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The Effect of Fungal Infection on The Outcome among Diabetic Patients with Foot Osteomyelitis

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ABSTRACT

Background: One of the most common diabetes-related reasons for hospitalization is diabetic foot infections (DFIs), which are a significant cause of morbidity. Osteomyelitis (OM) is a regrettable side effect of a DFU infection that spreads via soft tissues into the underlying bone.

Aim: to estimate the percentage of fungal infection in the pathogenesis of diabetic foot lesions and determine if adding antifungal drugs may affect the prognosis.

Patients and methods: A prospective cohort study, including 100 diabetic patients with infected diabetic foot ulcers with underlying osteomyelitis. Two wound swabs and bone biopsies were taken from the depth of the ulcer consisting of necrotic slough and granulation tissue, and carried immediately to the microbiology laboratory, at Assiut University to be examined. Once the fungal culture study is positive, oral fluconazole 150 mg every other day for 2-3 weeks was started for the patient with a maximum duration of two months or when healing occurs.

Results: The current study revealed that all the studied patients had positive bacterial growth. Out of them, 22 (22%) patients had mixed fungal and bacterial growth while the majority (78%) had only bacterial growth. Candida is the most common pathogen isolated in fungal OM.

Conclusion: Regarding the treatment of OM caused by fungi, there is no clear consensus. In the current study, patients with a lengthy history of foot ulcers were more likely to develop fungal foot infections. Furthermore, it's critical to stop the spread of resistance because there aren't any other effective antifungal treatments for treating severe fungal infections.

Keywords: Diabetic foot, Osteomyelitis, SINBAD score, Fungal Infection.

INTRODUCTION

Patients with diabetes mellitus (DM) are more likely to get bacterial and fungal infections[(1)]. Thrush complaints frequently serve as a reminder to check for undiagnosed type 2 diabetes or to reevaluate glycemic control, even in people with diabetes, systemic fungal infections are uncommon. They frequently occur in conjunction with extended hospital stays or other conditions that has immunocompromising effects [(2)].

Diabetic patients frequently develop foot ulcerations (DFUs), with lifetime incidence rates ranging from 19% to 34% [(3)].

At some time, more than half of individuals get an infection, harming clinical results [(4)]. We have largely been concentrating on bacterial infections up to this point, and we know relatively little about fungal diabetic foot disease. People with long-standing diabetes mellitus (DM) are known to have a lot of superficial fungus on their feet: studies have shown an overall 52% to 86% prevalence [(5)].

The interdigital gaps and toenails are the main sites, and as a result, there is a higher chance of developing classic diabetic foot disease. Longer DM duration, male gender, and older age are additional significant risk factors [(6)]. But, it is difficult to determine the prevalence rate and prognoses of genuine fungal infections in DFUs [(7-9)].

The current study aimed to estimate the percentage of fungal infection in the pathogenesis of diabetic foot lesions which remains unstudied, to assess the outcome of patients with fungal diabetic foot infections.

PATIENTS AND METHODS

Study setting& design:

A prospective cohort study included 100 patients suffering from infected diabetic foot ulcers accompanied by underlying osteomyelitis in which healing had failed despite intensive foot care. They were chosen from the Diabetic Foot Clinic in Assuit University Hospital from January 2021 to January 2022.

Inclusion criteria:

All diabetic patients with diabetic foot ulcers with underlying osteomyelitis.

Exclusion criteria:

Patients on corticosteroid therapy, long term antibiotic therapy for more than 28 days were excluded.

All patients in the present study were subjected to the followings:

Detailed history with an emphasis on type and duration of diabetes, duration of the ulcer, therapeutic history of either insulin or oral hypoglycemic drugs or both, and History of trauma.

Clinical examination of the ulcer, neuropathy, and Ankle-brachial index assessment and fundus examination. Laboratory investigation including glycosylated hemoglobin (HbA1c), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP),

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complete blood picture, and serum urea and creatinine. Swabs are obtained from pus for bacterial culture and fungal culture. Bone fragments and tissue biopsy from infected ulcers.

ETHICAL CONSIDERATION

The academic and ethical committee at Assiut University approved the study. All participants signed informed permission after being told of the study's goal. The Declaration of Helsinki, the World Medical Association's code of ethics for studies involving humans, guided the conduct of this work. The study was registered on Clinical Trials.gov Identifier: NCT04041739.

Statistical analysis

SPSS was used to gather and analyze the data (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York). The mean and standard deviation (SD) of quantitative data are reported and compared using the Student t-test. Numbers (n) and percentages (%) are used to represent nominal data. Such data were subjected to the Chi^2 test.

For patients with a fungal infection, the determinants for a full recovery were identified using logistic regression analysis. Additionally, a receiver operator characteristics (ROC) curve was utilized to assess how well an ulcer's size predicted its eventual healing. Therefore, the level of confidence was maintained at 95%. P value was deemed significant if it was less than 0.05.

RESULTS

*Characteristics of ulcers of enrolled patients (***Table 1***):*

The majority (57%) of patients had an ulcer at the forefoot while the ulcer was present in the midfoot and hindfoot in 28 (28%) and 15 (15%) of patients, respectively. The mean duration of the ulcer was 12.76 ± 2.09 (months). All studied patients had positive bacterial growth. Out of the studied patients; 22 (22%) patients had mixed fungal and bacterial growth while the majority (78%) of patients had only bacterial growth.

Table (1): Characteristics of ulcers of the studied patients

	N= 100
Age (years)	53.65 ± 12.27
Sex	
Male	63 (63%)
Female	37 (37%)
Duration of DM (year)	15.87 ± 2.22
Type of DM	
Type 1	14 (14%)
Type 2	86 (86%)
Therapy of DM	
Oral agents	24 (24%)
Insulin	70 (70%)
Both agents	6 (6%)
Ulcer duration (month)	12.76 ± 2.09
Site of the ulcer	
Forefoot	57 (57%)
Midfoot	28 (28%)
Hindfoot	15 (15%)
Size of ulcer (cm)	6.54 ± 1.11
Depth (cm)	2.01 ± 0.45
SINBAD Score	4.01 ± 0.55
Culture	
Mixed fungal and	22 (22%)
bacterial growth	78 (78%)
Only bacterial growth	

SINBAD: Site, Ischemia, Neuropathy, Bacterial Infection, Area and Depth.

*Type of fungal isolate among patients with fungal infection (***Table 2***):*

In the patients with fungal infection; the most frequent isolates were candida alibicans (50%) and candida tropicalis (27.5%) followed by candida glabrata (22.7%). Others isolates were present in 4 (18.2%) patients in form of Saccharomyces cerevisiae (13.6%) and Candida krusei (4.5%).

Table (2): Types of fungal isolate among patients with fungal infection

	N= 22
Candida albicans	11 (50%)
Candida tropicalis	6 (27.5%)
Candida *glabrata*	5 (22.7%)
Saccharomyces cerevisiae	3 (13.6%)
Candida krusei	1 (4.5%)

Data expressed as frequency (percentage).

The outcome of patients with fungal osteomyelitis (*Table 3*):

Seven (31.8%) patients achieved complete healing of the ulcer within a duration between two and 14 weeks. Resistant to fluconazole and not responding was reported in 10 (45.5%) patients who developed a chronic infection. The 5 (22.7%) patients required amputation secondary to acute ischemia.

Table (3): Outcome of patients with fungal osteomyelitis

	N= 22
Complete healing	7 (31.8%)
Duration (weeks)	4 (2-14)
Not Respond	10 (45.5%)
Amputation	5 (22.7%)

Data expressed as frequency (percentage), median (range) as appropriate.

Multivariate regression analysis for predictors of fungal osteomyelitis among diabetic foot patients (*Table 4-5, Figure 1*):

Based on the current study, the predictors for fungal osteomyelitis among those with diabetic foot were; duration of DM and ulcer, abnormal ankle-brachial index, size of the ulcer, peripheral neuropathy, and SINBAD.

It was found that SINDAD had the highest predictive value with an odd's ratio was 3.23, so we performed ROC curve analysis for SINBAD where at cutoff point > 3 points, it had 85.7% sensitivity, 100% specificity, 100% overall accuracy with area under was 0.933.

Table (4): Predictors of fungal osteomyelitis among diabetic patients

	Odd's ratio	95% CI	*P* value
Age (years)	1.13	1.09-2.26	0.09
Sex	0.98	0.56-1.45	0.23
Type of DM	1.11	0.56-2.56	0.10
Duration of diabetes mellitus	**1.34**	**1.20-2.01**	**0.02**
Duration of ulcer	**1.20**	**1.10-2.40**	**0.04**
Site of ulcer	1.09	0.78-2.18	0.10
Type of therapy	1.98	1.54-3.01	0.67
Abnormal ankle-brachial index	**1.68**	**1.34-2.22**	**0.01**
Size of ulcer	**2.13**	**1.50-4.56**	**< 0.001**
Glycosylated hemoglobin	1.11	0.87-2.22	0.13
Impalpable dorsalis pedis	0.19	0.18-1.91	0.24
History of trauma	0.45	0.33-1.09	0.09
SINBAD> 3	**3.23**	**2.34-7.23**	**< 0.001**

Table (5): Accuracy of SINBAD score in prediction of fungal osteomyelitis in diabetic patients

Indices	Value
Sensitivity	86.5%
Specificity	100%
Positive predictive value	100%
Negative predictive value	94%
Accuracy	95.7%
Cutoff point	>3
Area under curve	0.933
P value	< 0.001

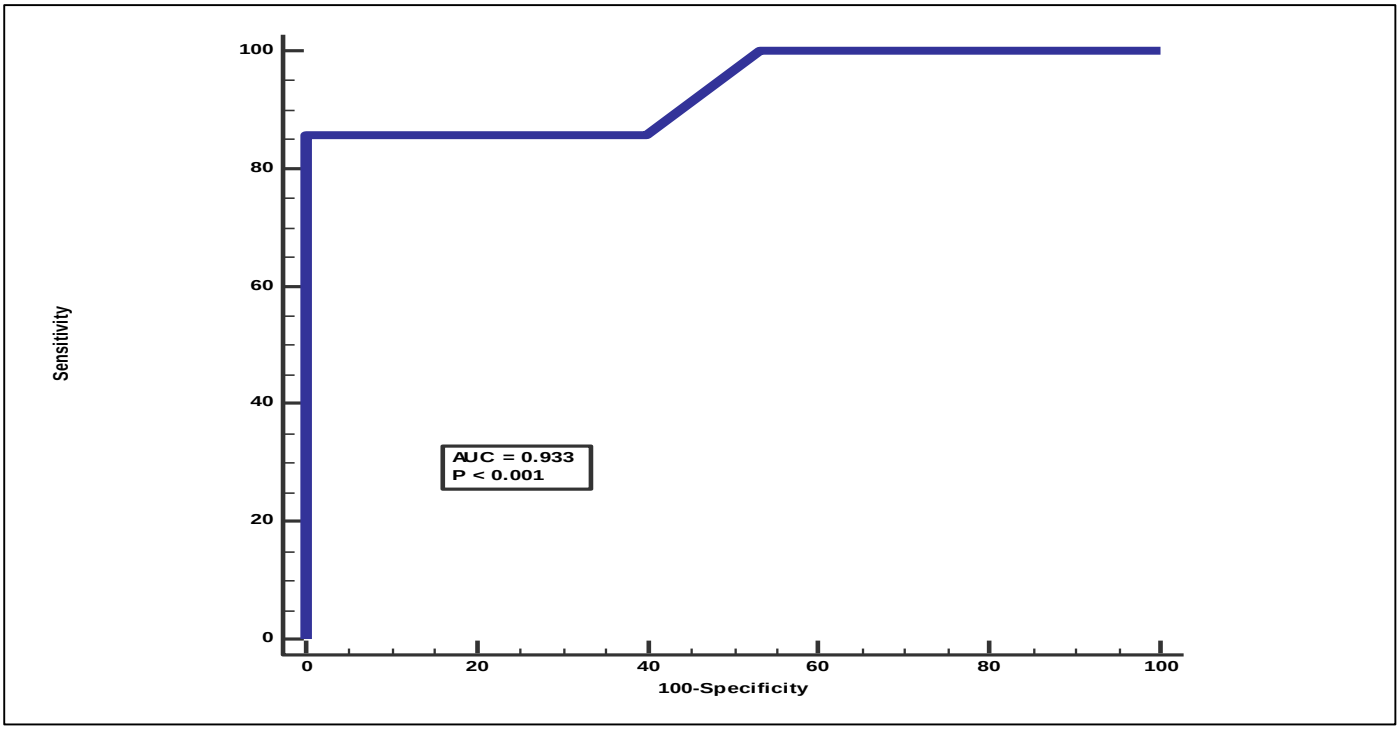

Figure (1): ROC curve for prediction of fungal osteomyelitis based on SINBAD

DISCUSSION

Most authors agree that managing an infected diabetic foot requires isolation and identification of the microbial flora, appropriate antibiotic therapy based on sensitivity pattern, careful selection and identification of chronic complications, and appropriate surgical intervention for these complications, even though the ideal course of treatment has not yet been determined [10-14].

The therapy of the patient and the outcome can be impacted by a fungal infection of the diabetic foot, which may be linked to particular specific disorders. Osteomyelitis (OM) is a regrettable side effect of an infected DFU in which the infection spreads via soft tissues into the underlying bone [15-20].

One hundred patients with diabetic foot osteomyelitis in total were enrolled in the current study. The goal of the study was to calculate the contribution of fungi to diabetic foot pathology. The average age of the enrolled patients was 53.65. Among them, there were 63 (63%) male patients and 37 (37%) female patients. The average time in DM was 15.87± 2.22 (years).

In line with the current study, **Torrence *et al.*** [17] studied a total of 35 patients who were diagnosed with OM. The mean age of surgically managed patients was 57 ± 12.4; 83% (29/35) of patients were men. The mean body mass index (BMI) of the overall cohort was 32 ± 5.8.

Also, another study of 216 diabetic patients with foot ulcers was studied. Out of the 261 patients, 156 [59.7%] were males, and 105 [40.2%] were females of mean age 58 years (±15 years) with a DFI. The majority of the DFIs were Grade III [18].

Torrence *et al.* [17] evaluated a total of 35 patients who were diagnosed with OM, which is similar to the current study. The average age of patients who underwent surgery was 57±12.4; 83% of the patients were men. The cohort as a whole had a mean body mass index (BMI) of 32±5.8.

In another study by **Saseedharan *et al.*** [18] 216 diabetic patients with foot ulcers were the subject. Out of the 261 patients, 156 (59.7%) were men and 105 (40.2%) were women with a DFI and a mean age of 58 years (15 years). A large percentage of DFIs were GradeIII.

In the current study, as regards fundus examination among those patients; it was found that only 16 (16%) patients had normal fundus examination while 30 (30%) and 54 (54%) patients had non-proliferative retinopathy and proliferative retinopathy, respectively. All patients had peripheral neuropathy while dorsalis pedis pulsation was absent in 28 (28%) patients

According to the American Diabetes Association standards, **Torrence *et al.*** [17] discovered that all patients (35/35) had peripheral neuropathy. An overall diagnosis of coronary artery disease was made in 25.7% (9/35) of the group. 31.4% (11/35) of individuals had chronic kidney disease. In 14.3% (5/35) of patients, the peripheral vascular disease was found. 51.4% (18/35) of the whole group had previously undergone a lower-extremity amputation.

The current study revealed that all studied patients had positive bacterial growth. Out of the studied patients; 22 (22%) patients had mixed fungal and bacterial growth while the majority (78%) of patients had only bacterial growth. Comparable with these findings; a previous study found that out of 35 patients treated surgically for DFI, 5/35 (14%) were identified as having fungal OM, and the other patients had (86%) bacterial OM (11). Also, **Arun *et al.*** [14] stated that the prevalence of positive fungal culture was 17.38% (250/1438).

In deep tissues of diabetic lower leg wounds, the fungus is highly prevalent (27.9%), according to a study by **Chellan *et al.*** [21]**.** In research by **Bansal *et al.*** [22]**,** 9% of the total isolates were due to fungi.

As regards bacterial isolates; the current study found that the most frequently isolated bacteria were E. coli (40%), and Staph. aureus (29%), and Streptococcus spp (29%) followed by pseudomonas spp (9%). Bacillus spp was present in only two patients. **Kareliya *et al.*** [23] concluded that the most frequently isolated bacteria were *S. aureus* (71%), Pseudomonas (49%), and *K. pneumonia* (10%).

In a prior study, 261 patients with diabetic foot infections contributed a total of 289 isolates, which were isolated from 178 tissue samples. 38 (17.6%) of the tissue samples showed no signs of growth. 55.7% of the samples were polymicrobial, while 44.3% of them were monomicrobial. Pathogens with a Gram-negative were more common (58.5%). Seven of the total isolates were fungi; 0.7% grew exclusively as fungi, and 1.7% combined with some bacteria to develop [18].

As regards candida isolates in the current study, the most frequent isolates were candida alibicans (50%) and candida tropicalis (27.5%) followed by candida glabrata (22.7%). Others isolates were present in 4 (18.2%) patients in form of Saccharomyces cerevisiae (13.6%) and Candida krusei (4.5%).

In agreement with the current study, **Manikandan *et al.*** [10] stated that the most frequent fungal isolates were candida alibicans (50%) and candida tropicalis (27.7%). Similar results were reported by previous studies [24-25].

As regards the outcome of fungal OM in the current study, 7 (31.8%) patients achieved complete healing of the ulcer within a duration between two and 14 weeks. Resistant to fluconazole and not responding was reported in 10 (45.5%) patients who developed chronic infection. The 5 (22.7%) patients required amputation secondary to acute ischemia.

The current study found both groups of patients had insignificant differences as regards different characteristics with exception of the duration of DM

which was significantly higher among patients with fungal infection (15.01 ± 3.30 vs. 20.18 ± 2.98 (years); p= 0.02) in comparison to those without fungal infection.

Based on the current study, the predictors for fungal osteomyelitis among those with diabetic foot were; duration of DM and ulcer, abnormal ankle-brachial index, size of the ulcer, and SINBAD score. It was found that SINDAD score had the highest predictive value with an odd's ratio was 3.23, so we performed ROC curve analysis for SINBAD where at cutoff point > 3 points, it had 85.7% sensitivity, 100% specificity, 100% overall accuracy with an area under was 0.933.

The current study acknowledges some limitations including a relatively small sample size, being conducted in a single center, and a short duration of follow-up. Also, we didn't compare the usage of fluconazole alone versus its combination with other antifungal agents. The main strength points of this study is being the first study to discuss such an issue in our locality. Also, all enrolled patients continued to follow-up till the end of the study.

CONCLUSION

In the current study, patients with a lengthy history of foot ulcers were more likely to develop fungal foot infections. Future researches are necessary to verify these results.

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