

ELEVATED SERUM PROLACTIN LEVELS AS A MARKER OF INFLAMMATION IN PSORIASIS VULGARIS – AWAKENED ISSUE

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Summary

Background and aims

Psoriasis vulgaris is well-known as a chronic, recurrent, immune-mediated inflammatory disease with a conceded genetic predisposition. Neither the etiology of the psoriasis, nor specific laboratory markers for its disease activity have been clearly elucidated. Prolactin (PRL) acts as a cytokine with immunomodulatory functions, therefore it plays a role in skin biology. However, the results of PRL as a marker remains unclear.

The aim of this study was to confirm whether serum PRL levels reflect the activity of the disease or systemic complications, like inflammatory joint disease.

Methods

An observational study of a total of 21 patients (12 with and 9 without psoriatic arthritis) suffering from psoriasis vulgaris were included. The control group included 20 sex and age matched healthy individuals. In all patients, we determined skin disease activity according to the PASI index and joint activity in patients with psoriatic arthritis measured by DAPSA score. The concentration of PRL in the serum was measured by electrochemiluminescence method (ECLIA).

Results

The serum PRL levels were significantly higher in psoriatic patients (369.61 ± 29.48 mIU/L) compared to healthy individuals (152.30 ± 7.49 mIU/L), $p < 0.0001$. Baseline prolactin demonstrated a significant positive correlation with the severity of psoriasis ($r = 0.984$, $p < 0.0001$). We noticed that correlations between HAMA and prolactin and DLQI and prolactin on group of psoriatic patients were not significant ($p > 0.05$), but correlation between HAMD and PRL is positive, medium-high and statistically significant ($p < 0.05$). The PRL serum levels in active PsA (determined as 4 swollen and tender joints) were significantly higher than in PV patients and controls, $p < 0.0001$ and $p = 0.002$, respectively, even though, we had two subgroups with a compact number of patients.

Conclusion

Our results showed that PRL serum levels are a marker of local skin activity and also of systemic complication like active arthritis.

Key-words: prolactin, psoriasis, psoriatic arthritis.

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Introduction

Psoriasis vulgaris (PV), chronic, inflammatory skin disease is a recurrent T-cell mediated hyperproliferative cutaneous disorder of multifactorial etiology resulted from polygenic predisposition connected with triggering factors (1). It affects approximately 1-3% of the general population, usually during adulthood (2). The trademarks of PV pathogenesis include inflammation of epidermis and dermis as a result of invasion of the activated immune cells, explicitly Th1, Th17 and Th22 lymphocytes and changes in keratinocyte differentiation leading to hyperproliferation. (3-6).

Psoriasis vulgaris is well-known being correlated with extracutaneous/systemic inflammation (like arthritis and uveitis) resulting in increased risk for associated comorbidities (7,8). Psoriatic patients, also frequently manifest obesity and metabolic syndrome like hypertension, dyslipidemia or diabetes (9). Clinical course of psoriasis may be complicated by the concomitant joint disease (psoriatic arthritis-PsA) in 7-40% of patients, although the relationship between skin and joints remains unclear (10,11). In 75% of psoriatic patients, PsA can develop during skin symptoms (approximately after 10 years from the skin disease onset); both manifestations may develop concomitant or the joint disease may precede the dermatosis (12). In most cases, severity of joint involvement doesn't reflect the intensity of skin eruption. Additionally, involvement of nails in psoriasis vulgaris is more common in PsA (13,14). Pathogenesis of PsA subsists of synovitis by cause of infiltration of inflammatory cells (especially CD163+ macrophages), local cytokines synthesis (as TNF- α , IL-6 and IL-17), neovascularization and proliferation of synovial tissue leading to bone destruction (Vandooren B et al absences of a classically activated macrophage cytosine signature in peripheral spondylarthritis, including PsA Arthritis Rheum 2009). Considerable clinical proof exists for the role of stress in the onset and exacerbation of psoriasis vulgaris. Gupta et al reported several psychocutaneous features, including increased exacerbations and worse disease correlated with stress activity (15).

The psoriasis area and severity index (PASI) is the ideal clinical marker to appreciate psoriasis

severity, besides being the most widely used tool to determine the disease severity in clinical trials and practice. It has the advantage to be sensitive to changes in the affection, hence to reflect improvement or worsening of this dermatosis (7). However, PASI has its limitations; for example, in the mild form it is not so sensitive in changes in small areas of involvement (16,17). Indeed, there are other approaches to assess psoriasis severity like the percentage of involved body surface area, the Physician's Global Assessment. Focusing on aspects of the quality of life that are affected by skin disease, we have the Dermatology Life Quality Index (DLQI) (18). Unfortunately, all of these tools are clinical markers.

Determining risk factors and biomarkers for PsA progression in psoriatic patients is crucial to early PsA diagnosis and management (5). Considerable genomic regions have been identified as linked to psoriasis, some of them interfere with PsA (19). Second, interplay between environmental and genetic factors is convincing for the development of the skin disease (20). Trauma, psychological stress and hormonal disturbances (pregnancy) are linked with both disease progression. These named situations are connected with hyperprolactinemia (21).

Prolactin (PRL), is an anterior pituitary hormone, added to its role in reproduction, it takes part of the hypothalamus-pituitary-adrenal (HPA) axis and it is released after stressful events (20,22). Furthermore, prolactin is produced by extra-pituitary sites, including immune cells. Current views point out the multilevel neuroendocrine-immune communication through the "brain-skin axis" in health and disease (23-25). Foitzik et al (20) mentioned the presence of PRL and PRLR in several cutaneous cell population including keratinocytes, fibroblasts, sweat and sebaceous glands (20). All of these works suggest that PRL contributes to a variety of both physiological and pathological cutaneous process (26).

Newly, it has been demonstrated that PRL boosts inflammation and Th17 and Th1 cytokine production in a mouse model with imiquimod-induced psoriasiform skin changes (27). PRL is overexpressed in psoriatic skin lesions. Dilmé-Carreras found a positive reciprocity between

serum PRL levels and the corresponding index PASI, after tacalcitol treatment (28). Contrarily, bromocriptine as a drug that downregulates PRL pituitary relief was found to be effective in PsA therapy.

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

Methods

Patients

A total of 41 subjects were enrolled in the study. This was a hospital-based, observational study on 21 patients with psoriasis vulgaris with or without psoriatic arthritis, and 20 age and gender-matched healthy controls. Patients and healthy subjects have provided their written informed consent. The study and consent procedure were approved by the involved Hospital's Ethics Committee. All the named institutional ethics committees specifically approved this study (ethics committees of University of Medicine and Pharmacy "Carol Davila" and of Infectious and Tropical Diseases "Dr. Victor Babeş", Bucharest).

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.

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 and 15, and severe psoriasis as a PASI of >15 (16).

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 phenothiazine (chlorpromazine), antidopaminergic agents (metoclopramide), antihypertensive agents (calcium channel blockers, methyldopa) and H2 blockers (cimetidine) and endocrinopathies, no topical or systemic treatment before the enrollment in the study (a period of 4 weeks for topic one and 6 months for the systemic one).

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) (29). 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 (30).

We screened for PsA to exclude subjects with any current or past musculoskeletal manifestations. The diagnosis of PsA was made by experienced rheumatologists (31).

Laboratory Analysis

As the PRL serum levels reflect physiological diurnal variation, the blood samples were taken in the morning hours (at least one hour after waking up) and after at least 20 minutes at rest before sampling. We use the immunoassay for the in vitro quantitative determination of PRL in human serum. The electrochemiluminescence immunoassay "ECLIA" is for use on Elecsys and cobase immunoassay analyzers. The principle of technique is "sandwich method" with a total duration of assay for 18 minutes. Samples (10 μ L) were incubated with 1st biotinylated monoclonal prolactin-specific antibody to form a first complex. After addition of a monoclonal prolactin-specific antibody labeled with a

ruthenium complex and streptavidin-coated microparticles, a sandwich complex is formed and becomes bound to the solid phase via interaction of biotin and streptavidin. The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are removed with ProCell/ProCellM. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier. Results were determined via a calibration curve which is instrument-specifically generated by 2-point calibration and a muster curve provided via the reagent barcode. The limit of sensitivity of the assay was 1.00 $\mu\text{IU}/\text{mL}$ (0.047 ng/mL). In the test there was no cross reactivity to other human hormones (hLH, hFSH, hTSH, hCG and HPL).

Statistical analysis

The data were collected and introduced to OpenOffice PC, version 4.1.1 Copyright © 2014 The Apache Software Foundation. The statistical analysis was shaped with the next programs: – R version 3.4.0 (2017-04-21) – "You Stupid Darkness" Copyright (C) 2017 The R Foundation for Statistical Computing Platform R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>, Inc. Beside standard R, we also used A Collection of Statistical Tools for Biologists. R package version 1.3-1. <https://CRAN.R-project.org/package=asbio>, asympTest: a simple R package for performing classical parametric statistical tests and confidence intervals in large samples The R Journal (Software: R Package, asympTest, version 0.1.2). și ggplot2 (c) H. Wickham. ggplot2: Elegant Graphics for Data Analysis. Springer-Verlag New York, 2009. Python version 3.6.0 with graphics and scientific modules on Anaconda(c) 2016 Continuum Analytics distribution was helpful, too.

Inferential statistics: due to the fact that each followed parameter into the two groups represents two random and independent variables, the combo algorithm between them was as follows: for binomial variables, if each possible value of the random variables, was at least 5 times in the study, it was considered that

the binomial distribution of the variable could be approximated by a Gaussian distribution. For statistical inferential, a bidirectional test χ^2 was used to test 2 independent proportions; if the distribution of the binomial variable could not be approximated with a normal one for comparison, a Fisher test was exactly bidirectional for independent proportions. If the distribution of the binomial variable could not be approximated with a normal one for comparison, a Fisher test was exactly bidirectional for independent proportions. For continuous variables, if the distributions of the variables on both batches could be approximated with the normal distribution, a Welch t bidirectional test was used for the difference of the averages for two independent normal distributions. If the distributions could not be approximated with the normal distribution, a Wilcoxon Rank-Sum Test for the difference of localization between two independent distributions was utilized.

The levels of prolactin were normally distributed, and therefore the student's test was used to analyse the differences between two groups. Spearman correlation coefficient was used for correlation 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. χ^2 test was used for the variables of the demographic data.

Results

Significant differences were found between patients and controls regarding the age ($p=0.0071$), but insignificant ones regarding the sex and skin type ($p>0.05$).

Twenty one patients with chronic plaque psoriasis had mean disease duration of 8.04 ± 1.29 years and a mean PASI of 12.98 ± 9.78 at baseline. Eleven patients had co-existing psoriatic arthritis. We compared HAMA and HAMD scales between the two groups and found significant differences. By the measurement of HAMA, we had on group A (PV) 16.38 ± 1.10 , respectively, group B (Controls) 1.60 ± 0.16 , $p<0.0001$. On HAMD scale, some high significant statistical differences were observed too, between the two groups, 15.90 ± 0.98 , 2.15 ± 0.31 , correspondingly, $p<0.0001$ (see also figure 1 and 2).

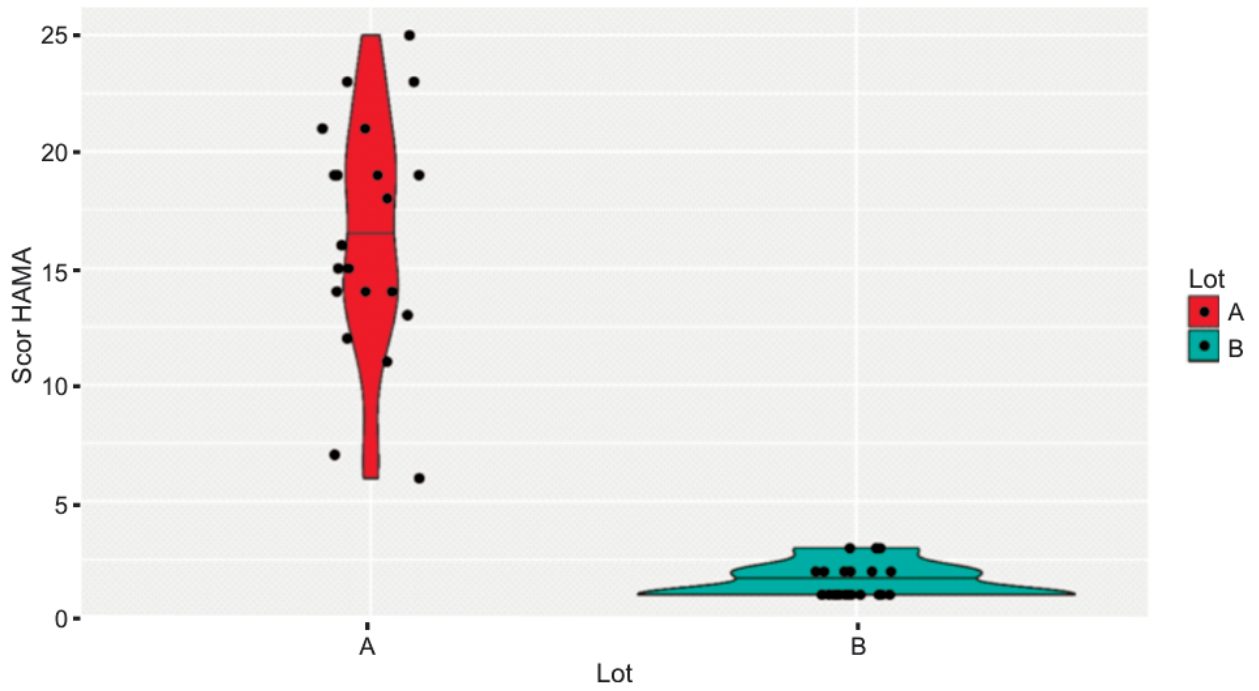


Fig. 1. The HAMA score statistically revealed in the two batches

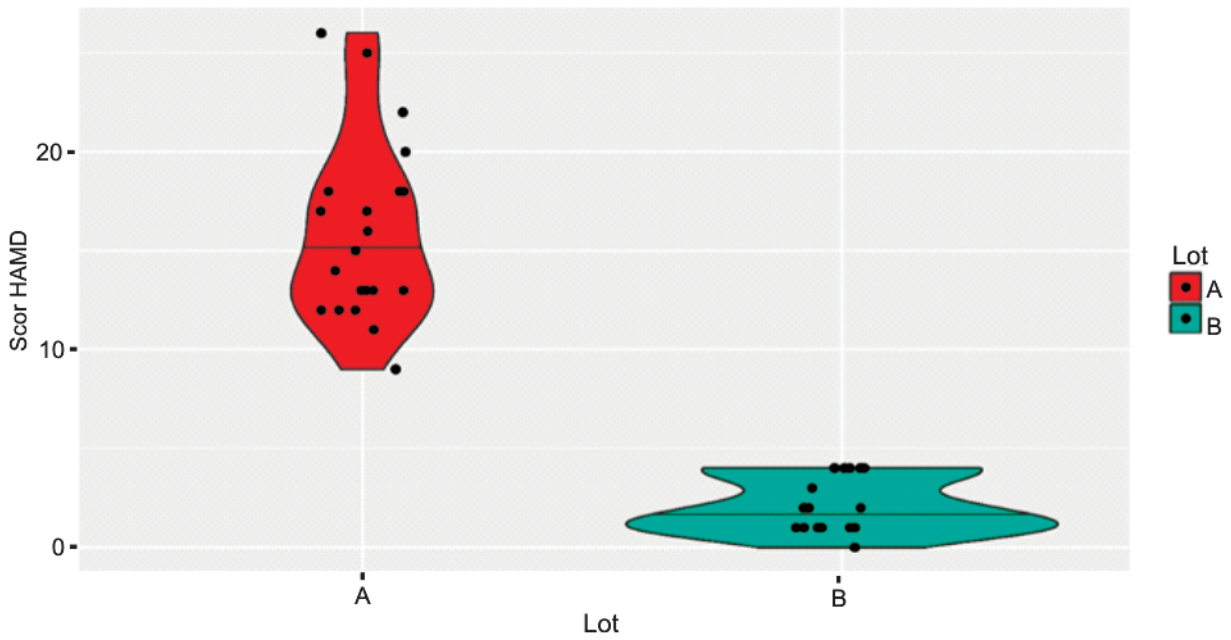


Fig. 2. Differences in HAMD score between the two batches A and B

Scatter HAMD vs Prolactin

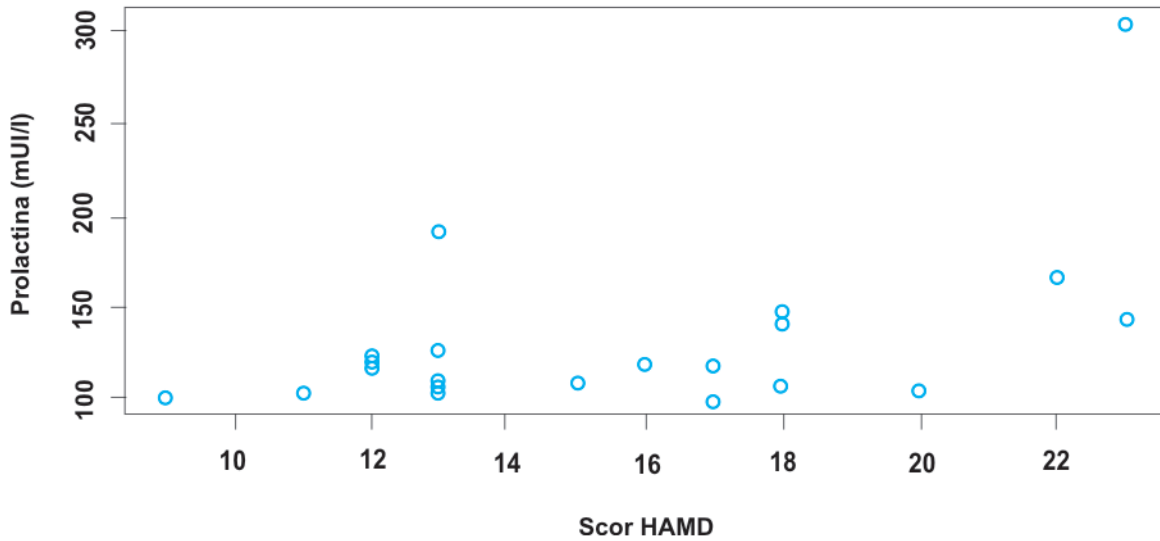


Fig. 3. HAMD-PRL correlation in the group of patients with vulgar psoriasis

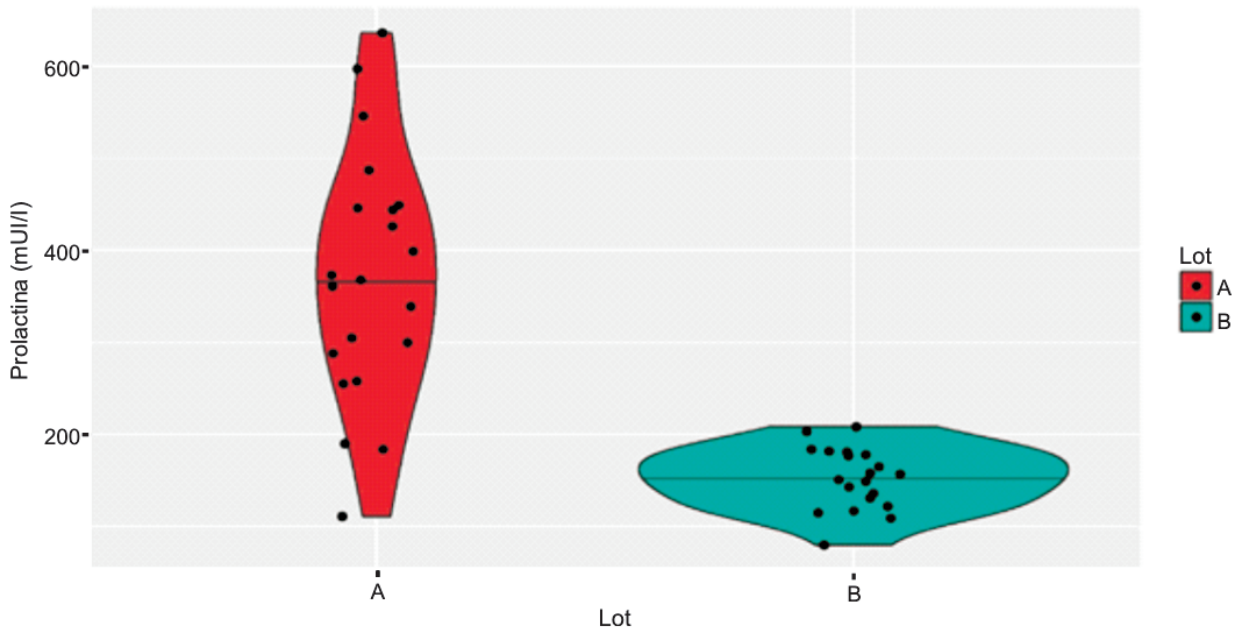


Fig. 4. PRL serum differences in the two analyzed groups

Increased serum PRL levels in Pv and disease severity

The serum PRL levels were significantly higher in psoriatic patients (369.61 ± 29.48 mIU/L) compared to healthy individuals

(152.30 ± 7.49 mIU/L), $p < 0.0001$ (figure 4). Baseline prolactin demonstrated a significant positive correlation with the severity of psoriasis ($r = 0.984$, $p < 0.0001$). The serum PRL levels might be influenced by several factors, including

gender, age, postmenopausal women and men have the psychological serum PRL levels similar and lower than premenopausal women. For this reason, we decided to divide PV and controls into two groups: premenopausal women (group 1) and postmenopausal women and men (group 2). We found that serum PRL levels were significantly higher in group 2 of PV (299.6 ± 32.38 mIU/L) than in controls (178 ± 14.02 mIU/L), $p < 0.001$. The levels of serum PRL were mildly increased in PV group 1 compared to controls, 289.02 ± 31.28 and 199.5 ± 23.95 mIU/L, respectively, however the differences were not significant.

We noticed that correlations between HAMA on group of psoriatic patients were not significant ($p > 0.05$), but correlation between HAMD and PRL is positive, medium-high and statistically significant ($p < 0.05$) (see figure 3).

There was no correlation between serum VSH and PRL levels ($r=0.2002$, $p=0.061$), data not shown. We found no significant differences in serum PRL levels in the PsA subtypes (oligoarthritis, polyarthritis) or in enthesitis in PsA. There was no differences in serum PRL levels in PsA with or without activity, 310.6 ± 41.2 and 273.4 ± 32.59 mIU/L, respectively, $p = ns$.

However, the PRL serum levels in active PsA (determined as 4 swollen and tender joints) were significantly higher than in PV patients and controls, $p < 0.0001$ and $p = 0.002$, respectively, even though, we had two subgroups with a compact number of patients.

Discussions

In our study, we observed significantly higher levels of prolactin in patients with psoriasis compared to controls and these levels correlated positively with the disease severity. We also looked for musculoskeletal manifestation of the disorder. We found eloquent data and the results showed a positive and higher correlation between PRL and PsA patients compared to PV group and healthy individuals. These results confirms the role of prolactin in pathogenesis of psoriasis vulgaris and moreover, its role in PsA. PRL appears to be a potential biomarker for PV and PsA.

Prolactin, a versatile polypeptide, secreted by the anterior pituitary has been implicated as an important immuno-modulator and has been found to labor a proliferative effect in cultured human keratinocytes via specific receptors (32). It is a member of the type I cytokine superfamily causing proliferation of lymphocytes during immune responses. PRL boosts proliferation of IFN-gamma, induces chemokine production in keratinocytes and develops infiltrates of Th1 cells. Prolactin and interleukin-17 (IL-17) participate in a positive feedback loop to increase CCL20 (chemokine ligand 20) production (33). This process may aggravate the Th17-mediated inflammation in psoriatic lesions.

Some clinical evidence has shown that hormonal changes, particularly with elevated PRL levels, like breastfeeding and prolactinoma precede psoriasis vulgaris onset or its flares (34,35). Previous small studies with 12 PV patients and 7 with PsA revealed elevated serum PRL levels in PV (36). In contrary, other studies confirmed the PRL impact on PsA and the role of treatment with bromocriptine, an alkaloid lowering which was successfully used in PsA disease (37,38). From 30 patients with psoriasis vulgaris, Kato et al. observed significantly high levels of prolactin among patients compared to controls, with significant decrease among patients after treatment. Significant positive correlation was found between serum PRL and PASI, both before and after treatment with methotrexate (39).

More recent publications have demonstrated the positive correlation between PASI score and serum PRL levels in patients with PV, treated with tacalcitol (28) and propylthiouracil (40), respectively, and the serum PRL levels were increased in both studies in PV patients compared to healthy individuals. However, two recent studies did not detect hyperprolactinemia or elevated PRL levels compared to healthy controls and although PRL levels decreased after treatment of newly diagnosed PV, no correlation with PASI was found (41). This varied discrepancy with some previous studies might be explained by patient characterization. While PRL release can be influenced by chronic emotional stress (42) and PV is recognized 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. On our study, due to the comparison between patients with PV, with no topical or systemic treatment at baseline and healthy individuals, data have shown high significant differences on serum PRL levels between the two groups associated with disease clinical severity (PASI score) and with systemic complication like PsA. On the other hand, we only found correlation between HAMD scale and serum PRL levels on psoriatic patients. Similar to other studies (5), our data have revealed higher correlation between PRL and PsA patients compared to PV group and healthy individuals. Hence, PRL basal levels reflect joint involvement and PsA activity independent of treatment. Moreover, PRL appears to be a novel marker of active PsA.

The limitations of our study include the following: relatively small number of subjects analyzed and the lack of immunohistochemistry for PRL receptors on skin biopsies in PV patients. The local PRL values might reflect disease activity better than systemic. Prolactin acts in extrapituitary tissues as a cytokine. In psoriasis vulgaris, it increases the production of CCL20 and CXCL (chemokine) 9, 10 and 11 of human keratinocytes which attract Th17 and Th1 cells into inflamed dermis (43). In further PRL human

studies on PV, it will probably be a necessity to divide patients according to gender, evaluate patient quality of life, and analyze cutaneous PRL, concomitant treatment.

In PsA, disease activity has been associated with elevated serum C-reactive protein and cytokines like IL-6, TNF- α among others (5). Elevated serum levels of prolactin might reflect the inflammatory activity of the disease. Further studies are necessary to explain the relationship between PRL and other inflammatory markers of PsA and to compare before and after the topical and systemic treatment in PV, respectively PsA. In future studies it will be interesting to analyze PRL levels in synovial fluid of psoriatic patients and look for an association with activity and radiological findings.

Conclusions

As psoriasis is often triggered or exacerbated by psychoemotional stress, prolactin may represent a link between psoriasis and stress, and elevated levels can be a cause or a consequence of psoriasis pathology. The exact source of this increase still remains to be established.

The elevated PRL serum levels is a marker of inflammation in patients suffering from psoriasis and reflects skin activity and systemic complications like psoriatic arthritis.

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Conflict of interest
NONE DECLARED

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