Correlation of Prolactin Serum Concentrations with Clinical Activity and Remission in Patients with Systemic Lupus Erythematosus. Effect of Conventional Treatment

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ABSTRACT. ***Objective.*** The role of prolactin (PRL) in the pathogenesis of systemic lupus erythematosus (SLE) is controversial. The effect of conventional treatment (steroids, antimalarials, immunosuppressor drugs) on PRL concentrations is unclear. We investigated correlation of PRL levels with lupus activity in patients at entry and after 6 months of conventional treatment.

Methods. We studied 43 female patients with active SLE, who were divided in 2 groups; Group 1: 16 patients with minor organ involvement (cutaneous and articular involvement), and Group 2: 27 patients with major organ involvement (glomerulonephritis). Controls were 36 healthy individuals. PRL levels were determined by an immunoradiometric assay at entry and after 6 months of treatment. PRL levels were correlated with SLE Disease Activity Index (SLEDAI) score.

Results. Mild hyperprolactinemia (HPRL, 20–40 ng/ml) was found in 30/43 (69.7%) SLE patients. After 6 months of treatment a reduction in PRL levels was found in both groups: Group 1: 24.3 ± 10.8 to 16.96 ± 10.87 ng/ml ($p < 0.001$); and Group 2: 23.6 ± 5.7 to 12.07 ± 11.13 ng/ml ($p < 0.001$). The SLEDAI score also decreased after treatment: Group 1: 16.5 ± 5.9 to 2.1 ± 1.3 ($p < 0.001$); Group 2: 16.8 ± 5.4 to 1.6 ± 1.4 ($p < 0.001$). At entry and after treatment, a significant correlation between PRL levels and SLEDAI score was found in all patients ($r = 0.4946$, $p = 0.0007$, and $r = 0.9086$, $p = 0.0001$, respectively).

Conclusion. HPRL was associated with SLE disease activity. Conventional immunosuppressive therapy decreased PRL levels in direct correlation with decreased SLE activity. This finding emphasizes that PRL may play a role in the pathogenesis and clinical expression of SLE. (J Rheumatol 2003;30:2140–6)

Key Indexing Terms:
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SYSTEMIC LUPUS ERYTHEMATOSUS ACTIVITY

Prolactin (PRL), a 23 kDa polypeptide hormone, is produced by the anterior pituitary gland as well as a variety of extrapituitary sites, including immune cells. PRL receptor is a member of the hematopoietin/cytokine receptor superfamily, making it possible that PRL plays a cytokine role in addition to its endocrine actions[1]. Experimental studies have suggested that PRL has a role in the regulation of humoral and cell mediated immune responses[2], and may play a role in the pathogenesis and clinical activity of systemic lupus erythematosus (SLE) and other autoimmune rheumatic diseases in humans and experimental animal models[3,4].

The prevalence of hyperprolactinemia (HPRL) in SLE is 20–30%, particularly in those patients with active disease[5-7]. However, controversy regarding the role of PRL in the pathogenesis of SLE has arisen primarily due to studies that found no correlation between PRL and lupus disease activity or any elevation of PRL compared to control populations[8-11]. The factors that may explain these discrepant findings include the heterogeneity of the SLE populations studied, variability of the indices used to measure lupus activity, variable disease duration, different treatments, circadian rhythms of PRL, and methods used to measure the concentrations of PRL[12-14]. In addition, power analysis of individual studies and anti-PRL antibodies could explain the

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inconsistent relationship between serum PRL levels and lupus activity[15,16].

Regardless of this controversy, recent human studies suggest that PRL can participate in major organ involvement, such as lupus nephritis and neuropsychiatric lupus[17,18]. Nevertheless, the role of PRL and the effect of conventional treatment in minor and major organ involvement of active SLE (steroids, antimalarials, and immunosuppressant drugs) on PRL levels are unclear.

We compared 2 subsets of patients with active SLE — those with minor organ and major organ involvement; and analyzed the effect of conventional treatment on serum PRL concentrations and SLE Disease Activity Index (SLEDAI) score.

MATERIALS AND METHODS

We studied 43 consecutive female patients with SLE who met the American College of Rheumatology 1982 criteria[19] for classification of SLE in the outpatient rheumatic clinic at the Hospital de Especialidades Centro Medico "La Raza," Instituto Mexicano del Seguro Social (IMSS). We included patients more than 16 years old with cutaneous, articular, and renal involvement. Patients with hypothyroidism, hepatic insufficiency or chronic renal failure, pregnant patients, or those being treated with drugs that modify PRL levels (bromocriptine, chloroquine, metoclopramide, verapamil, cimetidine, etc.) were excluded. At the start of the study, all patients had active disease according to the SLEDAI[20].

Patients were divided into 2 groups on the basis of renal involvement. A control population was also studied. Patient Group 1 comprised 16 patients with minor organ involvement (cutaneous and articular involvement); these patients were 27.7 ± 11.1 years old, and the duration of disease was 5.6 ± 3.1 years. All patients of Group 1 had normal urinary sediment, serum creatinine, and creatinine clearance. Group 2 comprised 27 patients with major organ involvement (lupus glomerulonephritis); the age of these patients was 28.6 ± 5.2 years and the duration of disease was 4.6 ± 2.8 years. All patients of Group 2 had active urinary sediment without renal failure. All patients had renal biopsy (21 patients had Class IV and 6 patients had Class III glomerulonephritis). The inclusion criteria were creatinine clearance > 60 ml/min and serum creatinine < 1.3 mg/dl. Group 3 comprised 36 healthy female controls, aged 28.3 ± 10.3 years. They were recruited from hospital employees, and all were healthy as established from their medical history based on an interview. Controls were matched according to the age of patients.

Basal levels of PRL were determined by an immunoradiometric assay (ELSA-PROL; CIS-Bio International, Gif sur Yvette, France) in patients and controls. All serum samples were taken during the morning (8:00 am to 12:00 pm) in active disease condition, before modifications of treatment were begun, and after 6 months of followup. Sera samples were stored at –20°C. Intra- and interassay variance coefficients were 3.5–5.5% and 4.2–6.1%, respectively. The normal serum values were 2–20 ng/ml. Hyperprolactinemia was defined as > 20 ng/ml and mild HPRL as > 20–40 ng/ml[21]. Prolactin levels were correlated with SLEDAI score at the onset and after 6 months of treatment. A patient's disease state was considered active with a SLEDAI score ≥ 1.

At entry, all patients of Group 1 were treated with low doses of prednisone (< 10 mg/day). The treatment was modified according to activity of SLE, and prednisone was increased to 15–20 mg/day and chloroquine 150 mg/day was added in 7 of 16 patients. At onset, all patients of Group 2 had low doses of prednisone and 11/27 had already been treated with intravenous (IV) cyclophosphamide. Treatment was modified according to renal activity. In all patients, prednisone was increased to 30–60 mg/day. Methylprednisolone pulses were added in 15/27 patients and 10 other patients received IV cyclophosphamide 0.5–1 g/m^2 of body surface area, once a month over a 6 month period. In addition, 10/27 also received chloroquine.

The study was approved by the Ethics Committee of the Hospital de Especialidades, Centro Médico "La Raza."

Statistical analysis. Results are expressed as mean ± standard deviation (SD). To compare basal PRL levels and basal SLEDAI versus final PRL levels and SLEDAI in Groups 1 and 2, the Wilcoxon signed-rank test was used. The unpaired t test was used to compare the basal serum PRL levels of all patients versus controls. ANOVA test was used to compare Groups 1 and 2 versus controls. The relationship between the serum PRL and SLEDAI score was assessed by linear regression.

RESULTS

Demographic and clinical characteristics. Table 1 shows patients' mean age, SLE duration, PRL levels, SLEDAI, and renal function at study entry. Mild HPRL was found in 30/43 patients with active SLE (69.7%). Mild HPRL was found in 10/16 (62%) active SLE patients in Group 1, and in 20/27 (74%) of Group 2.

PRL levels in patients and controls. The mean basal PRL levels were significantly higher in 43 SLE patients than in 36 healthy controls (23.55 ± 5.88 ng/ml vs 6.43 ± 2.24 ng/ml, respectively; $p < 0.0001$). Comparison between Group 1 (24.03 ± 6.38 ng/ml PRL) and Group 2 (23.6 ± 5.68 ng/ml), versus healthy controls (6.43 ± 2.24 ng/ml) also achieved statistical significance ($p < 0.001$).

PRL levels in patients at entry and after 6 months. We observed a significant decrease of PRL levels after 6 months of conventional treatment in 43 patients (23.55 ± 5.88 vs 13.88 ± 11.15 ng/ml; $p = 0.0001$). The basal PRL levels in patients of Group 1 were 24.03 ± 6.38 ng/ml (range 14.9 to 36.2 ng/ml). In Group 2, basal levels were 23.26 ± 5.68 ng/ml (range 13.5 to 35 ng/ml) (p = nonsignificant). After 6 months of followup, PRL levels decreased to < 20 ng/ml in 25/43 patients (58.1%). We observed a significant decrease of PRL levels in both groups; Group 1: 16.96 ± 10.87 ng/ml and Group 2: 12.07 ± 11.13 ng/ml ($p < 0.0001$), respectively. Figure 1 shows individual measures of PRL and SLEDAI before and after treatment.

SLEDAI score at entry and after 6 months. The SLEDAI score at the beginning of the study and after treatment in all patients showed a significant decrease after 6 months of treatment: 16.76 ± 5.54 vs 1.76 ± 1.85. The SLEDAI score in Group 1 was 16.5 ± 5.98 versus 2.06 ± 1.3 ($p < 0.0001$). In Group 2, the basal and final SLEDAI scores were 16.8 ± 5.4 versus 1.59 ± 1.4 ($p < 0.0001$).

Linear regression between serum PRL levels and SLEDAI score. At entry, SLE patients showed a significant linear regression of serum PRL levels and SLEDAI score ($r = 0.4946$, $p = 0.0007$). After treatment, a significant correlation was also observed ($r = 0.9086$, $p = 0.0001$) in all patients (Figure 2).

Patients in Group 1 showed a significant linear regression of serum PRL levels and SLEDAI score at entry ($r = 0.8616$, $p < 0.0001$) and after treatment ($r = 0.9135$, $p < 0.0001$).

Table 1. Demographic data of study groups.

	Group 1 (n = 16)	Group 2 (n = 27)	Group 3 (n = 36)
Age, yrs	27.7 ± 11.1	28.6 ± 5.2	28.3 ± 10.3
SLE duration, yrs	5.6 ± 3.1	4.6 ± 2.8	
Mean PRL, ng/ml	24.03 ± 6.38	23.6 ± 5.68	6.43 ± 2.24
SLEDAI score	16.5 ± 5.98	16.8 ± 5.4	
Mean creatinine clearance, ml/min	99.9 (90–110)	79.9 (60–128)	
Mean serum creatinine, mg/dl	0.95 (0.8–1.05)	1.19 (0.9–1.3)	

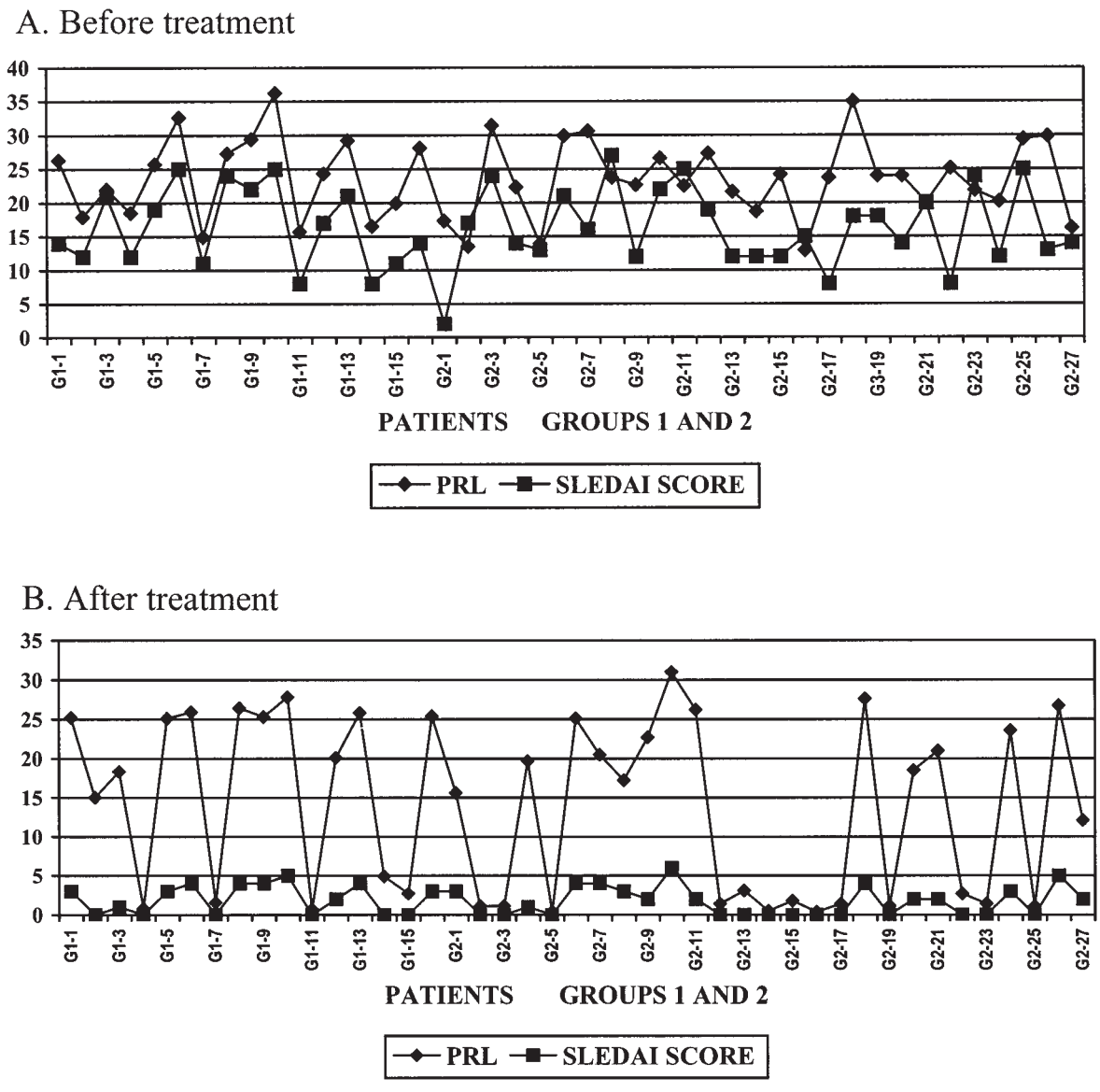

Figure 1. Individual behavior of prolactin (ng/ml) and SLEDAI score before (A) and after treatment (B).

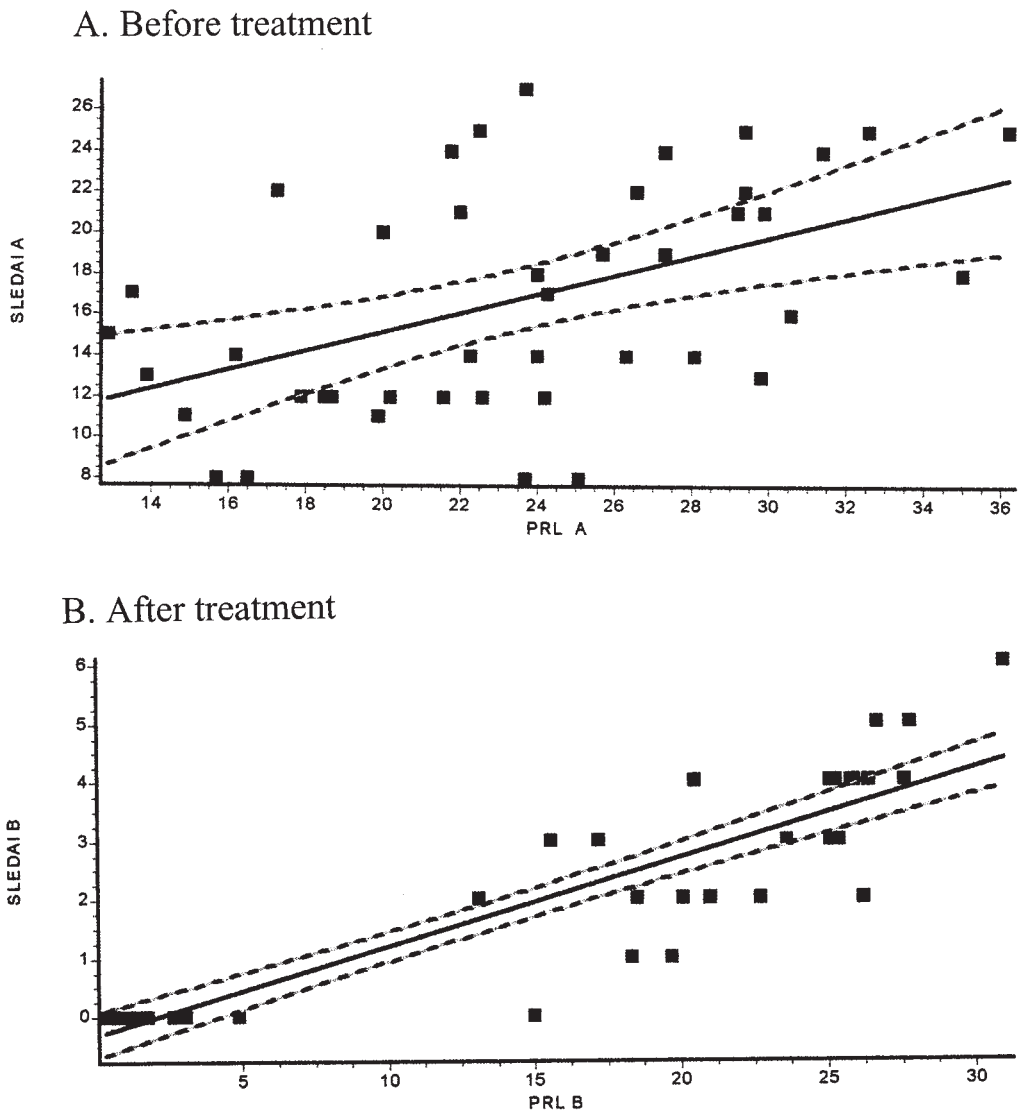

Figure 2. Linear regression between serum PRL concentrations and SLEDAI score before (A; r = 0.4946, p = 0.0007) and after treatment (B; r = 0.9086, p < 0.0001) in all patients.

We found no significant correlation between PRL and SLEDAI score in patients with lupus glomerulonephritis at the beginning of the study (Group 2) (r = 0.2376, p > 0.05). However, after treatment, we found a strong correlation between levels of PRL and SLEDAI (r = 0.9082, p < 0.0001).

DISCUSSION

Our data confirm previous observations of HPRL in patients with SLE, and also show that serum PRL levels correlated with both clinical activity and remission. Our findings also show that HPRL can be associated with both minor organ involvement (cutaneous and articular involvement) and major organ involvement (glomerulonephritis). Previously reported frequencies of HPRL in SLE have ranged from 2% to 37.5%[5-11,22-24], a frequency somewhat lower than our present findings (70%), although higher frequencies of up to 60% have been reported[25], but in contrast to other studies, at entry to our study all patients exhibited active disease with high SLEDAI scores.

The first correlation between HPRL and active lupus was noted in pregnant SLE patients[26], and it was concluded that HPRL present in pregnant women with SLE could be related to fetal wastage and disease activity. This finding was subsequently corroborated by a study of 51 pregnant patients with SLE, in whom there were strong positive correlations between serum PRL concentration and SLEDAI[27].

Our early study also showed a direct correlation between HPRL and clinical and serological activity in 45 consecutive SLE patients[5]. Over the past 10 years, several studies have

described similar findings[17,28,29], although others have not found an association between SLE disease activity and HPRL[8-11,30-32].

A number of possibilities may explain the inconsistencies noted, such as the design of the study, observational bias, inadequate use of statistical methods, or effects of medication, or they may be related to the hypothesis or the power of the study[25,33-38].

Blanco-Favela, *et al*[15] analyzed the statistical power of studies in the literature regarding the association between HPRL and SLE disease activity. They identified 5 articles that sought to establish a relationship between PRL and SLE activity. A power analysis of individual studies could be carried out in only 2 of the 5, but because of the low power of the studies, it could not be determined whether the differences in the frequency of HPRL were significant. However, joint analysis of the remaining 3 articles showed a significant association between HPRL and lupus activity, without establishing a formal causal relationship.

There are other factors, however, that may explain the contradictory results, such as the selection of patients according to SLE disease activity. The majority of patients included in the aforementioned studies included patients with inactive or mild activity according to the indices of clinical SLE activity, and in addition were receiving treatment for their SLE[6,8-10]. In contrast, in our study all patients had moderate to severe activity with high SLEDAI scores, and immunosuppressive therapy was not initiated before the first blood test for PRL.

Recent observations with similar groups of patients with high lupus disease activity as determined by established SLE indices corroborate our findings[39-41]. Jacobi, *et al*[39] studied the frequency of HPRL and the relationship to disease activity in 60 patients with SLE, including a followup of 20 patients (18 controls with rheumatic autoimmune disease other than SLE and 47 healthy subjects were studied). Clinical manifestations and disease activity (by European Community Lupus Activity Measure, ECLAM) were recorded. Patients with SLE and other autoimmune diseases had significantly higher PRL levels than controls. A significant correlation between serum PRL levels and ECLAM score was also observed in SLE patients. These results were confirmed by followup examinations. It was concluded that moderate HPRL was present in a subset of SLE patients, and this correlated with clinical and serological disease activity. Similar data were obtained by Pacilio, *et al*[40], who in addition found direct correlation between HPRL and minor (rash) and major (central nervous system) organ involvement.

Of interest is the report of Funauchi, *et al*[42] describing a case of SLE in a woman with a prolactinoma, in whom PRL, disease activity, and anti-DNA antibodies and CH50 activity were assessed serially. SLE flared when the plasma level of PRL increased, and disease activity subsided when PRL decreased after administration of bromocriptine. PRL in the 29 samples obtained during the course of the illness exhibited significant positive correlation with anti-DNA antibody titers and inverse correlation with CH50 activity.

It is probable that multiple factors are responsible for the HPRL seen in patients with active SLE[41]. It has been suggested that activated lymphocytes release proinflammatory cytokines in SLE patients. These cytokines may cross the blood-brain barrier and can stimulate PRL release from pituitary cells. Support for this theory is provided by the finding of PRL and interleukin 6 in cerebrospinal fluid from patients with active neuropsychiatric lupus[18]. Another possibility is that SLE patients may have defective control of PRL secretion, as indicated by the findings of decreased homovanillic acid (a metabolite of dopamine) and increased cyclo (His-pro), an inhibitor of PRL secretion[22,43].

An intriguing possibility is that active SLE lymphocytes might be the source of the PRL detected in patients with active SLE. Indeed, SLE patients with active disease have increased production by lymphocytes of PRL with different molecular weight forms[44,45]. The exact mechanism for the high levels of PRL in SLE patients remains unclear, but 2 potential explanations at the molecular level have been advanced. First, it has been reported that alteration in the CREB family proteins, which participate in lymphocyte PRL gene expression, may play a role. Indeed, variations in p-CREB (phosphorylated cAMP-responsive element binding protein) and p-CREM (phosphorylated cAMP-responsive element modulator) concentrations have been described in lymphocytes from SLE patients compared to controls[46]. More recently, Stevens, *et al*[47] demonstrated that one single nucleotide polymorphism (PRL-1149 G allele) in the lymphocyte-specific upstream promoter region affecting PRL transcription is overexpressed in SLE patients compared to controls. This provides a potential explanation for the increased PRL release by SLE lymphocytes.

Nagafuchi, *et al*[48] have described similar observations in rheumatoid arthritis (RA). They observed that synovium-infiltrating T cells in RA patients produced large amounts of intracellular PRL *in situ*, and concluded that locally produced PRL plays a distinct role in RA pathogenesis.

In experimental models, hypophysectomized rats retained 20–50% of the usual level of biologically active PRL in the circulation. Further, neutralization of the residual PRL resulted in immune dysfunction and death. Extrapituitary PRL, possibly secreted by immune cells, may therefore be capable of compensating for pituitary PRL[49].

Clinical data and studies in animals models suggest that HPRL can break immune tolerance in SLE. In this regard, Peeva, *et al*[50] describe that increased PRL breaks B cell tolerance in R4A-γ2b BALB/c mice. Treatment with PRL for 4 weeks induced a lupus-like phenotype with an increased number of B cells, elevated serum anti-DNA antibody titers, and glomerular immunoglobulin deposits.

Another interesting observation in our study was the finding of a significant decrease of PRL concentrations following treatment with immunosuppressive agents, suggesting that PRL secretion by activated lymphocytes in SLE can be inhibited by this therapeutic modality. This observation is in agreement with findings that dexamethasone and cyclosporine, inhibitors of immune activation, also affect PRL gene expression[51,52].

We found that HPRL was associated with SLE disease activity, and conventional immunosuppressive therapy decreased PRL concentrations in direct correlation with decreased SLE activity. These findings provide further support for the notion that PRL plays a role in the pathogenesis and clinical expression of SLE.

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