

Influence of prolactin and estrogen on disease activity in patients with systemic lupus erythematosus

Marwa Mahmoud Abdelaziz^a, Samar H. Goma^a, Sohair K. Sayed^b,
Dina H. El-Hammady^c, Rania M. Gamal^d, Doaa Samir Sayed^e

^aLecturer of Rheumatology and Rehabilitation, Faculty of Medicine, ^bAssistant Professor of Clinical Pathology, Faculty of Medicine, Assiut University, ^cAssistant Professor of Rheumatology and Rehabilitation, Faculty of Medicine, Helwan University, ^dAssistant Professor of Rheumatology and Rehabilitation, Faculty of Medicine, ^eAssistant professor of Dermatology and Venereology, Faculty of Medicine, Assiut University, Egypt

Correspondence to Samar Goma, Assiut University, Assiut, Egypt
e-mail: samarhassanein2010@yahoo.com

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Objective

The objective of this paper is to evaluate the role of prolactin and estrogen levels on disease activity in patients with systemic lupus erythematosus (SLE).

Patients and methods

This study included 60 female patients with SLE, with a mean age of 33.5±13.12 years. It was conducted between November 2014 and October 2015. Disease activity was defined according to Systemic Lupus Erythematosus Activity Index; score of at least 6 was considered as an active disease. Prolactin (PRL) and estrogen levels and other serological markers of lupus disease activity, namely, complement 3,4 (C3 and C4), erythrocyte sedimentation rate, C-reactive protein, and anti-double-stranded DNA (anti-dsDNA) titer were calculated.

Results

Hyperprolactinemia was present in 25.0% of patients, and low estrogen level was present in 33.3% of patients. There was no significant correlation between either of estrogen or prolactin levels and all clinical and laboratory features, except for a significant positive correlation between anti-dsDNA and hyperprolactinemia.

Conclusion

There was no significant correlation between either of PRL or estrogen levels and Systemic Lupus Erythematosus Activity Index score. Overall, 80.0% of patients with hyperprolactinemia and 80.0% with low estrogen level had SLE activity. There was a significant difference in the frequency of further indicators of disease activity in SLE such as raised erythrocyte sedimentation rate, raised C-reactive protein, or decrease in complement factors with high serum PRL and low estrogen level.

Keywords:

estrogen, prolactin, Systemic Lupus Erythematosus Activity Index, systemic lupus erythematosus

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Introduction

Systemic lupus erythematosus (SLE) is a potentially fatal and severe chronic autoimmune disease that affects multiple organ systems. It is remarkably heterogeneous, with diverse and dynamic symptoms manifested by flares of disease activity [1]. Hormonal, infectious, and environmental factors have been implicated in the etiology of the disease [2].

SLE is a disease of young women, which occurs from infancy to old age, with peak occurrence between ages 15 and 40 years. Females are affected far more than males (6–10 : 1) [3,4]. It seems highly plausible that female sex hormones contribute to the pathogenesis of lupus based on the tendency for disease onset during the child-bearing years [5], increased numbers of flares during high hormonal states such as pregnancy [6] and ovulation-induction therapy, and remissions after menopause [7]. It has been proved that steroid hormones such as 17 β -estradiol, testosterone, prolactin, progesterone, and dehydroepiandrosterone influence immune system regulation [8,9] and the activity of SLE [10].

Prolactin (PRL) participates in a number of important functions in the body: performs as a hormone, mainly owing to its pituitary production, and acts as a cytokine. Prolactin is also secreted by immune cells and its receptor belongs to the family of cytokine receptors type 1 [11], and it may play a role in the pathogenesis and clinical activity of SLE and other autoimmune diseases in human and experimental animal models [12]. PRL secretion is inhibited by the hypothalamus through dopamine. Thyroid-releasing hormone, hypothyroidism, and adrenal insufficiency stimulate PRL secretion by inhibiting dopamine secretion. The main cytokines stimulating PRL secretion are interleukin (IL)-1, IL-2, and IL-6, whereas interferon- γ and endothelin 3 are inhibitory [13].

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The prevalence of hyperprolactinemia in the general population is lower than 5%. Nevertheless, the average prevalence of hyperprolactinemia in patients with lupus is 20–30%, varying from 8 to 69.7% [14]. There is controversy about the existence of a correlation between the disease activity and the concentration of serum PRL in SLE. Some authors reported these two parameters to be positively correlated [15,16], whereas others denied an association [17,18].

In the classical mechanism of steroid hormone action, estradiol diffuses into target cells and binds to estrogen receptors located in the nucleus. The ligand-activated receptors interact at specific DNA sites, termed estrogen response elements, along target genes and alter the rate of transcription [19]. Estradiol can both activate and repress genes within a given signal transduction pathway contributing to abnormal signal transduction in SLE T cells [20]. Grimaldi *et al.* [8] found that estrogens play an important role in B-cell maturation, selection, and activation and, thus, can potentially weaken the immune system. There are conflicting opinion in the literatures about the influence of estrogens on the development of SLE [8,9,21–23].

We aimed in this study to evaluate the role of PRL and estrogen levels on disease activity in patients with SLE.

Patients and methods

This was a cross-sectional study, conducted between November 2014 and October 2015. It included 60 female patients with SLE aged from 16 to 58 years with a mean age of 33.5 ± 13.12 years who were diagnosed according to the American College of Rheumatology Criteria [24]. The study was carried out with the approval of the responsible ethics committee and in accordance with national law and the Helsinki Declaration of 1975 (in its current, revised form). Informed consent was obtained from all patients.

Demographic characteristics, clinical manifestations, and autoantibody profile such as anti-double-stranded DNA (anti-dsDNA) were recorded. Disease activity was defined according to Systemic Lupus Erythematosus Activity Index (SLEDAI) [25]; score of at least 6 was considered as an active disease.

Besides clinical assessment, venous blood was taken for measurement of the PRL, estrogen levels, and other serological markers of lupus disease activity, namely, C3, C4, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and anti-dsDNA titer.

Patients with renal and/or hepatic failure, pregnancy, lactation, hypothyroidism, taking medications known to affect PRL level, or taking sex hormones (oral contraceptives, hormone replacement, etc.) were excluded from the analysis.

Laboratory investigations

Samples collection

The patients under investigation were fasting. Overall, 10 ml of venous blood was taken from all patients between 8:00 and 10:00 AM and divided into the following: 3 ml in sterile EDTA-containing tubes for complete blood counts (CBC), 1.6 ml in tubes containing 3.8% sodium citrate for ESR, and the remainder was left in plain tubes for spontaneous clotting at room temperature before being centrifuged at 3000 rpm for 10 min. Serum samples were kept at -20°C for the hormonal determination (PRL and estrogen) and further analysis.

Laboratory tests

Kidney and liver function tests and lipid profile were performed using a chemical analyzer Hitachi 911 (Boehringer Mannheim, Germany). CBC was detected by Beckman Coulter (Brea, California, USA) HMX. ESR was performed using Westergren method.

Complete urine analysis was done by reagent strip 10 parameters (Polypharma, Boulevard de la réunification DOUALA, CAMEROON), whereas protein in 24 h urine was measured on COBAS Integra 400 autoanalyzer (Roche, Grenzacherstrasse, Basel, Switzerland) and creatinine clearance was calculated [26].

C3 and C4 serum level was assessed using BN Prospec System (Siemens Healthcare GmbH, Henkestr, Erlangen, Germany). Anti-dsDNA IgG autoantibodies were performed by Alegria, LongfieldKent, England, DiaSorine, Stillwater, Minnesota, USA. Antinuclear antibodies (ANAs) were determined by the indirect immunofluorescence technique on Hep2 cells (HEP2 cell line substrate; Dia Sorine). C-reactive protein was detected by latex agglutination test kit (Biotec Laboratories Ltd, Dorset, UK). PRL and estrogen levels were detected by VIDAS (Biomérieux, Marcy l'Etoile, France).

Statistical analysis

Data were analyzed using the statistical package SPSS, version 21. Data were expressed as mean \pm SD, median, and frequencies. Group differences were compared by using *t*-test, one-way analysis of variance, χ^2 , Mann-Whitney *U*-test, and Fisher's exact test when applicable. Pearson's correlation coefficient (*r*) between variables was calculated.

Linear regression analysis was performed. Serum PRL level was used as the dependent variable. Probability levels below 0.05 were considered significant.

Results

In this study, 60 female patients with SLE were included. The mean age was 33.5 ± 13.12 (range: 17–58) years, and the mean duration of the disease was 5.23 ± 2.87 (range: 0.50–16) years. The mean PRL level of all patients was 19.55 ± 12.59 (range 4.70–70.6) ng/ml. The mean estrogen level of all patients was 57.9 ± 65.7 (range: 13.4–284.8) pg/ml.

Hyperprolactinemia (defined as a level >25 ng/ml) was present in 15/60 (25%) patients.

Low estrogen level (defined as a level <25 pg/ml) was present in 20/60 (33.3%) patients. There were menstrual disturbances in 40/60 (66.6%) patients.

We had 20 (33.3%) patients with low estrogen level, 40 (66.7%) patients with normal estrogen level, but no patients with high estrogen level.

Table 1 shows the demographic and clinical features of the normoprolactinemic and hyperprolactinemic groups of patients. Nonsignificant difference was observed between normal and hyperprolactinemic groups regarding different clinical features such as photosensitivity, malar rash, discoid rash, oral ulcers, arthralgia, arthritis, pluritis, nephritis, pericarditis, and central nervous system manifestations ($P > 0.05$).

Table 2 shows the laboratory and serological profiles of the normoprolactinemic and hyperprolactinemic groups of patients and SLEDI score. There was no significant correlation between PRL level and red blood cells, white blood cells, platelets, hemoglobin level, 24H protein, and creatinine clearance. However, a significant positive correlation was observed with

Table 1 Clinical features of SLE patients in normal and hyperprolactinemia

Item	Normal prolactin (n=45)	Hyperprolactinemia (n=15)	P value
1-Age	32.74 ± 11.80	32.50 ± 14.80	ns
2-Disease duration	4.83 ± 2.53	3.96 ± 1.79	ns
3-Photosensitivity	29 (64.4%)	11 (73.3%)	ns
4-Malar rash	39 (86.6%)	10 (66.6%)	ns
5-Discoid rash	9 (20.0%)	3 (20.0%)	ns
6-Oral ulcers	35 (77.7%)	12 (80.0%)	ns
7-Arthralgia	38 (84.4%)	12 (80.0%)	ns
8-Arthritis	16 (35.5%)	6 (40.0%)	ns
9-Nephritis	30 (66.6%)	12 (80.0%)	ns
10-Pluritis	13 (28.8%)	2 (13.3%)	ns
11-Pericarditis	4 (8.8%)	3 (20.0%)	ns
12-CNS manifestations	8 (17.7%)	4 (26.6%)	ns

CNS, central nervous system; n, number; ns, nonsignificant.

Table 2 Laboratorial features of SLE patients in normal and hyperprolactinemia

Item	Normal prolactin (n=45)	Hyperprolactinemia (n=15)	P value
1-RBCs	3.99 ± 0.71	3.65 ± 0.65	ns
2-WBCs	5.81 ± 2.92	4.41 ± 1.46	ns
3-Platelets	247.80 ± 89.55	281.38 ± 79.82	ns
4-Hb	10.42 ± 1.78	10.31 ± 1.36	ns
5-ESR	36.00 ± 28.27	54.00 ± 14.06	ns
6-Elevation of ESR	30 (66.6%)	10 (66.6%)	ns
7-24 protein	1006.60 ± 1154.246	1929.59 ± 1359.15	ns
8-Cr. clearance	94.95 ± 38.54	67.42 ± 50.53	ns
9-Anti-dsDNA	78.11 ± 35.17	148.94 ± 96.62	<0.05
9-Low complement	30 (66.6%)	11 (73.3%)	ns
10-Elevation of CRP	30 (66.6%)	10 (66.6%)	ns
11-SLEDAI score	13.04 ± 6.40	16.62 ± 9.14	ns
<6	11 (24.4%)	3 (20.0%)	ns
≥ 6	34 (75.5%)	12 (80.0%)	ns

Anti-dsDNA, anti-double-stranded DNA; Cr. clearance, creatinine clearance; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; n, number; ns, nonsignificant; RBCs, red blood cells; SLEDAI, Systemic Lupus Erythematosus Activity Index; WBCs, white blood cells.

anti-dsDNA ($r=0.387$, $P<0.05$). Correlation was also tested between the PRL level and other serological markers of lupus activity. Again, no significant correlation could be demonstrated between PRL level and C3 ($r=0.234$, $P=0.190$), C4 ($r=0.208$, $P=0.531$), and ESR ($r=0.277$, $P=0.124$). On the basis of SLEDAI, 45/60 (75%) patients were identified with lupus activity ($\text{SLEDAI} \geq 6$); there was no significant correlation between PRL level and SLEDAI score ($r=0.177$, $P=0.323$). Overall, 12/15 (80%) patients with hyperprolactinemia had SLE activity.

Table 3 shows the demographic and clinical features of the groups of patient with normal and low estrogen level. There was no significant correlation between the estrogen level and all clinical features ($P>0.05$). Table 4 shows the laboratory and serological profiles of the normal and low estrogen groups of patients and SLEDAI score. There was no significant correlation between estrogen level and red blood cells, white blood

cells, platelets, hemoglobin level, 24H protein, creatinine clearance, and anti-dsDNA.

Correlation was also tested between the estrogen level and other serological markers of lupus activity. Again, no significant correlation could be demonstrated between estrogen level and C3, C4, and ESR. There was no significant correlation between estrogen level and SLEDAI score. Overall, 16/20 (80%) of low estrogen patients had SLE activity.

There was a significant difference in the frequency of several clinical manifestations and serological parameters between patients with SLE with normoprolactinemia and hyperprolactinemia (malar rash, discoid rash, nephritis, pleuritis, pericarditis, and central nervous system manifestations). Also, there was a significant difference in the frequency of several clinical manifestation parameters between patients with SLE with normal and low estrogen level (malar rash, oral ulcers, arthralgia, arthritis, pericarditis, and elevation of

Table 3 Clinical features of SLE patients As regards estrogen level

Item	Normal estrogen (n=40)	Low estrogen (n=20)	P value
1-Age	28.23±10.57	39.55±12.05	ns
2-Disease duration	3.66±1.57	6.64±2.39	ns
3-Photosensitivity	28 (70.0%)	14 (70.0%)	ns
4-Malar rash	36 (90.0%)	14 (70.0%)	ns
5-Discoid rash	8 (20.0%)	3 (15.0%)	ns
6-Oral ulcers	34 (85.0%)	15 (75.0%)	ns
7-Arthralgia	32 (80.0%)	18 (90.0%)	ns
8-Arthritis	17 (42.5%)	4 (20.0%)	ns
9-Nephritis	27 (67.5%)	14 (70.0%)	ns
10-Pluritis	10 (25.0%)	6 (30.0%)	ns
11-Pericarditis	8 (20.0%)	0 (0%)	ns
12-CNS manifestations	7 (1.5%)	4 (20.0%)	ns

CNS, central nervous system; n, number; ns, nonsignificant.

Table 4 Laboratorial features of SLE patients As regards estrogen level

Item	Normal estrogen (n=40)	Low estrogen (n=20)	P value
1-RBCs	5.16±0.47	4.40±0.57	ns
2-WBCs	5.17±2.68	6.06±2.73	ns
3-Platelets	267.13±94.17	226.55±65.11	ns
4-Hb	11.59±1.68	10.35±2.08	ns
5-ESR	38.00±25.13	43.00±39.17	ns
6-Elevation of ESR	26 (65.0%)	13 (65.0%)	ns
7-24 protein	1091.56±304.97	1309.70±387.12	ns
8-Cr. clearance	108.06±35.54	72.22±13.98	ns
9-Anti-dsDNA	92.33±20.45	102.47±27.94	ns
10-Low complement	27 (67.5%)	15 (75.0%)	ns
11-Elevation of CRP	26 (65.0%)	14 (70.0%)	ns
12-SLEDAI score	13.14±6.15	15.45±9.04	ns
<6	10 (25.0%)	4 (20.0%)	ns
≥6	30 (75.0%)	16 (80.0%)	ns

Anti-ds DNA, anti-double-stranded DNA; Cr. Clearance, creatinine clearance; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; n, number; ns, nonsignificant; RBCs, red blood cells; SLEDAI, Systemic Lupus Erythematosus Activity Index; WBCs, white blood cells.

CRP). Low complement appeared to be more common in hyperprolactinemic and in low estrogen groups, although the difference did not reach statistical significance.

Discussion

SLE is a complex autoimmune disorder that develops in genetically prone individuals under the influence of various environmental factors. It is an autoimmune disease with a wide array of clinical manifestations. It is characterized by the production of antibodies to components of the cell nucleus [3,4]. We aimed in this study to evaluate the role of prolactin and estrogen levels on disease activity in patients with SLE.

Hyperprolactinemia in patients with SLE may be caused by either enhanced secretion of pituitary PRL under the effect of inflammatory cytokines [27] or increased production of PRL by peripheral lymphocytes [28]. The immune complexes of PRL-anti-PRL (which are the macroprolactins) are not biologically active, as their large size interferes with transversing the capillary walls to reach target tissues. Delayed clearance of the PRL-IgG complex may account for increased serum levels of PRL in these patients [29]. A high number of patients with SLE were found to be hyperprolactinemic [30], but there is a controversy about the existence of a correlation between disease activity and the concentration of serum PRL in patients with SLE.

Most studies point to a positive correlation between PRL and SLE activity [15,16,31]. Yang *et al.* [32] proved that the serum level of PRL was increased in the patients with active SLE compared with patients with inactive SLE and that the serum level of PRL was closely related to SLE disease activity. In the study by Zahra *et al.* [33], mild to moderately elevated PRL levels were found in 10/30 (33.3%) of patients with SLE, and there was significant association between high PRL levels and clinical disease activity. Jacobi *et al.* [34] in their study revealed a positive correlation of the disease activity and the serum PRL concentration in patients with SLE. Patients with high disease activity had significantly higher serum PRL levels compared with patients with less active disease.

Other studies denied an association between PRL and SLE activity [35,36]. In a study by Pauzner *et al.* [37], mild hyperprolactinemia was found in 20/82 (24%) patients, and no association between hyperprolactinemia and clinical disease activity could be demonstrated. The study by Mansoor *et al.* [38] revealed that there was no significant correlation

between serum PRL levels and SLEDAI and other serological disease markers, namely C3, C4, and ESR. These disagreeing results about the correlation between PRL and SLE activity can be explained by the heterogeneity of the groups of patients studied, by the use of different index to measure SLE activity, by the inclusion of patients with variable disease duration and by the diverse methodologies used for PRL testing. The presence of hyperprolactinemia is associated with diverse autoantibodies like antinuclear antibody, anti-dsDNA, anticardiolipin and antimicrobial [39].

In our study, there was no significant correlation between PRL level and SLEDAI score ($r=0.177$, $P=0.323$). However, 12/15 (80%) patients with hyperprolactinemia and 34/45 (75.5%) patients with normoprolactinemia had SLE activity.

Antibodies directed toward nuclear antigens are characteristic of SLE, whereas anti-dsDNA antibodies are the hallmark for the disease [40]. Another finding suggesting a relationship between the serum PRL concentration and the disease activity in SLE is the positive correlation between the PRL level and the concentration of anti-dsDNA (IgG) [34]. Neidhart *et al.* [15] have shown these autoantibodies to be positively correlated with the serum PRL concentration in patients with SLE. In addition, Miranda *et al.* [41] reported a trend of anti-dsDNA-positive patients with lupus nephritis to be hyperprolactinemic compared with those who did not have anti-dsDNA antibodies. Zahra *et al.* [33] demonstrated that hyperprolactinemia in a subset of their patients correlated with high serum level of anti-dsDNA. Yang *et al.* [32] showed that increased serum levels of PRL were related to immunoglobulin and anti-ds-DNA antibody production. After treatment, the serum level of PRL was decreased with the reduction in the anti-ds-DNA antibody titer. This suggest that serum PRL might affect B-cell activation and antibody production, and that PRL might be implicated as a modulator of humoral immunity. Zhu *et al.* [42] showed a positive correlation in serum PRL levels and specific antibodies against dsDNA.

In our study, a significant positive correlation was observed between the serum PRL concentration with anti-dsDNA ($r=0.387$, $P<0.05$).

In addition, in the study by Jacobi *et al.* [34], the frequency of further indicators of disease activity in SLE, such as raised ESR or decrease in complement factors, was associated with high serum PRL.

In the study by Zhu *et al.* [42], a negative correlation was found between serum PRL levels and complement component C3.

In our study, there was a significant difference in the frequency of further indicators of disease activity in SLE such as raised ESR, raised CRP, or decrease in complement factors between normoprolactinemic and hyperprolactinemic patients. The influence of estrogens on the development of SLE remains unclear. Some studies underline the negative influence of these hormones on the immune system [8,9,21,43], especially in patients with some genetic predisposition [6,7], whereas others show the positive influence on health [22,23]. In one study, the hormonal replacement therapy was associated with SLE development. No association was found when analyzing the risk for SLE among oral contraceptive users [44]. Others studies have reported that there was a group of female affected with SLE in which the use of hormonal replacement therapy or oral contraceptive did not cause SLE exacerbation, but in a few number of patients with SLE, it did [45,46]. There are different opinions about the disease activity influence on ovarian function. Some studies stressed the relationship between SLE activity and menstrual cycle disturbances; in other studies, this fact was not confirmed [47,48]. In patients with SLE, the aromatic hydroxylase activity was found to be increased, which may partially explain the abnormalities of peripheral estrogen metabolism observed in these patients [49]. Concerning serum 17 β -estradiol (E2), its levels were reported to be increased, normal, or low in patients with SLE [43,50]. In the study by Shabanova *et al.* [51], the decrease of E2 level was dominant, and only in 2% of patients, its increase was observed. An investigation from Munoz *et al.* [50] obtained similar results: in SLE women during luteal phase of menstrual cycle, progesterone and E2 levels were decreased.

In our study, there were menstrual disturbances in 40/60 (66.6%) patients. We had 20 (33.3%) patients with low estrogen level, 40 (66.7%) patients with normal estrogen level, but no patients with high estrogen level.

There was no significant correlation between estrogen level and SLEDAI score; however, 16/20 (80%) of low estrogen patients and 30/40 (75%) of normal estrogen patients had SLE activity.

There was a significant difference in the frequency of further indicators of disease activity in SLE such as raised ESR, raised CRP, or decrease in complement

factors between patients with normal and low estrogen level.

In conclusion, this study demonstrate that no significant correlation existed between either of hyperprolactinemia or estrogen level and SLE disease activity. However, 80% of hyperprolactinemic and 80% of low estrogen patients had SLE activity.

There was a significant difference in the frequency of further indicators of disease activity in SLE such as raised ESR, raised CRP, or decrease in complement factors with high serum PRL and low estrogen level, and a significant positive correlation was observed between anti-dsDNA and hyperprolactinemia.

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Conflicts of interest

There are no conflicts of interest.

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