Original Article

Emergence of Fluconazole-resistant Candida Infections in Diabetic Foot Ulcers: Implications for Public Health

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Abstract

Background: It is well documented in the literature that fungal infections are common in diabetic foot ulcers (DFUs). This has led to an overuse of antifungal agents, namely fluconazole, with a consequent risk of emergence of resistance to this drug. Previous studies have shown a 3.9% prevalence of fluconazole resistance in DFU, but limited data exist regarding the change in resistance pattern over the last decade. **Objectives:** Our aim was to study the prevalence of resistance to fluconazole in patients with DFU and culture-proven fungal infections. **Materials and Methods:** We retrospectively studied 1438 patients with type 2 diabetes and nonhealing foot ulcers who had fungal cultures performed during the course of their treatment. The data were collected for all patients who presented to our foot clinic over a period of 18 months. **Results:** The prevalence of positive fungal culture was 17.38% (250/1438). 151/200 positive cultures belonged to *Candida* species. Resistance to fluconazole was observed in 9.3% (17/200). The most common organism with resistance to fluconazole was *Candida auris* (10/17). **Conclusions:** High prevalence of fluconazole resistance is a potential cause of concern, and the rational use of this drug is important in the community. The above results could have an impact on public health, as fluconazole is one of the safest and effective oral antifungal agents available. The spread of resistance could have implications for its use in other situations including systemic fungal infections.

Keywords: *Candida albicans*, Candida infection, *Candida parapsilosis*, diabetic foot ulcer, fluconazole resistance

Introduction

Diabetic foot ulcers (DFUs) are common in the community with prevalence rates ranging from 5% to 10%. The overall lifetime risk of developing DFU in patients with diabetes is estimated to be around 25%.[1,2] Poor and delayed healing with recurrent infections is a characteristic of DFU. Consequently, the risk of amputations in this group of patients is more than ten times in comparison to nondiabetic individuals.[2,3] While the predominant microorganism-causing infections in DFU are bacteria, few studies have reported the presence of filamentous fungi and low pathogenic yeast.[3-7] *Candida* spp. is the most commonly isolated yeast from these ulcers with a prevalence of 5%–21%.[8,9]

Fluconazole is recommended as the primary therapeutic option for the treatment of *Candida albicans*.[4] However, both inherent and acquired resistances to fluconazole are increasingly being reported and are a serious concern.[5,10] *Candida glabrata* and *Candida krusei* are reported to be more resistant to antifungal agents, particularly to fluconazole.[11] Protracted therapy and increased use for recurrent candidiasis are risk factors for the development of resistance to fluconazole.[12,13] The aim of our study was to document the current prevalence of fluconazole-resistant *Candida* infections in our patients with DFUs and identify any predisposing factors.

Materials and Methods

This was a retrospective study done on type 2 diabetes patients with DFU who attended the outpatient foot clinic at the endocrinology department of a tertiary care 1200-bedded teaching hospital in South India from January 2014 to October 2015.

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All patients with a positive fungal tissue culture during this period were included in the study. 1438 fungal cultures were done during this period, of which 17.38% (250/1438) were positive for *Candida* species. Nonrepetitive *Candida* isolates from DFU tissue were identified using VITEK 2 system (bioMérieux, Marcy I'Etoile, France). Antifungal susceptibility for fluconazole, amphotericin B, caspofungin, micafungin, flucytosine, and voriconazole were done using the Vitek 2 semiautomated system (AST-YSO1 cards, bioMérieux). Susceptibility of *Candida* spp. was interpreted using the CLSI M27-S4 guidelines.[14] Complete clinical and laboratory data were available in 200 patients. The data collected included age, sex, HbA1c, serum creatinine, details of type of procedure, type of organism, and sensitivity pattern. Statistical analysis was done using SPSS 21.

Results

Among the fungal culture isolates, 75.5% (151/200) belonged to *Candida* species and 6% (12/200) belonged to *Trichosporon* species. The most common fungal infection was *Candida parapsilosis* at 30% (60/200), followed by *C. albicans* (14.5%; 29/200) and *Candida auris* (5.5%; 11/200). Fluconazole resistance was observed in 17/182 (9.3%) isolates. Of 17 isolates with resistance, 10 were *C. auris*. 78.5% (157/200) of patients studied were male. The mean age of the study population was 62 ± 10 years and HbA1c 9.1% ± 2.0% [Table 1].

Of 17 patients with fluconazole resistance, 7 had undergone toe amputation, 9 had debridement, and 1 patient had foot reconstructive surgery. None of these patients had recurrence of nonhealing ulcers or required higher amputations. HbA1c in the fluconazole resistant group was 9.1% ± 1.5%, which was similar to those with sensitive fungal infection. Amphotericin resistance was 7% (12/183), flucytosine 7.9% (11/143), and voriconazole 4% (7/177) [Table 2].

Table 1: Baseline characteristics of patients with positive fungal cultures (*n*=200)

	Total (200)	Fluconazole sensitive (165)	Fluconazole resistant (17)
Age (years)	62.0±10.0	61.4±10.2	61.4±10.4
Sex (male:female)	157:43	15:2	127:38
HbA1C (%)	9.2±2.0	9.1±1.5	9.3±2.0
Serum creatinine (mg/dl)	1.5±0.9	1.6±1.2	1.5±0.9

HbA1C: Hemoglobin A1c

Table 2: Antifungal resistance pattern in diabetic foot wound cultures

Drug	Total cultures	Resistance (%)
Amphotericin	183	12 (7.0)
Fluconazole	182	17 (9.3)
Voriconazole	177	7 (4.0)
Flucytosine	143	11 (7.7)
Caspofungin	160	2 (1.6)
Itraconazole	11	2 (1.8)
Micafungin	112	2 (2.0)

Discussion

In our study, the prevalence of fluconazole resistance in fungal isolates from DFU was 9.3%. This is significant when compared to a previous study in 2008 from our center, which estimated resistance to fluconazole to be much lower (3.9%). A similar study by Tan *et al*.[15] showed a fluconazole resistance of 3.2% in all *Candida* infections in the bloodstream. The reason for this rise in resistance is unclear, although it could be the result of increasing use of fluconazole in our subset of patients.

The prevalence of positive fungal culture in our study was 17.4%. The previous study from our center had found a higher prevalence of 27.2%.[9] The reduction in positive fungal culture could be attributed to genuine reduction in infection secondary to increasing use of fluconazole.

A wide spectrum of fungal isolates was obtained in our study (28 in total) in keeping with previous reports. *Candida parapsilosis* was the most common infection, followed by *C. albicans* and *Candida tropicalis,* which is similar to the finding from our center in 2008.[9] There are previous reports which showed that *C. parapsilosis* has dramatically increased in significance and prevalence over the past two decades and is now one of the leading causes of invasive candidiasis.[16] A study from Singapore on blood-borne infection had shown similar fungal pattern with low resistance to fluconazole of 3.2%. *C. albicans* (37%), *C. tropicalis* (27%), and *C. glabrata* (16%) were more common in that study with *C. parapsilosis* less common.[16] Only 1/60 patients with *C. parapsilosis* infection had fluconazole resistance in our study, which is reassuring. Resistance to other antifungal agents was comparable to previous studies with amphotericin resistance 7%, flucytosine 7.9%, and voriconazole 4%. It is unclear at present whether this is due to limited use of these agents in the community compared to fluconazole.

Patients with fungal infections usually have poor glucose control.[5] Our study showed that those with fungal infection have uniformly poor control although this may not have any implication on antifungal resistance.

Follow-up of our patients with positive fungal culture and resistance to fluconazole showed that all underwent minor amputations or debridement with no evidence of recurrence. Hence, fluconazole resistance was not associated with any clinical deterioration or higher amputation level.

The strengths of our study are the large number of isolates studied and the reporting of the cultures from the same standardized laboratory. The limitations are the retrospective nature of study and the lack of information about previous fluconazole intake in these patients. A prospective study

including data on previous fluconazole use and a longer follow-up of these patients will help understand the magnitude of the problem better.

Meanwhile, the increase in antifungal resistance in the community is worrying as this could lead to spread of resistance to hematogenous or invasive fungal infection, which could be potentially lethal. Moreover, lack of other alternative antifungal agents in treatment of severe fungal infections makes it important to prevent spread of resistance.

Conclusions

A rise in fluconazole-resistant *Candida* infections in DFU raises concern regarding inappropriate use of these agents, especially in diabetes patients. Fluconazole is one of the most commonly used and safest antifungal agents in the primary care with very little side effects. The increase in resistance highlights the importance of drawing up a clear public health policy regarding the use of fluconazole in the community.

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Conflicts of interest

There are no conflicts of interest.

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