Original Article

Rheumatoid Arthritis and SLE in Females

Serum Prolactin: Biochemical Parameter for Assessing Disease Severity among Rheumatoid Arthritis and Systemic Lupus Erythematosus

Tehseen Iqbal, Syed Danish Haseen Ahmed, Sadia Ikhlaq Sheikh, Fauzia Imtiaz and Muhammad Ahsan

ABSTRACT

Objective: To find out the role of serum prolactin as a biochemical parameter for assessing the disease severity in female suffering from rheumatoid arthritis and systemic lupus erythematosus.

Study Design: Observational / case-control Study.

Place and Duration of Study: This study was conducted at the Basic Medical Sciences Institute, Jinnah Postgraduate Medical Centre, Karachi from January 2014 to June 2016.

Materials and Methods: A total of 105 female subjects of fertile age were included in this study, comprising of 35 newly diagnosed cases in each group of SLE and RA, while 35 healthy controls were enrolled for comparison. All the RA and SLE cases were diagnosed by using selection criteria based on American Rheumatology Association. Disease severity was measured by principally using Duke Severity of Illness score (DUSOI), while serum prolactin was analyzed by ELISA.

Results: Significantly higher disease severity, ESR and serum prolactin was found among SLE subjects when compared to both RA and control groups. Similarly, serum prolactin and ESR was found significantly higher among subjects in RA group when compared to controls. Statistically significant strong positive correlation of serum prolactin with disease severity in both RA and SLE subjects having r value (Spearman's correlation) of 0.686 and 0.729 were observed respectively.

Conclusion: In this study, statistically significant strong correlation of serum prolactin with disease severity confirms the role of prolactin as a biochemical parameter for assessing the disease severity among RA and SLE subjects. In addition, our findings also suggest that the therapeutic modulation of prolactin secretion may also help to decrease the disease severity among RA and SLE subjects.

Key Words: Prolactin, Autoimmune Diseases, Systemic Lupus Erythematosus, Rheumatoid Arthritis

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INTRODUCTION

Prolactin is a polypeptide hormone containing 199 amino acid residues secreted by the anterior pituitary[1]. It is primarily known for stimulating growth of mammary glands and maintaining lactation after childbirth. However, it also plays an important role in regulation of immune response, osmotic pressure, metabolism, behavior, and reproduction[2].

Department of Biochemistry, Dow University of Health Sciences, Karachi.

Correspondence: Dr. Syed Danish Haseen Ahmed, Associate Professor, Department of Biochemistry, Dow University of Health Sciences, Karachi.
Contact No: 0333-2352754
Email: danish-haseen@duhs.edu.pk

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Prolactin binds with its cognate receptor PRLr to manifests its physiological actions via autocrine, paracrine and endocrine[3]. Prolactin is not only secreted from pituitary but there are other extra-pituitary sites that are also responsible for its production[4]. This includes endothelium, brain cells, endometrium, prostate, skin and more importantly the immune system. The prolactin secreted from extra-pituitary cells has different biological activity due to variation in post-translational modifications[5].

Autoimmune diseases like rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are illnesses that occur when the body is mistakenly attacked by its own immune system[6]. In RA auto antibodies are formed against IgG that causes chronic inflammation of the joints and tissue around it. These auto antibodies are called rheumatoid factor and are of the IgM class. RA affect primarily women between the ages of 30 and

50 years. People with HLA-DR4 genes are predisposed to RA, the agents that induces these auto antibodies is unknown[7]. Similarly, SLE is an immune complex mediated disease in which auto antibodies are formed against DNA, histones, nuclear proteins and other component of the cell nucleus. Antibodies against double stranded DNA are the hallmark of SLE. The prevalence of RA and SLE in Pakistan is largely unknown, however the global prevalence of RA was estimated to be 0.24%[8], while the prevalence rate of SLE among Asian countries like China, India and Japan was found to vary from 30 to 50/ 100.000 population[9].

Hyperprolactinemia, other than causing galactorrhea, delayed puberty and disturbed menstrual cycles has also been linked with atherogenesis, various cancers including breast cancer, and autoimmune disorders[10]. Various research evidences have supported that elevation of serum prolactin participates in pathogenesis of autoimmune disease[7].The immune system, which is responsible for chronic autoimmune inflammatory diseases like RA and SLE is also an important site of extra-pituitary prolactin production[2]. In immune system Prolactin acts as a cytokine that is evident by the expression of both prolactin and its receptor in monocytes and lymphocytes, suggesting its role in auto and paracrine regulation[11].

Keeping in mind the disease burden and the role of prolactin in chronic autoimmune inflammatory diseases, the present study is aimed to find out the role of serum prolactin as a biochemical parameter for assessing the disease severity in female patients suffering from SLE and RA.

MATERIALS AND METHODS

This observational case-control study was conducted at the Basic Medical Sciences Institute, Jinnah Postgraduate Medical Centre, Karachi from January 2014 to June 2016. A total of 105 female subjects of fertile age were included in this study, comprising of 35 newly diagnosed cases in eachgroup of SLE and RA, while 35 healthy controls were enrolled for comparison. All the RA and SLE cases were diagnosed by using selection criteria based on American Rheumatology Association[12,13,14]respectively. Disease severity was measured by principally using Duke Severity of Illness score (DUSOI)[15]. DUSOI is based on a clinical judgment by a physician reflecting the severity of the disease. To match the score and compare RA with SLE, DUSOI was modified using method explained by Navarro-Cano et. al[16]. Subjects were examined and given scores on a scale of 0 to 4 each for symptoms, prognosis, treatability, and complications related to the disease. These four scores were then summed, divided by 16 and then multiplied by 100 to obtain the final score.

Subjects who were receiving steroid medication, hormone replacement therapy or contraceptive pills were excluded from the study. Likewise, Patients suffering from diabetes, liver diseases or any hormonal disorder were also excluded from the study. After informed consent, demographic data was recorded on a prescribed proforma. 5 ml of blood was collected after an overnight fast, which was centrifuged and serum was stored at -70 °C for later analyses. Prolactin was analyzed by using Monobind Accu-Bind Kit Product Code-725-300 by ELISA.Parameters were compared between groups and statistical significance was found by using one-way ANOVA. While post-hoc tukey's test was performed to see differences among the groups.Spearman's correlation was applied to explore the relationship between serum prolactin and disease severity.

RESULTS

Characteristics of subjects including demographic parameters, disease severity, ESR and serum prolactin are summarized in table.1. Raised ESR (> 20 mm/hr) and Hyperprolactinemia (> 29 ng/mL) was observed among females in RA and SLE groups. After comparison, statistically significant differenceswere observed among SLE, RA and controls.

Table No. 1: Comparison of Basic Demographic Parameters, Disease Severity, ESR And Serum Prolactin Between SLE, RA And Control Groups.

Parameters	SLE (mean ± SE) n=35	RA (mean ± SE) n=35	Control (mean ± SE) n=35	p-value
Age (yr)	23.48 ± 0.63†	31.45 ± 0.98	31.25 ± 0.88	0.00*
Age at menarche (yr)	12.74 ± 0.16	12.74 ± 0.18	12.54 ± 0.18	0.66
Parity	1.40 ± 0.18‡	2.82 ± 0.29	2.68 ± 0.27	0.00*
BMI (kg/m^2)	20.51 ± 0.31	21.80 ± 0.55	21.15 ± 0.41	0.11
Disease Severity (modified DUSOI)	62.48 ± 3.503†	37.97 ± 2.08	-	0.00*
ESR (mm/hr)	97.74 ± 3.13†	88.08 ± 2.06§	19.60 ± 1.02	0.00*
Serum Prolactin (ng/ml)	65.45 ± 4.08†	34.65 ± 1.01§	9.06 ± 0.59	0.00*

p-value was estimated by one way ANOVA, post-hoc tukey's test was performed to see differences among groups.* *p*-value < 0.05;† significantly higher in SLE group when compared to RA and controls; ‡significantly lower in SLE group when compared to RA and controls; §significantly higher in RA group when compared to controls.

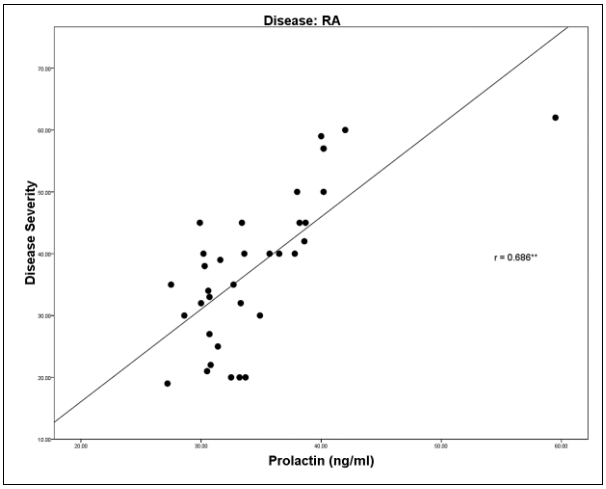

Figure No.1: Correlation between prolactin and disease severity in rheumatoid patients.

The scatterplot shows normal distribution of RA subjects. Data points were labelled as (●). Strength of association and relationship demonstrated by a linear trend line and values of correlation coefficient (r).

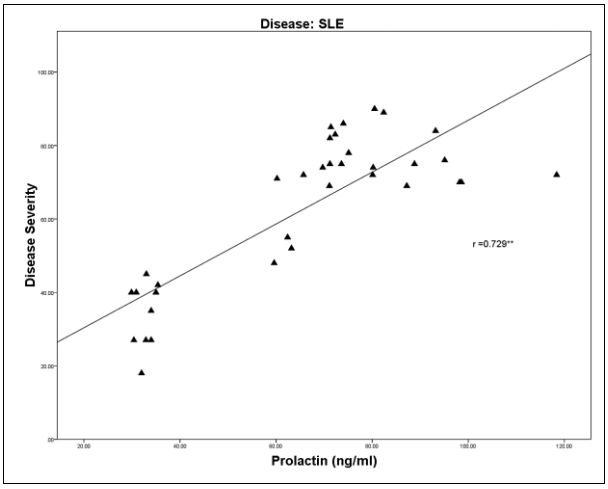

Figure No.2: Correlation between prolactin and disease severity in SLE patients.

The scatterplot shows normal distribution of SLE subjects. Data points were labelled as (▲). Strength of association and relationship demonstrated by a linear trend line and values of correlation coefficient (r).

Post-hoc Tukey's test revealed that subjects in SLE group found to be younger in age and have lower parity when compared to both RA and control groups. While significantly higher disease severity, ESR and serum prolactin was found among SLE subjects when compared to both RA and control groups. Similarly, serum prolactin and ESR was found significantly higher among subjects in RA group when compared to controls.Spearman's correlation was performed between variables to explore the possible relationship. A strong positive correlation of serum prolactin with disease severity in both RA and SLE subjects having r value (Spearman's correlation) of 0.686 and 0.729 were observed ($p<0.01$) (Figure 1 and 2).

DISCUSSION

The increasing burden of autoimmune diseases like RA and SLE have quizzed researchers to find newer modalities of treatment. Prolactin promotes autoimmunity by stimulating the immune system via disrupting the normal process of immunological tolerance among maturing B-cells towards self-antigen, enhances lymphocyte proliferative response to antigens and increase synthesis of cytokines, immunoglobulins, and autoantibodies[10].

The significant role of prolactin in the pathogenesis and severity of chronic autoimmune inflammatory diseases like RA and SLE among local population is demonstrated in our study by the higher serum prolactin levels among both RA and SLE subjects, while statistically significant strong correlation of serum prolactin with disease severity was also found. Other studies have also found higher prolactin levels and strong correlations between serum prolactin and disease severity of chronic autoimmune inflammatory diseases[17,18,19]. Contrary to findings of our study, fewer studies have also shown no correlation between serum prolactin and disease severity[20].

Various studies have indicated that prolactin act as immuno-stimulant and can directly influencedisease severity in chronic autoimmune inflammatory diseases[21]. Most immune cells secrete prolactin which stimulates proliferation, differentiation and maturation of T and B lymphocytes[22,23]. Not only the demonstration of higher serum prolactin among RA and SLE subjects but also higher prolactin levels in inflammatory tissue and synovial fluid with strong relation to disease activity suggests that the locally infiltrated immune cells, chondrocytes and fibroblasts secrete prolactin in higher amounts[19]. This locally produced prolactin in the inflammatory tissues stimulates the immune system and adjuncts by producing more inflammatory cytokines and matrix metalloproteinases leading to structural changes associated with RA and SLE[24].

Thus, the results of our study showing strong correlation between serum prolactin and disease severity among RA and SLE supports the hypothesis that serum prolactin may be used as a biochemical parameter to assess disease severity among RA and SLE subjects. However, the study design and small sample size warrant careful interpretation of the results. We further recommend multi-centric studies on larger population to establish the external validity.

CONCLUSION

In this study, statistically significant strong correlation of serum prolactin with disease severityconfirms the role of prolactin as a biochemical parameter for assessing the disease severity among RA and SLE subjects. In addition, our findings also suggest that the

therapeutic modulation of prolactin secretion may also help to decrease the disease severity among RA and SLE subjects.

Conflict of Interest: The study has no conflict of interest to declare by any author.

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