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REVIEW

Sex Hormones and Systemic Lupus Erythematosus

Review and Meta-Analysis

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Introduction

Systemic lupus erythematosus (SLE) is an acute and chronic autoimmune inflammatory disease known for its female predilection and peak incidence during the reproductive years. The increased female-to-male ratio of SLE patients suggests that sex factors modulate disease proclivity and development (1–3; for supplementary material, see www.sciencemag.org/feature/data/983519.shl). A multitude of sex factors could be responsible for the female predilection of SLE and other diseases. As recently reviewed (4), biologic differences between the sexes occur at genetic (X and Y chromosome–mediated), endocrinologic, metabolic, and environmental levels. However, the report in 1944 (5) of SLE flares corresponding to menstrual cyclicity focused an era of investigations on the potential contributions of estrogens, androgens, and prolactin to the development of SLE (6–8). Substantial evidence of immunoregulatory actions of 17β-estradiol (estradiol), testosterone, progesterone, dehydroepiandrosterone/dehydroepiandrosterone sulfate (DHEA/DHEAS), and prolactin supports the concept that sex hormones modulate the incidence and severity of disease in patients with SLE (3,9).

Clinical investigations of sex hormones in SLE have been relatively uniform in terms of enrollment of lupus patients and appropriately matched healthy controls. Small numbers of study participants, participant ethnicity, the relatively long time period over which studies have been reported, absence of sufficient statistical power to test respective hypotheses, and the variability of individual study results have confounded definitive conclusions about sex hormone concentrations and SLE. Menstrual cyclicity, endocrine feedback loops, hormonal interconversions (e.g., DHEA to progesterone to testosterone to estradiol), and chronobiologic relationships further complicate simple interpretation of cause-and-effect relationships and application of hormonal immunotherapy (10–12).

In this article, the sex-determined incidence and severity of SLE are reviewed. Clinical studies measuring serum 17β-estradiol, testosterone, progesterone, DHEA/DHEAS, or prolactin concentrations in adult women and men with SLE were identified by a computerized search of the medical literature and classified for presentation, analysis, and discussion.

SLE incidence and severity

The strongest risk factor for development of SLE appears to be female sex. The female-to-male sex ratio of 9:1 in SLE is observed during the peak reproductive years, with a gradual decline in the ratio after menopause. Among males with SLE, the age at disease onset is more evenly distributed (1,2). Specific evidence provides little support for the concept that strong correlations exist between disease severity and sex hormone concentrations. Moreover, serum sex hormone concentrations are not typically outside of physiologic ranges in patients with SLE (13), although the serum levels (within normal limits) have been found to be statistically higher or lower than those in healthy matched controls. Bias in ascribing sex differences in disease incidence or severity to sex hormones may be introduced by physiologic reality: levels of estrogens and prolactin are signif-

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Table 1. Controlled studies of serum 17β-estradiol concentrations in patients with systemic lupus erythematosus*

Authors, year (ref.)	Subjects	Conclusions
Female-only studies		
Jungers et al, 1983 (30)	19 SLE/12 controls	No significant difference
Feher et al, 1987 (31)	4–7 SLE/4–10 controls; 22 SLE/11 controls	No significant difference (regardless of cyclicity or menopause)
Lahita et al, 1987 (32)	12 SLE/pooled controls	No significant difference
Arnalich et al, 1992 (33)	26 SLE/21 controls	No significant difference
Folomeev et al, 1992 (34)	9 SLE/4 controls	No significant difference; aromatase activity varied inversely with SLE disease activity and positively with estradiol; no difference in female and male aromatase activity
Cheng and Li, 1993 (35)	140 SLE/20 controls	E_2 significantly higher in SLE; lupus activity related to incremental E_2 concentrations
Munoz et al, 1994 (36)	14 SLE/20 controls, premenopausal; 8 SLE/8 controls, postmenopausal	E_2 significantly lower in SLE; serum E_2 inversely related to disease activity at specific menstrual cycle stages; alterations in intermediate E_2 metabolism in SLE patients
Verthelyi et al, 2001 (37)	75 SLE/38 controls, premenopausal; 45 SLE/20 controls, postmenopausal	E_2 significantly higher in SLE (before or after menopause); cytokine imbalances did not correlate with hormone concentrations
Male-only studies		
Mackworth-Young et al, 1983 (38)	9 SLE/11 controls	No significant difference
Miller et al, 1983 (39)	49 SLE/49 controls	E_2 significantly higher in SLE; 18 of 49 had abnormally high E_2 concentrations
Carrabba et al, 1985 (40)	10 SLE/10 controls	No significant difference; lower testosterone/estradiol ratios in SLE men
Lavalle et al, 1987 (41)	8 SLE/11 controls	E_2 significantly lower in SLE
Folomeev et al, 1992 (34)	6 SLE/4 controls	No significant difference; trend toward increased E_2 and aromatase activity levels in SLE patients; however, aromatase activity varies inversely with SLE disease activity
Sequeira et al, 1993 (42)	14 SLE/17 controls	No significant difference
Cheng and Li, 1993 (35)	19 SLE/7 controls	E_2 significantly higher in SLE
Munoz et al, 1994 (36)	5 SLE/7 controls	No significant difference
Vilarinho and Costallat, 1998 (44)	7 SLE/10 controls	E_2 significantly lower in SLE
Chang et al, 1999 (43)	16 SLE/20 controls	No significant difference
Mok and Lau, 2000 (45)	35 SLE/33 controls	No significant difference
Verthelyi et al, 2001 (37)	8 SLE/28 controls	E_2 significantly higher in SLE; serum cytokine imbalances did not correlate with hormone concentrations

* SLE = systemic lupus erythematosus; E_2 = 17β-estradiol.

icantly higher and levels of androgens are significantly lower in women compared with men (4,14).

Observational phenomena suggesting that sex hormones modulate the incidence or severity of disease in patients with SLE include reports of lupus flares caused by use of oral contraceptives (for review, see refs. 15 and 16), administration of estrogen (17,18), and ovulation induction regimens (19,20). Conversely, ovarian failure (and, presumably, reduced estrogen concentrations) has been associated with reduced rates of lupus flares (21), although hormone replacement therapy is not clearly associated with recurrent lupus (for review, see ref. 22), and results of the ongoing Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) trial have not yet fully emerged. An association of lupus with Klinefelter's syndrome, and its amelioration following testosterone administration, also imply that sex hormones modulate the incidence or severity of SLE (23–25). Further complicating clinical interpretations are the dramatic hormonal fluxes that occur during pregnancy (26) and associated flares of SLE disease activity (27,28). In the following sections, differences between serum concentrations of estradiol, testosterone, DHEA/DHEAS, progesterone, and prolactin in adult nonpregnant female patients with SLE and male patients with SLE are examined.

Serum 17β-estradiol

Estradiol is the most potent and predominant estrogen in serum, is the aromatized end-product of the gonadal steroid metabolic pathway (14), and has been traditionally associated with development of SLE (6,7). Several studies have assessed serum estradiol concentrations in adult patients with SLE (29–47); those that included healthy age-matched controls and provide accessible data for analysis are shown in Table 1 and Figure 1. Two of 8 investigations involving adult female

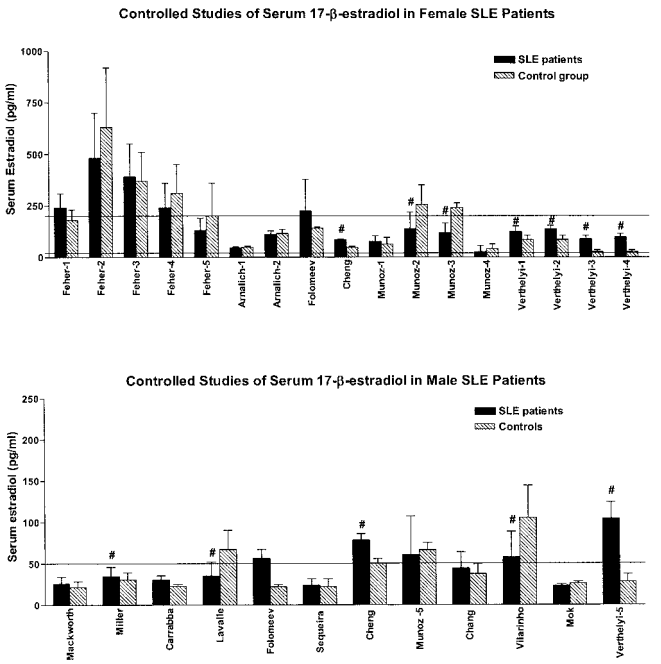

Figure 1. Controlled studies of serum estradiol concentrations (±SEM) in female and male patients with systemic lupus erythematosus (SLE). The studies by Jungers et al (30) and Lahita et al (32) are not included, because no SD was provided. Feher-1 through Feher-4 represent 4 consecutive weekly estradiol determinations, and Feher-5 represents postmenopausal women (31); Arnalich-1 represents the follicular phase and Arnalich-2 represents the luteal phase (33); Munoz-1 represents the follicular phase, Munoz-2 represents the mid-cycle, Munoz-3 represents the luteal phase, Munoz-4 represents postmenopausal patients, and Munoz-5 represents male patients (36); Verthelyi-1 represents premenopausal patients with inactive disease, Verthelyi-2 represents premenopausal patients with active disease, Verthelyi-3 represents postmenopausal patients with inactive disease, Verthelyi-4 represents postmenopausal patients with active disease, and Verthelyi-5 represents male patients (37). Horizontal lines show the upper and lower limits of normal for women and the upper limit of normal for men (14). Bars show the mean and SD. # = $P < 0.05$.

patients with SLE showed significantly increased serum estradiol concentrations in lupus patients compared with controls. One study demonstrated lower estradiol levels in SLE patients compared with controls (at 2 different menstrual cycle points), and 5 studies showed no difference between patients and controls (although Folomeev et al [34] reported a trend toward higher concentrations in SLE patients). Assessing serum estradiol levels in women was confounded, as shown in Figure 1, by 5-fold concentration changes in weekly determinations of estradiol (Feher-1 through Feher-4), phase of the menstrual cycle or postmenopausal status (Munoz-1 through Munoz-4), and pre/postmenopausal status in patients with inactive or active disease (Verthelyi-1 through Verthelyi-4).

Among 12 investigations of male SLE patients (Table 1), only 3 showed significantly increased serum estradiol concentrations in patients compared with controls, 7 studies showed no difference between patients and controls, and 2 showed significant suppression of serum estradiol in patients. In most of these studies, serum estradiol concentrations were within the normal physiologic range, although results of 3 studies suggested that some male lupus patients were hyperestrogenemic (18 of 49, 2 of 7, and 3 of 8 male SLE patients, respectively, had estradiol levels above the normal range) (39,44,46).

To formulate general conclusions regarding se-

Table 2. The Hedges common estimator of studies of sex hormones in SLE*

Sex hormone/ SLE group†	Hedges g_u	95% CI
Estradiol		
All patients	0.60	0.44, 0.76‡
Women only	1.23	0.99, 1.46‡
Men only	0.04	−0.18, 0.25
Testosterone		
All patients	−0.71	−0.89, −0.53‡
Women only	−1.22	−1.48, −0.97‡
Men only	−0.18	−0.44, 0.08
DHEAS		
All patients	−0.98	−1.17, −0.79‡
Women only	ND	ND
Men only	ND	ND
Progesterone		
All patients	ND	ND
Prolactin		
All patients	0.61	0.41, 0.82‡
Women only	0.30	0.10, 0.50‡
Men only	1.20	0.76, 1.65‡

* For meta-analysis, studies were included if they enrolled nonpregnant female or male patients with systemic lupus erythematosus (SLE) who met the American College of Rheumatology (formerly, the American Rheumatism Association) criteria for the classification of SLE, compared serum concentrations of the specified hormone using conventional measurement techniques, and had matched controls. Studies were excluded if they did not measure serum hormones in a healthy control population, did not provide clear data on statistical variation, or used nonconventional techniques for hormone assessment. Some studies examined female SLE patients in various hormonal states (i.e., follicular phase, luteal phase, postmenopausal) or included male SLE patients in a separate analysis, and were subclassified by first author name and a numeric designation for separate subset hormonal determinations (e.g., Munoz-1, Munoz-2). These data were treated as individual assessments of hormonal status. The Hedges common estimator and 95% confidence interval (95% CI) were calculated according to standard statistical methods. Hedges g_u is a measure of effect size. DHEAS = dehydroepiandrosterone sulfate; ND = not determined.

† The common estimator compared patients with respective controls for all SLE patients, female-only SLE patients, and male-only SLE patients, for the sex hormones listed.

‡ Statistically significant (not including zero).

Table 3. Controlled studies of serum testosterone in SLE patients*

Authors, year (ref.)	Subjects	Conclusions
Female-only studies		
Jungers et al, 1982 (60)	13 SLE/12 controls	Testosterone significantly lower
Jungers et al, 1983 (30)	19 SLE/12 controls	Testosterone significantly lower
Feher et al, 1987 (31)	54 SLE/44 controls	Testosterone significantly lower
Lahita et al, 1987 (32)	22 SLE/pooled controls	No significant difference; all androgen levels lower in SLE patients compared with controls, but not always statistically significant; androgens inversely correlated with disease activity
Arnalich et al, 1992 (33)	26 SLE/21 controls	No significant difference
Folomeev et al, 1992 (34)	9 SLE/4 controls	Testosterone significantly lower
Cheng and Li, 1993 (35)	140 SLE/20 controls	Testosterone significantly lower; decrements inversely proportional to lupus activity
Munoz et al, 1994 (36)	14 SLE/20 controls	No significant difference
Male-only studies		
Stahl and Decker, 1978 (61)	12 SLE/31 controls	No significant difference; hypogonadism or androgen deficiency not evident
Mackworth-Young et al, 1983 (38)	9 SLE/11 controls	Testosterone significantly lower; testosterone lower in SLE patients but not different from other chronic diseases
Carrabba et al, 1985 (40)	10 SLE/10 controls	No significant difference; lower testosterone/estradiol ratios in SLE men
Lavalle et al, 1987 (41)	8 SLE/11 controls	Testosterone significantly lower
Folomeev et al, 1992 (34)	6 SLE/4 controls	Testosterone significantly lower
Sequeira et al, 1993 (42)	14 SLE/17 controls	No significant difference
Cheng and Li, 1993 (35)	19 SLE/7 controls	Testosterone significantly lower; inversely related to disease activity
Munoz et al, 1994 (36)	5 SLE/7 controls	No significant difference
Vilarinho and Costallat, 1998 (44)	7 SLE/10 controls	No significant difference
Chang et al, 1999 (43)	16 SLE/20 controls	No significant difference
Mok and Lau, 2000 (45)	33 SLE/35 controls	No significant difference

* SLE = systemic lupus erythematosus.

rum sex hormone concentrations in adult female and male SLE patients compared with healthy controls, Hedges common estimator, a meta-analytic measure of effect size (48–50), was determined for all studies, female-only SLE studies, and male-only SLE studies, all of which included a population of healthy matched controls (Table 2). Using a weighted estimator based on within-study variances, calculation of the Hedges common estimator (see Appendix A) facilitates comparison of multiple studies that individually may not reach a definitive conclusion regarding association or effect (48,49). Additionally, 95% confidence intervals (95% CIs) for overall effect size are reported, and 95% CIs that do not include zero indicate a statistically significant difference. Because homogeneity of variances across all studies did not exist (which is one of the confounders in interpreting SLE sex hormone data), the Hedges common estimator results reported herein should be interpreted with caution until more definitive and verifiable results are available.

Nevertheless, calculation of the common estimator of serum estradiol studies in Figure 1 showed that estradiol was significantly higher in adult SLE patients compared with controls when all studies and female-only studies were considered (Table 2). No significant difference in serum estradiol levels between male-only lupus patients and healthy controls could be demonstrated (Table 2). The effect size for female-only SLE studies was large, and the 95% CI did not include zero, implying significantly increased serum estradiol concentrations in female lupus patients compared with controls, and likely accounting for the significant common estimator across all studies. Conversely, the 95% CI for the Hedges estimator for male-only SLE studies implies that no difference for estradiol concentrations exists between male SLE patients and healthy controls (Table 2).

Possible explanations for these findings include increased activity of aromatic hydroxylase or increased production of luteinizing hormone (LH) driving testosterone aromatization in women (14). Folomeev et al reported that aromatic hydroxylase activity was increased in SLE patients, but its activity was inversely related to SLE disease activity (34). To our knowledge, genotypic variations in the enzymes of gonadal steroid synthesis have not been identified in SLE patients, although abnormal metabolism of estrogen and testosterone has been reported (51–53), and other metabolic enzyme differences exist between women and men (4). Lupus patients have an increased 16α-to-2α hydroxylated estrogen metabolite ratio, resulting in production of more "feminizing" estrogens (51,52). In addition, female SLE patients have increased oxidation of testosterone (53), but these abnormalities do not explain increased serum estradiol concentrations in female lu-

pus patients. Increased estradiol concentrations in female SLE patients could, alternatively, be a response to disease activity (e.g., inflammation-stimulated aromatase activity) or the result of inflammatory cytokine action increasing LH release from the pituitary gland (54–56), increasing aromatization, and making estradiol a surrogate marker of inflammation rather than a modulator of disease activity.

Several observations call into question the true role of estrogens in the development or modulation of lupus. For example, in murine lupus, physiologic concentrations of estradiol, exclusive of its prolactin stimulatory effects, suppress autoimmune disease activity (57). Data in this review demonstrate that adult male SLE patients are not feminized by excessive serum estradiol concentrations. Moreover, estradiol concentrations are abnormally low in pregnant lupus patients compared with pregnant controls during periods of increased disease activity (58,59). Therapeutic administration of nonaromatizable (i.e., not convertible to estrogen) androgens does not improve and may worsen SLE disease activity (11), and estrogen receptor blockade with tamoxifen does not improve and may exacerbate SLE disease activity (10). Hence, a clear understanding of relationships between serum estradiol concentrations, steroid enzymes, metabolite effects, and disease activity in SLE remains elusive.

Serum testosterone

Testosterone, the immediate precursor of estradiol, is found in both men and women (14) and is generally accepted as being immunosuppressive (3,9). Most female-only SLE studies assessing serum estradiol also assessed serum testosterone concentrations; male-only SLE studies typically assessed only testosterone or other androgens and not estradiol or progesterone (60,61) (Tables 1 and 3). As shown in Table 3, 5 of 8 female-only SLE studies showed significantly decreased testosterone in patients with SLE compared with controls, whereas only 4 of 11 male-only SLE studies showed a significant suppression of testosterone in SLE patients. Although several studies showed a trend toward lower serum testosterone concentrations in SLE patients, results of many studies did not achieve statistical significance (Table 3 and Figure 2). Studies of testosterone also did not routinely identify the percentage of lupus patients who were hypoandrogenemic, although hypoandrogenism in patients with SLE and Klinefelter's syndrome, and SLE clinical improvement with testosterone administration, is documented, as noted above (23–25).

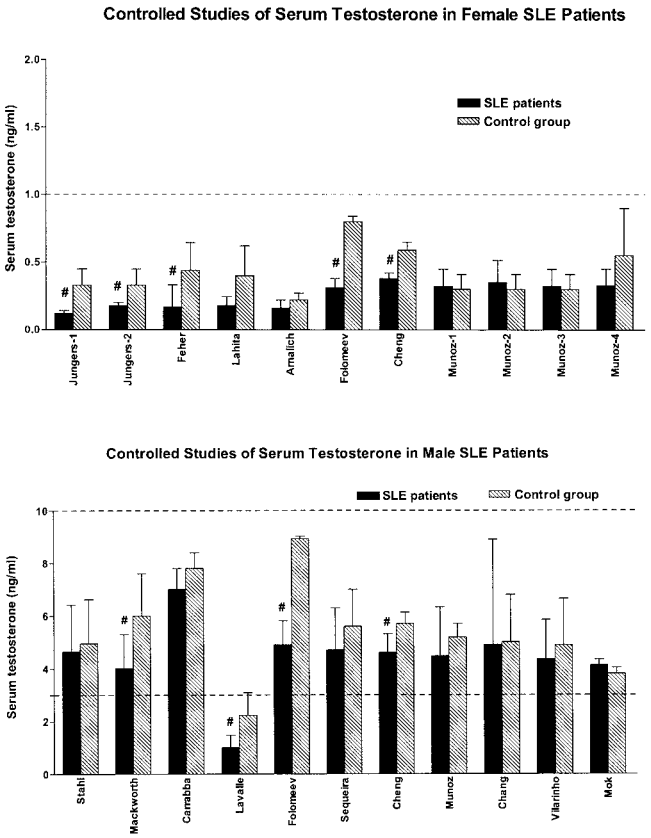

Figure 2. Controlled studies of serum testosterone concentrations (±SEM) in female and male SLE patients. Jungers-1 (60) and Jungers-2 (30) are 2 separately reported studies. Broken horizontal lines show the upper limits of normal for women and the upper and lower limits of normal for men (14). Bars show the mean and SD. # = $P < 0.05$. See Figure 1 for definitions.

Calculation of the Hedges common estimator across all studies of adult SLE patients showed significant serum testosterone suppression in lupus patients compared with healthy controls. However, female-only studies showed a large common estimator, a relationship that was not proved in male-only SLE studies (Table 2). Similar to the effect size for estradiol, the effect size for suppressed serum testosterone in female lupus patients was significant (because the 95% CI did not include zero). In contrast, the common estimator for testosterone concentrations was not significantly different between male SLE patients and controls.

A hypothesis consistent with observed sex hormone changes in female SLE patients is that a sex-determined accelerated metabolic conversion of upstream androgen precursors to estradiol occurs (a high throughput hypothesis). Alternative or adjunctive explanations include primary hypoandrogenism, hypopituitarism, accelerated catabolism or oxidation, hyperpro-

lactinemia, or combinations of these effects (14). Conversely, normal serum estradiol and testosterone concentrations in male SLE patients imply that lupus is not sex-steroid dependent in men. The etiology of low or suppressed androgen levels in male SLE patients observed in some studies remains unclear (62).

Serum DHEA/DHEAS

DHEA, an upstream precursor of progesterone, testosterone, and estradiol, is also an adrenal androgen with mild virilizing effects, whose primary form in the serum is DHEAS (14). As shown in Figure 3, a majority of studies of SLE in adults show serum DHEA or DHEAS to be significantly lower in SLE patients compared with controls. The common estimator of combined female-only and male-only SLE studies demonstrated a significant suppression of DHEAS in patients compared with controls (Table 2). However, the paucity of studies precluded sex subset classification for DHEAS as well as an assessment of common estimators for DHEA. Recently, several reports have documented that administration of DHEA to patients with SLE has therapeutic potential (63–66), although DHEA may exert its beneficial effects not only by increasing serum androgen levels (65) but also by increasing serum estradiol concentrations (67).

Serum progesterone

Progesterone is an upstream precursor of testosterone and estradiol (14). Few studies have systematically examined serum progesterone concentrations in adult SLE patients (33,36,37). Progesterone concentrations have been shown to be lower in SLE patients compared with healthy controls (Figure 3), although only one study (36) took into account menstrual cycles, during which progesterone levels were markedly lower during the follicular phase than during the luteal phase. As was true for DHEA, the paucity of progesterone-focused studies precluded meta-analysis.

In combination with the data showing reduced testosterone and DHEA/DHEAS concentrations, reduced levels of this upstream precursor again suggest increased metabolism toward the product of estradiol in female SLE patients, as the result of their primary multiple enzyme abnormalities, loss of feedback control, or increased levels of regulatory pituitary hormones (follicle-stimulating hormone [FSH] and LH). Abnormally low serum progesterone concentrations have also been documented in pregnant SLE patients during periods of increasing disease activity (58). Reports of the

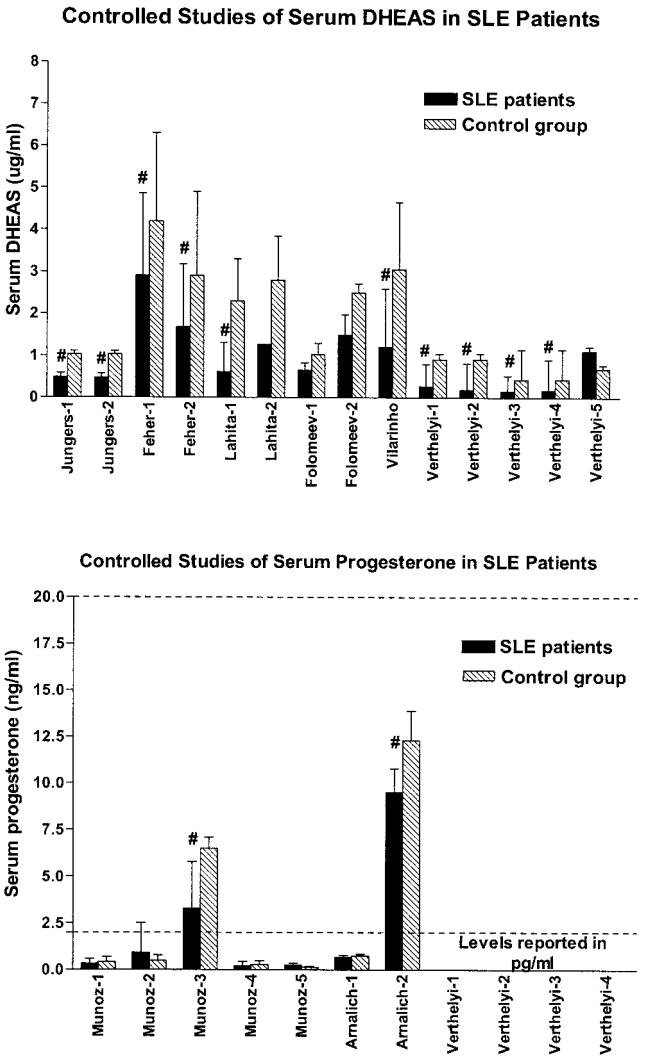

Figure 3. Controlled studies of serum concentrations (±SEM) of dehydroepiandrosterone sulfate (DHEAS) and progesterone in SLE patients. Jungers-1 (60) and Jungers-2 (30) are 2 separately reported studies. Lahita-1 represents females, and Lahita-2 represents males (32); Folomeev-1 represents females, and Folomeev-2 represents males. Broken horizontal lines show the upper and lower limits of normal for progesterone. Bars show the mean and SD. # = $P < 0.05$. See Figure 1 for other definitions.

effects of removal of or supplementation with progesterone are not available, although administration of combination estrogen/progesterone oral contraceptives may improve lupus disease activity (68).

Serum prolactin

Prolactin is a polypeptide pituitary sex hormone with relative concentration differences between sexes (69,70) and a broad array of immunoregulatory proper-

Table 4. Controlled studies of serum prolactin concentrations in SLE*

Author(s), year (ref.)	Subjects	Conclusions
Female studies		
Arnalich et al, 1992 (33)	26 SLE/21 controls	No significant difference
Jara et al, 1992 (71)	45 SLE/28 controls	Prolactin significantly increased; correlation with SLE disease activity; subset of patients were hyperprolactinemic
Munoz et al, 1994 (36)	14 SLE/20 controls; 8 SLE/8 controls	Prolactin significantly decreased (compared with controls at certain stages of the menstrual cycle)
Neidhart, 1996 (72)	29 SLE/29 controls	Prolactin significantly increased; increased prolactin associated with increased cortisol; significant correlation between serum prolactin and anti–double-stranded DNA
Huang and Chou, 1997 (73)	30 SLE/20 controls	Prolactin significantly increased
Rovensky et al, 1997 (77)	26 SLE/19 controls	Prolactin significantly increased
Ferreira et al, 1998 (74)	24 SLE/15 controls	Prolactin significantly increased
Gutierrez et al, 1998 (75)	10 SLE/10 controls	No significant difference
Jimena et al, 1998 (76)	36 SLE/20 controls	Prolactin significantly increased; no correlation found between prolactin levels and disease activity
Jacobi et al, 2001 (78)	60 SLE/47 controls	Prolactin significantly increased; correlation with lupus disease activity
Male studies		
Lavalle et al, 1987 (41)	8 SLE/11 controls	Prolactin significantly increased
Munoz et al, 1994 (36)	5 SLE/7 controls	No significant difference
Vilarinho and Costallat, 1998 (44)	7 SLE/10 controls	No significant difference
Chang et al, 1999 (43)	16 SLE/20 controls	Prolactin significantly increased

* SLE = systemic lupus erythematosus.

ties (7,8). Estradiol stimulates prolactin secretion, and prolactin suppresses gonadal steroid synthesis (69,70). As shown in Table 4 and Figure 4, several studies have examined the relationship of prolactin and SLE in adults, comparing either the mean concentrations in patients with those of controls or normal and abnormal prolactin concentrations (hyperprolactinemia), with or without a control population (71–87). Seven of 10 female-only and 2 of 4 male-only SLE studies showed significantly increased serum prolactin concentrations in adult lupus patients compared with controls. Of 5 additional prolactin studies (77–81), 2 showed increased prolactin concentrations in SLE patients; however, because the prolactin levels were reported in international units, these studies could not be included in the meta-analysis.

Computation of the common estimator demonstrated significantly increased prolactin concentrations across all studies and female-only studies (Table 2). Calculation of the Hedges common estimator of serum prolactin concentrations in male-only SLE studies also showed significantly increased serum prolactin concentrations in patients compared with healthy controls. The effect size was moderate for women and large for men (Table 2).

Determinations of the percentage of SLE patients with hyperprolactinemia (prolactin concentration >20 ng/ml) are shown in Table 5. Although 3 studies

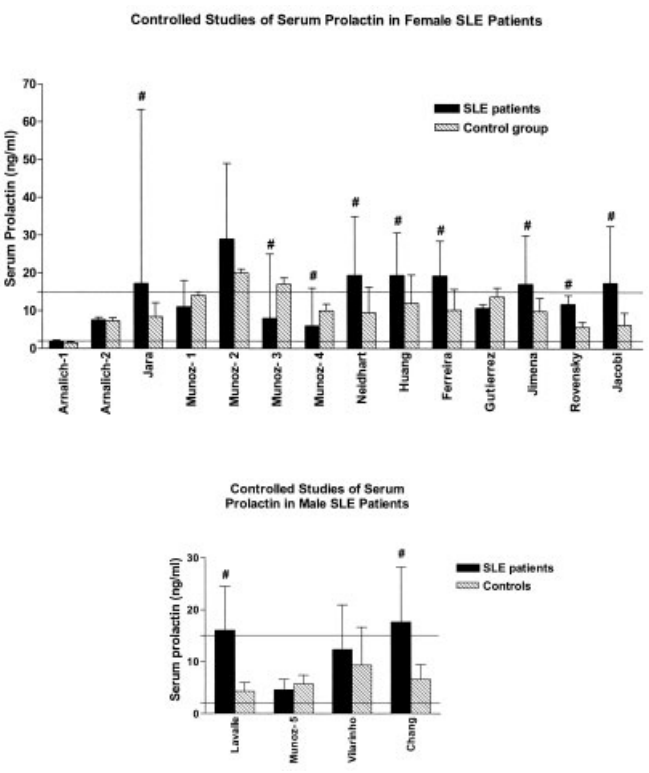

Figure 4. Controlled studies of serum prolactin concentrations (±SEM) in female and male SLE patients. Horizontal lines show the upper and lower limits of normal for prolactin (14). Bars show the mean and SD. # = $P < 0.05$. See Figure 1 for definitions.

Table 5. Prevalence of hyperprolactinemia in SLE patients and controls*

Author(s), year (ref.)	Serum hyperprolactinemia	
	Patients	Controls
Jara et al, 1992 (71)	10/45 (22)	0/28 (0)
Sequeira et al, 1993 (42)	0/14 (0)	0/13 (0)
Pauzner et al, 1994 (82)	16/82 (20)	ND
Buskila et al, 1996 (83)	10/63 (16)	ND
Formiga et al, 1996 (84)	6/20 (30)	ND
Neidhart, 1996 (72)	9/29 (30)	ND
Ostendorf et al, 1996 (85)	4/182 (2)	ND
Huang and Chou, 1997 (73)	12/30 (40)	2/20 (10)
Mok et al, 1997 (79)	25/72 (31)	ND
Rovensky et al, 1997 (77)	11/34 (31)	ND
Alvarez-Nemegyei et al, 1998 (93)	30/66 (45)	ND
Ferreira et al, 1998 (74)	9/24 (38)	2/15 (13)
Jimena et al, 1998 (76)	10/36 (28)	ND
Mok et al, 1998 (80)	4/13 (13)	ND
Vilarinho and Costallat, 1998 (44)	2/7 (29)	ND
Mok and Lau, 2000 (81)	0/35 (0)	0/33 (0)
Jacobi et al, 2001 (78)	17/60 (28)	0/47 (0)
Leanos-Miranda et al, 2001 (86)	41/259 (16)	ND
Pacilio et al, 2001 (87)	21/78 (27)	ND
Total†	237/1,149 (21)	4/156 (3)

* Values are the number (%). Serum hyperprolactinemia was defined as a concentration >20 ng/ml. SLE = systemic lupus erythematosus; ND = not determined.
† Mantel-Haenszel odds ratio estimator = 8.9 (95% confidence interval [95% CI] 3.1–16.6; 95% CI > 1.0 is statistically significant).

(43,80,85) did not show an abnormal percentage of hyperprolactinemic SLE patients, summation of all studies revealed that 21% of SLE patients were hyperprolactinemic compared with 3% of healthy controls. This >7-fold difference is also markedly higher than the 1–2% prevalence of hyperprolactinemia reported for general populations (69,88) and was statistically significant compared with healthy controls (Mantel-Haenzel odds ratio).

Prolactin probably stimulates lupus disease activity (89); serum prolactin and disease activity have been positively associated (71,87,90,91); abnormally high prolactin levels during pregnancy in SLE also correlate with disease activity (58,92); and 2 double-blind, placebo-controlled human studies have shown that suppression of prolactin with bromocriptine reduces SLE disease activity (93,94). Interestingly, bromocriptine not only suppresses prolactin but appears to increase estradiol concentrations (95) through increased aromatization of testosterone (96), implying a complex interaction for these hormones in lupus and its disease activity.

Explanations for the prolactin abnormalities in lupus patients are currently speculative. The prolactin gene is in close proximity to the HLA complex (97), and genotype aberrations could be genetically linked to disease predisposition in some subsets of SLE patients. Other possibilities include cytokine-stimulated pituitary prolactin release (54,55), production of immunoreactive prolactin peripherally (98,99), or aberrant pituitary prolactin secretion in lupus patients (74,75). Some of these explanations are, however, superficially not compatible with the other steroid hormone abnormalities seen in female SLE patients. Could aberrant secretion of prolactin, FSH, and LH release produce hyperprolactinemia as well as increased estradiol levels and its decreased precursors in female patients with SLE? Further delineation of abnormalities in pituitary hormone secretion and their effects on SLE is warranted.

Conclusion

Sexual dichotomy in the incidence of SLE and immunoregulatory properties of sex hormones have suggested that causal or modulatory relationships exist between lupus or lupus disease activity and estradiol, testosterone, DHEA, progesterone, or prolactin. The majority of studies, while documenting sex hormone aberrations in lupus, have examined relatively few patients and controls. Variability and nonhomogeneity of studies of serum hormonal concentrations in SLE patients confound necessary assumptions for statistical meta-analysis, further limiting conclusions derived from currently available data. The possibility of reporting bias also exists, but this argument is somewhat mitigated by the fact that >40% of sex-specific comparisons included in this review (Tables 1, 3, and 4) showed negative or "no difference" results for the sex hormones.

Although this review does not establish causal relationships, it emphasizes the altered sex hormone milieu of female SLE patients (Table 6), whether predisposing to disease development or resulting from the autoimmune process, with most hormones remaining within physiologic ranges. Hormonal differences be-

Table 6. Sex hormone changes in SLE patients*

Hormone	Women	Men
DHEA/DHEAS	↓	Probably ↓
Progesterone	↓	Unknown
Testosterone	↓	Normal
Estradiol	↑	Normal
Prolactin	↓ (stimulates) ↑	↑

* Compared with healthy controls. SLE = systemic lupus erythematosus; DHEA/DHEAS = dehydroepiandrosterone/dehydroepiandrosterone sulfate.

tween female and male SLE patients compared with their respective controls suggest that development of SLE in women is more closely related to gonadal sex steroid alterations. The results further suggest that a sex steroid enzyme abnormality in female lupus patients may predispose them to increased disease susceptibility, although increased mortality in females may be confounded by several nonhormonal factors. Supportive of the involvement of pituitary sex hormones in SLE are data that demonstrate aberrant prolactin levels in both female and male SLE patients. Abnormal provocative secretion of pituitary hormones (44,75) and aberrant regulatory pituitary secretagogues (74) further imply pituitary gland involvement in SLE hormonal aberrations. A better understanding of hormonal relationships in SLE could lead to novel and improved application of hormonal immunotherapy.

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APPENDIX A: THE HEDGES COMMON ESTIMATOR

The Hedges formulation is based on the usual *t*-statistic approach to testing for differences between the experimental (E) and control (C) group means. The pooled estimator of the SD is used for Hedges g:

$$s_p = \sqrt{\frac{(n_E - 1)s_E^2 + (n_C - 1)s_C^2}{n_E + n_C - 2}}$$

where s_E and s_C are the SDs from the experimental and control groups, respectively.

The Hedges estimator of the effect for the i^{th} study is:

$$g_i = \frac{\bar{Y}_{E_i} - \bar{Y}_{C_i}}{s_{p_i}}$$

where $\bar{Y}_E$ and $\bar{Y}_C$ are the sample means for the experimental and control groups.

Therefore, in a sense, g_i represents the standardized estimate of increase (decrease) in mean response over that of normal controls.

The variance of g_i is:

$$Var(g_i) = \frac{n_{E_u} + n_{C_u}}{n_{E_i} n_{C_i}} + \frac{g_i^2}{2(n_{E_i} + n_{C_i} - 2)}$$

The above formulae give g_i and $Var(g_i)$ for the i^{th} study. The combined estimator of the effect size is derived from the calculation above and summed over all studies using the following formula:

$$\hat{\delta} = \frac{\sum_{i=1}^{k} w_i g_i}{\sum_{i=1}^{k} w_i}$$

where the weight, w_i, is the inverse of the variance (weighted least squares)

$$w_i = \frac{1}{Var(g_i)}$$

The variance of the combined Hedges g estimator is:

$$Var(\hat{\delta}) = \frac{1}{\sum_{i=1}^{k} w_i}$$

The square root of the variance is the standard error, so a $100(1 - \alpha)\%$ confidence interval is computed:

$$\hat{\delta} \pm \frac{Z_{\alpha/2}}{\sqrt{\sum_{i=1}^{k} w_i}}$$

Thus, the Hedges common estimator provides a statistical measurement of effect size over a number of studies that, in and of themselves, do not arrive at a consistent conclusion.