Serum levels of sex hormones in men with chronic plaque psoriasis in comparison with a healthy control group

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Background: Psoriasis is a chronic inflammatory skin disease with extensive systemic effects. The role of sex hormones in the pathogenesis of psoriasis remains unknown. Therefore, in this study, the level of sex hormones in male chronic plaque psoriasis patients was evaluated.

Methods: This study was descriptive-analytic of the cross-sectional type, done with a total population of 60, including 30 patients with chronic plaque psoriasis and 30 healthy subjects in the control group. Serum levels of testosterone, estradiol, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) were measured in patients and the control group who did not have psoriasis. The two groups were matched based on the grouped matching technique. The two groups were matched for age (34 ± 9 years) and BMI (30 ± 3 kg/m^2), and the effects of these two variables on hormonal levels were eliminated. According to the results of the Kolmogorov-Smirnov test, the data had a normal distribution. The independent t-test and Pearson correlation coefficient were used for data analysis. A P-value less than 0.05 was considered significant.

Results: The levels of LH and FSH were significantly higher in the patient group than in the healthy group ($P = 0.01$ and $P < 0.001$, respectively). Testosterone and estradiol serum levels were lower in the patient group than in the healthy group ($P < 0.001$).

Conclusion: Our study suggests that male patients with chronic plaque psoriasis have higher levels of LH and FSH and lower levels of testosterone and estradiol than the general male population.

Keywords: psoriasis, luteinizing hormone, follicle stimulating hormone, estradiol, testosterone

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INTRODUCTION

Psoriasis is a chronic papulosquamous skin disorder that affects about 1–3% of the world's population [1]. Despite the unknown etiology of this disease, factors such as genetic, immune, and environmental factors are considered in its etiology. Among environmental factors, cigarette smoking and a high body mass index (BMI) are significant. Obesity, in addition to accompanying the disease, is also a risk factor for cardiovascular complications [2].

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Sex hormones are among psoriasis's most prominent hormonal causes [3]. Estrogen reduces the production of neutrophils, T cell type 1 and macrophage collector chemokines, CXCL8, CXCL10, and CCL5 by keratinocytes and suppresses the production of IL-12 and antigen-presenting cells. Accordingly, estrogen can reduce inflammation in psoriatic lesions. Estrogen alone or with progesterone prevents skin atrophy, dryness, and folds following photo-aging. These two hormones also stimulate keratinocyte prolapse, increase collagen synthesis, and inhibit collagen lysis by reducing metalloproteinase activity in the fibroblast matrix. Estrogen can maintain moisture in the skin by increasing mucopolysaccharides or hyaluronic acid in the dermis, and progesterone also increases the secretion of sebum. Estrogen antagonizes androgens by increasing vascular endothelial growth factor (VEGF) production in macrophages. This moderating effect of sex hormones can be used as a biomarker for treating or preventing psoriasis and its chronic ulcers. Unlike these two hormones, androgens prolong inflammation and disrupt extracellular matrix organization in wound healing, slowing wound healing [4].

Like other immune disorders, psoriasis patients are more likely to develop metabolic syndrome, atherosclerosis, and cardiovascular disease [5]. Chronic and systemic inflammation plays a vital role in the progression of these diseases, and there is a prominent similarity between molecular and inflammatory pathways in psoriasis and atherosclerosis [6]. Patients with psoriasis have a higher risk of developing obesity and diabetes mellitus [5]. Testosterone and sex hormone-binding globulin (SHBG) are sensitive biomarkers for insulin resistance [7-9] and indicate vascular damage [10]. There is an inverse relationship between testosterone and insulin levels in healthy men [11]. Cross-sectional studies have shown lower levels of androgens in diabetic men than in healthy men [12,13]. Men with low SHBG levels, similar to men with low testosterone levels, have an increased risk of developing metabolic syndrome.

The precise role of sex hormones in psoriasis pathobiology remains unknown [14]. It is known that estrogen affects inflammatory processes [15,16], elevated estrogen levels during pregnancy are associated with improved psoriasis [17], high levels of estrogen inhibit the immune response, and low estrogen levels facilitate immunological and inflammatory processes [18]. However, studies on sex hormones (especially testosterone and estradiol) in psoriasis patients are few. Hence, we investigated the level of sex hormones in male chronic plaque psoriasis patients.

METHODS

Study design

We conducted a cross-sectional, descriptive-analytical study. After obtaining informed consent and considering inclusion and exclusion criteria, 30 male patients with chronic plaque psoriasis referred to the dermatology clinic of Imam Reza Hospital (Mashhad, Iran) in 2016 were included in the study.

Sample size

To determine the sample size, we used the study of Cemil *et al.* [19], which compared the mean levels of male sex hormones in psoriasis and control groups. The mean testosterone level in patients with psoriasis was 392.29 ± 181.91 ng/dl and 506.91 ± 117.7 ng/dl in the control group. So considering a power of 80% and type I error of 5%, the required sample size per group was calculated as 29, and we sampled 30 individuals for each group [19].

Enrolment and data collection

Demographic data (age and occupation) and disease information were recorded, including disease duration, psoriasis area and severity index (PASI), family history of psoriasis, nail involvement, and joint involvement. The severity of psoriasis was measured based on the PASI score. Then, 5 ml of brachial blood was taken from patients to measure serum levels of testosterone, estradiol, FSH, and LH. The same was done for the control group, which included other clinic patients who had no psoriasis and met the inclusion criteria, and were matched regarding age and body mass index. Inclusion criteria were chronic plaque psoriasis approved by a dermatologist and, if necessary, by pathology; informed consent; and age over 18 years. Exclusion criteria were a previous history of cardiovascular disease, hormone-related malignancy or breast cancer, venous thromboembolism, diabetes, kidney and liver disease, hypertension, or the use of lipid-lowering, antidiabetic or systemic corticosteroid drugs, or hormonal therapy.

Data analysis

Data were entered into SPSS 21.0 software and analyzed using descriptive statistics for descriptive data analysis, independent t-test to compare the mean levels of hormones in both groups, and ANOVA to compare the mean between different hormone levels. Data distribution was normal and between -2 and 2 based on skewness and kurtosis tests.

Ethical consideration

This study was approved by the Ethics Committee of Mashhad University of Medical Sciences (code IRMUMS FM.REC.13550; project number 31). We explained the study protocols and objectives to all participants and ensured the confidentiality of the data. Written informed consent was obtained prior to enrollment. The tests were performed free of charge for the patients, and the results were returned to the patients or their physicians if necessary.

RESULTS

This study included 30 male chronic plaque psoriasis patients and 30 controls, all of whom were evaluated for sex hormone status. The Kolmogorov-Smirnov test was used to evaluate the normality of the results. Overall, 50% (n = 15) of the patients had nail involvement, 16.7% (n = 5) had joint involvement, and four (13.3%) had simultaneous nail and joint involvement. The mean age was 34 ± 9 years among patients and 34 ± 9 years among controls ($P = 0.96$). The BMI was 30 ± 3 kg/m^2 among patients, with an identical result among controls ($P = 0.73$). The two groups were matched for age and BMI, and these two variables' effects on hormone levels were eliminated.

The Kolmogorov-Smirnov test confirmed the normality of data for all sex hormone level distributions (Table 1). The levels of LH and FSH hormones in the patient group were significantly higher than in the control group ($P = 0.01$ and $P < 0.001$). Serum levels of testosterone and estradiol were lower in the patient group than in the healthy group, and there was a significant difference between the two groups (Table 2 and Figures 1-4).

Also, the correlation between patients' PASI scores and hormonal levels was measured by the Pearson correlation test. The mean PASI score was 12.1 ± 23, which decreased with increasing FSH and estradiol levels, but no significant correlation was found ($P = 0.71$ and $P = 0.28$, respectively). However, with increasing PASI scores, testosterone levels decreased significantly ($P < 0.001$). While there was a weak direct relationship between the PASI score and LH level, there was no significant correlation (Table 3). A strong, inverse correlation was found between the PASI score and testosterone level.

The relationship between sex hormone levels and nail and joint involvement was also evaluated. There was a significant association between nail or joint involvement and testosterone level ($P = 0.003$ and $P = 0.003$, respectively), but no relationship was

Table 1. Normality of data on hormone levels in each group

Indicator	Patient group N = 30	Healthy group N = 30
Luteinizing hormone level	Z = 0.94 , $P = 0.33$	Z = 1.16 , $P = 0.13$
Follicle-stimulating hormone level	Z = 0.59 , $P = 0.87$	Z = 0.91 , $P = 0.92$
Estradiol level	Z = 0.83 , $P = 0.49$	Z = 1.08 , $P = 0.19$
Testosterone level	Z = 1.07 , $P = 0.19$	Z = 0.74, $P = 0.63$

*Kolmogorov Smirnov test was used to assess the normality of variables.

Table 2. Comparison of sex hormones between patients and controls

Indicator	Patients N = 30	Controls N = 30	*P*-value*
Age, years	34 ± 9	34 ± 9	0.96
Body mass index, kg/m^2	30 ± 3	30 ± 3	0.73
Luteinizing hormone level, IU/l	5.1 ± 1.3	3.9 ± 1.4	0.01
Follicle-stimulating hormone level, IU/l	7.3 ± 1.4	4.8 ± 1.4	<0.001
Estradiol level, pg/ml	35 ± 17	54 ± 16	<0.001
Testosterone level, ng/dl	370 ± 70	485 ± 105	<0.001

*Independent t-test.

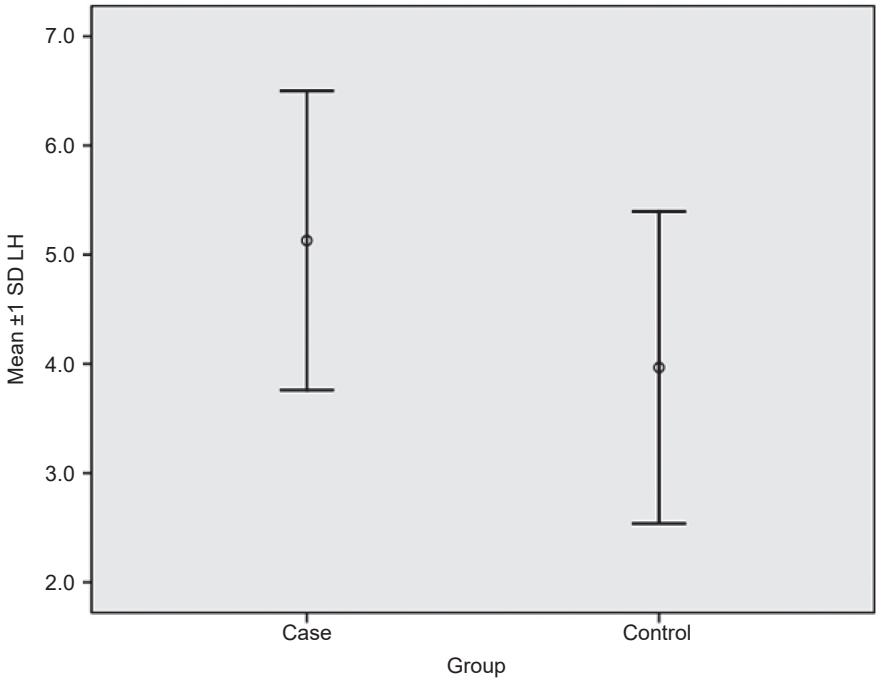

Figure 1. Mean serum luteinizing hormone (LH) level in patients and controls

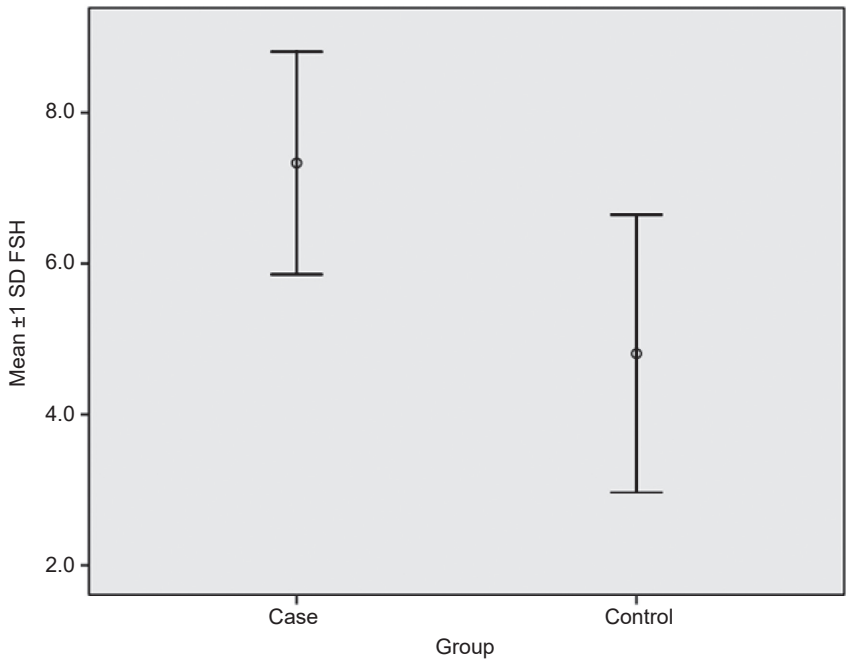

Figure 2. Mean serum follicle-stimulating hormone (FSH) level in patients and controls.

found between LH, FSH, and estradiol serum levels with nail and joint involvement (Table 4).

DISCUSSION

We investigated the sex hormone levels in male chronic plaque psoriasis patients and matched controls; the patients exhibited significantly higher LH and FSH levels and significantly lower testosterone and estradiol levels. Also, the testosterone levels correlated with the nail or joint involvement and with the PASI score, but such correlations were not detected regarding LH, FSH, and estradiol.

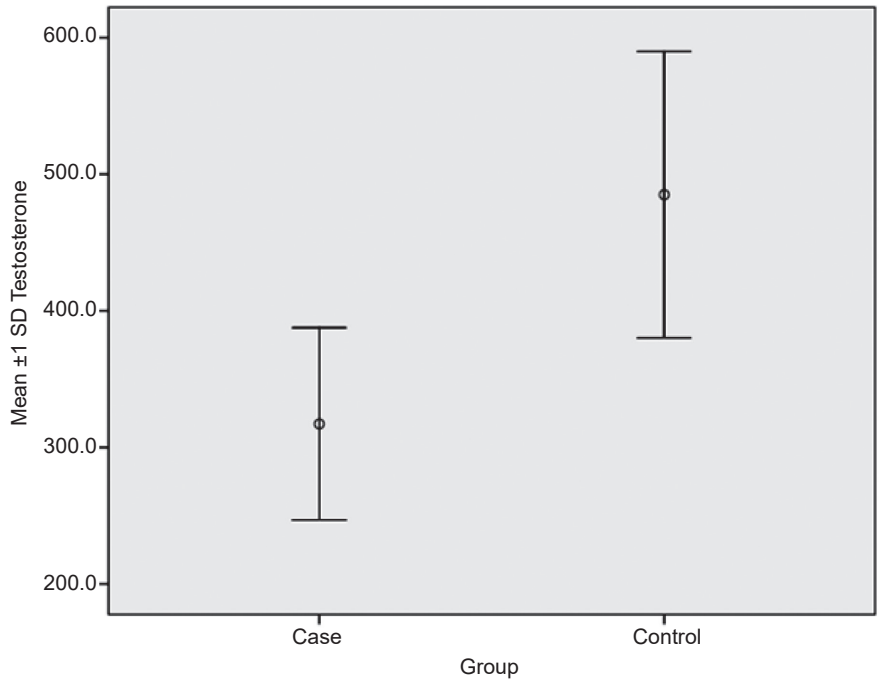

Figure 3. Mean serum testosterone level in patients and controls.

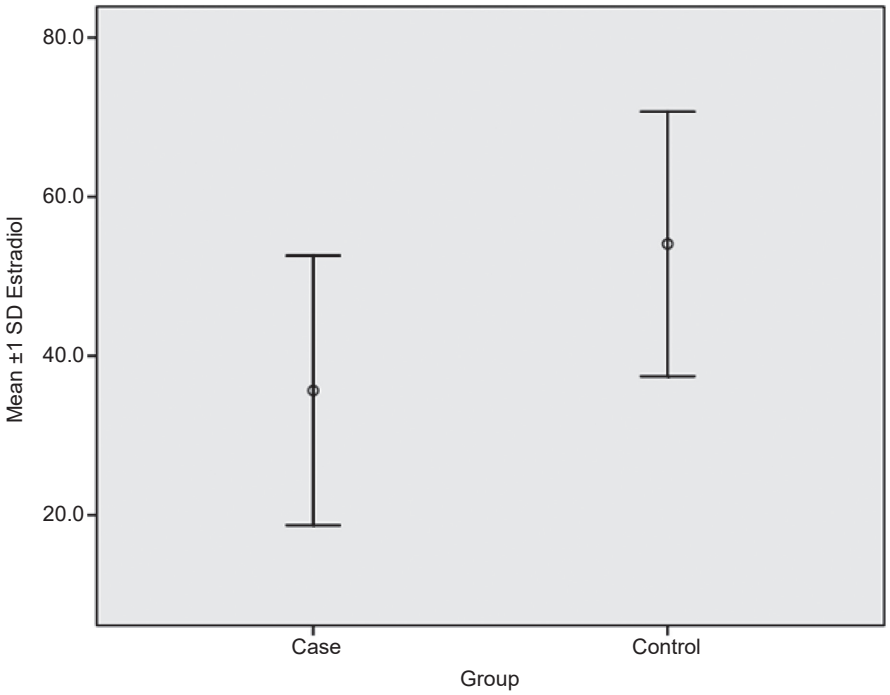

Figure 4. Mean serum estradiol level in patients and controls.

Despite previous research, the role of sex hormones in the pathophysiology of psoriasis is still unclear and is being investigated. The present study is one of the first studies in Iran regarding sex hormone profiles in male patients with chronic plaque psoriasis. The first research in this field began in 1981 with the Schwarz review. In line with our findings, they reported lower testosterone and dehydroepiandrosterone (DHEA) levels in men with psoriasis [20]. Similar to our study, Caldarola *et al.* recorded lower testosterone

Table 3. The relationship between PASI score and sex hormone levels among patients

Indicator	Patient group N = 30
PASI score & luteinizing hormone level	Pearson correlation = 0.14 *P* = 0.43
PASI score & follicle-stimulating hormone level	Pearson correlation = -0.06 *P* = 0.71
PASI score & estradiol level	Pearson correlation = 0.2 *P* = 0.28
PASI score & testosterone level	Pearson correlation = 0.71 *P* < 0.001

Table 4. The relationship between nail and joint involvement and sex hormone levels among patients

Indicator	Patient group N = 30					
	Joint involvement			Nail involvement		
	No (n = 11)	Yes (n = 19)	*P*-value*	No (n = 21)	Yes (n = 9)	*P*-value*
Luteinizing hormone level, IU/l	5.11 ± 1.1	5.04 ± 1.1	0.87	5.25 ± 1.1	4.88 ± 1.1	0.41
Follicle-stimulating hormone level, IU/l	7.5 ± 1.4	7.1 ± 1.2	0.78	7.62 ± 1.4	7 ± 1.3	0.27
Estradiol level, pg/ml	30 ± 18	40 ± 16	0.12	31.7 ± 18	38.4 ± 18	0.37
Testosterone level, ng/dl	323 ± 60	406 ± 75	0.003	311 ± 79	410 ± 70	0.003

*Independent t-test.

levels and higher FSH levels in psoriasis patients. However, they found higher estradiol levels and lower LH levels in psoriasis patients compared with controls [21]. In the Cemil *et al.* study [19], hormonal levels of FSH, LH, and testosterone were similar to this study, while estradiol levels were higher in patients; only testosterone and estradiol showed significant differences from controls. However, in the present study, all four hormones showed significant differences between groups.

Cemil *et al.* note that estradiol has bipotent effects on macrophages and monocytes; at low doses, it induces the production of proinflammatory cytokines (such as interleukin [IL]-1, IL-6, tumor necrosis factor [TNF-a]), while at high concentrations, it decreases the production of these cytokines, suggesting that lower levels of estradiol have a stimulating effect on psoriasis and that low serum estradiol is associated with high PASI scores [19]. Saad's study on 15 patients with concurrent hypogonadism and psoriasis showed that after testosterone therapy, skin lesions improved, and the PASI score decreased dramatically in the first 24 months [22].

Different hormonal levels obtained from the studies may be due to compensatory mechanisms following hypogonadism and testosterone reduction in these patients. Aromatase, the critical enzyme converting androgens into estrogen, is reduced in psoriasis following the excessive secretion of cytokines, making the deficiency of sex hormones predictable. In addition, high levels of estradiol and low testosterone levels play an essential role in inflammatory responses, so testosterone has an anti-inflammatory and estrogenic effect on both inflammatory and anti-inflammatory effects [23], which the present study confirms.

The study of Zanganeh *et al.* provided discrepant results regarding estradiol [24]. Murase *et al.*, however, showed that increased estradiol levels during pregnancy improved psoriatic lesions in women [17]. Ceovic *et al.* reported that high levels of estrogen (sex hormones) inhibit the immune response, and its low levels facilitate immunological and inflammatory processes [18].

Boehncke *et al.* recorded similar testosterone levels (median: 377.0 ng/dl) as this study in men with moderate to severe psoriasis [25]. Clinical and laboratory studies indicate that testosterone has anti-inflammatory effects. In several studies, placebo-controlled trials in hypogonadal men with metabolic syndrome by Kaplan, Tengstrand, and Corrales showed an apparent decrease in hs-CRP, TNF-alfa, and IL-1 beta (an inflammatory factor). Therefore, our results confirm the association between inflammation and testosterone deficiency [26-28]. Androgens may play a

unique anti-inflammatory role in T cells. In the Dalal study, when serum testosterone was reduced in a rat model with autoimmune orchitis (experimental), testosterone use led to a decrease in disease severity as well as a decrease in TNF alpha, IL-6, MCP-1 mRNA expression, and inhibition of macrophage activity [29].

Ruiz-Villaverde showed that fertility rates in men with psoriasis increase significantly after treatment [30]. In the study of Tuğrul Ayanoğlu *et al.* on 14 patients with psoriasis, FSH levels and FSH/LH ratio were reported to be higher than the control group, as in our study. Their study suggested that the increase in FSH levels, with the increase of angiogenic mediators such as VEGF as an angiogenic cytokine, can augment the speed of emptying of resting follicles by increasing the vessels of the ovarian cortex. This negatively affects the reserves of follicles and can cause premature ovarian failure (POF). In patients with psoriasis, these angiogenic mediators increase skin inflammation [31].

Different studies compared the effect of PASI levels on hormone levels. Saad's study showed that psoriasis patients had a 75% PASI score after testosterone therapy [22]; this figure was 50% in the Boehncke study [25]. In the Caldarola [21] study, the PASI score was much lower than in the present study, though testosterone levels were higher. Cemil's study found a poor inverse correlation between PASI score and estradiol levels, while the strongest association in our study was with testosterone [19]. In the Ruiz-Villaverde study, the PASI score decreased significantly in men and women after receiving psoriasis treatment, and similar to our study, there was a relationship between sex hormone levels and the PASI score [30].

Limitations faced during this study included the disinclination and lack of cooperation of patients and healthy people to complete the questionnaire and prepare blood samples, which was solved by explaining that the result can help improve the management of patients with psoriasis. It should be noted that the range of testosterone changes in our study was in the normal range, and hypogonadism was not seen. Prior studies did not evaluate the relationship between sex hormone levels and nail or joint involvement in psoriasis patients, and our study may be the first to investigate this issue.

CONCLUSION

Our study suggests that male patients with chronic plaque psoriasis have higher levels of LH and FSH and lower levels of testosterone and estradiol than the general male population. Also, the testosterone level correlates with PASI score and joint or nail involvement in these patients.

Acknowledgments

None.

Authors contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Yalda Nahidi, Naser Tayyebi Meibodi, Sima Davoodi, Farahnaz Abdolhoseinzadeh and Mostafa Izanlu. The first draft of the manuscript was written by Sima Davoodi and Mostafa Izanlu and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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