The Role of Prolactin as a Disease Activity Indicator in Some Rheumatic Diseases

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Abstract

Background: Autoimmune rheumatic diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and scleroderma, predominantly affect women and are characterized by systemic inflammation, leading to organ failure. Prolactin (PRL), a hormone produced by the pituitary gland and lymphocytes, significantly affects immune regulation and is implicated in the pathophysiology of these diseases.

Objectives: This study aimed to evaluate the relationship between PRL levels and disease activity in RA, SLE, and scleroderma.

Patients and methods: A cross-sectional case-control study involved 150 premenopausal women (50 with RA, 30 with SLE, and 20 with scleroderma) and 50 age-matched healthy controls. Clinical disease activity assessments (DAS28 for RA, SLEDAI for SLE, and MRSS for scleroderma) and laboratory estimation of serum PRL level were conducted.

Results: The mean PRL levels in RA (26.17 ng/ml), SLE (25.23 ng/ml), and scleroderma (32.07 ng/ml) were significantly higher than controls (15.48 ng/ml) ($P < 0.001$). 42% of RA patients, 30% of SLE patients, and 50% of scleroderma patients had elevated PRL levels. Hyperprolacinemia is correlated with disease activity (DAS28 ($r = 0.493$, $p = 0.0001$), SLEDAI ($r = 0.546$, $p = 0.002$), and MRSS ($r = 0.893$, $p = 0.0001$), respectively).

Conclusion: Serum PRL levels were significantly elevated in RA, SLE, and scleroderma, which is consistent with disease activity scores. Regular monitoring may be necessary because of the potential of PRL to function as a marker of disease activity. The therapeutic potential of dopamine agonists in autoimmune diseases warrants further investigation, as they have the potential to reduce flare-ups and organ involvement.

Keywords: Rheumatoid arthritis; Systemic lupus erythematosus; Systemic sclerosis; DAS28; SLEDAI.

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Introduction

Autoimmune rheumatic illnesses (rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and scleroderma) predominantly affect women and are characterized by systemic inflammation leading to organ failure**.** These diseases result from the breakdown of self-tolerance mechanisms in the immune system, where they react to autologous antigens in tissues and organs **(Marder et al., 2015).**

Prolactin (PRL), a polypeptide hormone produced by pituitary lactotrophs and lymphocytes, plays a significant role in immune system regulation. It controls the maturation of CD4-/CD8- thymocytes into mature CD4+/CD8+ T cells, increasing pro-B cell production **(Orbach and Shoenfeld, 2007).** PRL influences the local immune system, supporting immune cell maturation and autoreactive B-lymphocyte activity **(Fojtíková et al., 2010).**

PRL receptors, present in many cell types, are crucial for auto-reactivity and deletion, modification of apoptotic molecules, boosting humoral and cell-based immunity, and expanding costimulatory pathways. PRL also affects B-cell tolerance by preventing BCR-mediated clonal activation and reducing the threshold for anergic B-cell activation, increasing proinflammatory cytokine release, and T-cell cytotoxic activity **(Legorreta-Haquet et al., 2022).**

Clapp et al. (2016) proposed the PRL/vaso inhibin axis to play a role in RA pathogenesis. In the pathophysiology of rheumatic autoimmune illnesses, PRL is essential, as it regulates lymphocyte growth, antibody production, and cytokine release, disrupting B-lymphocyte tolerance mechanisms **(Mousavi et al., 2023).**

Elevated PRL levels have been reported in several systemic and organ-specific autoimmune disorders. This increase in PRL may result from enhanced PRL release from the anterior pituitary due to inflammatory cytokines that reduce suppressive dopamine levels **(Fojtíková et al., 2010).**

This study aimed to evaluate prolactin levels concerning disease activity in some rheumatic diseases (RA, SLE, and scleroderma).

Patients and methods

This hospital-based cross-sectional case-control study was conducted based on code **SVU/MED/PRR022/1/23/3/597**, from March 2023 to January 2024 in the outpatient clinic and inpatient department of physical medicine, rheumatology, and rehabilitation at Qena University Hospital.

Sample size calculation: the following simple formula was used to calculate the adequate sample size in the prevalence study:

$$n = \frac{Z^2 p(1-p)}{d^2}$$

Where n is the sample size, Z is the standard normal variant (at 5% type 1 error (P < 0.05) it is 1.96,

P (expected proportion in the population based on previous studies) = 56.9%, d (absolute error or precision) = 0.05.

The study involved 150 female patients with common rheumatic diseases, divided into four groups: 50 with RA, 30 with SLE, 20 with scleroderma or systemic sclerosis (SSc), and 50 healthy age-matched females as a control group.

Inclusion criteria: All participants were 18–50-year-old premenopausal women.

Exclusion criteria: Male patients, females under 18 or over 50, those with other causes of arthritis or autoimmune rheumatic diseases, diabetes mellitus, menopause, dopamine agonists, pregnancy, recent lactation, pituitary adenoma, thyroid and parathyroid disorders, certain antipsychotics, antiemetics, and hormonal contraception.

Group 1 included 50 patients with RA defined according to the 2010 ACR/EULAR criteria (**Aletaha et al., 2010).**

Group 2 included 30 patients with SLE diagnosed using the 2019 ACR/EULAR criteria **(Aringer et al., 2019).**

Group 3 included 20 patients with SSc diagnosed according to the 2013 ACR/EULAR criteria, where scleroderma-like illnesses were excluded **(van den Hoogen et al., 2013).**

Group 4 included a control group of 50 healthy age-matched women.

All subjects were evaluated for

Full personal data including name, age, residence, and special habits and patient's medical history, including visual disturbances, organic brain syndrome, seizures, psychosis, cerebrovascular accidents, severe persistent headaches, cardiopulmonary problems (dyspnea, cough, chest pain, lung fibrosis), vasculitis or Raynaud phenomenon, skin thickening, facial rash or photosensitivity, mucosal ulcers, and hair loss. Drug and family histories were recorded.

The systematic evaluation of the patients enclosed vital signs, pallor, jaundice, cyanosis, facial rash or photosensitivity in SLE, peripheral edema, arthritis, serositis, mouth ulcers, alopecia, and the central nervous, respiratory, cardiovascular, neurological, and gastrointestinal systems. The weight, and height were measured, and BMI was calculated.

Specific rheumatic diseases examinations assessed muscles and joints for arthritis (hotness, redness, swelling, discomfort, or limitation of mobility), synovitis, myositis, skin thickness, and fibrosis. Subcutaneous calcinosis, telangiectasia, skin hypo-/hyperpigmentation, active skin ulcers, and skin thickness measured using the modified Rodnan skin thickness score (MRSS) were specific assessments for SSc, in 17 body areas, on a scale from 0 (normal) to 3 (severe) for a total score (range 0–51) **(Lafyatis and Valenzi, 2022).**

Assessment of rheumatic disease activity scores

The disease activity score in 28 joints on both sides of the body (DAS28) and the erythrocyte sedimentation rate (ESR) are used to assess RA; based on the number of tender and swollen joints (TJC and SJC) in 28 joints, and the patient's overall health on a visual analog scale (0-100). Scores are interpreted as follows: < 2.5, remission; 2.5-5, moderate activity; and > 5, high activity **(Ton et al., 2012)**.

The SLE Disease Activity Index (SLEDAI) measures clinical symptoms and laboratory data across organ systems using 24 questions **(Gordon et al., 2018).** It rates organ participation from 1 to 8 (0-105). SLEDAI = 0, remission; 1-4, low activity; 5-10, moderate activity; and >10, high activity with clinical significance defined by increases of > 3 (flare), < 3 (improvement), and ± 3 (persistent activity) **(Fanouriakis et al., 2019).**

For SSc, the modified Rodnan skin score (MRSS), a semiquantitative score was used to evaluate the skin thickness at 17 different cutaneous sites (for a total score from 0 to 51) **(Lafyatis and Valenzi, 2022)**

Laboratory investigation

All patients provided 10 ml of venous blood during the follicular phase. Three ml placed in an EDTA tube for a complete blood count (CBC) using Celltac (Nihon Kohden, Rosbach, Germany), and the absolute numbers of platelets and neutrophils were divided by lymphocytes to calculate inflammatory indices, such as platelets to lymphocyte ratio (PLR) and neutrophils to lymphocyte ratio (NLR). 1.6 ml in tubes with 3.8% sodium citrate for ESR, and the rest in plain tubes for serum collection for chemistry analysis, and aliquots were maintained at -20 °C for the PRL assay.

An automated chemistry analyzer, Pentra c400 (HORIBA ABX SAS), was used to assess renal function, liver enzymes, and random blood glucose (RBG).

CRP level estimation using Beckman Coulter AU480, and semi-quantitative latex agglutination and indirect immunofluorescence were used to measure RF and anti-CCP levels in patients with RA.

Laboratory tests for serum PRL were performed using Calbiotech prolactin ELISA kits and a solid-phase double-antibody sandwich immunoassay. The PRL level was typically ≤ 25 ng/ml, with a reference range of 5-100 ng/ml and an analytical sensitivity of 5 ng/ml.

Antinuclear antibody (ANA), anti-dsDNA, C3, and C4 serum levels, and 24-hour urine protein tests were performed for patients with SLE. Patients with SSc were evaluated for ANA using indirect immunofluorescence.

Radiology Exams: For RA and SLE patients, a postero-anterior (P-A) plain radiograph of the hands, feet, and other affected joints was obtained.

Statistical analysis

Statistical analysis was conducted using IBM® SPSS® Statistics Version 26 for Windows. Data normality was assessed using Shapiro-Wilk test, indicating a non-parametric distribution. Categorical variables are presented as numbers and percentages, whereas continuous variables are presented as mean ± standard deviation, median, and range. Group differences were analyzed using t-tests, one-way analysis of variance, Kruskal-Wallis test, Mann-Whitney U-test, chi-square test, and Fisher's exact test. Spearman's rank correlation coefficients used to find relationship between variables. The receiver operator characteristic (ROC) curve analysis was used to determine the optimal cutoff values of PRL, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy assessed by the area under the curve (AUC) at a 95% confidence interval (CI), with significance set at $P < 0.05$.

Results

RA patients had a mean age of 36.62 ± 7.6 years, SLE patients 33.17 ± 8.4 years, and SSc patients 35.9 ± 6.47 years, while controls were 28.6 ± 8.11 years, (**Table.1**).

Table 1. Clinical and lab data among studied groups

Variables	RA (n = 50)	SLE (n = 30)	SSc (n = 20)	Control (n = 50)	P-value
Age	36.62 ± 7.6	33.17 ± 8.4	35.9 ± 6.47	28.6 ± 8.11	< 0.001* ^{KW}
Weight (kg)	66.54 ± 7.57	62.47 ± 5.91	61.55±4.67	67 ± 8.48	0.014* ^{KW}
Length (m)	1.59 ± 0.02	1.59 ± 0.02	1.59 ± 0.02	1.59 ± 0.02	0.352 ^{KW}
BMI (Kg/m2)	26.23 ± 2.79	24.86 ± 2.23	24.41 ± 2.27	26.4 ± 3.2	0.023* ^{KW}
Temperature ˚C	36.98 ± 0.35	36.87 ± 0.19	36.87 ± 0.31	36.89 ± 0.24	0.628 ^{KW}
Heart rate	77.24 ± 5.89	78.93 ± 4.23	78.3 ± 5.78	79.92 ± 4.1	0.104 ^{KW}
SBP mmHg	121.2 ± 8.72	119 ± 7.59	118.5 ± 7.45	116.96 ± 20.08	0.518 ^{KW}
DBP mmHg	74.04 ± 4.96	73.33 ± 4.79	73.5 ± 4.89	73.36 ± 10.67	0.737 ^{KW}
Respiratory rate	16.28 ± 0.78	16.27 ± 0.64	16.35 ± 0.49	16.38 ± 0.49	0.561 ^{KW}
Hb (g/dl)	11.48 ± 0.73	11.38 ± 0.97	12.2 ± 0.96	11.94 ± 0.94	0.002* ^{KW}
RBC $\times 10^{12}$/L	4.29 ± 0.46	4.29 ± 0.37	4.59 ± 0.79	4.39 ± 0.34	0.464 ^{KW}
Platelets $\times 10^{9}$/L	236 ± 50	221 ± 64	217 ± 48	221 ± 30	0.181 ^{KW}

WBCs × 10^9/L	7.21 ± 2.11	5.77 ± 2.36	8.31± 2.9	6.71 ± 1.92	0.012* ^{KW}
Monocyte ×10^9/L	0.52 ± 0.45	0.36 ± 0.23	0.54 ± 0.23	0.43 ± 0.27	0.006* ^{KW}
Neutrophil ×10^9/L	4.11 ± 1.37	3.54 ± 1.23	4.52 ± 1.77	4.05 ± 1.31	0.228 ^{KW}
Lymphocyte ×10^9/L	2.53 ± 0.88	2.21 ± 0.71	3.1 ± 0.94	2.43 ± 0.85	0.023* ^{KW}
NLR	1.98 ±1.51	1.87±1.31	1.52 ± 0.68	2.07 ± 1.58	0.461 ^{KW}
PLR	113.28 ± 77.11	117.22 ± 70.46	76.59 ± 29.69	110.61 ± 67.79	0.048* ^{KW}
CRP	6.26 ± 9.14	5.97 ± 4.54	7.21 ± 2.25	6.63 ± 1.78	0.030* ^{KW}
ESR 1 hour	31.94 ± 23.3	36.85 ± 19.24	23.35 ± 19.5	17.82 ± 11.86	< 0.001* ^{KW}
S. Urea	20.05 ± 3.79	28.34 ± 7.8	37.65 ± 7.92	20.59 ± 5.67	< 0.001* ^{KW}
S. Creatinine	0.87 ± 0.24	0.84 ± 0.1	0.78 ± 0.08	0.76 ± 0.12	0.009* ^{KW}
Urine analysis					
Urine proteins (Albumin)					
Negative	48(96%)	3(10%)	20(100%)	50(100%)	< 0.001* ^{Chi}
(+)	2(4%)	18(60%)	0(0%)	0(0%)	
(++)	0(0%)	8(26.67%)	0(0%)	0(0%)	
(+++)	0(0%)	1(3.33%)	0(0%)	0(0%)	
Epithelial cells					
Negative	0(0%)	0(0%)	9(45%)	0(0%)	< 0.001* ^{Chi}
(+)	27(54%)	17(56.67%)	4(20%)	33(66%)	
(++)	13(26%)	10(33.33%)	7(35%)	17(34%)	
(+++)	10(20%)	3(10%)	0(0%)	0(0%)	

*: significant; KW: Kruskal-Wallis test; Chi: Chi-square test; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; SSc: systemic sclerosis; Kg: kilograms; m: meter; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; Hb: hemoglobin; RBCs: red blood cells; WBCs: white blood cells; NLR: neutrophil lymphocyte ratio; PLR: platelets lymphocyte ratio; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

In this study, clinical and laboratory data were analyzed across four groups: rheumatoid arthritis (RA, n = 50), systemic lupus erythematosus (SLE, n = 30), systemic sclerosis (SSc, n = 20), and healthy controls (n = 50). Significant differences were observed in several parameters. Compared to controls, RA patients exhibited a significant increase in mean age (36.62 ± 7.6 years, p < 0.001*) and BMI (26.23 ± 2.79 kg/m2, p = 0.023*), while SLE patients showed a significant decrease in BMI (24.86 ± 2.23 kg/m2, p = 0.023*). Hemoglobin levels were significantly higher in SSc patients (12.2 ± 0.96 g/dl, p = 0.002*) compared to other groups. Additionally, markers such as urine proteins (p < 0.001* Chi) and epithelial cells (p < 0.001* Chi) also showed significant differences among the groups, indicating distinct physiological profiles across the studied conditions. (**Table.1**).

Table 2. Distribution of serum prolactin levels among the studied groups

Prolactin levels Mean ± SD	RA (n = 50)	SLE (n = 30)	SSc (n = 20)	Control (n = 50)	P-value
Prolactin (ng/ml)	26.17 ± 16.64	25.23 ± 16.11	32.07 ± 22.14	15.48 ± 4.75	< 0.001* ^{KW}
	No (%)	**No (%)**	**No (%)**	**No (%)**	

Normal (≤ 25ng/ml)	29(58%)	21(70%)	10(50%)	50(100%)	< 0.001* ^{Chi}
High (> 25ng/ml)	21(42%)	9(30%)	10(50%)	0(0%)	
P1	**P2**	**P3**	**P4**	**P5**	**P6**
0.769 ^{MW}	0.387 ^{MW}	<0.001* ^{MW}	0.400 ^{MW}	0.003* ^{MW}	0.005* ^{MW}

*: Significant; KW: Kruskal-Wallis test; Chi: Chi-square test; MW: Mann Whitney test; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; SSc: systemic sclerosis; P1: Comparison between RA and SLE groups; P2: Comparison between RA and SSc groups; P3: Comparison between RA and control groups; P4: Comparison between SLE and SSc groups; P5: Comparison between SLE and control groups; P6: Comparison between SSc and control groups.

PRL level among the studied groups

The study found that 58% of patients with RA have normal PRL levels, while 42% have HPRL. 70% of patients with SLE have normal PRL levels, while 30% have HPRL. 50% of patients with SSc have normal PRL levels, while 50% have HPRL. The mean PRL level was significantly higher in RA patients, SLE patients, and SSc patients compared to the control group (P < 0.001) (**Table .2**).

Table 3. Distribution of prolactin levels in rheumatic diseases groups

Rheumatic diseases	N	Prolactin Mean ± SD	P-value
Rheumatoid arthritis (RA) group			
DAS28 levels			
Remission	4 (8%)	13.53±8.95	<0.001* ^{KW}
Low activity	9 (18%)	14.14±5.46	
Moderate Activity	22 (44%)	26.11±17.62	
High activity	15 (30%)	36.86±14.43	
Anti-cyclic citrullinated peptide (Anti-CCP)			
Negative	18	25.02±19.33	0.486 ^{MW}
Positive	32	26.82±15.22	
Systemic lupus erythematosus (SLE) group			
Myositis			
• No	26	23.48±15.34	0.093 ^{MW}
• Yes	4	36.63±18.65	
Facial rash			
• No	11	25.68±16.23	0.763 ^{MW}
• Yes	19	24.97±16.48	
SLEDAI levels			
• Low	8	13.63±5.67	0.003* ^{KW}
• Moderate	16	16.06±4.01	
• High	6	39.27±15.49	
Antinuclear antibodies (ANA)			
• Negative	2	17.4±3.25	0.454 ^{MW}
• Positive	28	25.79±16.54	
Anti-dsDNA			
• Negative	19	20.73±9.82	0.143 ^{MW}
• Positive	11	33±21.78	
Complements C3 and C4			

• Low	9	36.14 ± 13.89	0.002* ^{MW}
• Normal	21	20.55 ± 14.92	
Casts			
• Absent	27	24.93 ± 16.75	0.768 ^{MW}
• Granular	3	27.9 ± 10.11	
Systemic sclerosis (SSc) group			
Prolactin level			
Normal (≤ 25)	10	14.28±6.56	0.0002*^{MW}
High (>25)	10	49.86±16.98	
Antinuclear antibodies (ANA)			
Negative	15	30.07 ± 21.84	0.407 ^{MW}
Positive	5	38.06 ± 24.48	
modified Rodnan skin score (mRSS)			
0-5	5	12.62 ± 7.33	0 .001*^{KW}
6-10	9	23.3 ± 9.90	
11-15	6	96.68 ± 11.61	

*: Significant; KW: Kruskal-Wallis test, MW: Mann-Whitney test; DAS28: disease activity score in 28 joints; SLEDAI: systemic lupus erythematosus disease activity score.

The Disease Activity Score 28 (DAS28) ranged from 2.08 to 6.44, with a mean of 4.32 ± 1.19. The distribution of prolactin levels was analyzed across rheumatic disease groups. In the rheumatoid arthritis (RA) group, prolactin levels varied significantly among DAS28 activity levels: 13.53 ± 8.95 in remission, 14.14 ± 5.46 in low activity, 26.11 ± 17.62 in moderate activity, and 36.86 ± 14.43 in high activity (p < 0.001* KW). Anti-cyclic citrullinated peptide (Anti-CCP) status did not significantly affect prolactin levels (p = 0.486 MW). In the systemic lupus erythematosus (SLE) group, prolactin levels were higher in patients with high SLEDAI scores (39.27 ± 15.49) compared to those with low (13.63 ± 5.67) or moderate (16.06 ± 4.01) scores (p = 0.003* KW). Levels did not significantly differ based on myositis or facial rash presence, ANA status, or anti-dsDNA status (p > 0.05). Prolactin levels also varied significantly across modified Rodnan skin score (mRSS) categories: 12.62 ± 7.33 for mRSS 0-5, 23.3 ± 9.90 for mRSS 6-10, and 96.68 ± 11.61 for mRSS 11-15 (p < 0.001* KW). Levels did not significantly differ based on ANA status (p = 0.407 MW). (**Table 3**).

Table 4.Correlation between RA group's prolactin levels with other parameters

Variables	Prolactin levels	
	r	P-value
RA clinical and laboratory parameters		
DAS28	0.493	0.0001*
Number of swollen joints	0.380	0.007 *
Number of tender joints	0.362	0.010 *
Patient global health	0.394	0.005 *
Rheumatoid factor (RF)	0.037	0.797
hemoglobin (g/dl)	0.090	0.535
Platelets × 10^9/L	0.166	0.249
WBCs × 10^9/L	0.121	0.401

Neutrophil-lymphocyte ratio (NLR)	-0.083	0.566
Platelets lymphocytes ratio (PLR)	-0.056	0.698
ESR 1st Hour	0.428	0.002*
CRP	0.216	0.133
SLE clinical and laboratory parameters		
SLEDAI	0.546*	0.002*
hemoglobin (g/dl)	0.148	0.435
Platelets × 10^9/L	-0.159	0.400
WBCs × 10^9/L	0.241	0.199
Monocyte count ×10^9/L	0.052	0.786
Neutrophil count×10^9/L	0.018	0.924
Lymphocyte count ×10^9/L	0.039	0.837
Neutrophil-lymphocyte ratio (NLR)	-0.073	0.702
Platelets lymphocytes ratio (PLR)	-0.149	0.432
Creatinine (mg/dl)	-0.183	0.334
Protein 24 hrs.	0.211	0.262
ESR 1st Hour	-0.00034	0.999
CRP	-0.059	0.753
SSc clinical and laboratory parameters		
Modified Rodnan skin score (MRSS)	0.893	0.0001*
hemoglobin (g/dl)	-0.008	0.974
Platelets × 10^9/L	0.091	0.702
WBCs × 10^9/L	-0.125	0.599
Monocyte count ×10^9/L	-0.012	0.961
Neutrophil count×10^9/L	-0.185	0.435
Lymphocyte count ×10^9/L	0.203	0.390
Neutrophil-lymphocyte ratio (NLR)	-0.380	0.099
Platelets lymphocytes ratio (PLR)	-0.146	0.540
Serum Creatinine	0.050	0.835
ESR 1st Hour	-0.215	0.363
CRP	-0.039	0.871

r: correlation coefficients; *****: significant; DAS28: disease activity score in 28 joints; WBCs: white blood cells; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate, SLEDAI: systemic lupus erythematosus disease activity score, SLE: systemic lupus erythematosus, SSc: scleroderma or systemic sclerosis.

(**Table.4**) show that: In RA patients, we found a significant positive correlation between PRL levels and DAS28 ($r = 0.493$, $p = 0.0001$), the number of tender joints ($r = 0.362$, $r = 0.010$), the number of swollen joints ($r = 0.380$, $r = 0.007$), patient global health ($r = 0.394$, $p = 0.005$), and ESR ($r = 0.428$, $p = 0.002$).

In the SLE group, we found a significant positive correlation between PRL levels and SLEDAI ($r = 0.546$, $p = 0.002$).

In the SSc group, MRSS was mild in all cases and we found a significant positive correlation between prolactin levels and MRSS ($r = 0.893$, $p = 0.0001$).

Table 5. ROC curve analysis of utility of prolactin cutoff value to differentiate between rheumatic diseases (RA, SLE, and SSc) and control groups

	AUC	Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy	P-value
RA	0.715	18.8 ng/ml	66	78	75	69.6	72	< 0.001*
SLE	0.696	23 ng/ml	46.67	96	87.5	75	71.3	0.004*
SSc	0.715	21.3 ng/ml	65	88	68.4	86.3	76.5	0.016*

*: significant; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; SSc: systemic sclerosis

Prolactin level at a cutoff value of > 18.8 ng/ml can significantly differentiate between RA patients and the control group (P < 0.001) with an AUC of 0.715, a sensitivity of 66%, a specificity of 78%, a PPV of 75%, a NPV of 75%, and an accuracy of 72% (**Table.5**, **Fig.1**).

Prolactin level at a cutoff value of > 23 ng/ml can significantly differentiate between SLE patients and the control group (P = 0.004), with an AUC of 0.695, a sensitivity of 46.67%, a specificity of 96%, PPV of 87.5%, an NPV of 75%, and accuracy of 71.3% (**Table.5, Fig.2**).

Prolactin level at a cutoff value of > 21.3 ng/ml can significantly differentiate between SSc patients and the control group (P = 0.016), with an AUC of 0.715, a sensitivity of 65%, a specificity of 88%, a PPV of 68.4%, an NPV of 86.3%, and an accuracy of 76.5% (**Table.5**, **Fig.3**).

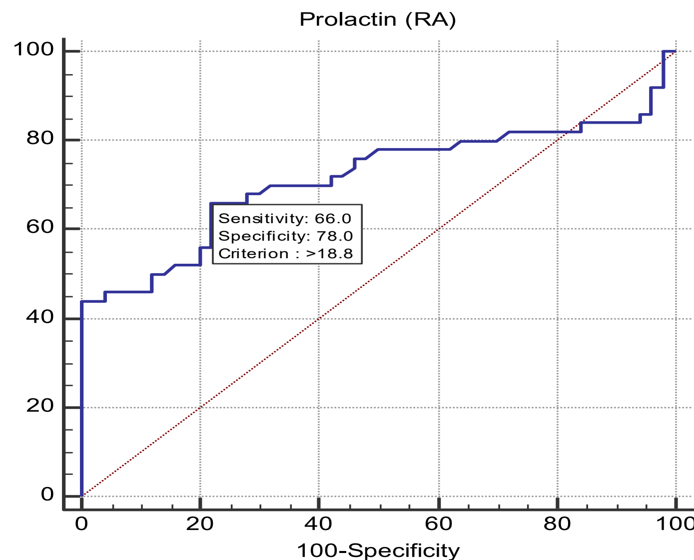

Fig.1: ROC curve of prolactin to differentiate between RA and control groups

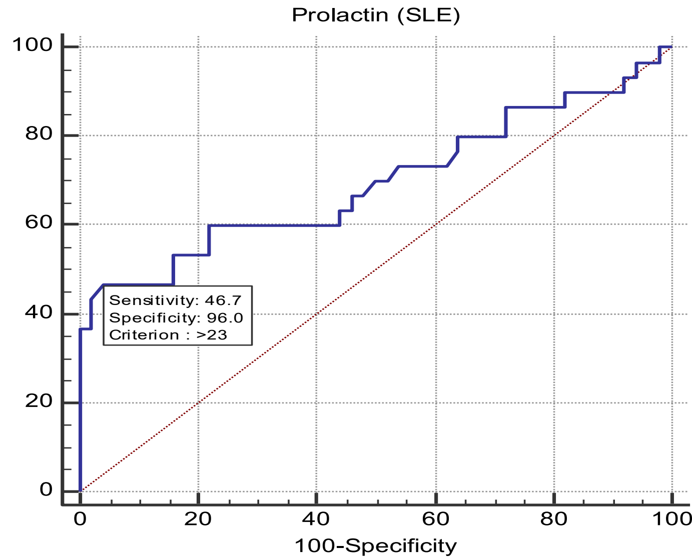

Fig.2. ROC curve of prolactin to differentiate between SLE and control groups.

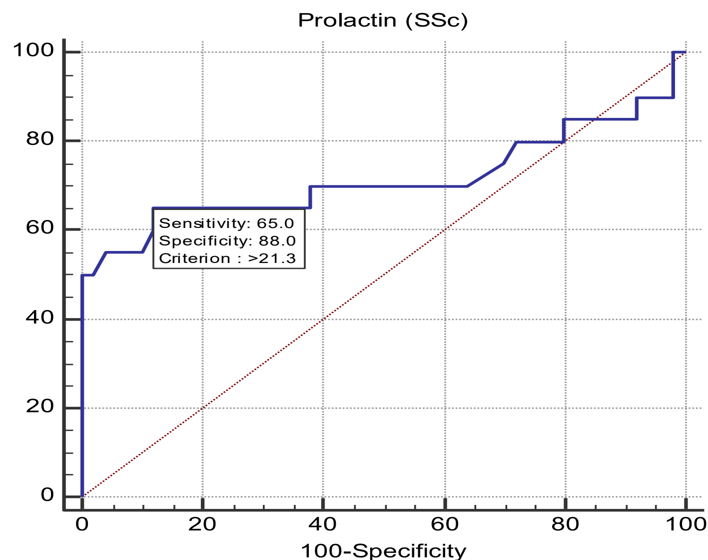

Fig.3. ROC curve of prolactin to differentiate between SSC and control groups

Discussion

Our study included 50 women with RA (mean age 36.62 ± 7.6 years) with significantly higher mean PRL (26.17 ± 16.64 ng/ml) than controls (15.48 ± 4.75 ng/ml), and that PRL level was correlated with disease activity and severity parameters (DAS-28 scores). HPRL (>25 ng/ml) was present in 42% of the patients. Disease activity: low, 18%; moderate, 44%; severe, 30%; remission, 8%. PRL level was significantly correlated with the disease activity groups ($P < 0.001$) and correlated with ESR values, but with no significant correlation with the inflammatory marker CRP or the inflammatory indices NLR and PLR. Our results were similar to those of **(Ghule et al., 2009; Fojtíková et al., 2010; Fayez et al., 2015; Wu et al., 2019; Yousif and Ibraheem, 2020; Haggag et al., 2022; Ali et al., 2023).**

Moreover, a meta-analysis reported higher circulating PRL in RA, positively correlating with CRP and ESR levels **(Wu et al., 2019). Tang et al. (2012)** found that premenopausal and postmenopausal women and non-responders to anti-TNF medication have greater PRL levels than men. **Tang et al. (2014)** estimated PRL in the synovium and blood of 15 RA patients and found HPRL and PRL in the synovial fluid (SF), suggesting a favorable association between PRL and disease activity. PRL, which is released systemically and locally, can cause inflammatory arthritis. RA SF contains PRL, macrophages, and other immune cells **(Tang et al., 2016).** Thus, they suggested that the treatment of inflammatory arthritis with PRLR targeting may be intriguing **(Tang et al., 2017).**

In the study by **Gupta et al. (2023)**, a significantly higher DAS28 in premenopausal women with RA was correlated with elevated serum PRL, FSH, and progesterone, with inverse correlations for testosterone and DHEAS. They suggested bromocriptine and testosterone supplementation for refractory RA with a documented deficiency.

In this study, we found a significant positive correlation between PRL and DAS28 ($r = 0.493$, $P < 0.0001$) and ESR ($r = 0.428$, $p = 0.002$). ROC analysis showed PRL > 18.8 ng/ml can differentiate RA from controls ($P < 0.001$), with an AUC of 0.715, sensitivity of 66%, specificity of 78%, PPV of 75%, NPV of 75%, and accuracy of 72%.

In this study, we evaluated 30 female patients with SLE, mean age 33.17 ± 8.4 years, and found significantly higher mean PRL levels (25.23 ± 16.11 ng/ml) than controls (15.48 ± 4.75 ng/ml) ($P = 0.003$), with 9 (30%) having HPRL. The SLEDAI was positively correlated with PRL ($r = 0.546$, $P = 0.002$), with no significant correlation with the inflammatory markers ESR, CRP, or the inflammatory indices NLR and PLR. Disease activity: 26.7%, low activity; 53.3%, moderate activity; and 20%, high activity. A significant negative relationship was observed between serum PRL levels and complement levels ($P = 0.003$). These findings were consistent with the following studies (**Jara et al., 1992; Jacobi et al., 2001; Pacilio et al., 2001; Zhu et al., 2015; Gómez-Hernández et al., 2016; Toffoli et al., 2016; Yang et al., 2016; Song and Lee, 2017; Mohammed et al., 2023).**

However, **Alam et al. (2022)** reported that 74% of patients with SLE have HPRL. Moreover, **Gómez-Hernández et al. (2016)** reported that all asymptomatic patients had normal PRL levels, and all patients with HPRL experienced lupus crisis. Additionally, **Zhu et al. (2015)** and **Yang et al. (2016)** reported that patients with active SLE exhibited significantly higher dsDNA antibody titers and specific binding of PRLR in patients with active SLE than that in controls ($P < 0.01$).

Liu et al. (2019) observed that 23.27% of women with HPRL presented with at least one autoantibody. **Alvarez et al. (1998)** found that bromocriptine administration reduced SLE flare severity and frequency.

In our study, we observed significant associations between malar rash, photosensitivity, arthritis, and high PRL levels, which are consistent with the findings of **Soliman et al. (2018).**

In contrast, **Jara et al. (1992)** found that HPRL is correlated with renal and hematological manifestations.

Moreover, PRLR mRNA expression levels were significantly higher in patients with active SLE than in controls ($P < 0.01$).

Contrary to our study, **Orbach et al. (2012)** found that PRL was associated with lupus manifestations but not with SLEDAI.

In contrast, our study contradicted the findings reported by **Pauzne et al., 1994; Ostendorf et al., 1996; Buskila et al., 1996; Jimena et al., 1998; and Soliman et al., 2018,** which reported an insignificant association between PRL levels and disease activity in SLE.

We observed a significant negative association between PRL levels and complement components C3 and C4 levels and a positive association with SLEDAI, consistent with previous reports **(Jara et al., 1992; Chang et al., 1999; Zhu et al., 2015; Iqbal et al., 2017).**

In our study, we included 20 SSc patients; they showed significantly higher PRL than controls (P = 0.005), with a significant positive correlation with MRSS (r = 0.893, P = 0.0001), but with an insignificant correlation with the inflammatory markers ESR, CRP, or the inflammatory indices NLR and PLR. Cardiopulmonary symptoms were prevalent in 8 (40%) of SSc patients (P < 0.001). This aligns with the findings of multiple studies **(Kucharz et al., 1996; Straub et al., 1997; Hilty et al., 2000; La Montagna et al., 2001; Shahin et al., 2002; Czuwara-Ladykowska et al., 2006; Mirone et al., 2006)** indicating significant correlations between PRL levels and SSc subtypes, disease duration, disease severity, and activity.

In the study by **Hilty et al. (2000),** serum PRL levels were compared between 73 SSc patients and age- and sex-matched controls using the metoclopramide stimulation test (MTCY). Younger patients (< 50 years) exhibited higher serum PRL levels, and mild HPRL was observed in SSc patients, with an altered diurnal rhythm of PRL secretion.

Our study findings were consistent with **Vera-Lastra et al. (2006),** who reported significantly higher basal serum PRL levels in SSc patients before and after metoclopramide (MTC) stimulation, along with a higher prevalence of HPRL and microadenomas detected via CT scans in SSc patients compared to controls. Moreover,

Wu et al. (2020), in a meta-analysis, comprising 9 studies including 293 SSc patients and 282 controls, found elevated PRL levels in SSc patients, particularly in females aged 45 years or younger with a disease duration of 7.5 years or less, compared to controls.

In **Shahin et al.'s (2002)** study, 23 non-smoking women with SSc were examined, including 10 with limited SSc (lSSc) and 13 with diffuse scleroderma (dSSc). Serum PRL levels were significantly higher in patients than controls (p < 0.001) and correlated significantly with disease duration (r = 0.42, p < 0.05). Eight (34.8%) patients had HPRL, and PRL levels in dSSc patients correlated significantly with the skin tethering rate (r = 0.72, p < 0.01).

Mirone et al. (2006) investigated 39 patients with SSc and reported elevated serum PRL levels in childbearing-aged women (associated with a significant decrease in serum testosterone and dehydroepiandrosterone sulphate than in controls), which was positively correlated with disease severity and duration.

La Montagna et al. (2001) found significantly higher PRL levels in childbearing-aged SSc patients than in controls. Additionally, the net AUC for PRL in response to TRH stimulation was significantly elevated in patients with SSc; regression analysis linked basal and stimulated PRL concentrations with skin sclerosis, peripheral vascular involvement, and lung involvement.

In contrast to our study, **La Montagna et al. (2004)** found no correlation between PRL levels and SSc subtypes, serological parameters, or disease activity. **Arnaud et al. (2017)** found no association between PRL levels and SSc subtypes or skin thickness scores. Similarly,

Khodamoradi et al. (2018) found an insignificant difference in serum PRL levels between scleroderma patients and controls and reported that PRL levels were correlated significantly with disease duration.

Study limitations include the small sample size, the cross-sectional design, hindering the evaluation of anti-inflammatory treatment effects on PRL levels in rheumatic disease patients.

Conclusion

Serum PRL levels are notably elevated in autoimmune rheumatic diseases (RA, SLE, and SSc) versus controls, correlating with disease activity scores but not with the inflammatory markers or indices. PRL may serve as a marker of disease activity, necessitating regular monitoring. That warrants the therapeutic potential of dopamine agonists in autoimmune diseases for further investigation, potentially mitigating flare-ups and organ involvement.

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