Review Article

Candidiasis: Its Relationship to Diabetes Mellitus

ABSTRACT

Candida causes candidiasis. The genus Candida contains about 200 different species, but only a small proportion of Candida are dangerous and cause more external or internal diseases when they enter the body. Candida albicans is a ubiquitous pathogen, associated with many bacteria in the mouth, throat, and intestines. The immune system and the bacteria present are monitored for Candida, and damage to the immune system or changes in the bacteria can cause Candida to become infected. In general, these infections are limited to the mouth, genital area, and skin, but people with cancer or other serious diseases, such as HIV, have very weak immune systems which make them suffer from more serious diseases.

Key words:*Candida albicans, Diabetes mellitus, Gastrointestinal tract, Yeast.*

1. INTRODUCTION

Candida is a diploid fungus that frequently causes mucosal and systemic infections in humans. This organism can grow normally in humans and animals, but it can cause serious diseases, causing disability and death (1). For the human pathogen Candida spp. A fungal infection occurs in different parts of the body called candidiasis (2). Yeast is a monomorphic, sometimes dimorphic fungus. There are many types of infections that can affect humans, called fungal infections. Fungal infections include superficial skin infections, mucosal infections, and infections that spread to multiple organs (2). Candida species are among the most common fungal infections in the world (candidiasis), but within this genus, Candida albicans is the most common. Although this yeast is responsible for 50% - 90% of

candidiasis in humans, C. albicans is part of the popular flora in half of healthy people. Controlling this yeast is beneficial to the host because it not only reduces the growth of other fungal infections but also improves immune system function (3). Since the end of the 20th century, fungi have been recognized as a major cause of human disease, and immunocompromised patients remain the most prevalent (2). Candidiasis covers a wide range of skin, mucosal, systemic or multiple infections caused by Candida albicans and other Candida species. Diseases can be acute or chronic. Candida is an opportunistic pathogen that can cause disease in debilitated or allergic patients. When Candida spp. Affecting the entire mouth, skin, genitals, respiratory system and digestive tract, the disease is usually superficial. Invasive candidiasis is a disease characterized by serious conditions such as candidemia (affects the blood), meningitis (affects the brain), and endocarditis (affects the heart) (4). Infectious diseases are a major cause of morbidity and mortality with high morbidity and mortality in hospitalized patients and patients with compromised immune systems. The pathogenesis of Candida is a multifaceted process that involves many processes and pathways. It is also a multi-factorial mechanism that involves both host and microbial factors (5). To establish infection, pathogens must escape, reproduce in the host environment, and persist in the host's immune system. The organism must also be able to spread to other body tissues and organs, especially for systemic diseases (6). The most common pathogen is Candida albicans, an endogenous commensal member of the human mucosal microbiota that can be isolated from 30% to 50% of healthy individuals (7). The characteristics of other species may be either ends or roots. Clinicians determine the significance of the Candida species they isolate by considering the following: (i) What type of specimen was obtained from the normal site? (ii) Number of samples with the same organism taken from the same location. If untreated, hospital-acquired bloodstream infections caused by Candida can lead to systemic or disseminated candidiasis. Although the disease is complex, mucosal candidiasis is important in (i) vulvovaginitis (recurrent in some women) and (ii) oropharyngeal and esophageal infections in AIDS patients (7). The genus Candida is one of the most common flora in the human body, and is known to cause fungal infections and infections (8). Changes in Candida spp. From commensal to pathogenic bacteria due to their harmful characteristics, such as adherence to host tissue, biomedical devices (catheters), and biofilm formation. In addition, extracellular hydrolases are also released (9).

Candidiasis is more common in old age and infancy. About 37% of newborns in the United States may develop it in the first few months of life. Children who use oral contraceptives have higher rates of oral candidiasis. In women, this happens during pregnancy. Oral ulcers are the first symptom of HIV infection. Oral disease is more common

and more common in people with food allergies. Cancer is similar in men and women. Although Candida albicans is the most common cause of candidiasis, non-Candida species have increased significantly in recent years. It is important to be aware of the non-albicans Candida species because this depends on the treatment and some drugs (such as the commonly used non-albicans Candida species) can become resistant to fluconazole. The incidence of invasive and disseminated candidiasis has increased worldwide, and people with weakened immune systems are the most vulnerable group (10). Worldwide, C. albicans is the most common pathogen responsible for infectious diseases, but its frequency of isolation is decreasing. This species includes C. glabrata, C. tropicalis, and C. parapsilosis. In particular, several studies have documented a significant increase in C. glabrata with increasing patient age and attendance at a cancer center (11). However, the number of Candida species varies worldwide, and C. glabrata is rarely found in Latin America and some Western European countries. Candida tropicalis and Candida parapsilosis are the most common non-albicans species in Latin America (11).

2. RELATIONSHIP BETWEEN CANDIDIASIS AND DIABETES

Adults with candidemia have higher rates of diabetes, heart disease and cancer. Several studies have been conducted on the relationship between diabetes and candidiasis (12), in part because diabetics are more susceptible to fungal infections than non-diabetics (13). There are several explanations for the prevalence of Candida infections in DM patients, depending on whether the infection is local or systemic. appearance. Yeast adhesion to epithelial cell surfaces, increased salivary glucose, decreased salivary flow, microvascular contraction, and decreased neutrophilic Candida activity are some of the host factors that leading to Candida overgrowth and subsequent infection. These conditions are more dangerous when glucose is present (14), a number of degradative enzymes are secreted, or the patient has systemic immunosuppression. These factors significantly affect the balance between the host and yeasts, promoting Candida spp transition from commensal to pathogen and resulting in infection. In fact, (15) reported in a recent study that diabetic patients have a higher prevalence of intestinal Candida albicans colonization. In fact, patients with a high prevalence of intestinal Candida albicans may be more likely to develop type 1 diabetes. Through a process known as phenotypic switch system, or white-opaque transition, Candida albicans is also known to wait for a change in some element of the host physiology that ordinarily

suppresses growth and invasiveness. This allows you to switch between different cell types in a flexible and traditional manner. In some cases, it occurs at the stage of the disease in diabetic patients and continues to occur throughout the disease (16). Although yeast is a natural part of the intestinal microbiota, the cell count does not exceed 10 colony forming units (CFU)/g feces. However, type 1 and type 2 diabetes patients with poor glycemic control have been found to have higher levels of Candida. Their stools are higher than healthy people. The first cause of this colon is a direct result of poor immune function or high blood sugar levels in diabetic patients without proper glycemic control, thus creating an environment good for fungal colonization (17). Another study showed that total intestinal CFU in type 1 diabetic patients colonized by Candida albicans was significantly increased, up to 40%, compared to 14.3% in healthy individuals. This may affect the reduction of commensal bacteria, due to competition between yeast and bacteria. In addition, type 1 diabetes affects the balance of the intestinal flora, and this flora can disrupt the balance of the intestinal flora (18). Kowalewska et al. Researchers investigated the relationship between serum levels of interleukin 12 (IL12) in the gastrointestinal tract in children and adolescents with type 1 DM and the proportion of remaining yeast-like fungal colonies. in the gastrointestinal tract. However, more studies are needed to verify the antifungal activity of IL12 (19). The emergence of drug resistance in Candida isolates has a significant impact on morbidity and mortality. and changes in the epidemiology of Candida spp. Natural plants. By shifting colonization to Candida species that are more naturally resistant, such as Candida glabrata, Candida dubliniensis, and Candida krusei, the widespread use of medications, especially azoles, has fostered the selection of resistant species (20). Presently, the world distribution of Candida sp. is a feature of the epidemiology in the area, but it indicates a predominance of Candida albican, Candida glabrata, Candida tropicalis, Candida parapsilosis and Candida krusei. It has been confirmed that 90% of fungemia cases are attributed to Candida spp. and the mortality has ranged from 40% to 80% in immunocompromised hosts. In addition, mortality rates are also high in non-immunocompromised patients (60%) and diabetic patients (67%) (21). The main sugars that affect the pathophysiology and diet of diabetes are glucose and fructose, but other simple carbon sources play an important role in the growth of Candida. in diabetic patients. To better understand nutrient

capture strategies and their possible association with hyperglycemic conditions in diabetic patients, (22) the growth rate of C. albicans was studied in the presence of various sugars and fructose. The authors found a direct correlation between sugar levels and the growth of Candida albicans, which may explain why people with diabetes do not control yeast infections. Surprisingly, fructose has the ability to inhibit Candida albicans. This suggests that foods rich in fructose can prevent the growth of candidiasis. This is a great benefit for individuals using oral candida remedies. biofilm (22).

3. PARTICULAR FEATURES OF CANDIDA SP. THAT INCREASE THE INCIDENCE OF CANDIDIASIS IN DIABETIC PATIENTS.

3.1 Enzymatic activity

Several studies have found a relationship between hydrolase activity and increased pathogenicity of Candida spp. (twenty-three). Research has shown that people with diabetes Candida spp. Due to the high concentration of sugar in the blood, the hemolytic activity and the esterase activity of the liver are high, because the activity of sulfur increases in diabetic patients. The same authors hypothesized that this species may be more pathogenic under different conditions such as DM (24). Aspartic acid protease (SAP) has also been studied and can degrade various substrates to form host proteins in the oral cavity. This enzyme is thought to be helpful against Candida spp. It gets the nitrogen it needs for growth, sticks and gets into the oral mucosa, or both. They can also increase vascular permeability, leading to inflammatory responses and clinical symptoms, which may compromise the host's humoral defenses (25). When these enzymes catalyze the accumulation of inflammatory cells and plasma proteins, a number of inflammatory mediators are released into the body. Recent studies have shown that C. albicans hyphae secrete a cytolytic peptide toxin called candilysin, which triggers epithelial damage and death (26). This was the first peptide toxin discovered in a bacterium. In oral epithelial cells, candidalicin causes the release of lactate dehydrogenase (LDH), a marker of membrane instability and cell damage. Importantly, this study also shows that C. albicans mutants that completely delete the ECE1 gene region, or the

kandolysin coding region, are highly invasive in vitro but unable to cause tissue damage, or release cytokines, and the mice are severely affected by those models.

3.2 Biofilm formation

Biofilms are microbial communities embedded in the extracellular matrix that offer significant resistance to antifungal treatment and enhance the host's immune response. These communities can develop on biotic (e.g. oral mucosa) and abiotic (e.g. ductal) surfaces (27). With a mortality rate of nearly 40%, candidemia is the most common fungal infection in the world. Candida species are often implicated as the cause of candidemia, urinary tract infections, and nosocomial pneumonia. Most of these diseases are related to the use of medical equipment and the formation of biofilms on them (28). Central venous catheters used for fluids, nutrition, and medications are the most commonly used medical devices. Contamination of catheters or IV fluids can occur from the patient's skin, from the hands of the healthcare provider, or from seeping into the catheter from existing wounds. In rare cases, if Candida spp. At first it remains in the pus as a symptom, then it begins to show pathogenic behavior, entering the intestinal mucosa and spreading throughout the bloodstream. Therefore, colonization of endogenous channels by circulating yeast may occur. This condition often occurs in cancer patients due to damage to the intestinal mucosa caused by chemotherapy (29). The main cause of bleeding in other patients is contaminated lungs, followed by widespread invasive candidiasis. In order to achieve blood elimination and improve results, it is recommended to remove the catheter in patients who have distributed Candida species. Infection. It is hypothesized that the high glucose requirement for Candida spp. Biofilms that form may require the formation of a polysaccharide matrix that is released by stagnant cells and provides protection against environmental threats (30). It has been determined that Candida spp. Its clinical origin is relevant for biofilm formation. Antifungal drugs are less effective in treating biofilm infections than infections caused by planktonic cells. In addition, isolates of Candida spp. Biofilms produced by DM patients have high pathogenic potential (30). Medical devices are common in society.

4. TYPES OF CANDIDIASIS

4.1 Oral Candidiasis

As one of the most common fungal infections, oral candidiasis is becoming increasingly common (31). Oral candidiasis can be recognized by different patterns of mucosal changes, such as erythema, pseudomembranes, and thick plaques (biofilms). If people with type 1 DM were compared to people with type 2 DM, the prevalence of Candida spp. Colonization was observed (84% and 68%, respectively), but occurred in 27% of the nondiabetic group. In addition, the study explains that the disease has no effect on this colony. However, if the immune system is weak, the disease can spread, which is the beginning of the disease. These diseases remain a major health problem (32). Causes and Risk Factors for Oral Candida Although there are many factors that can cause oral Candida infections, the most common are lesions on the tongue, smoking, wearing dentures, and Disease prevention (such as diabetes) can all affect oral Candida infections. Transmission and development of oral candidiasis (33). The factors influencing the high incidence of oral candidiasis in diabetic patients are shown in Table 1. Biofilm formation and higher levels of enzyme activity are the most striking features. two of oral candidiasis. A study by Samaranayake et al was done on glucose-infused saliva batch cultures. The results showed that pyruvate and acetate were the main ion species for the rapid decrease in pH of Candida spp. Some authors suggest that at low pH values around 2-4.14, the yeast is better able to adhere to the epithelial cells and the acrylic surface of the teeth. Balan and colleagues reported that changes in the oral environment during hyperglycemia increase glucose uptake and acid production, favoring the transition of Candida from commensal to pathogenic bacteria (34). Diabetes is a condition in which plasma glucose is above the normal range but below clinical diabetes. Javed and his colleagues isolated Candida spp. 100% of diabetic patients and 65.7% of controls were studied, and diabetic patients (48.7%) were found to carry more C. albicans than controls (25.7%). They also observed the presence of Candida spp. Salivary flow is low in prediabetic patients, independent of glycemic control (35).

Table 1. Physiopathology and etiology related to the occurrence of oral candidiasis in diabetics.

CONDITIONS	PATHOPHYSIOLOGY
Uncontrolled hyperglycemia (high HbA1c) and high glucose levels in saliva	-Uncontrolled hyperglycemia may cause intensification in salivary glucose levels because in diabetics the basement membrane of the parotid salivary gland is more permeable -High glucose levels allow *Candida* spp. to multiply, even in the presence of

	normal bacterial flora -During hyperglycemic episodes, the chemically reversible glycosylation products with proteins in tissues and the accumulation of glycosylation products on buccal epithelial cells may sequentially increase the number of available receptors for *Candida* spp. -Glucose suppression of the killing capacity of neutrophils, emphasizing colonization (immunosuppression) -Glucose, maltose, and sucrose boost the adhesion of *Candida* to buccal epithelial cells
Lower salivary Ph	-The growth of *Candida* in saliva is accompanied by a rapid decline in pH, which favors their growth and triggers the extracellular phospholipase (PL) and acid proteases, increasing the yeast adhesion to oral mucosal surfaces
Tissue response to injury is diminished	-Diabetes mellitus (DM) is known to diminish the host resistance and modify the tissue response to injury. This can result in severe colonization, even in the absence of any clinically evident oral candidiasis and possibly with further dissemination via the blood.
Oral epithelium	-It is most probable that the host oral epithelium of patients with diabetes favors the adhesion of colonization and subsequent infection.
Poor oral hygiene	The lack of control of the oral environment, especially concerning the prevention of dental caries (coronary, root, and periodontal), leads to a higher rate of oral candidiasis, especially in DM older patients
Aging Gender	Diabetic women, orally colonized with *Candida* spp. have higher oral glucose levels than diabetics without oral *Candida* spp.
Prostheses	Inadequate use of prostheses, together with inadequate hygienization, favours the growth of *Candida* spp.
Drugs	Xerostomia (abnormal lack if saliva): *Candida* spp. stagnation and growth on oral tissues

4.2 Vulvovaginal candidiasis

The exact relationship between DM and vulvovaginal candidiasis (VVC) remains to be elucidated, but several studies suggest that the decreased immune response associated with DM is the main cause of return of VVC. In addition, it is known that the complications associated with clinical vaginitis can be reduced through the management of diabetes, and the type, weight, and degree of diabetes control are risk factors. which may be related to the prevalence of VVC (37). Candida albicans was the most common species isolated, followed by Candida glabrata in both diabetic and nondiabetic patients. Studies have shown that NCAC infections increase over time, especially C. glabrata, which is more often associated with VVC in African and Asian countries (38). Table 2 lists cellular factors that increase the risk of VVC and can be reduced by proper diabetes management. Several studies have investigated the relationship between VVC and DM. Compared to non-diabetic women in Brazil, Guimarães et al. (39) studied the prevalence of isolates of Candida spp. and several clinical features: 18.8% of women with diabetes and 11.8% of control women had a type of fungus. The diabetic group had more symptoms (VVC + recurrent VVC (RVVC) = 66.66%) than colonic women (33.33%) and showed more colonics, VVCs, and RVVCs than controls. To identify microorganisms associated with VVC, Sherry et al. (40) studied the epidemiology of VVC in a cohort. Scientists found that although Candida albicans is the most common type of Candida, NCAC is now becoming more common. It has also been reported that the ability to form heterogeneous biofilms is associated with reduced susceptibility to antifungal drugs. On the other hand, C. glabrata was found in 61.3% of cases and C. albicans was found in 28.8% of VVC cases, as reported by (41) in in 11 diabetic patients. Similar findings for women with diabetes were also found in other studies. Many studies show the prevalence of asymptomatic Candida infections. in women with diabetes. Some studies suggest that pregnancy is another risk factor, although the results are tentative, and these studies are informative. Many studies have shown that pregnancy and uncontrolled diabetes increase the risk of the disease. Elevated blood sugar levels and changes in reproductive hormones during pregnancy may be the reasons why diabetic conditions provide the carbon needed for Candida infection and growth. (42), however, did not find a relationship between diabetes and the occurrence of yeast infections in pregnant women, so there is no clear relationship between infections and age, race, or education.

Table 2. Physiopathology and etiology related to the occurrence of vulvovaginitis in diabetics.

CONDITION	PATHOPHYSIOLOGY
Uncontrolled hyperglycemia (high HbA1c) and high glucose levels in vaginal mucosae	- The increased serum glucose level is thought to lead to impaired monocyte, granulocyte, and neutrophil adherence, as well as reduced chemotaxis, phagocytosis, and pathogen killing - Diabetics secretions contain glucose, which can be used as a nutrient by yeasts - pH, nutritional substance, temperature, and adherence capacity in the vulvovaginal tissue may induce *Candida* sp. virulence. The vaginal epithelial cell receptor of fucose supports the adhesion of Candida sp. to vaginal epithelial cells -The rise in vaginal glucose and secretions and activities of hydrolytic enzymes [e.g., secreted aspartyl proteinases (SAPs), PL] increases the pathogenicity of *Candida* spp. -Increased levels of glycogen increase colonization and infection by Candida sp. by lowering the vaginal pH, facilitating the development of vulvovaginal candidiasis (VVC)
Pregnancy	-The increased circulation of estrogen levels and the deposition of glycogen and other substrates in the vagina leads to a 10–50% higher incidence of vaginal colonization by *Candida* spp. -Variability of constitutive defensins (e.g., lactoferrins, peptides) and lysozyme, leading to a poor innate immune response -Hyperglycemia can rise the anaerobic glycolysis in vaginal epithelial cells, increasing lactic acid and acetone production, decreasing the vaginal pH, thus enabling fungal colonization and proliferation
Diabetes type	- The incidence of VVC related to the type 1 DM or type 2 DM and is variable among studies
Aging	- The older one is, the higher VVC prevalence is

4.3 Urinary tract candidiasis

The number of bacteria from the genus Candida associated with urinary tract infections (UTIs) continues to increase, accounting for 10% to 15% of UTIs in hospitals. Many factors can increase the risk of candiduria, including diabetes

mellitus (DM), urinary retention, urinary tract infection, kidney transplant, and hospitalization. In particular, the risk of severe and complicated urinary tract infections has been reported due to abnormalities of the urinary system (43). Fungal infections of the urinary tract increased dramatically in the 1980s; Candida albicans was the predominant species isolated, while NCAC sp. This species is currently the dominant species in many countries of the world (44). The physiology, pathology and etiology related to the development of urinary tract infections caused by Candida spp. Candida and diabetes are shown in Table 3. Therefore, reducing risk factors, such as improving glycemic control and removing a urinary catheter, can reduce candiduria (45). According to the findings of Falahati et al. (45) Studies have shown a significant relationship ($p < 0.05$) between candiduria and female gender, high fasting and urine glucose, nondiabetic (HbA1c $\leq$ 8), and urine pH acid. The pathogens identified were Candida glabrata (n=19.50%), Candida albicans (n=12,31.6%), Candida krusei (n=4,10.5%), Candida tropicalis (n=2.5, 3%) and Candida kefir (n). = 1, 2.6%). The study concluded that considering the prevalence of candidiasis in patients with diabetes, it is necessary to focus on the management of diabetes, previous conditions, and the relationship between the disease. diabetes and candidiasis. A 2018 study evaluated candiduria in patients with type 2 diabetes. In fact, the results showed that people with type 2 diabetes had a higher incidence of candida and poor blood sugar. Although NCAC sp. albicans, but this difference was not significant (42). Ismo et al. (46) identified fungi that cause urinary tract infections in asymptomatic and symptomatic diabetic patients, and the associated risk factors. This was done through a cross-sectional study. Major cancer occurred in 7.5% and 17.1% of asymptomatic and symptomatic type 2 diabetes patients, respectively. Among Candida isolates, 84.2% were found in asymptomatic diabetic patients and the remaining 15.8% were found in symptomatic patients. Rizzi and Trevisan studied the prevalence and importance of urinary and genitourinary (GI) infections in diabetes and the effect of sodium glucose cotransporter 2 (SGLT-2) inhibition on these complications. The results show that diabetics have a high risk of urinary tract and gastrointestinal infections. The authors concluded that only gastrointestinal medications were associated with poor glycemic control. In a one-year, single-center prospective study conducted at Dayanand Medical College and Hospital, Garg et al looked at 151 diabetic and non-diabetic female patients diagnosed with urinary tract infections. Uncontrolled diabetes is more common in acute urinary tract infections such as pyelonephritis and emphysematous pyelonephritis.

Table 3. Physiopathology and etiology related to the occurrence of urinary tract infections and systemic candidiasis in diabetics.

Condition	Pathophysiology
Uncontrolled hyperglycemia (high HbA1c) and high glucose levels in urinary tract (UT) mucosae or blood	- Favorable microenvironment for the gas-forming organisms, such as *Candida* spp to grow
Gender	- An association between candiduria and being female
Drugs	-SGLT2 inhibitors (e.g., dapagliflozin, canagliflozin, tofogliflozin) administration leads to a greater susceptibility to urinary tract infection (UTI) -Association with a persistent increase in urine glucose concentration

(36)

4.4 Systemic candidiasis

Diabetes is known to increase the risk of systemic candidiasis. The development of microvascular disease, impaired host defense, and diabetic vasculopathy are the most important factors (47), which increase hypoperfusion and hyperglycemia and lead to neutrophil and lymphocyte death. and reduce opsonization effects. A common clinical finding in hospitalized patients, especially in intensive care units, is catheter-associated candiduria, which is closely related to the biofilm. The main risk factor for Candida spp. The diagnosis was DM. According to other studies, Candida spp. According to Padawer et al., it is the second most common pathogen associated with catheter-related or asymptomatic colonic urinary tract infections. (36) Similar observations were made earlier. To identify common risk factors, clinical decision rules, risk prediction models, and published analyzes of invasive fungal disease (IFD) in critically ill older patients were systematically reviewed. The study showed a 16.6% prevalence of invasive candidiasis in patients with diabetes mellitus (DM), recent hemodialysis, total parenteral nutrition, or general antibiotics, compared to 16.6% in patients without diabetes mellitus (DM) and new patients. - starting hemodialysis. The prevalence of invasive candidiasis was 5.1% among patients undergoing hemodialysis, using total parenteral nutrition, or receiving systemic antibiotics. In addition, Michalopoulos et al. A univariate regression analysis study conducted between 1997 and 2002 found DM to be a significant risk factor for candidemia and a unique predictor of candidemia. Candida albicans (70%), *Candida parapsilosis* (10%), *Candida glabrata* (6.7%), *Candida tropicalis* (6.7%), and *Candida krusei* (6.7%) were isolated from candidemia patients. Central venous catheter tips and blood

(89.5%) were used simultaneously to isolate *C. albicans*. Khatib *et al* conducted another retrospective study of candidemia in hospitalized adults from 2007 to 2015. (48) Most of the isolates (97.5%) were *C. albicans*, and *C. glabrata* was more common in diabetic patients (52.9% versus 32.0% in non-diabetic patients; p = 0.004) from the womb. Findings suggest that species may differ in colonization dynamics or pathogenicity (48).

4.5 Other candidiasis

Patients with diabetes mellitus (DM), recent hemodialysis, total parenteral nutrition, or patients receiving general nutrition due to elevated blood glucose levels may more susceptible to dermatophyte infection. This disease is usually characterized by a large biofilm that requires the use of medical devices to reduce the lesion. Foot infections (tinea pedis and onychomycosis) are very dangerous in diabetic patients due to the high prevalence of diabetic foot in these patients (49), and onychomycosis is mainly caused by *Candida albicans*. and *Candida parapsilosis*, known to diabetics. suffering from tinea pedis and onychomycosis. Therefore, this disease is considered a predictor of the development of diabetes. Table 4 lists risk factors for tinea pedis and onychomycosis. Non-*albicans Candida* species may be responsible for the formation of biofilms that appear to be the main cause of diabetes, which is a major problem in diagnosis and treatment. According to recent studies, Candida tropicalis (34.6%), Candida albicans (29.3%), *Candida krusei* (16.0%), *Candida parapsilosis* (10.6%) and *Candida glabrata* (9.33%) are the most common species of *Candida* (50).

Table 4. Physiopathology and etiology related to the occurrence of nail fungal diseases linked to *Candida* spp. in diabetics.

Condition	Pathophysiology
Uncontrolled hyperglycemia (high HbA1c) and high glucose levels in vaginal mucosae	-Circulatory disorders affecting the lower extremities (peripheral circulation), peripheral neuropathy, and retinopathy - Nail thickness is associated with an elevated HbA1c value - Diabetics using hemodialysis exhibit a higher probability of onychomycosis

Duration of DM	-More time leads to a higher probability of onychomycosis
Gender Aging	-Being male and being older are directly associated with onychomycosis in diabetics

(36)

5. CONCLUSIONS

Most people with diabetes live in developing countries. Diabetes is a chronic metabolic disease. In patients with diabetes, the immunocompromised state is often accompanied by poor glycemic control and many secondary diseases. Biofilm fungal infections in diabetics are known to be more difficult to treat than in healthy individuals, especially when exposed to medical devices. Oral thrush, VVC, and severe candidiasis are the most common types of candidiasis in DM patients. Reporting these cases and the results of the chosen therapy is essential if we are to continue to treat these patients in the most effective manner.

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