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Sex Hormones and Prolactin Levels and Their Association with Anti Cardiolipin Antibody in Patients with Systemic Lupus Erythematosus

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ABSTRACT

Pathogenesis of systemic lupus erythematosus (SLE) is complex and multi-factorial. Among various suggested mechanisms for the disease, the hormonal theory has been considered as one of the most important mechanisms. Recently, the association of sex hormones with manifestations of antiphospholipid antibody syndrome (APLS) has been hypothesized. The aim of present study was to assess the serum levels of anticardiolipin antibody (ACA), sex hormones and prolactin in SLE female patients and their association with the disease.

This study comprised 40 SLE female patients and 41 healthy age-matched female subjects. For all patients and controls, the serum levels of ACA (IgG and IgM), estradiol, testosterone, progesterone, dehydroepiandrosterone sulfate (DHEA-S) and prolactin were measured by ELISA method.

Our study revealed that serum levels of testosterone, DHEA-S and progesterone were significantly lower in SLE patients than control (p<0.001). However, serum levels of estradiol and prolactin were significantly higher in SLE patients compared to controls (p<0.001). There was a significant difference between mild and moderate severity patients group for ACA positivity (95% CI 13.67-41.3; p=0.03). Also, SLE patients with positive ACA showed significantly lower (p<0.001) serum levels of testosterone, DHEA-S and progesterone and significantly higher (p<0.001) estradiol and prolactin serum levels compared to negative ACA patients.

The results of our study indicated that expression and metabolism of sex hormones and prolactin are different in female SLE patients compared to healthy subjects. It seems, change in serum levels of these hormones is related to higher SLE disease activity, increased thrombotic risks and increased renal involvement.

Keywords: Anticardiolipin antibody; Antiphospholipid syndrome; Sex hormones; Systemic lupus erythematosus

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INTRODUCTION

Systemic lupus erythematosus (SLE) is an acute and chronic autoimmune inflammatory disease characterized by overproduction of T helper type 2 (Th_2) cytokines. Symptoms of these diseases can affect many different body systems, including joints, skin, kidneys, blood cells, heart, and lungs. Anti-nuclear antibodies (ANA) are a group of autoantibodies against the cell nuclei and found in more than of 98% patients with systemic lupus. This laboratory test is the most sensitive diagnostic test for confirming the disease.

Females are more susceptible to the disease compared to men with a peak incidence during the reproductive years. The higher female-to-male ratio in SLE patients suggests a role for sex factors in modulation of the disease development.[1-3]A bulk of sex factors could be responsible for the higher susceptibility to SLE in females. Biologic differences between both sexes occur at genetic (X and Y chromosome -mediated), endocrinologic, metabolic, and environmental levels.[4,5] SLE demonstration during menstrual cycle suggested potential contributions of estrogens, androgens, and prolactin in the development of SLE.[6-9]

Sex hormones not only affect sexual differentiation and reproduction, but also influence the immune system. So, immune responsiveness in females may contribute to the greater susceptibility of women to autoimmune disease.[10-12]Sex hormones especially estrogen (also prolactin and testosterone) play important roles in these diseases.[13,14]It has been suggested that autoimmunity is associated with a breakdown of the neuroendocrine and the immune systems.[15] It seems that sex steroids differentially affect Th_1 and Th_2 cytokine production.[10,16]Estrogen enhances immunologic processes driven by CD4+ Th_2 cell activity. Autoimmune diseases mediated by Th_2 dominant immune-physiology are more prevalent in females.[17-20] Immunoregulatory actions of 17-estradiol (estradiol), testosterone, progesterone, dehydroepiandrosterone/dehydroepiandrosteronesulfate (DHEA/DHEA-S), and prolactin supports the modulatory role of sex hormones in the incidence and severity of the autoimmune disease.[3-9]

Studying the influence of gender on the pathogenesis of several autoimmune diseases through sex hormones provides a better understanding of the underlying mechanisms behind the sexual dimorphism of the immune system that may lead to the development of novel therapeutic approaches to autoimmunity.[21]SLE patients with low female sex hormone levels at disease onset have a lower relative risk of mortality compared to those patients with high female sex hormone levels.[22,23]

Recently, a hypothesis has been suggested that sexual hormones may be associated with manifestations of antiphospholipid antibody syndrome (APLS). This syndrome is defined by the presence of antiphospholipid antibodies in patients with a history of fetal loss and/or recurring venous and arterial thromboembolism.[24,25] The antiphospholipid antibodies comprise the lupus anti-coagulant, anticardiolipin (ACA) and anti-β2-glycoprotein I antibodies. The ACAs are detected by enzyme-linked immunosorbent assay (ELISA) and consist of IgG, IgM and IgA isotypes. IgG is strongly associated with thrombosis. The antiphospholipid antibodies can prolong phospholipid-dependent coagulometric tests including activated partial thromboplastin time. In patients with anti-phospholipid antibodies there is a higher risk of thromboembolic events compared to hemorrhagic events.[26,27]

The aim of the present study was to assess the serum levels of sex hormones and prolactin in SLE female patients, evaluating the role of these hormones in the pathogenesis and clinical expression of this disease. Also, the possible association between the presence of ACA (IgG and IgM) and sex hormones and prolactin levels was investigated in a sample of women with SLE at reproductive age.

MATERIALS AND METHODS

This study comprised 40 SLE female patients and 41 healthy female. The controls were age-matched with patients. l patients were recruited from Imam Reza Hospital of Kermanshah University of Medical Sciences. Fulfillment of 4 or more of 11 revised American College of Rheumatology (ACR) classification criteria of SLE was used as inclusion criteria for studying SLE patients.[2]

Pregnant patients, poly cystic ovary syndrome, breast feeding, menopausal volunteers, abnormal liver function tests (GOT, GPT or LDH), and thyroid function tests, concomitant presence of another autoimmune disease, or users of drugs that alter the circulating levels of sex hormones were excluded

from the study. Patients and controls were in their mid-menstrual cycle (day 5-14). According to declaration of Helsinki; informed written consent was obtained from all participants. For all patients and controls a full history, complete dermatological and physical examination was provided. Therapeutic history was carefully evaluated for all patients. The SLE activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). The active disease was defined as SLEDAI≥4, and inactive disease
was when SLEDAI<4(28). Active disease was divided in two groups, mild severity disease with SLEDAI 4-10 and moderate severity disease with SLEDAI 11-19.

Complete blood Count (CBC), erythrocyte sedimentation rate (ESR), complete urine analysis, estimation of total protein in 24 hours urine, renal function tests, anti-nuclear antibodies (ANAs) and anti-dsDNA antibodies were detected for SLE patients. Proteinuria ≥150mg/24h and/or creatinine≥1.5 were considered for renal involvement.

Hormonal assays for patients and controls were done after an overnight fasting in 0-6 days of menstrual cycle. Serum estradiol, testosterone, progesterone, DHEA-S and prolactin were measured by a microplate immunoenzymometric assay (Monobind Inc., Lake Forest, CA, USA) according to the manufacturer's instructions.

Positive or negative status of ACA (IgG and IgM) was assessed by Hemagen anticardiolipin kit (Hemagen Diagnostics, Columbia, USA). Values below 10 U GPL for IgG and below 10 U MPL for IgM were considered negative. The relative sensitivity of test was 95% with specificity of 100% (98% agreement when compared with the reference kit provided by the Antiphospholipid Standardization Laboratory). Based on these analyses, the patients were stratified into two groups: serum ACA-positive and serum ACA-negative (IgG or IgM).

The categorical variables were presented as absolute and percent relative frequencies. The quantitative variables were presented as mean±standard deviation when their distribution was symmetrical or as median and interquartile interval when their distribution was asymmetrical. Comparing quantitative variables was performed using the Student *t* test, for those parameters with asymmetrical distribution; Mann-Whitney test was used. The level of $p< 0.05$ was considered as significant. Data were analyzed using the SPSS software, version 16.0 (Chicago, IL, USA).

RESULTS

This study was conducted on 40 SLE female patients aged between 20 to 39 years. Median disease duration of the disease was5.8 years (from 2 to 10 years). Most of patients had SLE in remission phase or with mild activity as is presented by the SLEDAI scores (Table 1). Forty-one healthy female volunteers constituted the control group. The controls were age-matched with patients. The median of control group was 28.4±6.65 years old.

Our study revealed that serum levels of testosterone, DHEA-S and progesterone were significantly lower in SLE patients compared to controls ($p<0.001$). However, serum levels of estradiol and prolactin were significantly higher in SLE patients than control group ($p<0.001$).

Further, serum levels of testosterone, DHEA-S and progesterone were significantly higher ($p<0.001$) and serum levels of estradiol and prolactin were significantly lower ($p<0.001$) in SLE patients with mild severity of the disease compared to those with moderate severity (Table 2). A direct correlation between SLE severity and increased levels of estradiol and prolactin were observed. There was an inverse correlation between SLE severity and serum levels of testosterone, DHEA-S and progesterone (Figure 1).
There were 15 (37.5%) SLE patients with renal involvement that most of them (66.6%) had moderate severity disease with higher SLEDAI. There was a significant difference between the presence of renal involvement in moderate severity SLE versus mild severity SLE (95% CI 17.2-49.4; $p<0.01$). SLE patients with renal involvement showed significantly lower ($p<0.001$) serum levels of testosterone, DHEA-S and progesterone and significantly higher serum levels ($p<0.001$) of estradiol and prolactin compared to cases without renal involvement.

Table 1. Demographic and clinical characteristics of systemic lupus erythematosus patients.

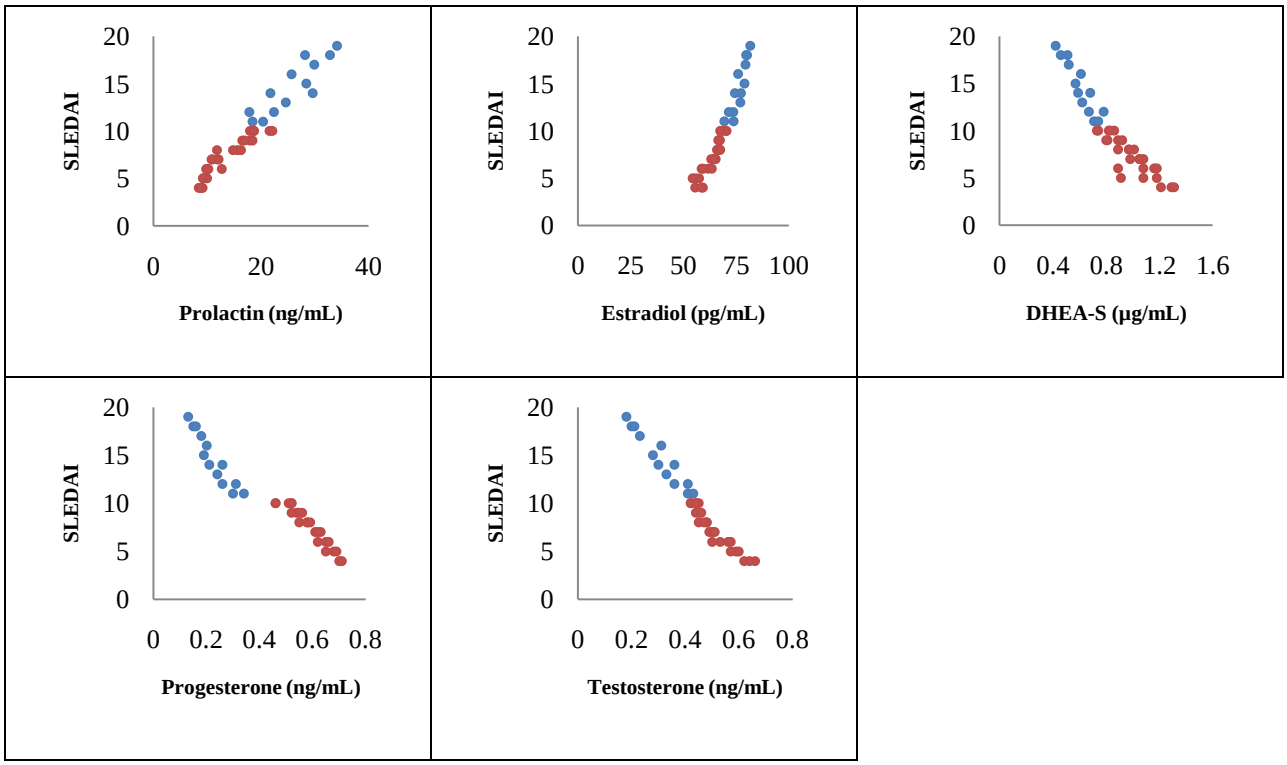
Parameters	SLE patients
Age, years (Mean±SD)	27.3±4.12
Duration of disease, years (Mean±SD)	5.8±3.21
Renal affection (%)	15 (37.5%)
Mild severity disease (4-10 SLEDAI)	27 (67.5%)
Moderate severity disease (11-19 SLEDAI)	13 (32.5%)

SLE: systemic lupus erythematosus
SLEDAI: systemic lupus erythematosus disease activity index

Table 2. Serum level of sex hormones and prolactin in systemic lupus erythematosus patients and control group

Parameters / Hormones	Total patients	SLE patients with mild activity of disease	SLE patients with moderate activity of disease	Controls
	N=40	N=27	N=13	N=41
Estradiol (pg/mL)	67.82±7.4	62.55±4.4	74.25±4.6	41.26±5.8
Prolactin (ng/mL)	17.61±7.2	12.34±3.2	24.06±5.3	5.98±1.8
DHEA-S (µg/mL)	0.86±0.2	1.03±0.1	0.66±0.1	1.96±0.2
Progesterone (ng/mL)	0.48±0.1	0.62±0.06	0.30±0.1	1.08±0.1
Testosterone (ng/mL)	0.44±0.1	0.52±0.07	0.34±0.9	0.80±0.08

SLE: systemic lupus erythematosus
DHEA-S: dehydroepiandrosterone sulfate



SLEDAI: systemic lupus erythematosus disease activity index
● Moderate severity● Mild severity

Figure 1. Serum level of sex hormones and prolactin according toSLEDAI

Also, SLE patients with renal involvement showed significantly higher SLEDAI compared to cases without renal involvement (p<0.001).

There were 11 SLE patients with positive ACA (IgG and/or IgM) that most of them (54.54%) had moderate severity with higher SLEDAI. There was a significant difference between patients with mild and moderate severity for ACA positivity (95% CI 13.67-41.3; p=0.03). Also, SLE patients with positive ACA showed significantly lower (p<0.001) serum levels of testosterone, DHEA-S and progesterone and significantly higher (p<0.001) serum levels of estradiol

and prolactin compared to patients negative for ACA. Further, in the ACA positive patients, there were more frequent renal complications. There was a significant association between positivity of ACA and renal involvement (95% CI 8.1- 34; $p<0.02$). Table 3 indicates parameters in patients stratified according to ACA (IgG and/or IgM) status.

Table 3. Characteristics of systemic lupus erythematosus patients according to anticardiolipin antibody (IgG or IgM) status

Parameters	ACA Positive	ACA negative	*p* value
Estradiol (pg/mL)	73.35±6.1	65.72±6.7	<0.001
Prolactin (ng/mL)	23.69±7.19	15.31±5.9	<0.001
DHEA-S (µg/mL)	0.68±0.1	0.93±0.2	<0.001
Progesterone (ng/mL)	0.35±0.1	0.52±0.1	<0.001
Testosterone (ng/mL)	0.36±0.1	0.48±0.1	<0.001
Renal involvement	9 (60%)	6 (40%)	0.02
Mild severity of the disease	5 (18.5%)	22 (81.4%)	0.03
Moderate severity of the disease	6 (46.1%)	7 (53.8%)	0.03

IgG: immunoglobulin G

IgM: immunoglobulin M

ACA: anticardiolipin antibody

DHEA-S: dehydroepiandrosterone sulfate

DISCUSSION

SLE is an autoimmune inflammatory disease with high incidence in females and peak of the disease occurrence during the reproductive years.[1-3,29]The pathogenesis of SLE is complex and multi-factorial. More attention has been focused on the role of hormones, especially sex hormones, in the pathogenesis of the disease. Although, hormones do not directly cause SLE but hormones might affect the risk of SLE through alteration in the function of immune cells and predisposition of individuals to the triggering effects of other genetic and environmental factors.[13,15,30]High mortality risk from this disease was observed in female SLE patients with high levels of sex hormones at disease onset.[22] Understanding the physiology of the interaction between sex hormones and immune function may provide new approach for treatment of the disease.[10]

Our study revealed that serum levels of testosterone, DHEA-S and progesterone were significantly lower and serum levels of estradiol and prolactin were significantly higher in SLE patients compared to controls (Table 3).

Estradiol as the most potent and predominant estrogen in serum, that is synthesized from testosterone by aromatization in gonadal steroid metabolic pathway,[31] has been suggested to be associated with development of SLE.[6,7] There are several studies that have determined serum estradiol levels in adult patients with SLE.[32-51]Few studies on adult female patients with SLE demonstrated a significantly increased serum estradiol levels in lupus patients compared withcontrols.[31]Lower estradiol levels in SLE patients compared with controls (at 2 different menstrual cycle points) has been observed, however, other studies showed no difference in the concentration of estradiol between patients and controls.[32]Serum estradiol levels change during the various phases of the menstrual cycle, in postmenopausal status, and in pre/postmenopausal status in patients with inactive or active disease.[32]However, considering females in all studies indicated a significantly higher level of estradiol in adult SLE patients compared with controls.[32] These findings could be interpreted by higher activity of aromatic hydroxylase or increased production of luteinizing hormone (LH) that drives testosterone aromatization in women.[52]Folomeevet al.[38] reported that aromatic hydroxylase activity has been increased in SLE patients, but enzyme activity was inversely related to SLE disease activity. Genotypic variations in the enzymes of gonadal steroid synthesis have not been identified in SLE patients, although abnormal metabolism of estrogen and testosterone, and the presence of differences in metabolic enzyme between women and men have been reported.[53-55]Lupus

patients have an increased ratio of 16α-to-2α hydroxylated estrogen metabolite that leads to production of more "feminizing" estrogens.[53,54] In addition, in female SLE patients the oxidation of testosterone is increased.[56]It seems the increased estradiol concentrations in female SLE patients could be a response to disease activity (e.g., inflammation-stimulated aromatase activity) or as the result of increasing LH release from the pituitary gland through the action of inflammatory cytokine[57-59] with increased aromatization and making estradiol as a marker for inflammation.

The true role of estrogens in the development or modulation of lupus has been investigated in several studies. In murine lupus, exclusive of prolactin stimulatory effects of estradiol physiologic concentrations of this hormone suppress autoimmune disease activity.[60] Further, estradiol concentrations are abnormally low in pregnant lupus patients compared with pregnant controls during periods of increased disease activity.[61,62] Therapeutic administration of non aromatizable androgens, compounds that could not convert to estrogen, does not improve and may worsen SLE disease activity,[63] and blockade of estrogen receptor with tamoxifen does not improve and may exacerbate SLE disease activity.[64]So, it needs a clear understanding of relationships between serum estradiol concentrations, steroid enzymes, metabolite effects, and disease activity in SLE.

Testosterone is the immediate precursor of estradiol. While some studies suggested a significantly decreased testosterone level in female patients with SLE compared with controls;[39] other studies failed to find a statistical significance.[38] Primary hypoandrogenism, hypopituitarism, accelerated catabolism or oxidation, hyperprolactinemia or combination of these conditions could result in significant serum testosterone suppression in female SLE patients. Testosterone could be considered as an immunosuppressive hormone since decreases immunoglobulin production from peripheral blood mononuclear cells (PBMCs) of both normal individuals and SLE patients.[65]

DHEA is an adrenal androgen that could be converted to progesterone, testosterone, and estradiol. Its primary form in the serum is DHEA-S (31). Significantly lower levels of DHEA or DHEA-S in serum of SLE patients compared with controls has been indicated in many studies[32] with a significant suppression of DHEA-S in patients compared with controls. Administration of DHEA to patients with SLE could bepotentiallytherapeutic,[66-70] that may exert its beneficial effects through increasing serum androgen levels[68]and also by elevating serum estradiol concentrations.[70]

Progesterone is an upstream precursor of testosterone and estradiol. In agreement with our study, Verthelyi et al. found progesterone concentration significantly lower in SLE patients compared to healthy controls.[41]Reduced levels of progesterone in SLE patients might be due to enhanced metabolism of it and the production of estradiol in female SLE patients, as a result of their primary multiple enzyme abnormalities.[32]Also, in pregnant SLE patients abnormal low serum progesterone concentrations have been documented during periods of increasing disease activity.[61] There are no available reports of the effects of removal of or supplementation with progesterone, although administration of combination estrogen/progesterone oral contraceptives may improve lupus disease activity.[63]In contrast to our study, Rastin et al,[66] showed no significant increase in the levels of serum progesterone in female SLE patients.

Our results showed a significant difference between serum prolactin levels in SLE patients compared to controls. In confirmation to our study, Abul-Saoud et al. found the mean of serum prolactin in SLE patients was higher than normal control group.[71]Estradiol stimulates prolactin secretion, and prolactin suppresses gonadal steroid synthesis.[32] Hyper prolactinemia in SLE patients might be resulted from stimulation of prolactin synthesis and release by estrogen, stimulation of prolactin secretion in the pituitary gland by cytokines and inflammatory mediators (IL1β, IL-6 and TNF- α).[32]Prolactin might stimulate lupus disease activity since serum prolactin level has been positively associated with disease activity. Also, abnormal high prolactin levels during pregnancy in SLE have been associated with disease activity.[63]Inplacebo-controlled human studies suppression of prolactin with bromocriptine decreased the SLE disease activity. Interestingly, bromocriptine not only suppresses prolactin levels but also through increased aromatization of testosterone enhances the estradiol concentrations. These observations suggest a complex interaction between these hormones in lupus and its disease activity.[32]

Since the prolactin gene is in close proximity to the

HLA complex,[72,73]genotype variations could increase predisposition to the disease in some subsets of SLE patients. Other reasons might be cytokine-stimulated pituitary prolactin release,[57,58] production of immune reactive prolactin peripherally, or aberrant pituitary prolactin secretion in lupus patients.[32]

SLE patients with renal involvement showed significantly lower serum levels of testosterone, DHEA-S and progesterone and significantly higher serum levels of estradiol and prolactin compared to those SLE patients without renal involvement. Also, SLE patients with renal involvement showed significantly higher SLEDAI compared to those without renal involvement. The kidney has receptors for prolactin and kidney damage or nephrectomy leads to hyper prolactinemia. Prolactin stimulates phagocytic function which mediates immune complex kidney damage.[32]

We found SLE patients with positive ACA had significantly lower serum levels of testosterone, DHEA-S and progesterone and significantly higher serum estradiol and prolactin levels compared to negative ACA patients. Moreover, in the ACA positive patients, there were more frequent renal involvement complications. Further, the present study assessed thrombotic events is correlated with the estradiol, other sex hormones and prolactin levels in a group of women with SLE at reproductive age. In confirm to our study, Abul-Saoudet al. found the mean of serum prolactin in SLE patients with ACA positive was higher than ACA negative SLE patients.[71]Our results showed that the presence of ACA in the serum was associated with higher estradiol levels. Our finding agrees with the suggestion that higher estrogen levels usually associate with the production of auto-antibodies.[74,75]

The results of our study demonstrated sex hormones and prolactin levels and metabolism are different in female SLE patients compared to healthy subjects. It seems, low serum levels of testosterone, DHEA-S and progesterone and high serum levels of estradiol and prolactin could be related to higher SLE disease activity, increase of thrombotic risks and higher renal complications. Knowledge of hormonal relationship in SLE could provide novel and improved application of hormonal immunotherapy.

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