Original Article

# Characterization and identification of candiduria due to *Candida* species in diabetic patients

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## Abstract

**Background and Purpose:** The presence of *Candida* yeasts in urine, known as candiduria, is an indicator of infection or colonization of the urinary tract by *Candida* species. This condition in diabetic patients can be hazardous due to diminished immune system response. The objective of this study was to investigate the incidence of candiduria in diabetic patients and to identify its causative agents. Furthermore, the demographic and laboratory ($HbA_{1c}$, urine glucose and pH, urine culture colony count, and fasting blood sugar) data and their possible associations with candiduria were investigated.

**Materials and Methods:** This cross-sectional, descriptive study was performed on 305 diabetic patients referred to the diabetes research center, Hamedan, Iran, during April 2015 to September 2015. Urine and blood specimens were collected and urine analysis, urine culture, FBS, and $HbA_{1c}$ tests were performed. Positive cases were subjected to colony count and the causative agents were subsequently identified through the routine identification tests, as well as colony color in CHROMagar Candida medium, and the assimilation patterns in API 20 C auxanographic method.

**Results:** Among the 305 cases, 38 (%12.5) were positive for candiduria. Causative agents were identified as *Candida glabrata* (n=19, 50%), *C. albicans* (n=12, 31.6%), *C. krusei* (n=4, 10.5%), *C. tropicalis* (n=2, 5.3%), and *C. kefyr* (n=1, 2.6%). According to the results of the statistical analyses ,there were significant association between candiduria and female gender, high FBS and urine glucose, uncontrolled diabetes ($HbA_{1c} \geq 8$), and acidic urine pH ($P<0.05$).

**Conclusion:** Considering the high incidence rate of candiduria in diabetic patients, control of diabetes, predisposing factors, and causal relationships between diabetes and candiduria should be highlighted.

**Keywords:** *Candida*, Diabetes, $HbA_{1c}$, Urinary tract infections

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## Introduction

*Candida* species are the most frequently recovered fungi from genital and urinary tract. Candiduria, which means the presence of *Candida* in urine, is caused by *albicans* and non-*albicans* species of the genus *Candida*. Identification of *Candida* isolates to the species level is required due to changes in dominant species and different antifungal susceptibility patterns observed in recent years [1, 2].

Broad- spectrum antibiotic therapy, application of catheters, endocrine disorders such as diabetes mellitus, prolonged hospitalization, primary or secondary weakness in immune system responses, and urinary system disorders and abnormalities are some of the common predisposing factors of candiduria [3].

Although the presence of *Candida* in urine may be a transient and asymptomatic condition and may not meet the typical requirements for systemic antifungal therapy [4], the high risk of morbidity and mortality associated with candiduria in immunocompromised individuals highlights the clinical importance of this condition [5].

Diabetes is the most common endocrine disorder worldwide. Owing to immunologic impairments following diabetes, it is a potent predisposing factor for a wide spectrum of infections. Patients with uncontrolled diabetes and high levels of blood sugar (hyperglycemia) leave the integumentary system, gastrointestinal and urinary tracts, and mucous membranes more susceptible to infectious agents due to reduced immunity of the body [6-8].

Urinary tract infection (UTI) is a frequent condition in diabetic individuals, and candiduria could be the onset of a disseminated infection [9, 10]. According to these data, investigation of the dominant *Candida* species and the relationships between candiduria and underlying factors seems imperative for effective prevention of severe consequences of disseminated *Candida* infections.

The objective of this study was to investigate the incidence of candiduria in diabetic patients in Hamedan, Iran, and to identify its causative agents. Furthermore, we aimed to investigate the associations between candiduria and demographics, laboratory values (such as glycated hemoglobin [$HbA_{1c}$], urinary glucose/pH, urinary culture colony count, and FBS) data.

## Materials and Methods

In this cross-sectional, descriptive study, performed during a six-month period (from April 2015 to September 2015), a total of 305 diabetic outpatients (age range: 17-74 years) of a referral diabetes research center in Hamedan, Iran, were included. Lack of any other predisposing and confounding factors such as vaginitis was the inclusion criterion. Demographic data and informed consent were obtained from all the patients and this study was approved by the Ethics Committee of Iran University of Medical Sciences, Tehran, Iran (Code IR.IUMS.REC.1395.861066003).

Clean catch midstream urine and venous blood specimens were collected from all the patients. Routine urine analysis, urine glucose test, and urine culture were performed on all the specimens and positive cases were subjected to culture colony count. Isolated *Candida* species were identified by routine laboratory tests, colony color in CHROMagar candida medium (CHROMagar, France), and the assimilation patterns in API 20C auxanographic method (bioMerieux, Marcy l'Etoile, France). FBS and $HbA_{1c}$ tests were performed using an automated biochemical analyzer (BT 1500, Biotecnica Instruments, Italy) on the serum specimens of the patients.

### *Statistical analysis*

The results of all the tests and demographic data were analyzed using Chi-square test and t-test in SPSS, version 15.

## Results

Among the 305 studied cases consisting of 223 females (73.1%) and 82 males (26.9%), 38 patients (12.5%) were positive for candiduria. Of these patients, 30 (9.8%) had colony count $\geq 10^3$. According to the statistical analysis, there was a significant association between female gender and candiduria (*P=0.005*).

*C. glabrata* was the most common cause of candiduria accounting for half of the cases in this study followed by *C. albicans*. The frequency of different *Candida* species in this study is presented in Table 1.

**Table 1.** The frequency of *Candida* species isolated from urine specimens of diabetic patients

| *Candida* species | Total | |
|---|---|---|
| | Frequency | Percentage |
| *C. glabrata* | ١٩ | ٥٠ |
| *C. albicans* | ١٢ | ٣١,٦ |
| *C. krusei* | ٤ | ١٠,٥ |
| *C. tropicalis* | ٢ | ٥,٣ |
| *C. kefyr* | ١ | ٢,٦ |
| total | ٣٨ | ١٠٠ |

The mean colony count of *Candida* species among 38 positive cases was $5.37\times10^4$ CFU/ml with the minimum and maximum values of $2\times10^2$ and $5.8\times10^5$ CFU/ml, respectively. The urine pH varied from 5 to 8 among all the patients, and the majority of candiduria cases were within the pH range of 5-6. A statistically significant association was observed between acidic urine pH and the occurrence of candiduria (*P=0.02*).

High FBS values (*P=0.001*), glucosuria (*P=0.022*), and uncontrolled diabetes ($HbA_{1c}\geq8$; *P=0.001*) also significantly associated with candiduria in the present study. Table 2 demonstrates the frequency of candiduria in the study population based on different characteristics of the patients.

## Discussion

*Candida* species are the leading fungal agents of UTI, particularly in patients with deficient immune responses [11]. The majority of candiduria cases are acquired as nosocomial infection due to application of catheters and wide spectrum antibiotic therapy [12].

*Candida* species are the causative agents of up to 10% of all nosocomial UTI cases [13], and some underlying factors such as advancing age, female gender, antimicrobial therapy, urinary catheter, surgery, and diabetes mellitus may facilitate their pathogenesis [14]. Also, biofilm formation, adhesion of fungi to the host tissue and medical devices, and extracellular hydrolytic enzymes production are considered as factors facilitating the commensal to pathogen shift of *Candida* species [15].

The recovery rate of *Candida* species from urine samples varies in different studies. In the present

**Table 2.** Distribution of candiduria among diabetic patients based on different variables

| Variables | Candiduria | | Total |
|---|---|---|---|
| | Negative | Positive | |
| Gender | | | |
| Male | 79 | 3 | 82 |
| Female | 188 | 35 | 223 |
| Total | 267 | 38 | 305 |
| Marital status | | | |
| Single | 18 | 0 | 18 |
| Married | 216 | 29 | 245 |
| Divorced | 33 | 9 | 42 |
| Total | 267 | 38 | 305 |
| Diabetes type | | | |
| I | 25 | 4 | 29 |
| II | 242 | 34 | 276 |
| Total | 267 | 38 | 305 |
| CFU[a] | | | |
| 0 | 267 | 0 | 267 |
| 1-$10^3$ | 0 | 8 | 8 |
| $10^3$-$10^4$ | 0 | 16 | 16 |
| $10^4$-$10^5$ | 0 | 10 | 10 |
| $10^5$-$10^6$ | 0 | 4 | 4 |
| Total | 267 | 38 | 305 |
| Urine pH | | | |
| 5-6 | 234 | 37 | 271 |
| >6-7 | 22 | 1 | 23 |
| >7-8 | 11 | 0 | 11 |
| Total | 267 | 38 | 305 |
| FBS[b] | | | |
| 50-150 | 135 | 7 | 142 |
| 151-250 | 106 | 20 | 126 |
| 251-350 | 23 | 10 | 33 |
| 351-450 | 3 | 1 | 4 |
| Total | 267 | 38 | 305 |
| $HbA_{1c}$[c] | | | |
| <8 | 176 | 13 | 189 |
| ≥8 | 91 | 25 | 116 |
| Total | 267 | 38 | 305 |

a. Colony forming unit/ml
b. Fasting blood sugar (mg/dl)
c. Hemoglobin $A_{1c}$ (% of total Hemoglobin)

study, 38 out of 305 patients (12.5%) were positive for candiduria, and among them, 30 (9.8%) had significant candiduria (≥$10^3$ CFU/ml). In a study conducted by Nademi et al. [11], nosocomial candiduria was reported in 4.3% (5 out of 115) of hospitalized patients. Furthermore, Yismaw et al. [10] reported significant candiduria in 7.5% and 17.1% of asymptomatic and symptomatic patients with diabetes, respectively. The overall candiduria rate was 8.3% (35 out of 422). Similarly, Goyal et al. [2], Zarei et al. [16], and Padawer et al. [17] reported candiduria in 2.36%, 16.5%, and 19.49% of their study populations, respectively. In a comparative study by da Silva Krenke et al. [18], candiduria was reported in 30% and 16% of diabetic and non-diabetic patients, respectively. The disagreements between the results of various studies may be due to differences in study populations, underlying factors, preventive measures of patients and hospitals, and geographical location.

Although *C. albicans* is reported as the major *Candida* species causing candiduria in some studies [3, 16, 19, 20], an increasing trend in the prevalence of candiduria due to non-*albicans Candida* species was shown by some researchers [2, 21-23]. In the present study, *C. glabrata* was the most isolated species (50%) followed by *C. albicans* (31.6%), *C. krusei* (10.5%), *C. tropicalis* (5.3%), and *C. kefyr* (2.6%).

The higher incidence of non-*albicans Candida* species, including *C. glabrata*, may be due to their ability to adapt to the urinary tract condition, as well as their intrinsic and/or acquired resistance to the conventional antifungals [2]. Considering the high drug resistance of non-*albicans Candida* species, especially *C. glabrata* [2, 22], their dominance should be considered as a health concern and a probable cause of treatment failure.

The association between candiduria and different demographic and laboratory data was assessed in the present study. Female gender, decreased (acidic) urine pH, high FBS followed by glucosuria, and uncontrolled diabetes ($HbA_{1c}$ ≥8) were associated with candiduria. Although the urine pH of diabetic cases was within the range of 5-8, all the cases of candiduria had acidic pH. Acidic pH is favorable for *Candida* species and alkaline pH decreases their growth. Strassner et al. [24] used potassium-sodium-hydrogen citrate for alkalinization of urine in patients with candiduria as a treatment technique. In so doing, candiduria disappeared in 89% (16 out of 18) of patients.

In agreement with the findings of the present study, Paul et al. reported high plasma glucose level as a correlated factor to the candiduria [13]. Also Geerlings et al. [25] believed that female gender, poor or uncontrolled diabetes ($HbA_{1c}$ ≥8), and some other factors like pregnancy, aging, and a history of UTI within the previous six months are the possible risk factors for candiduria in diabetic patients.

According to the data from a study conducted by Georgiadou et al. [23], female gender, multiple hospitalization, broad-spectrum antimicrobial therapy, renal dysfunction, intensive care unit admission, and diabetes mellitus are predisposing factors of candiduria in patients with hematologic malignancy. In addition to urinary system disorders following candiduria, candidemia is reported to be significantly associated with the candiduria [26], which underscores the importance of this condition.

The present study was conducted in a referral center for diabetes in Hamedan, Iran. The results

provided an update to the dominant *Candida* species in Hamedan and highlights the possibility of treatment failure due to high resistance of non-*albicans Candida* species. However, it is recommended to perform further studies with larger sample sizes and susceptibility testing to determine the efficient antifungal agents.

## Conclusion

Considering the high incidence rate of candiduria in diabetic patients, efficient control of diabetes, predisposing factors, and causal relationships between diabetes and candiduria should be emphasized. In addition, as the non-*albicans Candida* species were isolated more than *C. albicans*, their intrinsic resistance to antifungal drugs should be noted. Antifungal susceptibility testing for determination of susceptibility/resistance profile of isolates could be helpful for appropriate treatment.

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## Authors' contributions

All the authors of the present manuscript contributed sufficiently to the work.

## Conflicts of interest

None declared.

## Financial disclosure

None.

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