Purified Protein Derivative Skin Test in Patients With Psoriasis Vulgaris: A Case-Control Study

Psoriasis Vulgarisli Hastalarda Pürifiye Protein Türevi Deri Testi: Vaka Kontrollü Bir Çalışma

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ABSTRACT Objective: The diameter of purified protein derivative skin test (PPD) induration in evaluation of positive reaction varies according to patient's immune status, living area and BCG vaccination. A needle prick trauma and PPD extract may lead to Koebner phenomenon after 72 hours and these applications may be the cause of false positive or increase of diameter of PPD reaction in psoriatic patients. The aim of the study was to evaluate the results of PPD skin test in psoriatic patients and to compare with control subjects. **Material and Methods:** The test was performed on 117 consecutive patients with psoriasis vulgaris and 102 immunocompetant control patients. The Mantoux method was used for the test and skin reaction was measured at 72 hours. A positive skin reaction was considered > 10 mm. **Results:** A positive PPD test was detected in 49 psoriatic patients (41.8%) and in 31 of the control subjects (30.3%). Differences in positive PPD reactions (p=0.16) and the diameter of PPD indurations (p=0.36) between two groups were not statistically significant. The diameter of PPD indurations in psoriatic patients was not associated with sex, duration of the disease or psoriasis area and severity index score (p> 0.05). **Conclusion:** Our results show that psoriasis has no effect on the PPD skin test. We think that this test is appropriate to recognize latent tuberculosis infection in patients with psoriasis until more sensitive diagnostic tests become available.

Key Words: Psoriasis; tuberculosis

ÖZET Amaç: Pozitif bir reaksiyonun değerlendirmesinde PPD (saflaştırılmış protein türevi= Purified Protein Derivative) deri testi endürasyonunun çapı hastanın immun durumuna, yaşadığı yer ve BCG aşılanmasına göre değişkenlik göstermektedir. İğne travması ve PPD partikülleri 72 saat sonra Koebner fenomenine yol açabilir ve bu uygulama psoriatik hastalarda yanlış pozitifliğe veya PPD reaksiyon çapında artışa neden olabilir. Bu çalışmanın amacı psoriatik hastalarda PPD deri testinin sonuçlarını değerlendirmek ve kontrol grubuyla karşılaştırmaktır. **Gereç ve Yöntemler:** Test ardışık 117 psoriasis vulgarisli hastaya ve 102 immun olarak sağlam kontrol hastasına uygulandı. Test için Mantoux metodu kullanıldı ve deri reaksiyonu 72. saatte ölçüldü. Pozitif deri reaksiyonu > 10 mm olarak kabul edildi. **Bulgular:** Pozitif PPD testi 49 psoriatik hastada (%41.8) ve 31 kontrol hastasında (%30.3) saptandı. İki grup arasında pozitif PPD reaksiyonu (p= 0.16) ve PPD endürasyon çapında (p= 0.36) istatistiksel olarak fark saptanmadı. Psoriatik hastalarda PPD endürasyonunun çapı cinsiyet, hastalık süresi ve psöriazis alan ve şiddet indeks skoru ile ilişkili değildi (p> 0.05). **Sonuç:** Sonuçlarımız psoriasisin PPD deri testi üzerine herhangi bir etkiye sahip olmadığını gösterdi. Biz bu testin psoriasisli hastalarda daha duyarlı tanısal testler elde edilene kadar latent tüberküloz enfeksiyonunu tanımlamada uygun olduğunu düşünüyoruz.

Anahtar Kelimeler: Psoriazis; tüberkülozis

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PPD skin test is used widely in detection of latent tuberculosis infection (LTBI). The diameter of PPD induration in evaluation of positive PPD reaction varies according to patient's immune status, living area and BCG vaccination. Anti-TNF drugs, which antagonize the biologi-

cal activity of TNF-α started to be used in the treatment of rheumatological disorders and psoriasis vulgaris. One of major problems of these agents is appearance of tuberculosis infection. It is recommended that the risk of LTBI should be evaluated by a PPD skin test before initiating anti-TNF-α therapy.[1] The diameter of induration of positive PPD skin test is accepted as 10 mm in countries where BCG vaccination is used routinely. However a high incidence of anergy has been reported in some rheumatologic diseases. For this reason, it is suggested that this positive diameter of induration should be decreased to 5 mm in rheumatological disorders.[2,3]

The Koebner phenomenon is a known condition in psoriasis, and all traumatic process may lead to this phenomenon. The reported incidence of Koebner response in psoriasis varies from 11-75%. The latent period between injury to uninvolved skin and appearance of disease is usually 10-14 days, but it may range from three days to several years.[4] A needle prick trauma and PPD extract may lead to Koebner phenomenon after 72 hours and these applications may be the cause of false positive PPD reaction in psoriatic patients. On the other hand, psoriasis is an immunologically mediated disease caused by activation of T lymphocytes and many therapeutic agents such as cyclosporine in psoriasis work primarily through inhibition of T cell activation. Alteration of T cell function in psoriatic patients may result in inability to produce an adequate response to the PPD test, which is a T cell mediated type IV reaction. However there is no information about assessing this skin test in psoriatic patients. The purpose of this report was to evaluate the PPD reactivity and effects of Koebner phenomenon on this skin test in psoriatic patients and and to compare it with immunocompetant control patients.

MATERIAL AND METHODS

The study was conducted on 117 consecutive unrelated patients with psoriasis vulgaris (56 males, 61 females; mean ± SD age 35.4 ± 13.4 years, range 16-67 years) and 102 unrelated control subjects (47 males, 55 females; 35.9 ± 12.4 years, range 16-65 years), attended outpatient dermatology clinic between April 2006 and July 2007. Control subjects consisted of immunocompetent patients diagnosed with tinea pedis, palmoplantar warts, insect bites, male or female androgenetic alopecia, acne vulgaris, seborrhoeic dermatitis, actinic keratosis, corn and callus. HIV test was negative in the control subjects with warts, tinea and seborrhoeic dermatitis. Patients older than 15 years old were ,ncluded ,nto both study and the control groups. Exclusion criteria were the presence of a disease associated with non-specific immunosuppression (liver or renal disease, sarcoidosis, diabetes, malnutrition, and malignant diseases), use of immunosuppressive drugs, active tuberculosis, known hypersensitivity to PPD, acute infections, and positive serology for HIV. In addition, psoriatic patients who were treated with an immunosuppressive agent, PUVA, UVB, narrow band UVB in last three months, and patients were treated with acitretin in last two years were not included in the study. Personnel and psoriatic patients working in hospital were not included in the study. PPD was performed using the Mantoux method [5 tuberculin

TABLE 1: PPD test results in the groups.

	Psoriatic patients (n=117)	Control patients (n=102)	p
Age*	36 (23)	35 (19.25)	0.72
Diameter of PPD induration* (mm)	7 (6)	7 (6)	0.36
Positive PPD test**	49 (41.8)	31 (30.3)	0.16
Anergy**	16 (13.6)	20 (19.6)	0.25

*; median (IQR:interquartile range), **;number (%)

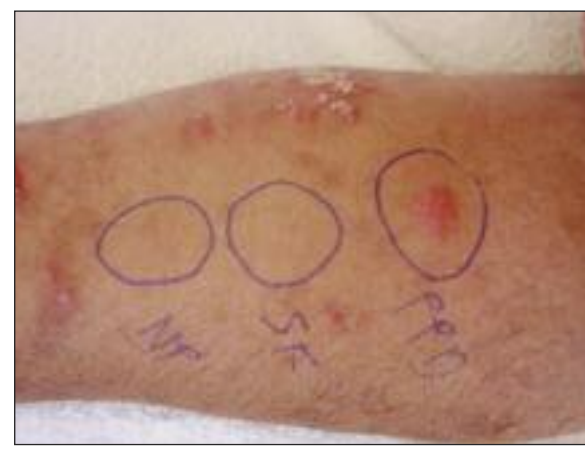

FIGURE 1: A positive PPD test in a Koebner-negative patient.

unit (0.1 ml) was injected intradermally by 26G disposable needle] and was evaluated by measuring the diameter of induration (not erythema) 72 hours later. In addition to PPD test, a needle prick and injection of 0.1 ml physiological saline were performed intradermally by using a 26G disposable needle in order to evaluate false positive of PPD test and Koebner phenomenon. All applications were performed to hairless volar site on the forearm by the same physician (MÖ) and the test areas were measured transversely to the long axis of the forearm using the pen method by the same observer (BE). PPD test was considered positive if a reactive induration exceeded 10 mm in diameter. Abnormal skin findings such as pustule or papulosquamous lesion on the test area were noted at evaluation. Patients who had the Koebner phenomenon before the test were noted. BCG vaccination was recorded in a personal interview and by verifying its scar. Duration of the disease, and psoriasis area and severity index (PASI) score were recorded in the patients with psoriasis vulgaris. The protocol was approved by the institutional ethics committee, and all subjects signed an informed consent form.

For statistical analysis, Mann-Whitney U test, χ^2 test and Spearman's correlation co-efficient were used.

RESULTS

The tests were performed on the anterior region of the brachium in five patients with psoriasis because of widespread psoriatic lesions on their forearms. BCG scar was detected in 107 psoriatic patients (91.4%) and 88 control subjects (86.2%). There were no significant differences between patients with psoriasis and controls in age (p= 0.72), sex (p=0.79) or BCG vaccination (p= 0.31). The median (IQR: interquartile range) diameter of induration on the PPD prick site in the psoriatic patients and controls were 7 (6) mm and 7 (6) mm, respectively (p=0.36) (Table 1). Positive PPD test was detected in 49/117 psoriatic patients (41.8%) and in 31/102 in the control group (30.3%) (p= 0.16) (Figure 1). BCG scar was detected in all PPD positive subjects except for two psoriatic patients. Twenty two subjects (eight psoratic and 14 control patients) who had no BCG scar were negative for PPD test. Sixteen (13.6%) psoriatic patients showed no reaction to PPD (0 mm) compared with 20 subjects (19.6%) in the control group (p= 0.25) (Table 2).

Koebner phenomenon was detected in 11 patients (9.4%) before the test (Table 3). Positive PPD test was detected in five of 11 patients. The median (IQR) diameter of induration on the PPD prick site in the Koebner-positive and negative patients were 8 (8) mm and 7 (6) mm, respectively (p=0.75). Anergy was not detected in the Koebner-positive patients. The phenomenon at other two test sites in these patients was not seen (Figure 2). An erythematous plaque with pustules located on the edge of the plaque was seen in a Koebner-negative patient who did not have any reactions at the other two tests areas. A papulosquamous lesion only at the needle prick site was detected in a Koebner-negative patient who had no reaction to the physiological saline and PPD (Figure 3). Minimal erythema at the physiological saline and only needle prick sites were seen in three Koebner-negative patients (Figure 4). We interpreted these nonindurative lesions as a Koebner reaction.

We performed an analysis to determine whether the diameter of PPD induration was influenced by factors such as duration of the disease and PASI score in psoriatic patients. The mean ± SD disease duration and PASI score were 12.6 ± 9.8 years and 9.8 ± 7.9, respectively. The range of PASI score and duration of the disease were 0.4-36.2 and 6 months-40 years, respectively. However, the diameter of PPD induration was not associated with sex (p= 0.20), duration of the disease (r_s= 0.01, p= 0.90) or PASI score (r_s= 0.07, p= 0.40). There was no association between the positive PPD test and PASI score.

Positive PPD test was not associated with age in psoriatic (p= 0.47) and control patients (p= 0.95). In 23 patients with psoriasis and 12 control patients, the duration of BCG vaccination was under 15 years. A positive PPD test was detected in 10 of 23 patients with psoriasis and four of 12 control patients. All of them had BCG scars. Chest X rays were performed in all subjects with positive PPD tests. Some findings such as parenchymal abnor-

TABLE 2: The diameter of PPD induration [No. (%)]

Group	BCG scar	0 mm	1-9 mm	>10 mm	Total
Psoriatic patients	Absent	5 (50)	3 (30)	2 (20)	10
	Present	11 (10.2)	49 (45.7)	47 (43.9)	107
	Total	16 (13.6)	52 (44.4)	49 (41.8)	117
Control patients	Absent	9 (64.2)	5 (35.7)	-	14
	Present	11 (12.5)	46 (52.2)	31 (35.2)	88
	Total	20 (19.6)	51 (50)	31 (30.3)	102

malities and granuloma like lesions on the chest X ray for latent tuberculosis were detected by a pneumologist in only 8 patients with psoriasis (16.3%) and one subject in the control group (16.1%).

DISCUSSION

In this case-control study, PPD test was evaluated in psoriatic and control patients. A positive PPD test result has been reported to vary from 0% to 90% in many studies from different countries.[5] PPD reaction can be influenced by some viral diseases, metabolic disorders, protein deficiencies, lymphoid tissue disorders and drugs. BCG gives some protection against tuberculosis and leads to a positive PPD skin test. In Turkey, BCG vaccination was performed in the first in two months of age and at the age of 7 years. There is no reliable method to distinguish between a positive PPD reaction associated with vaccination and *M. tuberculosis* infection. However, in a meta-analysis, it was demonstrated that when the PPD test is taken 15 years or later after BCG vaccination, the vaccination does not have any influence on PPD reaction.[5] In a recent study from Turkey, it was found that BCG scars did not have any influence on PPD reaction authors suggested that in adults and they suggested that a positive PPD response in adults living in high-prevalence countries might be due to LTBI rather than previous BCG vaccination.[6] In 35 subjects the duration of BCG vaccination was under 15 years in the present study, and 14 of them (40%) had positive PPD test. However, there was an abnormality on chest X ray for latent tuberculosis in 14 patients. We found a slight increase in positive PPD skin test (41.8%) in the psoriatic patients however this was not statistically significant. This slight high positive rate may be associated with excessive use of immunosuppressive agents and/or a long contact or hospitalization time in psoriatic patients than the control patients. Cross-reactions caused by the presence of atypical mycobacteria is another possibility, but there is limited data in Turkey.

TABLE 3: PPD test results in Koebner-positive and negative patients.

	Koebner-positive (n=11)	Koebner-negative (106)
Diameter of PPD induration*(mm)	8 (8)	7 (6)
Positive PPD test**	5 (45.4)	44 (45.8)
Anergy**	0	16 (16.6)
Abnormal skin finding***		
PPD test areas	0	1
Physiological saline areas	0	3
Needle prick areas	0	4

*; median (IQR:interquartile range), **;number (%), ***;pustule and/or papulosquamous lesion

A negative reaction to PPD (anergy) is detected in subjects who are not infected or unable to develop a delayed hypersensitive skin reaction. However, a high incidence of anergy has been reported in some viral and immunologic disorders such as rheumatoid arthritis and inflammatory bowel disease.[2] We did not detect a statistically significant difference between the psoriatic patients and the control for anergy. The Koebner phenomenon is a known condition in psoriasis and all traumatic conditions may lead to this phenomenon. The reported incidence of Koebner response in psoriasis varies between 11-75%. The latent period between injury to uninvolved skin and appearance of disease is usually 10-14 days, but it may range from three

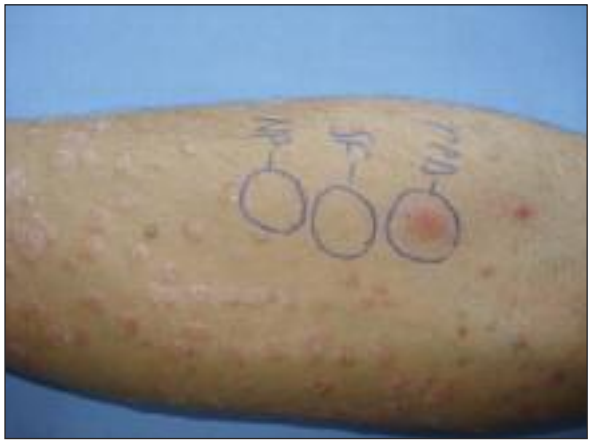

FIGURE 2: A negative PPD test in a Koebner-positive patient

days to several years.[4] A needle prick trauma and PPD extract may lead to Koebner phenomenon after 72 hours and these applications may be the cause of false positive PPD reaction in psoriatic patients. In the previous studies, an association between intradermal antigen tests (PPD, Candida, mumps, e.g.) and the Koebner phenomenon was not detected in psoriasis. This phenomenon was observed at all injection sites in three of of 42 psoriatic patients and one of the three patients was Koebner-positive psoriatic subject in these studies.[7,8] We observed this phenomenon at a needle prick site and a PPD injection site in two patients with psoriasis who were Koebner-negative. Interestingly, Koebner phenomenon or any reaction was not detected at the PPD and physiological saline injection sites in the only needle prick site Koebner positive patient, and at the needle prick and saline injection sites in the PPD injection site Koebner positive patient. We did not see the Koebner phenomenon at all test sites in our 11 Koebner-positive patients and positive PPD test was detected in five of them. In addition, there is no statistically significant difference in the diameter of induration on the PPD prick site between the Koebner-positive and negative patients. We believe that Koebner phenomenon may play a limited role on the positive PPD test. However this test should be evaluated in large series of Koebner-positive patients.

In conclusion, personal immune status and local epidemiological data are very important factors in interpretation of a positive PPD test in a person. The high positive PPD rates in this study may be result of the high prevalence of tuberculosis in Turkey. However, PPD positivity rate was not found higher or lower in the psoriatic patients when compared to the controls. This finding shows that psoriasis and the Koebner phenomenon do not influence the PPD reaction, and positive PPD test in a psoriatic patient living in high-prevalence countries may be related to latent tuberculosis rather than the BCG vaccination. We suggest that PPD skin test is appropriate to recognize LTBI in psoriatic patients who will be treated with the biologic or other systemic agents, until more sensitive diagnostic tests are available.

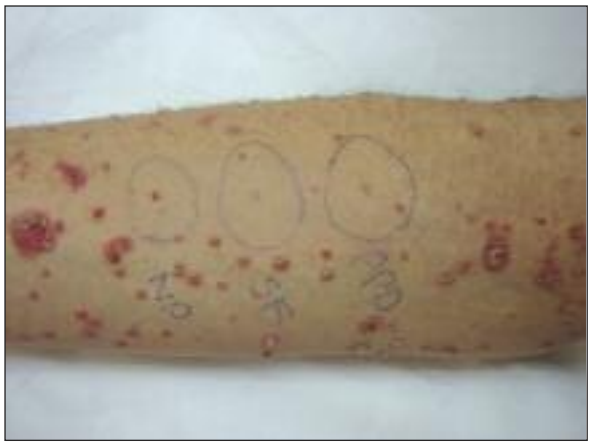

FIGURE 3: A papulosquamous lesion at the needle prick site in a Koebner-negative patient.

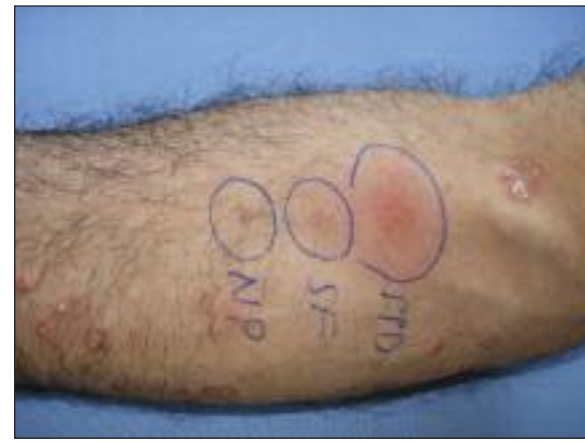

FIGURE 4: A positive PPD test, minimal erythema at the physiological saline and the needle prick sites in a Koebner-negative patient

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