Egyptian Journal of Medical Microbiology Volume 33 / No.3 / July 2024 19-24 Online ISSN: 2537-0979

ORIGINAL ARTICLE

Evaluation of Serum Programmed Cell Death–1 (PD-1) in Psoriasis Vulgaris: A Case-control Study

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Key words:
Programmed cell death – 1, Psoriasis vulgaris

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ABSTRACT

Background*: The actual mechanisms underlying the psoriasis pathogenesis and early diagnosis remain unclear. According to medical theory, psoriasis is a chronic, recurrent illness linked to T cell activation, namely T helper 1 and 17 (Th1 and Th17). The glycoprotein known as "programmed cell death-1," which is present on the surface of many immune cells, including T cells, reduces effector T cell activity and increases that of regulatory T cells.* ***Objectives****: To evaluate the levels of serum PD-1 and correlates it with the severity of the disease in patients with psoriasis vulgaris.* ***Methodology****: Thirty psoriatic patients and thirty healthy volunteers were selected as controls from the Dermatology, Andrology, and STDs department's outpatient clinic at Mansoura University Hospitals. For every patient and control group, the following informations were collected: age, sex, unique behaviors, family history, and length of illness. The Psoriasis Area and Severity Index (PASI) score was used to determine the severity of psoriasis. Every participant had completed a serum PD-1 laboratory test.****Results****: There was non statistically significant difference between studied groups as regard serum PD-1. There was a statistically significant positive thirty psoriatic patients and thirty healthy volunteers were selected as controls from the Dermatology, Andrology, and STDs Department's Outpatient Clinic at Mansoura University Hospitals. For every patient and control group, the following informations were collected: age, sex, unique behaviors, family history, and length of illness. The Psoriasis Area and Severity Index (PASI) score was used to determine the severity of psoriasis. Every participant has completed a serum PD-1 laboratory test correlation between serum PD-1 and the following; occupation, smoking and kobnerization. Serum PD-1 has poor area under curve in differentiating cases from control group.* ***Conclusion:*** *It could be concluded that there was no statistically significant difference between studied groups as regard serum PD-1 but there was a statistically significant positive correlation between serum PD-1 and occupation, smoking and koebnerization.*

INTRODUCTION

A chronic immune-mediated skin condition with variable prevalence that affects many ethnic groups is psoriasis [1]. Psoriasis is characterized by persistent inflammation that results in unchecked keratinocyte proliferation and defective differentiation [2].

On CD4+ and CD8+ T lymphocytes, the negative immunological checkpoint receptor known as programmed cell death protein-1 (PD-1) is expressed. By controlling T cell activation, the binding of PD-1 and its ligands, programmed death-ligands 1 (PD-L1) and 2 (PD-L2), promotes immunological tolerance in healthy individuals [3].

The mechanism of PD-1/PD-L1 has been thoroughly investigated in relation to comprehending T-cell activation and immunological checkpoint-targeted therapeutic interventions. Psoriasis aggravation is the result of immune checkpoint inhibition with anti-PD1 or anti-PD-L1 treatments [4,5].

The purpose of the current study was to assess the serum PD-1 level in psoriasis vulgaris patients and establish a correlation between it and the severity of their condition.

METHODOLOGY

Thirty patients with psoriasis vulgaris (group A) and thirty healthy matched controls (group B) participated in this case-control study. They were chosen from the Mansoura University Hospitals' Outpatient Clinic of Departments of Dermatology, Andrology, and STDs.

A written informed consent was obtained from all participants.

Patients on systemic treatment such as immunosuppressive or chemotherapy, pregnant and

lactating women, patients with other autoimmune diseases, were excluded from the study.

Patients with chronic plaque psoriasis over the age of 18 years old, of both sexes who did not receive any systemic treatment for at least 3 months were included in the study.

All the participants were subjected to:

- *Thorough history taking:*
  Personal history: age, sex, residence, occupation, special habits, marital status.
  Past history: systemic illness, drug intake and previous therapy.
- *Complete physical examination:* clinical data, such as height, weight, body mass index (BMI) and blood pressure, were collected.
- *Dermatological examination*: was performed on the skin, hair, nails and oral mucosa.
  Psoriasis area and severity index (PASI) score was calculated at enrollment. PASI evaluates the severity of lesions as well as the affected region into a single score in the range 0 (no disease) to 72 (maximal disease) [6].
- *Laboratory investigation:* All members of the study were subjected for measurement of serum level of soluble programmed cell death protein -1. It was measured using enzyme-linked immunosorbent assay (ELISA) Cat. No 201-12-7502.

Ethical consideration:

The Mansoura Medical College Institution Research Board (IRB) reviewed and approved the study protocol (Code number: R.22.04.1674). At every stage of the study, privacy and confidentiality were upheld. Every piece of data was only ever utilized for scientific research.

Statistical analysis:

The 2013 release of IBM SPSS Corp. was used to feed data into the computer and analyze it. Version 22.0 of IBM SPSS Statistics for Windows. NY / Armonk: IBM Corp. Numbers and percentages were used to describe the qualitative data. Once the Kolmogrov-Smirnov test had confirmed that the quantitative data were normal, the mean (minimum and maximum) and standard deviation were used to characterize the parametric data. The acquired results were deemed significant at the (0.05) level. Monte Carlo, Chi-Square, and Fischer exact tests can be used to compare two or more groups of qualitative variables.

The Kruskal Wallis and Mann-Whitney U tests were used to compare two or more independent groups. The direction and strength of a linear relationship between two non-normally distributed continuous variables and/or ordinal variables are ascertained using the Spearman's rank-order correlation.Receiver Operating Characteristic (ROC) curve analysis is used to assess a test's diagnostic performance, or how well it distinguishes between sick and non-diseased cases. From the curve, sensitivity and specificity were identified.

RESULTS

There was a non statistically significant difference between studied groups as regards serum PD-1. Median serum PD-1 is 15.91 ng/ml in psoriasis patients versus 14.86 ng/ml for controls (Table 1).

Table 1: Comparison between group A (psoriasis patients) and group B (controls)

Variables	Group A N=30	Group B N=30	test of significance
Age/years mean±SD	45.20±11.75	41.27±13.11	t=1.02 P=0.314
Sex: N (%)			
Male	13(43.3)	14(46.7)	χ^2=0.045
Female	17(56.70)	16(53.3)	P=0.832
Marital status: N (%)			
Single	4(13.3)	10(33.3)	χ^2=2.50
Married	26(86.7)	20(66.7)	P=0.114
Occupation: N (%)			
Not working	5(16.7)	0	MC=7.33
Manual worker	11(36.7)	8(26.7)	P=0.062
Employee	3(10.0)	12(40.0)	
Housewife	11(36.7)	10(33.3)	
Special habits: N (%)			
Non-smoker	24(80.0)	24(80)	FET
Smoker	6(20.0)	6(20.0)	P=1.0
Serum PD1 (ng/ml) median (min-max)	15.91(3.2-64.0)	14.86 (7.1-25.4)	Z=1.01 P=0.312

t: Student t test, **FET:** Fischer exact test, χ^2 **:** Chi-Square test**, MC**:Monte Carlo test**, Z**:Mann Whitney U test

There was a statistically significant relation between serum PD-1 and the followings; occupation, smoking and Kobnerization (Table 2). Higher median serum PD-1 was found among employees and manual workers (19.15, 16.2, respectively) (Table 2). Higher median serum PD-1 was found among smokers than nonsmokers (20.9 versus 15.69 ng/ml) (Table 2). Higher median serum PD-1 was detected among cases with positive koebnerization than negative Koebnerization (16.2 versus 8.84 ng/ml) (Table 2).

A non statistically significant correlation was detected between serum PD-1 level and the following: sex, age of the patient, marital status, family history, disease duration, and PASI score (p >0.05). (Table 2).

Table 2: Correlation between serum PD-1and sociodemographic and clinical findings among studied cases.

Variables	Serum PD1 (ng/ml) Median (min-max)	test of significance
Sex:		
Male	16.2(6.5-64)	Z=1.26
Female	15.88(3.2-21.11)	P=0.209
Occupation:		
not working	8.5(3.2-9.2)	KW=10.60
manual worker	16.2(7.4-64.0)	**P=0.014***
employee	19.15(15.3-19.6)	
housewife	16.02(11.6-21.11)	
Marital status :		
Single	15.89(9.2-15.92)	Z=0.580
Married	16.11(3.2-64.0)	P=0.562
Special habits:		
Non-smoker	15.69(3.2-21.11)	Z=2.62
Smoker	20.9(9.2-64.0)	**P=0.009***
Onset:		
Sudden/acute	15.92(7.4-21.11)	Z=0.646
Gradual	15.88(3.2-64.0)	P=0.519
Course:		
Recurrent	15.46(3.2-64.0)	z=1.63
Progressive	16.2(7.4-30.2)	P=0.103
Family history:		
-VE	16.02(3.2-64.0)	Z=1.09
+VE	13.6(9.2-16.2)	P=0.278
Kobnerization		
-VE	8.84(6.5-9.2)	Z=2.95
+VE	16.2(3.2-64.0)	**P=0.003***
Age/years	r=-0.105 p=0.569	
Duration of the disease/years Median (min-max) 6 (0.5-35.0)	r=-0.024 p=0.901	
PASI score Median (min-max) 8.8 (1.2-18.6)	r=0.137 p=0.470	

Z: Mann Whitney U test , *statistically significant , r:Spearman correlation coefficient.

Serum PD-1 had poor area under curve in differentiating cases from control group (AUC=0.593), with the best detected cut off point from the curve is 15.43 ng/ml yielding sensitivity of 63.3% and specificity of 66.7%.(Table 3. Fig 1).

Table 3: Validity of serum PD-1 in differentiating between studied groups.

Variable	AUC (95%CI)	P value	Cut off point	Sensitivity %	Specificity %
SerumPD-1 (ng/ml)	0.593 (0.422-0.765)	0.312	15.43	63.3	66.7

AUC: Area Under curve

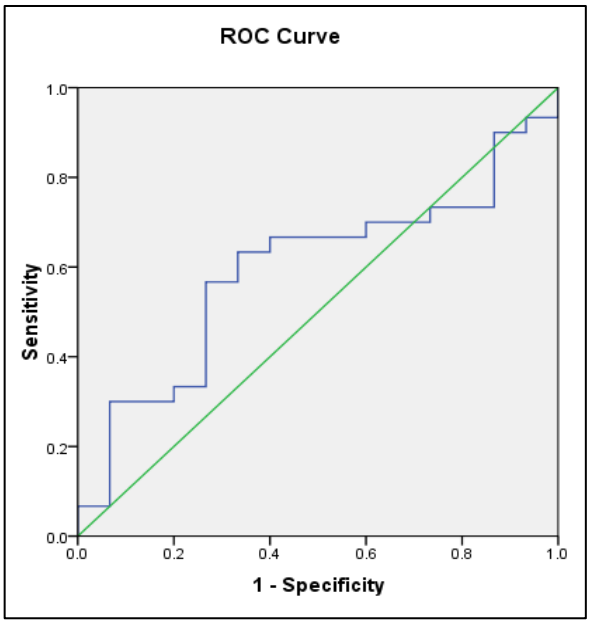

Fig. 1: Roc curve of serum PD-1 in differentiating between studied groups

DISCUSSION

In the present study, regarding serum PD-1, there was a statistically negligible difference between the groups under investigation. The control group's median serum PD-1 ranged from 7.1 to 25.4 ng/ml, while in psoriatic patients', it ranged from 3.2 to 64.0 ng/ml, with a median of 15.91 (Table 1). There was shown to be a non-statistically significant association (p >0.05) between the serum PD-1 level, the length of the disease, and the PASI score (Table 2).

Despite the fact that a great deal of research has been done on the pathophysiology of psoriasis, the function of the PD-1/PD-L1 pathway in the illness remains unclear. A member of the CD28/CTLA-4 superfamily, PD-1 is a T-cell regulator that inhibits T-cell activity[7]**.** To interact with cells expressing either PD-1 or PD-L1, dentritic cells (DCs) express both the PD-1 receptor and PD-L1[8]**.** The maintenance of psoriasis depends on T-lymphocyte activation, which is caused by a variety of pathways [9]**.**

According to Khatery et al.[10]**,** psoriatic patients had higher serum and tissue levels of PD-1 than controls. They found that the tissue levels of PD-1 and the PASI score correlated positively**.**[11] Observation from 2021 that PD-1 expression tends to be higher in individuals with severe persistent plaque psoriasis is consistent with current findings. Additionally, this was consistent with Phadungsaksawasdi et al.[12] study, which showed that PD-1+ CD8+ CD103+T cells were present in the active psoriatic epidermis and that these cells correlated with the severity and histopathology of the disease. Additionally, the number of epidermal PD-1+T cells in psoriasis skin lesions significantly decreased following remission brought on by biologic therapy.

However, a research done by Bartosińska et al.[13] revealed a favorable association between CD4+PD-1+ and CD8+PD-1+ T cells as well as a marked drop in protein PD-1 expression on both CD4+ and CD8+ T cells. They came to the conclusion that while PD-1 is involved in the normal immune response's silencing, psoriasis's chronicity and repeated recurrence may be caused by its decreased expression. According to Tanaka et al.[14]**,** in mice with PD-1 loss, psoriasiform dermatitis is induced, activated cytotoxic CD8+ T cells are recruited into the epidermis, and IL6 production is subsequently upregulated.

In psoriatic patients, Nagui et al.[15] measured the levels of membrane-bound PD1 and soluble programmed cell death-1 (sPD1). They discovered that patients' levels of sPD1 were considerably lower than those of controls. In terms of membrane-bound PD1, there was a non statistically significant difference between the controls and psoriatic skin samples. There was a substantial negative link with the severity of the disease and a statistically significant positive correlation between tissue and sPD1 levels.

In Chia and John [16] study, a 74-year-old man with metastatic lung cancer was treated with pembrolizumab, a PD-1 inhibitor, for two cycles before experiencing a severe flare-up of psoriasis. After stopping immunotherapy, topical corticosteroids, and phototherapy, the psoriasis cleared up. In a similar vein, Matsumura et al.[17] noted that an 87-year-old patient experiencing two cycles of nivolumab for metastatic melanoma experienced an aggravation of psoriasis.

A statistically significant positive connection was found in our study between serum PD-1 and smoking, profession, and Kobnerization (Table 2). Smoking was linked to higher levels of proinflammatory biomarkers (TNF-α, SAA, TNF-β, IL-1α, IL-1β, IL-1RA, IL-3, IL-6, IL-12/IL-23p40, IL-12p70, IL-15), chemokines (CCL11, CCL26, CXCL8/IL-8, CXCL10, CCL2, CCL13, CCL22, CCL3, CCL4, CCL17), growth factor, and vascular stress biomarkers (bFGF, Flt-1, Tie-2, IL-7, PlGF, VEGF-A, VEGF-C, VEGF-D, TSLP, GM-CSF, sICAM-1, sVCAM-1) and lower levels of T cell-derived biomarkers (IFN-γ, IL-2, IL-5, IL-9, IL-10, IL-13, IL-16, IL-17A, IL-17A/F, IL-17B, IL-17C, IL-17D)[18]. These results confirm the well-established pro-inflammatory effect of smoking and highlight the suppression or malfunction of T cells caused by smoking, which may be related to nicotine's recognized immunosuppressive effects[19, 20].

Workers who perform manual labor are susceptible to infections, oxidative stress, tissue hypoxia, and inhalation of harmful and irritating substances. Damage

to the epithelium is caused by these factors, which also trigger the nonspecific inflammatory response and release endogenous molecules known as danger-associated molecular patterns (DAMPs). Pattern recognition receptors (PRRs), which are expressed by fibroblasts, endothelial cells, dendritic cells, macrophages, monocytes, and neutrophils, among other cell types, recognize these compounds and release pro-inflammatory cytokines as a result[21]. When someone comes into contact with cigarette smoke, their PRRs are activated both directly by the smoke's constituent parts and indirectly by the epithelium's damage, which releases DAMPs [22].

It is unclear exactly what causes Koebner phenomenon (KP) and reverse KP. KP has a strong correlation with ongoing illnesses. Koebnerization is brought on by proinflammatory cytokine overexpression and epidermal damage[23].

A few limitations of our study were the small number of patients and the absence of tissue analysis. To further understand the involvement of PD-1 in the pathophysiology of psoriasis vulgaris, more research on a greater number of patients with long-term follow-up following therapy is advised.

CONCLUSION

It could be concluded that there was no statistically significant difference between studied groups as regard serum PD-1 but there was a statistically significant positive correlation between serum PD-1 and occupation, smoking and koebnerization.

Declarations:

Consent for publication: Not applicable

Availability of data and material: Data are available upon request.

Competing interests: The author(s) declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

This manuscript has not been previously published and is not under consideration in another journal.

Funding: Authors did not receive any grants from funding agencies.

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