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Clinical and Mycologic Characteristics of Onychomycosis in Diabetic Patients

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SUMMARY The aim of the study was to examine the relative prevalence of dermatophytic, yeast and non-dermatophytic mould onychomycosis among diabetic patients, and to compare it with nondiabetic patients. The study included 460 consecutive diabetic patients and the same number of nondiabetic age-matched subjects attending dermatology clinics at Farwaniya Hospital, Kuwait, over a period of 4 years. All patients were examined clinically and mycologically for any evidence of onychomycosis. All cases of clinically suspected and/or mycologically proven onychomycosis were prescribed terbinafine tablets 250 mg orally *per* day continuously for 6-12 weeks. The prevalence of clinical onychomycosis in the diabetic and control group was 18.7% (86 cases) and 5.7% (26 cases), respectively. Elderly diabetic patients were at an increased risk of developing onychomycosis. Toenails were affected in 54 (62.8%), fingernails in 20 (23.3%), and both fingernails and toenails in 12 (14%) cases in diabetic group. Distal subungual onychomycosis was the most common clinical presentation, recorded in 67.4% of patients, followed by total dystrophic onychomycosis in 11.6% of patients. Culture positivity alone was seen in 16 (18.6%), both culture and KOH positivity in 52 (60.5%), and positive KOH alone in 10 (11.6%) cases; 8 cases had negative KOH examination and culture, but were PAS positive. Dermatophytes were the most common isolate. Seven percent cases treated for onychomycosis from the diabetic group were evaluated as unsuccessful (relapsed) at the end of the study. This study confirmed that diabetic patients are at a high risk of having or contracting onychomycosis. Onychomycosis was found to correlate significantly with increasing age and male gender. These findings reinforce the importance of attending to infections in diabetics to reduce the associated morbidity. Managing onychomycosis in diabetics may require systemic antifungal treatment, physical measures and patient education.

KEY WORDS: diabetes, onychomycosis, risk factors

INTRODUCTION

Diabetes mellitus (DM) is a worldwide problem of increasing importance. The World Health Organization (WHO) estimates that the world population of diabetic individuals will double to over 200 million people by the year 2010. Diabetes mellitus is an important predisposing condition for cutaneous infections, including onychomycosis (1). Onychomycosis is one of the most common nail diseases

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with the prevalence varying from 2.8% to 11.1% and determined by a plethora of factors like age, predisposing conditions, social class, occupation, climate, living environment and frequency of travel (2). Onychomycosis can have four major types of clinical presentations: distal subungual (the most common form of the disease), proximal subungual (the most common form found in patients with human immunodeficiency virus infection), and superficial and total dystrophic onychomycosis (3). Onychomycosis, a mycotic infection of the nail unit, is caused by three groups of fungi, namely dermatophytes, yeasts, and non-dermatophyte moulds (4). While the majority of onychomycoses are caused by dermatophytes (over 90% of onychomycoses are caused by two dermatophytes: *Trichophyton rubrum* and *Trichophyton mentagrophytes*), yeasts and non-dermatophyte moulds are the pathogens in about 7% of fungal nail infections (4).

It is well known that diabetic patients often have problems with their feet, mainly due to neuropathy and arterial insufficiency. The risk of toe or lower leg amputation may be increased if fissures or traumatic ulcerations are followed by a secondary infection (5). Thus nail infections represent a risk factor in diabetic patients because of possible sequels (5-7). Infections are a common problem among diabetic patients and fungal infection constitutes the most common type of infection that exceeds 50% of all types of infections in diabetic patients (5). Diabetics are at least twice as likely to suffer from onychomycosis as normal individuals (5,8). Diabetic patients with onychomycosis have a higher percentage of gangrene and/or foot ulcer (12.2%) compared to those without onychomycosis (3.8%), i.e. a 3-fold higher risk (9).

As of 2007, Kuwait's population is estimated to be roughly 3 to 3.5 million people; about 15% of the adult Kuwaiti population have type 2 diabetes, while type 1 diabetes is also a common chronic disease in Kuwaiti children (1).

We designed this study to find out more about the clinico-epidemiologic factors related to onychomycosis in our significant diabetic population and to compare it with onychomycosis in nondiabetic patients.

MATERIALS AND METHODS

This prospective and comparative study was performed at Department of Dermatology, Farwaniya Hospital, Kuwait. The Hospital Ethics Committee approved the study and all participants signed a written informed consent. During the period from January 2005 to December 2008 , patients with DM type 1 or 2 and older than 18 years were recruited from outpatient clinics; this group of subjects corresponded to 460 consecutive diabetic patients presenting for consultation for any dermatologic problem. Control group included the same number of nondiabetic age- and gender-matched subjects presenting to our outpatient clinic. None of 920 subjects suffered from skin disorders known to alter the nail aspect. None of the recruited subjects was known to be suffering from a dermatosis with a potential to involve the nails.

Demographic data on diabetic patients and controls were obtained from patient history and medical records. Age, gender, duration and type of diabetes, medications taken by the patient, fungal infections at other sites, and mean blood sugar values over the last 6 months, socioeconomic factors (occupation, education level, income, hobbies, habits of nail cutting, and footwear), trauma to the nail, contact with pets/animals, and family history of fungal infection were the parameters recorded for each patient. History of associated medical illnesses such as hypertension, coronary artery disease, vascular disease, peripheral neuropathy, nephropathy and retinopathy was also obtained.

Clinical diagnosis of onychomycosis was made and the patients were classified according to the following four major clinical presentations of onychomycosis. These types included distal subungual, proximal subungual, superficial, and total dystrophic onychomycosis. The number of nails and the area of nail plate involvement, and the severity of onychomycosis were recorded. The severity of onychomycosis was evaluated globally for all nails as mild (<25% involvement or <4 nails involved), moderate (26%-74% involvement or 5-8 nails involved), or severe (>75% involvement or >9 nails involved) (10).

Patient nails were cleaned with a spirit swab, and nail scrapings were obtained with a number 15 sterile scalpel blade. In patients with distal and subungual onychomycosis (DSO) or total dystrophic onychomycosis (TDO), the nail was scraped from diseased area and scrapings were also collected from subungual debris. In patients with superficial white onychomycosis (SWO), minute scrapings were taken from the superficial layers of the affected parts of the nail plate. The nail clippings or scrapings were incubated in 40% potassium hydroxide for 30 minutes and examined under microscope for the presence of fungal elements. Culture was done on both cycloheximide-supplemented and cycloheximide-free Sabouraud's agar media,

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to identify dermatophytes and non-dermatophyte fungal pathogens, respectively. The cultures were carried out on all nail specimens obtained from patients in both diabetic and nondiabetic groups. Each set of medium was incubated at 25° C - 37 °C and examined regularly for 4-6 weeks, for any growth. If there was no growth after 6 weeks, the result was reported as negative. Separate samples were also taken if there was fingernail involvement in addition to toenail onychomycosis, or if different clinical types were observed in the same patient.

Onychomycoses were identified according to the nature of the fungus grown at culture. They were thus classified as dermatophyte, yeast or non-dermatophytic mould onychomycoses. When two distinct fungi were seen microscopically and isolated simultaneously from a nail sample, mixed fungal infection of the nail plate was diagnosed. Some onychomycoses remained unidentified because the culture remained negative. If neither microscopy nor culture yielded a diagnosis, histological analysis of crushed nail plate clippings was used to determine whether the pathogen was fungus. Nail plate fragment was sent for histopathologic examination in a 10% buffered formalin container. Periodic acid-Schiff (PAS) staining was done for all specimens.

Terbinafine 250 mg tablet orally *per* day was prescribed for all clinically suspected and/or mycologically proven cases for 6-12 weeks (fingernails 6 weeks and toenails12 weeks). Clinical and mycological examinations were repeated at 36 weeks after the end of treatment. The primary efficacy parameter was mycological cure, defined as negative results on microscopy and fungal culture of samples taken from the target nail. Secondary efficacy parameters included clinical cure (100% clearing of the target toenail) and complete cure (mycological cure plus clinical cure). Cure rates were evaluated at the end of the study (week 48). Cases evaluated as unsuccessful at the end of the study but noted as cured before the final visit were accepted as “relapsed”. Laboratory tests including complete blood count and biochemical assays of liver enzymes, urea, creatinine and glucose levels were studied before and at the end of therapy. Side effects such as gastrointestinal complaints, headache and skin eruptions were recorded.

Statistical analysis

Chi-square test was used to compare differences between diabetic and nondiabetic patients. Logistic regression models were used to measure the association between various groups (age, gender, severity, type of diabetes, etc.) and prevalence of onychomycosis in diabetic and nondiabetic patients. The level of significance was set at $P<0.05$.

RESULTS

The study included 460 diabetic patients, 302 (65.65%) men and 158 (34.35%) women, aged 18-65 (mean age, 36.5) years. Of the 460 nondiabetic controls, there were 276 (60%) males and 184 (40%) females. Most of the recruited patients in both groups were in the 46-65 age group (Table 1). Thirty six (7.8%) patients had type 1 diabetes and 424 (92.2%) patients had type 2 diabetes.

The prevalence of clinical onychomycosis in diabetic and control groups (Table 1) was 18.7% (86 cases) and 5.7% (26 cases), respectively. The mean duration of nail involvement was 1.8 years in the diabetic group and about 8 months in the control group. The duration of diabetes in patients with onychomycosis was 9.1±0.9 years. In diabetic group, 34 (39.5%) patients with clinical onychomycosis were in the 56-65 age group, followed by 24 (28%) patients in the 46-55 age group. Similarly, in

Table 1. Age distribution of patients with clinical onychomycosis in diabetic and control groups

Age group (yrs)	Diabetic group		Control group	
	Total number of patients recruited	Patients with clinical onychomycosis (n=86)	Total number of patients recruited	Patients with clinical onychomycosis (n=26)
18-25	36	2	30	2
26-35	48	8	56	2
36-45	70	18	64	4
46-55*	142	24	138	6
56-65**	164	34	172	12
Total	460	86	460	26

*$P<0.05$; **$P<0.001$

Table 2. Distribution of clinical onychomycosis cases according to types of onychomycosis

Clinical type	Diabetic patients with clinical onychomycosisn (%)	Control group patients with clinical onychomycosisn (%)
DSO	58 (67.4)	20 (77)
PSO	2 (2.3)	0
SWO	4 (4.7)	0
TDO	10 (11.6)	2 (7.7)
DSO + TDO	6 (7)	2 (7.7)
DSO + SWO	6 (7)	2 (7.7)
Total	86 (100)	26 (100)

DSO = distal subungual onychomycosis; PSO = proximal subungual onychomycosis; TDO = total dystrophic onychomycosis; SWO = superficial white onychomycosis

control group, the frequency of clinical onychomycosis was 46.2% (12 cases) and 23.1% (6 cases) in the 56-65 and 46-55 age groups, respectively. The presence of onychomycosis was found to correlate significantly with increasing age (P<0.01) and male gender (P<0.05) in both diabetic and control groups.

Of the 86 cases with clinical onychomycosis in diabetic group, toenails were affected in 54 (62.8%), fingernails in 20 (23.3%), and both fingernails and toenails in 12 (14%) cases. In control group, the frequency of involvement of toenails, fingernails, and both toenails and fingernails was 61.5% (n=16), 23.1% (n=6), and 15.4% (n=4), respectively. The degree of nail involvement was mild in 54.2%, moderate in 36.4% and severe in 9.4% of patients with onychomycosis. Statistical analysis showed that there was no significant difference in the distribution and severity of onychomycosis between cases and controls (P>0.1). In diabetic group with clinical onychomycosis, DSO was the most common clinical presentation, recorded in 67.4% (Table 2), and followed by TDO in 11.6% of patients.

Table 3. Fungal isolates of onychomycosis in diabetic patients

Fungal pathogen (N=68)	**Diabetic patients n (%)**
Dermatophytes	
Trichophyton (T.) rubrum	26 (38.2)
T. mentagrophytes	6 (8.8)
T. tonsurans	2 (3)
Microsporum gypseum	2 (3)
Yeasts	
Candida (C.) albicans	18 (26.4)
C. tropicalis	4 (5.9)
Moulds	
Fusarium sp.	6 (8.8)
Aspergillus niger	2 (3)
Mixed	
Trichophyton rubrum & Candida albicans	2 (3)
Total	68 (100)

Of the 86 patients with clinical onychomycosis, culture positivity alone was seen in 16 (18.6%), both culture and KOH positivity in 52 (60.5%), and positive KOH alone in 10 (11.6%) cases; the remaining 8 cases failed to show any fungal pathogens on KOH examination or on culture, but showed positive PAS stain on histopathologic examination. The distribution of fungal pathogens causing onychomycosis in diabetic group is shown in Table 3, among cases where species identification from culture was possible. In diabetic group, dermatophytes were the most common isolate (53%), followed by yeasts and moulds in 32.4% and 11.8%, respectively. In control group, the distribution of dermatophytes, yeasts and nondermatophyte moulds was 84%, 9.6% and 6.4%, respectively. In both diabetic and control groups, dermatophytes were the most common fungal pathogens isolated from toenails. However, yeasts were isolated more often from fingernails in diabetic group. Associated superficial fungal infections were present at other sites in diabetic and control groups in 40.4% and 4.6% of patients, respectively. The frequency of superficial fungal infections in diabetics with or without onychomycosis was significantly higher as compared with control group (P<0.001).

The type of DM was not a significant predictor for the development and severity of onychomycosis (P>0.01); however, both the prevalence and severity of onychomycosis were significantly more often associated with the duration of diabetes (P<0.01). The mean blood glucose level in the preceding 6 months was not found to correlate significantly with the prevalence of onychomycosis (P>0.01).

The significant predictors for onychomycosis in diabetic patients included a family history of ony-

Table 4. Success rates of terbinafine treatment

	Mycologic cure	Clinical cure	Relapse rate
Diabetic group			
N (%) Toenail: n=66	47 (71.2%)	41 (62.1%)	6/86 (7%)
N (%) Fingernail: n=32	26 (81.3%)	24 (75%)	
Control group:			
N (%) Toenail: n=20	17 (85%)	14 (70%)	
N (%) Fingernail: n=10	9 (90%)	8 (80%)	

chomycosis (P=0.0002), peripheral neuropathy (P<0.05), retinopathy (P<0.001), reduced or absent peripheral pulses in the extremities (dorsalis pedis or posterior tibial) (P<0.05), and concurrent intake of immunosuppressive therapy (P=0.030). However, various medical illnesses such as the history of hypertension, angina, myocardial infarction, hypercholesterolemia, intermittent claudication, and thyroid disorders were other non-significant predictors for onychomycosis in both diabetic and nondiabetic groups (P>0.05).

At the end of the follow up period (at week 48), mycological cure was obtained in 71.2% (47/66) and clinical cure in 62.1% (41/66) of diabetic patients treated with terbinafine for toenail infection; and in 81.3% (26/32) and 75% (24/32) of those treated for fingernail infection, respectively. The corresponding values for nondiabetic control group were 85% (17/20) of mycological cure and 70% (14/20) of clinical cure for toenail infections, and 90% (9/10) of mycological cure and 80% (8/10) of clinical cure for fingernail infections (Table 4). Seven percent (6/86) of diabetic group cases, 6 with toenail infection and 1 with combined toenail and fingernail infection, were evaluated as unsuccessful (relapsed) at the end of the study. There was no relapse in control group.

At the end of treatment, laboratory data on both diabetic and nondiabetic patients proved to be practically unchanged for hematologic parameters such as creatinine, aspartate aminotransferase, γ-glutamyltransferase and alkaline phosphatase level. Glucose levels were unchanged after the 12-week treatment period in all diabetic patients. No drug interaction, hypoglycemic episodes or reports of hypoglycemia were reported during the treatment. Therapeutic side effects (Table 5) were reported in 9 of 86 (10.5%) diabetic patients, and in 3 of 26 (11.5%) control patients. All side effects were minor, and none of the patients had to stop treatment due to side effects.

DISCUSSION

Onychomycosis in diabetics is far from being just a cosmetic problem. On the contrary, it is a potentially dangerous disease. It is known for quite some time that the morbidity linked to onychomycosis, the ever-growing size of diabetic population and the high frequency of foot disorders in diabetic patients present a considerable health problem (11,12).

In the past, only a few studies determined the prevalence of onychomycosis in diabetic subjects (5,13-16).

To our knowledge, this is the first study from Kuwait, which systematically determined the prevalence of and predisposing factors for the development of onychomycosis in diabetic patients. In our study, the presence of onychomycosis was found to correlate significantly with increasing age and male gender in both diabetic and control groups. The increase in the prevalence of onychomycosis with advancing age has been reported previously (17,18). Elderly men with diabetes were particularly prone to the development of onychomycosis (10). Whether the increased prevalence of onychomycosis in the elderly is related to changes in immunity or to an increased susceptibility due to diseases such as DM is not well understood (10). The increase in the number of cases with age may be

Table 5. Incidence of side effects

Side effect	Diabetic group, n (%)	Control group, n (%)
Gastrointestinal symptoms	5 (5.8%)	2 (7.7%)
Skin rash	1 (1.2%)	0
Disturbance of taste	3 (3.5%)	1 (3.8%)
Headache	3 (3.5%)	2 (7.7%)

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explained by repeated nail micro-trauma, due to a more prolonged exposure to pathogenic fungi, as well as greater work activity and venous insufficiency (19,20).

In our study, onychomycosis was more frequently observed in toenails, followed by fingernails, in both groups, which is consistent with a study from India (10).

The diagnosis of onychomycosis can be made clinically most of the times, but laboratory studies are important to confirm the clinical diagnosis, and also to identify the etiologic agents (21). The efficiency of direct microscopic examination emphasizes the importance of the method, when performed by experienced professionals, favoring the speed of diagnosis and treatment of patients. This approach, together with culture is considered as an extremely important procedure for the epidemiological study of onychomycosis (21). In this study, dermatophytes were the most common isolate causing onychomycosis in diabetic patients, followed by yeasts and non-dermatophyte moulds. Other authors also isolated dermatophytes as the most common pathogens. However, in one Indian study, yeasts were found to be the most common pathogen causing onychomycosis in diabetic patients, followed by dermatophytes and non-dermatophyte moulds (10). Another study from Saudi Arabia reports on *Candida* species as the most frequently isolated pathogen from infected nails (22).

Results of direct KOH examination correlated significantly with culture results in both diabetics and nondiabetics with onychomycosis, indicating KOH examination to have high sensitivity. Statistical analysis revealed that the probability of getting nail culture positive and direct KOH examination positive is the same in diabetics and nondiabetics with onychomycosis. There was no significant difference between diabetics and nondiabetics onychomycosis patients according to the severity of nail involvement.

Among dermatophytes, *T. rubrum*, was isolated as the most common pathogen in both groups of patients, as also reported elsewhere (23,24).

In some patients, trauma was a predisposing factor, emphasizing its role in onychomycosis (25-27). Peripheral neuropathy, impaired peripheral circulation, and retinopathy were observed to be significant predictors for the development of onychomycosis in this study. Previous studies also correlated onychomycosis with diabetic complications of neuropathy, retinopathy, and impaired peripheral circulation (3,10). Thus, diabetic subjects with one or more predisposing factors for the development of onychomycosis should have their feet and nails examined carefully and regularly.

In our study, there was no correlation between the prevalence of onychomycosis and the mean blood glucose level over the last 6 months, which is consistent with earlier results (3,10). In the present study, the prevalence and severity of onychomycosis were significantly more often associated with the duration of diabetes. Thus, early intervention while onychomycosis is less severe may be advisable because of the potentially progressive nature of fungal infection (29).

Terbinafine is currently the most active available antidermatophyte agent *in vitro*, and clinical studies strongly suggest that this is also the case *in vivo* (30). It has been reported to be superior to itraconazole, both *in vitro* and *in vivo*, for dermatophyte onychomycosis (31). It is licensed at a dose of 250 mg daily for 6 and 12 weeks in fingernail and toenail infection, respectively. A follow up period of at least 48 weeks from the start of treatment should be allowed both in order to allow the maximum effect to become apparent, and to identify relapse as far as possible.

A study of 104 diabetic patients treated with oral terbinafine 250 mg daily for 12 weeks showed a mycologic cure rate of 73% (32). Another study in diabetics of terbinafine 250 mg once daily for 12 weeks showed mycologic cure in 79.3%, with no adverse events or medication interactions (33). In a study by Bohannon and Streja (34), the results in diabetic patients were compared with those recorded in a much larger group of nondiabetic patients receiving terbinafine. There were no significant differences in mycological cure between diabetic and nondiabetic patients (64% *vs*. 73%). The same trend was also observed for clinical cure (37% *vs*. 45%).

At the end of treatment, laboratory data proved to be practically unchanged for hematologic parameters in both diabetic and nondiabetic patients. Laboratory examinations showed no abnormality including complete blood count and hepatic and renal functions. There were no drug interactions or reports of hypoglycemia during the treatment phase. Also, there were no significant side effects in the multicenter study by Farkas *et al*. (32), as only minor side effects were reported in 12% of cases. Adverse events were limited to gastrointestinal pain/upset, headache and taste changes. In 83% of patients, blood glucose levels remained the same as those at baseline, and there were no

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episodes of hypoglycemia in patients with insulin dependent diabetes mellitus or non-insulin dependent diabetes mellitus (32). We recorded a 7% relapse rate in diabetic group only, with no relapse in control group, which may be due to recurrence/reinfection.

CONCLUSION

This study confirmed diabetic patients to be at a high risk of having or contracting onychomycosis. Onychomycosis was found to correlate significantly with increasing age and male gender. Toenails were more commonly involved than fingernails in both diabetic patients and nondiabetic controls. The severity of onychomycosis is significantly associated with the duration of diabetes. Therefore, recognition and early intervention is advisable because of the potential progressive nature of fungal infections and the potentially serious sequels associated with persistence of untreated infected nails. The consequences of neglecting onychomycosis may carry more risk for diabetics compared with nondiabetic patients. Although it is the responsibility of the clinician to accurately diagnose and pertinently treat onychomycosis, education of diabetic patients about the importance of foot and nail care should form an essential component of diabetes management. This is especially important in patient groups at a higher risk for the development of onychomycosis, such as elderly diabetics, as found in the present study. In the group of non-insulin dependent DM patients taking oral antidiabetic agents and suffering from multiple concomitant diseases treated with different types of medication, most of the potentially serious drug interactions can be avoided with the appropriate selection of antifungal agent.

Terbinafine has a relatively low risk of drug-drug interaction and has a proven efficacy against typical pathogens that cause onychomycosis, which makes it especially attractive for diabetic population. Therefore, it should be the drug of choice in the treatment of onychomycosis in diabetics. Relapse is more common in diabetic patients than in nondiabetic patients, so managing onychomycosis in diabetics may require accompanying an antifungal agent with mechanical/physical measures, and patient education regarding proper foot care to improve treatment outcomes and prevent recurrence. Nails should be cut short and kept clean, and the feet need to be dried completely following a bath or shower.

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