Acta Dermatovenerol Croat 2005;13(2):85-92 ORIGINAL SCIENTIFIC ARTICLE

Species Distribution and Frequency of Isolation of Yeasts and Dermatophytes from Toe Webs of Diabetic Patients

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Received: November 2, 2004.
Accepted: March 27, 2005.

SUMMARY The paper identifies fungal species, looking at the incidence of fungal isolation and risk factors influencing the development of fungal infection and colonization of interdigital spaces of the feet in 509 diabetic outpatients. Using standard mycologic diagnostic methods, fungi were detected in toe webs of 122 (24%) diabetic patients. The finding of fungi was twice as common in interdigital spaces of one (85/16.7% of the patients) than both feet (37/7.3% of the patients). Yeasts were the most common isolates (95/18.7% of the patients), followed by dermatophytic moulds (24/4.7% of the patients), whereas coexistence of yeasts and dermatophytes was the most infrequent finding (3/0.6% of the patients). From toe webs, 24 fungal species, 21 yeast species belonging to nine genera (*Candida, Rhodotorula, Cryptococcus, Trichosporon, Saccharomyces, Blastoschizomyces, Geotrichum, Debaryomyces,* and *Ustilago*) as well as three species of dermatophytes of the genera *Trichophyton* and *Epidermophyton* were isolated. The most frequently isolated fungi were *Candida parapsilosis* (59/11.6% of the patients) and *Trichophyton mentagrophytes* (16/3.1% of the patients). Although there was no correlation between the incidence of toe web space colonization with yeasts and dermatophytosis with the criteria of patient sex and age, and duration of diabetes, the difference in the incidence according to type of diabetes was statistically significant. In non-insulin dependent diabetes mellitus patients, the incidence of fungal isolation from toe webs was statistically significantly higher (30.1%) than in insulin dependent diabetes mellitus patients (19.8%).

KEY WORDS: yeasts; dermatophytes; toe webs; diabetic patients

INTRODUCTION

Compared with nondiabetic population (1-4), certain mycotic infections (such as rhinocerebral zygomycosis, vaginal and oral candidosis) develop more frequently in diabetic patients. More severe clinical manifestations as well as a broader range of etiologic causative agents (from primary pathogenic to opportunistic species) are the main characteristics of fungal infections combined with diabetes (1-4).

Currently there are opposing views on whether diabetes is a risk factor for the development of colonization and/or infection of skin and nails with fungi (4). Although not fully explained, the etiologic mechanism of these processes is considered to be linked with a glucose metabolism disorder in these patients. A high level of blood and tissue glucose, and a low level of skin lactates favor the growth of yeasts and moulds (4,5). Reduced

Acta Dermatovenerol Croat
2005;13(2):85-92

neutrophil activity in diabetic patients due to the transformation of glucose into sorbitol that inhibits the oxidative mechanism of phagocytosis in fungal cells facilitates the development of mycotic infection of keratinized tissue (5). Also contributing to the development of fungal infections of the skin and nails are poor metabolic control in diabetics (6), advanced age, treatment with immunosuppressants and antibiotics, presence of peripheral vascular diseases, positive family medical history, occlusive footwear, vigorous physical activity, and frequent use of public swimming pools and swimming facilities (7-9). In diabetic patients with fungal infection, the affection of toenails is four times more common than that of fingernails (7).

Some yeast species (*Candida C. parapsilosis* and *C. guilliermondii*) constitute the physiologic flora of the feet (1,2,5,10,11). In contrast, *C. albicans* and *C. tropicalis* are rarely found on healthy smooth human skin. They are more often isolated from moist axillary skin, groins and toe webs. The incidence of foot skin colonization with *Candida* varies considerably depending on geographical area, patient occupation, hospital stay, and primary disease (5). There is a higher prevalence of *Candida* spp. in the toe webs among the populations from warm and wet areas, among farmers and hospitalized patients (5). However, it peaks in oncologic (47.1%-63.6%) and chiropody patients (50.0%) as well as in the elderly (38.1%) (5). Abel has described seasonal variation in the prevalence of *Candida* species in toe webs, finding an approximately equal incidence of *Candida* colonization in males and females (12). Maibach and Kligman have managed to cause vesicular-pustular skin lesions in volunteers only after covering the inoculation site of live blastoconidia of *C. albicans* with a strap, bandaging it with adhesive tape. Under the strap, increased sweating and elevated temperature created favorable conditions for the growth and replication of *Candida* (13).

Interdigital candidosis of feet manifests as white foci surrounded by a shiny dark-red rim, which soon begins to scale. Clinical signs of this infection readily cause confusion with interdigital dermatophytosis of feet (tinea pedis or athlete's foot). To emphasize that yeasts are etiologic causative agents, Kaufmann-Wolf has named this clinical picture "Erosio interdigitalis blastomycetica" (1,2,10), however, this term has not been widely accepted. *C. albicans* is the most common cause of interdigital candidosis, with sweaty skin being the most important predisposing factor in the development of infection (1,2,5,10,13).

Clinically, interdigital tinea pedis is manifested as erythematous-squamous skin lesions, maceration, desquamation, and as vesicles and/or blisters in toe web spaces. Some authors have reported an increased incidence of nail dermatophytosis (tinea unguium) and tinea pedis in diabetic patients in comparison with nondiabetic population (8,9,14-16), whereas others (6,17,20) failed to demonstrate an increased incidence of these infections in well-controlled diabetic patients. The findings of many studies have proved an association of skin mycoses with complications (secondary bacterial infections with staphylococci, streptococci, pseudomonas and enterobacteria, development of abscess and osteomyelitis of foot bones, as well as an increased incidence of minor and major low extremity amputations) in diabetic patients (5,7,10,14-16).

The present study investigated the incidence and etiology of interdigital tinea pedis and certain risk factors for the development of these infections in diabetic patients. It also examined the incidence of isolation of individual yeast flora species from the toe webs of diabetic patients free from the clinical signs of infection of these spaces.

PATIENTS AND METHODS

During three years (2000-2002), the study included 509 consecutive diabetic outpatients, 314 (61.7%) male and 195 female (38.3%), mean age 66.7 (range 25 to 90) years, presenting for periodic follow-ups. There were 303 (59.5%) patients with insulin dependent diabetes (IDDM) and 206 (40.5%) patients with non-insulin dependent diabetes (NIDDM), with the mean diabetes duration of 12.6 (range 0.08 to 54) years. Polyneuropathy, macroangiopathy and microangiopathy were present in 471(92.5%), 428 (84.1%) and 385 (75.6%) diabetic patients, respectively.

A total of 943 swabs of the toe web spaces of 509 diabetic patients were used for mycologic diagnosis. The material was cultured on Sabouraud glucose agar supplemented with chloramphenicol and cycloheximide. The seeded media were incubated at 25º C for 7 to 21 days (1).

Identification of yeast isolates was done by use of classic mycologic methods (1,10,11) (germination test, sugar and nitrate assimilation tests, sugar fermentation tests, growth on maize agar). Mould isolates were identified on the basis of their macro- and microscopic features (1,10,11).

Differences in the incidence of toe web colonization with yeasts and dermatophytosis in diabet-

ic patients according to sex and type of diabetes were analyzed by use of χ^2-test. Fisher's exact test was used to correlate the presence of interdigital tinea pedis and yeast colonization of toe webs with patient age and duration of diabetes.

RESULTS

The fungi isolated from toe web spaces of 122 (24.0%) of 509 diabetic patients were 2.3 times more common in these spaces of a single foot (85/16.7% of patients) than of both feet (37/7.3% of patients) (Table 1). Yeasts had the highest isolation incidence (18.7%), being isolated four times more often than dermatophytic moulds (4.7%) and 32 times more often than yeasts combined with dermatophytic moulds (0.6%). *C. parapsilosis* was the most commonly isolated yeast species. It was found in toe web spaces of 11.6% (59/509) of diabetic patients. The most commonly isolated dermatophytic mould was *T. mentagrophytes*. It was detected in 3.1% of patients (16/509) (Fig. 1).

One hundred eighty-nine fungal isolates involving 24 different species from 11 genera were isolated from the interdigital spaces of one foot or both feet (Table 2). Yeast isolations had a rate of 79.4%, with the isolates belonging to 21 yeast species from the genera C*andida, Rhodotorula, Cryptococcus, Trichosporon, Saccharomyces, Geotrichum, Debaryomyces, Blastoschizomyces* and *Ustilago*. Regarding the isolation rate (20.6%) for dermatophytes, it was 3.8 times lower than the rate of yeast isolation; as for isolates, they originated from three species belonging to the genera *Trichophyton* and *Epidermophyton*.

Yeasts belonging to the three genera *Candida* (111 isolates, 58.7%), *Rhodotorula* (14 isolates, 7.4%) and *Cryptococcus* (7 isolates, 3.7%) had the highest isolation incidence accounting for 69.8% of all fungal isolates from the interdigital spaces of both feet (Fig. 2). *C. parapsilosis* had the highest isolation rate (38.1%), followed by *C. famata* (7.4%) and *C. albicans* (5.5%). The rates of isolation of the remaining eighteen yeast species were much lower and varied between 0.5% and 4.2%. Regarding dermatophytic isolates, *T. mentagrophytes* was most common (11.6%); the rate of isolation of *T. rubrum* (6.3%) and *E. floccosum* (2.6%) was 2 to 4.5 times lower.

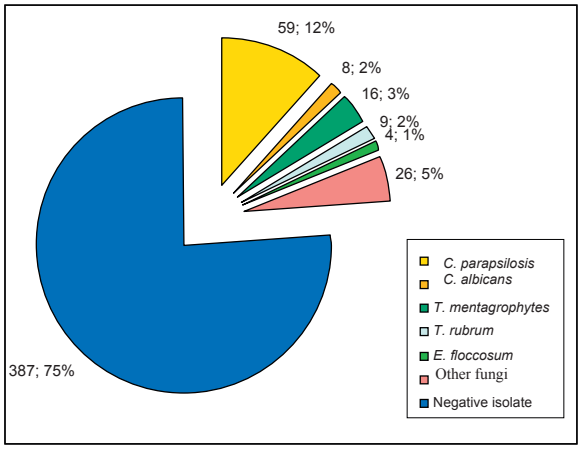

Figure 1. Isolation rate of *Candida parapsilosis, C. albicans, Trichophyton mentagrophytes, T. rubrum* and *Epidermophyton floccosum* from interdigital spaces of one foot or both feet of 509 diabetic patients.

Table 1. Incidence of yeast and/or dermatophytic mould isolates from interdigital spaces of one foot or both feet of 509 diabetic patients

	Diabetic patients with isolates of					
	Yeasts		Dermatophytes		Yeasts and dermatophytes	
	n	%	n	%	n	%
From one foot	70	13.8	14	2.8	1	0.2
From both feet	25	4.9	10	2.0	2	0.4
From neither foot	414	81.3	485	95.2	506	99.4
Total	509	100.0	509	100.0	509	100.0

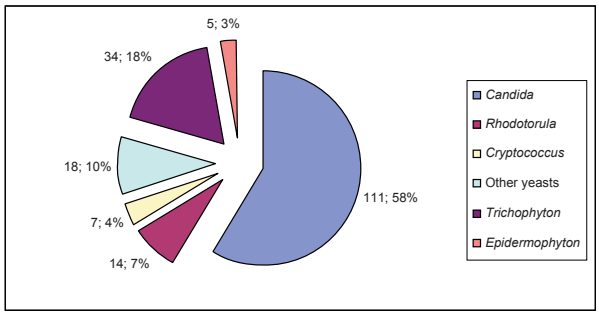

Figure 2. Proportion of isolates of individual yeast and dermatophyte genera in total fungal isolates obtained from interdigital spaces of one foot or both feet.

The significance of yeast isolates from toe web spaces was interpreted according to clinical finding and parameters of mycologic diagnosis (quantification of isolates), based on the knowledge about the pathogenic effect of individual yeast species. The following reasons led us to consider yeasts as toe web space colonizers: (i) absence of local signs of infection and absence of vesicles, ulcers and other skin lesions in toe web spaces, toenails and adjacent tissues; (ii) high isolation incidence of the species constituting the physiologic flora of the skin and the kind of low pathogenic potential; and (iii) isolation of 63.0% of the isolates (95/150) in a small number of colonies (up to 10). The rate of interdigital yeast colonization of one foot (71/13.9% of patients) was 2.6-fold that of interdigital colonization of both feet (27/5.3% of patients) (Table 1).

Interdigital tinea pedis was confirmed by culture in 5.3% (27/509) of diabetic patients (Table 1). It affected with approximately equal frequency the interdigital spaces of one foot (15/509) and of both feet (12/509).

Fungi were isolated with a roughly equal incidence from toe web spaces in diabetic male (67/21.3%) and female patients (55/28.2%) as well as from those of patients aged 70 (69/22.7%) and those aged 71+ (53/26.4%). There was no statistically significant difference in the incidence of colonization with yeasts and dermatophytosis of interdigital spaces of one foot or both feet in diabetic patients according to sex (χ^2=3.113; p=0.078) and age (Fisher's test, p=0.344).

NIDDM patients (30.1%) had a statistically significantly higher incidence (χ^2=7.132, p=0.008) of interdigital colonization with yeasts and dermatophytosis of one foot or both feet (Table 3) than IDDM patients (19.8%).

Yeasts and dermatophytes were found more commonly in the interdigital spaces of one foot and both feet of patients with IDDM (52/21.0%) and NIDDM (60/31.4%) duration of less than 20 years than in those with either type of diabetes duration of more than 21 years. Yet, there was no statistically significant association between the incidence of toe web space colonization with yeasts and dermatophytosis and the duration of diabetes in either IDDM (χ^2=1.169, p=0.28) or NIDDM patients (Fisher's test, p=0.24).

DISCUSSION

Dermatomycosis and onychomycosis are the oldest fungal infections described to have an incidence superior to the one expected in diabetic patients (5,7-9,15-17,19). The Alteras study findings (15) showed diabetics to be statistically significantly more commonly affected with foot infections caused by dermatophytic moulds (57.0%) and *Candida* species (31.0%) than nondiabetics (40.0%; 5.0%). Dogra *et al.* investigated the incidence of morbidity from fungal infections of toenails in 400 diabetic patients in India (8). The incidence of onychomycosis was statistically significantly higher in diabetic (17%) than in nondiabetic patients (6.8%). The most common isolates in diabetic patients were yeasts (48.1%), followed by dermatophytic (37.0%) and nondermatophytic moulds (14.8%). A study conducted in Canada and the US included 550 diabetics, mean age 56.1 years. While deformities of toenails were found in 46%, onychomychosis was confirmed (by culture) in 26% of the patients (7). The occurrence of toenail onychomycosis displayed a statistically significant association with older age and male sex. Affection with toenail onychomycosis was 2.99 times as common in male as in female diabetics. Statistical calculation revealed the rate of toenail onychomycosis in diabetic patients to be 2.5- to 2.7-fold that in healthy people of the same sex and age (8,9). The most common causative agents of fungal toenail infections were dermatophytic moulds (88.2%), followed by nondermatophytic moulds (9.1%), and *Candida* species (2.7%) being the rarest (9). One of the priorities of a one-year project (1997-1998) with 100,000 people from 11 European countries was to look at fungal foot infections in 19,588 diabetic patients (9). It found a statistically significantly higher (1.4 times) incidence of clinically manifest and mycologically confirmed fungal foot infections (toe web spaces and toenails) in diabetics compared with nondiabetics.

Table 2. Isolation rates of individual genera and species of yeast and dermatophytic moulds in total fungal isolates from interdigital spaces of one foot or both feet

	Genera and species of yeasts and dermatophytic moulds		One foot		Both feet		Total	
			n	%	n	%	n	%
Yeasts	***Candida***	*C. parapsilosis*	40	38.1	32	38.1	72	38.1
		C. famata	7	6.7	7	8.3	14	7.4
		C. albicans	5	4.8	5	6.0	10	5.3
		C. glabrata	6	5.7			6	3.2
		C. tropicalis	2	1.9	1	1.2	3	1.6
		C. guilliermondii	2	1.9			2	1.0
		C. zeylanoides	1	1.0	1	1.2	2	1.0
		C. solani	1	1.0			1	0.5
		C. catenulata	1	1.0			1	0.5
	Rhodotorula	*R. glutinis*	5	4.8	3	3.6	8	4.2
		R. rubra	4	3.8	2	2.4	6	3.2
	Cryptococcus	*C. laurentii*	1	1.0	2	2.4	3	1.6
		C. luteolus	2	1.9			2	1.0
		C. neoformans	1	1.0			1	0.5
		C. uniguttulatus			1	1.2	1	0.5
	Ttichosporon	*T. beigelii*	3	2.9	1	1.2	4	2.1
	Saccharomycess	*S. cerevisiae*	2	1.9	2	2.4	4	2.1
	Geotrichum	*G. candidum*	2	1.9	2	2.4	4	2.1
	Debaryomyces	*D. hansenii*	3	2.9	1	1.2	4	2.1
	Blastoschizomyces	*B. capitatus*	1	1.0			1	0.5
	Ustilago	*U. violaceum*	1	1.0			1	0,5
Moulds	***Trichophyton***	*T. mentagrophytes*	8	7.6	14	16.7	22	11.6
		T. rubrum	4	3.8	8	9.5	12	6.3
	Epidermophyton	*E. floccosum*	3	2.9	2	2.4	5	2.6
		Total	105	100	84	100	189	100

Examining toenail fungal infections among diabetic patients is important because of the simultaneous development of foot skin fissures that permit secondary deep and severe bacterial infections of the diabetic foot to occur (7,9,16). Studies have also shown the presence of skin lesions, most often interdigital tinea pedis, in more than two thirds of diabetics with a fungal toenail infection, which favors the occurrence of bacterial infections of deeper foot tissues (16.0% of diabetics with onychomycosis and only 6.0% of diabetics free from onychomycosis) (7,9,16). In diabetic patients with fungal toenail infection, foot ulcers and gangrene develop three times as often (in 12.2% of patients) as in diabetics who are free from these fungal infections (3.8%) (20).

Some studies failed to show an increased incidence of tinea unguium and tinea pedis in well-managed diabetic patients (6,18). Buxton *et al.* assessed the incidence of affection with dermatophytosis of toe web spaces and toenails in 100 metabolically regulated IDDM patients and 100 nondiabetics of the same age, sex, occupation and sporting activities (18). Tinea pedis and tinea unguium were found in 19% of diabetics and 17% of their nondiabetic controls. Romano *et al.* demonstrated dermatophytosis of toe web spaces and toenails in 4.1% (7/171) of metabolically managed diabetics and 6.1% (17/276) of nondiabetics (6).

Table 3. Incidence of yeast colonization and dermatophytosis of interdigital spaces of one foot or both feet according to type of diabetes

	Type of diabetes				Total
	Insulin dependent diabetes mellitus		Non-insulin dependent diabetes mellitus		
	n	%	No n	%	N
Positive	60	19.8	62	30.1	122
Negative	243	80.2	144	69.9	387
Total	303	100.0	206	100.0	509

Our finding of a low incidence of interdigital tinea pedis (5.3% of patients) is in agreement with the study by Romano *et al.* (6) proving the existence of these infections in 2.9% of diabetic patients. According to the results of other authors, the incidence of toe web dermatophytosis was significantly higher in diabetic patients. Interdigital tinea pedis was mycologically confirmed in 16% (21), 17% (18), 32% (19) and 57% (15) of diabetics. A possible explanation for the low incidence of interdigital tinea pedis in our diabetics would be proper education of these patients (mainly urban population and accessibility of physicians of any specialty) about appropriate daily foot care. Besides warm temperature, humidity, minor skin injuries, and poor foot hygiene favor the development of tinea pedis. Daily foot washing makes the penetration of dermatophytic moulds into the skin statistically significantly more difficult, also slowing down the development of dermatophytosis (22).

The species mycologically confirmed in the present study as the causative agents of interdigital tinea pedis in diabetic patients were *T. mentagrophytes* (3.1%), *T. rubrum* (1.8%) and *E. floccosum* (0.8%). This is in agreement with the results of some authors who claim that *T. mentagrophytes* is also the most common causative agent of tinea pedis in both diabetics and nondiabetics (10,12,23). In other studies, *T. rubrum* (7,9,15,18,19,21) and *E. floccosum* (6) were the most common dermatophytic moulds isolated from interdigital spaces of diabetic feet. Rothman was the first to describe (in 1953) an increased incidence of these infections with *T. rubrum*, drawing attention to the association between the level of glycemia and recurrent infections with dermatophytes, especially *T. rubrum* (6). In the study by Romano *et al.* (6), *E. floccosum* was the most common causative agent of interdigital tinea pedis (1.8%).

From the healthy skin, in addition to the most common *Candida* species (1,2,5,10-12,24), yeasts from the other genera, e.g., *Rhodotorula* (5,10-12,24), *Blastoschizomyces* (1,11,12), *Trichosporon* (11,12), *Debaryomyces* (24), *Geotrichum* (10,11), and *Ustilago* (11,25) have also been isolated. Species of the genus *Cryptococcus* were more commonly isolated from skin ulcers than from intact skin (10-12,24,25).

The present study found *C. parapsilosis* to be the most common colonizer of toe web spaces in diabetic patients. There are many reports (1,2,5,10-12,24,25) of an increased incidence of isolation of this *Candida* species (3.1-20.0%) from the skin of healthy individuals than of *C. albicans* species isolation (0-17.4%). The study also showed a similar relationship in the incidence of isolation of these

two *Candida* species in diabetics (*C. parapsilosis* in 11.6% and *C. albicans* in 1.6% of patients). Both the species distribution and the frequency of isolation of yeasts from interdigital spaces of diabetic foot in this study were consistent with the spectrum and incidence of yeast isolation from the skin of nondiabetic (healthy) subjects reported in the literature (1,2,5,10-12,24,25).

Our results suggested the type of diabetes to be a risk factor for the development of interdigital foot colonization with yeasts and dermatophytosis in diabetics. NIDDM patients had a statistically significantly greater incidence of yeast colonization and dermatophytosis of toe webs than IDDM patients (30.1% *vs.* 19.8%), suggesting that good metabolic management and maintenance of an optimally balanced circadian concentration of blood glucose (in IDDM patients) delays and reduces the incidence of yeast colonization and dermatophytosis of interdigital spaces of one foot or both feet. Some authors failed to demonstrate a statistically significant difference in the incidence of tinea pedis according to type of diabetes, existence of late complications of diabetes, levels of glycemia and concentration of glycosylated hemoglobin (6). Yosipovitch *et al.* (19) have described a statistically significantly higher incidence of tinea pedis in patients suffering from NIDDM for more than 5 years (32.0%) as compared with healthy subjects (7.0%). Other authors describe a higher incidence of paronychial toenail infection caused by different species of *Candida* as well as an association between this fungal infection with complications (secondary bacterial infections and development of abscesses and foot bone osteomyelitis) in diabetic patients (4,26).

CONCLUSION

Our findings did not show a high incidence of interdigital tinea pedis (5.3%) and yeast colonization (19.3%) in diabetic patients. Nevertheless, many authors have described the phenomenon of relapsing fungal infection and reinfection of toe webs, toenails and/or tissue around the nails with dermatophytes and yeasts. They have also described the risk of secondary bacterial infection of deep tissues developing due to bacterial penetration through the skin lesions originating from fungal infection (7,9,16,20,27). We therefore stress the importance of educating diabetic patients in the appropriate foot hygiene and the need of daily self-inspection of the feet in order to detect skin lesions in time. In fact, the studies conducted in several large clinical centers have shown a significant decline (44%-85%) in the incidence of lower extremity amputations in diabetic patients arising from the patients' education and involvement in diabetic foot control programs (7,26,28).

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My dear husband, you must take Nivea cream after shave every day.
From the Nivea collection of Zlatko Puntijar (1929)