Dentistry 3000
Vol 12 No 2 (2024) DOI 10.5195/d3000.2024.717

Inspecting Candida Oral Infections among Diabetics

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Abstract

Objective: Oral candidiasis infection is more prevalent in diabetic patients. There are numerous factors that can exacerbate the colonization of Candida species in the oral cavity, including salivary pH disorders and xerostomia. The study aimed to evaluate Candida spp. resistance to antifungal agents and compare their colonization levels in diabetics and nondiabetics oral cavities.

Methods: We conducted the investigation from February 2023 to April 2023. We conducted the following analyses after collecting 100 oral samples: gram stain, culture on Sabaroud dextrose agar, and direct microscopic inspection. The Vitek 2 System confirmed the yeasts through carbohydrate assimilation profiles.

Results: Out of 100 oral samples cultured, 69 yielded Candida species. Fifty-two samples were from diabetics and 17 were from nondiabetic patients. The frequencies of isolated Candida species, including C. albicans, were 28, C. tropicalis 17, C. krusei 16, C. glabrata 6, and C. dubliniensis 2. The results indicated that C. albicans exhibited higher resistance rates against clotrimazole, itraconazole, and voriconazole than the no albicans Candida species. Clotrimazole, itraconazole, and voriconazole, on the other hand, showed no effect on 11, 29, and 18 samples for all Candida species, respectively.

Conclusion: C. albicans was the most prevalent Candida species in people with diabetes; however, other Candida species were common. Fluconazole and nystatin often treat oral Candida infections.

Keywords: Diabetes mellitus, Oral Candidiasis, Antifungal, Candida albicans, Nystatin**.**

Citation: Al-Garawyi A, et al. (2024) Inspecting Candida Oral Infections among Diabetics. Dentistry 3000. 1:a001 doi:10.5195/d3000.2024.717
Received: August 28, 2024
Accepted: September 1, 2024
Published: September 30, 2024

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Introduction

One of the most prevalent opportunistic fungal diseases in humans is oral candidiasis. Of the 150 species of this genus that have been isolated from the oral cavity, Candida albicans is the source of most of them (80%) [1,2]. Patients with diabetes, immunocompromised patients, and neutropenic patients frequently encounter Candida infections, which significantly contribute to nosocomial infections [3]. Candida, which comes from the Latin word candid, is a harmless, two-skinned fungus that can make invasive, disease-causing pseudohyphae [4]. Diabetes mellitus is a metabolic disease marked by a partial or total reduction in the pancreatic production of insulin, either because of inadequate insulin production or an autoimmune reaction that affects the beta cells that are responsible for synthesizing insulin. Hyperglycemia, a condition caused by elevated blood sugar levels, can be particularly harmful to people with diabetes, especially those who have had the condition for an extended period. This is because it can induce a variety of physiological responses [5]. It is very important to figure out the types of Candida that cause infections because different isolates of Candida species have different levels of ability to cause infections [6] and resistance to antifungal drugs [7]. So, the main goal of this investigation was to identify the Candida species in people with and without diabetes, as well as to investigate how sensitive people with oral candidiasis are to antifungals.

Material and Methods

Sample collection:

Dentistry 3000
Vol 12 No 2 (2024) DOI 10.5195/d3000.2024.717

The current study included 100 oral samples from each diabetic and nondiabetic patients attending hospitals in Al-Muthanna Governorate. They were over 45 years old and of both sexes. Individuals were recruited from February 2023 to April 2023. Specialist doctors conducted the clinical examinations. Furthermore, the doctors questioned each patient about their general health history, age, sex, use of antibiotics, alcohol consumption, and other risk factors for Candida infection. We took samples using a sterile cotton swab and transported them to the laboratory for testing.

Candida isolation and identification:

To determining the occurrence of Candida spp. and differentiating among species, many tests were performed on all oral samples, such as Gram stain [8], streaked on sabouraud dextrose agar [Mumbai, India] containing 0.5 mg per 1000 ml chloramphenicol [9,10], and direct microscopic examination [11]. The yeasts were confirmed via carbohydrate assimilation profiles using the Vitek 2 System (BioMerieux, France) according to the manufacturer's instructions.

In vitro antifungal susceptibility tests:

We selected five to six Candida species colonies from a 24-hour-old culture on an SDA plate, inoculated them in 5 mL of sterile saline, and adjusted their turbidity to 0.5 McFarland standards to create a suspension. The excess fluid was removed by rolling a sterile cotton wool swab on the tube's inside surface, moistened in the adjusted inoculum suspension, and then distributed on the Muller-Hinton agar surface to form a lawn [12,13]. The disk diffusion method was employed to conduct antifungal susceptibility testing. The Clinical Laboratory Standard Institute (CLSI) recommended that antifungal discs (Thermo ScientificTM OxoidTM) be applied to MHA (Thermo ScientificTM OxoidTM) using disk dispensers (OxoidTM). The discs contained Voriconazole (10 µg), Clotrimazole (10 µg), Fluconazole (10 µg), Itraconazole (10 µg), and Nystatin (100 IU). The dishes were incubated at 35°C in ambient air for 24 hours. The Clinical and Laboratory Standard Institute (CLSI) interpretation criteria for voriconazole, fluconazole, nystatin, itraconazole, and clotrimazole are shown in Table 1 [14].

Table 1. Based on [14] interpretative criteria for resistance and susceptibility to utilized antifungal disks (mm).

Antifungal Agent	Sensitive	Dose dependent	Resistance
Fluconazole	≥19	15-18	≤ 14
Nystatin	≥ 25	17-24	< 16
Clotrimazole	>20	12-19	≤ 11
Itraconazole	> 16	10-15	< 9
Voriconazole	≥19	15–18	≤14

Results

The present study included the collection of one hundred (100) oral samples from 69 diabetic patients and 31 nondiabetic patients. The patients ages ranged from 45 to 80 years. Out of 69 oral

Dentistry 3000
Vol 12 No 2 (2024) DOI 10.5195/d3000.2024.717

swabs from diabetic patients, Candida species were isolated from 52 samples (Table 2). In contrast, Candida spp infection was detected in only 17 (54.8%) oral swab samples from nondiabetic patients. The statistical significance of the difference between these two categories was indicated by the P-value of 0.05. The study found that diabetic patients were 1.37 times more likely to contract

Candida spp. infection than nondiabetic patients, while nondiabetic patients have a relative risk of 0.54, as mentioned in Table 2.

Table 2. Candida infection rates in patient groups with and without diabetes.

Groups	Positive	Negative	Total	Odds Ratio	Relative Risk for diabetic patient	Relative Risk for nondiabetic patient
Diabetic	52	17	69	2.51	1.37	0.54
Nondiabetic	17	14	31			
Total	69	31	100			

We identified five species of Candida. Among 69 patients with and without diabetes, Candida albicans was the most common agent 28, followed by Candida tropicalis 17, Candida krusei 16, Candida glabrata 6, and Candida dubliniensis 2, as displayed in Figure 1.

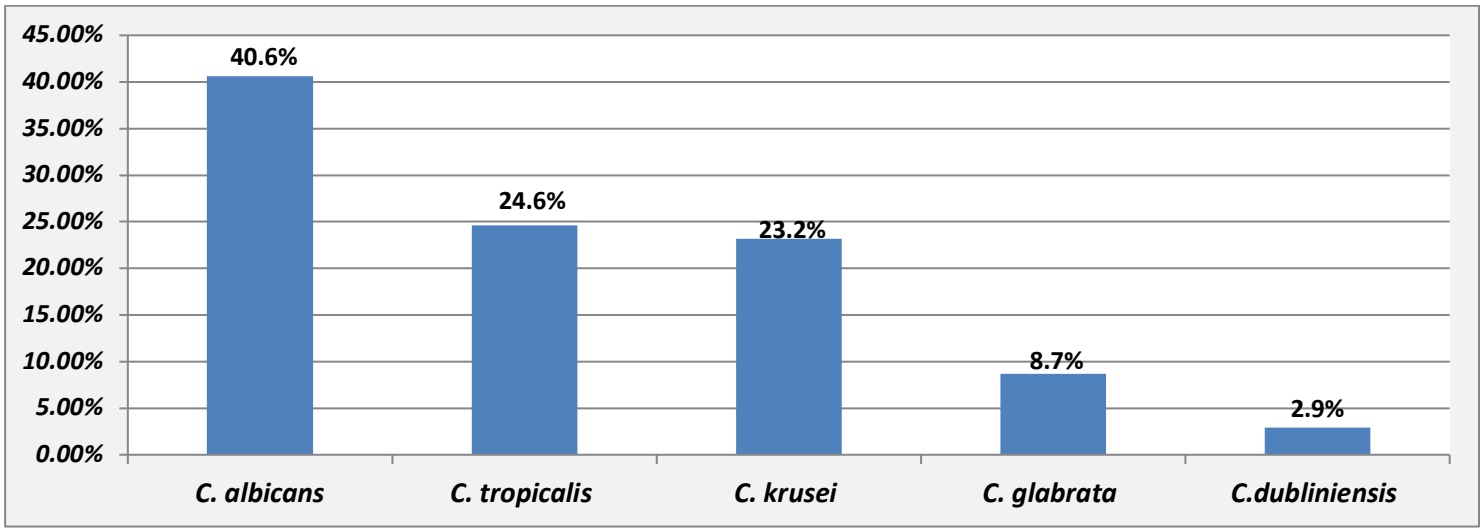

Figure 1. Various species of Candida isolated from oral cavity among diabetics and nondiabetics.

The prevalence of Candida spp. infection in diabetic and nondiabetic patients was analyzed using the Chi square test, and the results are summarized in Table 3. We found no statistically significant difference in the percentage of positive Candida infection cases between diabetic and nondiabetic patients across different age groups ($P > 0.05$).

Table:3 Demographical screening of Candida load in diabetic patients in comparison to nondiabetics.

Dentistry 3000
Vol 12 No 2 (2024) DOI 10.5195/d3000.2024.717

Age groups	Diabetic	Nondiabetic	Total	X2	P value
45-55	17	5	22	1.29	0.52
56-66	20	9	29		
> 67	15	3	18		
Total	52	17	69		
X2= 1.29, df=2, P> 0.05					

According to the chi-square test, we found a notable disparity in the occurrence of Candida spp. infection depending on sex. Table 4 shows a significant (P< 0.05) proportion of positive cases for Candida among patient with and without diabetic.

Table 4. The frequency of Candida infections depending on sex.

Sex		Diabetic	Nondiabetic	Total	X2	P value
	Males	37	6	43	7.01	0.008
	Females	15	11	26		
Total		52	17	69		
X2= 7.01, df=1, P< 0.05						

We found that 20 diabetic patients had oral ulcers, in whom the frequency of Candida spp. was 90.9%, while in those who were negative for oral ulcers, it was 68.1%. The observed difference was statistically significant (P< 0.05), as shown in Table 5.

Table 5. The frequency of Candida infections depending on oral ulcer.

Oral ulcer		Diabetic	Nondiabetic	Total	X2	P value
	Positive	20	2	**22**	**4.20**	**0.04**
	Negative	32	15	47		
Total		52	17	69		
X2= 4.20, df=1, P< 0.05						

We investigated the frequency of Candida spp. in relation to hypertension using the chi square test. Table 6 shows that out of the 52 diabetic individuals with a Candida infection, 71.4% had

Dentistry 3000
Vol 12 No 2 (2024) DOI 10.5195/d3000.2024.717

hypertension and 77.1% did not have hypertension (P > 0.05).

Table 6. The frequency of Candida infections depending on hypertension.

Hypertension		Diabetic	Nondiabetic	Total	X2	P value
	Positive	15	6(	21	0.25	0.61
	Negative	37	11	48		
Total		52	17	69		
X2=0.25, df=1, P> 0.05						

The sensitivity test results of all Candida spp. isolates toward all antifungal agents in the current study are shown in Table 7. Candida albicans, the most isolated species, was shown to be responsive to fluconazole, nystatin, clotrimazole, itraconazole, and voriconazole at ratios of 36.2%, 5.8%, 13%, 20.3%, and 15.9%, respectively. Candida albicans, the most isolated of 69 Candida species, was responsive to fluconazole, nystatin, clotrimazole, itraconazole, and voriconazole at 36.2%, 5.8%, 13%, 20.3%, and 15.9%, respectively. Conversely, fluconazole, nystatin, clotrimazole, itraconazole, and voriconazole had no effect in 0%, 0%, 8.7%, 15.9%, and 10.1%, respectively. Out of the 17 C. tropicalis isolates, 15.9% were sensitive to fluconazole, 21.7% to nystatin, 5.8% to clotrimazole, 7.2% to itraconazole, and 14.5% to voriconazole, while 4.3%, 8.7%, and 7.2% were resistant to clotrimazole, itraconazole, and voriconazole, respectively. In addition, 2.9% were resistant to clotrimazole, 11.6% to itraconazole, and 4.3% to voriconazole. Regarding C. glabrata, the findings showed that 4.3% were susceptible to fluconazole, nystatin, clotrimazole, itraconazole, and voriconazole, respectively; 2.9% and 4.3% were resistant to itraconazole and voriconazole, respectively. Additionally, of the two C. dubliniensis isolates that were found, both were resistant to itraconazole.

Table 7. Antifungal susceptibility testing of Candida spp. isolates.

Fluconazole	C. albicans	C. tropicalis	C. krusei	C. glabrata	C. dubliniensis	Total
Sensitive	25	11	15	3	2	56
Dose dependent	3	6	1	3	0	13
Resistance	**0**	**0**	**0**	**0**	**0**	**0**
Total	**28**	**17**	**16**	**6**	**2**	**69**
Nystatin						
Sensitive	**4**	**15**	**12**	**4**	**2**	**37**

Dentistry 3000
Vol 12 No 2 (2024) DOI 10.5195/d3000.2024.717

Dose dependent	24	2	4	2	0	32
Resistance	**0**	**0**	**0**	**0**	**0**	**0**
Total	28	17	16	6	2	69
Clotrimazole						
Sensitive	9	4	5	2	2	22
Dose dependent	**13**	**10**	**9**	**4**	**0**	**36**
Resistance	6	3	2	0	0	11
Total	**28**	**17**	**16**	**6**	**2**	**69**
Itraconazole						
Sensitive	**14**	**5**	**4**	**2**	**0**	**25**
Dose dependent	3	6	4	2	0	15
Resistance	**11**	**6**	**8**	**2**	**2**	**29**
Total	28	17	16	6	2	69
Voriconazole						
Sensitive	11	10	6	3	2	32
Dose dependent	**10**	**2**	**7**	**0**	**0**	**19**
Resistance	7	5	3	3	0	18
Total	**28**	**17**	**16**	**6**	**2**	**69**

Discussion

Globally, diabetes is a serious public health issue [15]. The study confirms that diabetes mellitus is a significant risk factor for symptomatic candidosis, whether oral or otherwise, in Iraqi patients with diabetes mellitus, as previously reported [16,17]. This is also consistent with several other studies, which have all shown that diabetes mellitus increases Candida colonization and growth [18,19]. According to research by Premkumar et al. [20], the most found species was C. albicans. However, they also saw C. parapsilosis, C. tropicalis, and C. dubliniensis. Candida albicans was the most prevalent species (43.1%) in the oral cavity of diabetes patients, as discovered by Mohammadi et al. [21]. Conversely, the prevalence of Candida spp. in the oral cavity of nondiabetic controls was lower (27%). Factors such as increased salivary glucose, pH, flow reduction, and smoking habits contribute to Candida colonization [22]. We investigated the prevalence of Candida spp. in diabetic and nondiabetic populations according to age and the results indicated that there was

Dentistry 3000
Vol 12 No 2 (2024) DOI 10.5195/d3000.2024.717

no statistically significant difference in the percentage of positive cases in diabetic and nondiabetic patients. Al-Awadhi et al. [23] found no association between diabetes and infection or age. Twenty diabetic individuals during our study reported oral ulcers. We examined the prevalence of Candida spp. in diabetic patients with oral ulcers and found a possible relationship between oral ulcers and presence of Candida spp. in 90.9% of diabetic individuals with mouth ulcers compared to 68.1% in those without ulcers. Additional research is warrented to confirm these findings and explore potential underlying causes. Our study found no statistically significant difference in the prevalence of Candida spp. between hypertension diabetic patients and no hypertensive diabetic patients. Candida spp. was more common specifically among hypertension diabetic patients (77.1%) than among hypertensive nondiabetic patients (28.6%). Comparing C. albicans to other no albicans candida species, the findings showed that itraconazole, variconazole, and clotrimazole demonstrated increased resistance rates. This result is in line with another study, which showed that C. albicans was more resistant to clotrimazole and itraconazole than no albicans candida species [24]. The presence of point mutations, insertions, and deletions in the genes encoding target proteins in C. albicans may explain these results. These mutations often cause antifungal medication resistance. Gene overexpression often upregulates oxidative damage and antifungal resistance proteins. Gene overexpression of the multidrug efflux pump is one example [25,26]. However, a significant level of resistance was detected in Itraconazole and Voriconazole, with rates of 42% and 26.1%, respectively, for all Candida species. This conclusion aligns with the results of earlier investigations [27,28]. The present investigation demonstrated that fluconazole and nystatin were effective against all isolated Candida spp., with a sensitivity rate of 81.2% and 53.6%, respectively. This information is in accordance with numerous other studies [29,30]. Consequently, nystatin typically functions by interacting with ergosterol and distracting the fungal cytoplasmic membrane. Nystatin creates the pores in the cell membrane that serve as an exit for magnesium cellular components and potassium ions. This damages the proton gradient of the cell membrane, thereby promoting fungal cell death. Nystatin binds ergosterol somewhat well and binds 3 hydroxy or oxysterol rather poorly. Consequently, the indications are less than those of the azole group [31]. Fluconazole inhibits the formation of ergosterol, a crucial component of the fungal cell membrane, by interacting with 14-demethylase, a cytochrome P-450 enzyme. Fluconazole prevents yeast formation and endogenous respiration by preventing sterol loss, which is parallel to the accumulation of 14-methyl sterols in fungi, which is the primary cause of its perceived fungistatic activity [32]. Fluconazole and nystatin are recommended antifungals for treating Candida infections due to their susceptibility to most fungal species.

Conclusion

We found a high prevalence of Candida spp. and a greater frequency of Candida species in individuals with diabetes compared to those without the disease, indicating an association between diabetes and Candida infection. This investigation also found a nonsignificant correlation between mouth ulcers, hypertension, and Candida infection. While there is a substantial variation in the incidence of Candida infection depending on sex, there is no significant correlation between age

Dentistry 3000
Vol 12 No 2 (2024) DOI 10.5195/d3000.2024.717

groups and Candida infection. With a frequency of 40.6%, C. albicans was the most often found Candida species; C. dubliniensis was the least common (2.9%). Fluconazole and nystatin showed a high degree of sensitivity among candida species, suggesting that fluconazole is the more effective therapy for oral candida infections. Regular monitoring of Candida infections is crucial as they potentially pose a risk for developing diabetes. The research supports informing the general public about Candida infections and their health consequences.

Conflicts of interest

The authors declare no competing interest.

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Dentistry 3000
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Dentistry 3000
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