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RELATION OF SERUM PROLACTIN LEVEL TO SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE

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Background: Systemic lupus erythematosus (SLE) is an autoimmune disease that involves multiple organ systems. Prolactin accelerates the breakdown of immune tolerance by promoting the survival, maturation and activation of autoreactive B and T cells, dendritic cells and macrophages and may play a role in the pathogenesis of autoimmune diseases, including systemic lupus erythematosus. Premature cardiovascular disease is the leading cause of morbidity in lupus which may be directly associated with altered lipid metabolism in systemic lupus erythematosus patient.

Objective: To find out the relation of serum prolactin and lipid profile with systemic lupus erythematosus patients.

Methodology: This cross sectional study was conducted in the Department of Biochemistry, Dhaka Medical College, Dhaka from January 2017 to December 2017. In this study, fifty diagnosed patients of SLE (Group A) and fifty apparently healthy individuals (Group B) of both sexes were selected according to the selection criteria from Department of Medicine, Dhaka medical college hospital, Dhaka (Group A) and by personal contact (Group B). Baseline parameters (body mass index, blood pressure and fasting plasma glucose) of both groups were measured. Serum prolactin was estimated by enzyme immune assay.

Results: Out of 100 patients included in our study. Mean ± SD of serum prolactin level was significantly higher (p <0.001) in SLE patients (37.95 ± 18.47) ng/ml when compared to healthy controls (14.82 ± 2.86) ng/ml. Distribution of serum prolactin status in SLE patients shows among 50 patients 37 (74%) has hyperprolactinemia and 13 patients have normal prolactin level. Among age (mean ± SD), gender distribution and duration of disease of study subjects among groups. There were no significant differences in terms of age and gender between SLE patients and healthy subjects show homogenecity of both groups. Shows serum prolactin of the study subjects in both groups. Serum prolactin level was significantly higher in SLE patients than healthy individual. Serum prolactin showed significant positive correlation with SLE (p<0.001). In Group A thirty seven SLE patients had raised serum prolactin & thirteen had normal prolactin level. The correlation of serum prolactin with SLE. There was significant positive correlation of serum prolactin.

Conclusion: From present study it can be concluded that systemic lupus erythematosus is related to increased serum prolactin level and with dyslipidemia.

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INTRODUCTION

Systemic lupus erythematosus (SLE) is the prototypic multisystem autoimmune disorder with a broad spectrum of clinical presentations encompassing almost all organs and tissues [1]. The complex pathogenesis of SLE is characterized by immunological abnormalities including involvement of T-cells, dendritic cells and B-cell hyperactivity with auto-antibody production resulting in the formation of immune complexes causing organ damage in host tissues [2]. SLE primarily is a disease of young women, with a peak incidence between the ages of 15 to 40 and a female: male ratio of 6 to 10:1. The age at onset, however, can range from infancy to advanced age. In both pediatric and older onset patients, the female: male ratio is approximately 2:1.Systemic lupus erythematosus (SLE) is a rare disease with a prevalence that ranges from about 0.03% in Caucasians to 0.2% in Afro-Caribbean, although the prevalence varies with race, ethnicity and socioeconomic status [3].While the prevalence, severity, and outcome of the disease show considerable variation across the globe, there is little evidence to indicate its relative prevalence in Asia. However, clinical manifestations of the disease as observed in one study were of greater severity in Asia, with greater renal involvement in particular [4]. Prolactin (PRL) is produced by the anterior pituitary gland and has been primarily identified as a major stimulating factor for lactation in the postpartum period. PRL is mainly secreted by the lactotrophs, cells that constitute 20-50% of the anterior pituitary cells. There are also many extrapituitary sources of PRL, including lymphocytes, skin fibroblasts, the brain, the breast, the decidua, and prostate and adipose tissue cells [5]. Like cytokines, PRL functions not only in an endocrine hormone but also in a paracrine and autocrine manner. PRL is known to stimulate the humoral and cellular immune response. In relation to the immune processes, PRL accelerates the breakdown of immune tolerance by promoting the survival, maturation and activation of autoreactive B and T cells, dendritic cells and macrophages [6]. PRL is considered a cytokine for many reasons: it is secreted by immune cells; its

receptor belongs to the family of cytokine receptors type 1 (interleukins, erythropoietin, thrombopoietin, leptin, granulocyte macrophage colony stimulating factor, granulocyte colony-stimulating factor); it shares the intracellular signalization route with other cytokines [7]. The immune–neuroendocrine system participates in the pathogenesis and clinical expression of autoimmune rheumatic diseases. During inflammatory stimulation and active disease, the interaction between the hypothalamic–pituitary–adrenal, hypothalamic–pituitary gonadal, hypothalamic–pituitary– thyroid, and prolactin (PRL) axes with the immune system is evident. Therefore, the abnormal response of the immune–neuroendocrine system May participate in breaking immune cell tolerance [8]. Hyperprolactinaemia has often been associated with autoimmune conditions such as RA, MS, autoimmune thyroiditis, myasthenia gravis and diabetes mellitus. However, the dynamic changes of PRL in SLE patients are not clearly defined [9]. Moreover, the presence of PRL may reflect an abnormal communication between the immune system and the neuroendocrine system in active SLE. Lymphocytes from patients with active SLE produce increased amounts of PRL. This extrapituitary PRL may participate in abnormal immune processes in SLE. There is exciting new evidence that high PRL in SLE may be explained by stimulation of pituitary PRL secretion by cytokines. The interactions between PRL, cytokines, autoantibodies and organ involvement suggest that PRL participates in local and generalized immune and inflammatory processes and acts as a bridge between the neuroendocrine and immune systems in SLE 10].

METHODOLOGY

Study design: A cross sectional study.

Study period: January 2017 to December 2017.

Place of study: Department of Biochemistry, Dhaka Medical College, Dhaka, Bangladesh.

Study population: Diagnosed cases of systemic lupus Erythematosus.

Sample size: One hundred (100)

Grouping of subjects: Group A- 50 diagnosed systemic lupus Erythematosus Patients Group B- 50 Apparently healthy Individuals.

Inclusion Criteria:

For study group

- Diagnosed case of SLE on the basis of 2015 ACR/SLICC revised criteria for diagnosis of SLE (Appendix II) by Department of Medicine, Dhaka Medical College, Dhaka.
- Sex: Both male and female.
- Age between 18-44years.

For control group:

- Healthy subjects with age between 18-50years

Exclusion Criteria:

- Pregnant and lactating women.
- Known case of liver diseases & renal diseases (other than SLE).
- Patients taking lipid lowering drugs & any drugs that affects prolactin level (Bromocriptine, SSRI, Phenothiazine).

In this cross-sectional study, by purposive sampling, 100 (one hundred) individuals were enrolled. A total of 50 (fifty) diagnosed SLE patients (Group A) were selected according to 2015 ACR/SLICC revised criteria for diagnosis of SLE (Appendix-II) were from Department of Medicine, Dhaka Medical College Hospital. Fifty apparently healthy individuals (Group B) were selected according to the selection criteria from hospital premises by personal contact among nurses, doctors & patient's attendants. The objectives, natures, purpose and potential risk of all procedures used for the study were explained in details and informed written consent was taken from both the patients and healthy individuals. Initial evaluation of the patients by history and clinical examination were performed and recorded in the preformed data collection

sheet (Appendix-V). Proper counseling of SLE patients and their attendants were done and SLE patients were requested to be on at least 8 hours overnight fast till collection of blood sample on the next day morning, as well as healthy individuals were also counseled and requested to come on next day following 8 hours overnight fast. Base line parameters such as BMI & blood pressure were measured. Then with all aseptic precaution, blood samples were collected to estimate serum prolactin, FPG. Collection and preservation of blood samples: With all aseptic precautions, 6 ml fasting venous blood sample was collected from median cubital vein of each study participant by disposable syringe in the early morning after an overnight fast for at least 8 hours. The needle was detached from the nozzle and 2ml blood was transferred in NaF containing test tube for the estimation of plasma glucose. Rest 4 ml blood from the syringe was transferred into a dry, clean and plain test tube with a gentle push to avoid hemolysis, test tubes were labeled and coded for identification and kept in slanting position till formation of clot, then centrifuged at 3000 rpm for 5 minutes and the separated serum was kept in labeled eppendorf after proper labeling. From each eppendorf about 25µL of serum was used for prolactin, 10µL for TC, 10 µL for TG, 200µL for HDL-C and 10µL for blood glucose estimation. Serum prolactin was measured by enzyme immune assay.

Laboratory Methods: All the analytical measurements were done in the Department of Biochemistry, Dhaka Medical College, Dhaka**.**

Serum prolactin (PRL): Serum prolactin was estimated by enzyme immune assay [11]. Normal value: Haring et al. [12]. In females: 4-23ng/ml or mcg/L (non-gravid/non-lactating). In males: 2-18 ng/ml or mcg/L.

Data analysis: All data were recorded in a predesigned data collection sheet. Continuous variables were expressed as mean ± SD and were compared between groups of patients by unpaired student's t' test. Categorical variables were compared using Fisher's exact test and were presented as absolute frequencies with percentages. Spearman's rank correlation coefficient (r) tests were performed to compare relationship between parameters and SLE. Level of significance was defined as p value <0.05 at 95% confidence interval. All analysis was done using the SPSS version 22 package for windows.

RESULTS

The present study 'Association of Serum prolactin and Systemic lupus erythematosus patients' was a cross sectional analytical study, which was conducted in the Department of Biochemistry, Dhaka Medical College, Dhaka. The study was aimed to see the association of serum prolactin and systemic lupus erythematosus patients.

Table-1: Age and gender distribution of the subjects in both groups (N=100)

Parameters	**Group A** (n=50)	**Group B** (n=50	**p value**
Age in years (mean ± SD)	33.38 ± 7.88	32.22 ± 8.03	0.468[a]
Sex%			
Male	4(8)	6 (12)	0.741[b]
Female	46 (92)	44 (88)	
Duration of disease in years (mean ± SD)	3.68 ± 1.13		

a =Unpaired Students 't' test was performed to compare between the groups. b =Fisher's exact test was performed to compare male and female between the group.

Values within the parenthesis indicate in percentage.

Group A: SLE patients.

Group B: Apparently healthy individual. Level of significance $p < 0.05$

Table 1 shows age (mean ± SD), gender distribution and duration of disease of study subjects among groups. There were no significant differences in terms of age and gender between SLE patients and healthy subjects show homogenecity of both groups.

Table 2: Prolactin level in systemic lupus erythematosus and control groups (N=100)

Parameters	**Groups**		**p value**
	Group A (n=50) mean ± SD	**Group B (n=50) mean ± SD**	
Serum Prolactin (ng/ml)	37.95 ± 18.47	14.82 ± 2.86	**<0.001***

Unpaired student's t' test was done to measure the level of significance.

*= significant

Table 2 shows serum prolactin of the study subjects in both groups. Serum prolactin level was significantly higher in SLE patients than healthy individual.

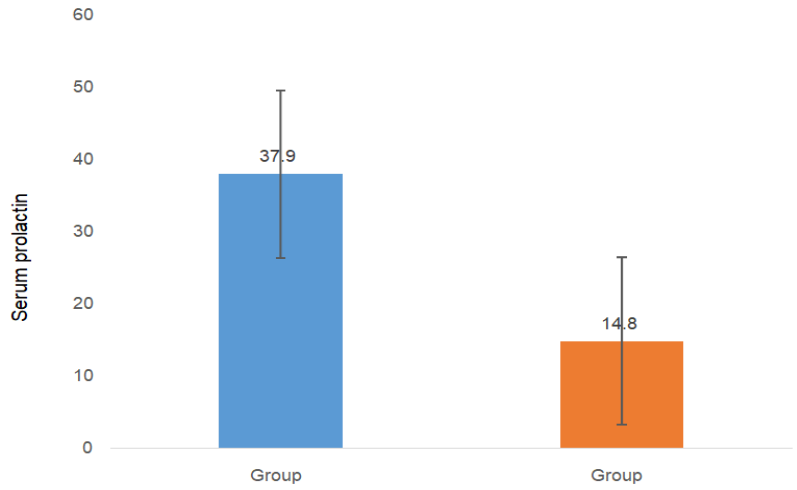

Figure 1: Simple bar diagram showing serum Prolactin status of study subjects in both groups.

Table 3: Distribution of group A patients according to prolactin status (N=50)

Parameter	**n= 50**	**Percentage (%)**
Hyperprolactinemia (Male > 18ng/ml) (Female> 23ng/ml)	**37**	**74**
Euprolactinemia (Male 2-18ng/ml) (Female 4-23ng/ml)	**13**	**26**

Table 3 shows in Group A thirty seven SLE patients had raised serum prolactin & thirteen had normal prolactin level.

Table 4: Correlation of serum prolactin with SLE (N=50)

	Study parameters	**r value**	**P Value**
SLE	**Serum Prolactin (ng/ml)**	**+0.751**	**<0.001***

Spearman's correlation coefficient (r) test was performed to measure the level of Significance.
* = significant, Level of significance $p < 0.05$

Table 4 shows correlation of serum prolactin with SLE. There was significant positive correlation of serum prolactin.

DISCUSSION

SLE is the prototypic multisystem autoimmune disorder with a broad spectrum of clinical presentations encompassing almost all organs and tissues. The extreme heterogeneity of the disease has led some investigators to propose that SLE represents a syndrome rather than a single disease. The exact pathological mechanisms of SLE remain elusive. The etiology of SLE is known to be multifactorial, involving multiple genes, sex hormones, and environmental factors including sunlight, drugs, and infections [13].The present study was undertaken to observe the serum prolactin and lipid profile in patients with systemic lupus erythematosus. For this purpose, 50 diagnosed systemic lupus erythematosus patients were considered as group A and age and gender matched 50 apparently healthy individuals were included in group B. Female are found to be more affected than male may be due to pathogenic effects of estrogen and X-chromosome-linked disease susceptibility. In this study, there were no statistically significant differences in terms of mean BMI (kg/m^2), FPG (mmol/l) and DBP (mm of Hg) among both groups but mean SBP (mm of Hg) in SLE patients were significantly higher as compared to healthy subjects ($p < 0.001$). Almost similarly as Bhat et al., [14] who found significant differences in terms of systolic blood pressure in between groups ($p < 0.001$). But it disagrees with studies with Hatef -Fard et al., [15] who found BMI, FPG, SBP & DBP higher significantly in SLE patients. He stated that might not be related to disease but also aggravated by due to physical inactivity & diet habit. In present study, mean ± SD of serum prolactin level in group A and group B were 37.95±18.47 ng/ml and 14.82 ± 2.86 ng/ml. Serum prolactin was found significantly higher ($p < 0.001$) in group A when compared to group B. These results were in agreement with studies done by Kandasamy et al., [16], Iqbal et al., [17], Zhu et al., [18], Zamora-Ustaran et al., [19] and Yang et al.,[20]. They observed significant increase of serum prolactin in patients with systemic lupus erythematosus compared to others. There is a study done by Karimifar et al., [7] whose findings shows no association of higher serum prolactin in the mean prolactin level of systemic lupus erythematosus patients (12.2 ± 5.1 ng/ml) which was inconsistent with present study. The disagreeing results about the correlation between PRL and SLE 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 prolactin testing. Distribution of serum prolactin status in Systemic lupus erythematosus patients shows 50 patients 37 (74%) has hyperprolactinemia (serum prolactin level > 18ng/ml in male and >23ng/ml in women) and 13(26%) normal prolactin level, which agrees with studies Zhu et al., [18] and Zamora-Ustaran et al.,[19]. Spearman's rank correlation test was done to observe relationship between serum prolactin and with SLE which shows statistically strong significant ($r=+0.751$, $p<0.001$) positive correlation between serum prolactin and SLE. This finding is almost similar to the study result of Iqbal et al., [17] showing ($r =+0.729$ & $p <0.001$). This controversy 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

indices to measure SLE activity, by the inclusion of patients with variable disease duration, and by the diverse methodologies used for PRL testing [21]. This was against the findings of Karimifar et al [7] who found that there was a significant difference in the frequency of several clinical manifestations (renal involvement and hematological manifestations) and between patients with SLE with normoprolactinemia and those with hyperprolactinemia, where P values were 0.002 and 0.02, respectively. However, the study by Jokar et al. [22] found no significant differences when the frequency of SLE clinical and serological features was compared among hyperprolactinemic and normoprolactinemic groups. Our study and the publications that suggest that there is no alteration in pituitary PRL secretion in patients with SLE reinforce the hypothesis that the increase of PRL in some patients was because of the local production by immune cells. The analysis of the aforementioned data suggests that chronic inflammation may affect serum PRL concentration. However, serum PRL levels are not likely to be used as a marker of the disease activity in patients with SLE.

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Conflicts of interest: There are no conflicts of interest.

CONCLUSION

In conclusion, the study demonstrates that hyperprolactinemia and dyslipidemia are related with systemic lupus erythematosus. Therefore, it is advocated that regular screening of serum prolactin level along systemic lupus erythematosus patients might help to reduce severity of flare up and involvement of major organ and prevent complication of dyslipidemia.

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