Leptin and sex hormones in psoriasis and correlation with disease severity

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Background: Leptin, a 16-KDa peptide hormone secreted from the adipose tissue, plays an important role in the regulation of energy intake and expenditure and body weight regulation; furthermore, it has a regulatory function on the reproductive system. The aim of this study was to assess the relationship between serum leptin levels and sex hormones in psoriatic patients and control group and to determine the serum levels of leptin and sex hormones in patients and their association with disease severity.

Method: This case-control study included 43 male patients with psoriasis and 42 age- and sex- matched healthy controls. We measured serum levels of leptin, sex hormone-binding globulin (SHBG), luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactin, and total testosterone in both groups.

Result: Psoriatic patients had significantly higher levels of leptin and lower levels of FSH than healthy controls. Psoriatic patients did not differ significantly in the serum concentrations of LH, total testosterone, SHBG, and PRL in comparison with healthy controls. The severity of the disease (PASI score) was positively correlated with leptin (p<.0001), Body Mass Index (p=0.001), and waist circumference (p=0.001), and was inversely correlated with serum LH levels (p=0.03). No significant associations were found between the severity of the disease and serum levels of FSH (p=0.38), total testosterone (p=0.14), SHBG (p=0.98), and PRL (p=0.76).

Conclusion: Our results suggest that the serum leptin level is associated with psoriasis severity and duration; moreover, we found a relationship between LH and psoriasis severity. This association needs more extensive studies.

Keywords: leptin, psoriasis, sex hormone-binding globulin, sex hormones, testosterone

INTRODUCTION

Psoriasis is a chronic, autoimmune, papulosquamous dermatosis that can be associated with systemic manifestations. It affects 2-4% of the general population [1]. Leptin, a 16-kDa peptide hormone secreted from the adipose tissue, plays an important role in the reproductive function, regulates energy homeostasis, and also modulates immune responses [2-4]. Leptin has been found to exert important effects on reproductive organs and an abnormal leptin level is correlated with fertility problems in males [5-9]. It seems to be due to the expression of functional leptin receptors on the surface of Leydig cells [10].

It is reported that sex steroid hormones, estrogen, progesterone, or androgen manifest a variety of biological and immunological effects in the

skin [11,12]. Female hormonal changes, especially estrogen, during the pregnancy, menstruation, and menopause influence the natural course of psoriasis [13,14]. Moreover, some studies have evaluated the associations between lower levels of testosterone, free testosterone, and sex hormone-binding globulin (SHBG) and the metabolic syndrome [15]. In a recent study, SHBG has been proposed as a sensitive biomarker for insulin resistance and systemic inflammation in psoriatic patients [16], and another small study investigated testosterone levels in men with psoriasis [17].

According to previous studies, prolactin seems to have a role in the pathogenesis of autoimmune disease [18,19] and contributes to the pathogenesis of psoriasis due to its effects on keratinocytes proliferation [20]. Although no difference has been reported between PRL levels in psoriatic patient and healthy controls [21,22], some other studies have shown that PRL levels are higher in psoriatic patients [23,24]. Moreover, some investigations have reported a decrease in PRL following treatment [21]. Serum leptin has been reported to be significantly higher in patients with psoriasis when compared to healthy controls [25,26].

Therefore, given the fact that few studies have been performed in this area, we decided to measure leptin, LH, FSH, PRL, SHBG, and testosterone in male psoriatic patients to evaluate the correlation between the levels of these hormones and disease activity.

PATIENTS AND METHODS

This study was performed on 43 male patients (age >18 years) with clinically or pathologically confirmed plaque-type psoriasis who were selected from two reference centers (Loghman-e-Hakim and Shohada-e-Tajrish University Hospitals, Tehran, Iran) from June 2012 through June 2013. All patients signed written informed consent and were included after receiving approval from the university ethics board. Also, 42 age-matched healthy male controls were enrolled into the study. In the patient group, exclusion criteria were any dermatologic or systemic disease, consumption of hormonal medications, eating disorders, phototherapy, endocrine disorders, alcoholism, smoking, and any malignancy or psychiatric condition. Patients previously treated with systemic agents within the past three months

or topical therapies within one month were excluded from the study, as well. Age-matched controls with a negative history of the skin or systemic inflammatory disease, family history of psoriasis or psoriatic arthritis, consumption of drugs and alcohol, and smoking were enrolled in our study. Demographic and clinical information including age, family history of psoriasis, weight, height, waist circumference, disease duration, drug and alcohol consumption, and smoking was collected from each participant. The PASI score was used to assess the severity of psoriasis.

From each participant, a 5-ml blood sample was obtained to measure the concentration of hormones. Blood samples were centrifuged for 10 min in the room temperature to separate the plasma; then, the plasma was stored at −70°C. Afterwards, we measured FSH, LH, SHBG, PRL and testosterone levels by ELISA (Diagnostics Biochem Canada Inc.) and leptin by Human Leptin (ELISA, Biovendor, Brno, Czech Republic) in the laboratory of Endocrine Research Centre of the University. Blood samples were collected between 8–9 am both from psoriatic patients and the control group after 12 hours of overnight fasting.

Statistical Methods

Continuous variables were reported as mean±SD or as median with total and interquartile ranges (25th-75th percentiles). Categorical data was expressed as number (percentage). The Shapiro-Wilk's W-test was applied for checking the normality assumption of the continuous variables. Chi-square and Fisher's exact test, wherever appropriate, were performed for data analysis. Independent two-sample t-test or Mann-Whitney-U test, wherever appropriate, were used to compare the continuous variables between the two groups. Correlations between hormonal values, clinical parameters, and disease severity (PASI) were assessed by Spearman's correlation test. In addition, multiple regression analysis with a forward step-wise approach was applied to choose variables entering in the final standard least square model. These models were fitted to determine the items most predictive of leptin, total testosterone, and SHBG. Only those parameters that entered the model at P<0.1 were included in the final model. The logarithmic transformation of leptin and total testosterone was used to improve

the fit of the models, according to analysis of the residuals. The statistical software SPSS 16.0.0 (SPSS Inc. Chicago, IL, USA) was used for statistical analyses. Two-sided P-values less than 0.05 were considered statistically significant.

RESULT

Forty-three patients with psoriasis and 42 age-matched healthy controls were included in this study. Baseline characteristics and clinical features of the subjects are summarized in Table 1. The two groups were similar in age, BMI and waist circumference (Table 1).

Laboratory findings

Patients had significantly higher levels of leptin and lower levels of FSH than healthy controls (Table 2). Psoriatic patients did not differ significantly in the serum concentrations of LH, total testosterone, SHBG, and PRL in comparison with healthy controls (Table 2). The two groups were similar in the abnormal levels of serum LH, total testosterone; FSH and PRL (Table 2). Thirty-two patients with psoriasis (74.4%) and 30 healthy controls (71.4%) showed at least one abnormal level of LH, FSH or total testosterone, with no statistical difference between the two groups (Table 2).

Table 1. Demographic and clinical features of patients with psoriasis and healthy controls

Characteristic	Patients with psoriasis (n = 43)	Healthy controls (n = 42)	P-value
Age, years			0.27
Mean ± SD	34.09 ± 10.53	31.76 ± 8.99	
Median (range)	34 (18-59)	30 (18-59)	
BMI			0.21
Mean ± SD	25.84 ± 3.81	24.82 ± 3.58	
Waist circumference, cm			0.06
Mean ± SD	93.19 ± 12.49	88.40 ± 10.27	
Duration of disease , years			
Median (range); IQR	9 (0.2-27); (3-15)	-	
PASI score			
Mean ± SD	26.82 ± 12.95	-	
Median (range)	25.9 (1.8-61.7)	-	

Abbreviations: BMI, Body Mass Index (calculated as weight in kilograms divided by height in meters squared); SD, Standard Deviation; IQR, Interquartile range (25th -75th percentiles); PASI: Psoriasis Area and Severity Index

Table 2. Laboratory findings and sex hormone abnormalities in patients with psoriasis and healthy controls

Characteristics	Patients with psoriasis (n=43)	Healthy controls (n=42)	P-value
FSH, IU/L	1.40 (1-7.32); (1.3-1.7)	2 (1.3-22.1); (1.7-2.32)	<.0001
LH, IU/L	6.89 (2.22-16.46); (4.11-9.16)	7.15 (1.8-15.2); (4.6-8.92)	0.78
Total testosterone, nmol/L	8.88 (4.13-35.71); (5.59-13.05)	9.49 (3.47-42.78); (5.92-13.91)	0.44
PRL, µIU/mL	193 (64-492); (128-286)	243 (86-700); (140.75-367.5)	0.06
SHBG, nmol/L	45.8 (10.4-121); (36.4-71.9)	43.1 (15.4-129.7); (29.32-57.62)	0.39
Leptin, ng/mL	5.44 (1.01-45.14); (2.45-9.97)	2.67 (1-27.02); (1.55-4.5)	0.0002
Sex hormone abnormalities			
High LH (>9.3 IU/L)	10 (23.26%)	8 (19.05%)	0.63
Low T (<10.41 nmol/L)	25 (58.14%)	24 (57.14%)	0.92
High FSH (>18 IU/L)	0 (0%)	1 (2.38%)	0.49
High SHBG (>70 nmol/L)	12 (27.91%)	8 (19.05%)	0.33
Hyperprolactinaemia (>390 µIU/mL)	4 (9.3%)	5 (11.9%)	0.74
High FSH/ high LH/ low T	32 (74.42%)	30 (71.43%)	0.76
High LH/ low T	32 (74.42%)	30 (71.43%)	0.76

Values are expressed as median (range); IQR or as no. (%)
Abbreviations: IQR, Interquartile range (25th -75th percentiles); FSH, Follicle stimulating hormone; LH, Luteinizing hormone; PRL, Prolactin; SHBG, Sex hormone-binding globulin

Correlation between serum leptin levels and all other evaluated parameters

Leptin was positively correlated with BMI and waist circumference in both study groups. In patients with psoriasis, leptin was negatively associated with testosterone and positively associated with the severity (PASI) and duration of the disease. Leptin was inversely associated with SHBG and directly associated with age in healthy controls. No significant associations were found between serum leptin concentrations and serum levels of LH, PRL and FSH in both groups of study. When the two groups were combined, serum leptin concentration was significantly related to testosterone, FSH, BMI, age and waist circumference.

Multiple regression analyses were applied including all subjects (patients with psoriasis and healthy controls) and introducing "group of study" to the model as a dummy variable. According to the results of step-wise forward regression, BMI and the presence of psoriasis were positively associated with log-transformed leptin levels (adjusted R^2=0.36, F=24.88, p<.0001). Also, waist circumference and the presence of psoriasis predicted 38% of the log-transformed leptin changes (F=26.35, p<.0001). When the two groups were combined, BMI and serum testosterone were significantly associated with log-transformed leptin levels (adjusted R^2=0.31, F=19.70, p<.0001). Also, waist circumference and serum testosterone concentration predicted 33% of the log-transformed leptin changes (F=21.55, p<.0001). In psoriatic patients, the severity (PASI) and duration of the disease were significantly correlated with log-transformed leptin levels (adjusted R^2=0.50, F=21.87, p<.0001).

Correlation between disease severity (PASI) and other evaluated parameters

The severity of the disease (PASI score) was positively associated with leptin (r_s=0.70, p<.0001), BMI (r_s=0.50, p=0.001), and waist circumference (r_s=0.50, p=0.001) and inversely correlated with serum LH levels (r_s=-0.33, p=0.03). No significant associations were found between the severity of the disease and serum levels of FSH (r_s=-0.14, p=0.38), total testosterone (r_s=-0.23, p=0.14), SHBG (r_s=0.005, p=0.98), and PRL (r_s=-0.05,

p=0.76). According to the multivariable regression modeling, to avoid multicollinearity, leptin, BMI, and waist circumference were alternatively entered in the regression model. When leptin was entered in the statistical model, leptin was the only significant predictor of the severity of the disease (adjusted R^2=0.52, F=45.79, p<.0001). In the model including BMI instead of leptin, LH and BMI were significantly associated with the severity of the disease (adjusted R^2=0.22, F=7.03, p=0.002). Also, waist circumference and LH predicted 28% of the PASI changes (F=9.26, p<.001).

Correlation between disease duration and laboratory findings

The duration of the disease was positively associated with leptin and negatively associated with total testosterone (Table 3). There were no significant associations between the duration of the disease and serum levels of LH (r_s=0.02, p=0.90), FSH (r_s=-0.09, p=0.56), PRL (r_s=0.17, p=0.27), and SHBG (r_s=0.02, p=0.90).

DISCUSSION

In this study, serum levels of FSH, LH, PRL, SHBG, total testosterone, and leptin were measured in patients with psoriasis and the results were compared with that of age-matched healthy controls. There was no significant difference between the two groups of the participants in age, BMI, and waist circumference. It helped us to remove the confounding effect of these parameters on leptin between the two groups because several studies have shown the effects of these parameters on leptin [25,27,28].

Based on our findings, the serum leptin level in psoriatic patients was significantly higher than healthy individuals; in addition, a positive correlation was observed between serum leptin and both disease severity and duration. These findings are consistent with a previous study conducted by Cerman et al [25]. This is an important finding that patients with high leptin levels have an increased risk of developing metabolic syndrome [29]. Therefore, elevated levels of leptin in patients with severe psoriasis may be a contributing factor for the increased prevalence of metabolic disease. Although leptin levels failed to correlate with the PASI score

in psoriatic patients in two recent studies, serum leptin levels were significantly higher in patients with psoriasis than healthy controls [26,30].

In our study, a significant negative correlation was found between serum leptin and testosterone in psoriatic patients. Because low total testosterone and SHBG levels both predict the development of metabolic syndrome [15], this finding may predict the increased prevalence of metabolic disease in psoriatic patient.Higher leptin levels were observed in men with fertility problems in the previous studies [5-9]. Nevertheless, the serum level of testosterone in our patients was lower than the control group although it was within normal limits. There was no significant difference between the two groups in serum levels of LH, SHBG, and total testosterone. Also, we did not detect any significant relationship between the severity of the disease and serum levels of these parameters except for LH. However, in a study conducted on 33 male patients with psoriasis in Germany in 2011, SHBG was introduced as a marker for insulin resistance and systemic inflammation in psoriasis [16]. Although a significant negative correlation was observed between serum levels of SHBG and serum leptin levels in healthy subjects in our study, no statistically significant association was observed between serum levels of SHBG and other disease parameters that were evaluated in this study in the two groups. Although the association between metabolic syndrome and lower levels of testosterone, free testosterone, and SHBG has been studied [15], only one small study investigated the testosterone level in men with psoriasis [17] and Boehncke et al assessed the effect of SHBG on psoriasis [16].

There was no significant difference in the serum level of prolactin between the two groups, which is consistent with previous studies [21,22]. In a study in 2010, serum prolactin levels were assessed at baseline and six weeks after local treatment with Tacalcitol ointment in patients with plaque type psoriasis and a direct relationship was observed between serum levels of prolactin with disease severity based on PASI before and after treatment [24]. However, we did not detect such an association. Although we found that the severity of the disease (PASI score) was inversely correlated with serum LH levels, such a relationship is not consistent with previous studies [16,17]. Given that very few

studies have measured the level of sex hormones in psoriasis, these findings may be incidental and further studies are required.

In our study, the severity of the disease (PASI score) was also positively associated with BMI and waist circumference. In a previous study, an association was reported between psoriasis and obesity [31]. The duration of the disease was positively associated with leptin and negatively associated with total testosterone, but there were no significant associations between the duration of the disease and other parameters. It suggests a possible relationship between testosterone and chronic inflammation which is perhaps the result of the effect of age on the hormonal levels in psoriasis. However, further studies are recommended to prove this hypothesis. In summary, it appears that increased levels of leptin are related with the severity and duration of psoriasis, but further more extensive studies are required to evaluate the association between hormonal levels and the disease activity.

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