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Serum level of prolactin in psoriatic patients

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Abstract

Background: Psoriasis is a chronic inflammatory hyper-proliferative disease of the skin, scalp, nails, and joints. It has been hypothesized that prolactin (PRL) may modulate the skin immune system and may be involved in the pathogenesis of psoriasis. Psoriasis exerts significant, negative impact on patients' quality of life. Relatively high rates of depression are reported in patients with psoriasis.

Objectives: The aim of this work was to study the possible role of PRL in the pathogenesis of psoriasis and its correlation with the disease activity and emotional status of the patients.

Subjects and methods: This study included 30 patients with chronic generalized psoriasis and 10 healthy subjects served as controls, attending the Outpatient Clinic of Dermatology and Venereology Department, Tanta University Hospital. Serum samples were taken from all patients before and after 4 weeks of treatment with 25 mg / week of methotrexate (MTX) (I.M injection) for detection of PRL serum levels by ELISA, while serum samples were taken from control subjects once for comparison. Psychological instruments; [The Hamilton Depression Scale(HAMD) and The Hamilton Anxiety Scale(HAMA)] were used to screen the broad range of psychological factors that have been implicated in psoriasis.

Results: Serum PRL levels were statistically highly significant among patients compared to controls, with significant decrease among patients after treatment. A significant positive correlation was found between PRL serum levels and PASI score before and after treatment. Correlations between HAMA and HAMD with PASI were statistically significant before and after therapy, and so the correlations between HAMA and HAMD with PRL serum levels were also statistically significant before and after therapy.

Conclusion: Prolactin seems to have a role in the pathogenesis of psoriasis. This role may represent a cause and/or a consequence of psoriasis pathology. The most likely scenario is that PRL enhances interferon-induced chemokine production in keratinocytes, thereby facilitating cutaneous T-cell infiltration. This raises the intriguing prospect that PRL may offer a novel future therapeutic target in psoriasis and other skin diseases that worsen in response to psychological distress.

Introduction

Psoriasis is an inflammatory disease characterized by hyper-proliferation of keratinocytes and accumulation of T cells in the epidermis and dermis of psoriatic lesions. [1] Evidence for the central role of T helper (Th1) lymphocytes comes from both animal models of psoriasis and from trials of treatment with T-cell inhibitors. [2] There is some evidence that psoriasis worsens at ages when hormonal changes such as puberty and menopause are taking place, and may also worsen or improve during pregnancy. [3]

Prolactin (PRL), a neuropeptide secreted by the anterior pituitary gland, possesses a variety of physiological actions. It has been implicated as an important immuno-modulator and exerts a proliferative effect in cultured human keratinocytes via specific receptors. Some studies have indicated an increase in serum PRL levels in psoriasis and exacerbation of psoriasis when a prolactinoma is present. [4,5]

Emotional disturbances are one of the most important causes of hyper-prolactinaemia, [6] and stress is significantly associated with exacerbations of psoriasis, thus secondary hyper-prolactinaemia due to stress cannot be excluded, nevertheless some authors believe that PRL may play a role in the pathogenesis of psoriasis. [7,8]

Aim of the work

The aim of this work was to study the possible role of PRL in the pathogenesis of psoriasis and its correlation with the disease activity and emotional status of the patients.

Patients and Methods

This study included 30 patients with chronic generalized psoriasis; 24 males & 6 females. Their age ranged from 21-70 years with a mean of 47.833 ±12.123 and 10 healthy subjects served as controls, they are age and sex matched with the studied patients. Their age ranged from 20-66 years with a mean of 42.100±14.685. They included 7 males and 3 females attending the Outpatient Clinic of Dermatology and Venereology Department of Tanta University Hospital during the period from October 2010 to May 2011. The patients were subjected to:

1- Full history taking:

Including personal history, history of the disease (age of onset, duration and extension of the disease), past history (history of drug intake, lactation, menstrual irregularities in females and andrological complaints in males) and family history.

2- Full clinical examination including:

A complete dermatological examination was done for each patient so as to determine the extent and distribution of the disease .Clinical severity of psoriasis was assessed by using the Psoriasis Area Severity Index (PASI) score. Points for erythema, infiltration and desquamation of the skin ranged from 1 to 4, and the involved area from 1 to 6, thus theoretically the PASI ranges from 0 to 72, with higher scores indicating more severe condition. In our study mild psoriasis was classified as a PASI less than 7, moderate psoriasis as a PASI between 7 and15, and severe psoriasis as a PASI of >15. [9]

The following patients were excluded from the study:-

-Hepatic and renal patients, pregnant or lactating females, patients who are receiving any medications affecting PRL such as phenothiazines (chrompromazine), antidopaminergic agents (metaclopromide), antihypertensive agents (calcium channel blockers, methyldopa) and H2 blockers (cimetidine) and endocrinopathies

3- Therapeutic management:

Each patient received 1cm / 25 mg / week of methotrexate (MTX) for 4 weeks (I.M injection).

4- Clinical assessment:

Clinical assessment consisted of clinical response determination after 4 weeks. Photographs of the body sites affected by psoriasis were taken for each patient before and after the end of treatment. The clinical response to therapy was scored by using PASI score.

5- Laboratory investigation:

All studied patients were subjected to the following laboratory investigations:-Complete blood picture, liver and renal function tests, chest and brain x ray and abdominal Ultrasonography.

Hormonal assay that included serum PRL measured by ELISA technique before and after the duration of treatment with MTX (4 weeks). The PRL was measured by using DRG kit supplied by Clinilab (Louhi-Finland). The specimen was taken between 8-10AM, blood was collected by veinpuncture, allowed to clot, the serum separated by centrifugation at room temperature and stored at 20°C until used. 25μl of each standard, control and samples were dispensed into appropriate wells,100 μl Enzyme Conjugate was dispensed into each well, and incubated for 30 minutes at room temperature, then the wells was rinsed 5 times with distilled water,100 μl of Substrate Solution was added to each well and was incubated for 10 minutes at room temperature, the enzymatic reaction was stopped by adding 50 μl of Stop Solution to each well.[10]

6- Specific and generic measures of psychological distress:

The psychological instruments were as follows:

-The Hamilton Depression Scale (HDS, HAMD or HAD) is a depression test measuring the severity of clinical depression symptoms. It consists of 21 items, each defined by series of symptoms. Some items were rated on a 5-points scale, ranging from 0 (not present) to 4 (severe), another items were rated on a 3-points scale, ranging from 0 (not present) to 2 (severe). The scoring is based on the first 17(0-7 = Normal, 8-13 = Mild Depression, 14-18 = Moderate Depression, 19-22 = Severe Depression,≥23 = Very Severe Depression). [11]

- The Hamilton Anxiety Scale (HAMA) is a rating scale developed to quantify the severity of anxiety symptomatology. It consists of 14 items, each defined by a series of symptoms. Each item is rated on a 5-point scale, ranging from 0 (not present) to 4 (severe), with a total score range of 0-56, where <17 indicates mild severity, 18-24 mild to moderate severity and 25-30 moderate to severe. [12]

The questions of the 2 questionnaire were asked to the patients before and after the duration of the treatment with MTX.
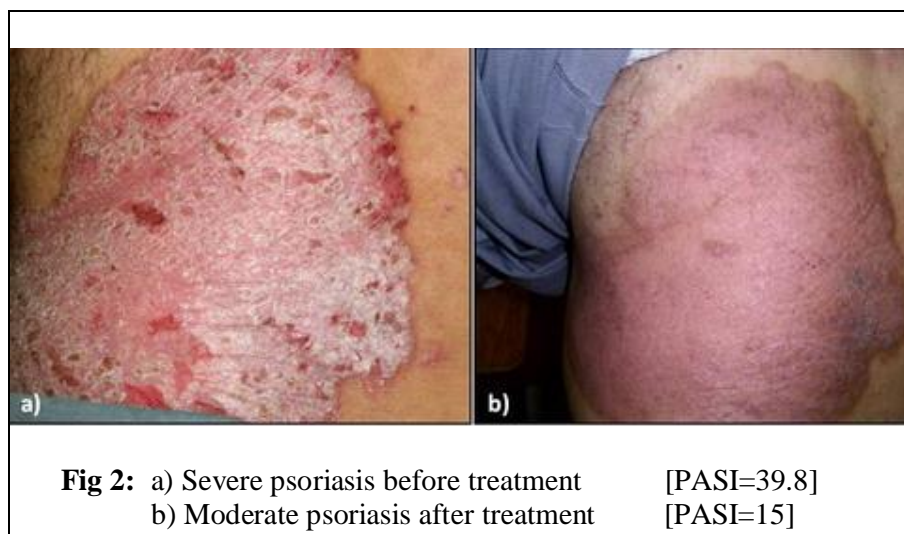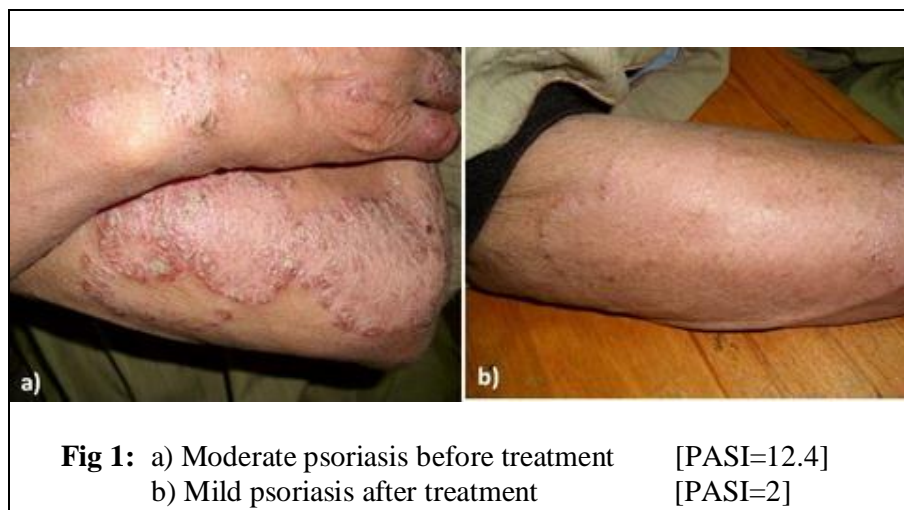
Statistics

Statistical presentation and analysis of the present study was conducted, using the mean, standard error, student t- test and Chi-square, by SPSS V17. Statistical significance was determined at a level of $P < 0.05$.

Results

Clinical results:

In this study the duration of the psoriasis ranged from 2 years to 43 years, with a mean of 14.0 ±12.382 years. As regards family history, 2 out of the 30 patients had positive family history (6.67%). According to PASI score, 7 patients (23.33%) were classified as moderate psoriasis, 6 of them became mild (**Fig 1**) and 1 remained moderate after therapy, 23 patients (76.67%) were classified as severe psoriasis, 8 of them became mild, 9 became moderate (**Fig 2**) and 6 remained severe after therapy. There is a significant decrease in the value of PASI before and after therapy (**Table 1**).

Fig 1: a) Moderate psoriasis before treatment   [PASI=12.4]
        b) Mild psoriasis after treatment   [PASI=2]

Fig 2: a) Severe psoriasis before treatment   [PASI=39.8]
        b) Moderate psoriasis after treatment   [PASI=15]

| PASI score before ttt		PASI score after ttt			
		Mild	Moderate	Severe	Total
Moderate	N	6	1	0	7
	%	20	3.33	0	23.33
Severe	N	8	9	6	23
	%	26.67	30	20	76.67
Total	N	14	10	6	30
	%	46.67	33.33	20	100
Chi-square	X^2	6.973			
	P-value	0.031*			

ttt: treatment   *: significant

Table (1): The values of PASI score before and after therapy.

Laboratory results:

Serum levels of PRL in the group of patients ranged from 31.5 ng/ml to 80.6 ng/ml with a mean and SD of 49.590 ng/ml ± 15.473 in comparison with controls that ranged from 7-20 ng/ml with a mean and SD of 14.00 ± 5.228, so the cutoff point between control group and patients group is 20 ng/ml **(Fig 3)**. There is statistically highly significant increase among patients (P=0.000). As regards the serum levels of PRL after therapy, they ranged from 9.0 to 40.0 ng/ ml with a mean and SD of 20.553 ± 8.276 with significant decrease in comparison with values before treatment **(Table 2)**.
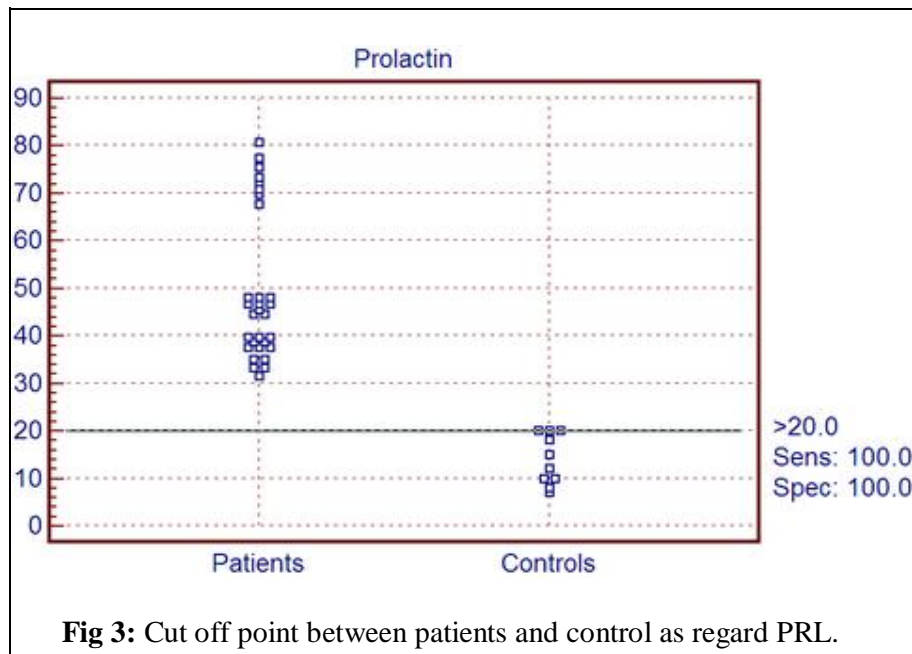
Fig 3: Cut off point between patients and control as regard PRL.

	Prolactin			Paired T-test	
	Range	Mean	± SD	T	P-value
Before ttt	31.5 - 80.6	49.59	± 15.473		
After ttt	9 - 40	20.553	± 8.276	15.823	0.000*

Table (2): Serum PRL levels in psoriasis patients before and after

therapy.

Psychological results:

The values of HAMA score before therapy ranged from 3.0 to 29.0 with a mean and SD of 13.733 ± 6.938, while after therapy the values significantly decreased, they ranged from 1.0 to 18.0 with a mean and SD of 7.600 ± 5.076 (p=0.000) (Table 3). The values of HAMD score before therapy ranged from 2.0 to 23.0 with a mean and SD of 9.700 ± 6.353, while after therapy the values significantly decreased, they ranged from 1.0 to 18.0 with a mean and SD of 5.100 ± 3.772 (p=0.000) as shown in **(Table 3)**.

	HAMA			Paired T-test	
	Range	Mean	± SD	t	P-value
Before ttt	3 - 29	13.733	± 6.938		
After ttt	1 - 18	7.6	± 5.076	8.279	0.000*
	HAMD			Paired T-test	
	Range	Mean	± SD	t	P-value
Before ttt	2 - 23	9.7	± 6.353		
After ttt	1 - 18	5.1	± 3.772	7.367	0.000*

Table (3): Comparison between the values of HAMA and HAMD scores

before and after therapy.

Correlations between HAMA and HAMD with PASI and PRL before therapy were statistically significant **(Table 4)**.Correlations between PRL with HAMA, HAMAD and PASI were statistically significant after therapy **(Table 5)**.

Correlations		PASI before ttt	PRL Before ttt	HAMA before ttt
HAMA before ttt	r	0.848	0.822	
	P-value	0.000*	0.000*	
HAMD before ttt	r	0.918	0.9	0.794
	P-value	0.000*	0.000*	0.000*

Table (4): The correlation between HAMA and HAMD with PASI and PRL before therapy.

Correlations		PASI after ttt	Prolactin after ttt	HAMA after ttt
Prolactin after ttt	r	0.923		
	P-value	0.000*		
HAMA after ttt	r	0.839	0.835	
	P-value	0.000*	0.000*	
HAMD after ttt	r	0.918	0.808	0.816
	P-value	0.000*	0.000*	0.000*

Table (5): The correlation between PRL with PASI, HAMA and HAMD, and the correlation between HAMA and HAMD with PASI after therapy.

Discussion

Stress and hormonal factors have been reported to be implicated in the pathogenesis of psoriasis. [13] It has been hypothesized that PRL may modulate the skin immune system and may be involved in the pathogenesis of psoriasis. Functional PRL receptors are detected on keratinosis and PRL effectively increased the in vitro growth of keratinocytes in psoriasis. [14] PRL acts as a neuroendocrine modulator of both skin epithelial growth and the skin immune system. It is hypothesized to be integrated in a multilevel neuroendocrine-immune communication along the "brain-skin axis". Stress has been reported to trigger and exacerbate psoriasis; therefore, it may represent a link between prolactin and the disease pathogenesis. [15] So, the aim of this study was to study the possible role of PRL in the pathogenesis of psoriasis and its correlation with the disease activity and emotional status of the patients.

Our results revealed that serum level of PRL was significantly higher in psoriatic patients than controls and were significantly reduced after treatment and there was a correlation between serum PRL levels and PASI. These results are consistent with those of Dilme-carreras et al. [8], their study included 20 patients of psoriasis, and 20 healthy controls. PRL levels were measured by Enzyme- linked Immuno Assay (EIA) in serum of patients of psoriasis before and after treatment with tacalcitol ointment

4µ/g once a day for 6 weeks and disease severity was assessed by PASI in all patients. Serum levels of PRL were significantly higher in patients than controls before treatment. They also found that PRL levels were significantly reduced after treatment with tacalcitol and there was a correlation between pretreatment serum PRL levels and PASI. Also in a study done by El-Khateeb et al. [16], who initiated a study including 15 psoriasis patients and 15 healthy volunteers as controls, PASI score was evaluated, and PRL levels in serum and blister fluid were assessed by (ELISA). PRL levels were significantly elevated in blister fluid of psoriatic lesional skin. Correlations between PASI score and different serum PRL levels in lesional and non-lesional skin were insignificant. Significant positive correlations of prolactin level were observed between lesional and non-lesional skin in psoriasis and between serum and clinically normal skin in both psoriasis and control subjects.

Regana and Millet, 2000 reported three cases of women with plaque-type psoriasis that severity and extent of the skin lesions correlated with development of a prolactinoma [17]. All three patients were treated with bromocriptin. They had normalization of PRL level and also improvement of psoriatic lesions. Then, they discontinued bromocriptin and all cases had relapsed in psoriasis. On the other hand Azizzadeh et al. [14] found that although levels of serum PRL, which were determined by ELISA in 30 psoriatic patients compared with 30 controls using Pishtaz Teb kit, has a mean level in psoriatic patients was not significantly higher than the control group. However, there was statistically significant relation between severity of disease and serum prolactin.

Our results revealed also that, values of HAMA and HAMD score were significantly high in all psoriatic patients, they were significantly decreased after treatment, and there was a correlation between these values and PASI. These results are in accordance with Verhoeven et al. [18] who found a significant association between stress and disease severity. This prospective study of 62 psoriasis patients determined high levels of daily stressors to be related to an increase in disease severity 4 weeks later. In another study carried out by Erick Chern et al. [19], thirty-six patients with psoriasis receiving conventional treatment and 48 patients receiving the Goeckerman regimen (UV irradiation and coal tar) were recruited to the study. Clinical severity was evaluated weekly using PASI. Psoriasis Disability Index (PDI) and Hospital Anxiety and Depression Scale (HADS) questionnaires were applied at admission and one month after discharge. The mean PASI score in the Goeckerman group decreased and PDI scores decreased. HADS scores for anxiety and depression decreased significantly. In comparison with conventional therapy, the modified Goeckerman regimen showed similar clinical efficacy, with additional benefits in improving overall quality of life and psychosocial distress in patients with moderate/severe psoriasis, and more cost-effectiveness. Unlike the above studies Zachariae et al. [20] showed that stress responders differed significantly from non-stress responders. Stress responders tended to self-report greater disease severity than non-stress responders, even though clinical measures of disease severity (e.g. PASI)

did not vary between groups. Stress responders were, however, found to have more plaques of psoriasis on visible areas than non-visible regions.

The PRL may be locally produced in the skin, and such production revealed a relatively marked increase in psoriatic lesions. The cutaneous contribution of PRL may be diluted in the circulation before it reaches a threshold from which it can begin to influence the serum level of PRL, accordingly, it seems to have a role in the pathogenesis of psoriasis. This role may represent a cause and/or a consequence of psoriasis pathology. [16] There was a study involved 10 patients with early-onset chronic plaque psoriasis and 10 controls, skin biopsies were taken from all of them, that were subsequently analyzed immuno-histochemically. Both PRL and prolactin receptors were detected in epidermal keratinocytes, dermal fibroblasts, and sweat glands of healthy controls. By comparison, however, expression of PRL and PRL receptors was markedly up-regulated throughout the epidermis in psoriasis plaques, especially in the basal layer, probably because of local cutaneous production. No significant difference was noted between expression in the uninvolved skin of psoriasis patients and samples from normal controls. [21]

Prolactin enhances proliferation of IFN-γ production in T cells or natural killer cells and potentiates IFN-γ -induced chemokine production in keratinocytes which, in turn, generates abundant infiltrates of type I T cells. It stimulates the hyper-proliferation of keratinocytes and induces angiogenesis through the production of vascular endothelial growth factor. PRL induces CCL20 secretion from epidermal keratinocytes in psoriatic lesions, which recruit Th17 cells that release IL-17. PRL and IL-17 cooperate in a positive feedback loop to increase CCL20 secretion. This process may aggravate the Th17-mediated inflammation in psoriatic lesions. It stimulates antigen-presenting cells by increasing the expression of MHC class II or co-stimulatory molecules, CD40, B7-1, or B7-2. [16] Given that cyclosporine A (CsA) is an effective treatment for psoriasis, [22] it deserves mentioning that PRL reportedly competes with CsA for a common binding site on T lymphocytes and that stimulation of PRL secretion reverses the immuno-suppression induced by CsA. CsA also inhibits PRL-mediated induction of ornithine decarboxylase, and bromocriptine and CsA have synergistic effects in the treatment of autoimmune diseases. If PRL can indeed blunt the efficacy of CsA therapy, this might be countered by co-administration of bromocriptine or related dopaminergic agents, or by previously unreported PRLR antagonists. This might allow more effective, but less toxic, lower-dose CsA therapy in psoriasis. [23] It is possible that differences in peripheral or lymphocyte, rather than pituitary production of PRL may worsen disease activity in certain patients. Of the currently available prolactin-lowering drugs, bromocriptine at least has been shown to decrease both peripheral and pituitary PRL production and may represent a useful adjunctive therapy in certain patients, particularly those with refractory disease. [24]

In conclusion

Prolactin seems to have a role in the pathogenesis of psoriasis. This role may represent a cause and/or a consequence of psoriasis pathology. This raises the intriguing prospect that PRL may offer a novel future therapeutic target in psoriasis and other skin diseases that worsen in response to psychological distress.

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