The Significance of Dehydroepiandrosterone for Fatigue in primary Sjögren's Syndrome and Systemic Lupus Erythematosus

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De rol van dehydroepiandrosteron in moeheid bij
het primaire syndroom van Sjögren en
systemische lupus erythematosus
(met een samenvatting in het Nederlands)

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof. dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op dinsdag
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Door

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Promotoren: Prof. dr. R.H.W.M. Derksen
Prof. dr. R. Geenen

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Chapter 1

General Introduction

GENERAL INTRODUCTION

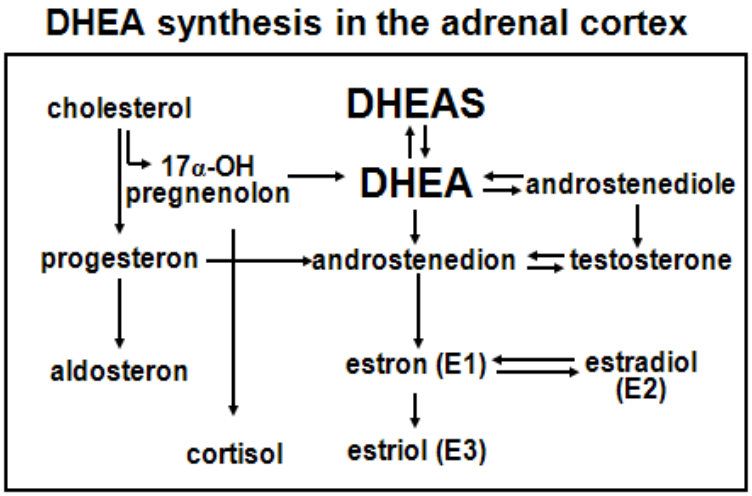
Fatigue is a major complaint in many patients suffering from the chronic autoimmune disorders primary Sjögren's syndrome (pSS) or systemic lupus erythematosus (SLE).[1,2] Patients with these disorders frequently consider fatigue as their major handicap with influences on many aspects of daily life. Doctors very much recognize the existence of this problem, but are unable to treat it. Besides fatigue, patients with pSS or SLE have been noticed to have reduced well-being and physical functioning compared to the general population.[3-26]

There are many suggestions that the weak androgen hormone dehydroepiandrosterone (DHEA) relates to these abnormalities.[55,57,68]

This thesis examines relationships between DHEA and fatigue, well-being, physical functioning, and (surrogate parameters of) disease activity in patients with pSS and SLE.

Dehydroepiandrosterone(-sulphate)

Dehydroepiandrosterone (DHEA) and its sulfate ester DHEA-S are weak androgens secreted by human adrenal glands in response to corticotrophic hormone.[39]



DHEA and DHEA-S are interconvertable and DHEA can be converted both in the adrenal gland and peripheral target tissues into active androgens and estrogens.[38] In humans, serum levels of DHEA(-S) progressively decline from peak levels in the third decade of life with approximately 70-80% over the next five decades.[40-42]

Several studies concluded that DHEA, administered to elderly people, can improve age-related phenomena and sense of well-being.[43-48] Positive effects of administration of DHEA on fatigue, mood, anxiety, depression and overall well-being has also been described in a variety of disease states.[49-54] Strong support for positive effects of DHEA suppletion (apart from cortico- and mineralocorticoid substitution) on well-being comes from a double-blind cross-over study in women with DHEA deficiency due to adrenal insufficiency.[54] In patients with pSS and SLE decreased serum levels of DHEA have been described. [34,55-57,62,63] The studies suggest that DHEA(S) may be a mediator of fatigue, well-being, and functioning in primary Sjögren's syndrome (pSS) and systemic lupus erythematosus (SLE).[34-38]

Primary Sjögren's syndrome

Primary Sjögren's syndrome (pSS) is a chronic autoimmune disorder characterized by lymphocytic infiltration of exocrine glands. Hallmark symptoms are dryness of the eyes (keratoconjuncivitis sicca) and mouth (xerostomia). This exocrinopathy can be encountered alone (primary Sjögren's syndrome, pSS) or in presence of another autoimmune disease, such as rheumatoid arthritis, systemic lupus erythematosus, or systemic sclerosis (secondary Sjögren's syndrome, sSS). The disease has female preponderance and manifests itself most frequently in the fourth and fifth decade of life.[1]

There is no global accepted diagnostic set of criteria for the diagnosis of primary Sjögren's syndrome, but recently the American-European Consensus group suggested a new set of classification criteria (Table 1).[73]

Many patients with pSS experience severe fatigue and reduced well-being and physical function.[3-16,27-31,33]
Studies with small numbers of included patients suggested that women with pSS can be androgen deficient with reduced serum levels of DHEA or DHEA-S relative to age matched controls. [55-57] One study reported a positive relationship between circulating levels of DHEA-S and mental well-being in pSS.[57] Interestingly, studies in a female mouse model of Sjögren's syndrome showed that administration of androgens strongly suppresses inflammatory manifestations.[58-60] A possible mode of action of DHEA is inhibition of proinflammatory cytokines.[61] Proinflammatory cytokines are known to trigger a complex set of events leading to fatigue and psychological and functional malaise known as sickness behaviour.[75,76]

The first part of this thesis includes three studies in patients with pSS. The aim of these studies was an evaluation of the role of dehydroepiandrosterone in fatigue, depressive mood, mental well-being, and physical functioning in this disease. By analysis of surrogate inflammatory parameters, we also assessed influences of the disease process itself.

Table 1. Revised international classification criteria for Sjögren's syndrome.[73]

I. Ocular symptoms: a positive response to at least one of the following questions:

1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
2. Do you have a recurrent sensation of sand or gravel in the eyes?
3. Do you use tear substitutes more than 3 times a day?

II. Oral symptoms: a positive response to at least one of the following questions:

1. Have you had a daily feeling of dry mouth for more than 3 months?
2. Have you had recurrently or persistently swollen salivary glands as an adult?
3. Do you frequently drink liquids to aid in swallowing dry food?

III. Ocular signs—that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:

1. Schirmer's I test, performed without anaesthesia (≤5 mm in 5 minutes)
2. Rose bengal score or other ocular dye score (≥4 according to van Bijsterveld's scoring system)

IV. Histopathology: In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score ≥1, defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm2 of glandular tissue

V. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:

1. Unstimulated whole salivary flow (≤1.5 ml in 15 minutes)
2. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary or destructive pattern), without evidence of obstruction in the major ducts[19]
3. Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer[20]

VI. Autoantibodies: presence in the serum of the following autoantibodies:

1. Antibodies to Ro(SSA) or La(SSB) antigens, or both

Rules for classification for primary SS

In patients without any potentially associated disease, primary SS may be defined as follows:

a. The presence of any 4 of the 6 items is indicative of primary SS, as long as either item IV (Histopathology) or VI (Serology) is positive.

b. The presence of any 3 of the 4 objective criteria items (that is, items III, IV, V, VI).

c. The classification tree procedure represents a valid alternative method for classification, although it should be more properly used in clinical-epidemiological survey.

Exclusion criteria:

Past head and neck radiation treatment, Hepatitis C infection, Acquired immunodeficiency disease (AIDS), Pre-existing lymphoma, Sarcoidosis, Graft versus host disease, Use of anticholinergic drugs (since a time shorter than 4-fold the half life of the drug).

Chapter 2.

This chapter describes a cross-sectional study in a relatively large sample of patients and matched healthy control subjects. Aim of the study was to compare serum DHEAS levels and

clinical and laboratory indicators of pSS between patients and controls. In the pSS patients, the presence or absence of an association between serum DHEAS levels and fatigue, well-being and physical functioning was evaluated.

Chapter 3.
If there is a direct association between serum levels of proinflammatory cytokines and fatigue in pSS, this can have direct therapeutical consequences, given the current possibilities of direct anti-cytokine treatment with so-called biologicals. This chapter describes a study that evaluates serum levels of interleukin (IL)-1β, IL-2, IL-6, IL-10, and tumor necrosis factor alpha (TNF-α) with multiple dimensions of fatigue.

Chapter 4.
Several observations suggest that administration of DHEA might have beneficial effects on fatigue, well-being, and functioning in patients with pSS. These include, among others, the following observations: 1. women with pSS appear androgen deficient.[55] 2. reduced serum levels of DHEA or DHEAS have been observed in patients with pSS.[56-57] 3. circulating levels of DHEAS associate with mental well-being.[57] 4. in a mouse model of Sjögren's syndrome androgens suppressed inflammation.[58-60] Based on this, we performed a double-blind placebo-controlled trial to study effects of daily oral administration of 200 mg DHEA on fatigue, well-being, functioning, and surrogate parameters of disease activity.

The second part of this thesis includes three studies in patients with SLE. These studies describe the possible role of DHEA on fatigue, depressive mood, mental well-being, physical functioning, disease activity, and bone mineral density.

Systemic lupus erythematosus

SLE is a chronic multisystem autoimmune connective tissue disorder with a broad range of clinical presentations. SLE has a female preponderance with a women to men ratio of 9 to 1. The course of SLE is characterized by remissions and exacerbations. SLE can be life threatening when major organs are affected.[2]

The American College of Rheumatology (ACR) developed widely accepted classification criteria for SLE (Table 2).[74]

Table 2. The 1982 revised criteria for classification of systemic lupus erythematosus.[74]

Criterion	Definition
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Arthritis	Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	a) Pleuritis--convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion *OR* b) Pericarditis--documented by ECG or rub or evidence of pericardial effusion
7. Renal disorder	a) Persistent proteinuria greater than 0.5 grams per day or grater than 3+ if quantitation not performed *OR* b) Cellular casts--may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic disorder	a) Seizures--in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance *OR* b) Psychosis--in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic disorder	a) Hemolytic anemia--with reticulocytosis *OR* b) Leukopenia--less than 4,000/mm^3 total on 2 or more occasions *OR* c) Lymphopenia--less than 1,500/mm^3 on 2 or more occasions *OR* d) Thrombocytopenia--less than 100,000/mm^3 in the absence of offending drugs
10. Immunologic disorder	a) Positive LE cell preparation *OR* b) Anti-DNA: antibody to native DNA in abnormal titer *OR* c) Anti-Sm: presence of antibody to Sm nuclear antigen *OR* d) False positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test
11. Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome

* The proposed classification is based on 11 criteria. For the purpose of identifying patients in clinical studies, a person shall be said to have systemic lupus erythematosus if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.

Many patients with SLE experience disabling fatigue and reduced well-being and physical function.[17-26,28,32,33] When was asked what the most disabling symptom of their disease was, over half of the patients with SLE reported that this was fatigue, despite the fact that this group of interviewed patients comprised many patients with previous severe manifestations that required strong immunosuppressive treatment, like nephritis.[17]

Low serum levels of DHEA(S) in patients with SLE have been reported irrespective of glucocorticoid use.[34,62,63]

In SLE several studies in which DHEA was administered have been published. Patients included had mild to moderate active SLE,[36,64-69] and improvement or stabilization of signs

and symptoms of the disease were reported. DHEA was noted to have steroid sparing effects and reduced the number of flares of the disease.[64-69]
In a small open study improvement in overall well-being and fatigue was noted when DHEA was given,[68] and in steroid-using SLE patients administration of low dose DHEA (20 or 30 mg per day) improved mental well-being and sexuality.[70]
Not surprisingly, there is an association between circulating DHEA(S) levels and bone mineral density (BMD),[71] and in SLE patients with active disease the addition of 200 mg DHEA a day to treatment with high-dose glucocorticoids prevented significant reduction in BMD.[65] The latter is of special interest since in patients with SLE a high incidence of osteopenia and osteoporotic vertebral fractures were found.[72]
Of importance, all studies conclude that administration of DHEA is well tolerated with acne being the most frequently noted side effect.

Chapter 5.
Based on observations that 1. SLE patients have low DHEA(S) levels, 2. fatigue is an important problem in most SLE patients, and 3. suggestions on correlations between DHEAS levels and well-being, we performed a cross-sectional study on the association between levels of DHEA(S) and fatigue.
Included in the study were only patients with a low level of disease activity since it had been shown that both disease activity and glucocorticoid administration may influence both serum levels of DHEAS and fatigue. Analysis for patients with and without use of glucocorticoids were done separately.

Chapter 6.
This chapter describes a randomized double-blind placebo-controlled study of the effects of daily oral administration of 200 mg DHEA on fatigue, well-being, functioning, and disease activity in patients with SLE. Only patients with quiescent SLE were included to avoid confounding by disease activity and the use of more than small doses of prednisone.

Chapter 7.
This chapter evaluates the presence of possible beneficial effects of administration of 200 mg DHEA per day on bone density as measured in the lumbar spine (bone mineral density, BMD).

Methods

The studies described in this thesis were performed in 120 outpatients of the departments of Rheumatology and Clinical Immunology of the University Medical Centers in Utrecht and Groningen. Both correlational and clinical experimental designs, using standardized questionnaires as well as laboratory and clinical variables, examined the possible significance of dehydroepiandrosterone in pSS and SLE. The cross-sectional studies compared 60 female patients with pSS and 60 female patients with SLE with for each patient group 60 age-matched healthy, female control subjects. The experimental studies involve double-blind, randomized, placebo-controlled clinical trials with 30 patients receiving 200 mg oral DHEA (Fagron, Nieuwerkerk a/d IJssel, Netherlands) and 30 patients on placebo per patient group. At baseline, after 3, 6, and 12 months on study medication, and 6 months after cessation of treatment, outcome parameters were assessed.

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Chapter 2

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

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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 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 auto-immune 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 function, eventually in order to search for guidance in developing more effective interventions.

PATIENTS 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.

General fatigue, depressed mood, mental well-being, and physical functioning.
Fatigue was assessed with the general fatigue scale of the Multidimensional Fatigue Inventory (MFI, range 4-20).[8] The Zung self-rating depression scale (range 20-80) assessed depressive mood.[9] The RAND short form-36 (SF-36) health survey[10] measured physical functioning (physical component summary (PCS)) and mental well-being (mental component summary (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

χ-square tests, Mann-Whitney tests, and independent samples *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*-value s < 0.05 were considered statistically significant.

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 1).

Table 1. 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			
Tender point count, median	4 (2-11)	0 (0-1)	<0.001
Laboratory assessments			
Fatigue, well-being, and physical functioning			
General fatigue, median (25th and 75th perc.)	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 25th and 75th 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 amenorrhea 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.

Clinical observations.

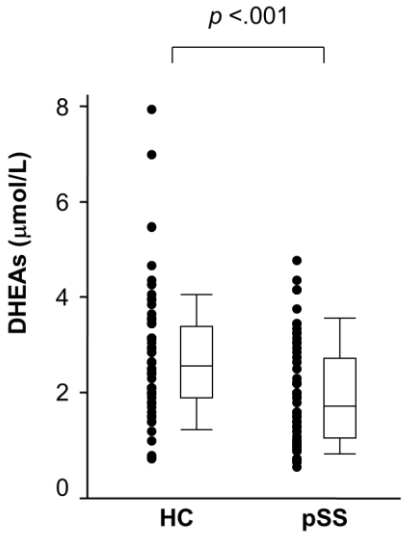
An abnormal Schirmer I test was found in 52% of pSS patients and in one healthy participant (χ^2 = 37.79, p < 0.001). PSS patients had more tender points than control participants (U = 571, p < 0.001); 23% (14/60) of pSS patients and none of the healthy participants met the fibromyalgia criteria.

Laboratory assessments.

Mean serum haemoglobin concentration was lower in pSS patients than in healthy controls (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 participants.

Figure 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.

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 general 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 general 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 general 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 auto-immune 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-behavioural, physical exercise, and sleep hygiene interventions should be considered.

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Chapter 3

Serum cytokine levels related to multiple dimensions of fatigue in patients with primary Sjögren's syndrome

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ABSTRACT

Objective: To test whether serum levels of selected cytokines relate to different dimensions of fatigue in patients with primary Sjögren's syndrome (pSS).

Methods: Sixty female patients with pSS filled out a questionnaire to assess multiple dimensions of fatigue. Scores were compared to values in a population-based control group. Levels of interleukin (IL)1β, IL2, IL6, IL10, and tumor necrosis factor alpha (TNFα) were measured in serum with commercial sandwich ELISAs. The relationship between self-reported dimensions of fatigue and these serum cytokine levels was determined.

Results: Patients with pSS had high scores at all dimensions of fatigue ($p<0.001$): general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue. Fatigue levels were not related to serum cytokine levels. The incidental finding that reduced motivation was higher in patients with detectable serum levels of IL10 ($p=0.04$) disappeared after correction for multiple testing.

Conclusion: Fatigue is prominent in patients with pSS and involves all dimensions of fatigue. The findings do not suggest a widespread effect of circulating cytokines on multiple aspects of fatigue.

INTRODUCTION

Primary Sjögren's syndrome (pSS) is a chronic autoimmune disease that primarily affects the exocrine glands. The disease has a female preponderance and manifests itself most commonly in the fourth and fifth decade of life. The clinical picture varies from mild complaints of ocular and oral dryness to severe keratoconjuctivitis sicca and a variety of extraglandular features.[1] For many patients with pSS fatigue is a prominent and disabling feature.[2]

In pSS, both cells constituting the characteristic glandular periductal infiltrates as well as the ductal epithelial cells actively produce a variety of (pro-inflammatory) cytokines. Compared with healthy controls, patients with pSS have increased serum levels of IL2,[3] IL6,[3,4] and IL10.[3,5] Several observations link cytokines to fatigue. In animal studies administration of IL1β, tumor necrosis factor α (TNFα), or lipopolysaccharide leads to decreased activity and increased somnolence.[6] In man, cytokine treatment with TNFα,[7] IL2,[8] or IL6,[9] is associated with flu-like symptoms including fatigue, depressed mood, and cognitive disturbances. In patients with rheumatoid arthritis reduction of fatigue is seen with TNFα blocking therapy.[10] These data strongly suggest a role of cytokines as triggers for a complex set of events leading to physiological, behavioural, affective, motivational, and cognitive changes known as sickness behaviour.[6] The finding of a significant association between serum cytokine levels and fatigue provides a rationale to direct future treatments at proinflammatory cytokines. In this study we test whether serum levels of selected cytokines relate to multiple dimensions of fatigue in patients with pSS.

PATIENTS AND METHODS

Participants were 60 patients from the departments of Rheumatology and Clinical Immunology of the University Medical Centre Utrecht and the University Hospital Groningen, The Netherlands, who consecutively gave informed consent to participate in a placebo-controlled study on the effects of administration of dehydroepiandrosteron (DHEA) on fatigue and general well-being. Inclusion criteria were female sex, a focus score ≥ 1 on minor salivary gland biopsy, meeting at least four of the European criteria for the classification of primary Sjögren's syndrome,[11] normal serum creatinine and thyroid stimulating hormone levels, and no use of corticosteroids in the preceding year. The mean (SD) age of patients was 53.3 (13.1) years. The current study took place before the start of treatment with DHEA or placebo.

All patients completed the Multidimensional Fatigue Inventory (MFI)[12], a 20-item self-report questionnaire covering five dimensions of fatigue: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue. This scale has been used and

validated in a variety of conditions, including pSS.[2]

As surrogate parameters of disease activity erythrocyte sedimentation rate (ESR), haemoglobin concentration (Hb), and total serum immunoglobulin G (IgG) were used.

Levels of IL1β, IL2, IL6, IL10, and TNFα were measured in undiluted serum samples by enzyme linked immunosorbent assay (ELISA) according to the manufacturer's instructions (BioSource International, Inc. Camarillo, Ca., USA). The range of detection for the assay used is for IL1β: 0.19-20 pg/ml, for IL2: 0.1-30 U/ml, for IL6: 0.104-10 pg/ml, for IL10: 0.2-50 pg/ml, and for TNFα: 0.09-32 pg/ml.

Statistical analyses.

The fatigue scores and disease activity parameters were normally or nearly normally distributed; the skewness of the distribution of the scores was between 0.16 for 'reduced motivation' and –1.57 for 'general fatigue'. It was decided to not resort to non-parametric statistics or improve normality by transforming variables, because it was considered not valid to change these scores by transformation and because of the impossibility of adjusting non-parametric scores for the effect of age. Univariate analysis of variance was used to compare the disease activity and fatigue scores for patients with cytokine levels below and above the detection limit of the assay used. As cytokine levels, surrogate measures of disease activity, and fatigue levels may all depend on age, analyses were adjusted for age.

The fatigue scores of our patients were compared with the scores of a normal healthy control population as described by the investigators who developed the MFI questionnaire.[13] This group comprised 78 women and 61 men with a mean (SD) age of 46 (16) years. Effect-sizes were computed to quantify the extent to which the scores of our group deviated from scores of the control group. [14] An individual score of a patient (*X)* minus the control group average (*M*) divided by the standard deviation of a control group results in the effect-size: *(X – M)/ SD* . Effect-sizes of 0.2, 0.5, and 0.8 indicate small, moderate, and large deviations from the norm, respectively. Univariate analyses of variance with age as covariate were applied to compare patients with cytokine levels below and above the lower detection limit for disease activity parameters and fatigue scores.

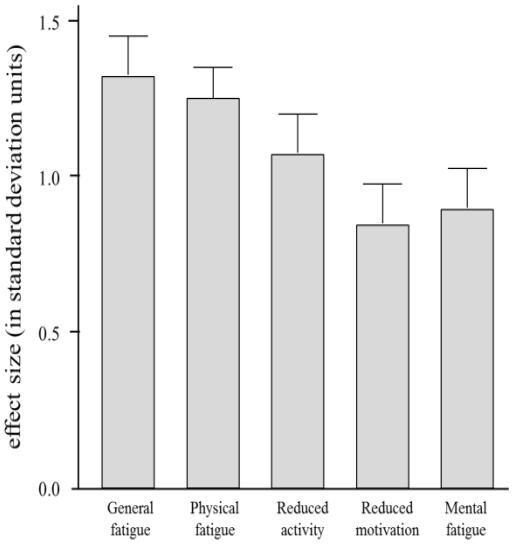
Analyses were done with SPSS. All tests were 2-sided, and p values < 0.05 were considered significant. To take account of multiple testing, the Bonferroni criterion (the normal α divided by the number of tests) was used to interpret findings and determine significance.

RESULTS

The mean scores of the patients showed for all dimensions of fatigue an effect size deviation of the control group that was large and highly significant ($p<0.001$; Figure 1).

Taking a large effect-size deviation of 0.8 standard deviation from the norm or more as classification criterion for fatigue for each MFI subscale, general fatigue and physical fatigue was present in 45 (75 %) of the patients, reduced activity in 38 (63%), and reduced motivation and mental fatigue in 31 (52 %) of patients.

Figure 1.



Effect sizes (mean (SEM)) at five dimensions of fatigue of the Multidimensional Fatigue Inventory (MFI). Effect sizes compare scores assessed in 60 patients with primary Sjögren's syndrome with a normal control population.

Within the group of 60 patients a cytokine level above the lower range of detection of the assay used was present in 8 (13%) patients for IL2, 5 (8%) for IL6, 19 (32%) for IL10, and 50 (83%) for TNFα. No sample had detectable levels of IL1β. The mean (SD) ESR, haemoglobin, and IgG levels were 32.4 mm (26.1) mm/1st h, 8.1 (0.7) mmol/L, and 18.3 (8.3) g/L, respectively. Mean levels of ESR, haemoglobin, and IgG were significantly higher in patients with detectable IL2, IL6, IL10, and TNFα levels than in patients with levels below the lower detection limit ($p \leq 0.01$), except for mean IgG levels in patients below and above the detection limit for TNFα ($p=0.06$). Fatigue scores did not correlate with ESR, IgG, or haemoglobin, except for a correlation between the dimension reduced motivation and IgG ($r = 0.27$, $p = 0.04$).

Table 1 shows the mean fatigue scores of patients with or without detectable levels of IL2, IL6, IL10, and TNFα. The only significant association between reduced motivation and IL10 disappeared when the level of significance was set to the Bonferroni criterion.

Table 1. Mean (SD) fatigue levels of patients with serum cytokine levels below (<) and above (>) the detection limit

	IL2 U/mL			IL6 pg/mL			IL10 pg/mL			TNFα pg/mL		
	<	>	p	<	>	p	<	>	p	<	>	p
General fatigue	16.7 ± 4.4	18.0 ± 3.0	0.38	16.7 ± 4.3	18.0 ± 3.5	0.55	16.5 ± 4.7	17.5 ± 2.8	0.56	17.0 ± 3.6	16.8 ± 4.4	0.73
Physical fatigue	14.9 ± 3.9	15.5 ± 4.1	0.67	14.9 ± 4.0	15.6 ± 2.7	0.72	14.6 ± 4.4	15.7 ± 2.5	0.39	15.6 ± 4.4	14.8 ± 3.8	0.52
Reduced activity	13.6 ± 4.3	13.8 ± 4.9	0.90	12.5 ± 4.3	14.4 ± 5.3	0.69	13.3 ± 4.7	14.3 ± 3.6	0.44	14.3 ± 5.3	13.5 ± 4.2	0.54
Reduced motivation	11.5 ± 3.8	12.4 ± 4.7	0.58	11.4 ± 3.9	14.2 ± 2.9	0.11	11.0 ± 3.8	12.9 ± 3.8	0.04	12.3 ± 3.6	11.5 ± 4.0	0.64
Mental fatigue	12.6 ± 5.0	12.9 ± 5.9	0.88	12.9 ± 5.0	8.8 ± 4.4	0.08	12.5 ± 5.5	12.9 ± 4.2	0.74	13.0 ± 5.2	12.5 ± 5.1	0.80

The numbers of patients with serum cytokine levels below (<) and above (>) the detection limits of the assays were: 52 and 8 for IL-2, 55 and 5 for IL-6, 41 and 19 for IL-10, and 10 and 50 for TNF-α, respectively; the range of the fatigue subscales is 4 to 20.

DISCUSSION

Our study confirms that many patients with pSS have abnormally high fatigue levels at all dimensions of fatigue. We hypothesized that in the chronic inflammatory disorder pSS, persistent fatigue is mediated by overproduction of cytokines and that serum levels of cytokines might relate to fatigue. As expected, we found an association between serum levels of cytokines and markers of disease activity in pSS, i.e. ESR, haemoglobin and IgG. We consider this finding as a sign of validity of our data on serum cytokine levels.

There are only a limited number of studies on serum cytokine levels to which our data can be compared. With the assays used, we found levels above the lower detection limit in none of the patients for IL1β, in 8-32% for IL2, IL6, and IL10 and in 83% for TNF-α. Levels above the detection limit of the assay used were reported in 29/31 (93%) patients with pSS for IL-6,[4] and 31/53 (58%) patients with pSS for IL10.[5] The frequency for detectable levels of IL6 (8%) in our study was relatively low. Possible explanations are the different sensitivities of sandwich ELISAs used and differences in pSS populations studied. It has been reported that pSS patients have higher mean serum levels of IL2,[3] IL6,[4] and IL10[5] than healthy controls, and

that mean TNFα[3] levels are similar. However, these studies did not indicate how many patients had undetectable levels.[3,4]

Few studies have investigated the possible association between fatigue and serum cytokine levels. In patients with systemic lupus erythematosus, no association was found between fatigue and circulating levels of cytokines,[15] but in fatigued breast cancer survivors higher levels of serum markers of proinflammatory cytokine activity were found than in non-fatigued survivors.[16] In contrast to our study, these studies did not use multidimensional fatigue assessments, which have been shown to be useful in patients with breast cancer during radiotherapy, where physical and cognitive fatigue were increased, while affective fatigue was not changed.[17] We found that although patients with pSS are fatigued at all dimensions, levels of serum cytokines were definitely not related to physical dimensions of fatigue. The small number of patients with detectable IL6 and IL10 levels might have reduced the possibility of finding a significant association between levels of these cytokines and reduced motivation.

The absence of an association between serum levels of cytokines and dimensions of fatigue does not necessarily mean that the theory that cytokines are related to fatigue is wrong. The pronounced physiological and behavioural changes noted when cytokines are given to patients[7-9] might be due to the much higher levels of circulating cytokines that are thus induced. Furthermore, levels of circulating, peripherally produced cytokines may not reflect the local situation in the central nervous system as proinflammatory cytokines can induce synthesis and release of cytokines by glial, vascular, and immune cells in the brain itself.[6]

In conclusion, with the exception perhaps of the motivational aspect of fatigue, our findings do not reflect a widespread effect of serum cytokines on multiple aspects of fatigue.

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Chapter 4

Effect of dehydroepiandrosterone administration on fatigue, well-being, and functioning in women with primary Sjögren's syndrome: a randomized controlled trial

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ABSTRACT

Objective: Dehydroepiandrosterone (DHEA) administration has been reported to improve fatigue, psychological distress, and physical disability. These are common features of primary Sjögren's syndrome (pSS). We investigated the effects of DHEA administration on fatigue, well-being, and functioning in women with pSS.

Methods: In a double-blind, randomized placebo-controlled clinical trial, 60 female patients with pSS received 200 mg oral DHEA or placebo. Primary outcome measures were general fatigue, depressive mood, mental well-being, and physical functioning. In addition, pain, sicca complaints and disease activity parameters were measured. Patients were assessed before treatment, after 3, 6, and 12 months on study medication, and 6 months after cessation of treatment.

Results: Patients from both the DHEA- and placebo-treated group improved on general fatigue ($p < 0.001$), mental well-being ($p = 0.04$), and depressive mood ($p = 0.008$). Physical functioning did not change ($p = 0.44$). Of the secondary outcome variables, complaints of a dry mouth diminished during treatment in both groups ($p = 0.006$), the erythrocyte sedimentation rate showed a decrease for the DHEA group ($p = 0.02$), and complaints of dry eyes improved in the placebo group ($p = 0.01$). The belief to have used DHEA was a stronger predictor for improvement of fatigue and well-being than the actual use of DHEA.

Conclusions: Our study does not support a superior effect of DHEA over placebo in female patients with pSS. Both DHEA and placebo induce improvement of fatigue and well-being. This may suggest possibilities for cognitive-behavioral interventions.

INTRODUCTION

The chronic autoimmune disorder primary Sjögren's syndrome (pSS) is characterized by lymphocytic infiltration of exocrine glands. Hallmark symptoms are dryness of the eyes (keratoconjuncivitis sicca) and mouth (xerostomia). The disease has female preponderance and manifests itself most frequently in the fourth and fifth decade of life.[1] Many patients with pSS experience disabling fatigue and reduced mental well-being and physical functioning.[2-6] Chronic widespread pain is frequent with 10 to 55 percent of patients fulfilling the criteria of fibromyalgia.[7]

Attention has been drawn to the influence of dehydroepiandrosterone (DHEA) and its sulfate ester DHEAS on autoimmune diseases.[8] DHEA and DHEAS are weak androgens secreted by human adrenal glands in response to adrenocorticotrophic hormone. DHEA administration can improve fatigue and well-being in elderly[9-11] and in a variety of disease states.[12-17] In female patients with systemic lupus erythematosus (SLE), improved well-being and fatigue,[18] and reduced disease activity[19,20] were observed with oral DHEA (200 mg per day).

Women with pSS appear androgen deficient.[21,22] Reduced serum levels of DHEA or DHEAS were observed as well as a correlation between circulating levels of DHEAS and mental well-being.[21,23] Androgens suppressed inflammation in a mouse model of Sjögren's syndrome.[24] Based on these previous studies, we expected to find, in a randomized double-blind placebo-controlled study, beneficial effects of daily oral administration of 200 mg DHEA on fatigue, well-being, and functioning in women with pSS.

PATIENTS AND METHODS

Design

In a double-blind, randomized placebo-controlled clinical trial, patients received 200 mg oral DHEA (Fagron, Nieuwerkerk a/d IJssel, the Netherlands) or placebo during one year. At baseline, after 3, 6, and 12 months on study medication, and 6 months after cessation of treatment, patients had a physical examination (by AH), filled out questionnaires, and donated blood. Patients who stopped medication intake prematurely, were evaluated 6 months after the last capsule was taken and these data were considered as being obtained at 18 months. Patients, physicians, and researchers were blinded to the treatment.

Participants

Patients were recruited from the outpatient clinics of the departments of Rheumatology and Clinical Immunology of the University Medical Centers in Utrecht and Groningen, the Netherlands. The study was approved by the institutional review boards of both hospitals,

and all participants provided written informed consent.

Charts of 395 patients with sicca complaints were evaluated for eligibility resulting in 155 eligible women, who fulfilled the European criteria for classification of pSS including a focus score ≥ 1 on minor salivary gland biopsy,[25] and were ≥ 18 years. Exclusion criteria were pregnancy or wish to conceive, a malignancy within the preceding 5 years, use of glucocorticosteroids in the preceding year, and abnormal thyroid stimulating hormone (TSH), serum creatinin, or liver function.

Outcome variables

The primary outcome measures were general fatigue, depressive mood, physical functioning, and mental well-being. For the general fatigue scale of the Multidimensional Fatigue Inventory (MFI, range 4-20),[26] patients responded to four statements indicating fatigue during the previous three days (range 1-5). The Zung self-rating scale (range, 20-80) assessed affective, psychological, and somatic characteristics of depressive mood;[27] patients responded to 20 statements (range 1-4). The RAND (short form-36, SF-36) Health Survey[28] was used to measure physical component summary (PCS) and mental component summary (MCS) scores.[29]

Secondary outcome measures were self-reported pain and ocular and oral dryness, presence of fibromyalgia, tear production, and surrogate parameters of disease activity: erythrocyte sedimentation rate (ESR), hemoglobin concentration, and serum-immunoglobulin-G (serum-IgG). Patients indicated on a 100 mm visual analogue scale (VAS) their pain during the last two days between the extremes "no pain" (0 mm) and "the most pain ever" (100 mm), and the degree of ocular and oral dryness between the extremes "not troublesome" (0 mm) and "extremely troublesome" (100 mm). Tender point count was performed according to the criteria for fibromyalgia.[30] The Schirmer I test was used to measure mean tear production.[25] ESR, hemoglobin concentration, and serum-IgG were determined according to standard procedures.

Control variables

Laboratory tests included whole blood count, serum creatinin, gamma glutamic transpeptidase (GGT), and alanine aminotransferase (ALT) according to standard procedures.

DHEAS levels were measured using an Advantage Chemiluminescense System (Nichols Institute Diagnostics, San Juan Capistrano, USA). The lower limit of detection was 0.2 µmol/L and interassay variation <11%. Normal values in our laboratory are 0.5-9 µmol/L. Testosterone was measured after diethylether extraction using an in house competitive radio-immunoassay with a polyclonal antibody with [1,2-^{3}H(N)]-Testosterone as a tracer. The lower limit of detection was 0.12 nmol/L, interassay variation 5 - 7%, and crossreactivity to DHEA <0,1%. Samples were stored at –80° C and analysed in single runs.

Patients indicated if they had noted, as compared to pretreatment, an increase in body hair, acne, oily skin or capital hair, or changes in the regularity or duration of the menstrual cycle or postmenopausal blood loss.

At the 18 months visit, when the patients were able to judge their status during and after treatment, they indicated whether they believed to have used DHEA or placebo.

Statistical analysis

Patients were analysed on an intention-to-treat basis; for missing values the last observation was carried forward. We also performed an analysis in patients who fully adhered to the treatment.

χ^2 tests examined self-reported side-effects of the two groups. Schirmer I, ESR, and IgG (skewness > 1.5) were logarithmically transformed before parametric analysis. The primary and secondary outcome measurements were evaluated with repeated measures analysis of variance. The quadratic time effect examined whether both the DHEA and placebo medication induced a change. The quadratic group x time interaction effect examined whether this change was different for patients on DHEA and placebo. The mean auto-correlation between the 5 assessment points varied form $r = 0.56$ for general fatigue to $r = 0.76$ for depressive mood. With an auto-correlation of $r = 0.65$ to achieve a moderate effect size of $f = 0.25$, analyses of variance (5 repeated measures, 2 groups with 30 participants each, 2-tailed $\alpha = 0.05$) achieves a high power of $\beta = 0.99$ for both the time effect and the time x group interaction; the power to detect a small effect ($f = 0.10$) of $\beta = 0.63$ is below the $\beta = 0.80$ criterion.[31]

Ancillary analyses examined by repeated measures analyses of variance whether effects on primary outcomes were dependent on whether patients believed to have used DHEA or placebo and, within the patients who had used DHEA, whether effects were dependent on menopausal status, age, fibromyalgia, baseline DHEAS levels, the change of DHEAS in response to DHEA administration, and baseline levels of general fatigue, depressive mood, and mental well-being. In case of non-dichotomous variables, two subgroups were created by median split. The power of ancillary analyses in the group of 30 patients on DHEA is low ($\beta = 0.33$) for a small effect and high ($\beta = 0.99$) for a moderate effect.

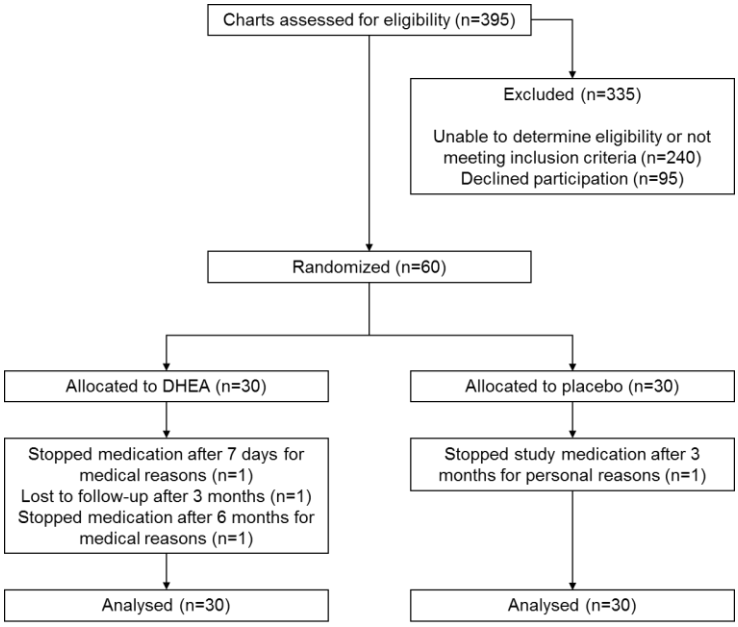
Statistical analyses were performed using SPSS 11.5 for windows (SPSS, Chicago, Illinois). A 2-sided p-value < 0.05 was considered statistically significant.

RESULTS

Patients

In all, sixty patients were randomly assigned to receive DHEA or placebo. Figure 1 is a flow chart of the research participants. Of 155 eligible patients, 95 declined participation because of fear of side-effects (44%), trial considered too much a burden (33 %), traveling expenses (13%), absence of fatigue and distress (9%), and chance to be allocated to placebo medication (2%). Three patients in the DHEA group and one in the placebo group stopped the study medication prematurely.

Figure 1.



Flowchart of patient selection and randomization. All patients, except the one that was lost to follow-up, had a final assessment 6 months after intake of the last capsule with study medication.

Table 1 Baseline characteristics of the research participants

	DHEA	placebo
Patients, n	30	30
Age: mean (range) yrs	55 (23-76)	52 (19-76)
Disease duration: mean (range) yrs	8 (0.1 - 24)	6 (0.3 - 16)
Caucasian race, n (%)	26 (87%)	29 (97%)
Education level, n (%)		
primary	2 (7)	1 (3)
secondary	20 (67)	23 (77)
tertiary	8 (27)	6 (20)
Marital status, n (%)		
single	3 (10)	4 (13)
married	22 (73)	23 (77)
widowed/divorced	5 (17)	3 (10)
Postmenopausal, n (%)	19 (63)	18 (60)
Schirmer I test, median (mm)	4.5	6.0
≤5 mm/5 min, n (%)	18 (60)	13 (43)
Circulating SS-A antibodies, n (%)	23 (77)	23 (77)
Circulating SS-B antibodies, n (%)	16 (53)	11 (37)
Fibromyalgia, n (%)	6 (20)	8 (27)
Medication, n (%)		
Acetaminophen	8 (27)	11 (37)
NSAID	9 (30)	10 (33)
Hydroxychloroquine	3 (10)	7 (23)
Beta blocker	2 (7)	4 (13)
Antidepressant	4 (13)	2 (7)
Anti acne drug, Isotretinoin	0 (0)	1 (3)

Postmenopausal status was defined as amenorrhea for one year or more in women with a uterus in situ and by FSH > 35 IU/L in hysterectomised women; none of the differences between treatment groups was significant. DHEA, dehydroepiandrosterone; NSAID, non steroidal anti inflammatory drug.

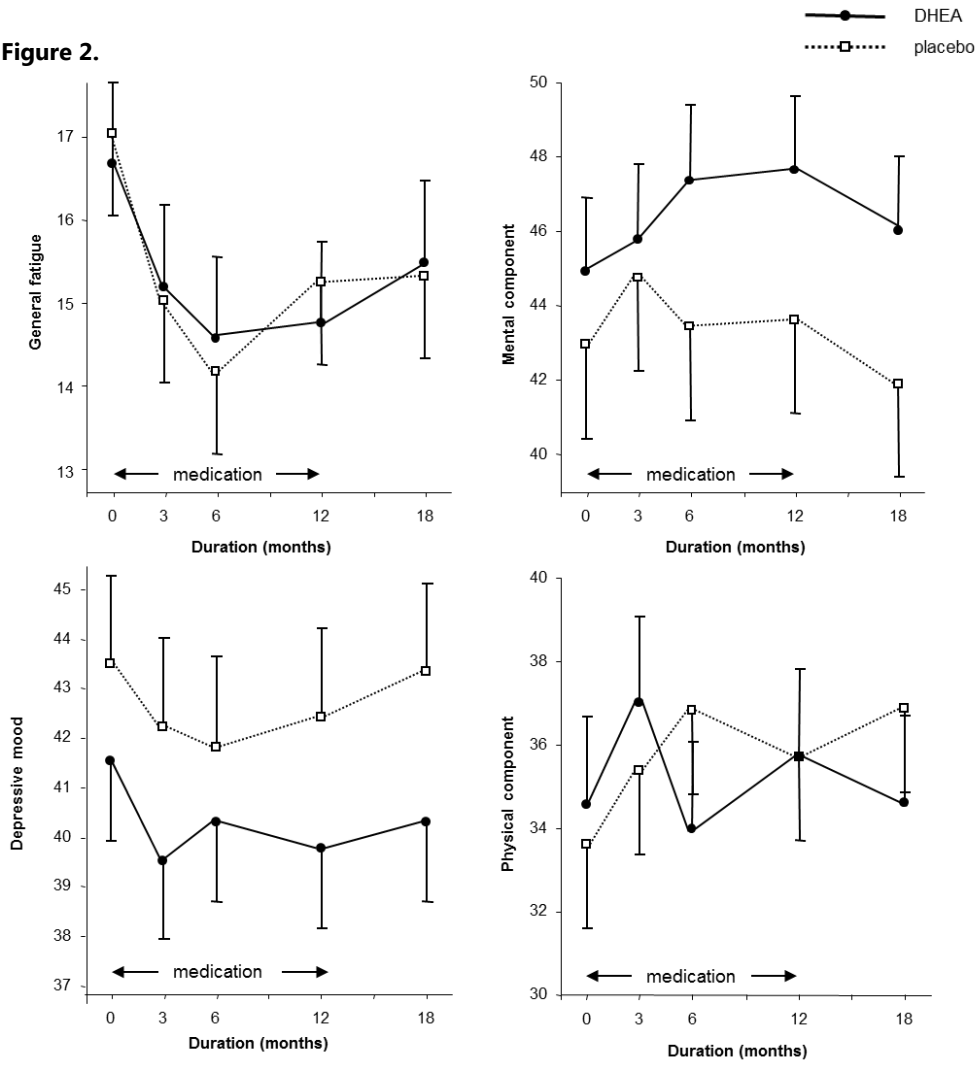
Patient characteristics at enrollment were similar for both treatment groups.

DHEAS and testosterone levels

At baseline, mean serum DHEAS was 1.9 (SD 1.1) and 1.7 (SD 1.1) µmol/L for the DHEA and placebo groups, respectively. Mean serum testosterone was 0.9 (SD 0.4) nmol/L in both groups. During treatment with DHEA, mean levels of DHEAS and testosterone increased to supraphysiological values of 20.0 µmol/L and 4.3 nmol/L, respectively. DHEAS and testosterone values were within normal limits at baseline, after discontinuation of treatment, and during treatment with placebo.

We suspected that four patients did not take DHEA study medication regularly. In these patients the change in DHEAS levels after 12 months DHEA intake was between - 0.4 and 2.6 µmol/L. This is in the range of changes observed in the placebo group (-1.60 to 3.20 µmol/L). In the other patients on DHEA, the increase in DHEAS levels varied from 4.9 to 48.7 µmol/L.

Figure 2.



Scores (means and standard errors) of primary outcome measures in 60 patients with primary Sjögren's syndrome (pSS) (n=30 dehydroepiandrosterone (DHEA) vs. n=30 placebo) at baseline, and after 3, 6, 12, and 18 months.
Higher scores indicate more fatigue, a better mental and physical health status, and more depressive mood. At baseline, the four primary outcome variables did not differ between treatment groups ($p > 0.32$).

Side effects

Androgenic.

An increase of acne and body hair was reported more often by patients on DHEA than those on placebo: 37, 47, and 43 % of the patients on DHEA reported an increase of acne at the 3, 6, and 12 months assessment (10, 7, and 10 % of the patients on placebo) and 20, 40, and 63

% of the patients on DHEA reported an increase of body hair (0, 3, and 7 % of the patients on placebo). The frequencies of menstrual abnormalities and oily skin or capital hair did not differ between the groups with increased oily skin or capital hair after 12 months (17% in DHEA and 0% in placebo) as the only exception. One patient of the DHEA group stopped study medication after 3 months because she feared increase of hirsutism.

Other.
In the DHEA group one patient stopped participation after 7 days because she experienced restlessness, malaise, nightsweats, and skin rash and another patient stopped after 6 months, because of increased ocular pain and dryness, restlessness, and sleep disturbance.

Two patients in the DHEA group had a severe deterioration in health during the study period. Both continued DHEA treatment and had all evaluations. One patient, known to have mitral valve insufficiency, developed heart failure 5 months after the start of DHEA treatment when she had a pulmonary infection. The second patient had progressive dyspnoea 12 months after the start of DHEA. A diagnosis of lymphocytic interstitial pneumonitis was made; she was treated with high dose glucocorticoids and 6-monthly intravenous infusions with cyclophosphamide.

Primary outcomes

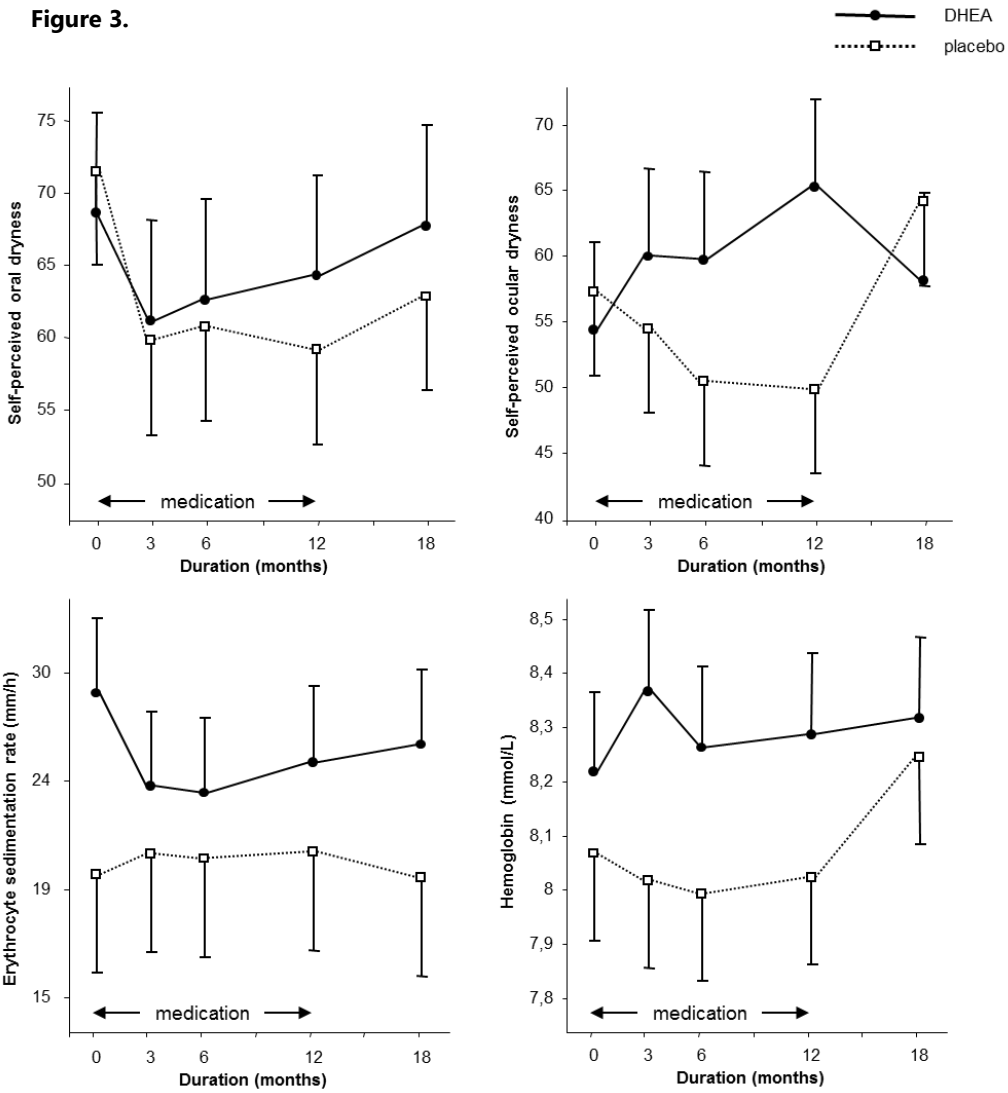
Figure 2 shows the change during the study period of the four primary outcome measures for the DHEA and the placebo group. General fatigue showed a significant change for both treatments ($p < 0.001$): it decreased during the first six months of medication use and steadily increased after this period. There was no differential effect of medication: the change in fatigue did not differ for the DHEA and placebo group ($p = 0.77$). Also the mental component score ($p = 0.04$) and depressive mood ($p = 0.01$) showed a significant change during the study for both medication groups; the best scores were observed during the treatment period. For the mental component score ($p = 0.90$) and depressive mood ($p = 0.65$) no significant differences were found between the change in the DHEA and in the placebo group. In both treatment groups no systematic change ($p > 0.33$) was found for the physical component score.

Secondary outcomes

Of eight secondary outcome measures, a significant change for both groups was only detected for self-perceived oral dryness with least complaints during intake of study medication ($p = 0.005$, Figure 3).

For three secondary outcome measures, i.e. self-perceived ocular dryness, ESR, and hemoglobin, the change was significantly different between the treatment groups (Figure 3).

Figure 3.



Scores (means and standard errors) of four secondary outcome measures in 60 patients with primary Sjögren's syndrome (pSS) (n=30 dehydroepiandrosterone (DHEA) vs. n=30 placebo) at baseline, and after 3, 6, 12, and 18 months. Higher scores indicate more perceived oral and ocular dryness. At baseline, these four secondary outcome variables did not differ significantly between treatment groups (p = 0.07 for ESR, and p > 0.41 for the other variables). Not shown are the scores of self-reported pain, fibromyalgia tender points, Schirmer I test, and serum IgG.

Ocular dryness complaints became worse for patients on DHEA as compared to patients on placebo (p = 0.01). The ESR decreased with the use of DHEA and was stable with placebo (p = 0.03). Hemoglobin levels showed a different change for the DHEA and placebo group (p

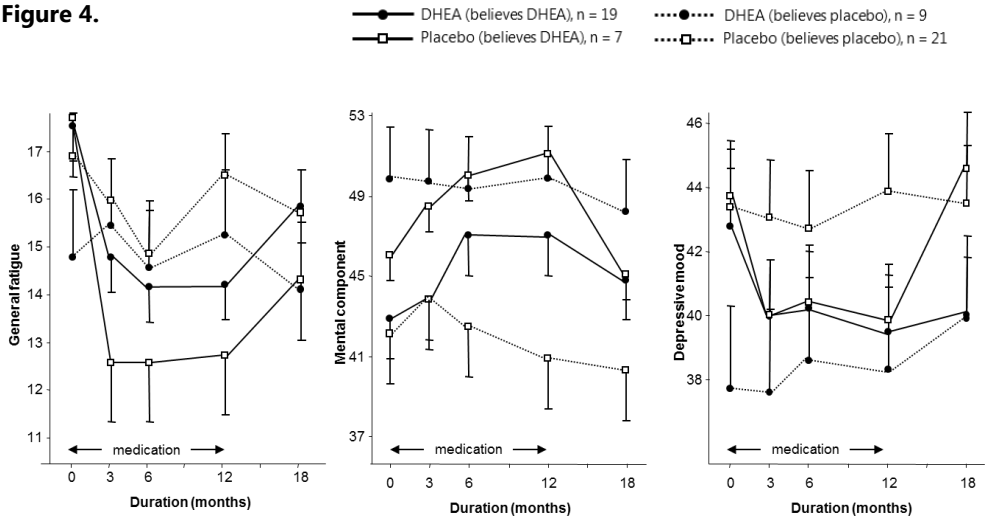
= 0.04), but these changes did not reflect an improvement during the medication intake for either group.

Ancillary analyses

We examined whether the change of general fatigue, mental well-being, and depressive mood was related to the patient's belief to have used DHEA or placebo, menopausal status, age, presence of fibromyalgia, baseline DHEAS serum level, the change in DHEAS level in response to DHEA administration, perceived side effects, and baseline levels of the primary outcome measures.

Of the 30 patients with DHEA, 19 believed to have used DHEA, 9 placebo, and 2 did not know. Of the 30 patients with placebo, 21 believed to have used placebo, 7 DHEA, and 2 did not know. Excluding the 4 patients who did not know, we analysed the change of general fatigue, mental well-being, and depressive mood in relation to actual and believed medication used (Figure 4).

Figure 4.



General fatigue, the mental component score, and depressive mood at baseline, and after 3, 6, 12, and 18 months as a function of DHEA (filled circle) or placebo (open circle), and patient's belief to have used DHEA (straight line) or placebo (dashed line). Higher scores indicate more fatigue, a better mental status, and more depressive mood.

The change of general fatigue (p = 0.15), the mental component score (p = 0.43), and depressive mood (p = 0.22) did not differ as a function of actual medication use, whereas the change of general fatigue (p < 0.001), and depressive mood (p = 0.02), but not the mental component score (p = 0.13), were significantly different as a function of believed medication

use: the patients who believed to have used DHEA demonstrated an improvement on fatigue and depressive mood.

In the DHEA-treated group, the change of general fatigue, mental well-being, and depressive mood did not depend on menopausal status ($p > 0.26$), age ($p > 0.31$), fibromyalgia ($p > 0.51$), extent of change in serum DHEAS levels during treatment ($p > 0.07$), or perceived side effects ($p > 0.62$). Patients with higher baseline serum levels of DHEAS improved more on general fatigue than patients with lower levels ($p = 0.03$), while changes in depressive mood and the mental component score ($p > 0.66$) were not dependent on baseline DHEAS. The change in general fatigue, depressive mood, and the mental component score did not depend on baseline levels of these three variables with one exception: the decrease of depressive mood from baseline to the first assessment after 3 months was higher for the group with more depressive mood ($p = 0.04$).

Adherers-only analyses

Results of analyses with exclusion of 4 patients with missing values and 4 patients with extraordinarily small changes in serum DHEAS levels, did not differ from the intention-to-treat analyses.

DISCUSSION

Our placebo controlled double-blind study in women with pSS demonstrates a beneficial effect on fatigue and well-being with both DHEA and placebo treatment and disproves a beneficial effect of DHEA over placebo.

These results apply to a pharmacological dose of 200 mg a day, which has been used and shown safe in inflammatory diseases.[16,19,20,32] A substitution dose of 50 mg DHEA might be sufficient to affect mood, while a higher dose also affects disease activity.[33] Our study showed that administration of DHEA induced physiological effects: serum DHEAS and testosterone raised to supraphysiological levels, androgenic side effects were reported, and a decrease of ESR was measured.

The suggestion of a positive effect of DHEA administration on physical and psychological parameters comes from some,[9-11] but not all[34-36] studies in elderly healthy participants and studies in a variety of disease states.[12-18] Several of these studies had a small sample size,[13-15,18] lacked a placebo controlled design,[11,15,18] or did not analyse according to intention to treat.[16,17] A sound demonstration of a positive effect of DHEA replacement on well-being was given in women with subnormal DHEA serum levels caused by adrenal insufficiency.[14]
One can argue that we could not prove an effect of DHEA administration, because our patients were not DHEAS deficient, were not on glucocorticoid therapy which decreases

serum DHEA(S) levels,[37,38] and because also premenopausal women were included, while supplementation is more plausible after the menopause. The sample size of the ancillary analyses in our study was too small to detect small effects and thus prohibits the generalisation of results to DHEA-deficient groups, groups on glucocorticoid therapy, or postmenopausal women. Our analyses did not, however, find a differential effect of DHEA of moderate magnitude in these subgroups.

Our primary aim was not to examine whether DHEA would affect disease activity in women with pSS, but we included ESR, hemoglobin concentration, and serum-IgG in our study as surrogate disease activity parameters. Studies in SLE,[19,20] and in a mouse model of Sjögren's syndrome[24] reported less disease activity with administration of androgens. In contrast with a previous study in pSS,[39] in our study as in female patients with pSS treated with nandrolone decanoate,[40] ESR decreased with DHEA compared to placebo.

Our study suggested favorable outcomes for both DHEA and placebo. Ancillary analyses demonstrated that fatigue and mood varied as a function of believed medication use instead of actual medication use. Two mechanisms may explain this observation: either the believe to have DHEA induced improvement, or improvement induced the believe to have DHEA. The suggestion that a placebo effect instead of regression to the mean explains the improvement of fatigue and well-being, is strengthened by the observation that the extent of improvement of general fatigue and the mental component score did not depend on baseline levels. Definite prove of a placebo effect warrants a study that also includes a waiting list control group.

Biological and psychological factors contribute to fatigue, inactivity, and depressed mood. Although these symptoms are reflex-like responses to the inflammatory process, it is, to a certain extent, possible to not give to them depending on motivation.[41] The willingness of the patients to participate in our intervention demonstrates their positive expectation and motivation, which may have increased their vitality and well-being.

Our study does not support efficacy of 200 mg oral DHEA over placebo. Both oral administration of DHEA and placebo improved fatigue and well-being in patients with pSS. We did not examine the mechanisms underlying this unexpected placebo effect, but its presence suggests that it is possible to ameliorate fatigue and well-being in some women with pSS through non-pharmacological mechanisms. This may indicate possibilities for cognitive behavioral interventions.

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Chapter 5

Fatigue in patients with systemic lupus erythematosus: the role of dehydroepiandrosterone

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ABSTRACT

Fatigue is a major problem in systemic lupus erythematosus (SLE), but the physiological substrate of this fatigue is largely unclear. To examine if low levels of dehydroepiandrosterone (DHEA) and its sulfate DHEAS play a role in SLE fatigue, we compared 1) DHEAS levels and fatigue between 60 female SLE patients with low disease activity (31 using, 29 not using prednisone) and 60 age-matched healthy women, and 2) fatigue between SLE patients with low and normal DHEAS levels. Serum DHEAS levels were determined with an Advantage Chemiluminescense System. The Multidimensional Fatigue Inventory (MFI) was used to assess fatigue. Patients were more fatigued ($p \leq .001$) than healthy women and more often had below normal DHEAS levels ($p < 0.001$). Patients using prednisone with low and normal DHEAS levels reported a similar level of fatigue ($p \geq 0.39$). Patients with low DHEAS levels not using prednisone reported less fatigue than those with normal DHEAS levels ($p \leq 0.03$). Thus, our results indicate that low DHEAS levels in SLE are not –or even inversely– related to fatigue. After our previous finding that DHEA administration does not reduce fatigue, this result further indicates that low serum DHEA(S) levels alone do not offer an explanation for SLE fatigue.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with clinical presentations such as inflammation of joints, skin, visceral membranes and kidneys.[1,2] Fatigue is a prominent, often debilitating feature of the disease.[3-9] Up to 80% of patients experience fatigue, even when the disease is in remission.[4,8,9] To date, the physiological origin of fatigue in SLE is largely unclear. Some studies suggested a correlation between fatigue and SLE disease activity, cytokine or autoantibody levels,[8,10] while other studies were inconclusive,[11] or argued against any relation.[5,6,9,12]

Attention has been directed towards the possible anti-inflammatory and vitalizing influence of the hormone dehydroepiandrosterone (DHEA) and its sulfate ester (DHEAS) in SLE.[13] DHEA and DHEAS are the most abundantly produced androgens in humans, secreted by the adrenal glands in response to activity of the hypothalamic pituitary adrenal axis (HPA-axis). Compared to healthy subjects, mean levels of DHEA(S) are low in SLE patients.[13-15] Studies in ageing people and some patient populations suggested that lower levels of circulating DHEA(S) are related to more fatigue.[13] In patients with adrenal insufficiency, DHEA substitution therapy reduced fatigue.[16,17] In SLE, most studies examining DHEA supplementation did not specifically assess fatigue as an outcome measure, but improvement in health, global well-being and functioning was observed.[18-21]

The low mean DHEA(S) levels in SLE, together with fatigue being a major problem in most SLE patients, was the basis for our attempt to examine the association between endogenous levels of DHEA(S) and fatigue in SLE. We used baseline data of our previous intervention trial[22] to compare serum DHEAS levels and multiple dimensions of fatigue between female SLE patients and age-matched healthy women, and to compare fatigue between SLE patients with low and normal DHEAS levels. Since disease activity may influence both DHEAS levels and fatigue,[8, 10] only SLE patients with a low level of disease activity were included in the study. Moreover, because prednisone may reduce serum DHEA(S) levels[13] and improve perceived health,[23] this study, unlike previous studies, differentiated between patients using and not using prednisone. SLE patients were expected to have lower levels of serum DHEAS and higher fatigue levels than healthy controls. Furthermore, SLE patients with low DHEAS levels were expected to report more fatigue than those with normal DHEAS levels.

PATIENTS AND METHODS

Participants

Included were 60 female patients with SLE with a low level of disease activity who were willing to participate in a placebo-controlled study on effects of administration of DHEA on

well-being and fatigue[22] and 60 age-matched healthy women. Patients were recruited from the departments of Rheumatology and Clinical Immunology of the University Medical Centers of Utrecht and Groningen. They fulfilled at least four American College of Rheumatology (ACR) SLE classification criteria[24] and were ≥ 18 years. All of the patients were in clinical remission according to assessment by an experienced rheumatologist. Exclusion criteria were pregnancy, wish to conceive, malignancy within the preceding 5 years, daily use of glucocorticosteroids > 10 mg in the preceding 6 months, and abnormal thyroid stimulating hormone or creatinin levels, or abnormal liver function. Age- and sex-matched control subjects were recruited by patients among friends, family members, and acquaintances. They did not take medications and were not known with a disease. The research and ethics committee of both institutions approved of the study. All participants provided written informed consent.

Assessments

The assessments of the SLE patients involved the baseline data of our placebo-controlled trial on effects of DHEA administration.[22] Serum levels of DHEAS were measured using an Advantage Chemiluminescense System (Nichols Institute Diagnostics, San Juan Capistrano, USA)[25] with a lower detection limit of 0.2 μmol/L and an inter-assay variation of < 11%. Normal values in our laboratory are 1-9 μmol/L, 1-7 μmol/L, and 0.5-5 μmol/L for women aged 20-40, 40-50, and > 50 years, respectively. Clinical assessments included serum anti-double-stranded DNA (anti-dsDNA) antibodies, serum C3 and C4, SLE disease activity index (SLEDAI),[26] and erythrocyte sedimentation rate (ESR). Fatigue was measured with five dimensions of the Multidimensional Fatigue Inventory (MFI): general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue. The score range per dimension is 4 - 20, with higher scores indicating more fatigue.[27]

Statistical analysis

χ^2-tests, independent samples *t*-tests, and Mann-Whitney U tests were used to examine differences between SLE patients using prednisone, SLE patients not using prednisone, and healthy controls with respect to frequencies (Caucasian y/n, education level, marital status, pre- or postmenopausal status, low/normal DHEAS level, medication use), continuous variables with a normal score distribution (age, disease duration, C3), and continuous variables with a non-normal score distribution (SLEDAI, anti-dsDNA, C4, ESR, DHEAS, MFI fatigue scores). The possible influence of differences in menopausal status between patients and controls was checked. Within the two SLE groups, Mann-Whitney U tests were used to examine differences in fatigue between patients with low and normal DHEAS levels. Common threshold values were used to differentiate between these low and normal DHEAS levels. Statistical analyses were done with SPSS 16.0. All tests were two-sided, and $p < 0.05$

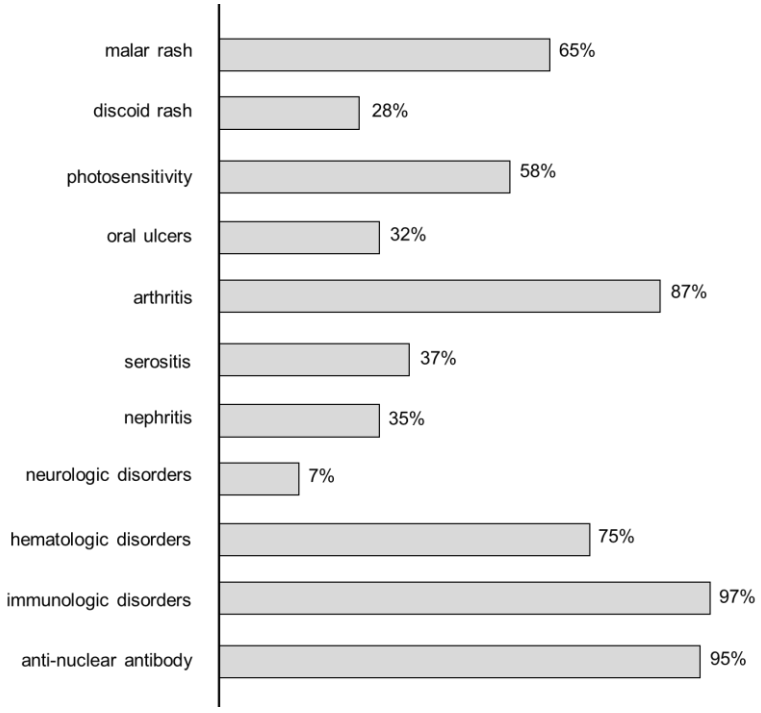
was considered significant.

RESULTS

Participant characteristics

Figure 1 gives an impression of the study population by indicating the ACR criteria for the classification of SLE[24] that were fulfilled at the time of study. Apart from serological findings, arthritis and hematological abnormalities were the most frequent clinical manifestations. About one third had a history of lupus nephritis. In all patients, SLE was in stable clinical remission. This is also reflected in the low SLEDAI scores,[26,28,29] with only serological and hematological findings being the cause of scores above zero. Overall, 85% of patients had a SLEDAI score of ≤ 4 and the maximum score was 6. These scores are within the range of previous established SLEDAI cut-off scores for inactive disease.[28,29]

Figure 1.



ACR criteria for the classification of SLE fulfilled by our patients.

Thirty-one patients with SLE used a low dose of prednisone (median dose 5 mg, range 2.5-10.0 mg). As shown in Table 1, patients with SLE using prednisone, patients with SLE not using prednisone, and healthy control subjects did not significantly differ from each other on demographic variables ($p \geq 0.11$). Patients with SLE using prednisone did have lower C4 levels ($p = 0.047$) and more often used azathioprine ($p = 0.004$) than those not using prednisone, but the two patient groups did not significantly differ on other disease activity variables (SLEDAI, $p = 0.18$; anti-dsDNA, $p = 0.33$; C3, $p = 0.052$; ESR, $p = 0.50$) or other medication use (paracetamol, non-steroidal anti-inflammatory drugs, hydroxychloroquine, methotrexate, β-blockers, and antidepressants; $p \geq 0.16$; data not shown).

Table 1. Characteristics of patients with SLE using and not using prednisone and healthy controls.

	SLE using prednisone (n = 31)	SLE not using prednisone (n = 29)	p1	Healthy controls (n = 60)	p2
Demographic variables					
Age, years, mean ± SD (range)	41.8 ± 10.6 (21-64)	43.8 ± 10.9 (28-71)	.48	43.2 ± 10.7 (21-70)	.85
Disease duration in years, mean ± SD (range)	12.8 ± 7.4 (2-32)	12.3 ± 6.9 (2-28)	.80	n/a	
Caucasian, n (%)	27 (87)	25 (86)	.92	57 (95)	.36
Education level, n (%)[a]			.97		.66
Low	12 (39)	12 (41)		21 (35)	
Middle	13 (42)	12 (41)		24 (40)	
High	6 (19)	5 (17)		15 (25)	
Marital status, n (%)			.75		.13
Single	4 (13)	6 (21)		5 (8)	
Married	22 (71)	18 (62)		51 (85)	
Widowed/divorced	5 (16)	5 (17)		4 (7)	
Postmenopausal status, n (%)[b]	10 (32)	8 (28)	.69	9 (17)[c]	.11
Fatigue, median (interquartile range)					
MFI general fatigue	15.0 (13.0-18.0)	14.0 (11.5-17.5)	.49	5.0 (4.0-8.0)	<.001
MFI physical fatigue	14.0 (11.0-16.0)	12.0 (8.5-16.0)	.63	5.0 (4.0-7.8)	<.001
MFI reduced activity	10.0 (8.0-13.0)	12.0 (8.5-13.5)	.76	5.0 (4.0-7.8)	<.001
MFI reduced motivation	10.0 (7.0-12.0)	9.0 (6.0-12.0)	.57	4.0 (4.0-6.0)	<.001
MFI mental fatigue	8.0 (6.0-13.0)	11.0 (6.0-12.5)	.81	5.5 (4.0-8.8)	<.001
DHEAS, nmol/litre, median (interquartile range)	0.46 (0.10-0.82)	1.90 (0.73-3.15)	<.001	2.95 (2.00-4.18)	<.001
DHEAS level, n (%)			<.001		<.001
low	24 (77)	7 (24)		1 (2)	
normal	7 (23)	22 (76)		59 (98)	

[a] Education level was defined as low (primary school or lower vocational secondary education), middle (intermediate general secondary education or intermediate vocational education), and high (higher general secondary education, higher vocational education, or university education).

[b] Postmenopausal status was defined by amenorrhea for at least one year in women with a uterus in situ and in hysterectomised patients by serum follicle-stimulating hormone level > 35 IU/litre.

[c] In 7 healthy controls, menopausal status was not determined.

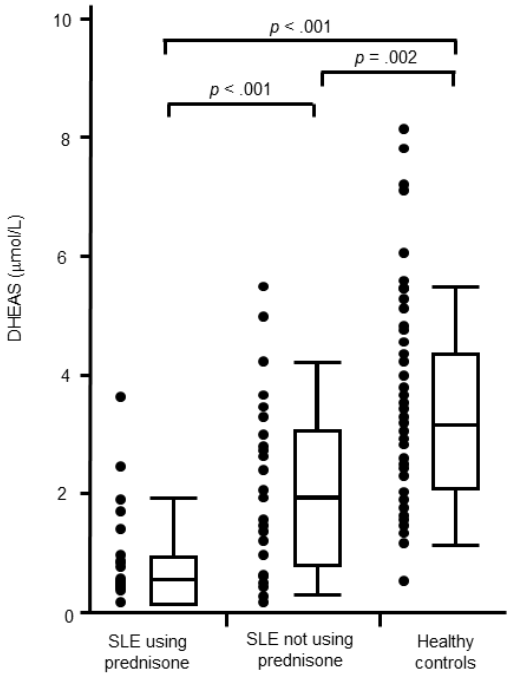
DHEAS: Dehydroepiandrosterone sulfate; MFI: Multidimensional Fatigue Inventory with higher scores reflecting more fatigue (range 4-20); p_1: significance of the difference between the two SLE groups; p_2: significance of the difference between the total SLE group and the control group; SLE: systemic lupus erythematosus.

Fatigue and DHEAS levels in the SLE group versus the control group

The bottom of Table 1 shows the median scores for the five fatigue dimensions, median DHEAS levels, and the number of participants with serum DHEAS levels below or above the lower limit of normal. Patients with SLE using and not using prednisone did not differ from each other on any of the five fatigue dimensions ($p \geq 0.49$), but compared to healthy control subjects, patients with SLE reported more fatigue on all dimensions ($p \leq 0.001$).

DHEAS levels differed significantly between the three groups (Figure 2). DHEAS levels of patients with SLE using prednisone were lower than those of patients with SLE not using prednisone ($U = 184.0$, $p < 0.001$) and DHEAS levels of the total SLE group (*median* = 0.79) were lower than of the control group ($U = 620.0$, $p < 0.001$). In the SLE group, 77 per cent of the patients using prednisone and 24 per cent of the patients not using prednisone had below-normal serum DHEAS levels ($\chi^2 = 17.0$, $p < 0.001$). Only one (premenopausal) control participant had a below-normal serum DHEAS level.

Figure 2.



DHEAS levels in patients with SLE using and not using prednisone and healthy controls. Data are shown as dots for every participant and as boxplots. Each box represents the 25th to 75th percentile. Bars outside the boxes represent the 10th to 90th percentile. DHEAS: Dehydroepiandrosterone sulphate ; SLE: systemic lupus erythematosus. The median patient score on the SLE Disease Activity Index was 4 (interquartile range 2-4, maximum 6).

The control group included less postmenopausal women than the SLE group, but repeating the analyses for only premenopausal women did not change the results: premenopausal SLE patients were more fatigued on all dimensions ($174.0 \leq U \leq 578.0$, $p \leq 0.002$) and had lower DHEAS levels ($U = 355.0$, $p < 0.001$) than premenopausal controls.

Fatigue in SLE subgroups with low versus normal DHEAS levels

Within the entire SLE group, patients with low and patients with normal DHEAS levels did not differ on any of the five fatigue dimensions ($U \geq 349.5$, $p \geq 0.14$; data not shown). Table 2 shows the median fatigue scores of the patients with SLE related to DHEAS level and use of prednisone. In patients with SLE using prednisone, fatigue did not differ between patients with low and normal DHEAS levels. In the SLE group not using prednisone, those with low DHEAS levels reported less fatigue than those with normal DHEAS levels on four of the five fatigue dimensions ($U \leq 33.5$, $p \leq 0.03$); this is illustrated in Figure 3 for the general fatigue dimension. These findings were not due to differences in inflammation; ESR did not differ between patients with low DHEAS levels and patients with normal DHEAS levels ($U = 61.5$, $p = 0.43$ in the SLE group not using prednisone and $U = 62.0$, $p = 0.30$ in the SLE group using prednisone).

Table 2. Median MFI fatigue scores (interquartile ranges) in SLE subgroups with low versus normal DHEAS levels.

	SLE using prednisone				SLE not using prednisone			
	Low DHEAS (n = 24)	Normal DHEAS (n = 7)	U	p	Low DHEAS (n = 7)	Normal DHEAS (n = 22)	U	P
MFI general fatigue	15.5 (13.0-18.8)	13.0 (12.0-17.0)	66.0	.39	10.0 (8.0-12.0)	15.0 (13.0-19.3)	22.0	.005
MFI physical fatigue	14.0 (11.0-16.5)	12.0 (8.0-16.0)	67.0	.42	9.0 (7.0-12.0)	13.5 (9.8-17.0)	33.5	.03
MFI reduced activity	10.5 (8.0-13.0)	10.0 (5.0-19.0)	74.0	.64	5.0 (5.0-12.0)	12.0 (10.8-14.3)	26.0	.009
MFI reduced motivation	10.0 (7.0-12.8)	10.0 (6.0-12.0)	69.0	.48	6.0 (4.0-8.0)	11.0 (7.8-12.0)	24.5	.007
MFI mental fatigue	8.5 (5.5-13.0)	8.0 (6.0-12.0)	84.0	1.00	8.0 (4.0-12.0)	11.0 (6.8-13.0)	60.0	.38

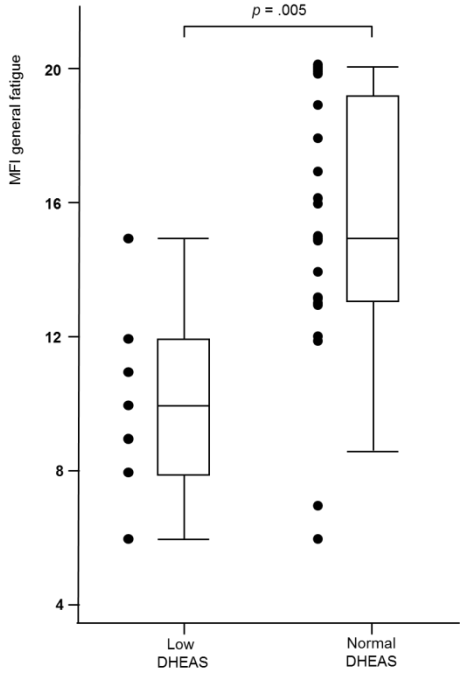
DHEAS: Dehydroepiandrosterone sulphate; MFI: Multidimensional Fatigue Inventory with higher scores reflecting more fatigue (range 4-20); SLE: systemic lupus erythematosus; *U*: Mann-Whitney *U*-test.

DISCUSSION

To elucidate the possible role of endogenous DHEAS levels in SLE fatigue, serum DHEAS levels and fatigue were examined in female patients with SLE with a low level of disease activity and in female healthy control subjects. As expected, more SLE patients had low

DHEAS levels and they also reported more fatigue than healthy controls. Contrary to our expectations, patients with SLE with low DHEAS levels reported similar or even less fatigue than patients with SLE with normal DHEAS levels.

Figure 3.



MFI general fatigue scores in patients with SLE not using prednisone with low versus normal DHEAS levels. Data are shown as dots for every patient and as boxplots. Each box represents the 25th to 75th percentile. Bars outside the boxes represent the 10th to 90th percentile. DHEAS: Dehydroepiandrosterone sulphate; MFI: Multidimensional Fatigue Inventory with higher scores reflecting more fatigue (range 4-20); SLE: systemic lupus erythematosus; Of patients not using prednisone, the median score on the SLE Disease Activity Index was 2 (interquartile range 0-4, maximum 6).

In SLE,[13-15] but also in other chronic autoimmune diseases with high levels of fatigue, such as rheumatoid arthritis[30] and Sjögren's syndrome,[25] DHEAS levels are found to be low. In contrast, in non-inflammatory disorders characterized by fatigue, such as chronic fatigue syndrome (CFS), depression and burnout, both low[31-33] and high[34-38] DHEA(S) levels have been found. Therefore, it could be that low levels of DHEAS are rather a marker of chronic inflammation than of fatigue. Nevertheless, the low DHEAS and high fatigue levels in SLE patients suggest an association between the two.

In the total SLE group, fatigue and DHEAS levels were unrelated and in the absence of prednisone, fatigue was even less in patients with low DHEAS levels than in patients with normal DHEAS levels. A possible explanation for this unexpected result may be that fatigue is

not influenced by low DHEA(S) levels as such, but rather by an overall physiological imbalance involving DHEA(S) and other hormones, such as cortisol. Previous studies in SLE suggest a hypo-responsive hypothalamic-pituitary-adrenal (HPA) axis related to inflammation.[39-41] In non-inflammatory disorders involving fatigue, a higher than normal DHEA(S)/cortisol ratio has been observed,[35,38] as well as simultaneously elevated levels of both DHEA(S) and cortisol.[34,36] Our current results do not rule out the existence of a DHEA(S)/cortisol imbalance reflecting impaired HPA-axis functioning due to inflammation, or fatigue in SLE. This is a topic for future inquiry.

Research on the relation between endogenous DHEA(S) levels and fatigue in SLE is scarce. As reviewed,[1] most studies examined the effects of administering DHEA in SLE patients, who often simultaneously used glucocorticoids and had clinically relevant disease activity. Our study is the first that specifically focused on the possible role of endogenous DHEAS levels in fatigue of SLE patients with low disease activity. Our study has various strengths. Patients and controls were matched on sex and age, prednisone use was taken into account, and the possible effect of disease activity was minimized by only including patients with a low level of disease activity. However, our study also has some limitations. Perhaps DHEAS levels in the brain are more relevant to fatigue than serum levels; serum DHEAS levels may not optimally reflect neural DHEAS.[42] In addition, although DHEAS and DHEA levels are related, our findings do not necessarily fully generalize to DHEA.[13,43] For future research it is recommended that, besides disease activity and use of immunosuppressive drugs, also other aspects of HPA-axis functioning, such as cortisol and DHEA, are taken into account to examine the possible imbalance of adrenal products which may be associated with SLE fatigue.

The results of the current study indicate that fatigue in patients with SLE is unrelated to low endogenous DHEAS levels. In the group of patients not using prednisone, levels of fatigue were even higher with higher DHEAS levels. Together with the results of our randomized controlled trial showing no effect of DHEA administration on fatigue over the placebo effect,[22] this suggests that neither DHEA nor its sulfate are instrumental alone in determining the level of fatigue in SLE.

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Chapter 6

Effects of dehydroepiandrosterone on fatigue and well-being in women with quiescent systemic lupus erythematosus: a randomized controlled trial

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ABSTRACT

Objective: Dehydroepiandrosterone (DHEA) has been reported to improve fatigue and reduced well-being. Both are major problems in patients with systemic lupus erythematosus (SLE), even with quiescent disease. Low serum DHEA levels are common in SLE. The present work investigates the effects of DHEA administration on fatigue, well-being, and functioning in women with inactive SLE.

Methods: In a double-blind, randomised, placebo-controlled study, 60 female patients with inactive SLE received 200 mg oral DHEA or placebo. Primary outcome measures were general fatigue, depressive mood, mental well-being, and physical functioning. Assessments were made before treatment, after 3, 6, and 12 months on medication, and 6 months after cessation of treatment.

Results: Patients from both the DHEA and placebo group improved on general fatigue ($p < 0.001$) and mental well-being ($p = 0.04$). There was no differential effect of DHEA. The belief to have used DHEA was a stronger predictor for improvement of general fatigue than the actual use of DHEA ($p = 0.04$).

Conclusions: The trial does not indicate an effect of daily 200 mg oral DHEA on fatigue and well-being, and therefore DHEA treatment is not recommended in unselected female patients with quiescent SLE.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a connective tissue disease with clinical presentations such as inflammation of joints, skin, visceral membranes, and kidneys.[1] Fatigue and decreased well-being and functioning are frequent issues, even when disease activity is low.[2,3] Attention has been drawn to the influence of dehydroepiandrosterone (DHEA) and its sulfate ester DHEAS on autoimmune diseases.[4] Beneficial effects of DHEA administration on fatigue and well-being have been reported in elderly and in several disease states.[4]

Androgens have anti-inflammatory properties.[5] Serum DHEA(S) levels in SLE are low irrespective of glucocorticoid use.[6] Beneficial effects of DHEA on fatigue and well-being in women with SLE were suggested by a small open study[7] and in a study in patients on glucocorticoids.[8] Our randomised double-blind placebo-controlled study was conducted in patients with quiescent SLE to avoid confounding by disease activity and intermediate or high doses prednisone, a drug that improves perceived health[9] and reduces serum DHEA(S) levels.[4] We expected to find beneficial effects of daily oral administration of 200 mg DHEA on fatigue, well-being, and functioning.

PATIENTS AND METHODS

Design

The present study was a double-blind, randomised placebo-controlled clinical trial. In all, 60 female patients with SLE received 200 mg oral DHEA (Fagron, Nieuwerkerk a/d IJssel, The Netherlands) or placebo. At baseline, after 3, 6, and 12 months on study medication, and 6 months after cessation of treatment, outcome parameters were assessed.

Participants

Evaluation of 342 charts of patients with SLE from the departments of Rheumatology and Clinical Immunology of the University Medical Centers in Utrecht and Groningen yielded 181 potential candidates based on predefined criteria. Inclusion criteria were fulfillment of at least four American College of Rheumatology (ACR) SLE classification-criteria,[10] female gender and age ≥18 years. Exclusion criteria were pregnancy or wish to conceive, malignancy within the preceding 5 years, daily use of glucocorticoids >10 mg in the preceding 6 months, and abnormal thyroid stimulating hormone, serum creatinin, or liver function. The study was approved by the institutional review boards of both hospitals. Participants provided written informed consent.

Variables

Primary outcome measures were general fatigue, depressive mood, mental well-being and physical functioning. Fatigue was assessed with the general fatigue scale of the Multidimensional Fatigue Inventory (MFI, range 4-20).[11] The Zung self-rating scale was used to assess depressive mood (range 20-80).[12] The RAND short form-36 (SF-36) Health Survey was used to measure mental well-being (mental component summary) and physical functioning (physical component summary).[13]

Secondary outcome measures were self-reported pain (100 mm visual analogue scale (VAS)), fibromyalgia tender point count,[14] SLE disease activity index (SLEDAI),[15] erythrocyte sedimentation rate (ESR), hemoglobin concentration, serum C3 and C4, and serum anti-double-stranded DNA (anti-dsDNA) antibodies

DHEAS levels were measured using an Advantage Chemiluminescense System (Nichols Institute Diagnostics, San Juan Capistrano, USA) and testosterone with polyclonal antibody with [1,2-^{3}H(N)]-Testosterone as tracer.[16] At the 18-months visit, patients indicated whether they believed they had been using DHEA or placebo.

Statistical analysis

Patients were analysed on an intention-to-treat basis; for missing values the last observation was carried forward.

Friedman and Mann-Whitney tests were used to examine anti-dsDNA antibody levels. Other primary and secondary outcome measurements were evaluated with repeated measures analysis of variance. The quadratic time effect was used to examine whether DHEA and placebo affected the outcome variables. The quadratic group x time interaction effect was used to examine whether this change was different for patients on DHEA and placebo.

We considered the finding of a small effect (f=0.10) irrelevant, and a moderate effect (f=0.25) an overestimation of expected effects. We aimed for an inbetween effect size of f=0.175. We calculated a requirement for 2 groups of 30 patients to examine a differential effect of DHEA versus placebo administration (auto-correlation 0.25, 2-sided α-level 0.05, power 0.80, 5 repeated measurements).

In statistical analyses with SPSS 15.0 (SPSS, Chicago, Illinois, USA), a two-sided p-value < 0.05 was considered statistically significant.

RESULTS

Patients

The flow chart is shown in supplementary figure S1. In all, 60 patients were randomly assigned to receive DHEA or placebo. One patient in the DHEA group stopped the study

medication prematurely after six months. Her final evaluation was 6 months later. Patient characteristics at enrollment were similar for both treatment groups (Table 1).

Table 1 Baseline characteristics of research participants

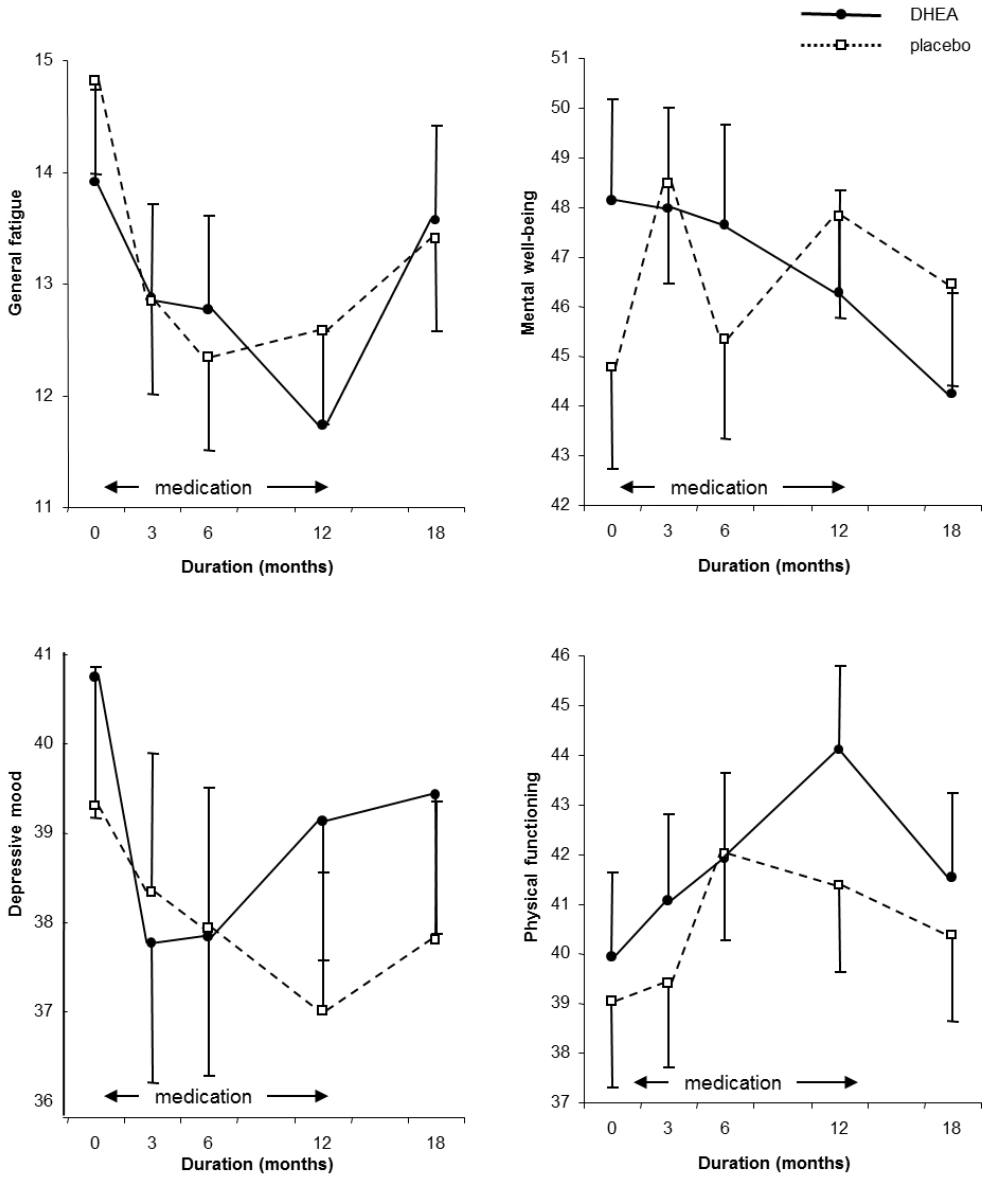
	DHEA	**Placebo**
Patients, n	30	30
Age: mean (range) yrs	45 (28-71)	41 (21-62)
Disease duration mean (range) yrs	13 (3-32)	12 (2-28)
Caucasian race, n (%)	24 (80%)	28 (93%)
Education level, n (%)		
primary	2 (7)	1 (3)
secondary	25 (83)	21 (70)
tertiary	3 (10)	6 (27)
Marital status, n (%)		
single	4 (13)	6 (20)
married	18 (60)	22 (73)
widowed/divorced	8 (27)	2 (7)
Postmenopausal, n (%)	12 (40)	6 (20)
Fibromyalgia, n (%)	2 (7)	4 (13)
SLEDAI: mean ± SD	2.77 ± 2.40	3.40 ± 1.83
anti-dsDNA: median (interquartile range) IU/ml	19 (5-86)	27 (10-38)
C3: mean ± SD (range) g/L	0.89 ± 0.26 (0.40 - 1.44)	0.90 ± 0.23 (0.55 - 1.67)
C4: mean ± SD (range) g/L	0.14 ± 0.06 (0.04 - 0.25)	0.13 ± 0.05 (0.06 - 0.28)
DHEAS: mean ± SD (range) µmol/L	1.2 ± 1.3 (0.1 – 5.5)	1.5 ± 1.4 (0.1 – 4.9)
Testosterone: mean ± SD (range) nmol/L	0.8 ± 0.6 (0.1 – 2.6)	0.9 ± 0.6 (0.1 – 3.6)
Prednisone use		
never used, n (%)	2 (7)	4 (13)
current use, n (%)	15 (50)	16 (53)
dose, mean ± SD (mg/day)	6.0 ± 2. 5	5.9 ± 1.5
Medication, n (%)		
Acetaminophen	9 (30)	12 (40)
NSAID	7 (23)	9 (30)
Hydroxychloroquine	16 (53)	20 (67)
Azathioprine	8 (27)	11 (37)
Methotrexate	0 (0)	1 (3)
Beta blocker	0 (0)	2 (7)
Antidepressant	2 (7)	3 (10)

None of the differences between treatment groups was significant. Postmenopausal status was defined as amenorrhea for 1 year or more in women with a uterus in situ and by FSH > 35 IU/litre in hysterectomised women.
DHEA, dehydroepiandrosterone; DHEAS, DHEA sulfate; dsDNA, double-stranded DNA; FSH, follicle stimulating hormone; NSAID, non-steroidal anti-inflammatory drug; SLE, systemic lupus erythematosus; SLEDAI, SLE disease activity index.

DHEAS and testosterone levels

In the DHEA and placebo group, DHEAS levels at baseline were lower in patients on glucocorticoids (DHEAS: 0.6 versus 1.9 µmol/litre for patients with and without prednisone, respectively; p = 0.01; placebo: 0.8 versus 2.2 µmol/litre, respectively; p = 0.002).

Figure 1.



Scores (means and standard errors) of primary outcome measures in 60 patients with systemic lupus erythematosus (SLE) (n=30 dehydroepiandrosterone (DHEA) vs. n=30 placebo) at baseline, and after 3, 6, 12, and 18 months. Higher scores indicate more fatigue, a better mental and physical health status, and more depressive mood. At baseline, the four primary outcome variables did not differ between treatment groups ($p > 0.21$).

During treatment with DHEA, mean levels of DHEAS and testosterone increased to supraphysiological values of 22.8 μmol/litre (SD 13.7) and 4.2 (SD 3.1) nmol/litre, respectively. The increase of serum levels DHEAS after administration of DHEA was significant only in the DHEA group ($p < 0.001$). The change of DHEAS did not differ for patients with and without prednisone ($p = 0.82$ for DHEA; $p = 0.17$ for placebo).

Primary outcomes

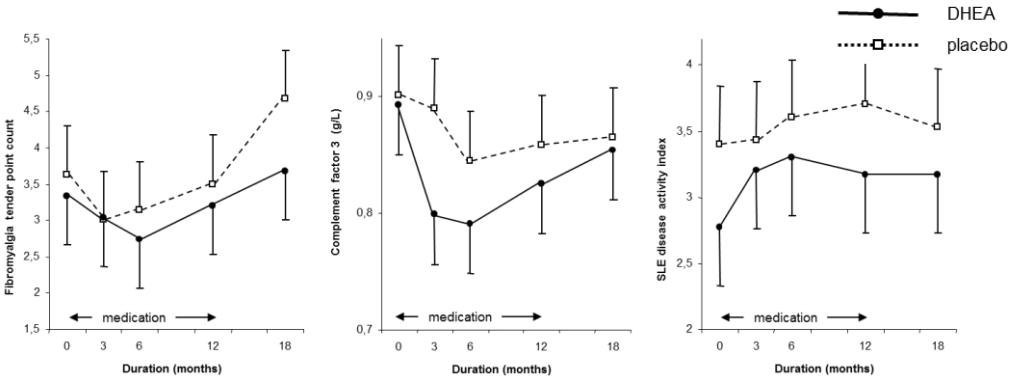
Figure 1 shows the change in the four primary outcome measures for the DHEA and the placebo groups. General fatigue showed a significant change for both treatments ($p < 0.001$): best scores were observed during treatment. Depressive mood ($p = 0.04$) showed a significant change for both treatment groups with lower scores during treatment and at follow-up. For mental well-being ($p = 0.23$) and physical functioning ($p = 0.06$) no significant changes were found in either group.

There was no differential effect from the study medication: the change in the primary outcome measures did not differ for the DHEA and placebo groups (p values > 0.31).

Secondary outcomes

For three out of eight secondary outcome measures, a significant change was detected during treatment (Figure 2): tender point count ($p = 0.003$), serum C3 levels ($p < 0.001$, lowest scores during intake of study medication), and anti-dsDNA antibodies ($p < 0.001$, decreasing levels from baseline to 6 months after cessation of medication).

Figure 2.



Scores (means and standard errors) of 3 secondary outcome measures in 60 patients with systemic lupus erythematosus (SLE) (n=30 dehydroepiandrosterone (DHEA) vs. n=30 placebo) at baseline, and after 3, 6, 12, and 18 months. At baseline, these three secondary outcome variables did not differ significantly between treatment groups ($p > 0.25$). Not shown are the scores for self-reported pain, erythrocyte sedimentation rate, hemoglobin concentration, serum levels of complement factor 4, and anti-double stranded DNA (dsDNA) antibodies.

For C3 levels, the change differed between the treatment groups: during the medication period, the decrease of C3 levels was most pronounced in patients treated with DHEA (p = 0.03). Decreases in serum C3 levels did not correlate with changes in disease activity. Self-reported pain, SLEDAI, ESR, hemoglobin concentration and serum C4 levels did not change significantly during treatment, and there was no differential effect for the DHEA and placebo groups.

Ancillary analyses

Of the 30 patients on DHEA, 16 and 7 believed to have used DHEA or placebo, respectively. Seven stated they were not sure. Of the 30 patients on placebo, 16 and 13 believed to have used placebo or DHEA. One was not sure. Excluding the eight patients who were not sure, we analysed the change in primary outcomes in relation to actual and believed medication used (see supplementary figure S2). The change of general fatigue (p =0.63), mental well-being (p =0.66), depressive mood (p =0.48), and physical functioning (p =0.59) did not differ with actual medication use. The change of general fatigue (p =0.04) was related to believed medication use: patients who believed to have used DHEA demonstrated an improvement. The change of mental well-being (p =0.07), depressive mood (p =0.39), and physical functioning (p =0.38) was not different with believed medication use.

Side effects

Androgenic side effects and disease exacerbations occurred more often with DHEA (n=5) than placebo (n=2) (see supplementary table S1).

DISCUSSION

No effect of daily 200 mg oral DHEA over placebo was found on fatigue and well-being. Beneficial effects were observed with DHEA and placebo. General fatigue varied with believed instead of actual medication use.

An open study in SLE showed improvement of well-being and fatigue after a daily dose of 200 mg DHEA.[7] Double-blind, placebo-controlled studies suggested a reduction of perceived disease activity[17-19] and corticosteroid requirement.[20] Studies assessing fatigue as a secondary outcome measure found no effect of DHEA.[19,20] Similar to other studies,[17,19,20] we found an increase of serum DHEAS and testosterone to supraphysiological levels and a decrease of serum C3 levels. Despite these physiological effects, no disease modulating activity of DHEA was observed.

Our study demonstrated a favorable change of fatigue and depressive mood for DHEA and placebo. Fatigue varied with belief of use instead of actual medication use. The belief that DHEA was used may have induced improvement, but it is also possible that improvement induced the belief DHEA had been used. Regression to the mean may also have played a role.

Biological and psychological factors contribute to fatigue and mental well-being. The willingness of patients to participate in this intervention study demonstrates a positive expectation, which by itself may have increased their vitality and well-being. Our findings do not generalise to all female patients with inactive SLE and may not apply to selected patients with uniformly high fatigue levels, serum DHEAS levels below normal, prednisone treatment >10 mg per day, or patients who are postmenopausal. The size of our sample was not large enough to detect small effects or to thoroughly examine the possibility that DHEA treatment may be effective in selected patients.

In summary, fatigue and well-being improved with DHEA and placebo administration. Therefore, our study does not support the suggestion that fatigue, well-being and functioning might be treated with daily 200 mg oral DHEA. Hence we cannot recommend DHEA substitution in unselected female patients with quiescent SLE.

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ONLLINE SUPPLEMENT

Side effects

Patients indicated if they had noted, as compared to pretreatment, an increase in body hair, acne, oily skin or capital hair, or changes in the regularity or duration of the menstrual cycle or postmenopausal bleeding. Androgenic side effects are shown in table s1 (p-values of χ^2 tests).

		3 months	6 months	12 months	18 months
Acne					
	DHEA	12 (40)	14 (47)	15 (50)	4 (13)
	placebo	7 (23)	4 (13)	4 (13)	1 (3)
	p	0.17	0.005	0.002	0.16
Body hair					
	DHEA	1 (3)	8 (26)	13 (43)	7 (23)
	Placebo	4 (13)	5 (17)	4 (13)	1 (3)
	p	0.16	0.35	0.01	0.07
Menstrual abnormalities					
	DHEA	1 (3)	3 (10)	4 (13)	4 (13)
	Placebo	3 (10)	7 (23)	7 (23)	7 (23)
	p	0.61	0.30	0.51	0.51
Oily skin or hair					
	DHEA	5 (17)	5 (17)	5 (17)	2 (7)
	Placebo	0 (0)	0 (0)	1 (3)	0 (0)
	p	0.05	0.05	0.05	0.05

Body hair: facial, axillary, or pubic hair, or hair on extremities.
Menstrual abnormalities: changes in regularity or duration of the menstrual cycle, or postmenopausal blood loss.

Table S1. *Number (and percentages) of patients with SLE with DHEA (n=30) or placebo (n=30) reporting an increase of self-perceived side effects compared to baseline.*

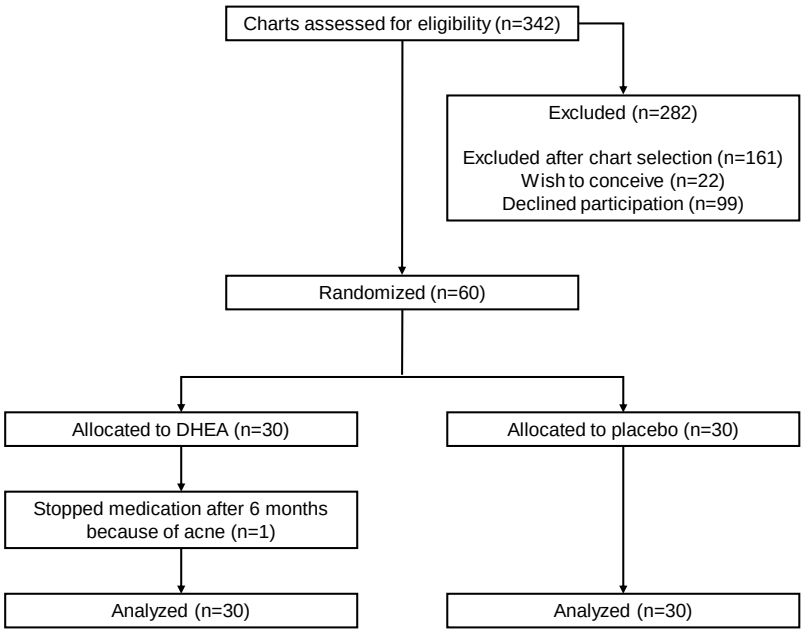
Other side effects.

An increase in disease activity necessitating glucocorticoid treatment occurred in five and two patients on DHEA and placebo, respectively. Two patients of the DHEA group developed active lupus nephritis; one patient had a severe flare of cutaneous discoid lupus erythematosus, and another polyarthritis. One patient received a daily dose of prednisone >10 mg because of severe malaise, arthralgia, and rising anti-dsDNA levels. In the placebo group, indications for daily prednisone use > 10 mg were disease exacerbation with lupus nephritis, inflammatory skin rash and pleuritis in one patient and polyarthritis in another. All patients continued study medication and had all evaluations.

FLOW CHART

Of 181 eligible patients selected from medical charts, 18% had a wish to conceive (exclusion criterion). Reasons to decline participation were fear of side-effects (45%), trial considered too much a burden (33%), traveling expenses (7%), and prolonged stay abroad (6%). The flow chart is shown in Figure S1.

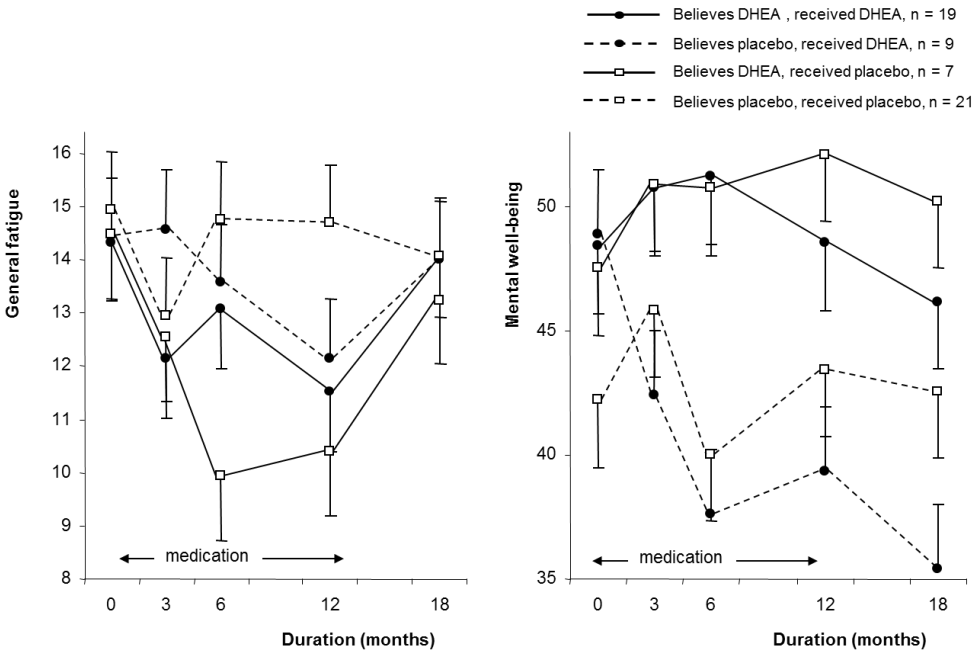
Figure S1.



Flow chart

ANCILLARY ANALYSES

Figure S2.



General fatigue and the mental component score at baseline, and after 3, 6, 12, and 18 months as a function of DHEA (filled circle) or placebo (open circle), and patient's belief to have used DHEA (straight line) or placebo (dashed line).

Note: Higher scores indicate more fatigue and a better mental status (the non-significant scores on depressive mood and the physical component score are not shown)

Chapter 7

The effect of dehydroepiandrosterone on lumbar bone mineral density in patients with quiescent systemic lupus erythematosus

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ABSTRACT

Objective: Because dehydroepiandrosterone (DHEA) is an adrenal steroid hormone with weak intrinsic androgenic properties that can be converted in peripheral tissues into more potent sex hormones, one might expect a positive effect of DHEA on bone mineral density (BMD). We evaluated the effects on lumbar BMD of oral DHEA, 200 mg/day, for one year in female patients with quiescent systemic lupus erythematosus (SLE).

Methods: The study subjects were 60 women with SLE. All participants gave informed consent to participate in a double-blind, placebo-controlled study on the effects of DHEA on fatigue and general well being. BMD was measured with dual-energy x-ray absorptiometry (DEXA) at baseline and after 12 months.

Result:. Fifty-eight patients (mean age 42.6 years) could be evaluated; 2 patients (both in the DHEA group) refused to undergo DEXA a second time. In premenopausal women, DHEA did not influence BMD significantly. There was a significant increase in BMD with use of DHEA in postmenopausal women who were not receiving bisphosphonates or estrogen-containing medications. This increase was not observed in the group receiving placebo.

Conclusion: In premenopausal women with quiescent SLE, use of DHEA does not have a significant effect on BMD. DHEA may increase BMD in postmenopausal SLE patients, if they are not already protected from bone loss by use of estrogens or bisphosphonates. Small numbers, due to absence of stratification for menopausal status, and the use of anti-resorptive agents at randomization preclude firmer conclusions based on the results of this study.

INTRODUCTION

Dehydroepiandrosterone (DHEA) and its sulfated derivate DHEAS are steroid hormones that are produced by the adrenal cortex. DHEA(S) has weak intrinsic androgenic properties, but in peripheral tissues DHEA(S) is converted into testosterone, dihydrotestosterone and estrogens.[1] Serum levels of DHEAS progressively decrease with age from the third decade on,[2] and a variety of age-related abnormalities, including low energy levels, osteoporosis and immune senescence, have been linked to this decrease.[3] Patients with systemic lupus erythematosus (SLE) have low levels of circulating DHEAS compared to age-matched healthy controls,[4,5] and an association between circulating DHEAS levels and bone mineral density (BMD) has been reported.[6]

In SLE, oral administration of DHEA can reduce disease activity as well as the daily glucocorticoid dose needed to control disease activity.[7,8] Fatigue and low energy levels are frequent symptoms in patients with SLE, even when the disease is in remission. We performed a double-blind, placebo controlled study in female patients with quiescent SLE to test whether administration of 200 mg/day DHEA has a positive effect on well-being and fatigue. We report the effects of this treatment for 1 year on lumbar spine BMD.

PATIENTS AND METHODS

Participants were 60 female SLE patients[9] from the departments of Rheumatology and Clinical Immunology of the University Medical Center Utrecht and the University Hospital Groningen, the Netherlands, who consecutively gave informed consent to participate in a placebo-controlled study on the effects of administration of DHEA on fatigue and general well-being. The institutional review boards approved the study. Eligible patients were not receiving > 10 mg of prednisone daily (or an equivalent dosage of glucocorticoids) at the time of inclusion and in the preceding 6 months. Both physicians and patients were instructed to keep the daily dose of glucocorticoids, calcium, vitamin D, bisphosphonates, and estrogen-containing medications constant during the 12-month study period during which patients received a capsule containing either DHEA (200mg) or placebo once daily. Identical capsules were provided by the hospital pharmacy. DHEA was purchased from Fagron (Nieuwekerk aan den IJssel, The Netherlands).

Clinical evaluations were performed at study entry and at 3, 6, and 12 months. At these visits disease activity was scored by the SLE Disease Activity Index (SLEDAI).[10] At baseline and at 12 months, BMD of the lumbar spine (first through fourth lumbar vertebrae) was measured with a multiple detector, fan-beam, dual energy, x-ray absorptiometry (DEXA) bone densitometer (QDR DELPHI, Hologic Europe NV, Zaventem, Belgium). Daily quality control was accomplished using a calibrated spine phantom to verify that the system's

performance was within established parameters. Results are reported in gm/cm^2. In a single patient, the minimum change between 2 scans that can be considered statistically significant (i.e. cannot be attributed to measurement error with 95% confidence) is 0.023 gm/cm^2. We defined normal BMD, osteopenia, and osteoporosis according to World Health Organization (WHO) criteria, with T score cutoffs set at –1.0 and –2.5. Two patients (both in the DHEA group) refused to undergo a second BMD measurement. Therefore, the study group comprised 58 patients.

Women with regular menses (n=42) were considered premenopausal. Postmenopausal status was defined as amenorrhea for at least one year in women with an uterus in situ (n=16), and in hysterectomized women by presence of a follicle stimulating hormone (FSH) level of > 35 IU/liter (n=0). In order to evaluate the effects of DHEA on BMD, we divided the patients into 2 groups: bone-protected and bone non-protected. The bone-protected group comprised, irrespective of the use of bisphosphonates, premenopausal women (n=42), postmenopausal women using estrogen containing medications (n=1), and postmenopausal women who were not on estrogen containing medications but did use bisphosphonates (n=6). The non-protected group consisted of postmenopausal women who did not take estrogen containing medications or bisphosphonates (n=9).

Having ascertained that BMD scores were normally distributed, parametric statistics were applied for their evaluation. Independent-sample t-tests, the χ^2 test, bivariate correlations, and univariate analysis of variance were used for statistical analysis, as appropriate. An alpha level of $p < 0.05$ was considered significant in all tests.

RESULTS

As shown in Table 1, most baseline characteristics were similar for patients receiving DHEA (n = 28) and those receiving placebo (n = 30). The only significant difference between the 2 groups was the percentage of postmenopausal patients (39% in the DHEA group and 17% in the placebo group (p=0.02)).

Based on their BMD at baseline, 26% of patients were osteopenic and 7% osteoporotic. BMD at baseline was significantly associated with postmenopausal status, current use of prednisone, age, and body mass index (data not shown). No such association was observed for disease duration and the SLEDAI score.

In 53 patients, use of prednisone, calcium, vitamin D, bisphosphonates, and estrogen-containing medications remained unchanged during the study period. One patient in the placebo group who was receiving prednisone (5 mg/day) at the start of the study stopped taking this medication after 8 months. Four patients (all in the DHEA group) required an increase in their daily dose of prednisone. In the first patient, the increase was from 7.5 mg/day to 60 mg/day, 4 months after study entry because of an exacerbation of chronic

obstructive pulmonary disease. Over 2 months the daily dose was tapered to 7.5 mg. In the second patient, prednisone was increased from 10 mg/day to 20 mg/day, 6 months after study entry, because of active skin lesions. In 4 months, the daily dose was tapered to 12.5 mg and remained constant for the rest of the study period. Both of these patients were receiving calcium and bisphosphonate therapy from the beginning of the study. In 2 other patients, active lupus nephritis developed 6 months after the start of the study. In both patients the daily dose of prednisone was increased to 1 mg/kg for 4 weeks, followed by tapering over 4 months to 10 mg/day. One of these patients began receiving oral contraceptives simultaneously with the increase in her daily prednisone dose.

Table 1: Patient characteristics at study entry

	DHEA 200 mg (n = 28)	Placebo (n = 30)	p-value***
Age in years, mean ±SD	44.6 ± 11.9	40.7 ± 9.4	0.17
Caucasian, no (%)	23 (82.1)	28 (93.3)	
BMI, mean ± SD	25.0 ± 5.2	26.0 ± 5.7	0.49
Disease duration, mean ± SD in years	12.6 ± 7.0	12.3 ± 7.4	0.88
SLEDAI*, mean ± SD (range)	2.82 ± 2.42 (0-10)	3.40 ± 1.83 (0-6)	0.31
Postmenopausal state, no. (%)	11 (39.3)	5 (16.7)	0.02
Prednisone:			
Never used, no (%)	2 (7.1)	3 (10.0)	
Current use, no (%)	14 (50.0)	17 (56.7)	0.61
Mean dose ± SD (gram/day)**	5.71 ± 2.32	5.54 ± 2.00	0.82
Current use of:			
calcium, no (%)	17 (60.7)	15 (50.0)	0.41
bisphosphonates, no (%)	6 (21.4)	6 (20.0)	0.89
vitamine D, no (%)	3 (10.7)	3 (10.0)	0.58
estrogens no (%)	4 (14.3)	7 (23.3)	0.38
Osteopenia or osteoporosis lumbar spine, no (%)	9 (32.1)	10 (33.3)	0.92

* SLEDAI = Systemic Lupus Erythematosus Disease Activity Index (score: 0-108).

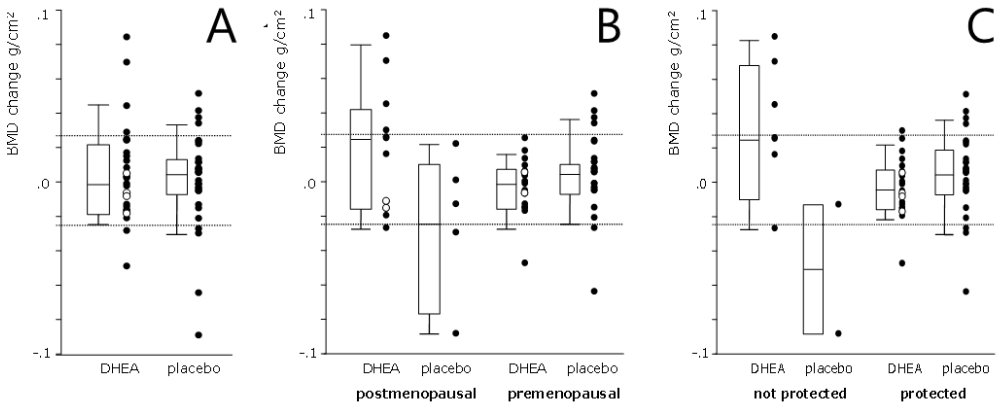
** in patients on steroids at start of the study.

*** unpaired T-tests were used for continous outcomes and χ-square for proportional outcomes.

At study entry, the BMD (mean ± SD) was 0.987 ± 0.144 gm/cm^2 in the DHEA group and 1.009 gm/cm^2 ± 0.120 in the placebo group (p = 0.53). After 12 months, these values were 0.992 gm/cm^2 ± 0.147 and 1.008 gm/cm^2 ± 0.122, respectively (p = 0.65). Changes in BMD were not significantly different between the 2 groups groups (p = 0.46) (Figure 1A).

A change of 0.023 gm/cm^2 between 2 BMD measurements in a single patient was considered significant. Based on this definition, a significant change over 12 months was observed in 31% of patients. In the DHEA group, an increase in BMD was noted in 7 patients (25%) and a decrease was observed in 2 patients (7%). In the placebo group, 4 patients (13%) had an increase in BMD and 5 patients (17%) patients had a decrease in BMD (Figure 1A).

Figure 1.



Change in lumbar bone mineral density (BMD) after use of dehydroepiandrosterone (DHEA) or placebo for 12 months in grams/cm^2 after the use of dehydroepiandrosterone (DHEA) or placebo for 12 months. A, Total study group (n = 58). B, Effects of DHEA in relation to menopausal status. C, Effects of DHEA in relation to the presence or absence of bone protection (defined as premenopausal status and use of bisphosphonates or estrogen-containing medications). Data are shown as boxplots. Each box represents the 25th to 75th percentiles. Lines outside the boxes represent the 10th and 90th percentiles. Lines inside the boxes represent the median. The broken horizontal lines reflect a change of 0.023 gm/cm^2. The four open circles in de DHEA group represent 4 patients for whom the daily dose of prednisone was increased significantly during the study period.

Subgroup analyses showed that the change in BMD was dependent on menopausal status (p = 0.006) (Figure 1B). In premenopausal women, the change in BMD was not related to DHEA treatment. In contrast, all postmenopausal women who experienced an increase in BMD had received DHEA. Among postmenopausal patients, the mean change was 1.80 % with DHEA and –2.32 % with placebo.

Figure 1C shows a subgroup analysis based on the presence (n=49) or absence (n=9) of 'bone protection' (defined as premenopausal status and use of estrogen-containing medications, bisphosphonates, or combinations of these). The effect of DHEA on BMD depended on whether or not the patient was otherwise protected for bone loss (p = 0.000). In absence of bone protection, the mean change in BMD was 3.22 % with DHEA and –5.61% with placebo. In the presence of bone protection, a change in BMD was unrelated to DHEA treatment.

The change in BMD in response to DHEA or placebo did not depend on the presence of osteopenia or osteoporosis at baseline (p = 0.59) or current prednisone treatment (p = 0.60) (data not shown). Repetition of the statistical analyses, excluding the 5 patients who had a change in their glucocorticoid dose during the study period, did not alter the results. Symptomatic vertebral fractures were not observed during the study period.

Over 12 months, the SLEDAI score (mean ± SD) changed from 2.82 ± 2.42 to 3.25 ± 2.55 in the DHEA group, and from 3.40 ± 1.83 to 3.70 ± 2.51 in the placebo group. The difference in the two groups was not statistically significant (p = 0.79).

DISCUSSION

A robust finding of our study is that administration of DHEA, 200 mg/day for one year, does not affect the lumbar spine BMD in premenopausal women with quiescent SLE. Furthermore, our data suggest that DHEA may have a protective effect on bone in postmenopausal SLE patients who are not receiving estrogens or bisphosphonates (Figure 1B and C). A protective effect of oral DHEA on BMD is consistent with the observation of a small but significant increase in BMD at the hip that was observed in 14 postmenopausal women who received daily applications of a 10% DHEA cream for 12 months.[11] The mean percent increase in BMD we observed with the use of DHEA for 1 year in postmenopausal women who did not receive estrogens or bisphosphonates (3.2%) is comparable with the 4% increase that was reported for the use of bisphosphonates in postmenopausal women with osteoporosis,[12] and in glucocorticoid treated postmenopausal women who did not use estrogens.[13]

Although our findings are consistent with our expectations, this study has some limitations. Due to the absence of stratification for menopausal status and the use of antiresorptive medication, there was a skewed distribution for the use of DHEA and placebo among the (relatively small number of) postmenopausal patients who were studied. This prevents firmer conclusions.

Van Vollenhoven et al.[14] observed that administration of 200 mg of DHEA to patients with active SLE who received high-dose glucocorticoids prevented the significant reduction in BMD that occurred over a 6 month-period in the placebo group; this finding suggests that DHEA may have bone-sparing effects. Our observations, however, cannot be compared with those findings, because the patients in the study by van Vollenhoven and colleagues had SLE that was more active (mean SLEDAI score 12.6 versus 3.1 in our study), more often used prednisone (100% versus 53% in our study), received a higher daily dose of prednisone (mean 46.7 mg versus 5.6 mg among users in our study), and were younger (mean age 37.3 years versus 42.7 years in our study). Furthermore, data on menopausal status and bone-protective medications were not provided. Because glucocorticoid-induced bone loss is most marked early in the course of treatment with glucocorticoids,[15] it is conceivable that the bone-sparing effects of medications are most pronounced in the first months after the start of glucocorticoid treatment.

We conclude that the use of DHEA in premenopausal patients with quiescent SLE has no significant effects on lumbar BMD. In contrast, DHEA may improve BMD in postmenopausal patients with SLE, especially if they do not also use bisphosphonates or estrogens. This can

be relevant for patients in whom bone-sparing therapy with bisphosphonates or estrogen-containing medications is not tolerated or is contraindicated.

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Chapter 8

Summary and General Discussion

This thesis examined the possible significance of dehydroepiandrosterone for fatigue in patients with primary Sjögren's syndrome (pSS) and systemic lupus erythematosus (SLE) as well as effects of DHEA(S) on well-being, physical functioning, disease activity, and bone mineral density (BMD). This chapter summarizes and discusses the findings of this thesis with a main focus on fatigue and its possible physiological determinants, such as disease activity, serum cytokines, and DHEA and the possibility to reduce fatigue with exogenous DHEA.

The studies described in this thesis were performed in 120 outpatients of the departments of Rheumatology and Clinical Immunology of the University Medical Centers in Utrecht and Groningen. Both correlational and clinical experimental designs used standardized questionnaires as well as laboratory and clinical variables. The cross-sectional studies compared 60 female patients with pSS and 60 female patients with SLE with for each patient group 60 age-matched healthy, female control subjects. The experimental studies involved double-blind, randomized placebo-controlled clinical trials with 30 patients receiving 200 mg oral DHEA and 30 patients on placebo per patients group. At baseline, after 3, 6, and 12 months on study medication, and 6 months after cessation of treatment, outcome parameters were assessed. Effects of twelve-month DHEA administration on bone mineral density were examined in SLE patients.

Fatigue

Compared to healthy control participants, pSS patients reported more general fatigue and depressed mood as well as reduced mental well-being and physical functioning; these differences were highly significant (Chapter 2). In this patient group, more than 75% of the patients rated their fatigue as more severe than the worst scoring 25% of healthy participants. Also the fatigue levels of patients with SLE, both in patients using and not using prednisone, were significantly higher than those of healthy control participants (Chapter 5). Overall, the high presence of fatigue observed in the patients of the current study is in agreement of previous surveys of fatigue in these patient groups and underlines the importance of finding determinants and treatment options of fatigue in these patient groups.

Correlational analyses in patients with pSS showed that fatigue, well-being and functioning were not correlated with tear production (Schirmer I test) and laboratory indicators of expression of disease (haemoglobin concentration, erythrocyte sedimentation rate, and serum immunoglobulin G) (Chapter 2). Thus, although the high prevalence of fatigue and reduced functioning in pSS patients might suggest a mediating role of generalized immunological processes, in the present study, the investigated surrogate indicators of disease activity in pSS are not correlated with persistent fatigue and reduced functioning. Because only SLE patients with a low level of disease activity were included in the study no meaningful correlations between the SLE disease activity index and fatigue could be calculated for this patient group (Chapter 5).

It is important to take account of the difference between variations in fatigue within an individual and between individuals as different processes may underlie these differences.[1] Intra-individual levels of fatigue may covary with disease activity. As a consequence, the symptom of fatigue can be a sign for the physician to evaluate disease activity. However, intra-individual variations in fatigue and disease activity were not examined in our studies; the assessment of fatigue in our survey highly reflects stable individual differences in chronic fatigue, which do not or barely correlate with disease activity. In this survey, as well as in earlier studies, associations were found between fatigue and psychological variables.

Cytokines and fatigue

In pSS, both cells constituting the characteristic glandular periductal infiltrates as well as the ductal epithelial cells actively produce a variety of (pro-inflammatory) cytokines. Compared to healthy controls, patients with pSS have increased serum levels of IL-2,[2] IL-6,[2,3] and IL-10.[2,4] Proinflammatory cytokines may trigger a complex set of events leading to fatigue and psychological and functional malaise known as sickness behavior.[5,6] In confirmation of this model, several observations link cytokines to fatigue. In animal studies administration of IL-1β, TNF- α, or lipopolysaccharide leads to decreased activity and increased somnolence.[5] In men, cytokine therapy with TNF-α,[7] IL-2,[8] or IL-6,[9] is associated with flu-like symptoms including fatigue, depressed mood, and cognitive disturbances. Reduction of fatigue is seen with biological therapies blocking proinflammatory cytokines, such as TNF-α blocking therapy in patients with rheumatoid arthritis.[10,11]

In chapter 3 we examined whether serum levels of selected cytokines relate to multiple dimensions of fatigue in patients with pSS. Fatigue levels were not related to serum levels of interleukin (IL)-1β, IL-2, IL-6, or TNF-α. The occasional finding that reduced motivation was higher in patients with detectable serum levels of IL-10 ($p=0.04$) disappeared after correction for multiple testing. Our findings did not reflect a widespread effect of circulating cytokines at multiple aspects of fatigue.

The absence of an association between serum levels of cytokines and dimensions of fatigue does not necessarily mean that the theory that cytokines are related to fatigue is wrong. The pronounced physiological and behavioural changes noted when cytokines are administered to patients,[7,9] might be due to much higher levels of circulating cytokines that are induced in such situations. Furthermore, levels of circulating, peripherally produced cytokines may not reflect the local situation in the central nervous system as pro-inflammatory cytokines can induce synthesis and release of cytokines by glial, vascular, and immune cells in the brain.[5] Thus, our negative finding with respect to the association between fatigue and serum cytokine levels does not rule out the possibility that (pro-inflammatory) cytokine-directed therapies could still have an effect on fatigue, which should be a topic investigation in future studies.

Endogenous DHEA(S) serum levels

The main focus of this thesis was to examine the possible role of DHEA(S) in fatigue, well-being and functioning. First, we examined whether fatigue was associated with endogenous DHEAS levels. Previous studies in small samples of women with pSS indicated reduced serum levels of DHEA[12] or DHEAS,[13] and a positive correlation between circulating levels of DHEAS and mental well-being.[13] In this thesis, although DHEAS levels in pSS patients were low compared to levels in healthy controls, the correlations between serum DHEAS and general fatigue, depressed mood, mental well-being, and physical functioning were not significant (Chapter 2)**.** Compared to healthy subjects, mean levels of DHEA(S) have also been observed to be low in SLE patients,[14-16] which was confirmed in our study (Chapter 5). In the SLE group, 77% of the patients using prednisone and 24% of the patients not using prednisone had below normal serum DHEAS levels, while only one control participant had a below normal serum DHEAS level. As in patients with pSS, the results in patients with SLE indicated that low DHEAS levels are not –or even inversely– related to fatigue (Chapter 5). In conclusion, although endogenous serum DHEA(S) levels are low in both patients groups and fatigue is high, correlational analyses indicate that DHEA(S) does not play a critical role in the high levels of fatigue, or in well-being and functioning.

High levels of fatigue in conjunction with low DHEA(S) serum levels have been observed in chronic autoimmune diseases,[14,16,17,18] as well as in non-inflammatory disorders, such as chronic fatigue syndrome (CFS), depression and burnout,[19-21] while others found high DHEA(S) levels in non-inflammatory disorders.[22-25] Therefore, it could be that low levels of DHEAS are a consequence of chronic inflammation rather than a cause of fatigue.

A possible explanation for this unexpected result may be that fatigue is not influenced by low DHEA(S) levels as such, but rather by an overall physiological imbalance involving DHEA(S) and other hormones, such as cortisol. This so called "disproportion principle" reflects an inadequately low secretion of cortisol and/or ACTH (and thus DHEAS) in relation to stimulating cytokines in human chronic inflammatory diseases.[26] Taken into consideration the increased proinflammatory status in these patients, the hypothalamic-pituitary-adrenal (HPA) axis response is relatively inadequate and lower than one might expect. This suggests that a supraphysiological response of the HPA-axis might be expected to counteract the ongoing inflammatory status and as a consequence possibly improve fatigue.

Previous studies in pSS[12] and SLE[27-29] suggest a hypo-responsive HPA axis in relation to inflammation. Our current results in SLE do not rule out the existence of a DHEA(S)/cortisol imbalance reflecting impaired functioning of the HPA-axis due to inflammation, or fatigue and its consequences. This is a topic for future inquiry.

In summary, low DHEA(S) serum levels are found in patients with pSS and SLE, which might be the result of the disease process, glucocorticoid-medication or other consequences of the disease, such as sleep disturbance, pain, and physical deconditioning. This thesis does

not yield evidence to assume a central role for endogenous DHEAS in fatigue, well-being and functioning.

Effect of administration of DHEA

Having summarized and discussed the effects of DHEA administration on fatigue, the effects on bone mineral density will be discussed.

Fatigue

The observation of lack of association between low DHEA(S) and fatigue does not rule out the possibility that raising DHEA(S) levels to supraphysiological serum levels could have a beneficial effect on fatigue in patients with chronic inflammatory diseases. Moreover, "the disproportion principle" might be a reason to add DHEA(S). The possible usefulness of DHEA administration is also indicated in empirical studies; positive effects on fatigue, mood, anxiety, depression and well- being were described in elderly people,[30-35] in a variety of disease states,[36-40] and in women with DHEA deficiency due to adrenal insufficiency. [38,41]

Empirical studies indicated that DHEA(S) serum levels might be low in patients with pSS,[12,13,42] that treatment with an anabolic-androgenic steroid improved subjective xerostomia, well-being, and decreased ESR,[43] and that circulating levels of DHEA-S and mental well-being were related.[13] Moreover, in a female mouse model of Sjögren's syndrome administration of androgens strongly suppressed the inflammatory reaction.[44-46]

Also in patients with SLE, low serum levels of DHEA(S) have been reported.[14-16] Oral administration of DHEA was shown to stabilize or improve activity of SLE, to reduce the number of flares, to have steroid sparing effects,[47-53] to improve mental well-being and sexuality,[54] and fatigue.[52] Moreover, circulating DHEA(S) levels and bone mineral density (BMD) were found to be correlated,[55] and reduction in BMD could be prevented by DHEA administration.[49] In animal models for SLE, administration of DHEA at young age showed prevention of development of manifestations of autoimmunity and prolonged life.[56,57]

Motivated by these previous studies, we examined in a randomized double-blind placebo-controlled study in women with pSS and women with SLE the effects of daily oral administration of 200 mg DHEA on fatigue, well-being, functioning, and (surrogate parameters of) disease activity. In patients with SLE also effects on bone mineral density were examined.

Our study demonstrated that patients with pSS (Chapter 4) and patients with SLE (Chapter 6) from the DHEA-treated group but also from the placebo-treated group improved on general

fatigue, mental well-being, and depressive mood. The improvement of fatigue and well-being was stronger associated with the belief to have used DHEA than the actual use of DHEA. Our study was the first with a strong study design. As effects on fatigue were similar to that of placebo, we clearly demonstrated a lack of a pharmacological beneficial effect of DHEA treatment 200 mg/day.

In patients with pSS, the negative findings in our study are in line with another study observing no significant effects of DHEA 200 mg a day for ocular and oral objective tests and serological measures.[58] Similar to our study, another study that was published later also employed a randomized placebo-controlled design including 107 patients with pSS.[59] In contrast to our study, 50 mg DHEA a day was given and enrolling patients had to fulfill two essential inclusion criteria: first, patients had to suffer from significant fatigue, defined as a general fatigue score ≥ 14 on the MFI-20 scale (MFI). Second, serum DHEAS levels had to be lower than the mean of age- and sex-matched healthy control participants. As in our study, intention-to-treat analysis showed no difference in fatigue between treatment with DHEA and placebo; fatigue improved similarly in both patient groups. All 5 MFI-subscales and theVAS-fatigue improved from the baseline levels as a result of treatment ($p < 0.001$), but with negligible differences between the two treatment arms. The authors concluded that substitution treatment with 50 mg DHEA a day in DHEA-deficient and severely tired patients with pSS did not help against fatigue better than placebo.

Our findings were also in agreement with a study finding no correlation between serum or salivary androgen levels (including serum DHEAS) in pSS patients with MFI-20 fatigue scores.[60]

Some of our study results were confirmed in two other randomized, controlled, double-blind trials using 50 mg DHEA/day orally in patients with pSS.[61,62] This included that DHEA increases serum androgen levels, that serum DHEAS levels and ESR are inversely correlated, and that neither subjective dryness of eyes and mouth, nor the (un)stimulated salivary flow rate improves with DHEA treatment. Unfortunately, both studies did not evaluate fatigue or well-being.

In patients with SLE, the first publication mentioning beneficial effects of DHEA 200 mg/day on fatigue in female patients with SLE dates from 1994.[52] In this open study, lacking a control group, 8 of -in total- 10 patients reported that DHEA 200 mg/day improved well-being, fatigue, energy and other subjective consequences of the disease. The reported improvement of fatigue using DHEA 200 mg/day was confirmed in our study. However, our double blind, placebo-controlled randomized trial also observed similar effects for the placebo group, which clearly demonstrates that the effect is not due to DHEA administration. Petri et al.[53] performed a randomized, double blind, placebo-controlled clinical trial using DHEA 200 mg/day in female patients with SLE and evaluated the effect of DHEA on fatigue

as secondary outcome measure. In line with our results, no statistically significant difference between DHEA and placebo treated groups were found. They did, however, report a beneficial effect of DHEA using a composite end point that integrated all three SLE domains: disease activity, organ damage, and health-related quality of life (QoL). There were no significant differences in overall analyses, but subgroup analysis in patients with active disease (SLEDAI > 2) showed significantly more improvement or stabilization without clinical deterioration in DHEA treated patients compared to the placebo group. This composite responder score was newly developed and not applicable to our study group. Therefore, comparison of results in that study with our data is not possible.

Another study evaluated effects of dehydroepiandrosterone 20-30 mg/day on health-related quality of life in glucocorticoid treated female patients using a double-blind, randomized, placebo-gecontrolled study during 6 months, followed by a 6 months open label phase.[54] They found no superior effect of DHEA over placebo in physical component score (PCS), general health and vitality, which is in agreement with our results. The mental component score (MCS) improved significantly in the DHEA-treated patient group during the 6 months double-blind treatment phase, but worsened during the subsequent 6 months open label phase of the study. The MCS in the initial placebo group did not improve in the second open label phase with DHEA supplementation. Thus, at best short-lived improvement in mental well-being was observed, but not an improvement of fatigue (defined as the opposite of vitality in this study).

Our study could not find beneficial effects of DHEA treatment on SLE disease activity measured by SLEDAI. A previous open study reported a significant decrease in SLEDAI score after 3 – 6 months DHEA 200 mg/day in 8 of in total 10 patients who elected to continue DHEA treatment, introducing a possible survivor bias, while SLEDAI scores did not change significantly during the first 3 months.[52] The lack of statistically significant improvement in SLE disease activity with DHEA 200 mg/day compared to placebo was confirmed by other investigators.[47,51,53] The beneficial effects of DHEA in the latter studies were based on an improvement in patients overall assessment of disease activity (P-VAS), and a reduction in (time to first) lupus flares in DHEA treated patients compared to placebo treated patients, although statistical significance was reached only in subgroup analysis for most of these outcome variables or not at all.

Serum complement factor 3 was the only physiological variable that differentially changed in response to DHEA versus placebo, which was also found in earlier reports.[50,51,53] This decrease in C3 serum levels is not likely to be caused by an overall increase of disease activity since the SLEDAI did not significantly change in both groups. Decreases in complement levels without SLE flare during DHEA treatment were also observed in several other clinical studies.[50,51,53] The observed reduction in C3 level may be a direct physiologic androgen effect on hepatic complement synthesis as indicated in a study in men with Klinefelter syndrome during testosterone replacement therapy.[63] Another explanation for

this phenomenon could be an anti-inflammatory effect of DHEA on the proinflammatory cytokine production.[64] In vitro incubation of human peripheral blood mononuclear cells and bone marrow cells with DHEA has been demonstrated to reduce the production of IL-6.[64,65] Since IL-6 levels are elevated in active SLE[66,67] and can stimulate hepatic secretion of C3 as acute phase reactant,[68] decreased levels of C3 during DHEA treatment may be the result of reduced IL-6 levels.

Bone mineral density

In patients with SLE a high prevalence of low bone mineral density (BMD) has been reported.[69-71] Osteoporosis and osteoporotic fractures are likely one of the most preventable forms of musculoskeletal organ damage in this disease.[72] In SLE, low levels of circulating DHEA(S) compared to age-matched healthy controls have been found[14-16] and low DHEA(S) levels have been correlated with low BMD.[55] This correlation is likely to be expected since the pro-hormone DHEA(S) is converted into testosterone, dihydrotestosterone and estrogens in peripheral tissue.[73] The combined findings suggests that administration of DHEA could prevent bone mineral loss due to disease activity or glucocorticoid use. We evaluated the possible beneficial effect of administration of 200 mg DHEA per day on lumbar bone mineral density (BMD) in female patients with systemic lupus erythematosus (Chapter 7).

Our study indicated that administration of 200 mg DHEA per day for one year did not affect lumbar BMD of premenopausal women with quiescent SLE. However, our results did suggest a protective effect of DHEA on bone in postmenopausal SLE patients who did not use estrogens or bisphosphonates: of 9 postmenopausal women without bone protective co-medication the mean change in lumbar BMD was 3.22% in the group treated with DHEA versus -5.61% in the placebo treated group. This beneficial effect of DHEA on bone loss in systemic lupus erythematosus was also indicated in other double-blind, placebo-controlled, randomized clinical trials.[49,74,75] In 19 patients with active SLE (nefritis, serositis, or haematological abnormalities) necessitating the start of high-dose glucocorticoids, addition of 200 mg DHEA a day to treatment prevented significant reduction in lumbar BMD, while in the placebo-treated group lumbar BMD decreased.[49] It is difficult to compare our observations with these findings as in this study patients had more active SLE (mean SLEDAI 12.6 versus 3.1 in our study), more often used prednisone (100% versus 53% in our study), had a higher daily dose of prednisone (mean 46.7 mg versus 5.6 mg among users in our study), were younger (mean age 37.3 years versus 42.7 years in our study), and data on menopausal status and bone-protective medications were not provided. More comparable with our study design is a later published double-blind, placebo controlled trial evaluating effects of DHEA 200 mg/day on bone mineral density in women with systemic lupus erythematosus receiving chronic low dose glucocorticoid therapy.[74] They reported a significant improvement in BMD in patients treated with DHEA compared to placebo, with a mean BMD gain at the lumbar spine of 1.7% in 200 mg DHEA group compared to a mean

loss of 1.1% in the placebo group. In the DHEA treatment group, the mean gains from baseline at both the lumbar spine and total hip were statistically significant. Sanchez-Guerrero et al[75] examined effects of DHEA 200 mg/day on BMD in women with SLE receiving chronic glucocorticoid therapy excluding patients using hormonal replacement therapy and bisphosphonates. The study population comprised almost 60% postmenopausal patients. Postmenopausal women who received DHEA showed a significantly higher gain in lumbar BMD than premenopausal patients. DHEA 200 mg/day was found to be protective against BMD loss at the lumbar spine in patients with SLE receiving glucocorticoids. The greater effects of DHEA on BMD in postmenopausal patients might be mediated by its metabolism to androgenic or estrogenic steroids by bone cells,[75-77] which could affect local production of growth factors, cytokines, and other regulatory pathways.[65,78-80]

Thus, we conclude that the use of DHEA in premenopausal patients with quiescent SLE has no significant effects on lumbar BMD. However, DHEA may improve BMD in postmenopausal SLE patients, especially if they are not already protected for bone loss by the use of bisphosphonates or estrogens. Since alternative treatment of (glucocorticoid induced) bone loss, like bisphosphonates, are widely available and has been proven safe and effective and is associated with low costs, we would not advise DHEA as treatment option for this purpose, especially since the long-term consequences of treatment with this steroid hormone have yet to be determined.

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Chapter 9

Addendum

Nederlandse samenvatting

Dankwoord

Curriculum Vitae

Publications

NEDERLANDSE SAMENVATTING

Inleiding

Vermoeidheid is één van de belangrijkste klachten van patiënten met het primair syndroom van Sjögren (pSS) en Systemische Lupus Erythematosus (SLE). Veel patiënten vinden vermoeidheid en gebrek aan energie de meest invaliderende klacht van hun ziekte. Het heeft op veel aspecten van hun dagelijkse leven een negatieve invloed. Dokters met ervaring in deze ziektebeelden erkennen het ook als een groot probleem en vinden het frustrerend dat ze er zo weinig aan kunnen doen.

Van het gebruik van dehydroepiandrosteron (DHEA), een zwak mannelijk geslachtshormoon dat geproduceerd wordt in de bijnieren, wordt beweerd dat toediening ervan aan mensen het algemeen welbevinden, inclusief moeheid, gunstig kan beïnvloeden. Op het internet kan men vele sites vinden waarin het gebruik van DHEA door ouderen wordt aanbevolen ter verbetering van hun energie. De onderzoeken waarop dergelijke aanbevelingen steunen zijn echter van zeer matige wetenschappelijk kwaliteit. DHEA is niet als geneesmiddel erkend, maar toch is het als "natuurproduct" te koop.

Het primair syndroom van Sjögren (pSS) en Systemische Lupus Erythematosus (SLE) rekent men tot de auto-immuunziekten. Dit zijn aandoeningen waarbij het afweersysteem (immuunsysteem) zich (onder andere) richt tegen componenten van het eigen lichaam. Dergelijke aandoeningen komen vaker voor bij vrouwen. Oestrogenen, de vrouwelijke geslachtshormonen, hebben op deze ziektes in het algemeen een negatieve invloed. Dit geldt niet voor androgenen, de mannelijke geslachtshormonen.

Omdat DHEA een (zwak) mannelijk geslachtshormoon is en omdat er in de literatuur diverse aanwijzingen waren dat DHEA bij auto-immuunziekten moeheid en verminderd welbevinden gunstig zou kunnen beïnvloeden, besloten wij een placebo-gecontroleerd onderzoek uit te voeren met als belangrijkste doel om vast te stellen of toediening van DHEA aan patiënten met pSS of SLE een gunstig effect heeft op hun kwaliteit van leven.

Nadat achtergrond informatie is gegeven over de aandoeningen waarop het onderzoek zich richt (pSS en SLE) en de te onderzoeken stof (DHEA), bespreken wij kort de bevindingen van het onderzoek.

Het primair Syndroom van Sjögren

Het primair syndroom van Sjögren (pSS) is een auto-immuunziekte die wordt gekenmerkt door een chronische ontsteking van klieren, zoals de traan- en speekselklieren. Indien het syndroom van Sjögren samengaat met andere auto-immuunziekten zoals reumatoïde artritis, SLE of systemische sclerose spreekt men van een secundair syndroom van Sjögren.

Met het woord primair wordt bedoeld dat er geen bijkomende auto-immuunziekte aanwezig is.

De ontstekingen in de traan-en speekselklieren bij pSS leiden tot klachten van droogheid van de ogen (keratoconjunctivitis sicca) en mond (xerostomia). Naast deze organen kunnen ook andere weefsels en organen door het ziekteproces worden aangedaan. Tot deze zogenaamde extra-glandulaire manifestaties rekent men onder andere gewrichtsklachten, huiduitslag, ontstekingsverschijnselen van kleine bloedvaatjes, aantasting van zenuwen of longafwijkingen die de opname van zuurstof in het bloed bemoeilijken. Vaak is het nodig om deze extra-glandulaire verschijnselen bij pSS te behandelen met het krachtig ontstekings-remmend werkende medicijn prednison.

Diverse onderdelen van het afweersysteem (immuunsysteem) zijn betrokken bij de voor de ziekte pSS kenmerkende ontstekingsverschijnselen. De precieze oorzaak van pSS is (vooralsnog) niet achterhaald. Dat geldt ook voor de oorzaak van de zo vaak bij deze ziekte aanwezige moeheid.

Het pSS is niet zeldzaam: circa 0.5-1.0 % van de volwassen bevolking voldoet aan de criteria van deze aandoening. Vrouwen hebben de ziekte veel vaker dan mannen (verhouding 9 : 1) en de ziekte openbaart zich meestal tussen het 30ste en 40ste levensjaar.

Systemische lupus erythematosus

Systemische Lupus Erythematosus (SLE) is een auto-immuunziekte die vrijwel ieder orgaan in het lichaam kan aantasten. Functiestoornissen in die organen worden veroorzaakt door ontstekingsreacties die het gevolg zijn van het neerslaan van immuuncomplexen (dit zijn verbindingen tussen auto-antistoffen en de moleculen waartegen zij gericht zijn) in bloedvaatjes. Een normaal immuunsysteem maakt alleen afweerstoffen tegen lichaamsvreemde binnendringers. Patiënten met SLE maken (net als vele andere patiënten met een auto-immuunziekte) ook afweerstoffen tegen lichaamseigen bestanddelen (men spreekt van auto-antistoffen). Bij SLE patiënten is de vorming van afweerstoffen tegen substanties die in normale celkernen aanwezig zijn (zoals DNA, de bouwsteen van chromosomen) een bekend verschijnsel. Verder is kenmerkend voor SLE dat er in het bloed zogenaamde circulerende immuuncomplexen aantoonbaar zijn en dat men in aangedane weefsels neerslagen van dergelijke immuuncomplexen kan aantonen, met name in vaatwandjes. De reacties die volgen op de neerslag van immuuncomplexen in de vaatjes van organen worden algemeen gezien als de basis waarop de beschadiging van organen volgt.
De ziekte SLE kent een enorme verscheidenheid aan verschijnselen. Tot de meest voorkomende verschijnselen bij het begin van de ziekte behoren gewrichtsklachten (al dan niet vluchtige pijnen of ontstekingen in diverse gewrichten) en huiduitslag, vaak op aan de zon blootgestelde huid. Bij ongeveer de helft van de SLE patiënten raken de nieren bij de ziekte betrokken. Onbehandeld leidt betrokkenheid van de nier vaak tot verlies van de nierfunctie.

Het verloop van SLE kenmerkt zich door perioden waarin de ziekte activiteit vertoont (opvlamming, exacerbatie), afgewisseld door perioden met weinig tot geen ziekteactiviteit (remissie). Veel patiënten met SLE gebruiken het ontstekingsremmende middel prednison om ziekte activiteit af te remmen.

De ziekte SLE komt bij circa 1 op de 4000 Nederlanders voor, waarbij vrouwen de ziekte vele malen vaker hebben dan mannen (verhouding 9 : 1). De ziekte openbaart zich meestal tussen het 20ste en 40ste levensjaar.

Dehydroepiandrosteron(-sulfaat)

Dehydroepiandrosteron (DHEA) en het daarvan afgeleide dehydroepiandrosteron-sulfaat (DHEA-S) behoren tot de hormonen die gemaakt worden door de bijnier van de mens en die worden uitgescheiden naar het bloed. DHEA(-S) is op zichzelf een zwak werkend mannelijk geslachtshormoon (androgeen). Het kan echter zowel in de bijnier zelf als in andere weefsels omgezet worden in sterker werkende mannelijke geslachtshormonen, zoals testosteron, of in vrouwelijke geslachtshormonen (oestrogenen). De hoeveelheid DHEA(-S) in het bloed van mensen is het hoogst tussen het 20e en 30e levensjaar en daarna neemt de hoeveelheid in het bloed geleidelijk af . Rond de leeftijd van 80 jaar is gemiddeld nog maar 20-30% over van de maximale spiegel op jeugdige leeftijd.

Diverse onderzoeken suggereren een verband tussen deze met de leeftijd samenhangende “normale”, fysiologische afname van het DHEA(-S) gehalte in het bloed en uiteenlopende, met de ouderdom komende “gebreken” zoals vermoeidheid, verlies van energie, hart-en vaatziekten, geestelijke achteruitgang en zelfs achteruitgang in de functie van het afweersysteem.

Daarnaast wordt, vooral op het internet, volop geadverteerd dat het toedienen van DHEA aan ouderen veel van deze “ouderdomsverschijnselen” kan tegengaan. Hoewel op de kwaliteit van de onderzoeken waarop deze beweringen steunen veel aan te merken is, wordt DHEA wel “de fontein van de jeugd” genoemd.

Er zijn ook over toediening van DHEA bij ziektebeelden, zoals depressie, anorexia nervosa, het chronisch vermoeidheidssyndroom en bij een verminderde werking van de bijnier diverse publicaties verschenen. Daarin worden overwegend positieve effecten beschreven. Het toedienen van DHEA lijkt gunstige effecten te kunnen hebben op klachten van moeheid, stemming, stress, depressie en het algemeen welbevinden.

Diverse onderzoekers hebben aangetoond dat bij een aanzienlijk deel van patiënten met pSS en SLE de hoeveelheid DHEA(-S) in het bloed verlaagd is. Dat is zeker het geval indien een patiënt behandeld wordt met prednison. Prednison behoort tot de glucocorticoïden. Deze krachtige ontstekingsremmende middelen onderdrukken de productie van verschillende in de bijnieren geproduceerde hormonen, waaronder het DHEA.
Bij pSS en SLE komen verlaagde waarden voor DHEA in het bloed ook los van prednison-gebruik voor. De DHEA productie in de bijnier lijkt dus bij pSS en SLE patiënten “spontaan”

vaak afgenomen.
Goed uitgevoerd, placebo-gecontroleerd onderzoek naar de effecten van toediening van DHEA bij pSS en SLE op vermoeidheid en het algemeen welbevinden is niet voorhanden. Bij SLE is wel onderzocht of het middel actieve ziekte tot rust kan brengen. Daarbij werden nauwelijks tot geen nadelige effecten van het middel gevonden.

Het placebo-gecontroleerde prospectieve onderzoek

De basis van de onderzoeken die in dit proefschrift worden beschreven wordt gevormd door twee studies waarin bij 60 vrouwelijke patiënten met pSS en 60 vrouwelijke patiënten met SLE het effect van dagelijkse inname van 200 mg DHEA wordt vergeleken met het gebruik van een nep-medicijn (placebo).

De in de studie gebruikte uiterlijk identieke capsules werden door de apotheek van het Universitair Medisch Centrum Utrecht (UMCU) gemaakt volgens de richtlijnen voor het maken van geneesmiddelen. De grondstof DHEA werd ingekocht bij de firma Fagron uit Nieuwerkerk a/d IJssel. Welke capsule een patiënt uiteindelijk ging gebruiken werd door loting bepaald .

Uiteindelijk hebben 30 patiënten met pSS en 30 patiënten met SLE gedurende 12 maanden dagelijks een capsule die óf DHEA óf placebo bevatte ingenomen. Een half jaar na het staken van de inname kwamen de patiënten voor de laatste metingen en werd hen gevraagd of zij meenden placebo of DHEA te hebben gebruikt.

De aan het onderzoek deelnemende patiënten waren afkomstig uit de groepen patiënten met pSS en SLE die begeleid en behandeld werden binnen de poliklinieken van de afdelingen Reumatologie en Klinische Immunologie van het UMCU en het Academisch Ziekenhuis in Groningen.

Patiënten met pSS die korter dan 1 jaar voor aanvang van de studie prednison hadden gebruikt en patiënten met SLE die in de 6 maanden voorafgaande aan de studie meer dan 10 mg prednison per dag hadden gebruikt werden uitgesloten van de studies.
Behalve patiënten deden in sommige onderdelen van het onderzoek ook gezonde vrouwen mee als controles (in totaal 99). Zij kwamen qua leeftijd overeen met de patiënten.
Vóór de deelname aan het onderzoek kregen patiënten en controle personen uitvoerige schriftelijke en mondelinge voorlichting over de voor- en nadelen van het meedoen aan het onderzoek en gaven zij schriftelijk toestemming.

De beschreven onderzoeken waren mogelijk dankzij financiële steun van het Reumafonds.

Resultaten van het onderzoek

In hoofdstuk 2, 3 en 4 van dit proefschrift worden drie onderzoeken beschreven bij de vrouwelijke patiënten met pSS.

Het onderzoek in **hoofdstuk 2** laat zien dat de aan de studie deelnemende patiënten met pSS, ten opzichte van gezonde vrouwen met eenzelfde leeftijd, duidelijk meer vermoeid waren en vaker een depressieve stemming, een verminderd gevoel van algemeen welbevinden en meer pijn hadden. Bij laboratorium onderzoek bleken patiënten ten opzichte van de controle personen minder DHEA-S in het bloed te hebben. Daarnaast waren, zoals te verwachten bij pSS patiënten, bij de patiënten meer klachten van droogheid aanwezig en toonde het bloed een hogere bezinkingssnelheid van rode bloedcellen, een lager hemoglobine gehalte (Hb) en een overmaat aan afweerstoffen (IgG). Een eenduidig verband tussen gerapporteerde klachten van vermoeidheid en de hoeveelheid DHEA-S in het bloed konden wij echter niet aantonen.

Cytokinen zijn door cellen uitgescheiden moleculen die een activerende of remmende invloed hebben op cellen die beschikken over een ontvangersmolecuul (receptor) waaraan het cytokine kan binden. Cytokinen vormen onder andere een belangrijke schakel in de communicatie tussen cellen die betrokken zijn bij ontstekingsprocessen. Van de zogenaamde pro-inflammatoire (ontstekingsbevorderende) cytokinen wordt algemeen aangenomen dat zij een belangrijke rol spelen in wat men ziekte-gedrag ("sickness behaviour") noemt. Hieronder verstaat men vermoeidheid, psychologische en functionele malaise die kan optreden na de complexe cascade van met het ziekteproces samenhangende gebeurtenissen.

In **hoofdstuk 3** beschrijven wij het onderzoek dat wij deden bij vrouwelijke patiënten met pSS naar samenhang tussen verschillende aspecten van moeheid en de hoeveelheid van verschillende cytokinen in het bloed. In dit onderzoek betrokken wij de volgende cytokinen: interleukine (IL)-1b, IL-2, IL-6, IL-10 en tumor necrosis factor (TNF)-α. De resultaten lieten zien dat er géén relatie was tussen de circulerende hoeveelheid van de afzonderlijke cytokinen en aspecten van vermoeidheid bij vrouwelijke pSS patiënten.

De belangrijkste studie bij pSS, het placebo-gecontroleerde onderzoek dat hoopte voor de patiënt relevante, gunstige effecten van de toediening van dagelijks 200 mg DHEA op moeheid en algemeen welbevinden aan te tonen wordt beschreven in **hoofdstuk 4.**

De resultaten lieten inderdaad spectaculaire verbeteringen zien van DHEA gebruik op moeheid, algemeen welbevinden en depressieve stemming. Ook verminderde bij de patiënten de hinder van een droge mond en daalde de BSE significant. Echter, met uitzondering van het effect op de BSE, werden dezelfde spectaculaire verbeteringen gezien bij pSS patiënten die het "nepmedicijn" (placebo) hadden gebruikt.

De resultaten geven een duidelijke aanwijzing dat het geloof dat de patiënt heeft over het gebruik van een werkzaam middel of placebo in belangrijke mate het effect bepaalt.

Hoewel de resultaten dus als negatief moeten worden beoordeeld, laat dit onderzoek heel goed zien hoe ongelooflijk belangrijk het is om bij klinisch onderzoek een placebo groep te betrekken. Zonder placebogroep zou ons onderzoek tot geheel andere conclusies hebben geleid.

De hoofdstukken 5, 6 en 7 betreffen vrouwelijke patiënten met SLE.

Hoofdstuk 5 beschrijft de samenhang tussen de in het bloed aanwezige hoeveelheid DHEA-S en moeheid bij de 60 vrouwelijke patiënten met SLE en qua leeftijd overeenkomende gezonde vrouwen. Daarnaast wordt bij SLE patiënten onderzocht of er een samenhang is tussen diverse aspecten van door patiënten gerapporteerde moeheid en de aan-of afwezigheid van een verlaagde DHEA-S hoeveelheid in het bloed.

Wij vonden binnen de totale groep van SLE patiënten geen verschil in de mate van moeheid tussen patiënten met een verlaagde of normale hoeveelheid DHEA-S in het bloed. Binnen de groep patiënten die (een lage dosis) prednison gebruikten werd geen verschil in moeheid vastgesteld tussen patiënten met verlaagde en normale DHEA-S waarden in het bloed.

Opmerkelijk was de bevinding dat bij de patiënten die géén prednison gebruikten degenen met verlaagde waarden voor DHEA-S in het bloed minder vermoeid waren dan degenen met een normaal DHEA-S gehalte.

Concluderend: wij konden in deze studie géén eenduidig verband vaststellen tussen verschillende aspecten van moeheid bij vrouwelijke SLE patiënten en het al dan niet verlaagd zijn van de hoeveelheid DHEA-S in het bloed.

Hoofdstuk 6 beschrijft de effecten van de toediening van 200 mg DHEA per dag aan SLE patiënten in vergelijk met de effecten die toediening van placebo heeft op algemeen welbevinden en vermoeidheid. De uitkomst van het onderzoek was vrijwel identiek aan de uitkomst bij pSS patiënten (hoofdstuk 4).

Ook bij patiënten met SLE werden zowel in de groep die DHEA kreeg toegediend als in de placebogroep een duidelijke verbetering van moeheid en algemeen welbevinden gevonden en wederom leek het geloof in de medicatie van doorslaggevende betekenis.

Geslachtshormonen bevorderen de kalkhoudendheid en daarmee de stevigheid van botten; denk maar aan het feit dat door sterk dalen van de hoeveelheid oestrogenen in het bloed na de menopauze bij vrouwen het risico op botontkalking (osteoporose) sterk toeneemt. Omdat DHEA een hormoon is dat na uitscheiding door de bijnieren in krachtig werkende geslachtshormonen kan worden omgezet is het aannemelijk dat het toedienen van DHEA

een gunstig effect op de kalkhoudendheid van botten (de botmineraal dichtheid, BMD) kan hebben.

In **hoofdstuk 7** onderzochten wij dit bij vrouwen met SLE die deelnamen aan het in hoofdstuk 6 beschreven placebo-gecontroleerde onderzoek. Van 28 patiënten die DHEA gebruikten en 30 patiënten uit de placebogroep was aan het begin van de studie en na 12 maanden een beoordeelbare botdichtheidsmeting voor evaluatie beschikbaar. Het effect van DHEA op de botdichtheid bleek afhankelijk van of de vrouwen voor- of na de menopauze zaten en of zij reeds medicatie gebruikten waarvan bekend is dat zij de botdichtheid bevorderen. Gevonden werd namelijk dat bij vrouwen die nog niet in de menopauze zijn, het gedurende 1 jaar gebruiken van 200 mg DHEA géén toename van de botdichtheid liet zien, maar wel bij vrouwen die voorbij de menopauze waren en die geen botdichtheidbevorderende medicatie gebruikten.

Conclusies

De conclusies van de in dit proefschrift beschreven onderzoeken betreffende DHEA zijn als volgt:

Patiënten met pSS en SLE zijn duidelijk vermoeider en hebben vaker een depressieve stemming en verminderd gevoel van algemeen welbevinden vergeleken met gezonde controlepersonen. De DHEA-S spiegel in het bloed was zowel in de groep patiënten met pSS als SLE duidelijk lager dan in deze gezonde controles. In tegenstelling tot onze verwachting kon echter geen relatie worden aangetoond tussen vermoeidheid of algemeen welbevinden en de hoeveelheid DHEA-S in het bloed.

Van pro-inflammatoire cytokinen wordt beweerd dat zij een belangrijke rol spelen in ziekte-gedrag ("sickness behaviour"). Het aantonen van een direct verband tussen enerzijds vermoeidheid en de concentratie van pro-inflammatoire cytokinen in het bloed en anderzijds tussen pro-inflammatoire cytokinen met parameters van "ziekteactiviteit" bij patiënten met pSS zou derhalve consequenties kunnen hebben voor de behandeling. Wij vonden wel een samenhang tussen parameters van ziekteactiviteit en de hoeveelheid in het bloed aanwezige (pro-inflammatoire) cytokinen, maar geen verband tussen vermoeidheid en de circulerende cytokinen spiegels. Geconcludeerd wordt dat de concentratie van (pro-inflammatoire) cytokinen in het bloed geen goede parameter is voor moeheid. Dit betekent niet noodzakelijkerwijs dat de theorie van de veronderstelde relatie tussen deze cytokinen en vermoeidheid niet juist is. Mogelijk weerspiegelen de in het bloed circulerende cytokinen niet de locale situatie in ontstoken weefsels of in het centrale zenuwstelsel. Of op weefselnivo dit verband wel gevonden kan worden behoeft nader onderzoek.

Het placebo-gecontroleerde onderzoek bij patiënten met pSS en SLE met 200 mg DHEA per dag toonde een duidelijke verbetering aan met gebruik van DHEA op moeheid, algemeen welbevinden en depressieve stemming. Echter, dezelfde verbetering werd gezien bij patiënten die het "nepmedicijn" (placebo) hadden gebruikt. Het effect van een

"geneesmiddel" lijkt dus in belangrijke mate bepaald te worden door het geloof dat de patiënt heeft in het gebruikte middel. Er zijn twee mechanismen die deze observatie kunnen verklaren: óf het geloof DHEA te gebruiken induceert verbetering óf verbetering induceert het geloof DHEA te gebruiken. Om te concluderen of hier mogelijk sprake is van het zogenaamde "placebo-effect" moet men eerst dé definitie van hét placebo-effect formuleren en deze definitie is niet éénduidig. Waargenomen effecten in placebogroepen bestaan uit meerdere componenten, zoals het natuurlijke beloop, het – meestal positieve – effect dat optreedt bij onderzochten wanneer ze weten dat zij onderwerp van onderzoek zijn, regressie naar het gemiddelde en een eventueel placebo-effect. Wij mogen uit ons onderzoek dan ook niet concluderen dat hier sprake is van het "placebo-effect"; voor deze conclusie zou een onderzoek nodig zijn waarbij ook nog een controle groep patiënten op een wachtlijst betrokken wordt. Aangezien de bereidheid van patiënten om deel te nemen aan een onderzoek al verbetering kan geven suggereert dat middels psychologische interventie, zoals cognitieve gedragstherapie, gunstige effecten bereikt kunnen worden.

Hoewel de resultaten van ons onderzoek dus als negatief moeten worden beoordeeld, laat dit onderzoek heel goed zien hoe belangrijk het is om bij klinisch onderzoek een placebo groep te betrekken. Zonder placebogroep zou ons onderzoek immers tot geheel andere conclusies hebben geleid.

Zoals te verwachten bleek het gebruik van DHEA een gunstig effect te hebben op botdichtheid in postmenopauzale patiënten met SLE. Toch zouden wij niet adviseren DHEA als behandeloptie voor dit doel voor te schrijven, aangezien de lange termijn effecten van deze hormonale behandeling nog niet zijn vastgesteld en er alternatieve behandeling voor (gluco-corticoïd geïnduceerd) verlies aan kalkhoudendheid van bot voorhanden is, zoals bisfosfonaten, die bewezen effectief en veilig is.

Gebaseerd op onze onderzoeksresultaten kunnen wij helaas het gebruik van DHEA als geneesmiddel voor vermoeidheid en afgenomen stemming niet aanbevelen. De zoektocht naar effectieve interventie moet doorgaan, waarbij op dit moment cognitieve gedragstherapie nog het meest succesvol lijkt ter bestrijding van chronische moeheid.

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CURRICULUM VITAE

André Hartkamp werd geboren op 8 februari 1963 in Apeldoorn. Na het behalen van het VWO diploma in 1981 aan de "Koninklijke Scholengemeenschap Apeldoorn Prins Hendrik der Nederlanden" begon hij met de studie psychologie aan de Rijksuniversiteit Utrecht. In 1982 werd het propedeutisch examen behaald. In 1983 veranderde hij van studie toen hij werd ingeloot voor de studie Geneeskunde die eveneens aan de Rijksuniversiteit Utrecht gevolgd werd. Na het behalen van het arts-examen in 1990 was hij als dienstplichtig militair van april 1990 tot augustus 1991 werkzaam als arts op de 836 Keuringsraad op de Korporaal van Oudheusden kazerne in Hollandse Rading. Van augustus 1991 tot 1 januari 1993 werkte hij als arts-assistent interne geneeskunde (niet in opleiding) in het Elisabeth Ziekenhuis in Amersfoort. In januari 1993 begon hij met de opleiding tot internist in het Academisch Ziekenhuis Utrecht (opleider Prof. dr. D.W. Erkelens). Van 1 mei 1996 tot 1 januari 1998 vervolgde hij de opleiding in het Sint Antonius Ziekenhuis te Nieuwegein (opleider Dr. H.C.M. Haanen). Vanaf januari 1998 werkte hij in het kader van het "vrije jaar" in de opleiding tot internist als arts-assistent en klinisch onderzoeker op de afdeling Reumatologie en Klinische Immunologie van het Academisch Ziekenhuis Utrecht en werd een start gemaakt met het onderzoek wat beschreven wordt in dit proefschrift. Hij werd op 1 januari 1999 geregistreerd als internist. Van januari 1999 tot januari 2002 was hij arts-assistent in opleiding tot reumatoloog in het Academisch Ziekenhuis Utrecht (opleider Prof. dr. J.W.J. Bijlsma). Na zijn registratie als reumatoloog (1 januari 2002) was hij tot september 2003 als staflid werkzaam binnen de afdeling Reumatologie en Klinische Immunologie. Daarna maakte hij de overstap naar het Jeroen Bosch Ziekenhuis te 's-Hertogenbosch waar hij tot op heden als reumatoloog werkzaam is.

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