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Diabetes As A Major Risk Factor For Candiduria: Pathophysiology And Clinical Implications

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Abstract
In healthy people, candiduria is uncommon. On the other hand, it is frequently observed in hospitalized patients, particularly in intensive care units (ICUs), where there are numerous risk factors, such as diabetes mellitus, indwelling urinary catheters, and exposure to antibiotics. Patients with diabetes are more susceptible to genitourinary fungal infections caused by Candida albicans and other non-albicans Candida species, according to an increasing number of research studies. Males and females with type II diabetes are more likely to develop UTIs and candiduria due to Candida species. These clinical problems will surely grow more common in the future due to the gradually rising worldwide burden of diabetes. Fungal infections and diabetes are two major contributors to the global illness burden, and both have been on the rise in most developed and developing nations in recent decades. We have emphasised important virulence factors of Candida species in this review work. We have also demonstrated how a variety of pathophysiological variables can interact to cause a candidic infection. Genitourinary fungal infections will surely grow more common in the future due to the continually rising worldwide prevalence of diabetes.

Keywords: *non albicans Candida, Candida albicans, fungal infection, urinary tract infection, Candida spp., diabetes, candiduria*

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I. Introduction

Candiduria (the presence of *Candida* in the urine sample) poses a challenge for medical professionals due to a lack of evidence, in contrast to bacteriuria (the presence of bacteria in the urine).[1-7] The chance of developing candiduria might be raised by predisposing circumstances such as diabetes mellitus, renal transplantation, urine stasis, and hospitalisation. However, one of the primary risk factors for its development is diabetes.[8-10]

In the past few decades however, there has been a rise in the prevalence of non-albicans *Candida* (NAC), being found in 35-65% of all systemic candidiasis, which was 10-40%.[11,12] Growing prevalence rates of non-albicans species of *Candida*, including *Candida glabrata, Candida tropicalis, Candida krusei,* and *Candida parapsilosis*, have been noted throughout the past two to three decades. This has led to significant issues for hospitalised patients because of their high resistance to antifungal medications.[13-15]

Diabetes mellitus is a complex metabolic condition marked by hyperglycemia caused by reduced insulin product, defective insulin action, or both. (American Diabetes Association (ADA) Expert Committee, Report of the expert commission on the opinion and bracket of diabetes mellitus, 1997).[16]

Prediabetes and diabetes mellitus

A person is considered to have "prediabetes" if their glycated haemoglobin(A1C) is between 6.0 and 6.4%, their disabled fasting glucose (IFG), or their disabled glucose forbearance (IGT) are each at high threat of developing diabetes and associated complications.[17]

A collection of metabolic diseases collectively referred to as diabetes are distinguished and characterised by the existence of hyperglycaemia when therapy is not received. The diverse etiopathology involves abnormalities in the metabolism of carbohydrates, fats, and proteins as well as deficiencies in the secretion, action, or both of insulin.[18]

II. Type 2 Diabetes

Type 2 diabetes is the most prevalent form of diabetes, counting for 90 - 95% of all diabetes circumstances. It's distinguished by insulin action and stashing diseases, with either being the major characteristic. These people don't bear insulin treatment to survive when they're diagnosed with this type of diabetes, and they constantly do so throughout their lives. There are conceivably multitudinous reasons for this type of diabetes. Although the particular aetiologies are unknown, autoimmune destruction of β- cells isn't observed. The maturity of type 2 diabetes cases, but not all, are fat, redundant weight produces some position of insulin resistance. The threat of developing type 2 diabetes increases with age, rotundity, and lack of physical exertion. Type 2 diabetes has significant family aggregation, so individualities who have a parent or sibling with the condition are at an advanced threat. Women with a history of gravid diabetes and those who are fat, hypertensive, or dyslipidemic are also at advanced threat.[19]

Risk factor of diabetes

Diabetes is a prevalent medical condition. Environmental, behavioural, and genetic variables may all have an impact on its development. The risk factors for diabetes type 1 and type 2 differ. When the insulin-producing cells of the pancreas are damaged, type 1 diabetes results. Although the exact origin of the harm to these cells is unknown, the body's unusual response to the cells is most likely responsible for it. A viral or other infection may be the cause of this. Usually diagnosed in persons in their forties or fifties, type 2 diabetes is also known to affect Black and South Asian people at earlier ages. However, it is increasingly being detected in younger, overweight individuals. The development of type 2 diabetes is caused by either insufficient insulin production or improper use of the insulin that is generated. Type 2 diabetes risk might be decreased by improving one's lifestyle.[20]

Diabetes and infection

In addition to organ problems including neuropathy, retinopathy, and nephropathy, diabetics also have both simple and complex infections. Additionally, people with diabetes mellitus are more likely to have infections, and these infections lead to complications and death more often than they would in healthy people.[19]

1. Respiratory infections
2. Urinary tract infections
3. Gastrointestinal and liver infections
4. Skin and soft tissue infections
5. Head and neck infections

Pathogenesis and risk factors of UTI in diabetes

Most studies indicate that people with diabetes mellitus (DM) have a three-fold higher prevalence of Asymptomatic bacteriuria (ASB, and there is evidence that ASB increases the risk of symptomatic UTIs (Urinary tract infection) in this particular population).[21-24] Patients with diabetes may be more susceptible to UTIs due to a number of possible processes specific to their condition.[25] Pathogenic bacteria may proliferate in urine with higher glucose contents.[26,27] Nevertheless, a number of studies failed to detect a correlation between diabetes patients' risk of UTI and their HbA1c level, which is a proxy for glycosuria; also, sodium glucose cotransporter 2 inhibitors, which raise glycosuria, did not raise the incidence of UTI.[28] Although haematogenous seeding of the urinary system is rare, UTI can sometimes happen after *Candida sp.* fungemia or *Staphylococcus aureus* bacteraemia. It is unknown how significant lymphatic dissemination of uropathogens is in the pathophysiology of UTI.[19]

Mechanisms involved

Differences in the host response between diabetic and non-diabetic patients, differences in the infecting microbial strains, or a combination of the two could be the cause of the higher incidence of UTIs in diabetics. Although the precise mechanisms are still partially explained, several possible theories have been proposed to shed light on the relationship between UTI and diabetes, including changed growth circumstances (caused by diabetes-related neuropathy and glucosuria), as well as changed pathogen-host relationships like diabetes-related.[29,30]

III. Funguria

Candida species are the most commonly identified fungi in urine and candiduria is the presence of *Candida species* in the urine.[31] Although they are less frequent in the community, *Candida* UTIs are primarily observed in hospitalised patients. The most frequent cause of candiduria in patients is either colonisation or contamination. It's critical to determine if this discovery is the result of colonisation or a genuine *Candida* UTI. Regretfully, there are no precise standards or recommendations for diagnosing *Candida* UTIs or differentiating between infection and colonisation.[32]

Candida

Candida is a form of yeast-like fungus that can be identified by its oval or round yeast cells, pseudo hyphae, and true hyphae.[33] There are about 200 species in the genus *Candida*. This genus of yeasts is a unicellular fungus that mostly reproduces by budding. Hippocrates was the first to describe a yeast infection and the first to describe thrush in the fifth century.[34] The most harmful species to humans is *Candida albicans*, which is also considered commensal in the vaginal tract, Gastro intestinal tract (GIT), and oral cavity. It causes systemic and local infections, especially in immunocompromised people, such as those with HIV/AIDS, diabetes, steroids, antibiotics, cancer patients undergoing chemotherapy and radiation therapy, people with urinary and central line catheters, and others.[33] About five species of *Candida* with medicinal significance had been identified by 1963. The species were *Candida albicans, Candida stellatoidea* (now used interchangeably with *Candida albicans), Candida parapsilosis, Candida tropicalis,* and *Candida gulliermondii*.[35] However, the advent of novel cancer treatment modalities in the 1960s, the rise in central venous catheter use, improvements in average life expectancy, and other medical advancements led to a corresponding increase in the central venous catheter use, improvements in average life expectancy, and various other advances in medicine. Seven of the minimum 17 species of *Candida* that are now known to exist have been connected to human disease.[36] However, a trend of infections with these non-albican *Candida species* has just emerged, and these infections have been increasing in frequency recently.[37]

Taxonomic classification:

The taxonomical classification of *Candida species* are as follows:
Kingdom - Fungi
Phylum - Ascomycota
Subphylum - Saccharomycotina
Class - Saccharomycetes
Order - Saccharomycetales
Family – Saccharomycetaceae
Genus - Candida

Species of Candida

Here are some common species of *Candida: Candida albicans, Candida glabrata, Candida parapsilosis, Candida tropicalis, Candida krusei, Candida dubliniensis, Candida guilliermondii, Candida kefyr, Candida famata, Candida viswanathii*

Medical importance

Numerous yeast species have the capacity to induce illness in the environment that predisposes them. Risk factors for yeast infections include having HIV, diabetes mellitus, using broad-spectrum antibiotics, catheters, burns, surgery, steroids, neutropenia, and cellular immunological weaknesses. All things considered; *Candida* continues to be the most commonly isolated fungal agent. The sixth most prevalent nosocomial infection in the US is *Candida*. *Candida* is the fourth most common cause of bloodstream infections, after coagulase-negative *Staphylococcus* and *Enterococcus species*, according to a study by Pfaller and colleagues that examined nosocomial bloodstream infections that occurred in 55 medical centres in the United States between 1995 and 1998. This data was the same as that produced by the Centres for Disease Control and Prevention (CDC) in the late 1980s and early 1990s, and it indicated that the crude mortality rate of *Candida* was 40% (crude mortality is a measure of population illness).[33]

IV. Virulence Factors Of *Candida*

Due to several virulence factors that aid in pathogenesis, *Candida albicans* is typically the organism most frequently responsible for *Candida* infections. These include adhesion (the biomolecules that recognise the host), morphogenesis (the reversible change from unicellular yeast cells to filamentous growth forms), and secreted phospholipases and aspartyl proteases. To put it simply, a virulence factor is any characteristic of a fungus that makes it more virulent in the host or boosts the organism's ability to bind to host cells.[38]

1. Morphogenesis (polymorphism):

The polymorphic fungus *Candida albicans* can develop in various forms, mainly yeast, pseudohyphae, and hyphae. Its parallel-walled, true hyphae and ovoid-shaped budding yeast forms are the most significant for its pathogenicity. While the yeast form is thought to play an important role in the spread of *Candida albicans*, the hyphae form is more common for an infection. Other than serving as a transitional phase between yeast and hyphae, the function of pseudohyphae is not well understood.[39] Changes in pH, temperature, carbon dioxide levels, nutrient availability, and quorum-sensing chemicals (farnesol, tyrosol, and dodecanol) are some of the variables that might alter morphology.[40]

2. Adhesion:

Special sets of glycosylphosphatidylinositol (GPI)-linked cell surface glycoproteins enable *Candida albicans* to adhere to microorganisms' surfaces. The eight sets of agglutinin-like sequence (ALS) genes that encode these glycoproteins are Als1-7 and Als-9. Since the Als-3 gene is elevated when oral and vaginal epithelial cells are infected, it seems to be the most significant gene for adhesion. It also aids in adhesion, which promotes the production of biofilms.[41]

3. Invasins:

Als-3 proteins have the ability to act as invasions in addition to adhesion, assisting in *Candida albicans's* invasion of host endothelium and epithelial cells. Ssa-1 is another significant invasion gene that often codes for heat-shock proteins. In essence, the pathogen's surface-specialised proteins mediate binding to host ligands, such as endothelial cells' N-cadherin and epithelial cells' E-cadherin, which causes the host cells to absorb the fungal infection. The active entry of *Candida albicans* into host cells through an unidentified hyphae-related mechanism is another invasion strategy.[42]

4. Hydrolytic enzymes*:*

Many pathogenic microorganisms have constitutive and inducible hydrolytic enzymes that break down, modify, or degrade membrane integrity, causing host cell malfunction or disruption and assisting in the invasion of host tissues. Aspartic proteinases (Sap) and phospholipases (PL), two of the several secreted hydrolases produced by pathogenic species of *Candida*, have been the subject of extensive research.[38]

5. Aspartic proteinases:

Extracellular aspartic proteinases (Saps) are secreted by medically significant yeasts of the genus *Candida* and are particularly interesting as virulence factors. *C. albicans, C. dubliniensis, C. tropicalis,* and *C. parapsilosis* all share this trait. These yeasts generate carboxyl proteinases, which are enzymes that can break down human proteins such as albumin, haemoglobin, keratin, and secretory immunoglobulin A.[43] The Sap family consists of at least ten proteins. According to in vivo research, only yeast cells express SAP genes 1, 2, and 3, while *C. albicans* undergoing a transition from yeast to hyphae at neutral pH have been found to express SAP genes 4, 5, and 6.[44]

6. Phospholipases and lipases:

Extracellular phospholipase (PL) has been studied in a number of pathogenic fungi, such as *Aspergillus fumigatus, Cryptococcus neoformans,* and *Candida albicans*, as a possible virulence factor.[45] Thus far, these enzymes have been divided into four PLs (A, B, C, and D) based on the distinct and particular ester bond that is broken. In *C. albicans*, only Phospholipase B (PLB) activity has been shown. This 84-kDa glycoprotein exhibits lysophospholipase transacylase and hydrolase (fatty acid release) activity.[46] Additionally, *C. glabrata, C. parasilosis, C. tropicalis, C. krusei,* and *C. lusitaniae* have been shown to exhibit phospholipase activity.[45] The adherence-phospholipase and adherence-aspartic proteinase characteristics of *C. parasilosis* strains were found to be correlated in studies by Dagdeviren et al.; PL production seemed to be a significant virulence component in bloodstream infections brought on by *C. parasilosis*.[47]

7. Haemolytic activity:

By exploiting haemoglobin or heme as a source of iron, pathogenic microbes can proliferate within the host. *Candida species* use haemolysins to break down haemoglobin and remove elemental iron from host cells. Haemolysins are hence important virulence factors that can lyse erythrocytes and release haemoglobin.[48,49] The presence of glucose in the growth media may control the production of this haemolytic factor. Moreover, *C. glabrata, C. parapsilosis,* and *C. tropicalis* can also produce total haemolysins (in an absent, partial, or total manner), even though the activity varies by species and strain.[50]

8. Biofilms:

Candida can grow biofilms on both living and non-living surfaces, including catheters and mucosal membranes. In the upper portion of the biofilm, hyphae cells grow following the adhesion of yeast cells to the surface. This ultimately results in a more resilient, developed biofilm and the spread of yeast cells, both of which increase the pathogen's pathogenicity. Bcr1, Tec1, and Efg1 are crucial transcriptional factors in the biofilm development process.[51] According to recent research, biofilms prevent reactive oxygen species from forming and shield *C. albicans* colonisation from neutrophil attack.[52]

V. Types Of Urogenital Candidiasis In Patients With Diabetes:

1. Vulvovaginal candidiasis in females with diabetes
2. Balanitis/balanoposthitis due to Candida spp. in males with diabetes
3. Candidiasis in the urinary tract of diabetic patients

Candidiasis in the urinary tract of diabetic patients

Diabetes increases the risk of urinary tract infections (UTIs) and their associated consequences, including kidney abscesses, pyelonephritis, and emphysematous cystitis.[53-56] Moreover, UTIs are connected with catheterisation and after renal transplantation, but type 2 diabetes mellitus is a known risk factor for acquired UTIs in the community and in clinical settings.[57,58] Due to glycosuria, immune system dysfunction brought on by hyperglycemia, and enhanced *Candida* virulence, patients with diabetes are naturally more susceptible to candiduria.[59-61] Since there are no apparent laboratory standards, it is still debatable how to distinguish candiduria from a frank UTI. *Candida* is also known to be a commensal of the urogenital tract. As a result, its presence in the urine sample raises questions about whether a *Candida* UTI diagnosis can be made with certainty.[62]

In any event, research conducted globally has found that the prevalence of candiduria in people with type 2 diabetes mellitus ranges from 2.27% to 30.00%, with significantly higher rates in females.[63] Significant candiduria was discovered in 7.5% of asymptomatic and 17.1% of symptomatic individuals with diabetes in Ethiopian research; the most frequently implicated species were *Candida albicans, Candida glabrata,* and *Candida tropicalis*.[64] Uncontrolled diabetes, elevated fasting blood sugar, and urine glucose were all significantly associated with candiduria in one Iranian study by Falahati et al..[65] *Candida glabrata* and *Candida albicans* were the most common species, accounting for 50.0% and 31.6% of cases, respectively, followed by *Candida krusei, Candida tropicalis,* and *Candida kefyr*.[54] Another study from Iran supported this, showing that people with type 2 diabetes mellitus who had poor blood glucose control also had a significant risk of candiduria.[63]

VI. Chemotherapy Of Candidiasis:

Since fungi and their human hosts are both eukaryotic, there are very few possible targets for therapeutic action. The range of distinguishable *Candida* infections has changed in recent years, despite the fact that *Candida albicans* is considered to be the most prevalent pathogen among *Candida species*.[66] Making the diagnosis as soon as feasible and choosing the optimal antifungal medication for treatment are especially crucial given the high morbidity and mortality rates linked to invasive fungal infections. Thankfully, the creation of novel antifungal drugs within the past 20 years has enhanced the prevention and management of invasive fungal infections. Four categories of antifungal medications have been authorised thus far to treat invasive fungal infections: (1) Polyenes (amphotericin B and amphotericin B liposomal formulations) that cause fungal cell membranes to become unstable; (2) Analogues of nucleosides (5-fluorocytosine) that disrupt the production of DNA and RNA. (3) Azoles (itraconazole, fluconazole, ketoconazole, and more recent azoles like voriconazole, posaconazole, and ravuconazole) that disrupt sterol synthesis and threaten the integrity of fungal cell membranes; and (4) Echinocandins (caspofungin) that prevent glucan synthesis, increasing permeability and lysis of cell walls.[67,68] The mechanism of action of antifungal drugs are shown in the table 1.[37]

TABLE 1: ***Mechanism of action of antifungal drugs.***

Antifungal Drug Class	Example	Mechanism of Action
Polyenes	Amphotericin B Nystatin	Creates channels that allow cellular contents to escape by interacting with sterols in cell membranes.
Antibiotic	Griseofulvin	Inhibits the movement of microtubules during fungal mitosis.
Azoles	Fluconazole, Itraconazole, Ketoconazole, Etc.	Block the production of ergosterol at the C 14-demethyalse level.
Allylamines	Terbinafine	Squalene epoxidase-level inhibition of ergosterol production
Thiocarbamate	Tolnaftate	Stop ergosterol production at the squalene epoxidase level.
Antimetabolite	Flucytosine	Make 5-fluorocytosine into 5-fluoricil to prevent the production of DNA and RNA.

Profens	Flurbiprofen Ibuprofen	The fungal cytoplasmic membrane is directly damaged.

Source: Rakesh K, Mukhia. Virulence factors, Molecular characterization & Clinical correlation of Candida species isolated from various specimens in a tertiary care hospital. shodhganga. Department of Microbiology, MGM Institute of Health Sciences, India; 2016.

Treatment of candidiasis in patients with diabetes

Even for UTIs brought on by various forms of *Candida*, antifungal treatment is frequently not warranted.[69] It is believed that treating those with risk factors (such as diabetes) should come first, as this could help to eradicate the infection.[70] Fluconazole is recommended to people with symptomatic UTIs brought on by *Candida spp*. and when it is believed that risk factors were eliminated or at least decreased because it has the potential to produce high concentrations in urine.[54] It can be taken orally in a single dose of 200-400 mg daily for 14 days. Because of low levels of echinocandins and other azole antifungals in the urine, amphotericin B deoxycholate is frequently employed for infections caused by *C. krusei* and *C. glabrata*.[54,69] For cystitis, amphotericin B is given intravenously at a dosage of 0.3 - 0.6 mg/kg per day; for pyelonephritis caused by resistant *Candida species*, the dose is 0.5 to 0.7 mg/kg per day or high-risk individuals.[71] Flucytosine at a dose of 25 mg/kg is administered orally four times a day to treat refractory pyelonephritis. Two weeks is the typical course of treatment. It is important to consider the patient's kidney function. Despite being highly successful in eliminating *Candida species*, flucytosine should be used with additional caution because of its toxicity.[72] Since resistance to it develops quickly if taken alone, therapy is not continued for more than seven to ten days. Additionally, a dose of 25 mg/kg of the medication is given every 6 hours.[73] It's crucial to remember that infections brought on by *Candida species* frequently recur.[74]

VII. Conclusions

In conclusion, hospitalised patients, especially those with diabetes, are more likely to have candiduria and genitourinary fungal infections. The incidence of these infections may increase in tandem with the ongoing growth in the global burden of diabetes. For efficient therapy and prevention, it is essential to comprehend the virulence factors of *Candida* and the interactions between different pathophysiological factors.

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