

Elevated serum prolactin levels as a marker of inflammatory arthritis in psoriasis vulgaris

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Background and Aims. Psoriasis vulgaris (PV) is complicated in up to 40% patients by the inflammatory joint disease psoriatic arthritis (PsA). Neither the aetiology of the arthritis nor specific laboratory markers for its disease activity have been clearly elucidated. Prolactin (PRL) acts as a cytokine with immunomodulatory functions and plays a role in skin and joint biology. The results on PRL however as a marker are unclear. The aim of this study was to confirm whether serum PRL levels reflect systemic complications of PV, like inflammatory joint disease and/or can serve as a marker of disease activity in both cases.

Methods. A total of 70 patients with PV without arthritis and 40 patients suffering from PsA were included. In all patients, we determined skin disease activity according to the PASI index and in PsA, active disease assessed as swollen or tender joints. The control group included 27 age and sex matched healthy individuals. The concentration of PRL in the serum was measured by immunoradiometric assays.

Results. The PRL serum levels were significantly increased in PsA patients (299.2 ± 28.29 mIU/L) compared to PV only patients ($201.4.2 \pm 11.72$ mIU/L), $P = 0.0003$ and healthy individuals (198.2 ± 15.31 mIU/L), $P = 0.007$. The serum PRL levels in PsA with active disease 336.8 ± 42.50 (mIU/L) were higher than in PV and controls, $P < 0.0001$ and $P = 0.002$ respectively. In PV only patients, there was no correlation between PASI and PRL levels.

Conclusion. Our results showed that PRL serum levels are a marker of active arthritis in PsA and reflects systemic complication rather than local skin activity.

Key words: prolactin, serum levels, psoriasis vulgaris, psoriatic arthritis, arthritis, immune cells

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INTRODUCTION

The inflammatory skin disease, psoriasis, affects approximately 1-3% of the population usually during adulthood^{1,2}. This disorder presents as a number of many subtypes including guttate, pustular and palmoplantar psoriasis. However, psoriasis vulgaris (PV) which manifests as plaque psoriatic lesions affecting variously, large areas of the body with varying intensity is the most common type. The hallmarks of PV pathogenesis include inflammation of dermis and epidermis due to invasion of activated immune cells particularly Th17 and Th1 lymphocytes and changes in keratinocyte differentiation leading to hyperproliferation^{3,4}.

The clinical course of psoriasis may be complicated by the concomitant joint disease, psoriatic arthritis (PsA), in 7-40% of patients^{5,6}. The relationship between skin and joint manifestation is not clear. Although PsA can develop in 75% of psoriatic patients during the skin manifestation (approximately 10 years after skin disease onset), the joint disease may precede the skin disease or both manifestations may develop in the same time⁷. The severity of joint

involvement usually does not reflect the intensity of skin manifestation. On the other hand some types of skin involvement particularly nail psoriasis are more common in PsA (ref.⁸). PsA is member of the spondylarthropathies and the arthritis is usually seronegative⁹. Clinically it appears as asymmetric oligoarthritis as the most frequent image of PsA, although in a half of patients there may occur symmetric polyarthritis or distal interphalangeal arthritis^{10,11}. On the other hand, the most severe subtype of PsA, arthritis mutilans is rare while spondylitis and/or sacroiliitis including HLA B27 positivity are found in only 5-10% of patients^{10,11}. In addition to arthritis, one third of patients develop dactylitis or inflammatory enthesopathy^{10,11}. The pathogenic background of PsA consists of synovitis due to infiltration of inflammatory cells (particularly CD163+ macrophages), local cytokines synthesis like TNF- α and IL-6 and IL-17, neovascularisation and proliferation of synovial tissue leading to bone destruction^{12,13}.

Determining risk factors and biomarkers for PsA development in psoriatic patients is a key to early PsA diagnosis and management. To date, several genomic regions have been identified as linked to psoriasis but

some of them overlap with PsA (ref.¹⁴). Second, other factors such as trauma, psychological stress and hormonal disturbances (e.g. pregnancy) are connected with both disease progressions. All of these situations are associated with hyperprolactinemia. Prolactin (PRL) is an anterior pituitary hormone and besides its role in reproduction, it is part of the hypothalamus-pituitary-adrenal (HPA) axis and it is released after stressful events^{15,16}. Prolactin is also produced by extra-pituitary sites including immune cells. The PRL receptor is thus expressed on many cell types including immune cells and keratinocytes and several PRL immunomodulatory functions have been described¹⁶. Experimentally, keratinocytes under PRL, synthesize chemokines with C-X-C and C-C motif which support Th1 and Th17 lymphocyte migration into psoriatic plaques^{17,18}. Recently it has been shown that PRL enhances inflammation and Th17 and Th1 cytokine production in a mouse model with imiquimod-induced psoriasisiform skin changes¹⁹. PRL is overexpressed in psoriatic skin lesions²⁰. Dilmé-Carreras found a positive correlation between serum PRL levels and the corresponding index PASI (psoriasis area and severity index) after tacalcitol treatment²¹. Conversely, bromocriptine as a drug that downregulates PRL pituitary release was found to be effective in PsA treatment²².

The aim of this study was to determine whether serum PRL levels reflect systemic complications of PV, like inflammatory arthritis and/or may serve as marker of disease activity in PV and/ PsA.

METHODS

Patients

A total of 70 patients with psoriasis vulgaris (PV) and 40 patients suffering from PsA (determined as seronegative arthritis in psoriatic patients⁹) were enrolled in the study. The control group consisted of 27 healthy age and

sex matched individuals. For demographic description and characterisation of PV and PsA patients, see Table 1. All PV patients were assessed for skin disease activity according to the Psoriasis Area and Severity Index (PASI) (ref.²³). We screened for PsA to exclude subjects with any current or past musculoskeletal manifestations. In the PsA group, active disease was defined as at least 4 swollen and tender joints. Joints were investigated clinically by experienced physicians. In the case of unclear findings, the investigation was confirmed independently by two rheumatologists. In all patients we assessed the type of PsA, performed x-rays and immunological analysis to exclude rheumatoid factors. Concomitant diseases and medication were noted in both groups. Local treatment was allowed in both groups. Patients and healthy individuals were screened for other autoimmune diseases and those suffering for some of these illnesses were excluded. All participants were asked for the other diseases (like hypothyreosis, hypertension, diabetes, ischemic diseases, infections and others) and all individuals with any known disease or new problems were excluded from the study. Moreover, pregnant or breastfeeding women or individuals using drugs affecting PRL secretion were not included in this study. The study was approved by the Ethical Committee of the Institute of Rheumatology in Prague, and all patients agreed with participation by signing the informed consent.

Laboratory Analysis

As the PRL serum levels reflect physiological diurnal variation, the blood samples were taken in the morning hours (at least 1 h after waking up) and after at least 20 min at rest before sampling. The concentration of PRL in serum and synovial fluid was measured in duplicate using an immunoradiometric assay (IRMA, Immunotech, Prague). Samples (50 µL) were incubated with ¹²⁵I-labelled antibody (150000 cpm/500 µL) in tubes pre-coated with mice monoclonal antibody for one hour

Table 1. Demographic Data: Psoriasis Vulgaris (PV), Psoriatic Arthritis (PsA) and Healthy Individuals (Controls).

	PV n=70	PsA n=40	Controls n=27	
Age	46.30±1.629	48.55±2.170	45.74±1.856	ns
Women/Men	32/38	20/20	18/9	ns
Postmenopausal Women (%)	43.8	45.0	33.0	ns
Biologic Therapy	21 (30%)	1 (2.5%)		<i>P</i> <0.001
DMARDs	0	30 (75%)		<i>P</i> <0.001
Peripheral arthritis	0	40 (100%)		<i>P</i> <0.001
oligo/monoarthritis	0	29 (72.5%)		<i>P</i> <0.001
polyarthritis	0	11 (27.5%)		<i>P</i> <0.001
arthritis mutilans	0	0		ns
Enthesitis	0	18 (45%)		<i>P</i> <0.001
Sacroiliitis /Spondylitis	0	2 (5%)		ns
Dactylitis	0	1 (2.5%)		ns
Nail involvement	0	10 (25%)		<i>P</i> <0.001

Abbreviations: Biologic therapy: etanercept, infliximab, adalimumab, ustekinumab, efalizumab; DMARDs – Disease-Modifying Antirheumatic Drugs (methotrexate, sulfasalazin, cyclosporin A); ns – not significant. *P* value was determined by Chi² test.

at room temperature by continuous shaking. The contents of tubes were then aspirated. The tubes were washed twice with 2 mL of wash solution, and the radioactivity bound to the tubes was measured using a gamma counter. The standards supplied with the kits were calibrated using the international standard WHO 84/500 (1 ng/mL=30.3 mIU/L). The limit of sensitivity of the assay was 30 mIU/L. The intra- and inter-assay coefficients of variation were determined with the use of pooled patients' serum samples and were 4.5 and 8.8%, respectively. In the test there was no cross reactivity to other human hormones (hLH, hFSH, hTSH, hCG, hGH and HPL). The levels of IgM rheumatoid factor (IgM-RF) were analysed by ELISA (Test Line s.r.o., Czech Republic), C-reactive protein (CRP) by nephelometry.

Statistical analysis

The IBM statistics software SPSS version 17 (<http://www.spss.com>) was used for statistical analysis. The levels of PRL were normally distributed, and therefore the student's t-test was used to analyse the difference between the two groups. *Spearman* correlation coefficient was used for correlations between PRL and selected variables. Data are presented as the mean \pm standard deviation. A p value less than 0.05 was considered statistically significant. Chi² test were used for the analysis of the variables of the demographic data.

RESULTS

Increased serum PRL levels in PsA patients

The serum PRL levels were significantly higher in PsA patients (299.2 \pm 28.29 mIU/L) compared to healthy individuals (198.2 \pm 15.31 mIU/L), $P = 0.007$, and PV patients (201.4.2 \pm 11.72 mIU/L), $P = 0.0003$. However, there were no differences between PRL levels in PV patients and controls, see Fig. 1. Because 30% of PV patients were treated by biologics we looked for the differences in serum PRL levels in these groups. There were no significant differences in serum PRL levels in group with or without biologics, however, the levels of PRL in PsA group were significantly higher than in both PV groups, with (206.9 \pm 23.15 mIU/L) and without (199.1 \pm 13.63 mIU/L) biologic treatment, $P = 0.034$ and $P = 0.001$, respectively.

The serum PRL levels might be influenced by several factors including age and gender, postmenopausal women and men have the physiological serum PRL levels similar and lower than premenopausal women. For this reason we divided PV, PsA and controls into two groups: premenopausal women (group 1) and postmenopausal women together with men (group 2). We found that that serum PRL levels were significantly higher in group 2 of PsA (299.7 \pm 34.38 mIU/L) than in PV (198.9 \pm 13.08 mIU/L) or controls (187.4 \pm 15.03 mIU/L), $P = 0.0017$ and $P = 0.020$ respectively. The levels of serum PRL were mildly increased in PsA group 1 compared to PV and controls, 298.0 \pm 51.28 and 208.6 \pm 26.09 mIU/L and 216.5 \pm 32.95 mIU/L, respectively, however the differences were not significant (see Fig. 2).

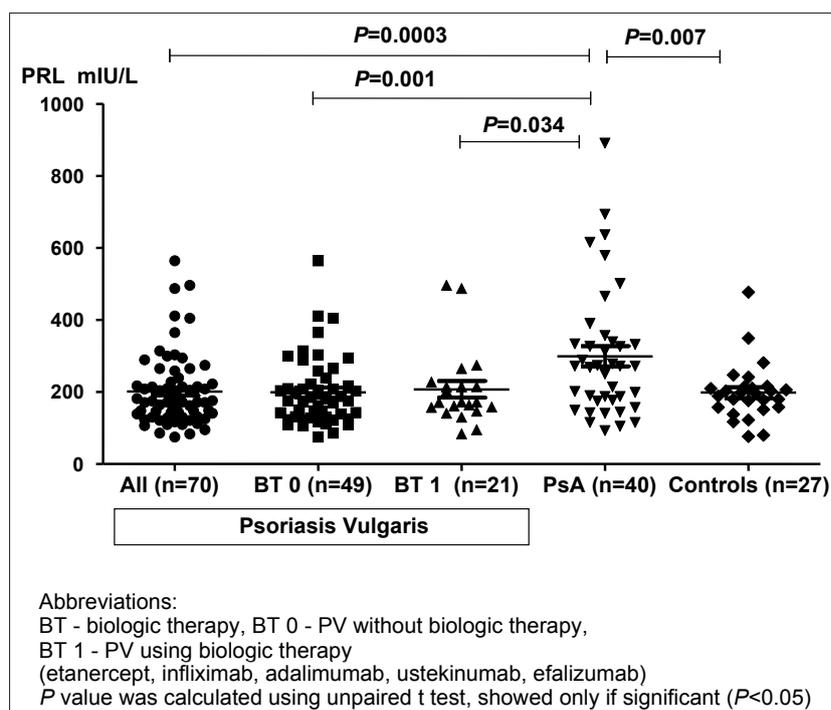


Fig. 1. Differences between serum prolactin (PRL) levels in patients with Psoriasis Vulgaris (PV), Psoriatic Arthritis (PsA) and Healthy Individuals (Controls).

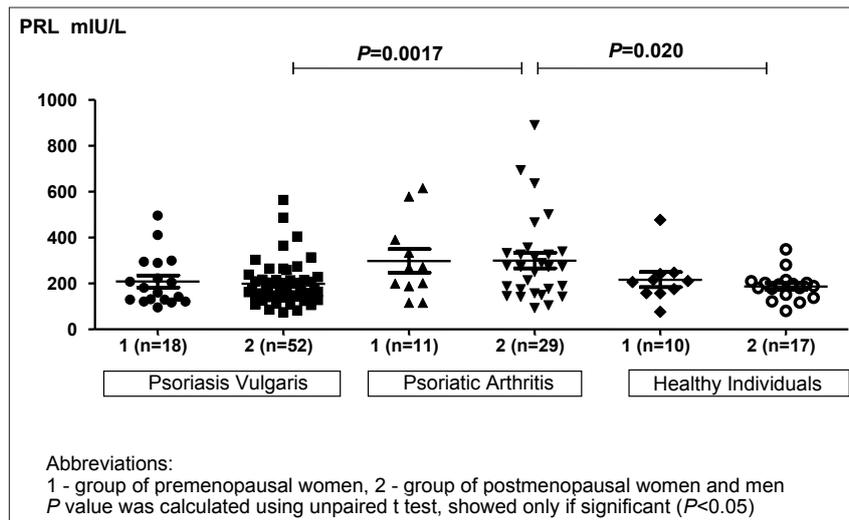


Fig. 2. Differences between serum prolactin (PRL) levels in premenopausal, postmenopausal women and men with Psoriasis Vulgaris, Psoriatic Arthritis and Healthy Individuals.

The correlation of serum PRL levels and disease activity

In our PV group the average PASI was 9.301 ± 11.72 and there was no correlation between PASI and serum PRL levels ($r = 0.1366$, $P = \text{ns}$), data not shown. Similarly, when we divided PV patients into three groups according to severity [group 1 PASI ≤ 10 ($n = 43$), group 2 PASI $= 10-20$ ($n = 18$) and group 3, PASI > 20 ($n = 7$)] we found nonsignificant differences in serum PRL levels for all other groups or controls (199.2 ± 13.71 , 213.6 ± 29.65 and 179.8 ± 33.82 mIU/L, respectively, $P = \text{ns}$), data not shown.

In the PsA group, 22 (55%) patients had active arthritis (determined as 4 swollen and tender joints). There were no differences in serum PRL levels in PsA with or without activity, 336.8 ± 42.50 and 253.3 ± 33.59 mIU/L, respectively, $P = \text{ns}$. However, the PRL serum levels in active PsA were significantly higher than in PV patients and controls, $P < 0.0001$ and $P = 0.002$ respectively, see Fig. 3. On the other hand, there was no correlation between serum CRP and PRL levels ($r = 0.2004$, $P = 0.071$), data not shown. We found no significant differences in serum PRL levels in the PsA subtypes (oligoarthritis, polyarthritis) or in enthesitis in PsA.

DISCUSSION

In this study we looked for differences in serum PRL levels in PV and musculoskeletal manifestation of the disorder, PsA. The results showed that serum PRL levels reflect the systemic involvement of psoriasis since the serum PRL was higher in particularly active PsA than PV without arthritis or healthy individuals. This result confirms the role of PRL in PsA pathogenesis and moreover, appears to be a potential biomarker for PsA. On the other hand, we found no correlation between serum PRL levels and PV disease activity.

PRL is a versatile polypeptide produced mainly by the pituitary gland and partially in some extrapituitary tissues like immune cells^{15,16}. PRL influences differentiation

and maturation of T and B lymphocytes via its receptor expressed on several immune cells including their precursors (e.g. thymocytes, B lymphocytes) (ref.^{24,25}) and is one of the factors supporting their autoreactivity.

Although the psoriatic skin and joint manifestation develop irrespective of sex some clinical evidence has shown that hormonal changes particularly with elevated PRL levels like breastfeeding^{26,27} and prolactinoma²⁸ precede disease onset or flares. Earlier small studies with 12 PV patients and 7 with PsA showed elevated serum PRL levels in PV (ref.²⁹) but not in PsA (ref.³⁰). Other studies, however, confirm the PRL impact of PsA severity while the treatment of bromocriptin, an alkaloid lowering the serum PRL levels, has been successfully used in the treatment of patients suffering from PsA (ref.^{22,31,32}). More recent publications have demonstrated the positive correlation between PASI score and serum PRL levels in 20 and 23 patients with PV treated with tacalcitol²¹ and propylthiouracil³³, respectively, and the serum PRL levels were increased in both studies in PV patients compared to healthy individuals. However, two recent studies with 30 PV patients did not detect hyperprolactinemia or elevated PRL levels compared to healthy controls^{34,35} and although PRL levels decreased after treatment of newly diagnosed PV, no correlation with PASI was found³⁵. In our study on 70 patients with PV, we found neither elevated serum PRL levels nor correlation between PRL and PASI. However, this discrepancy with some previous studies might be explained by patient characterization. In our cross sectional study, topical treatment was allowed and all patients used it. 30% of patients were treated by biologics. This is in contrast to Dilmé-Carreras²¹ and Malligarjunan³³ as in these studies, systemic and topical treatment was unwarranted before enrollment. While PRL release can be influenced by chronic emotional stress³⁶ and PV is recognised as a disease with a psychological component, the small differences in treatment might have an impact on the perception of the disease and levels of psychological stress.

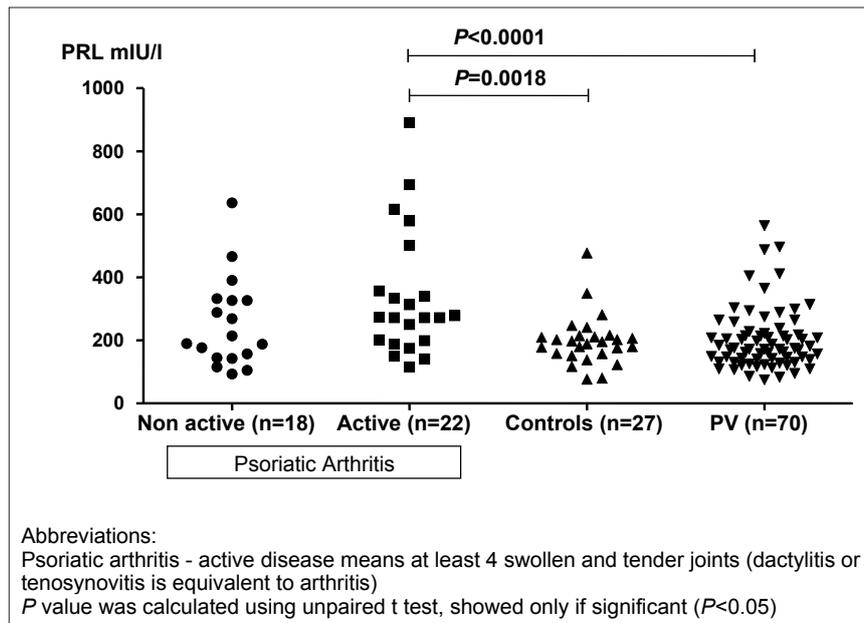


Fig. 3. Differences in serum prolactin (PRL) levels in Psoriatic Arthritis patients with and without active disease, Psoriasis Vulgaris (PV) and Healthy Individuals (Controls).

On the other hand, we found no differences in serum PRL and biologic treatment. Our finding confirms previous studies on the other autoimmune diseases and anti-TNF- α treatment and serum basal PRL levels. Daza et al. found no differences in serum basal PRL levels in patients with rheumatoid arthritis (RA) treated by adalimumab, RA patients without anti-TNF- α treatment or healthy controls³⁷. Recently, Kreiner et al. found no influences of etanercept on serum PRL levels in patients with polymyalgia rheumatica³⁸. Similarly, we found no differences in serum PRL levels in PsA patients with or without treatment by Disease-Modifying antirheumatic drugs (DMARDs). No role of DMARDs in serum basal PRL levels in RA was found in the Eijsbouts study - 20 RA patients were treated by sulfasalazine or methotrexate (MTX) for 6 months and there were no changes in basal PRL levels after 2 weeks and 6 months³⁹. Rovinsky et al. analysed the response to hypoglycaemia in patients suffering from RA and ankylosing spondylitis (AS) (ref.⁴⁰). Both groups were treated by MTX or non-steroidal antirheumatic drugs but the basal levels of PRL were similar to controls⁴⁰. Thus, PRL basal levels reflect joint involvement and PsA activity independent of treatment.

The disadvantage of our work was the absence of skin biopsies of PV patients. The local PRL values might reflect disease activity better than systemic. PRL acts in extrapituitary tissues as a cytokine and in psoriasis PRL increases the production of chemokines CCL20 and CXCL9, 10 and 11 of human keratinocytes which attract Th17 and Th1 cells into inflamed dermis^{17,18}. Moreover, PRL may influence keratinocytes directly while in one in vitro study its proliferative effect on these cells was demonstrated⁴¹. In further PRL human studies in PV, it will probably be necessary to divide patients according to

gender, concomitant treatment, evaluate patient quality of life and analyse cutaneous PRL.

Although early diagnosis may lead to early treatment and benefits for PsA patients, the prediction of PsA development in PV has not been clearly elucidated yet⁴². Recently, the GRAPPA group established serum biomarkers including IL-6, matrix metalloproteinase (MMP)-3 and others as markers distinguishing PV from PsA⁴³. In our study we demonstrated increased serum PRL levels in PsA patients compared to healthy individuals and to PV patients. Moreover, serum PRL levels were higher in PsA with current active disease and thus PRL appears to be a novel marker of active PsA.

In PsA, disease activity has been associated with elevated serum C-reactive protein and cytokines like IL-6, TNF- α among others⁴⁴. The regulation of pituitary PRL synthesis, the main source of serum PRL levels, is positively regulated by stress, exercise, circadian rhythms, the levels of estrogens and proinflammatory cytokines such as TNF- α and IL-6 (ref.^{16,45}). Thus elevated serum levels of PRL might reflect the inflammatory activity of the disease. In further studies, it will be necessary to explain the relationship between PRL and other inflammatory markers of PsA. Moreover, there might be link between PRL and joint inflammation. The synovium of the inflamed joint and entheses of PsA contains mononuclear cells and the local cytokine environment including IL-6, IL-1 β , TNF- α initiates and maintains local inflammation. In rheumatoid arthritis, PRL influences TNF- α production of peripheral CD14 monocytes⁴⁶ and might be involved in the inflammatory response. In future studies it will be necessary to analyse PRL levels in synovial fluid of psoriatic patients and look for an association with activity and radiological findings.

CONCLUSION

The elevated PRL serum levels is a marker of inflammatory joint disease in patients suffering from psoriasis and reflects systemic complications and active arthritis rather than local skin activity.

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Author contribution: MH, ZL, JL: literature search; MH, JL: Manuscript writing; MH, JS, LS, KP: detection and identification of PsA patients; JL, MH: screening of PsA in PV patients; PA, JL: investigation of PV patients; ZL, MH: lab analysis.

Conflict of interest statement: None declared.

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