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LOW PLASMA ANDROGENS IN WOMEN WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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The high ratio of women with systemic lupus erythematosus (SLE) has remained unexplained, despite the recent description of metabolic abnormalities of estrogen and androgen metabolism. Alterations of steroid metabolism in patients with SLE could be important in the pathogenesis of this disease, since it has been reported that gonadal steroids modulate the immune system. Moreover, research with inbred lupus mice has shown that estrogens have adverse effects on the disease in both sexes, whereas androgen therapy or oophorectomy is protective in females. Recently, the finding of elevated testosterone oxidation at C-17 in females with SLE suggested that plasma androgen levels in males and females with SLE should be examined more closely. We studied the varying degrees of clinical activity, with regard to plasma levels of 4 significant androgens: testosterone, androstenedione, dehydroepiandrosterone, and dehydroepiandrosterone sulfate in a series of 5 male and 42 female SLE patients. Decreased levels of all androgens were observed in women with SLE. The lowest levels of plasma androgens were found in female patients who had active disease, as determined by laboratory and clinical assessment. These data support the fact that specific abnormalities of androgen metabolism in the female are associated with SLE, and may contribute in some way to morbidity and mortality. More importantly, these data may have implications for future therapeutic regimens based on male hormone replacement.

Abnormalities of estrogen and androgen metabolism have been described in systemic lupus erythematosus (SLE) patients (1–3), and there is evidence from animal models and from humans to support several hypotheses (4,5). The actual mechanism of action for sex steroids may be modulation of the immune system (6).

Recently, low testosterone levels have been described in a small group of female patients with active SLE (7), testosterone oxidation has been reported to be increased in female patients with SLE (3), and suppression of free testosterone in men has been believed to worsen the illness (8,9). The observations on testosterone oxidation in women are the only hormonal abnormality described, to date, that is restricted to females with this disease.

In this investigation, the major plasma androgens were measured in men and women with SLE during various stages of clinical activity. For this study, care was taken to separate patients taking corticosteroids from those patients not taking cortico-

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steroids. Data presented here suggest that an abnormality of androgen metabolism may be confined to women with SLE, in general, and to women with SLE that is active, in particular.

PATIENTS AND METHODS

Patients. Patients with SLE were selected from the Rockefeller University Hospital, the Downstate Medical Center, and the Hospital for Joint Diseases/Orthopedic

Table 1. Clinical activity in 47 patients with systemic lupus erythematosus (SLE)

Patient*	Age	Duration of SLE (years)	No. of SLE criteria fulfilled	Disease severity				
				Disease activity†	Nephritis	Cerebritis	Pericarditis/ pleuritis	Steroid therapy
BF	54	13	7	1+	–	–	+	Off 4 years
WF	39	18	7	0	–	–	–	Off 2 years
BF	46	1	5	1+	–	–	–	Never
BF	48	13	6	1+	+	–	–	Off 5 years
BF	40	13	6	0	–	–	–	Off 4 years
WF	41	9	8	0	+	–	–	Off 4 1/2 years
BF	32	17	9	0	–	+	+	Off 21 months
BF	48	2	7	2+	+	–	–	Never
BF	23	4	7	3+	+	–	+	Never
BF	47	6	8	1+	+	+	–	Off 1 year
BF	57	12	7	1+	–	+	–	Off 11 1/2 years
BF	25	4	9	1+	–	–	+	Off 20 months
BF	43	15	7	1+	–	–	–	Never
WF	28	13	7	0	+	+	–	Off 6 1/2 years
WF	39	15	6	2+	+	–	–	+
WM	21	7	8	3+	+	–	–	Off 5 years
WM	50	3	4	2+	–	–	–	Off 3 years
WM	43	10	10	4+	+	+	–	+
WF	27	13	7	1+	+	–	–	Off 4 years
BF	30	12	9	4+	+	+	–	+
BF	35	10	6	2+	–	–	+	Never
BF	49	8	9	4+	+	–	–	+
BF	26	10	11	4+	+	+	–	+
WF	35	10	8	1+	+	–	–	Off 8 years
WF	35	2	6	4+	–	–	–	+
WF	43	1	6	4+	–	–	–	Never
WF	18	12	11	4+	+	+	–	+
WF	55	8	5	1+	+	–	–	Off 7 years
WF	40	20	6	1+	+	–	–	Off 10 years
WF	50	12	6	1+	–	–	–	Off 2 years
WF	72	2	5	4+	–	–	–	+
WF	44	10	6	1+	–	+	–	Never
WF	35	10	6	2+	+	–	+	Off 8 years
WF	56	15	6	1+	–	+	–	Off 2 years
WF	30	17	4	0	+	–	–	Off 10 years
WF	24	10	6	4+	+	–	–	Never
WF	38	6	6	0	–	–	–	Off 5 years
WF	20	4	6	1+	–	–	–	Never
WF	22	3	5	0	–	–	–	Never
WM	25	5	7	4+	+	+	–	+
WF	33	9	7	1+	–	–	–	Never
WF	61	1	6	4+	+	+	–	+
BF	61	15	5	1+	–	–	+	Off 10 years
WF	26	13	7	1+	+	–	–	Off 10 years
WF	35	6	5	1+	–	–	+	Off 3 years
WF	72	10	5	0	–	–	–	Never
WF	36	17	6	2+	+	–	+	+

* B = black; F = female; W = white; M = male.

† As used by Dr. Ellen Ginzler at Downstate Medical Center: 0 = none; 1 = false-positive serologies, elevated erythrocyte sedimentation rate, leukopenia, arthritis, rash, low-grade fever, mild cutaneous vasculitis; 2 = hemolytic anemia, thrombocytopenia without bleeding, pleuropericarditis, nephritis without azotemia, neurologic symptoms, severe anemia, or significantly elevated blood pressure; 3 = more severe nephritis (creatinine ≤2.0), neurologic symptoms, mild central nervous system symptoms, peripheral vasculitis with gangrene; 4 = life-threatening: creatinine >3.0, coma or obtundation, pulmonary hemorrhage, central nervous system vasculitis.

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Table 2. Serologic characteristics of systemic lupus erythematosus patients not taking steroids

	No.	ssDNA (%)*	DNA (%)†	Complement (CH50)‡
Male				
Inactive	2	6	7	158 (1)
		33	6	
Active	3	34	17	
		83	57	ND
		85	80	
Female				
Inactive	12	38 ± 26	14 ± 21	165 ± 59 (3)
Active	24	48 ± 28	27 ± 30	161 ± 51 (10)

* Anti–single-stranded DNA (ssDNA) antibodies measured by radioimmunoassay (normal 0–15%); values for female patients are the mean ± SD, actual values are given for the male patients.
† Anti-DNA antibodies measured by radioimmunoassay (normal 0–15%)
‡ Complement values are total hemolytic complement, (normal 150–250 hemolytic units); numbers in parentheses indicate separate sample numbers; ND = not done.

Institute. All patients fulfilled the 1982 American Rheumatism Association revised criteria for SLE (10). For the most part, patients were selected who had never been treated with prednisone, or who had not been taking prednisone for more than 1 year (Table 1). Forty-seven patients met the criteria for SLE. Eleven patients were taking corticosteroids at the time of the study and were grouped separately. Twelve patients were newly diagnosed and had never taken corticosteroids. Twenty-three patients in the study were free of corticosteroid therapy for 20 months or more. Control subjects were obtained from a pool of healthy normal volunteers.

Disease activity. Disease activity in each patient was assessed by clinical and laboratory parameters (Table 2). The therapeutic profiles, including specifics on the duration of therapy with steroids, are reported in Table 1. Measurement of anti-DNA antibodies (11) and total hemolytic complement levels (CH50) (12) confirmed the clinical impression of disease activity (values are given in Table 2). In several women, laboratory assessment was done during the inactive and the active stages of disease (Table 2). CH50 values were not always provided because these levels decrease even with storage of frozen specimens.

Measurement of plasma androgens. Twenty-milliliter blood samples were drawn in heparinized tubes from each patient, and samples were centrifuged at 1,200 revolutions per minute for 10 minutes. The extracted plasmas were immediately frozen at −80°C until radioimmunoassay (RIA). Plasma androgen levels were measured using RIA techniques previously described (13–15), and were run in triplicate where possible. Each steroid was assayed in 1 series on the same day. Levels of the 4 major androgens, androstenedione, testosterone, dehydroepiandrosterone (DHEA), and dehydroepiandrosterone sulfate (DHAS), were measured.

Plasma cortisol and estradiol levels. In order to be certain that patients had normally functioning adrenal glands, plasma cortisol levels were determined, according to the method of Braumsberg and James (16). Separate samples for plasma cortisol determinations were drawn in the morning clinic.

Plasma samples to measure estradiol levels were taken from females during the interfollicular phase of their menses to preclude active menstruation, a time when elevated androgen levels have been reported to occur (17).

Adrenocorticotropic hormone (ACTH) stimulation tests. Three women with low plasma androgen levels underwent ACTH stimulation testing (according to the method of Grieg et al [18]) to assess adrenal function. Briefly, 4- and 8-hour stimulation tests were performed by injecting 0.25 μg of Cortrosyn (Organon, West Orange, NJ) at time 0. Plasma samples were drawn at 0, 1, and 4 hours for the 4-hour study, while plasma samples were obtained at 0, 8 hours, and the following morning for the 8-hour study.

Statistical analysis. Statistical analysis was carried out using the BMDP statistical programs (P1D for simple data description and P3D for comparisons) on a Vax 780 computer.

RESULTS

Comparison of plasma androgen levels in the study population. The androgen levels, determined by RIA of plasma obtained from male SLE patients, are shown in Table 3. The results were compared with levels found in normal males. Three men had inactive disease; 2 had active disease. No significant differences in testosterone levels were noted. However, isolated values of DHEA and DHAS were compared, and those in the SLE patients seemed to be lower. Statistics from the male population were meaningless, however, because of the low numbers of patients.

Table 3. Androgen studies in male systemic lupus erythematosus (SLE) patients

Subjects	Testosterone (ng/dl)	Androstenedione (ng/dl)	Dehydroepiandrosterone (ng/dl)	Dehydroepiandrosterone sulfate (μg/dl)
Normal*	582 ± 192 (n = 8)	103 ± 50 (n = 14)	522 ± 256 (n = 18)	280 ± 104 (n = 30)
Active SLE†	681 (n = 2)	92 (n = 2)	131 (n = 2)	ND
Inactive SLE†	836 (n = 3)	125 (n = 3)	271 (n = 3)	126 (n = 2)

* Values are the mean ± SD.
† Values are the mean; since they were lower than was expected, they may reflect lower synthesis or clearance of these metabolites. ND = not done.

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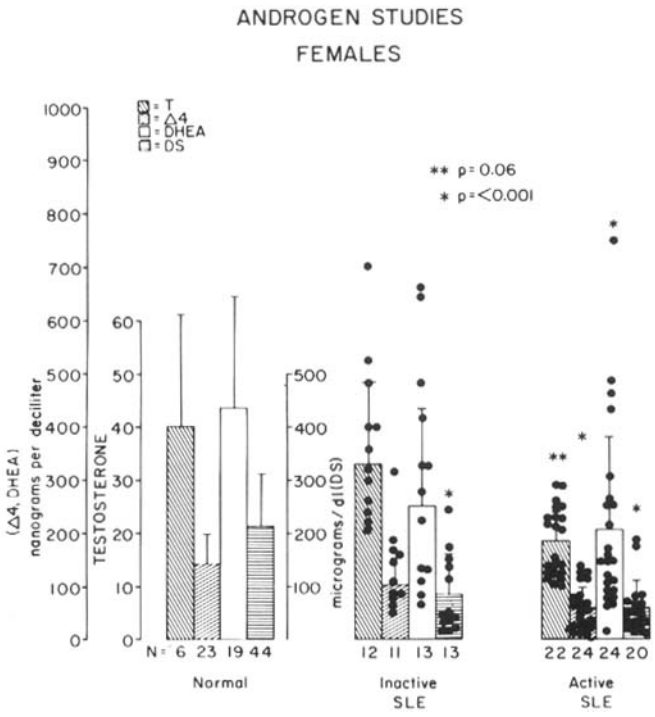

Figure 1. Plasma androgen levels in female systemic lupus erythematosus (SLE) patients compared with those in normal women. Significant decreases in androstenedione (Δ4), dehydroepiandrosterone (DHEA), and dehydroepiandrosterone sulfate (DS) are observed in the total female population with SLE, compared with normal subjects. When patients were grouped according to clinical activity, the patients with active SLE had significant depression of all androgens measured. T = testosterone.

RIA data obtained on plasma from female SLE patients are given in Figure 1. A decrease in levels of plasma testosterone was found in the female SLE patient group and in 22 patients with active SLE (active SLE, mean ± SD 18.0 ± 6.5 versus normal 40 ± 22; $P = 0.06$), although these did not reach significance. It is possible that inclusion of more female control subjects might help to achieve more significance. Androstenedione levels were significantly depressed in all female subjects, particularly in the female patients with active SLE. The lowest values were obtained for the 24 patients with active SLE (58.9 ± 36.4; $P < 0.001$) and in the total female SLE population (72.5 ± 46.7; $P < 0.001$). Dehydroepiandrosterone levels were similarly decreased in 24 women with active SLE (209.4 ± 174.9; $P < 0.001$) and in the total female SLE population (224.2 ± 177.5; $P < 0.001$). Women with inactive SLE had decreases in both androstenedione and DHEA ($P = 0.04$ and $P = 0.02$, respectively) but these levels barely reached significance.

The most significant decrease of androgens in females was found in the levels of DHAS; patients with active and inactive disease had significantly lowered values. A significant decrease in mean DHAS ($P < 0.001$) was found in all SLE patients (61.6 ± 69.8), in those 20 patients with active SLE (61.3 ± 51.3), as well as in the 13 patients with inactive SLE (82.9 ± 75). The mean DHAS value (±SD) for 30 male control subjects was 280 ± 104; for 44 female control subjects it was 230 ± 100.

Estradiol levels. Blood samples were taken from all female patients during the intrafollicular stage of the menstrual cycle; no patient was menstruating at the time the samples were obtained. Nevertheless, estradiol levels were obtained to assure normal ovarian function. All patients had menstrual periods, although some menses were reported to occur irregularly. Estradiol levels were determined in random samples of plasma from 15 patients (Table 4). Data show estradiol values of 16 ± 11 ng/dl for women with inactive SLE and 11.7 ± 6.4 ng/dl for women with active SLE. High estradiol levels were not found in any of the women studied. This fact is not inconsistent with previously reported findings of normal estradiol levels in male and female SLE patients studied radiometrically (2) or by analysis of urinary metabolites (1). In the latter studies, 16α-hydroxyestrone and estriol levels were elevated, whereas estradiol and estrone levels were normal.

Table 4. Cortisol and estradiol levels in male and female systemic lupus erythematosus patients

	Male (inactive)	Male (active)	Female (inactive)	Female (active)
Cortisol*	7.3 (2)	10.8 (6)	8.3 ± 3.7 (12)	8.9 ± 3.9 (15)
Estradiol†	–	–	16.0 ± 11.0 (12)	11.7 ± 6.4 (15)

* Normal 3–18 μg/dl; numbers in parentheses are no. of patients tested.
† Normal 13 ± 8 ng/dl; midcycle 30 ± 20 ng/dl. Estradiol levels were measured at the mid-follicular phase of the menstrual cycle to rule out hypo- or hyperestrogenism.

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Table 5. Adrenocorticotropic hormone (ACTH) stimulation in 3 female systemic lupus erythematosus (SLE) patients and 21 normal subjects*

Patient no.	ACTH (hours after dose)	Cortisol (μg/dl)	DHEA (ng/dl)	DHAS (μg/dl)	Androstenedione (ng/dl)	Testosterone (ng/dl)
1	0	21.3	679	189	163	50
	1	37.8	1157	211	160	72
	4	42.5	905	248	294	76
	8	46.9	1288	268	245	76
2	0	14.4	594	223	253	7
	1	41.8	1307	230	357	23
	4	38.3	1096	264	343	–
	8	34.5	1183	294	139	–
3	0	7.6	342	147	139	5
	1	24.6	638	149	194	–
	4	14.0	122	159	82	14
	8	38.0	639	225	174	58
Normal subjects (range)	0	5–14	175–575	38–326	61–295	12–53
	1	19–34	175–700	100–427	98–538	24–66

* DHEA = dehydroepiandrosterone; DHAS = dehydroepiandrosterone sulfate. No marked decrease in any androgen was observed in the 3 SLE patients by either a 4- or 8-hour Cortrosyn stimulation test.

Adrenal function. Adrenal function was normal in all patients who were studied. This was established by 2 methods: (a) by measurement of plasma cortisol levels (Table 4), and (b) by ACTH stimulation assays (Table 5). Cortisol levels were normal for all males and females tested. ACTH stimulation assays demonstrated a normal 4- and 8-hour cortisol response in the 3 female patients studied. The response of DHEA to ACTH was low, and further studies to explain this finding are underway.

Patients taking steroids. As expected, significant sex steroid differences were observed in patients receiving corticosteroid treatment for SLE (10–30 mg/day). Plasma testosterone levels were suppressed by corticosteroids in a female SLE patient (9 ± 7 ng/dl; normal 37.7 ± 19 ng/dl).

DISCUSSION

Despite the fact that fewer men have SLE, no significant sexual differences in estrogen metabolism were observed between male and female SLE patients (1,2). Nevertheless, laboratory and clinical evidence support the importance of estrogens as modulating factors in the morbidity of this disease (1,2,19). After puberty, the female to male ratio is 9:1 for reasons that may include variations in estrogen and androgen metabolism, and the as-yet-undetermined effects of the products of such metabolism on the immune system. The hydroxylation of estradiol at C-16 was previously reported to be increased in SLE patients of both sexes (1,2), yielding the potent estrogen 16α-hydroxyestrone (Figure 2). However no correlation of the clinical activity, sex of the patient, or abnormal estrogen metabolism was apparent (2). Other data suggested that first-degree relatives of patients with SLE had similar elevations of 16 hydroxylation (20).

Using techniques similar to those employed in our estrogen studies, we found that testosterone metabolism was accelerated in the female patient (3). Oxidation at C-17 was elevated only in female SLE patients and in patients with Klinefelter's disease (3), even though such findings were never reported in normal subjects (21,22). Moreover, Jungers et al reported low plasma testosterone values in 5 female patients with active SLE (7).

The results reported here confirm that plasma androgens are lower in female SLE patients than in male SLE patients, or in normal subjects of either sex. Such decreases in plasma androgens could be associated with groups whose clinical and serologic activity were greatest. Care was taken to avoid the effects of exogenous corticosteroids, which are known to lower androgen levels (23).

These studies show that androstenedione, DHEA, and DHAS are significantly lowered in all female SLE patients, but are lowered most strikingly in those patients with active disease. The small numbers of men studied prevented a statistical comparison, but data available on androgen levels (exclusive of testosterone levels) in a few male patients suggested that a similar mechanism might be operative. In light of these findings, it would seem that the decreased androgen levels in female SLE patients might repre-

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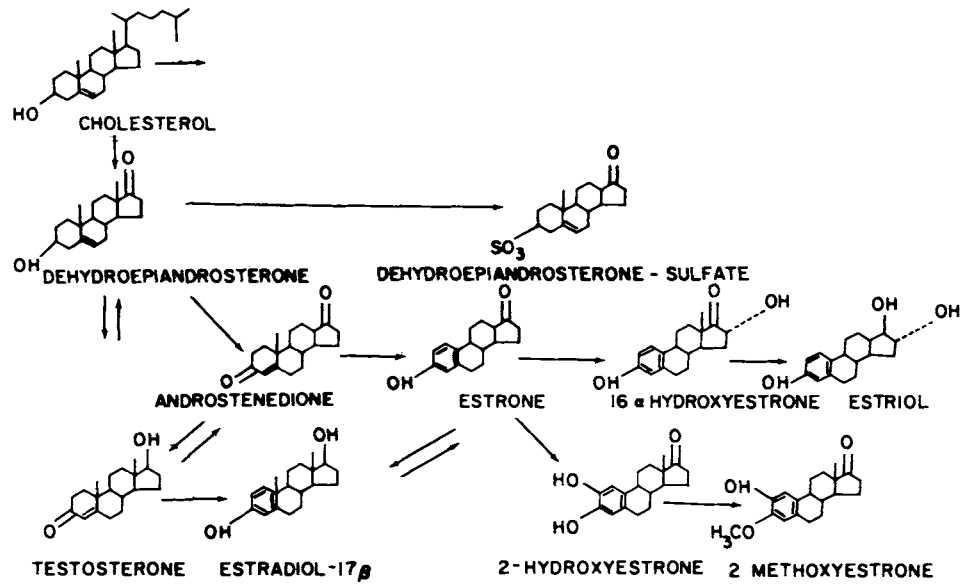

Figure 2. Human metabolism of estrogen and androgen. Previous data have shown an abnormality of hydroxylation of estrone at C-16 to 16α-hydroxyestrone and estriol, and abnormally rapid oxidation of testosterone to androstenedione at C-17. The latter finding is specific to female systemic lupus erythematosus patients.

sent a secondary effect of their disease state, or represent one of several potential determinants of disease susceptibility. It is also possible that these values represent abnormalities of clearance of gonadal steroids. This is probably reflected in the fact that low androgen levels have been reported in men with uremia (24). However, despite the fact that 4 of them had nephritis, the male patients studied here were not uremic. The values reported here in women are consistent both with the previously reported values from the small study (7) and the elevated testosterone C-17 oxidation data (3). Normal findings on cortisol and ACTH stimulation studies in many patients indicate the absence of an overall adrenal defect, despite the marked decrease of adrenal androgens. While the stress of a chronic illness might result in an overall decline in adrenal steroidogenesis, it should not result in a specific decrease in 17,20-lyase activity, nor should this be manifested only in women.

These data on the SLE patient may be of interest for several reasons. First, testosterone and related androgens have been reported to be effective in the control of murine SLE (25), and a variety of potent immunosuppressive effects have been described (26). Though reports are few, similar responses have not been observed to date in female patients treated with androgens. It has been hypothesized that testosterone in the human female may have a protective effect on disease severity and that low levels may have a significant effect on the morbidity of the disease, although this has not been shown. Moreover, the finding of worsening SLE in men taking substituted androgens makes this a possibility (8,9).

Animal and human studies have suggested that androgen levels might be of greater importance to the integrity of the immune system than was previously thought. The description of H2-associated genes for testosterone oxidation in mice indicates that testosterone metabolism is closely linked to immune function in that species (27,28). It is of interest that one clinical state of testosterone excess, HLA-linked nonclassical 21-hydroxylase deficiency, is negatively associated with HLA–B8, an allele found with high frequency among SLE patients (29). Though HLA–D data are not available for all patients included in this study, a large majority of these patients had HLA–B8 and HLA–D3 alleles. Moreover, the associated increase in suppressor cell activity (26) and interleukin-2 levels in animals (30) in response to testosterone may have relevance for these patients who have low-to-undetectable levels of such steroids.

Experimental data showing that lowering of

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plasma androgens changes the severity of disease will be reported later. Preliminary aromatization studies in several of our SLE patients suggest that aromatization in SLE is not elevated (data not shown). Fundamental questions which still have to be addressed concern the differences in androgen metabolism which might exist in these patients before puberty, and the overall significance and effects that such differences have in the manifestations of disease and the integrity of the immune system in humans.

Last, it is possible that the findings reported in this paper reflect problems of androgen clearance or androgen production in SLE. It should be noted, however, that the normal response to an ACTH stimulation test indicates that there is adequate adrenal reserve to make androgens. The problem, therefore, might be caused by metabolic clearance.

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