

Fungal Infection: A Hidden Enemy in Diabetic Foot Ulcers

¹Saravanan Sanniyasi, ²Jagan Balu, ³Cunnigaiper Dhanasekharan Narayanan

ABSTRACT

Diabetic foot ulcers are on the rise and increasingly associated with amputations. Fungal infections have recently been implicated in the nonhealing nature of these wounds. One hundred five patients treated as in-patients with nonhealing diabetic ulcers in a tertiary care hospital were included in this prospective study. Wound swabs and deep tissue biopsies were taken from these ulcers for fungal stain and culture and bacterial culture. Once the fungal stain or the culture study is positive, oral Fluconazole was started. Nineteen patients grew fungus in the ulcer, commonest species being *Candida tropicalis* (10.5%). The most common bacterial organism isolated with fungal infection is *Pseudomonas* followed by *Enterococcus*. Patients on prolonged antibiotic therapy showed statistically significant increase in fungal infection. Patients who underwent amputation within 15 days of admission were higher in fungal culture positive group, due to progression of ulcer in spite of antibiotic therapy. There is a definite correlation between incidence of amputation and fungal infection in whom antifungal therapy was not started, though not statistically significant. Fourteen patients, who did not undergo amputation, had faster wound healing and lesser progression of disease, with none of them requiring amputation after initiating antifungal therapy. Our study reveals that there is a definite relation between fungal infections and nonhealing nature of diabetic ulcers. Further randomized trials are necessary to substantiate this finding.

Keywords: Amputation, Antifungal therapy, Diabetic foot, Fungal infection.

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INTRODUCTION

Diabetes mellitus has reached a pandemic proportion affecting almost every country in the world.¹ Diabetic foot ulcers are one of the most common complications of long-standing diabetes mellitus, resulting in increased economic burden.² The plethora of bacterial infections,

which may be present in a diabetic ulcer and the treatment protocol based on it, has now been clearly defined.³ But, the chronic nonhealing ulcers, many of which end up in amputation, are found to be increasingly associated with fungal infections.⁴ Hence, this study was embarked upon with the objective of finding out the prevalence and the profile of fungal infections in chronic nonhealing diabetic foot ulcers and to find whether these fungal infections have a bearing on a future amputation.

MATERIALS AND METHODS

Patients who were treated as in-patients with nonhealing diabetic foot ulcers in a tertiary care hospital from April 2011 to September 2013 were included in this prospective study. A total of 105 patients were enrolled for the study.

A proforma was developed to record history, examination details and investigation reports. Details regarding type of diabetes mellitus, its duration and treatment were taken. Blood sugar levels, HbA1c levels, pus culture and sensitivity, fungal culture, X-ray foot and arterial Doppler were taken. Ulcer was cleaned with sterile normal saline before collecting samples. Wound swab was taken using pus culture tubes. Tissue samples were taken from the depth of the ulcer including edges consisting of necrotic slough and granulation tissue.⁵ Samples are taken from the depth of the ulcer after cleaning it with normal saline to differentiate fungal infection from fungal colonization. Superinfections in the form of fungal infections are known to occur in patients on long-term antibiotic therapy.⁶ The specimen was transported with saline soaked gauze in a sterile container for fungal culture.

Once the fungal stain or the culture study is positive, oral fluconazole 150 mg daily for 2 weeks was started for the patient. Fungal infection and type was confirmed with growth on Sabouraud's dextrose agar culture media.⁷ The other supportive wound care measures like glycemic control with insulin/oral hypoglycemic agents, antibiotics as per pus culture and sensitivity, and relieving pressure over the affected part of the foot were continued and the progression of the wound was studied.

Dressing of the wound was done regularly using hydrocolloid under sterile conditions. Any surgical intervention (wound debridement/split skin grafting/secondary suturing/disarticulation/amputations) required during the course of the study, based on ulcer progression was done as deemed necessary.

¹Associate Professor, ²Senior Resident, ³Professor

^{1,3}Department of General Surgery, Sri Ramachandra University Chennai, Tamil Nadu, India

²Department of Surgical Gastroenterology, Sri Ramachandra University, Chennai, Tamil Nadu, India

Corresponding Author: Saravanan Sanniyasi, Associate Professor, Department of General Surgery, Sri Ramachandra University, Chennai, Tamil Nadu, India, Phone: 04424768027 e-mail: saravan_s_2000@yahoo.com

Each ulcer was followed up to 6 months or till the healing of the ulcer, whichever is earlier. Fungal positive patients who were started on antifungal therapy were followed up every 15 days and fungal negative ulcers were followed once a month. The progression of the ulcer based on ulcer grade, duration of ulcer healing and the surgical intervention, including amputations, required during the course of ulcer healing was properly documented.

Statistical analysis was done using SPSS software version 14.0 and statistical significance was arrived at using Mann-Whitney test.

RESULTS

Samples were taken from 105 diabetic nonhealing foot ulcer patients, to study the prevalence of fungal infection and its correlation with various clinical features (Table 1).

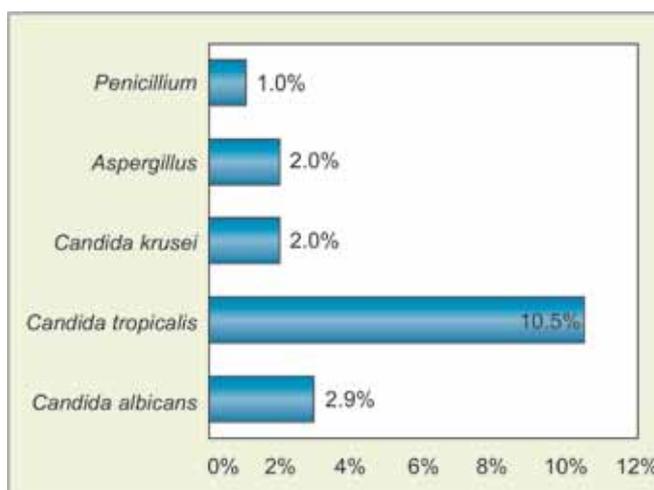
Majority of the study subjects were males (72.4%). Forty-two percent of the patients had a Wagner’s grade III ulcer.⁸ The most common bacterial organism identified was *Staphylococcus aureus* 25.7% followed by *Pseudomonas* 16.2 % and *Escherichia coli* 16.2 % (Table 2).

Nineteen patients grew fungus in the ulcer, commonest species being *Candida tropicalis* 10.5% (Graph 1). The most common bacterial organism isolated with fungal infection is *Pseudomonas* followed by *Enterococcus*.

Patients on prolonged antibiotic therapy showed statistically significant increase in fungal infection (Table 3). Patients who underwent amputation within 15 days of admission were higher in fungal culture positive group, due to progression ulcer in spite of antibiotic therapy. There is a definite correlation between incidence of amputation and fungal infection in whom antifungal therapy was not started. Fourteen patients, who did

Table 3: Statistical analysis

	Fungal positive	Fungal negative	p-value
Number of patients	19	86	—
Duration of diabetes mellitus (years)	12.26	6.84	<0.05
Duration of ulcer (months)	7.97	3.35	<0.05
Duration of antibiotics (days)	13.2	9	0.354
Number of amputations	5 (26.3%)	13 (15.2%)	>0.05



Graph 1: Spectrum of fungal infections

not undergo amputation, had faster wound healing and lesser progression of disease, with none of them requiring amputation after initiating antifungal therapy.

DISCUSSION

Fungal infection was present in 16.2% (19 out of 105) of our patients, which is higher compared to Bansal E et al⁹ 9% (9 out of 103 patients) and Emilija et al⁴ 4.5% (23 out of 509 patients). Chellan et al showed 27.9% positivity in their fungal cultures.⁵ In our study, the commonest fungal pathogen in diabetic foot ulcer was *Candida* species, which is in accordance to various other studies.^{4,9,10} Commonest among them was *C. tropicalis* which is similar to Bansal E et al.⁹ The duration of ulcer in fungal positive patients was between 2 and 36 months and the mean duration was 7 months. In Missoni et al¹⁰ study, the duration was found to be 3 months.

Chincholikar et al¹¹ and Emilija et al⁴ found *S. aureus* and *Pseudomonas* to be the commonest bacteriae to infect diabetic ulcers. The commonest bacterial organisms identified in our study were *S. aureus* 25.7%, followed by *Pseudomonas* 16.2%.

The commonest bacterial organism found in fungal positive patients was *Pseudomonas* followed by *Enterococcus*

Table 1: Patient demographics

	Minimum	Maximum	Mean
Age	44 years	85 years	58.77
Duration of ulcer	2 months	36 months	3.8
Duration of diabetes	1 year	23 years	7.46
Random blood sugar	76 mg/dl	670 mg/dl	250
Hb A1C	7	15	9.18

Table 2: Spectrum of bacterial flora

	Percentage
<i>Staphylococcus aureus</i>	25.7
<i>Pseudomonas</i>	16.2
<i>Escherichia coli</i>	16.2
<i>Enterococcus</i>	15.2
<i>Klebsiella</i>	8.6
<i>Enterobacter</i>	6.7
<i>Streptococcus</i>	4.8
<i>Proteus vulgaris</i>	3.8
<i>Acinetobacter</i>	2.9

compared to the study by Emilija et al⁴ where *Enterobacter* followed by *Pseudomonas* were the commonest organisms.

In our study group, we have found that ulcers of duration more than 7 to 8 months showed significant increase in fungal positivity ($p < 0.05$), when compared to ulcers of shorter duration. Also prolonged antibiotic therapy (13–14 days) was found to have increased incidence of fungal infection ($p < 0.05$).

There is a definite correlation between duration of diabetes mellitus and incidence of fungal positivity, patient with longer duration of diabetes more than 12 years have increased incidence of fungal infection compared with fungal culture negative patients who had around 6 years duration of diabetes mellitus. We could not find any correlation between glycemic control and fungal growth.

CONCLUSION

The prevalence of fungal infection in our study group was 18.1%; commonest fungus isolated was *Candida* species. Polymicrobial nature of nonhealing diabetic foot ulcer flora was seen; commonest bacterial organism identified was *Staphylococcus* and *pseudomonas*. Fungal infections were more commonly seen in long standing (7–8 months) nonhealing diabetic foot ulcers on antibiotic therapy. There were no isolated pure fungal infections; all the patients either had pure bacterial infections or mixed bacterial and fungal infections. *Pseudomonas* and *Enterococcus* were the two bacteriae which coexisted commonly with fungus in nonhealing diabetic foot ulcers.

There is a definite correlation between duration of diabetes mellitus and occurrence of fungal infection. We could not demonstrate correlation between glycemic control and the incidence of fungal infection in nonhealing diabetic foot ulcers.

There is also definite correlation between duration of antibiotic therapy (13–14 days) and incidence of fungal infection. Incidence of amputation was higher in patients group with mixed microbial infections both bacterial and fungal than in the group with only bacterial infection. Patients who were started on antifungal therapy

showed faster wound healing rates and less progression of the disease.

The present study signifies the need for mycological evaluation of nonhealing diabetic foot ulcer of a longer duration, with rapid progression despite antibacterial therapy and foot care, as introduction of prudent anti-fungal treatment results in faster wound healing rate of nonhealing diabetic foot ulcers. We believe that our results will create awareness among clinicians, of the need to treat fungal infections, as well as encourage further research in the infections. We need further randomized control trial comparing the treatment groups with and without antifungal therapy.

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