Original Article

Unveiling the Clinical Correlation between Candida Tropicalis Presence, Symptomatology and Urinary Yeast Quantification in Diabetic Patients

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Abstract

Objective: This study investigates the association between candiduria and diabetes mellitus, focusing on the presence of fungal elements in urine, associated symptoms, and the most prevalent Candida species in diabetic patients. It also provides a basis for comparing Vitek with advanced molecular techniques.

Methods: This cross-sectional study conducted at a tertiary care setting in Pakistan involved 116 participants recruited through non-probability sampling. The diagnostic workup for urinary tract infections was urinalysis and urine culture and sensitivity. The VITEK 2 System was used for the identification of Candida species and to assess their antifungal susceptibility.

Results: Involving 116 participants, 36 (31%) males and 80 (69%) females, urine analysis revealed Escherichia coli 56 (48.3%), Enterococcus faecium 16 (13.8%), Candida tropicalis 6 (5.2%), and 38 (32.8%) with no growth. Common symptoms included fever, dysuria, urgency, and lower abdominal pain. The frequency distribution of yeast levels in the study reveals that in many cases, 61 (52.6%) were categorized as "NILL," indicating no yeast presence. "MODERATE" yeast levels were observed in 28 (24.1%) cases, "MANY" in 25 (21.6%), and "FEW" in 2 (1.7%). Chi-square analyses showed no significant association between yeast frequency and gender ($\chi^2 = 2.32$, p = 0.510), lower abdominal pain ($\chi^2 = 1.29$, p = 0.733), or urgency to urinate ($\chi^2 = 0.39$, p = 0.942). However, significant associations were observed with fever ($\chi^2 = 11.27$, p = 0.010) and dysuria ($\chi^2 = 9.98$, p = 0.019). Likelihood ratio and linear-by-linear association tests supported these findings.

Conclusion: High prevalence UTIs are common in patients (especially in females) with type 1 and type 2 diabetes mellitus. The prevalence of Candida species, particularly Candida tropicalis, in our study highlights diverse uropathogens in diabetics; otherwise, Candida albicans is the most prevalent organism causing UTIs. Fungal UTIs in the elderly present challenges. With SGLT2 inhibitors emerging as a major risk factor for fungal urinary infections, it is crucial to consider this complication, especially in patients with cardiovascular disease. The Vitek technique offers a reliable, fast, and cost-effective method in low-income countries.

Keywords: Diabetes Mellitus, Urinary tract infection, Uropathogens prevalence, VITEK

Introduction

Urinary tract infections (UTIs) are common bacterial infections that represent a serious public health problem.[1] In uncomplicated UTIs, uropathogens originating from the gut colonize the periurethral area, ascend to the bladder, and adhere to superficial urothelial cells, leading to cystitis. Some bacteria evade host immune responses, multiply, and form biofilms that damage host tissues and may ascend to the kidneys, producing toxins; UTIs can subsequently progress to bacteremia and renal damage.[2] UTIs are a frequent concern in patients with type 2 diabetes mellitus (DM) due to impaired immunity, poor metabolic control, and autonomic neuropathy. In diabetic patients, UTIs range from asymptomatic bacteriuria to severe pyelonephritis and urosepsis. Moreover, individuals with DM are at increased risk of infection with antibiotic-resistant pathogens, posing significant clinical and economic challenges.[3] A cross-

sectional study from West Bengal, India, reported a 24.3% prevalence of culture-confirmed UTIs, while 32.7% of patients experienced symptomatic UTIs. Female patients with DM, particularly housewives, were more susceptible. Escherichia coli was the predominant uropathogen, especially among symptomatic cases. Gram-negative bacteria were more prevalent than gram-positive organisms (65.3% vs. 28.57%), and 34.37% of gram-negative isolates were extended-spectrum beta-lactamase (ESBL) producers.[4] UTIs are also a frequently recurring problem among women of all age groups due to anatomical susceptibility and proximity of the urinary and reproductive tracts. Conditions such as pregnancy, post-menopause, diabetes, epilepsy, urinary catheterization, and surgical interventions further increase the risk. Recurrent UTIs, defined as multiple infections within a specific period, affect 25–50% of women with UTIs.[5]

Patients with DM are more prone to complicated UTIs, including pyelonephritis, renal abscesses, emphysematous infections, and severe urosepsis. The bacterial spectrum is generally similar to that in non-diabetic patients, with E. coli being the most common pathogen. Preventive measures include adequate hydration, complete bladder emptying, and avoidance of unnecessary catheterization. Some evidence suggests that cranberry products and Lactobacillus may help prevent recurrence in women.[6] Additionally, a systematic review and meta-analysis of 86 randomized controlled trials on SGLT-2 inhibitors (canagliflozin, dapagliflozin, and empagliflozin) demonstrated a significant threefold increased risk of genitourinary infections among diabetic patients.[7]

A large Tanzanian study involving 1327 patients with community-acquired UTIs found a 27.4% prevalence with E. coli as the most common gram-negative isolate and Staphylococcus aureus and Staphylococcus haemolyticus as frequent gram-positive pathogens. Resistance patterns varied across antibiotics; carbapenems, third-generation cephalosporins, and nitrofurantoin showed lower resistance rates. Multidrug-resistant organisms were common, including methicillin-resistant S. aureus (MRSA), methicillin-resistant coagulase-negative staphylococci (MR-CoNS), and ESBL-producing Enterobacteriaceae.[8] Assessing the significance of candiduria is challenging, as it may represent infection, colonization, or contamination. Cases should be stratified based on patient risk factors and specimen validity, with management tailored accordingly, including catheter removal when necessary.[9] Fungal pathogens, particularly Candida species and occasionally Cryptococcus and other non-yeast fungi, can cause urinary and disseminated infections, especially in immunocompromised individuals.[10] This study explores the association between candiduria and DM, focusing on fungal elements in urine, symptomatology, fungal load, and predominant Candida species, while also enabling comparison between Vitek-based identification and advanced molecular diagnostic techniques.

Methods

This cross-sectional study was conducted at Fatima Memorial Hospital, Lahore (Nov 2023-May 2024) on 116 diabetic patients; 80 (68.96%) females, 36 (31.03%) males selected via non-probability sampling.

Inclusion criteria specified that participants must have a documented diagnosis of Diabetes Mellitus (Type 1 or Type 2), confirmed through medical records, physician diagnosis, or elevated blood glucose levels indicated by laboratory tests (HbA1C > 7%). The participants in this study, spanning both genders and aged 18 years and older, were required to have a confirmed diagnosis of urinary tract infection (UTI), based on clinical symptoms and laboratory evidence.

Exclusion criteria were applied to patients with immunocompromised conditions (chronic kidney disease, HIV/AIDS, cancer, transplant recipients, autoimmune disorders [rheumatoid arthritis (RA), systemic lupus erythematosus (SLE)], chronic steroid use, a history of cerebrovascular accidents, hemolytic disorders (hereditary spherocytosis, sickle cell disease, thalassemia, autoimmune hemolytic anemia, G6PD deficiency), significant organ compromise or multiple organ dysfunction (congenital abnormalities, end-stage heart failure, severe chronic obstructive pulmonary disease (COPD), and chronic liver cirrhosis), and those with a history of psychiatric illness or cognitive impairment.

The diagnostic workup for UTIs involved two primary tests: Urinalysis provided an initial assessment of urinary abnormalities, including leukocyte esterase, nitrites, pH, protein, red blood cells (RBCs), white blood cells (WBCs), and the presence of bacteria or yeast. Urine culture and sensitivity was performed to identify the causative microorganism and determine its antimicrobial or antifungal. The VITEK 2 System was employed to identify Candida species and assess their antifungal susceptibility in the urine culture and sensitivity process. This system works by detecting colour changes in biochemical tests that reflect the microorganisms' metabolic activities. The identification results were validated by comparing them with known reference strains, such as Candida albicans (ATCC 90028), Candida parapsilosis (ATCC 22019), and Candida krusei (ATCC 6258). Although Candida tropicalis ATCC 750 is a recognized reference strain, it is not routinely used as a standard control strain in systems like VITEK 2.

Data was analyzed using IBM SPSS 26 (chi-square for categorical variables, mean ± SD for continuous variables). Bias was minimized through standardized procedures. Ethical approval was obtained (IRB No. FMH-04/10/2023-IRB-1322), informed consent was taken, and confidentiality was maintained.

Results

The mean age of the study participants was 45.20 years, with a standard deviation of 21.16 years. Yeast presence was categorized into four groups: NIL 61 (52.6%), FEW 2 (1.7%), MODERATE 28 (24.1%), and MANY 25 (21.6%) (Figure I).
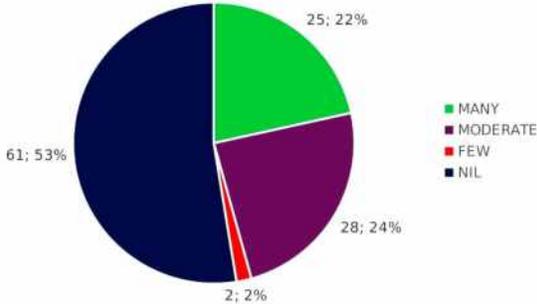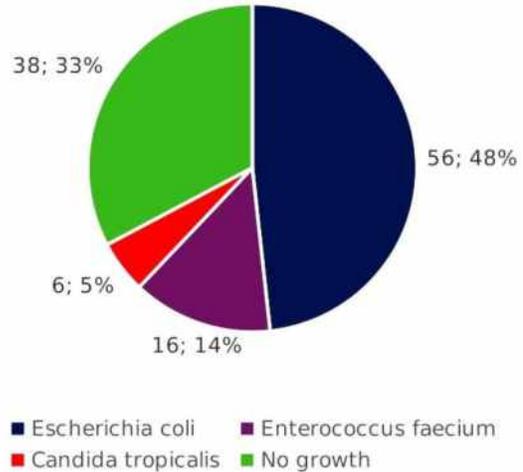

Figure I: *Pie chart representing yeast on urine analysis*
The provided data indicates the distribution of yeast levels categorized by gender. Among males, 19 (16.37%) had no yeast (NILL), 7 (6.03%) exhibited a moderate presence (MODERATE), 10 (8.62%) had a substantial presence (MANY), and 0 patients had a few (FEW). In females, 42 (36.20%) had no yeast, 21 (18.10%) showed a moderate presence, 15 (12.93%) had a substantial presence, and 2 (1.7%) had a few, with a total count of 116 (Figure II). A chi-square test was performed to examine the association between yeast frequency categories and the gender of participants. The results showed no statistically significant association (χ^2 = 2.32; p = 0.510). The likelihood ratio test and linear-by-linear association also confirmed no significance.
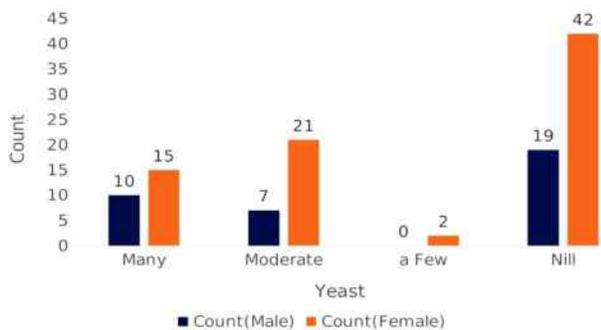
Figure II: *Gender-Based Distribution of yeast*

Analysis of urine culture and sensitivity revealed distinct patterns among uropathogens. Escherichia coli (E. coli) was the most prevalent, accounting for 56 (48.3%), followed by Enterococcus faecium at 16 (13.8%), Candida tropicalis at 6 (5.2%), and 38 (32.8%) showing no growth (figure III).

Figure 3: *Pie chart representing Organisms on urine culture and sensitivity*

The association between yeast levels and symptoms highlights that higher yeast levels correlate with increased frequency of fever, dysuria, lower abdominal pain, and urgency to urinate (Table 1). A Pearson chi-square test was conducted to assess the association between yeast frequency categories and participants having fever. The test revealed a statistically significant association (χ^2 = 11.27; p = 0.010). The likelihood ratio test and linear-by-linear association also supported this result. A Pearson chi-square test revealed a statistically significant association between yeast frequency categories and participants suffering from dysuria (χ^2 = 9.98, p = 0.019). The likelihood ratio and the linear-by-linear association were also significant. A Pearson chi-square test showed no significant association between yeast frequency categories and participants having lower abdominal pain (χ^2 = 1.29, p = 0.733); the likelihood ratio and linear-by-linear association also confirmed this non-significance. A chi-square test was conducted to examine the association between yeast frequency categories and participants suffering from urgency to urinate. The results indicated no significant

Table 1: *Correlation between yeast presence in urine samples and four common urinary tract symptoms: fever, dysuria, lower abdominal pain and urgency to urinate.*

Yeast	Fever n (%)	Dysuria n (%)	Lower Abdominal Pain n (%)	Urgency To Urinate n (%)
NILL	33 (28.44)	57 (49.13)	45 (38.79)	55 (41.41)
MODERATE	15 (12.93)	24 (20.6)	19 (16.37)	26 (22.41)
MANY	5 (4.3)	17 (14.6)	17 (14.6)	23 (19.82)
FEW	2 (1.7)	2 (1.7)	2 (1.7)	2 (1.7)

association ($\chi^2 = 0.39$; p = 0.942). Similarly, the likelihood ratio test and linear-by-linear association were also not significant.

Discussion

Patients with diabetes are highly susceptible to UTIs, which can lead to severe complications such as sepsis and septic shock. Diabetic kidney disease, or nephropathy, further increases infection risk due to factors like neurogenic bladder and urine stasis. Decreased immune response in diabetic patients can also facilitate microbial adhesion to uroepithelial cells, compounded by the promotion of bacterial growth by hyperglycemia. We observed the prevalence of Candida species in approximately 6 (5.2%) patients, a finding that aligns with the results reported in a similar study. However, in our setting, Candida tropicalis is more prevalent in diabetic patients.[4] Fungal UTIs in adults, particularly among the elderly and those with conditions like diabetes, were the focus of our extensive study. Many patients, primarily women, displayed funguria, but over half went untreated or received varied treatments like fluconazole or amphotericin B irrigation, with similar outcomes observed. Importantly, funguria resolved without antifungal therapy in many cases, highlighting the need for a nuanced clinical approach. Our study primarily observed funguria and physicians' responses rather than conducting treatment trials, revealing gaps in follow-up urine cultures and raising questions about clinical judgments. Further research is necessary to understand physicians' attitudes towards funguria and the efficacy of different treatment approaches.[9,10] Assessing candiduria's clinical significance-whether it indicates infection, colonization, or contamination, is challenging. Our study found varied yeast levels; most had no yeast 61 (52.6%), followed by moderate 28 (24.1%) and many 25 (21.6%) levels, with few cases showing minimal yeast 2 (1.7%). Co-occurrences of yeast and fever varied: 33 cases with no yeast and fever, 15 cases with moderate yeast and fever, 5 cases with many yeasts and fever, and 2 cases with few yeasts and fever. We also explored yeast presence and urgency to urinate, as well as yeast presence and dysuria and lower abdominal pain, with similar distributions across yeast levels. Literature suggests only 2-4% of funguria had symptoms suggesting urinary tract infection, including dysuria, frequency, urgency, flank pain, or hematuria. Fever is not definitively linked to funguria; these symptoms may be due to bacteriuria. The urinalysis results in both our study and the literature align, indicating a lack of consistency in symptoms and signs of infection among patients with funguria.[9] The observed gender distribution in our study, with a higher prevalence of females in UTI cases; 80 (68.96%), aligns with the existing literature highlighting the increased susceptibility of women to UTIs due to anatomical factors, such as shorter urethral length, and peri- and postmenopausal women include hormonal changes (estrogen insufficiency) and connective tissue aging (urinary incontinence, pelvic organ prolapse). In our study, the estimated mean age was 45.20 years, with a standard deviation of 21.16 years, and this age group is consistent with findings from previous studies.[12] The debate continues regarding the interpretation of yeast in urine laboratory findings. Some authors suggest that funguria, particularly in intensive care unit patients, may indicate systemic infection, while others emphasize its often-benign nature in many adults. Earlier work described the natural progression of asymptomatic funguria, highlighting the influence of underlying conditions such as diabetes and the ongoing challenge of distinguishing between true infection and colonization.[13,14] The assumption is that antibiotics alter the usual flora in the perineum, leading to an overgrowth of yeasts. This overgrowth is believed to facilitate their entry along the urethra, resulting in colonization and/or infection of the bladder.[15] Fungi, particularly Candida, are recognized to coexist in the vaginal mucosa as symbiotic organisms, creating a complex ecosystem alongside other bacteria. The defensive role of fungi involves various mechanisms, such as pH regulation, bioactive compound production, competition for nutrients and adhesion sites, and modulation of host immune responses. The composition of the vaginal microbiome varies among individuals, influenced by factors like sexual habits, menstrual hygiene practices, flushing habits, chronic stress, geography, socioeconomic status, and psychosocial pressure, as well as community characteristics.[16,17]

Our study faced limitations in comparing data with non-diabetic patients. An additional constraint was observed: the phenomenon of no growth in around 38 (32.8%) of cases. This phenomenon, potentially linked to faulty techniques and prior antibiotic use, underscores the necessity for careful interpretation and implies opportunities for improving diagnostic methods in urinary tract infections among individuals with diabetes. Collecting data from a single hospital setting using a non-probability sampling technique may result in findings that lack generalizability to the larger population. This method does not allow for the calculation of traditional sampling errors.

Conclusion

In the context of Diabetes Mellitus, UTIs are of particular importance due to various factors such as compromised immunity, altered urinary tract function, and glycosuria.

High prevalence UTIs are common in patients with Type 1 and Type 2 Diabetes Mellitus. It is noteworthy that these urinary tract infections have an increased severity

and are characterized by pathogens with increased levels of resistance, leading to less favourable outcomes as compared to non-diabetics. The prevalence of Candida species, particularly the abundance of Candida tropicalis, in our study highlights diverse uropathogens in diabetics, as Candida albicans is more common in some settings. Gender distribution patterns align with existing literature, emphasizing women's increased susceptibility. Fungal UTIs, notably in the elderly, present challenges. With SGLT2 inhibitors emerging as a major risk factor for fungal urinary infections, it is crucial to consider this complication, especially in patients with cardiovascular disease. We used the Vitek technique for Candida species identification, as it offers a reliable, fast, and cost-effective method in low-income countries. The ongoing debate over yeast in urine analysis findings underscores diagnostic complexities, urging further research for refined approaches. Treatment recommendations focus on treating symptomatic cases, considering the common occurrence of asymptomatic funguria and the possibility that antibiotic treatment contributes to bacterial resistance and colonization of normal flora.

Ethical Approval: The IRB/EC approved this study via letter no. FMH-04/10/3023-IRB-1322 dated November 16, 2023.

Conflict of Interest: None

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Authors' Contribution

SA: Conception.

MKR, MARB: Design of the work.

FS, MMS, AA: Data acquisition, analysis, or interpretation.

MKR, MARB, FS, MMS: Draft the work.

SA, AA: Review critically for important intellectual content.

All authors approve the version to be published.

All authors agree to be accountable for all aspects of the work.

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