PROLACTIN SERUM LEVELS IN PEMPHIGUS PATIENTS

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ABSTRACT

Objectives: Pemphigus is an autoimmune blistering disease. Prolactin is a hormone that affects the immune system; elevated serum prolactin levels may reduce the destruction of autoimmune B-cell lines, lower the activation threshold of B-cells, and promote autoimmune responses. This study aims to investigate the difference in serum prolactin levels between pemphigus patients and a control group.

Subjects and methods: A case-control study was conducted on 30 pemphigus patients and 20 controls who visited Ho Chi Minh City Dermatology Hospital between January 20, 2022, and September 30, 2022, for serum prolactin level testing.

Results: Serum prolactin levels were significantly higher in the pemphigus group compared to the control group [12.9 (9.2 - 20.1) ng/ml vs. 6.7 (4.3 - 9.5) ng/ml; p = 0.0001]. The study also found a moderate positive correlation between serum prolactin levels and the extent of skin lesions in the patient group (r = 0.39, p = 0.03).

Conclusions: Serum prolactin levels were significantly higher in pemphigus patients compared to the control group.

Keywords: *Pemphigus, prolactin.*

1. INTRODUCTION

Pemphigus is a chronic, life-threatening autoimmune blistering disease characterized by intraepidermal separation and acantholysis. Pemphigus vulgaris and pemphigus foliaceus account for 90-95% of diagnosed pemphigus cases[1]. The pathogenesis of pemphigus involves B-cells losing tolerance to the self-antigen Desmoglein (Dsg), producing IgG autoantibodies against Dsg-1 and Dsg-3.

Prolactin, a hormone found in both men and women, is secreted by the anterior pituitary gland. It plays a role in both innate and adaptive immunity, influencing the maturation of CD4+ and CD8+ T cells. Serum prolactin levels are also linearly correlated with the number of CD4+ T cells and B lymphocytes. Elevated serum prolactin levels may reduce the destruction of autoimmune B-cell lines, halt receptor editing,

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lower the activation threshold of B-cells, and promote autoimmune responses. Additionally, prolactin enhances immunoglobulin production and stimulates the development of antigen-presenting cells[2].

Several previous studies have shown an association between serum prolactin levels and pemphigus[3-6], though some have yielded contradictory results[3,7]. However, each study had limitations such as not using immunofluorescence for diagnosis, assessing disease severity only by skin lesion area, or only measuring prolactin levels in untreated patients. Furthermore, prolactin levels are influenced by many factors that were not tightly controlled, such as physical activity, circadian cycles, and menopausal status.

In Vietnam, no studies have yet examined serum prolactin levels in pemphigus patients. Therefore, this study aims to investigate the difference in prolactin levels between pemphigus patients and healthy controls, and to explore the relationship between serum prolactin levels and the epidemiological and clinical characteristics of pemphigus. By focusing on eliminating confounding factors in serum prolactin measurements, this study includes both untreated and treated pemphigus patients. The findings may contribute to a deeper understanding of prolactin's role in pemphigus and its relationship to the clinical features of the disease, serving as a foundation for further research and clinical trials in the future.

2. SUBJECTS AND METHODS

2.1. Study subjects

The study group consisted of 30 patients diagnosed with pemphigus based on clinical, histological, and/or immunofluorescence findings. Patients with conditions that could alter prolactin levels, such as pregnancy, breastfeeding, prolactin-secreting pituitary tumors, kidney failure, and liver cirrhosis[8], were excluded. Patients who had taken medications affecting prolactin levels within the last two weeks, such as antipsychotics, antidepressants, opioids[9], and dopamine agonists[8], were also excluded. The control group included 20 healthy individuals.

2.2. Study methods

Study design

This case-control study was conducted at Ho Chi Minh City Dermatology Hospital from January 2022 to September 2022.

Study procedure

Patients visiting the hospital were diagnosed with pemphigus by physicians at Ho Chi Minh City Dermatology Hospital through medical history, clinical examination, and histopathological tests. For unclear cases, immunofluorescence was used for confirmation.

Patients diagnosed with pemphigus and meeting the inclusion criteria without exclusion criteria were thoroughly informed about the study's objectives and procedures. Those who agreed to participate signed a consent form. Data collection and necessary information were then recorded in the data collection form. To minimize the effects of circadian rhythms and physical activity, blood samples were collected between 8:00 and 10:00 AM, after patients had rested for at least 30 minutes. One milliliter of venous blood was drawn into a 5 ml syringe. The blood sample was placed in a 2 ml vial, stored in an ice container, and transported within two hours to the Medic Medical Center for free prolactin level testing using the electrochemiluminescence

immunoassay (ECLIA) method, performed on a Cobas e 801 immunoassay analyzer.

The Pemphigus Disease Area Index (PDAI) is a widely accepted measure of pemphigus disease activity. PDAI uses a scoring system from 0 to 263, with 250 points measuring disease activity (number and maximum size of lesions on the skin, scalp, and mucous membranes) and 13 points for post-inflammatory lesions. Disease activity is classified as mild if the PDAI score is < 15, moderate if the score is 15 - 45, and severe if the score is > 45[10].

Data Analysis

Data were entered, coded, and processed using Stata 16.0 software. The Chi-square test (χ^2) was used to compare two or more qualitative variables. The Student's t-test (for normal distribution) or Mann-Whitney U test (for non-normal distribution) was used to compare two means. The Spearman rank correlation test was employed to find correlations.

2.3. Research ethics

The researchers ensured that the study adhered to the ethical guidelines of the Helsinki Declaration. The study was approved by the Ethics Committee of the University of Medicine and Pharmacy, Ho Chi Minh City, under decision number 642/HĐĐĐ-ĐHYD, dated November 23, 2021.

3. RESULTS

3.1. General characteristics of study participants

The average age of the patient group was 52.5 (standard deviation: 14.3), while the control group had an average age of 52.6 (standard deviation: 14.4). The male-to-female ratio was 1:1 in both groups (Table 1).

Table 1. General characteristics of study participants in patient and control groups

Characteristic		Patient group	Control group	p
Age (mean ± SD)		52.5 ± 14.3	52.6 ± 14.4	0.98[a]
Age group	< 40 years, n (%)	8 (26.7)	5 (25)	0.95[b]
	40 - 59 years, n (%)	12 (40)	8 (40)	
	≥ 60 years, n (%)	10 (33.3)	7 (35)	
Gender	Male, n (%)	15 (50)	10 (50)	1.00[b]
	Female, n (%)	15 (50)	10 (50)	
Total		30	20	

[a]Mann-Whitney test.

[b]Chi-square test.

3.2. Pemphigus disease activity classification according to pdai in the patient group

Among female participants, the ratio of premenopausal to postmenopausal women was 1:1.1. There were 26 patients with pemphigus vulgaris and 4 with pemphigus foliaceus. Twenty patients had normal body mass index (BMI), while 5 were overweight and 5 were obese. The median age of disease onset in the patient group was 50 years (interquartile range: 37 - 64 years), and the median disease duration was 6.5 months (interquartile range: 1 - 12 months). The median

skin lesion area was 19.5% (interquartile range: 12%-31%). Among the patients, 15 (50%) had skin lesions covering < 20% of their body, 9 (30%) had lesions covering 20% - 39%, and 6 (20%) had lesions covering ≥ 40%. Pemphigus Disease Area Index (PDAI) scores ranged from 12 to 154, with a median of 19.5 (interquartile range: 12 - 31). Among patients, 16 (53.3%) had severe disease (PDAI > 45), 10 (33.3%) had moderate disease (PDAI 15-45), and 4 (13.3%) had mild disease (PDAI < 15) (Figure 1).

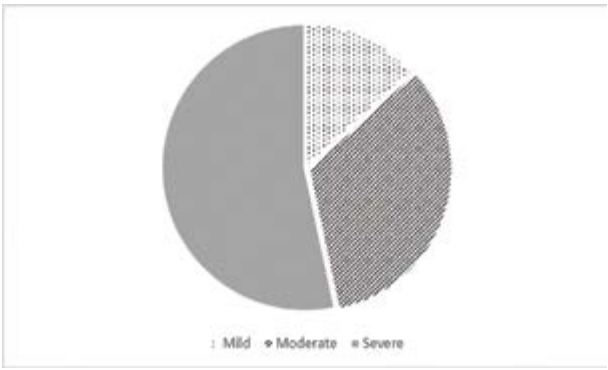

Figure 1. Pemphigus disease activity classification according to pdai in the patient group (N = 30)

3.3. Serum prolactin levels in patient and control groups

The median serum prolactin level in the patient group was 12.9 ng/ml (interquartile range: 9.2 - 20.1), compared to 6.6 ng/ml (interquartile range: 4.3 - 9.5) in the control group. Serum prolactin levels were significantly higher in the patient group (p = 0.0001) (Figure 2).

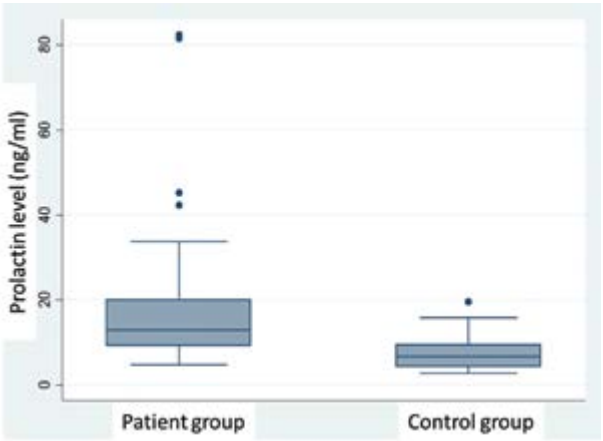

Figure 2. Serum prolactin levels in patient and control groups

3.4. Serum prolactin levels and clinical characteristics in the patient group

Table 2. Serum prolactin levels and clinical characteristics

		Median (ng/ml) (IQR)	p[a]
Gender	Male (n = 15)	11.5 (8.3 - 16.3)	0.08
	Female (n = 15)	15.4 (10.6 - 42.3)	
Menopausal status	Premenopausal (n = 7)	33.8 (18.7 - 45.2)	0.06
	Postmenopausal (n = 8)	11.8 (9.3 - 14.6)	
Disease type	Pemphigus vulgaris (n = 26)	13.6 (10.6 - 25.4)	0.13
	Pemphigus foliaceus (n = 4)	8.9 (7.5 - 12.3)	

[a]*Mann-Whitney test.*

No significant associations were found between serum prolactin levels and clinical characteristics such as gender, menopausal status, or disease type (Table 2).

3.5. Correlation between serum prolactin levels and clinical characteristics in the patient group

Table 3. Correlation between serum prolactin levels and clinical characteristics in the patient group

Variable	Correlation (r)	p[a]	Significance
Serum prolactin and age	- 0.12	0.54	No correlation
Serum prolactin and age of onset	- 0.13	0.49	No correlation
Serum prolactin and disease duration	- 0.14	0.47	No correlation
Serum prolactin and BMI	0.04	0.85	No correlation
Serum prolactin and disease activity (PDAI)	0.14	0.45	No correlation
Serum prolactin and skin lesion area	**0.39**	**0.03**	Moderate positive correlation

[a]Spearman rank correlation test.

There were no significant correlations between serum prolactin levels and variables such as age, age of onset, disease duration, BMI, or disease activity as measured by PDAI. However, a moderate positive correlation was observed between serum prolactin levels and skin lesion area (Table 3).

4. DISCUSSION

Normal prolactin levels in men are 4 - 22 ng/ml, and in women, 6 - 30 ng/ml. Our study recorded the median and interquartile range of serum prolactin levels in the patient group as 12.9 (9.2 - 20.1) ng/ml, and in the control group as 6.6 (4.3 - 9.5) ng/ml, both within the normal range. However, the serum prolactin levels in the patient group were significantly higher than in the control group ($p = 0.0001$). All individuals in the control group had normal prolactin levels, while in the patient group, 1 male and 5 females had elevated prolactin levels above normal.

Similar to our findings, Mohammad Kazem Fallahzadeh's study reported higher serum prolactin levels in the patient group compared to the control group (21.6 ± 3.5 ng/ml vs. 11.4 ± 0.7 ng/ml, $p = 0.048$)[4]. Maryam Yousefi's research[11] also noted significantly higher total and free serum prolactin levels in pemphigus patients compared to controls (both with $p = 0.01$). Amina Toumi's study[6] similarly found higher prolactin levels in the patient group compared to the control group (16.1 ± 15.8 ng/ml vs. 5.9 ± 1.2 ng/ml, $p = 0.023$). In contrast, Afaf Helmy's research[7] found no statistically significant difference between the patient and control groups (14.5 ± 12.5 ng/ml vs. 8.4 ± 2.5 ng/ml, $p = 0.4$). Thus, the majority of studies, including ours, found that serum prolactin levels in pemphigus patients were significantly higher than in controls.

Prolactin acts as a cytokine that regulates immune responses[12]. Prolactin receptors are found on human T and B lymphocytes, and some data suggest that T lymphocytes depend on prolactin to maintain immune competency[13].

It prevents B lymphocytes from undergoing programmed cell death and enhances the production of autoantibodies[14]. Prolactin stimulates the synthesis of TNF-alpha, increases interleukin-2 secretion, and promotes lymphocyte proliferation[15]. At high concentrations, prolactin enhances the differentiation of monocytes into immature dendritic cells and promotes the maturation of these cells, which are highly efficient antigen-presenting cells. This may be significant in initiating responses against autoantigens expressed by major histocompatibility complexes, potentially explaining the association of high prolactin levels with autoimmune diseases[16].

Elevated prolactin levels have been observed in several autoimmune diseases such as systemic lupus erythematosus, diabetes, Graves' disease, and multiple sclerosis. This correlation may depend on the bidirectional communication between neuroendocrine disorders and immune diseases[17]. Pemphigus is an autoimmune blistering disease in which B cells lose tolerance to self-antigens (Dsg) and produce IgG autoantibodies against Dsg-1 and Dsg-3. CD4+ Dsg-specific T cells help stimulate B cells to produce these antibodies. Elevated serum prolactin may increase B lymphocytes, boost autoantibody production, and thus play a role in autoimmune conditions like pemphigus.

Khandpur and Reddy reported a strong association between the severity of pemphigus vulgaris and serum prolactin levels in a 21-year-old woman with idiopathic hyperprolactinemia and widespread mucocutaneous pemphigus. The authors found a positive correlation between the severity of pemphigus vulgaris, serum prolactin levels, and circulating IgG autoantibody titers measured by indirect immunofluorescence. The patient was treated with bromocriptine (a prolactin-lowering drug), and the lesions improved. When the treatment was stopped, the pemphigus lesions recurred, but improved again after resuming bromocriptine and prednisolone. The patient was then maintained on bromocriptine. This study concluded that the correlation between serum prolactin levels and circulating IgG autoantibody titers, along with a good response to bromocriptine therapy, may suggest a causal relationship between pemphigus vulgaris severity and prolactin levels[18].

Our study found a moderate positive correlation between serum prolactin levels in the patient group and the extent of skin lesions ($r = 0.39$, $p = 0.03$). This result is consistent with previous studies: Mohammad Kazem Fallahzadeh[4] also reported a positive correlation between serum prolactin levels and skin lesion area ($p < 0.01$). Afaf Helmy's study[7] recorded a strong positive correlation between serum prolactin levels and the extent of skin lesions ($r = 0.79$, $p < 0.001$). Helmy also found that patients with skin lesion areas ≥ 40% had higher serum prolactin levels compared to those with 20 - 39% lesion areas, and the lowest levels were found in patients with less than 20% lesion areas ($p = 0.001$).

Our study aligns with global research, demonstrating a positive association between serum prolactin levels and the extent of skin lesions in pemphigus patients. This suggests that patients with high prolactin levels may be at greater risk for severe disease with widespread skin lesions.

5. CONCLUSIONS

The serum prolactin levels in pemphigus patients were significantly higher than in the

control group. In the patient group, serum prolactin levels showed a moderate positive correlation with the extent of skin lesions. This result suggests that serum prolactin levels may be used as a prognostic test for the spread of pemphigus.

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Conflict of interest statement: The authors declare that there is no conflict of interest in this study.

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