Effects of dehydroepiandrosterone supplement on health-related quality of life in glucocorticoid treated female patients with systemic lupus erythematosus

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Abstract
The objective of this study was to evaluate the efficacy of low dose dehydroepiandrosterone (DHEA) on health-related quality of life (HRQOL) in glucocorticoid treated female patients with systemic lupus erythematosus (SLE). Forty one women (≥ 5 mg prednisolone/day) were included in a double-blind, randomized, placebo-controlled study for 6 months where DHEA was given at 30 mg/20 mg (#45/#46 years) daily, or placebo, followed by 6 months open DHEA treatment to all patients. HRQOL was assessed at baseline, 6 and 12 months, using four validated questionnaires and the patients' partners completed a questionnaire assessing mood and behaviour at 6 months. DHEA treatment increased serum levels of sulphated DHEA from subnormal to normal. The DHEA group improved in SF-36 "role emotional" and HSCL-56 total score (both p < 0.05). During open DHEA treatment, the former placebo group improved in SF-36 "mental health" (p < 0.05) with a tendency for improvement in HSCL-56 total score (p = 0.10). Both groups improved in McCoy's Sex Scale during active treatment (p < 0.05). DHEA replacement decreased high-density lipoprotein (HDL) cholesterol and increased insulin-like growth factor I (IGF-I) and haematocrit. There were no effects on bone density or disease activity and no serious adverse events. Side effects were mild. We conclude that low dose DHEA treatment improves HRQOL with regard to mental well-being and sexuality and can be offered to women with SLE where mental distress and/or impaired sexuality constitutes a problem.

Keywords: SLE, DHEA, health-related quality of life, glucocorticoid

Introduction
Systemic lupus erythematosus (SLE) is an autoimmune chronic inflammatory disease affecting multiple organ systems. SLE occurs predominantly in females with a peak incidence during the fertile years and the disease may flare during pregnancy [1] and in patients using oral contraceptives [2]. In an animal model of lupus, female NZB/NZW mice are more frequently and severely affected and the disease can be improved using androgens [3].

Lower than normal levels of the weakly androgenic adrenal steroid hormone dehydroepiandrosterone (DHEA) and its sulphated form DHEA sulphate (DHEAS), have been reported in women with SLE. This is partly explained by ongoing glucocorticoid treatment which suppresses the adrenal cortex, but serum levels are reduced even in untreated SLE patients [4]. DHEA is the main adrenal steroid and is sulphated into DHEAS in the adrenal gland and peripheral tissues. DHEA is also further metabolised to more active steroids such as androstenedione, testosterone and estrogens [5] and the effects of DHEA are probably partly mediated through this conversion. No specific nuclear receptor for DHEA has yet been identified.

Patients with adrenal insufficiency and growth hormone (GH) deficiency due to hypopituitarism...
have almost undetectable serum levels of DHEAS [6,7]. DHEA supplementation to women with Addison’s disease has shown positive effects on wellbeing and sexuality at 50 mg daily [8], whereas another smaller study failed to show any improvements in quality of life [9]. Lower doses of DHEA given to hypopituitary androgen-deficient women have improved their behaviour [7].

A number of trials treating SLE patients with DHEA have been performed, all primarily aimed at decreasing disease activity [10–15]. Doses of 50–200 mg/day have been employed, resulting in supraphysiological serum DHEAS levels. The results on disease activity have been modest and androgenic side effects a reason for discontinuation of the drug [11,14].

Patients with SLE have a worse perception of health and well-being compared to controls, measured by the widely used health-related quality of life (HRQOL) instrument Short-Form 36 (SF-36) [16–18]. The aim of this investigation was to supplement SLE patients with low dose DHEA in order to obtain normal DHEAS serum levels, in a placebo-controlled trial for 6 months, followed by 6 months open labelled DHEA treatment, and assess primarily the effects on HRQOL and behaviour, using health questionnaires. In addition, the effects on hormonal levels, bone densitometry and bone metabolism, body composition, serum lipids, disease activity, side effects and safety were studied.

Patients and methods

Patients

Forty-one female patients with SLE, treated at the rheumatology clinics in Uppsala (n = 23) and Lund (n = 18), Sweden, were included in the study. Inclusion criteria were age 20–65 years and treatment with ≥ 5 mg prednisolone daily, where the dose had been stable for at least two months. Present or planned pregnancy was the only exclusion criterion. Three patients withdrew because of side-effects and one patient died shortly after completion of the study due to a widespread malignancy and was excluded from analysis. The results are based on 37 patients aged 21–65 years, treated with 5–15 mg prednisolone daily. Patient characteristics are shown in Table I.

Study protocol

The study was a two-phase trial with an initial 6 months, randomized, double blind, placebo-controlled period, followed by a further 6 months of open labelled DHEA treatment for all patients. Patients were stratified into two equal age groups, ≤ 45 years and ≥ 46 years, which received 15 or 10 mg DHEA or placebo twice daily, respectively. The production unit of the National Corporation of Swedish Pharmacies (Stockholm, Sweden) prepared capsules containing DHEA (Sigma, St. Louis, MO) or placebo according to Good Medical Practice standards. The use of a low dose regimen of DHEA was designed to result in serum DHEAS levels in the midnormal range and was based on the results from a study in women with hypopituitarism [7]. The prednisolone dose was allowed to increase if needed.

Patients were assessed before treatment and at 3, 6, 9 and 12 months of follow-up and a last visit at 15 months. Before treatment and at 6 and 12 months the following physical assessments were made: bone densitometry, body composition, handgrip, body hair growth, body weight and blood pressure. The patients responded to four validated questionnaires and their partners completed a questionnaire after the 6 months placebo-controlled period. At every three monthly visit, blood and urine samples for safety monitoring (haemoglobin, liver enzymes, creatinine, plasma glucose and urinalysis) were taken, disease activity assessed using a modified SLE disease activity index (mSLEDAI) [19] where complement levels and anti-double-stranded DNA antibodies are excluded. The Systemic Lupus International Collaborating Clinics/ American College of Rheumatology (ACR) damage index was recorded before treatment and after twelve months. Informed consent was obtained from each patient and the study was approved by the local ethics committee, Faculty of Medicine, Uppsala University, Sweden.

Biochemistry and clinical immunology

DHEAS and total testosterone were measured with a competitive solid-phase radioimmuno assay (RIA) (Coat-A-Count, Diagnostic Products Corporation, Los Angeles, CA, USA) and androstenedione was measured using an RIA (Diagnostic System Laboratories, Webster, Texas, USA). Serum osteocalcin was

Table I. Patient baseline characteristics.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>DHEA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (≤ 45/≥ 46 year)</td>
<td>20 (7/13)</td>
<td>17 (9/8)</td>
</tr>
<tr>
<td>Age (year)</td>
<td>47.6 ± 12.8</td>
<td>46.5 ± 11.7</td>
</tr>
<tr>
<td>Disease duration (year)</td>
<td>17.2 ± 11.6</td>
<td>15.4 ± 9.3</td>
</tr>
<tr>
<td>ACR-criteria</td>
<td>5.6 ± 1.7</td>
<td>5.5 ± 1.7</td>
</tr>
<tr>
<td>Prednisolone dosage (mg/day)</td>
<td>7.1 ± 2.8</td>
<td>5.8 ± 1.5</td>
</tr>
<tr>
<td>mSLEDAI† score [19]</td>
<td>2.8 ± 3.5</td>
<td>1.2 ± 2.0</td>
</tr>
<tr>
<td>SLICC‡ score [20]</td>
<td>2.2 ± 2.3</td>
<td>1.0 ± 1.5</td>
</tr>
</tbody>
</table>

* n = 37, mean ± S.D. No significant differences between the groups using Mann-Whitney U-test. † Modified SLE Disease Activity Index where complement levels and anti-double-stranded DNA antibodies are excluded. ‡ The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (ACR) damage index.
measured using an enzyme linked immunosorbent assay (ELISA) (Osteometer BioTech A/S, Copenhagen, Denmark) and carboxy-terminal propeptide of type I procollagen (PICP) using an RIA (Orion Diagnostica Espoo, Finland). High sensitive C-reactive protein (hsCRP) was analyzed in serum samples utilizing a BN Prospec nephelometer (Dade Behring, Deerfield, IL, USA) with latex enhanced reagents (Dade Behring). Cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, alanine transaminase, adrenocorticotropic hormone (ACTH), homocysteine, sexual hormone binding globulin (SHBG) and insulin-like growth factor I (IGF-I) were analysed according to routine methods. Sera were investigated by routine analysis for the presence of anti-nuclear antibodies (ANA), anti-dsDNA antibodies and complement levels.

**Bone densitometry, body composition, handgrip and body hair**

Bone mineral density (BMD) in lumbar spine (L2–L4), total hip and total body as well as lean body mass, fat mass and bone mineral content, were determined using dual energy X-ray absorptiometry (DXA). Handgrip strength was measured in both hands using an electronic grip force instrument [21]. Body hair was assessed using a scoring system for neutral body hair (forearm and leg, 0–8 points) and hormonal body hair in eleven other skin areas (0–43 points), where axillary and pubic skin areas were added to the previously described protocol [22].

**Questionnaires**

SF-36 reflects health status for the last four weeks and comprises 36 questions divided into eight different domains: Physical function (PF), role limitation due to physical problems (RP), bodily pain (BP), general health (GH), vitality (VT), social function (SF), role limitation due to emotional problems (RE) and mental health (MH). A higher score indicates better health (range 0–100) [23]. Normative data for Swedish women are available [24]. The physical component summary (PCS) (PF, RP, BP, GH) and mental component summary (MCS) (VT, SF, RE, MH) scores were calculated as previously described [17,25]. The Hopkins Symptom Check List (HSCL) is composed of 56 items covering psychiatric and somatic problems related to mental distress during the last seven days. Each item is scored on a four-point scale where 1 means no symptoms and 4 severe symptoms and a lower total score indicates better mental health [26]. Normative data for Swedish women are available [27]. The Psychological General Well-Being index (PGWB) is a validated self-assessed inventory comprising 22 items on a 1-6 scale, with a total score range of 32–122 where a higher score indicates greater well-being [28]. Normal values for Swedish women are available [29]. A Swedish version of the McCoy Sex Scale Questionnaire [30] was used for assessment of sexuality. This questionnaire measures sexual experience over the last 30 days and consists of nine items on a 1–7 scale. Scores were adjusted so that higher scores indicate a better sexual life in all items. Five items were grouped into the variable “sexual satisfaction”, two items into the variable “sexual problems” and two items comprised the variable “partner satisfaction”. Values for healthy postmenopausal Swedish women are available [31]. A 12-item questionnaire assessing changes in mood and behaviour in response to treatment was completed by the patients’ partners after the 6 months placebo-controlled period [7,32].

**Statistical analysis**

Data are reported as mean ± SD, unless otherwise stated. The overall within-group effect was analysed using Friedman’s test for repeated measurements. The within group treatment effect was analysed using Wilcoxon’s signed rank sum test and the comparison between groups was analysed using Mann-Whitney U test. Correlations were calculated using Spearman’s rank coefficient. P < 0.05 was considered significant for all analyses.

**Results**

**Patients**

Three out of 41 (7%) patients withdrew before completion of the study due to adverse events, two due to increased body hair during DHEA treatment and one because of weight gain, where most of the gain was during the placebo period. No serious adverse events were recorded during the study. One patient who completed the study was later excluded due to a widespread pulmonary malignancy that was unrelated to her SLE and study drug. The results of 37 women were analysed. One woman in the DHEA treated group (20 mg daily) experienced an exceptionally increased vitality during the placebo controlled period with difficulties sleeping. Her DHEA dose was reduced to 10 mg daily during the open treatment.

**Serum androgens, SHBG, ACTH and IGF-I**

The mean values for serum DHEAS levels were markedly reduced in both groups at baseline (study onset), and correlated inversely to current prednisolone dose ($r = -0.38, p < 0.01$). Ten/37 women (27%), five each in the DHEA and placebo groups respectively, that all were on 5 mg prednisolone daily, had normal or just below normal serum levels
of DHEAS at baseline (1.74–4.56 μmol/l). 35/37 (95%) and 23/37 (62%) had normal serum testosterone and androstenedione levels respectively. DHEA treatment increased serum DHEAS to the normal midrange. Two women, both in the ≥45 age group, had values just above the upper normal limit. Testosterone and androstenedione increased markedly within normal limits and SHBG decreased during DHEA treatment in both groups (Table II). Serum concentration of ACTH did not change, but there was a significant increase in serum IGF-I during DHEA treatment in both groups: 188 ± 54 to 209 ± 67 μg/l in the DHEA group 0–12 months, and 202 ± 72 to 221 ± 75 μg/l in the former placebo group during open treatment 6–12 months (both p < 0.01).

Health-related quality of life assessments and sexuality

The SF-36 scores at baseline (study onset) were similar to those previously published in patients with SLE [16] and on average 20 points lower than in healthy Swedish women aged 15–80 years [24]. There were no significant baseline differences in the scores for the DHEA and placebo groups respectively. During the 6 month placebo-controlled treatment period the DHEA group improved in role physical (RP) and role emotional (RE) (p < 0.05) (Figure 1A). The improvement in RE after the 6 months double-blind period was significantly higher in the DHEA group (+23.3 ± 37.6) compared with the change in the placebo group (−14.6 ± 40.2) (p = 0.008), whereas the improvement in RP was not significantly better than placebo. The improvement in RP and RE were not completely sustained for 12 months and there was a small decrease in the score for physical function (PF) in the DHEA group between baseline and twelve months (p < 0.05). There were no significant changes in the placebo group during the first 6 months double-blinded period. During the open labelled DHEA treatment period (6–12 months), the former placebo group showed a decrease in RP whereas the score for mental health (MH) improved (p < 0.05) (Figure 1B). There were no correlations between serum levels of DHEAS and the SF-36 scores and no difference in increase in serum levels of DHEAS between those who improved in the SF-36 domains compared to those who did not.

The MCS score also improved significantly in the DHEA group between baseline and 6 months: 53.9 ± 24.4 to 62.4 ± 17.9 (p < 0.05) with a decrease at twelve months to 58.7 ± 24.9. In the former placebo group the MCS score did not improve significantly during the open labelled DHEA treatment period (6–12 months), and 202 ± 72 to 221 ± 75 μg/l in the former placebo group during open treatment 6–12 months (both p < 0.01).
level of mental distress among SLE patients. DHEA treatment improved the total score in the DHEA treated group at six months to 92.6 ± 17.9 (p < 0.05). There was a tendency for improvement in the total score when the placebo group received open labelled DHEA treatment between 6 months (101.7 ± 34.0) and twelve months (94.3 ± 32.7, p = 0.10).

A separate analysis of the 10 women with normal serum DHEAS levels at baseline revealed no significant differences in their baseline scores in SF-36 and HSCL-56, compared to those 27 women with low serum levels at baseline. The women with normal serum DHEAS levels also showed the same improvements in these questionnaires as those with low levels. The patient numbers in each group were generally too small to reach significance, but the five women in the placebo group with normal serum DHEAS levels improved significantly in SF-36 MH during open labelled treatment 6–12 months, (68.0 ± 19.6 to 78.8 ± 11.5, p < 0.05).

The PGWB baseline score was 84.6 ± 16.7 in the DHEA group and 92.6 ± 20.2 in the placebo group (p = NS) which is lower than the previously reported...
score of 101 for healthy Swedish women [29]. After the six months placebo-controlled treatment period the DHEA group tended to improve its score to 90.0 ± 13.9 (p = 0.12 compared to baseline). During the DHEA treatment period 6–12 months, the score also increased, although not significantly, in the former placebo group from 90.1 ± 21.0 to 94.6 ± 22.0 (p = 0.14) (not shown). There was a correlation at study onset between the SF-36 RE and MH scores respectively (higher score better mental health), and the HSCL-56 total score (lower score better mental health): $r = -0.60$, $p = 0.0004$ for RE and $r = -0.80$, $p < 0.0001$ for MH. The same correlation was seen when SF-36 RE and MH scores were compared with the PGWB total score (higher score better mental health): $r = 0.62$, $p = 0.0002$ for RE and $r = 0.82$, $p = < 0.0001$ for MH. The scores for SF-36 RE, MH and HSCL-56 and PGWB correlated equally well at both 6 and 12 months.

Fifteen women (DHEA = 8, Placebo = 7) completed the McCoy scale at 0, 6 and 12 months. Six women did not have a partner or an active sexual life and 16 women did not complete the full questionnaire at all time points and were therefore not analysed. In the DHEA treatment group there was an improvement in the variable “sexual problems” at 12 months compared to baseline meaningless vaginal dryness and dyspareunia. In the placebo group there was no improvement during the placebo treatment period, but total score as well as the variable “sexual satisfaction” increased during the DHEA treatment period 6–12 months (Figure 3). There was a tendency for a correlation at twelve months between serum levels of DHEAS and “sexual satisfaction” ($r = 0.71, p = 0.06$) and “sexual problems”, respectively ($r = 0.68, p = 0.07$). At study onset there was a correlation between the scores for SF-36 RE and MH respectively, and the variables “sexual problems” (RE, $r = 0.63$, $p < 0.05$), sexual satisfaction (MH, $r = 0.65$, $p < 0.05$) and the total McCoy score (MH, $r = 0.54$, $p < 0.05$). These correlations were not seen at twelve months.

Figure 2. Hopkins symptom checklist-56 (HSCL-56) total scores during 6 months of DHEA (black bars) or placebo (white bars) followed by 6 months open DHEA treatment to both groups. Higher scores indicate higher mental distress. Bars denotes S.E.M. *p < 0.05 DHEA treated group 0–6 months.

Figure 3. McCoy’s sexuality scores during 6 months of DHEA or placebo followed by 6 months open DHEA treatment. Nine items on a 1–7 scale are grouped into the variables “partner satisfaction” (2 items), “sexual problems” (2) and “sexual satisfaction” (5). Higher scores indicate a better sexual life. Bars denotes S.E.M. *p < 0.05 as compared with commencement of DHEA treatment, baseline in the DHEA group and 6 months in the placebo group.
Thirty-one women had a partner who completed the partner questionnaire assessing changes in mood and behaviour, after the first six months double blinded period. No significant differences between the DHEA treated group and the placebo group were observed (not shown).

**Bone densitometry, body composition, handgrip strength and bone metabolism**

There was no increase in BMD (g/cm²) in lumbar spine, total hip or total body, body composition measured by DXA, or handgrip strength during DHEA treatment. In the DHEA treated group between baseline and 12 months there was a tendency for an increase in total body weight (71.2 ± 14.5 to 72.5 ± 15.8 kg) and body mass index (BMI, kg/m²) (25.3 ± 5.2 to 25.8 ± 5.6) (both p = 0.06) and the waist/hip ratio increased significantly (0.85 ± 0.08 to 0.88 ± 0.06, p = < 0.01). Markers of bone metabolism showed a significant decrease in the formation marker PICP in the DHEA treated group between baseline (140.8 ± 44.8) and 12 months (127 ± 37.4, p < 0.05). There were no changes in the other formation markers osteocalcin and bALP.

**Lipoproteins, safety parameters and side effects**

DHEA supplement significantly reduced serum HDL from baseline to six months (1.66 ± 0.54 to 1.55 ± 0.56 mmol/l, p < 0.05) and the same tendency was seen in the placebo group during open DHEA treatment 6–12 months (1.64 ± 0.45 to 1.54 ± 0.36 mmol/l, p = 0.09). No changes were seen in other lipids, homocysteine or alanine aminotransferase. Haematocrit was measured in 22 patients with a significant increase in both groups during DHEA treatment from 36.9 ± 1.9 to 40.4 ± 3.3% in the DHEA group and from 37.7 ± 3.7 to 40.0 ± 3.5% in the placebo group during open labelled DHEA treatment (both p < 0.05). Hormonal body hair score increased in both the DHEA group 0–12 months (6.85 ± 2.43 to 7.30 ± 2.74) and the placebo group during open labelled DHEA treatment 6–12 months (6.71 ± 2.44 to 7.35 ± 2.87), (both p < 0.05).

**SLE disease activity and damage**

There was no change in SLE disease activity as measured by mSLEDAI score, but a small but nonsignificant increase in prednisolone dose in the DHEA treated group between six and twelve months (6.7 ± 1.9 to 8.2 ± 3.8 mg/day, p = 0.18) and a significant increase in hsCRP from baseline to six months, which remained unchanged at twelve months (2.44 ± 2.65 to 4.22 ± 5.8 mg/l, p < 0.05). Anti-dsDNA antibody titers remained unchanged and there were no changes in the placebo group in any of the disease activity parameters at any time. Damage according to SLICC was unchanged in both groups.

**Discussion**

This is the first low dose DHEA treatment trial in women with SLE aimed at normalisation of serum DHEAS levels and investigating the patient’s HRQOL. Our main findings from SF-36 were an improvement in limitations due to emotional problems (RE) in the DHEA group during the blinded placebo-controlled treatment period (0–6 months), and an improvement in mental health (MH) in the former placebo group during open DHEA treatment (6–12 months). Both the RE and MH domains mainly reflect mental strength. None of the other domains changed consistently, indicating that DHEA treatment did not improve physical function, general health or vitality.

In a previous trial treating female SLE patients with DHEA, no improvements in SF-36 scores were found, bearing in mind that the study design was not aimed for a HRQOL improvement [13]. A recent placebo-controlled study in women with SLE showed an effect of DHEA 200 mg daily on a composite endpoint including disease activity and HRQOL (patient’s global assessment and the Krupp Fatigue Severity Score) [14]. A trial comparing LJP 394 and placebo, found improvements in SF-36 scores during LJP 394 treatment, where the improvement in RE after a renal flare was most pronounced compared to placebo, similar to our observation [33].

We noted a high standard deviation (SD) in some of the results including the significant improvement in RE after the 6 months double-blinded period: DHEA group (+23.3 ± 37.6), placebo group (−14.6 ± 40.2) (p = 0.008). This is partly explained by the domain RE having only four possible levels, and a high SD in SF-36 scores has previously been observed in SLE patients but not in controls [17].

SF-36 is well validated in SLE and considered the medical outcome survey of choice in this disease [34]. We have also used the HSCL-56 and PGWB questionnaires, which showed good correlations with the SF-36 scores reflecting mental well-being, i.e. RE and MH, at all timepoints. HSCL-56 has been used mainly in psychological settings and has shown to be a sensitive measure of treatment response to psychiatric drugs [35]. In this study, DHEA treatment improved the total score as well as subscores for cognition and depression. The results of the PGWB questionnaire, although nonsignificant, showed the same tendency for improved well-being during DHEA treatment, in both the DHEA and former placebo group. A high prevalence of anxious and depressive manifestations in SLE patients have previously been reported [18] which is in agreement with our results. These manifestations have also been shown to have a major
influence on the SF-36 scores in SLE patients [18], indicating the importance of mental well-being on HRQOL in SLE.

The McCoy questionnaire was completed by fewer than half the women at all timepoints and the results should, therefore, be interpreted cautiously. The improvement in the variable “sexual problems”, i.e. lubrication and dyspareunia, in the DHEA-treated group is consistent with other studies [31] and may reflect physiological changes due to sexual hormones. The improvement in total score as well as “sexual satisfaction” in the placebo group during the open labelled DHEA treatment period 6–12 months reflects both physiological and mental improvement.

The combined results of the questionnaires all support a mild improvement in mental health and sexuality during DHEA treatment and the results are therefore considered relevant despite multiple statistical comparisons. The improvements in the DHEA treated group during the placebo controlled period 0–6 months in both SF-36 RE and HSCL-56 total score, and the apparent tendency for improvement in PGWB total score were not sustained for the full 12 months. A possible explanation would be an initially activating effect of DHEA, to which the patients become adapted later. Another explanation might be that there was an increased disease activity among some of the patients in the DHEA group between 6 and 12 months, which is seen as a need for a higher prednisolone dose, which could have affected quality of life. An increase in glucocorticoid treatment would also suppress the endogenous DHEAS production further and therefore reduce the effect of low dose DHEA supplementation. It is possible that an increased dose of DHEA to 50 mg daily throughout the study would have been optimal.

An increased well-being after DHEA administration has been reported in normal elderly men and women [36]. An antidepressant effect of DHEA treatment has been suggested [37] and among the neurotropic effects in mice is an anxiolytic effect and increased hypothalamic serotonin levels [38,39]. The improved mental but not physical well-being and the lack of correlation between clinical outcome and serum levels of DHEAS in the present study may support the concept of DHEA as a neurosteroid, where CNS levels rather than peripheral serum levels are of importance. A lack of correlation between changes in serum sex hormone levels during DHEA treatment and responder outcome, including HRQOL, has also been noted by others [14].

DHEA has immunomodulatory properties, including suppression of interleukin-6 (IL-6) production from human peripheral blood mononuclear cells (PBMC) in vitro [40]. IL-6 levels are elevated in sera from SLE patients [41] and in cerebrospinal fluid from SLE patients with central nervous system involvement [42]. IL-6 affects several brain functions [43] and a DHEA-induced suppression of IL-6 might contribute to the observed positive effects on mental well-being. More specific neuropsychological instruments would be needed to better evaluate a possible effect of DHEA on neuropsychological symptoms in SLE.

The low dose and relatively short treatment period might explain the lack of improvement in BMD, since other studies have indicated a bone-sparing effect of DHEA [12]. Similarly, this dose was not expected to have an effect on disease activity. The decrease in HDL cholesterol, increase in hematocrit and IGF-I are known androgenic metabolic features of DHEA. The patients experienced mild or no androgenic side effects at all, implying that the study was truly blinded for the first six months. The increase in waist/hip ratio in the DHEA group after 12 months might be the combined effect of an androgen and glucocorticoid induced fat distribution.

In conclusion, we found that a DHEA supplement of 20–30 mg daily in women with SLE is well tolerated with few side effects. Significant improvements in HRQOL measurements were seen regarding mental well-being and sexuality, whereas other health related variables were unaffected. We therefore suggest that low dose DHEA supplement can be offered to glucocorticoid-treated women with SLE, where mental distress and/or impaired sexuality constitute a problem, despite an otherwise inactive disease. Larger studies of longer duration are needed to confirm the beneficial effect of DHEA and evaluate androgen replacement in women with SLE.

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