Low Serum Dehydroepiandrosterone Sulfate in Women with Primary Sjögren's Syndrome as an Isolated Sign of Impaired HPA Axis Function

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ABSTRACT. ***Objective.*** To assess the hypothalamic-pituitary-adrenal (HPA) and thyroid axes in women with primary Sjögren's syndrome (pSS).

Methods. In 10 women with pSS and 10 age matched female controls, we evaluated serum dehydroepiandrosterone sulfate (DHEA-S), testosterone, androstenedione, follicle stimulating hormone, luteinizing hormone, thyroid stimulating hormone, prolactin, growth hormone, sex hormone binding globulin, cortisol, and adrenocorticotropin hormone (ACTH), in both basal condition and after stimulation with corticotropin releasing hormone, thyrotropin releasing hormone, and luteinizing hormone releasing hormone intravenously. Patients had not previously been treated with glucocorticoids.

Results. Patients with pSS had significantly lower basal mean DHEA-S values compared with healthy controls (2.4 ± 0.4 vs 3.9 ± 0.3 μmol/l; $p < 0.05$) and significantly lower DHEA-S values after stimulation. The cortisol/DHEA-S ratio in the patient group was higher than in controls (171 ± 39 vs 76 ± 5; $p < 0.05$). A correlation was found between basal ACTH and DHEA-S values in the patients ($r = 0.650$; $p = 0.05$). No correlation was seen between disease activity or age and the serum concentration of DHEA-S. The levels of other hormones both at baseline and after stimulation were similar in patients and controls.

Conclusion. The results show that women with pSS have intact cortisol synthesis but decreased serum concentrations of DHEA-S and increased cortisol/DHEA-S ratio compared with healthy controls. The findings may reflect a constitutional or disease mediated influence on adrenal steroid synthesis. The thyroid axis and gonadotropin secretion were similar in patients and controls. (J Rheumatol 2001;28:1259–65)

Key Indexing Terms:
PRIMARY SJÖGREN'S SYNDROME HYPOTHALAMIC-PITUITARY-ADRENAL AXIS
DEHYDROEPIANDROSTERONE SULFATE

Research exploring the interactions between the hypothalamic-pituitary-gonadal axis and adrenal androgen functions and the immune system has significantly advanced our understanding of the pathogenesis and expression of autoimmune disease. Studies of the hypothalamic-pituitary-adrenal (HPA)-glucocorticoid axis in patients with rheumatoid arthritis (RA) suggest that they have a relatively hypofunctional axis with defective central and peripheral components[1]. In patients with systemic lupus erythematosus (SLE), several studies have documented low serum levels of androgenic-anabolic hormones including dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S)[2,3]. Few clinical observations exist from patients with primary Sjögren's syndrome (pSS) regarding their HPA axis or sex hormone status. However, experimental studies in mouse SS models have revealed that androgens reduce lymphocytic infiltration in lacrimal and salivary glands, the major target organs in pSS[4-6].

Primary Sjögren´s syndrome (pSS) is a disease that, like rheumatoid arthritis (RA) and SLE, primarily affects females[7]. It is a B cell driven autoimmune disease characterized by keratoconjunctivitis sicca and xerostomia[8,9], but it may also extend to a systemic process affecting the parenchymal tissues of the lungs, kidneys, and gastrointestinal tract[10,11]. Patients with pSS often express neuropsychiatric features such as fatigue, anxiety, and depressed mood[12-14]. These chronic stress symptoms may be associated with various disturbances in neuroendocrine reactivity. Many stress related diseases also involve significant disturbances in thyroid axis function, and hyperprolactinemia has been reported in patients with SLE[15] and pSS[16-18].

To explore the HPA axis in pSS, we investigated adrenocorticotropin hormone (ACTH) and cortisol responses to

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intravenous administration of corticotropin releasing hormone (CRH) in females with this disease. As the adrenal androgens are also under the control of ACTH[19], and adrenal androgen production may be a more sensitive indicator of adrenocortical hypofunction, we also measured DHEA-S. Thyroid stimulating hormone (TSH) and prolactin responses to thyroid releasing hormone (TRH) were studied to elucidate the thyroid axis and prolactin status. The gonadotropin responses to luteinizing hormone releasing hormone (LHRH) and circulating levels of testosterone and progesterone were measured as well. To control the possible influence of treatment with glucocorticoids or hormonal replacement therapy, patients with prior or ongoing therapy of this kind were excluded. The results reveal intact cortisol secretion but decreased serum concentrations of DHEA-S in our patients compatible with dysregulation of adrenal androgen production in women with pSS.

MATERIALS AND METHODS

Patients. Ten female patients (mean age 54 yrs, range 44–69) with pSS according to the preliminary European criteria[20] were studied. The patients also fulfilled the Copenhagen criteria[21]. Each patient therefore had keratoconjunctivitis sicca confirmed by the pathological Schirmer eye test (< 5 mm/5 min) and/or a short breakup time (< 10 s) and/or positive rose bengal staining (2 of 3 tests abnormal); xerostomia was confirmed by a total salivary gland secretion rate of < 0.7 ml/min and/or abnormal lower lip glandular biopsy and/or pathological salivary gland scintigraphy (2 of 3 tests abnormal).

The onset of disease occurred one to 15 years (mean 5 yrs) prior to the study. Five patients had extraglandular manifestations — 4 Raynaud's phenomenon and one sun sensitivity. Six patients had positive serology — 5 had antinuclear antibodies and 4 were anti-SSA and SSB positive. No patient was treated with disease modifying drugs, apart from one who was treated with hydroxychloroquine. No patient was taking or had previously been treated with glucocorticoids or hormone replacement therapy. No patient had any signs of diabetes mellitus or thyroid dysfunction or any other endocrine disorders. The laboratory inflammatory activity was estimated by measuring the erythrocyte sedimentation rate (ESR) according to Westergren (normal value 2–15 mm) and serum C-reactive protein (CRP; normal value < 10 mg/l).

All subjects were studied as inpatients at the Department of Rheumatology, Uppsala University Hospital, after giving informed consent, with the approval of the local Committee of Medical Ethics.

Controls. Ten healthy women not taking medication served as controls. Their mean age was 53 years (range 44–61). No patient or control was a smoker.

Multiple releasing hormone test. A multiple releasing hormone test (MRH test) was performed at 8 A.M. after an overnight fast by injecting 100 μg of CRH (Bissendorf, Hannover, Germany), 100 μg of LHRH (Hoechst, Frankfurt, Germany), and 200 μg of TRH (Hoechst, Frankfurt, Germany) intravenously. Venous blood samples for hormone analyses were drawn via an indwelling needle 10 min before and immediately prior to the injections of the 3 releasing hormones and then after +10, +20, +30, +45, +60, and +90 min.

Hormone measurements. Follicle stimulating hormone (FSH), luteinizing hormone (LH), thyroid stimulating hormone (TSH), prolactin, growth hormone (GH), sex hormone binding globulin (SHBG), and cortisol were measured using time resolved fluoroimmunoassays (autoDelfia™ hFSH, autoDelfia™ hLH Spec, autoDelfia™ hTSH ultra, autoDelfia™ Prolactin, autoDelfia™ hGH, autoDelfia™ SHBG, and autoDelfia™ cortisol; Wallac OY, Turku, Finland). ACTH was measured by a chemiluminescence immunoassay (Nicholas Institute Diagnostics, San Juan Capistrano, CA, USA). 17α-hydroxyprogestrone was measured using a radioimmunoassay kit (OPH-CT; Cis Bio International, Gif-sur-Yvette, France). Androstenedione was measured with a radioimmunoassay kit (Ortho-Clinical Diagnostics, Dallas, TX, USA). Total testosterone was measured with a solid phase radioimmunoassay (Coat-A-Count total testosterone; Diagnostic Products Corporation, Los Angeles, CA, USA). DHEA-S was measured with a chemiluminescence immunoassay (Nichols Institute Diagnostics).

Statistical analysis. Values are given as the mean ± SEM (range). Nonparametric tests, the Mann-Whitney U test, and Spearman's rank correlation test were used to analyze data between groups and correlations to clinical data.

RESULTS

The mean ESR value was 10 ± 3 mm/h (range 4–15) and the mean serum CRP level was 10 ± 1 mg/l. The patients therefore had moderate or no inflammatory activity according to these laboratory tests.

Basal hormone concentrations. Baseline serum levels of ACTH and cortisol, prolactin, TSH, and GH, and the gonadotropins FSH and LH were similar in patients with pSS and controls (Table 1). Patients had significantly lower mean DHEA-S values (2.4 ± 0.4 vs 3.9 ± 0.3 μmol/l, respectively; $p < 0.05$) and their cortisol/DHEA-S ratio was significantly higher than the controls (171 ± 39 vs 76 ± 5, respectively; $p < 0.05$). A correlation was found between the basal values of ACTH and DHEA-S in patients ($r = 0.650$; $p = 0.05$) but not in the controls. The androgens testosterone and androstenedione, as well as hydroxyprogesterone, were

Table 1. Age, sex, disease duration, serum DHEA-S (μmol/l), plasma ACTH (ng/l), and serum cortisol (nmol/l) in 10 patients with pSS and 10 healthy controls.

	Age, yrs	Disease Duration, yrs	DHEA-S μmol/l	ACTH, ng/l	Cortisol, nmol/l
Patients					
1	58	4	3.8	16	409
2	58	4	3.1	17	142
3	50	15	2.9	29	258
4	60	6	1.5	15	349
5	45	1	2.1	21	296
6	69	5	1.3	17	322
7	55	4	0.8	10	311
8	54	8	4.8	31	376
9	52	1	1.4	12	329
10	44	2	3.0	18	301
Controls					
1	45	C	4.0	17	283
2	51	C	3.1	17	260
3	44	C	5.1	26	315
4	52	C	2.7	10	152
5	61	C	5.1	42	475
6	52	C	4.0	18	308
7	57	C	3.7	18	279
8	61	C	2.9	34	322
9	54	C	3.3	31	194
10	54	C	5.2	38	374

Table 2. Baseline concentrations of FSH, LH, prolactin, TSH, GH, testosterone, androstenedione, 17-α-hydroxyprogesterone, SHBG, ACTH, cortisol, and DHEA-S in 10 patients (p) with pSS compared with 10 controls (c).

Hormones	Patients	Controls
FSH, IU/l		
Fertile (p = 4, c = 4)	37.5 ± 19.5	8 ± 2
Postmenopausal (p = 6, c = 6)	59 ± 17.5	56 ± 10
LH, IU/l		
Fertile (p = 4, c = 4)	15.6 ± 7.2	8.4 ± 4.8
Postmenopausal (p = 6, c = 6)	28.8 ± 5.4	28.2 ± 5.4
Prolactin, μg/l	5.0 ± 0.8	6.2 ± 1.3
TSH, mU/l	3.1 ± 0.9	2.2 ± 0.3
GH, mU/l	2.1 ± 0.9	2.2 ± 1.2
Testosterone, nmol/l	0.8 ± 0.1	0.8 ± 0.1
Androstenedione, nmol/l		
Fertile (p = 4; c = 4)	5.3 ± 0.6	4.8 ± 0.5
Postmenopausal (p = 6, c = 6)	4.0 ± 0.5	5.6 ± 0.9
17-α-hydroxyprogesterone, nmol/l		
Fertile (p = 4, c = 4)	3.8 ± 1.4	2.6 ± 1.3
Postmenopausal (p = 6, c = 6)	1.1 ± 0.1	1.4 ± 0.2
SHBG, nmol/l	56 ± 10	40 ± 6
ACTH, ng/l	18.7 ± 2	23.7 ± 3.3
Cortisol, nmol/l	309 ± 23	296 ± 28
DHEA-S, μmol/l	2.4 ± 0.4	3.9 ± 0.3*

Data are mean ± SEM. *Mann-Whitney U test, $p < 0.05$. FSH: follicular stimulating hormone, LH: luteinizing hormone, TSH: thyroid stimulating hormone, GH: growth hormone, SHBG: sex hormone binding globulin, ACTH: adrenocorticotropin hormone, DHEA-S: dehydroepiandrosterone sulfate.

similar in patients and controls. A nonsignificant increase in SHBG was seen in the patient group. The baseline levels of measured hormones did not correlate to the inflammatory activity (defined by ESR and CRP), disease duration, or extraglandular manifestations. Subgrouping into pre- or postmenopausal patients and controls had no effect on the results (Table 1).

Stimulation tests. The ACTH response in the MRH test was lower in patients compared with controls but not at a significant level (Figure 1A); more specifically, the peak value of the ACTH response (ng/l) in patients vs controls was 51.7 ± 29 vs 75.5 ± 34 ($p > 0.05$). In terms of cortisol, the responses in patients and controls were similar (Figure 1B). Significant correlations were seen in patients but not in the controls between the responses in ACTH and cortisol at the various times after CRH injection: +20 min ($r = 0.67$; $p < 0.05$), +30 min ($r = 0.7$; $p < 0.05$), +45 min ($r = 0.88$; $p < 0.01$), +60 min ($r = 0.67$; $p < 0.05$).

The response for serum DHEA-S for both groups is shown in Figure 2. Patients had significantly lower serum values both at baseline and after the MRH test, but no appreciable peaks in DHEA-S were detected in either patients or controls. The post-MRH test values for androstenedione and testosterone were not different in the groups, as shown in Figure 3.

The responses of FSH, LH, TSH, GH, prolactin, or 17α-hydroxyprogesterone during the MRH test were similar in patients and controls (Table 3).

DISCUSSION

Studies of HPA axis function revealed normal basal and CRH stimulated cortisol levels in female patients with pSS, in spite of a tendency to low ACTH levels at baseline and after stimulation. A study of the cortisol/ACTH secretion pattern in 8 women with pSS[22] revealed slightly yet significantly reduced basal levels of ACTH and cortisol, while their CRH induced incremental responses of these hormones appeared to be parallel. Assuming that there is a physiolog-

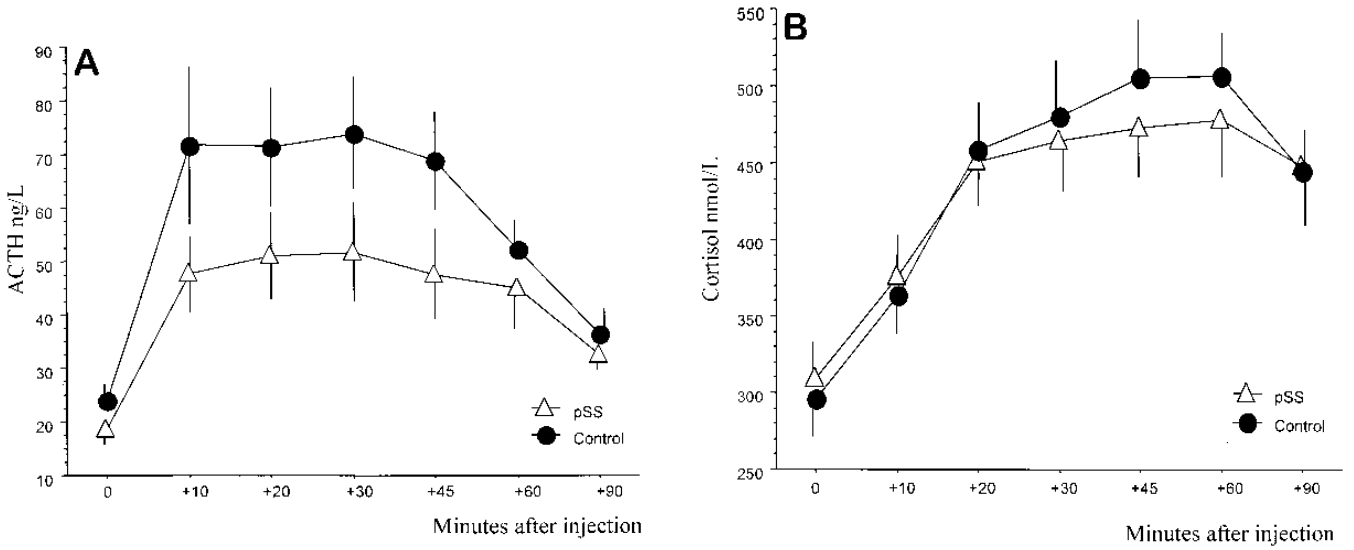

Figure 1. Levels of (A) plasma ACTH and (B) serum cortisol before and after intravenous MRH test in 10 patients with pSS compared with 10 healthy controls. Data are mean ± SEM.

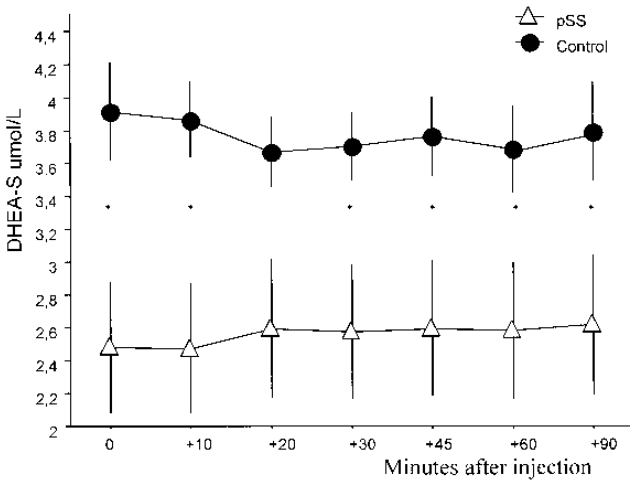

Figure 2. Serum levels of DHEA-S before and after intravenous MRH test in 10 patients with pSS compared with 10 healthy controls. Data are mean ± SEM. Significant difference by Mann-Whitney test between patients and controls; *p < 0.05.

ically intact HPA-glucocorticoid axis function in pSS, both plasma ACTH and basal serum cortisol levels would be expected to be elevated as a result of an inflammatory process. Products of the immune system, such as proinflammatory cytokines, stimulate parts of the central nervous system including the hypothalamus, thereby activating the HPA-glucocorticoid axis through both an endocrine and a neural spinal route[23]. The result in that case would be a suppression of the inflammatory response through the potent antiinflammatory/immunosuppressive effects of the endogenous glucocorticoids. A number of observations support such a concept; for example, rats with genetic pituitary-adrenal hyporesponsiveness are more susceptible to develop experimental arthritis and encephalitis[24,25]. In chronic inflammation, adaptations of the HPA axis would be expected to take place. Assuming that chronic inflammation induces enhanced ACTH secretion and, secondary to that, adrenal hypertrophy, a high secretion rate of glucocorticoids in response to normal ACTH stimulation would be expected, as seen in chronically stressed animals or major depression. However, in a chronic inflammatory disease like RA, a different pattern is seen, characterized by a relative reduction in cortisol responses in spite of elevated plasma ACTH levels[26]. These findings might therefore be related to genetic or constitutional factors[27]. The intensity of the inflammatory reaction might also influence the HPA axis function. Like our patients, patients with pSS often demonstrate a systemic inflammatory reaction of low grade intensity, in contrast to patients with RA.

DHEA, DHEA-S, and androstenedione are the major circulating adrenal androgens in women. Testosterone is produced to a limited extent, but has a stronger androgen activity[28,29]. In women, the adrenal cortex is a more important source of androgenic-anabolic hormones than the ovaries. Under control of LH, androstenedione in particular and testosterone are synthesized by the ovarian thecal-interstitial cells[30]. In contrast, DHEA and DHEA-S in circulation are probably exclusively dependent on adrenal synthesis in women[31]. ACTH is the documented hormone stimulating the adrenal cortical synthesis of androgens but there exists no feedback control[29]. Adrenal androgen stimulating hormones other than ACTH have been debated, but generally have not been accepted[32]. We observed that women with pSS have normal serum levels of testosterone/androstenedione, LH, and ACTH at baseline and after stimulation. However, they had decreased circulating levels of DHEA-S. Admitting that the adrenal androgen steroidogenesis is profoundly complex and incompletely understood[29], our findings of normal testosterone/androstenedione but

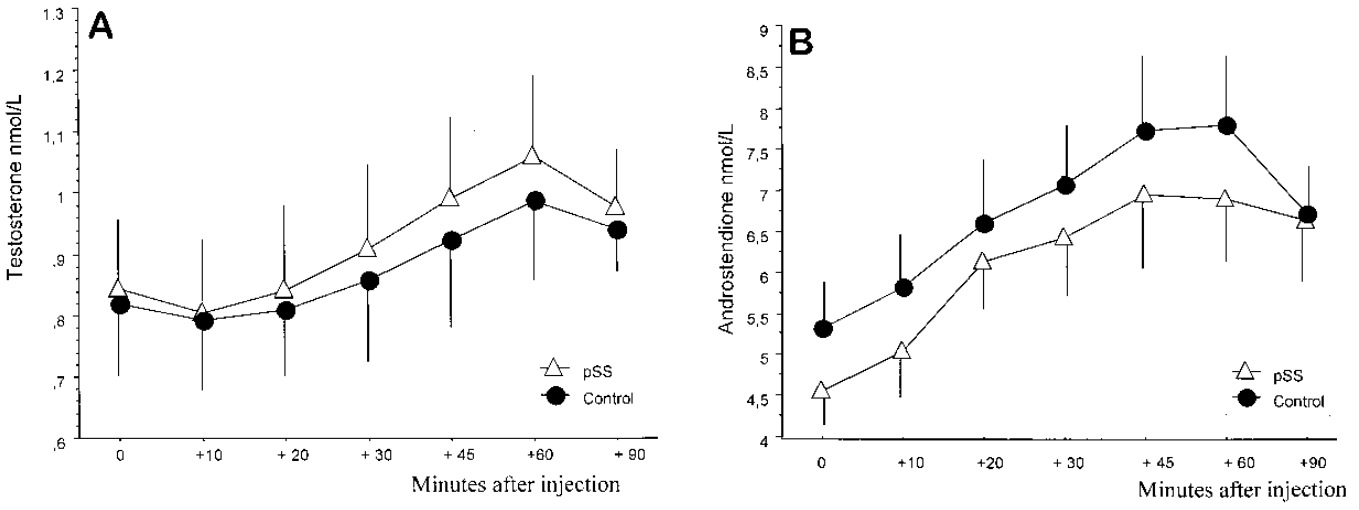

Figure 3. Serum levels of (A) testosterone and (B) androstenedione before and after intravenous MRH test in 10 patients with pSS compared with 10 healthy controls. Data are mean ± SEM.

Table 3. Response of FHS, LH, TSH, GH, prolactin, 17-α-hydroxyprogesterone, and SHBG to intravenous MRH in 10 patients (P) with pSS compared with 10 controls (C).

	0 min	+ 10 min	+ 20 min	+ 30 min	+ 45 min	+ 60 min	+ 90 min
FSH							
P	50.5 ± 13	57 ± 14	62 ± 15	68.5 ± 16.5	75 ± 17.5	77.5 ± 18	79 ± 18
C	36.5 ± 9.5	41.5 ± 11.5	45.5 ± 11.5	50 ± 11.5	53 ± 13	58 ± 14	60.5 ± 13.5
LH							
P	23.4 ± 4.8	51 ± 7.8	74.4 ± 10.2	90.6 ± 12	100.8 ± 13.2	102 ± 14.4	93.6 ± 13.8
C	19.8 ± 4.8	42.6 ± 10.8	60.6 ± 13.8	73.8 ± 16.2	83.4 ± 17.4	87 ± 18	82.8 ± 16.8
TSH							
P	3.1 ± 0.9	13.8 ± 3.2	19.5 ± 5.2	20.4 ± 5.8	17.3 ± 5.1	14.5 ± 4.4	10.1 ± 3.2
C	2.2 ± 0.4	12.5 ± 2.2	16.7 ± 2.7	16.7 ± 2.5	14.0 ± 2.3	11.3 ± 1.8	7.9 ± 1.3
GH							
P	2.1 ± 0.9	2.4 ± 0.6	1.9 ± 0.5	1.4 ± 0.4	0.9 ± 0.3	0.5 ± 0.1	0.4 ± 0.1
C	2.5 ± 1.3	2.5 ± 0.9	1.7 ± 0.5	1.7 ± 0.5	1.0 ± 0.2	0.6 ± 0.2	0.3 ± 0.1
Prolactin							
P	5.0 ± 0.8	50.0 ± 6.1	51.0 ± 6.7	46.4 ± 6.8	35.5 ± 5.8	26.0 ± 4.4	16.5 ± 2.8
C	6.2 ± 1.4	51.3 ± 4.9	52.5 ± 4.7	45.6 ± 4.1	33.9 ± 3.4	25.8 ± 2.9	17.0 ± 2.0
17-α-hydroxyprogesterone							
P	2.2 ± 0.7	3.2 ± 0.8	4.0 ± 0.9	3.9 ± 0.9	4.0 ± 0.8	4.1 ± 0.8	3.5 ± 0.8
C	1.9 ± 0.5	3.4 ± 0.7	4.3 ± 0.8	4.1 ± 0.8	4.4 ± 0.8	4.1 ± 0.8	2.8 ± 0.4
SHGB							
P	55.7 ± 10.4	56.4 ± 10.3	54.9 ± 10.3	54.9 ± 10.0	54.8 ± 10.1	52.9 ± 9.6	54.2 ± 9.4
C	40.3 ± 6.4	40.8 ± 6.3	40.0 ± 6.3	39.7 ± 6.3	39.9 ± 6.7	40.8 ± 6.8	40.7 ± 6.6

FSH: follicular stimulating hormone, LH: luteinizing hormone, TSH: thyroid stimulating hormone, GH: growth hormone, SHBG: sex hormone-binding globulin.

decreased DHEA-S serum levels in women with pSS are compatible with an adrenal hypofunction. A recent study[33] has also shown that women with primary and secondary SS are androgen deficient, in accord with our findings. The absence of diurnal variation of DHEA-S and its low metabolic clearance are other qualities making DHEA-S a reliable indicator of adrenal androgen production in women[34]. The interpretation that low DHEA-S serum levels in pSS may reflect dysregulation of adrenal function is not contradicted by the normal cortisol levels seen in our patients before and after ACTH stimulation. The balance between adrenal synthesis of glucocorticoid and androgenic-anabolic steroid synthesis varies greatly during the life stages[29]. While glucocorticoid concentrations are quite stable over time and well controlled by the HPA feedback system, the adrenal androgens vary considerably with age without identified mechanisms. A marked variability of individual serum DHEA-S values is reported among boys and girls from birth through adolescence[35] and also among adult women and men[36]. After factoring out age, heritability explains most of the variation[37]. Thus, the low serum DHEA-S levels in pSS might reflect a genetic influence.

DHEA-S deficiency similar to that seen in pSS has been presented as a nonspecific consequence of disease or its therapy. For example, acute and chronic glucocorticoid therapy can significantly reduce the circulating levels of DHEA-S[38,39]. Administration of sex hormones, diet, adiposity, exercise, age, and serum binding globulin levels are examples of the numerous factors that can affect hormonal blood concentrations[1,40]. Studies of adrenal androgens and autoimmune diseases have suggested low plasma concentrations of DHEA/DHEA-S due to ongoing or previous glucocorticoid therapy[2,3,41,42]. However, such an influence can be excluded in our study of women with pSS since they had never undergone such therapy. An age dependent dissociation of adrenal androgen and glucocorticoid synthesis is evident. With advancing age, the responsiveness of DHEA-S to ACTH stimulation decreases, unlike that of cortisol, resulting in an increase in the cortisol/DHEA-S ratio in the blood[19,43]. In this study, the cortisol/DHEA-S serum ratio was 2 times higher in our patients with pSS than in the controls. This finding illustrates a non-age dependent dissociation due to either a selective adrenocortical androgen hypofunction or an induced shift from DHEA-S synthesis to cortisol production. Immune adrenal interactions may be involved in the dissociation of adrenal androgens and cortisol seen in pSS and other autoimmune diseases. It has been proposed that intra-adrenal lymphocytes and macrophages may influence androgen secretion, either by direct cellular contact with androgen producing cells of the zona reticularis of the adrenal glands or by local release of cytokines such as transforming growth factor-ß or tumor necrosis factor-α[44].

Stress related states may also involve hypothalamic-pituitary-thyroid axes. We found similar basal and TRH stimulated levels of TSH in patients and controls. In another study in pSS, marginally but significantly elevated basal TSH levels were reported[22]. Prolactin is an anterior pituitary

hormone and is known to exert profound proinflammatory effects by stimulating humoral and cellular responses[45-47], and hyperprolactinemia has been associated with a number of autoimmune diseases, including SLE[15,17]. However, the association of hyperprolactinemia with SLE has been questioned in recent studies[48,49]. The release of prolactin to the blood circulation is stimulated by TRH. We found similar serum prolactin levels in patients with pSS and controls, both at baseline and after TRH stimulation. In another study, moderately increased levels of basal serum prolactin were reported in patients with pSS and especially in those who had active disease with internal organ disease[16].

Epidemiological correlations and cross sectional data in women with RA, who also have significantly lower levels of DHEA-S than healthy controls have suggested that preexisting or coexisting low serum androgen levels may contribute to the incidence and severity of RA[1,32,37,50,51]. Several studies have also documented low levels of androgens, including DHEA-S, in patients with SLE[3,52]. Thus, the most frequent autoimmune connective tissue diseases, RA, SLE, and pSS, afflict predominantly women with low serum levels of DHEA. Questions whether low DHEA-S levels predispose to these diseases, or whether the levels are influenced by biological and disease variables, remain unsettled. Of importance in this context is that DHEA and DHEA-S have been found to display immunomodulatory activities by effects on T cells and the synthesis of cytokines[6,53]. In particular, the observation that DHEA induces increased secretion of interleukin 2 (IL-2) and decreased production of IL-4, IL-5, and IL-6[52,53] may reflect important DHEA activities relevant to the induction and maintenance of autoimmune diseases. Administration of androgens including DHEA has been used to ameliorate disease signs in autoimmune animal models, e.g., SS, SLE, and polyarthritis, and to decrease various symptoms in humans with SLE and RA[6,32,41]. These reported beneficial effects illustrate the potential effects androgens may have on physiopathogenetic events in these diseases. Thus, irrespective of the mechanisms underlying low serum levels of DHEA-S in women with pSS, it seems reasonable to explore the possible beneficial effects DHEA treatment may have in this disease.

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