

Fungal foot infections in patients with diabetes mellitus – results of two independent investigations

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Summary

In diabetic patients, mycotic infections may increase the risk of developing diabetic foot syndrome. However, little data are available on the prevalence of fungal foot infections in patients with diabetes. In a first study published using data obtained during a conference attended by patients with long-term diabetes mellitus type 1 (DM1), 78/95 patients (82.1%) showed probable pedal fungal infections, of which 84.6% (66/78) were mycologically confirmed by direct microscopy and/or culture. The dermatophyte *Trichophyton rubrum* was the most common (69.2% of isolates). Significant correlation was found between infection and the gender (men more frequently affected) and the age of the patients. Marked mycoses on the soles of the feet were often considered to be dry skin by the patients. In a second study, 174 [31 DM1, 112 DM2 and 29 healthy accompanying persons (HAP), family members without DM] participants at a regional patients' symposium on diabetes took part in an examination for fungal infections and neuropathy of the feet. In addition to the items of the first study, we gathered data on the quality of blood glucose control (HbA1c), peripheral neuropathy (neuropathy symptoms and deficit score) and measurement of sudomotoric activity by Neuropad™. Mean duration of disease was 23.6 (DM1) and 11.2 (DM2) years, mean HbA1c 7.56% (DM1) and 6.89% (DM2) and fungal foot infections were confirmed at 35.5% (DM1), 53.1% (DM2) and 37.9% (HAP) respectively. In DM2, the prevalence of positive fungal samples is significantly higher for participants with less controlled blood glucose (higher HbA1c) ($P = 0.04$). Mycotic foot infection is also correlated with age, gender and duration of diabetes disease. Of special interest is the finding of relatively high numbers of black fungi ('Dematiaceae') ($n = 10$), *Phialophora europaea* ($n = 3$) being the most common one. The sudomotoric activity was impaired in a very high number of participants [107/171 (61.5%)], and was found positively correlated with the prevalence of fungal foot infection in DM2 but not in DM1 and HAP. The high prevalence of fungal infections detected in DM1 as well as in DM2 diabetics is remarkable, especially considering this highly motivated collective. Therefore, it appears that the feet of diabetics require more diagnostic, therapeutic and preventive care in terms of mycotic infections and sudomotoric dysfunction than previously thought.

Key words: diabetic foot, fungal foot infections, moccasin-type tinea, sudomotoric activity.

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Introduction

With an estimated 60 million people worldwide, all populations and age groups are affected by diabetes mellitus (DM).¹ The annual incidence of new cases of type 1 and type 2 DM (DM1 and DM2) in the USA is estimated to be 30 000 and 6 25 000 respectively.² Diabetic foot disease is a polyaeiological disease of

great importance; its prevention through inspection, hygiene, callus removal, appropriate foot wear, awareness of neuropathy and peripheral arterial occlusive disease is crucial. Bacterial and mycotic infections may worsen diabetic foot syndrome.³ Pedal mycosis may become a potential entry site for bacterial infection, especially cellulitis.³ Severe onychomycosis is a predictor of diabetic foot ulcer⁴ and particularly problematic in the presence of polyneuropathy, as pressure erosions of the nail bed and hyponychium may be noted late because of impaired sensation, increasing the risk of subsequent bacterial infections involving bone. Diabetics with onychomycosis show a higher rate for gangrene and diabetic ulcers (12.2%) compared with patients without onychomycosis (3.8%).⁵ However, data on the prevalence of fungal foot infections in diabetic patients are rare and heterogeneous.^{2,5–13}

During a first meeting organised by the Diabetes Academy Bad Mergentheim, we were able to assess the point prevalence of fungal foot infections in patients with DM1. Apart from examining each patient's clinical situation, fungal spectrum, risk factors and complications, attention was focused on each patient's individual knowledge as well as the nature and scope of preventive measures taken by each patient. In a second meeting during a regional symposium on diabetes for diabetic patients (9th Giessen Symposium on diabetes), the investigational setting was expanded to include the quality of blood glucose control (HbA1c) and neurological parameters, such as neuropathy symptom and deficit scores as well as assessment of sudomotoric capacity.

Research design and methods

In both studies, a four-page questionnaire was sent to everybody who was going to attend either the meeting of long-term DM1 at the Diabetes Academy Bad Mergentheim or the supraregional Giessen Symposium with DM1, type 2 (DM2) or healthy accompanying persons (HAP). In addition to the basic data (age, sex, duration of disease, current therapy, history of vascular disease and peripheral neuropathy), it contained questions about the delegates' level of knowledge concerning frequency of, previous therapy for, and possible prevention of fungal infections. Following introductory lectures on the day of the event, patients were invited to have their feet examined for fungal infections. The size and distribution of skin and nail lesions were recorded by an experienced physician. The severity of onychomycosis was classified for all toenails

as follows: minimal (<20% involvement of nail bed and plate), moderate (20–60%) and severe (>60%). Skin scrapings and nail clippings were taken from any lesions suggesting mycotic infection. If more than one toenail appeared clinically abnormal, the two toenails that were clinically most likely to have onychomycosis were sampled. To ensure data protection, the questionnaires submitted and the clinical/mycological findings were coded for blind evaluation and later assignment. Under their code, the patients could call for their results after 4 weeks in the first study. In our second study, results of mycological tests were sent to participants by regular mail with the recommendation to visit their family doctor for further instructions. In our mycological laboratory in Giessen, the specimens were analysed by direct microscopy (KOH and Uvitex 2B) and conventional culture technique using Kimig's agar and selective agar for pathogenic fungi (with chloramphenicol and cycloheximide) (both Merck, Darmstadt, Germany). Incubation was performed at 30 °C for 4 weeks and at room temperature for 4–6 weeks respectively. Differentiation of dermatophytes was based on gross and microscopic criteria according to De Hoog *et al.* [14]. Differentiation of yeast was made by means of rice agar and the ID32C auxanogram (BioMérieux, Marcy-l'Etoile, France). Infection was considered to be present in subjects with positive microscopy and/or culture of a dermatophyte. According to Gupta *et al.* [2], in the case of a yeast or non-dermatophyte mould non-dermatophyte fungal spores, filaments or pseudomycelium have to be observed by microscopy, in addition to the culture being positive for these organisms. It was not within the scope of both studies to summon patients for repeat sampling.

At the Giessen Symposium, additional data were obtained for HbA1c, the Neuropathy Symptome Score and Neuropathy Deficit Score (NDS)¹⁵ for the assessment of neuropathy [perception of pressure (Semmes-Weinstein monofilament)], temperature (Tip-Therm® Gesellschaft für neurologische Diagnostik mbH, Düsseldorf, Germany) and vibration (Rydell-Seiffer tuning fork) as well as achilles tendon reflexes and assessment of sudomotoric capacity by Neuropad™ (Most Active Health Care GmbH, Riegel, Germany).¹⁶ Test-battery was started with mycological sampling and clinical examination for the NDS to have the feet of all patients out of their shoes and socks for about 10 min before fixing the Neuropad™-plaster plantar at the region of the first metatarsal caput on both feet. The indicator plaster Neuropad™ was read out exactly after 10 min. Corresponding grade of sudomotoric

activity was given as intact, impaired and lost. At the end blood samples were drawn for HbA1c-testing.

Statistics

Fisher's exact test, Pearson's test and the chi-square test were used for statistical evaluation, and the program SPSS 6.1.3. (SPSS Inc., Chicago, Illinois) was used for all statistical calculations.

Results

The data of the first study have already been published.¹⁷ Briefly, of 95 volunteered to be examined, no clinical indication of foot mycosis was seen in 17 patients (17.9%). Of those in whom there was clinical suspicion of disease (82.1%, $n = 78$), mycotic infections were mycologically confirmed in nine patients (5× toe webs, 4× soles), onychomycosis in 28, and combined skin and nail mycoses in another 28 patients (8× toe webs, 20× soles). Forty-seven per cent (47.4%) of these patients had positive cultures, particularly for the dermatophyte *Trichophyton rubrum* (69.2% of isolates). Skin/nail mycosis was found to correlate significantly with increasing age ($P = 0.03$) and male sex ($P = 0.01$). The actual frequency of mycoses was underestimated by the patients. This correlated with the assessment of their own knowledge level concerning fungal infections: 83.2% of patients with skin mycoses and 88.4% of those with onychomycosis of the feet felt that they needed more information about their disease. Marked mycoses on the soles were often considered to be dry skin by the patients.

In the second investigation, 174 volunteers were examined including 31 with DM1, 113 with DM2 as well as 30 HAP out of the same household of diabetic participants. Demographics are shown in Table 1. Because of an HbA1c of 6.6% one HAP and because of incomplete data one DM2 had to be withdrawn from further analysis. In all, 374 samples of toenails and skin scrapings from sole and interdigital regions were gathered for mycological assessment by microscopy and culture. Positive direct microscopy and/or culture were found in 81 patients [DM1 11/31 (35.5%), DM2 59/112 (52.7%), HAP 11/29 (37.9%)], 49 with

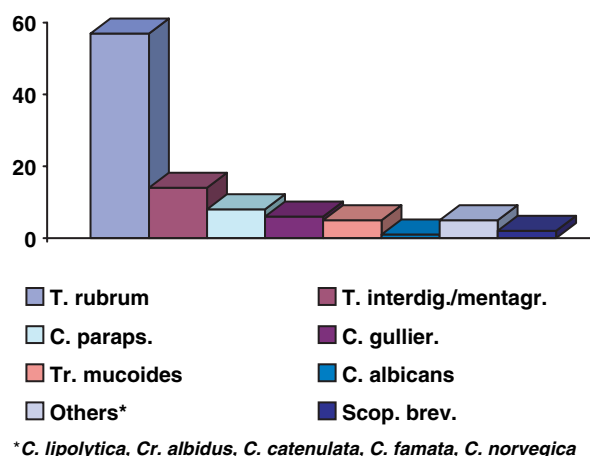


Figure 1 Spectrum and absolute numbers of fungal pathogens isolated ($n = 98$).

onychomycosis, 47 with moccasin-tinea and 41 with tinea pedis interdigitalis. Onychomycosis, moccasin-tinea or interdigital mycosis only were found in 18/16/6 cases, co-infection with onychomycosis and moccasin-tinea in eight cases, respectively, co-infection with onychomycosis and interdigital mycosis in further eight cases and co-infection with moccasin-tinea and interdigital mycosis in other eight cases. Sixteen patients were found to be positive for all three regions, all with a clinical picture of severe fungal infection.

The spectrum of fungal pathogens isolated is shown in Fig. 1. Again, most often the anthropophilic dermatophyte *T. rubrum* was found ($n = 57$, 58.2% of all isolates). The yeast *Candida guilliermondii* ($n = 6$), *C. parapsilosis* ($n = 8$) and *T. mucoides* ($n = 5$) are well-known pathogens in onychomycosis.¹⁸ *Candida albicans* was only found in one case of onychomycosis. Co-infections were found in seven cases: *T. rubrum* and *C. parapsilosis* ($n = 3$) and *T. rubrum*/*C. guilliermondii*, *T. rubrum*/*T. mucoides*, *T. mentagrophytes*/*C. parapsilosis* and *C. albicans*/*C. parapsilosis* in one case each. In Table 2, the frequencies of mycological confirmed fungal infections in the three groups are depicted. A significant correlation was seen between fungal foot infection and age ($r = 0.166$, $P = 0.03$) and gender ($r = 0.17$, $P = 0.025$), whereas men were more often

	Type 1 ($n = 31$)	Type 2 ($n = 112$)	HAP ($n = 29$)
Age (years)	56.3 ± 2.4 (27–76)	66.2 ± 0.9 (37–89)	58.5 ± 2.4 (28–81)
Diabetes duration (years)	23.2 ± 2.3 (0.25–53)	11.6 ± 0.9 (0.5–44)	–
HbA1c (%)	7.56 ± 0.22 (6.0–11.7)	6.89 ± 0.1 (4.2–10.8)	5.44 ± 0.05 (5.0–6.1)

HAP, healthy accompanying person; HbA1c, glycosilated hemoglobin A1c.

Table 1 Demographics of participants [mean ± SD; (min.–max.)]

Table 2 Frequency of mycologically confirmed fungal infections in the three groups ($n = 172$)

	Positive (native and/or culture, %)	Negative (%)
DM1 ($n = 31$)	11 (35)	20 (65)
DM2 ($n = 112$)	59 (52.7)	53 (50.5)
HAP ($n = 29$)	11 (38)	18 (62)

DM1, type 1 diabetes mellitus; DM2, type 2 diabetes mellitus; HAP, healthy accompanying person.

Table 3 Fungal foot infections (without Dematiaceae) with regard to HbA1c (at median HbA1c of 6.7%)

Fungal infection	No (%)	Yes (%)	n
DM1			
HbA1c ≤ 6.7	4 (80)	1 (20)	5
HbA1c > 6.7	16 (66.7)	8 (33.3)	24
DM2			
HbA1c ≤ 6.7	29 (26.9)	22 (43.1)	51
HbA1c > 6.7	24 (44.4)	30 (55.6)	54

DM1, type 1 diabetes mellitus; DM2, type 2 diabetes mellitus; HbA1c, blood glucose.

infected than women. Another significant factor, influencing the frequency of foot mycosis is the duration of diabetes (DM1 $r = 0.44$, $P = 0.014$; DM2 $r = 0.195$, $P = 0.041$).

The prevalence of positive fungal samples was found to be higher for diabetic participants with less controlled blood glucose levels (Table 3) but the Pearson's correlation is only significant for DM2 ($P = 0.04$). Data on frequency of fungal foot infections in HAP in comparison with their diabetic counterpart are shown in Table 4. Of special interest is the finding of relatively high numbers of black fungi (Dematiaceae), [$n = 10$ (2 DM1, 7 DM2, 1 HAP)], whereas *Phialophora europaea* ($n = 3$) was identified among other more rare types. Individuals, in whom Dematiaceae were found, used public swimming facilities more often and showed more intensive sporting activities than the other participants.

Table 4 Frequency of fungal foot infections in diabetics and their HAPs

Fungal infection in the same household	HAP	
	No (%)	Yes (%)
Diabetics		
DM1/DM2		
No	13 (72.2)	5 (27.8)
Yes	4 (44.4)	5 (55.6)

DM1, type 1 diabetes mellitus; DM2, type 2 diabetes mellitus; HAP, healthy accompanying person.

Associations of fungal foot infection and participant's hygienic and preventive behaviour are shown in Table 5. A total of 40.4% of the patients with confirmed fungal foot infection reported regular physician contact including check for mycosis, 47.2% inspected their feet daily themselves, 42.4% used skin cream or oil in a regular manner, 50.0% went to specialised foot care (chiropractors), 38.3% reported sporting activities and 41.2% wore bathing-shoes when visiting a swimming bath. However, analysing these data did not bear out significant correlations. The sudomotoric activity, measured by Neuropad™, was found to be surprisingly impaired in a very high number of participants (107/171, 61.5%), interestingly as many in diabetics (DM1 21/31, 67.7%), DM2 (67/112, 59.8%) as in HAP (19/28, 67.9%). Not only impaired but also totally lost perspiration was found in 47/171 (27.0%), among in DM1 7/31 (22.6%), DM2 35/112 (31.3%) and in HAP 5/28 (17.9%). In patients with DM2, we found a significant correlation between a reduced perspiration at the plantar foot and the prevalence of fungal foot infection ($r = 0.236$, $P = 0.012$). Significance was not reached in DM1 or HAP.

Discussion

Both our studies assessed the point prevalence of pedal skin and nail mycoses in patients with DM. The first study focused on DM1. In the second study, attention was given to a heterogeneous group either with DM1 or DM2 as well as on accompanying non-diabetic persons living in the same household. Our data are supplemented by the results of a questionnaire evaluating patients' knowledge of their condition. The results are surprising in several respects, as the examined groups of patients were highly motivated as demonstrated by their attendance at the diabetes meetings, showing their interest by a high level of cooperation and, not the least, by their exceedingly good level of glucose control. In the first investigation, 78 patients (82.1%) showed lesions suspicious of fungal infection, which were mycologically confirmed by direct microscopy and/or culture in 84.6% of these patients (66/78). Organisms were cultured in 47.4% (37/78) of the patients, *T. rubrum* predominating with 69.2%. Our results are in accordance with previous investigations.^{2,5-13} Significant relationships were found with regard to gender (men more frequently affected) and age of the patients. The unexpectedly high number of mycoses in a highly motivated group of DM1 patients is particularly remarkable because 64.2% of them examined their feet daily for injuries or infections; 32.6% received regular medical

Table 5 Association between prevalence of fungal foot infection and hygienic and preventive behaviour (number of patients)

	Confirmed fungal infection	Regular physicians control with respect to mycosis		Daily self-inspection of the feet		Regular use of skin cream or oil		Regular treated by specialised chiropodist		Former use of antifungal agents		Regular sporting activity		Regular use of bathing shoes	
		N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y
DM1	No	11	7	7	13	5	15	16	4	13	6	5	15	3	9
	Yes	6	3	3	5	2	7	8	1	5	4	4	5	2	1
DM2	No	29	24	18	34	10	42	44	9	29	24	36	14	1	21
	Yes	30	18	14	37	16	35	36	12	25	26	39	13	2	20
HAP	No	17	1	15	3	7	11	18	–	14	4	11	7	3	6
	Yes	8	1	5	5	5	5	10	–	7	3	4	6	2	4

DM1, type 1 diabetes mellitus; DM2, type 2 diabetes mellitus; HAP, healthy accompanying person.

care with attention to fungal infections, and 41% were regularly treated by a chiropodist. The probable reason for this is that even marked mycoses on the soles ('moccasin-type tinea'), which were mycologically confirmed in 24 patients, were often misinterpreted as dry skin, which is well-known symptom of diabetic polyneuropathy. This might explain why moccasin-type tinea was misjudged even by experienced specialist physicians and chiropodists.¹⁷ It may also reflect the fact that in cases of severe moccasin-type tinea, topical therapy is rarely curative because of the thick horny layer of the soles. However, the newer systemic antimycotics (itraconazole, fluconazole, terbinafine) are effective and safe drugs in diabetes.^{2,19}

In our second study, we again found a high number of fungal foot infections in DM1, DM2 and even in HAPs. The prevalence of 35–52% was lower than in our first investigation of long-term DM1, but the duration of disease was shorter than in the former study (35.8 vs. 11.6 and 23.2 years respectively). However, the prevalence is higher than that found in the Achilles-Project.²⁰ Again, as in our first study, a significant correlation was found between infection and gender (men more frequently affected) and the age of the patients. A correlation of HbA1c and the frequency of mycotic foot infection was only found to be significant in the DM2 group. This might be relativised by the small number of patients with DM1 tested and on the other hand by the relatively short timeline which is reflected by measurement of a one point HbA1c. The latter is in contrast to the foot infections e.g. with *T. rubrum*, which are known to show a chronical course, often over several years.

With regard to the sudomotoric neuropathy measured with the new tool Neuropad™, we found a very high level of impaired and/or lost plantar perspiration

activity in DM1, DM2 and even in HAP. In contrast to studies for evaluation of the usefulness of the Neuropad™ tool, we did not measure the time until the colour changed but considered the read out result in three categories (normal, impaired, lost) after exactly 10 min as recommended by Zick *et al.* [21]. With respect to factors, which might influence the reaction of the sudomotor test plaster, we were careful to be sure that all patients had the same conditions in terms of time from taking off their shoes and socks and applying the pads (10 min.), but the room temperature in our setting was probably higher than 25 °C as in studies from Zick *et al.* [21] and Papanas *et al.* [16], which may have influenced the read outs. This might contribute to the relative high number of HAP showing impaired sudomotor activity. Nevertheless, we found a significant correlation between reduced plantar perspiration and fungal foot infection in the DM2 group ($P = 0.012$). Diabetic neuropathy with loss of sensible perceptions, impaired sudomotor activity and reduced secretion of sebum lead to a defect skin barrier with high risk for injury, complicated wound healing and mycotic infections as well as bacterial superinfections.³ We have to be aware that the very high prevalence of loss of sensitivity, as a result of peripheral neuropathy, inactivates one of the most effective mechanisms for early intervention in the case of seemingly banal traumata or lesions. Thus, diabetic patients with onychomycosis were shown to have a higher rate of gangrene/diabetic ulcer (12.2%) than patients without onychomycosis (3.8%)² and severe onychomycosis is a significant predictor of diabetic foot ulcer.⁴

In summary, patients with diabetes seem to have diagnostic, therapeutic and preventive needs with regard to mycotic diseases of the feet that have hitherto been underestimated. As shown in both our studies, the

patients themselves are highly interested in these matters. In particular, the frequency of moccasin-type tinea is apparently underestimated, because of the low grade of inflammation and the similarity to dry seborrheic skin often seen in diabetics. Autonomic neuropathy, such as impaired sudomotor activity, shows a high prevalence (about 60%) and may make substantial contribution to mycotic infection. In addition to regular inspection, basic neurological and angiological assessment, as directed by actual guidelines on diagnosis and treatment of the diabetic foot (e.g. Working Group on the Diabetic Foot of the German Diabetes Association),²² are early tools in the diagnosis of feet at risk for fungal infection. Skin care with creams or lotions containing about 10% urea should be performed in a regular manner on occasion of dry, rough and chapped plantar skin. However, tinea pedis should be excluded by experienced physicians. With regard to the high number of healthy accompanying people with plantar mycoses we recommend, that family members of high-risk patients should be examined and, if affected, treated for mycotic foot infections as well. It would be interesting to compare our findings with results obtained from less motivated groups of patients.

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