert, PhD
Hendrika Bootsma, MD, PhD
Johannes W.J. Bijlsma, MD, PhD
Ron H.W.M. Derksen, MD, PhD

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

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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 ($p \leq 0.001$). 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 Chemiluminescense 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.

	Patients	Healthy controls	*p*-value
Characteristics			
Age in years, mean (SD) range	53.3 (13.1) 19–76	52.5 (12.1) 19–75	0.72
Education level, n (%)			0.72
Primary	3 (5)	5 (8)	
Secondary	43 (72)	43 (72)	
Tertiary	14 (23)	12 (20)	
Postmenopausal, n (%)	37 of 60 (62)	28 of 52 (54)	0.40
Clinical observations			
Abnormal Schirmer I test, n (%)	31 of 60 (52)	1 of 59 (2)	<0.001
Tender point count, median (25^{th} and 75^{th} percentile)	4 (2–11)	0 (0–1)	<0.001
Laboratory assessments			
Haemoglobin in mmol/L, mean (SD) range	8.1 (0.7) 6.8–9.7	8.5 (0.6) 7.2–10.0	0.001
DHEAs in μmol/L, mean (SD) range	1.85 (1.08) 0.35–4.60	2.63 (1.33) 0.53–7.70	0.001
Fatigue, well-being, and physical functioning			
General fatigue, median (25^{th} and 75^{th} percentile)	19 (14–20)	5 (4–8)	<0.001
Depressed mood, mean (SD) range	42.5 (7.5) 23–58	33.2 (8.1) 20–60	<0.001
Mental well-being, mean (SD) range	43.9 (10.8) 10.7–59.2	51.3 (9.1) 24.3–63.4	<0.001
Physical functioning, mean (SD) range	34.1 (9.6) 10.1–54.6	53.4 (5.5) 37.5–64.4	<0.001

Notes: Statistical tests for variables of which the mean and SD are shown were *t*-tests, for variables of which numbers are shown χ^2-tests, and for variables of which median and the interquartile ranges between the 25^{th} and 75^{th} percentile are shown Mann-Whitney tests.

For General Fatigue (MFI) and Depressed mood (Zung), a higher score reflects more fatigue and more depressive symptoms, respectively. For mental well-being and physical functioning, a higher score reflects better quality of life.

Women with a regular menses were considered premenopausal. Postmenopausal status was defined by amenorrhoea for at least one year in women with a uterus in situ and in hysterectomised women by serum follicle stimulating hormone (FSH) level >35 IU/L. Because FSH was not assessed in healthy women, menopausal status of 8 healthy women aged 48 to 54 years was not known.

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 (χ^2=0.65, p=0.72), or menopausal status (χ^2=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 (χ^2=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.

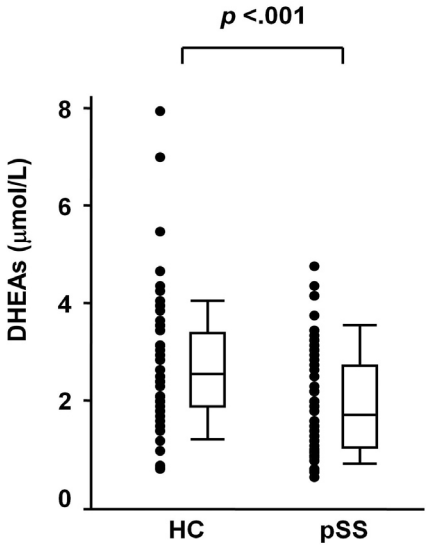

Fig. 1. Dehydroepiandrosterone sulphate (DHEAS) levels in female patients with pSS and age-matched female healthy control (HC) participants. Data are shown as dots for every participant and boxplots. Each box represents the 25^{th} to 75^{th} percentiles. Bars outside the boxes represent the 10^{th} to 90^{th} 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 were 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 (t=6.57, p<0.001), reduced mental well-being (MCS, t= -4.07, p<0.001) and, reduced physical functioning (PCS, t= -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.

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