MYCOSES **44,** 77–81 (2001) ACCEPTED: OCTOBER 14, 1999

Incidence of *Candida* in psoriasis – a study on the fungal flora of psoriatic patients

Die Häufigkeit von *Candida* bei Psoriasis: Untersuchungen zur Pilzflora bei Psoriasis-Patienten

A. Waldman[1,2], A. Gilhar[2], L. Duek[1] and I. Berdicevsky[1]

Key words. *Candida*, psoriasis, colonization, quantitation.

Schlüsselwörter. *Candida*, Psoriasis, Kolonisierung, Quantifizierung.

Summary. The presence of *Candida albicans* and other *Candida* species in saliva and faeces of 50 psoriatic patients compared with a control group of 50 healthy donors was examined quantitatively. The quantity of *Candida* in saliva and faeces of the psoriatics proved to be significantly higher than in the controls. *Candida* was detected in 78% of the saliva samples of the psoriatics but in only 50% of the controls, and in the faeces samples in 72% of the psoriatics, but in only 46% of the controls. Qualitative analysis revealed a predominance of *Candida albicans* (saliva, 77%; faeces, 64%) and *Candida rugosa* (saliva, 28%; faeces, 28%). We did not find a correlation between the severity of the psoriasis according to the Psoriasis Area and Severity Index and the amount of *Candida* in the saliva or in the faeces. Our results reinforce the hypothesis that *C. albicans* is one of the triggers to both exacerbation and persistence of psoriasis. We propose that in psoriatics with a significant quantity of *Candida* in faeces, an antifungal treatment should be considered as an adjuvant treatment of psoriasis.

Zusammenfassung. Es wurde die Besiedlung von 50 Psoriasis-Patienten im Vergleich zu 50 gesunden Kontrollpersonen mit *Candida albicans* und anderen *Candida*-Arten in Speichel und Fäzes quantitativ untersucht. Psoriatiker sind gegenüber den Kontrollen signifikant stärker mit *Candida* besiedelt: *Candida* fand sich bei 78% der Psoriatiker-Speichelproben (Kontrollen: 50%) und in 72% der Stuhlproben (Kontrollen: 46%). *Candida albicans* fand sich in 77% der Speichel und in 64% der Stuhlproben, *Candida rugosa* zu 28% im Speichel und zu 28% im Stuhl. Es fand sich keine Korrelation des Psoriasis-Schweregrades nach PASI und der *Candida*-Quantität in Speichel oder Fäzes. Unsere Ergebnisse bestärken die Hypothese, dass *C. albicans* ein Trigger sowohl für die Exazerbation als auch für die Persistenz der Psoriasis darstellt. Wir empfehlen, bei Psoriatikern mit einer signifikant hohen *Candida*-Kolonisation im Stuhl eine antimykotische Behandlung als adjuvante Psoriasistherapie zu erwägen.

[1]The Department of Microbiology and the [2]Laboratory of Dermatological Research, Rappaport Institute, Faculty of Medicine, Technion, Institute of Technology, Haifa, Israel.

Correspondence: Professor Dr Israela Berdicevsky, Department of Microbiology, P.O.B. 9649, Bat-Galim, Haifa, 31096 Israel. Tel: +972 4 8295293 Fax: +972 4 8295225

Introduction

Psoriasis is a skin disease which is characterized mainly by abnormal proliferation and differentiation of keratinocytes. Psoriasis combines a genetic defect as well as external triggers that affect the features of the disease. The recent hypothesis indicates that the cellular immune system plays a dominant role in exacerbation of psoriasis [1]. Micro-organisms such as β-haemolytic streptococci, *Staphylococcus aureus* and *Candida albicans* have been suggested as external triggers that release factors which serve as superantigens, and stimulate the T cells to initiate the pathogenic circle of psoriasis [2–8]. The source of the micro-organisms may be in the skin itself

but may also be in other parts of the body such as the throat regarding *Streptococcus* or the gut regarding *Candida albicans*. From these locations the micro-organisms release their superantigens and through the vascular system these superantigens reach the skin and start the psoriatic process [9].

The purpose of this study was to examine the presence of *Candida albicans* and other species of *Candida* in the saliva and faeces of 50 psoriatic patients compared with a control group of 50 healthy people. We also investigated the correlation between the severity of the psoriasis [determined by the Psoriasis Area and Severity Index (PASI), or by other methods] and the amount of *Candida* in the saliva or in the faeces.

Materials and methods

Patients

Fifty Israeli Jewish patients with chronic plaque psoriasis were recruited (33 males, 17 females; mean age, 51 years; age range, 10–82 years). Fifty healthy control subjects were also recruited (27 males, 23 females; mean age, 49 years; age range, 15–70 years).

Laboratory tests

Saliva samples. Whole unstimulated saliva samples were collected over a period of 10 min. These samples were cultured on MI medium. MI is a new fungal growth and isolation medium, which is selective for fungi, that has been developed and tested in our laboratory. This medium is based on a plant extract (the plant name is not mentioned for reasons of confidentiality). The uniqueness of this medium is its capacity to enhance the morphological differentiation of fungal colonies and its ability to inhibit bacteria without addition of antibiotic agents. The final identification was based on the ability of the yeasts to assimilate and ferment different sugars.

The plating was carried out according to standard procedures and the results were evaluated after 48 h of incubation at 32 °C. The quantity of *Candida* was established by decimal dilutions in saline solutions and plated in duplicates on Sabouraud glucose agar (Difco, Detroit, USA).

Growth was assessed according to the number of yeast colonies per 1 ml saliva as follows: <100 colony-forming units (CFU) ml^{-1}, absent; 100–1000 CFU ml^{-1}, moderate growth; 1000–10 000 CFU ml^{-1}, strong growth; $>10\,000$ CFU ml^{-1}, massive growth.

Faeces samples. Faeces samples were collected from all the participants of the study. From each sample, a volume of 10 μl was taken by a special loop. This volume was spread onto the MI medium and incubated for 5 days at 32 °C. Differentiation of the yeasts was carried out by using the diagnostic features of the MI agar, and by the ability of the yeasts to assimilate different sugars.

Growth was assessed according to the number of yeasts colonies per g faeces as follows: 50–500 CFU g^{-1} faeces, moderate growth; 500–5000 CFU g^{-1} faeces, strong growth; >5000 CFU g^{-1} faeces, massive growth.

Clinical tests

We interviewed the psoriatic patients and made a thorough clinical examination. The severity of psoriasis was determined according to PASI. This method evaluates the severity of psoriasis according to the affected psoriatic area and the features of the plaques, which include the infiltration, the erythema, and the desquamation of the plaques.

The PASI method gives a numeral index to the severity of psoriasis. The range spreads between 0 and 72. In addition to PASI, we determined the character of the disease by other measurements as follows: (a) the initial age of the psoriasis and (b) the medical treatment the patients receive in order to control the psoriasis.

Finally, we compared the severity of the disease according to the above measurements and the quantity of *Candida* in saliva or in faeces.

Results

Candida *in saliva*

In the psoriatics, *Candida* was detected in 78% of the saliva samples, whereas in the controls only 50% were positive carriers of *Candida* (Fig. 1). This difference between the psoriatics and the controls was statistically significant. ($P<0.01$). The different species of *Candida* in the saliva of the psoriatics patients are presented in Table 1 and the quantity of *Candida* in the saliva of the psoriatic patients is presented in Table 2.

Candida *in faeces*

In the psoriatics, *Candida* was detected in 72% of the faeces samples, whereas in the controls only 46% were positive carriers of *Candida*. (Fig. 2). This difference was statistically significant. ($P<0.01$). The species of *Candida* in the faeces of

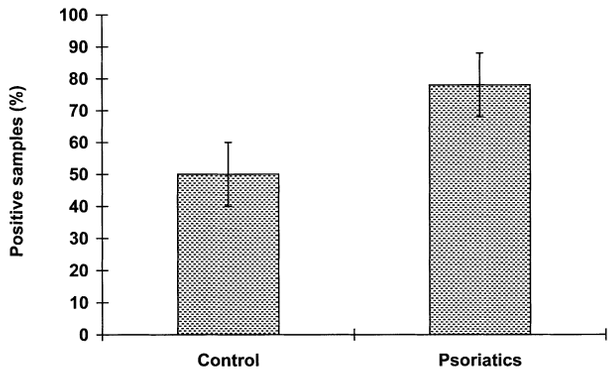

Figure 1. Quantitative analysis of *Candida* in saliva: psoriatics and controls. In the psoriatics ($n=50$) there was a significantly high incidence of *Candida* in the saliva, 78% with positive samples, whereas in the controls ($n=50$) there was only 50% positive samples ($P<0.01$).

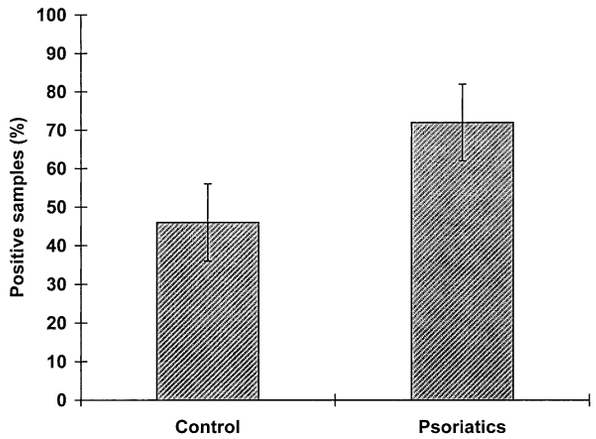

Figure 2. Quantitative analysis of *Candida* in faeces: psoriatics and controls. In the psoriatics ($n=50$) there was a significantly high incidence of *Candida* in the faeces, 72% with positive samples, whereas in the controls ($n=50$) there was only 46% positive samples ($P<0.01$).

Table 1. Qualitative analysis of yeast positive saliva samples in the psoriatics ($n=39$)

Species of *Candida* in saliva	No. of patients (%)
Candida albicans	77
Candida rugosa	28
Candida zeylanoides	10
Torulopsis (*Candida*) sp.	5.2
Candida langeroni	2.6
Candida tropicalis	2.6
Candida guillermondii	2.6
Candida lipolytica	2.6

Table 2. The titer of *Candida* in the saliva of the psoriatics: 78% were positive carriers. In this group, 56% had a titer of above 1000 CFU ml^{-1}

Quantity of *Candida* in saliva of the psoriatics (CFU ml^{-1})	No. of patients (%) $n=50$
<100 (absent)	22
100–1000 (moderate growth)	22
1000–10 000 (strong growth)	30
>10 000 (massive growth)	26
Total	100

Table 3. Qualitative analysis of yeast positive faeces samples in the psoriatics ($n=36$). Some harboured two or more species in their faeces samples

Species of *Candida* in faeces	No. of patients(%)
Candida albicans	64
Candida rugosa	28
Candida zeylanoides	5.6
Torulopsis (*Candida*) sp.	5.6
Candida stellatoidea	2.8
Candida marina	2.8
Rhodotorula sp.	2.8

Table 4. The number of yeast colonies in faeces of the psoriatics: 72% were positive carriers. In this group, 26% had a number of colonies above 500 CFU g^{-1} faeces

No. of yeast colonies in faeces of the psoriatics (CFU g^{-1} faeces)	No. of patients (%) $n=50$
0 (absent)	28
50–500 (moderate)	46
500–5000 (strong)	10
>5000 (massive)	16
Total	100

the psoriatics are presented in Table 3 and the quantitative analysis of the yeast-positive faeces samples is presented in Table 4.

Correlation between the severity of psoriasis and the quantity of Candida *in saliva or in faeces*

In the psoriatics the average of PASI was 13.5 (SD = 12.6) with a range of 1.0–63.2. There was no correlation between the index of PASI and the quantitative analysis of *Candida* in the saliva (Table 5). With regard to the faeces, we did find a partial correlation between the index of PASI and the quantity of *Candida* in the faeces samples (Fig. 3). We also found another interesting correlation between the initial age of the psoriasis and the quantity of *Candida* in the faeces. The results are presented in Fig. 4. This correlation was statistically significant. ($F=4.42$, $P<0.017$).

Table 5. The correlation between the index of PASI and the quantitative analysis of *Candida* in saliva of the psoriatics. There was no correlation. ($F=1.35$, $P<0.26$)

Quantity of *Candida* in saliva of psoriatics (CFU ml^{-1})	Average of PASI	Standard deviation	No. of patients (n)
<100	19.00	20.50	11
100–1000	12.90	8.00	11
>1000	11.70	9.70	28
Total	13.60	12.55	50

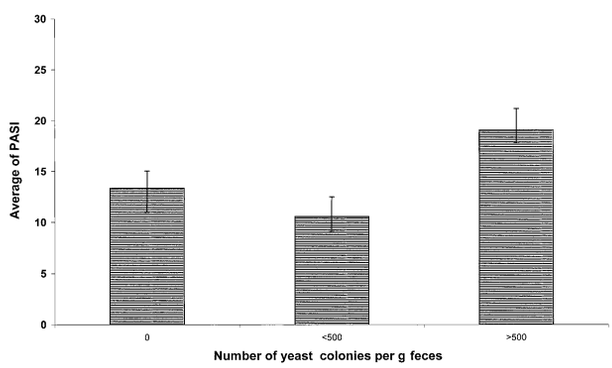

Figure 3. The correlation between the index of Psoriasis Area and Severity Index (PASI) and the quantitative analysis of *Candida* in faeces of the psoriatics. A partial correlation was found: the most severe psoriatics with the highest PASI had the highest amount of *Candida* in the faeces, ($F=1.95$, $P<0.15$).

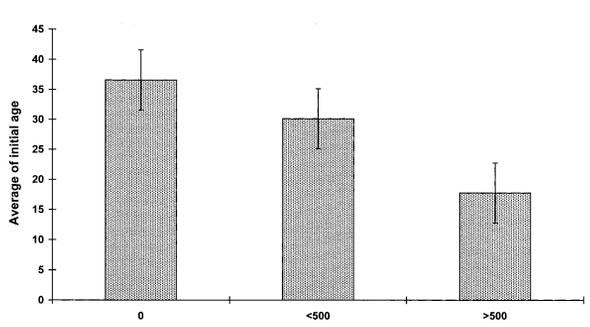

Figure 4. Quantitative analysis of faeces samples in the psoriatics regarding the initial age of psoriasis. The difference is statistically significant ($P<0.017$).

Discussion

The linkage between *Candida* and psoriasis has been investigated since the early 1980s. Two groups of researchers have studied this subject thoroughly: one group from the University of Memphis, Tennessee, USA [10], and another group from the university of Frankfurt, Germany [11].

The researchers from Tennessee, USA claimed that various microbial factors, mainly bacteria and yeasts, provoke the psoriatic process. They suggested that the yeast *Malassezia furfur* is a trigger of psoriasis capitis [12] and that cutaneous or intestinal *Candida* is a trigger of plaque psoriasis [13]. Based on these theories, they tested antifungal treatment against psoriasis. The results of these and other studies [14] showed that a treatment of systemic ketoconazole or nystatin was very effective in some of the psoriatic patients.

The researchers from Frankfurt/Main, Germany, had a similar theory that intestinal *Candida* is a possible trigger for psoriasis [15]. Hence, they tested for the presence of *Candida* in faeces samples in 100 psoriatic patients. The results indicated that 92% were positive carriers whereas in the controls, only 50% were positive to *Candida* [16].

This group from Germany also tested systemic antifungal treatment (nystatin) in 50 psoriatic patients and more than 50% showed a remarkable improvement [17].

Another group from Hamburg, Germany, also tested for the presence of *Candida* in faeces samples of 65 psoriatic patients and they found that 78% were positive carriers of *Candida* species, whereas in 652 controls, *Candida* was present in the faeces of only 29% of the patients [18].

In our study we made some further steps in detecting the linkage between *Candida* and psoriasis. We examined both saliva and faeces for colonization of *Candida* and we also examined the correlation between the quantity of *Candida* and the severity of the psoriasis according to PASI and other severity measures.

Our study showed that there is a remarkable level of *Candida* in psoriatic patients in comparison with the control groups, both in saliva and in faeces. We did not find any correlation between the quantity of *Candida* in saliva or in faeces and the severity of psoriasis according to PASI.

In our opinion PASI is not a sufficient index to describe the whole character of psoriasis. PASI describes only the current status of the disease, but psoriasis is a chronic disease with sudden acute flares. Therefore, we looked for other ways to estimate the features of the disease, by focusing on the medical treatment the patient receives to control psoriasis and on the initial age of the disease. These qualities are additional measures which express the pathogenic potential of the disease.

The initial age of psoriasis is considered as a prognostic measure to the character of the disease. The earlier the disease appears, the more severe will be the prognosis [19].

Researchers have already proved that psoriasis which started at an early age, has a strong genetic connection. Patients with early initial age have a high presence of HLA-CW6 and their offspring inherit the disease very frequently [20].

In our study we found a remarkable connection between the initial age and the quantity of *Candida* in the faeces.

In addition, we considered the presence of *Candida* in the faeces to be more reliable than the presence of *Candida* in saliva because with regard to saliva there are many factors other than psoriasis that influence the positive carriers of *Candida*; for example, denture wearers, antibiotic treatment [21], advanced age as well as early age [22], etc. In contrast, the presence of *Candida* in faeces is not generally influenced by such factors.

It is important to emphasize that *Candida* is only one of the triggers that can induce or exacerbate psoriasis [23].

Some recent research proved that the kinds of T cells which are found in the psoriatic plaque differ according to the trigger which caused the process. This research showed that when *Candida albicans* was the trigger of the disease, an increased expression of T cells with T-cell receptor (TCR) containing Vβ 5.1 or Vβ 8 is found. On the other hand, when there is another trigger, the kinds of T cells and their Vβ – TCR are specifically different [24, 25].

We concluded that *Candida albicans*, and other *Candida* species, can be a trigger of the psoriatic process. The reservoir can be intestinal *Candida* apparently secreting superantigens to the skin and inducing proliferation of specific T lymphocytes of restricted Vβ – TCR.

A significant presence of *Candida* in the faeces samples of psoriatic patients is a reasonable hint that in such cases *Candida* contributes to the induction or the persistence of psoriasis. Hence, in such cases we recommend the use of an antifungal agent as an additional treatment for psoriasis.

References

1 Gilhar, A., David, M., Ullman, Y., Berkutski, T. & Kalish, R. S. (1997) T-lymphocyte dependence of psoriatic pathology in human psoriatic skin grafted to SCID mice. *J. Invest. Dermatol.* **109**, 283–288.

2 Valbimarsson, H., Baker, B. S. & Fry, L. (1995) Psoriasis: a T-cell-mediated autoimmune disease induced by streptococcal superantigen? *Immunol. Today* **16**, 145–149.

3 Leung, D. Y., Walsh, P., Girono, R. & Norris, D. A. (1993) A potential role for superantigens in the pathogenesis of psoriasis. *J. Invest. Dermatol.* **100**, 225–228.

4 Ortonne, J. P. (1996) Aetiology and pathogensis of psoriasis. *Br. J. Dermato1.* **135** (Suppl. 49), 1–5.

5 Yamamoto, T., Katayama, I. & Nishioka, K. (1998) Clinical analysis of staphylococcal Superantigen hyper-reactive patients with psoriasis vulagris. *Eur. J. Dermatol.* **8**, 325–329.

6 Sayama, K., Midorikawa, K., Hanakawa, Y., Sugai, M. & Hashimoto, K. (1998) Superantigen production by *Staphylococcus aureus* in psoriasis. *Dermatology* **196**, 194–198.

7 Leung, D. Y., Travers, J. B., Giorno, R. & Norris, D. A. (1995) Evidence for a streptococcal superantigen-driven process in acute guttate psoriasis. *J. Clin. Invest.* **96**, 2106–2112.

8 Skov, L. & Baadsgaard, O. (1995) Superantigens – do they have role in skin diseases? *Arch. Dermatol.* **131**, 829–832.

9 Crutcher, N., Rosenberg, E. W. & Belew, P. W. (1984) Oral nystatin in the treatment of psoriasis. *Arch. Dermatol.* **120**, 435–436.

10 Rosenberg, E. W. & Belew, P. W. (1982) Microbial factors in psoriasis. *Arch. Dermatol.* **118**, 143.

11 Buslau, M., Menzel, I. & Holzman, H. (1988) Fungal flora of human feces in psoriasis and atopic dermatitis. *Mycoses* **33**, 90–94.

12 Rosenberg, E. W. & Belew, P. W. (1982) Improvement of psoriasis of the scalp with ketoconazole. *Arch. Dermatol.* **118**, 370–371.

13 Rosenberg, E. W. & Noah, P. W. (1988) The Koebner phenomenon and microbial basis of psoriasis. *J. Am. Acad. Dermatol.* **18**, 151–158.

14 Farr, P. M., Marks, J. M. & Krause, L. B. (1985) Response of scalp psoriasis to oral ketoconazole. *Lancet* **26**, 921–922.

15 Hänel, H., Menzel, I. & Holzman, H. (1988) High phospholipase-A activity of *Candida albicans* isolated from the intestine of psoriatic patients. *Mycoses* **131**, 451–453.

16 Menzel, I. & Holzman, H. (1986) Yeast flora in feces from patients with seborrheic dermatitis of scalp or psoriasis capilliti. *Z. Hautkr.* **61**, 451–455.

17 Buslau, M., Hanel, H. & Holzman, H. (1989) The significance of yeasts in seborrheic dermatitis. *Hautarzt* **40**, 611–613.

18 Sneff, H., Bothe, C. & Busacker, J. (1990) Studies on the yeast flora in patients suffering from psoriasis capillitii or seborrheic dermatitis of the scalp. *Mycoses* **33**, 29–32.

19 Melski, M. & Stern, R. S. (1981) The separation of susceptibility to psoriasis from age at onset. *J. Invest. Derm.* **77**, 474–477.

20 Brenner, W., Gschnait, F. & Mayr, W. R. (1978) HLA B-13, B-17, B-37 and CW-6 in psoriasis vulgaris: association with the age of onset. *Arch. Derm. Res.* **262**, 337–339.

21 Berdicevsky, I., Ben-Aryeh, H. & Szargel, R. (1980) Oral Candida in asymptomatic denture wearers. *Int. J. Oral Surgery* **9**, 113–115.

22 Berdicevsky, I., Ben-Aryeh, H. & Szargal, R. (1984) Oral *Candida* in children. *Oral Surg.* **57**, 37–40.

23 Krueger, G. & Eyre, R. (1982) Response to injury of skin involved and uninvolved with psoriasis and its relation to disease activity: Koebner and reverse Koebner reactions. *Br. J. Dermatol.* **106**, 153–159.

24 Moss, P., Charmely, P., Mulvihill, E., Ziegler, S., Raugi, G. L., Kern, D., Piepkorn, M. & Gelinas, R. (1977) The repertoire of T cell antigen receptor beta-chain variable regions associated with psoriasis vulgaris. *J. Invest. Dermatol.* **109**, 14–19.

25 Boehricke, W. H., Dressel, D., Manfras, B., Zollner, T. M., Wettstein, A., Bohm, B. O. & Sterry, W. (1995) T cell receptor repertoire in chronic plaque stage psoriasis is restricted and lacks enrichment of superantigen – associated V beta regions. *J. Invest. Dermatol.* **104**, 725–728.