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Review Article

Is diabetes a risk factor for fungal infections?

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Abstract

Diabetes is a metabolic disease characterized by abnormally high blood glucose levels and associated with complications. In diabetes, with dysregulation and the loss of functions of immune system cells, phagocytic activity, which is necessary to control and kill pathogens and process them for antigen presentation, is reduced. Thus, individuals with diabetes are more prone to infections and more susceptible to certain complications related to infections. Diabetic patients are particularly susceptible to fungal infections because their vascular and immunological systems are compromised. Many different types of fungal infections occur in people with diabetes, but one type with a particularly serious risk of death is mucormycosis. To obtain successful results from combined antifungal treatment and surgical interventions, it is necessary to address the underlying predisposing factors.

Keywords: Diabetes, fungal infections, mucormycosis.

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INTRODUCTION

Diabetes is a metabolic disease characterized by abnormally high blood glucose levels and associated with complications. Over time, high levels of blood glucose can damage blood vessels, causing microvascular and macrovascular complications (1). These complications affect all systems of the body. Moreover, diabetes and its complications increase oxidative stress. Increased oxidative stress causes damage to cellular organelles and enzymes together with impairment of defense mechanisms (2). Type 1 diabetes (T1D) is characterized by hyperglycemia caused by direct deficiency of insulin, while type 2 diabetes (T2D) is characterized by hyperglycemia caused by indirect deficiency of insulin (3). Gestational diabetes (GDM), or glucose intolerance that occurs during pregnancy, is one of the most common medical complications of pregnancy and affects more than 14% of women worldwide (4). It has been reported that the risk of developing T2D in women with GDM is approximately 40% higher in the 10-15 years after pregnancy (5). People with diabetes are more prone to infections and more susceptible to certain complications related to infections. This is because in cases of diabetes, with dysregulation and the impairment of functions of immune system cells, phagocytic activity, which is necessary to control and kill pathogens and process them for antigen presentation, is reduced. Both neutrophil function and glucose control are critical in reducing the risk of fungal infections. Polymorph nuclear neutrophils (PMNs) from individuals with diabetes have also demonstrated lower phagocytic capacity compared to PMNs obtained from individuals without diabetes (1,6). There may be an increase in urinary tract infections due to a decrease in the antimicrobial activity of the urine. Skin ulcers and lesions characterized by poor wound healing may occur as a result of comorbid neuropathy. Retinopathy, chronic kidney disease, neuropathy, and cardiovascular diseases are other common complications of poorly managed diabetes. Inadequate metabolic management of diabetes can lead to increased mortality (7). Due to the presence of high levels of glucose, free iron, and ketone bodies in the tissue microenvironment of diabetic patients, suitable conditions are provided for the growth of fungi. The high glucose levels provide the fungus the energy it needs, the free iron meets the metabolic needs of the fungus, and the ketone bodies provide the acidic environment preferred by many pathogenic fungi, especially *Candida*, *Dermatophytes*, *Zygomycetes*, *Aspergillus*, and *Fusarium* species (5,8). According to a report by the American Diabetes Association, the cost of diabetes in the United States in 2017 was 327 billion dollars. Patients with diabetes are susceptible to infection and usually require more hospitalization compared to the general population. Furthermore, 12% of deaths among people with diabetes are caused by infectious diseases (9,10). Diabetes causes both a direct decrease in serum albumin and a loss of albumin through urine due to diabetic nephropathy. There is a predisposition to serious invasive fungal infections that may result in mortality due to hypoalbuminemia (10). Levels of iron and pH also have close relationships with the risk of mycosis. Patients with high levels of serum iron are particularly susceptible to infections by Mucorales species (11,12). In cases of rhino-orbital-cerebral mucormycosis, mortality rates vary between 25% and 62% depending on the presence of underlying factors (13).

Association between fungal infections and diabetes

Candida taxa display dimorphism and can exist in both yeast and hyphal forms. The yeast form is observed in the commensal carriage of oral *Candida*, while the hyphal form is associated with tissue invasion and disease (14). Candidal infections may be an early sign of undiagnosed diabetes. This is of significant importance in terms of controlling hyperglycemia and protecting diabetic patients from complications. Worldwide, more than 60% of patients with diabetes have poor glycemic control, which makes them susceptible to opportunistic infections such as mucormycosis (5). Opportunistic fungal infections, and especially mucormycosis, have been shown to increase the number of deaths among patients with diabetes on a global scale (15). Diabetic patients are vulnerable to fungal infections; the risk of mycoses is increased 1.38-fold in patients with diabetes. Uncontrolled hyperglycemia contributes

to poor prognosis for diabetic patients with cryptococcosis (10). The microvascular damage and vascular dysfunction evident in patients with diabetes often lead to heightened susceptibility to *Candida* infections and more rarely to infections by *Geotrichum* species, which are yeast-like fungi (7). Fungi in patients with diabetes have increased rates of drug resistance. Biofilms constitute a major physical barrier to reducing the absorption of antifungals, leading to antifungal tolerance (10).

Association between diabetes and oral candidiasis

Yeasts inhabit the gastrointestinal tract, mouth, and vaginal mucosa at rates of 40%-60% in healthy adults as commensal organisms, but they may cause disease in immunocompromised individuals (4). In a case-control study that included 250 patients with T2D and 81 non-diabetic controls, yeast growth in culture was significantly higher for the diabetic patients, but the oral prevalence of *Candida* species was similar between the groups (16).

Association between diabetes and urinary tract fungal infections

Advanced age, female sex, diabetes, the use of broad-spectrum antibiotics, urinary system abnormalities, the long-term presence of catheters, and admission to intensive care units are the most common risk factors for urinary tract fungal infections. According to a retrospective observational case study from the United Kingdom, the risk of developing a urinary tract fungal infection is twice as high in patients with diabetes compared to individuals without diabetes (17). Progression of the infection and the development of pyelonephritis is pose serious risks for patients with diabetes. Mechanisms such as diabetic nephropathy, neuropathy, immune system disorders, and glycosuria increase the risk of urinary tract infections (17). *Candida* species are the second most common pathogens isolated from diabetic patients with urinary tract infections after *Escherichia coli* (10).

Association between diabetes and onychomycosis

Diabetes affects millions of people worldwide, but the most affected patients live in low-income countries. It is estimated that approximately 25% of these patients will develop diabetic foot ulcers. Ulceration and infection of foot tissues in an individual diagnosed with diabetes is defined as diabetic foot (18). Diabetic patients are particularly susceptible to superficial fungal infections because their vascular and immunological systems are compromised. In patients with diabetic foot, polymorph nuclear leukocytes and phagocytic functions are impaired and the immune system is damaged. These conditions contribute to the development of fungal and bacterial skin infections as well as fungal nail infections in diabetic foot patients (19). Fungal infection of the nails is called onychomycosis. Advanced age, male sex, diabetes, peripheral artery disease, and immunodeficiency are risk factors that increase the incidence of the disease. According to a systematic review of 10 articles, the prevalence rate of onychomycosis in patients with diabetes is 29% (19). The most frequently isolated organisms in cases of onychomycosis are dermatophytes. The most common causative species among dermatophytes is *Trichophyton rubrum*. Non-dermatophyte molds and yeasts may also be causative agents, albeit less frequently. The most common causative species among yeasts is *Candida albicans* (8). It is of utmost importance to start treatment after determining the viability of the fungus and the identity of the causative microorganisms. Thus, an effective fungal species-specific treatment protocol can be applied. Methods used for fungal detection and identification include direct microscopy with potassium hydroxide, microbiological culture, polymerase chain reaction (PCR), and histological techniques. It is recommended to use a combination of methods for the early and accurate diagnosis of onychomycosis. Onychomycosis, characterized by thickening, hyperkeratosis, onycholysis, and discoloration of the nails, has various clinical presentations including distal and lateral subungual onychomycosis, proximal subungual onychomycosis, superficial white onychomycosis, and total onychomycosis with diabetic

foot syndrome. Depending on the affected area and the causative agent, topical treatments, oral treatments, laser treatments, iontophoresis, photodynamic therapy, or combined treatments may be indicated (20,21). In a systematic study, both the presence of onychomycosis and nail thickening with onychomycosis were found to be associated with high levels of glycosylated hemoglobin (19). Fungal skin and nail infections of the feet, such as tinea pedis and onychomycosis, were significantly more frequent among patients with diabetes. A total of 600 patients with diabetes and 152 control subjects without diabetes were analyzed in a previous study. The frequencies of both onychomycosis and tinea pedis were significantly higher in the diabetic group compared to the control group. Furthermore, the development of onychomycosis or tinea pedis correlated significantly with increasing age, male sex, and duration of diabetes. As expected, both types of fungal infection were significantly more frequent among diabetic patients (14.2%) compared to the control group (5.9%) (2,22). Nail changes in diabetic patients may predispose them to life-threatening complications by increasing the risk of traumatic injury, as the affected nails can cause serious injury or ulceration of the surrounding skin. These areas can serve as entry points for fungal and bacterial infections. In the event of reduced blood flow in diabetic patients, improper wound healing can lead to an increased risk of lower extremity amputation or death (2). Studies have shown that diabetic patients with such infections have complete cure rates similar to those of non-diabetic patients, but the duration from infection to complete cure is longer. In addition, diabetic patients are at a greater risk of developing complications of onychomycosis such as secondary bacterial infections due to the poor circulation, impaired wound healing, and sensory neuropathy caused by diabetes (2).

Association between diabetes and cryptococcosis

Cryptococcosis is an opportunistic fungal infection whose clinical presentation varies depending on the anatomical location of the infection and the immunological status of the host. *Cryptococcus neoformans* and, less commonly, *Cryptococcus gattii* are responsible for human infections. The World Health Organization lists *Cryptococcus neoformans* as a fungal pathogen of critical priority (23). The disease depends on the affected anatomical location, with cases being classified as pulmonary, cerebral, cutaneous, skeletal, and disseminated infections. The anatomical location of the infection and the immunological status of the host also affect the clinical course of the disease (24). Diabetes mellitus may be a risk factor for worse cryptococcosis outcomes as basic functions of the immune system such as polymorph nuclear leukocyte chemotaxis, phagocytosis, and cell-mediated immunity are impaired in cases of diabetes due to hyperglycemia (25,26). Furthermore, Archuleta et al. demonstrated a relationship between uncontrolled diabetes and increased mortality in cases of pulmonary cryptococcosis (26). The frequency of diabetes among cryptococcosis cases may vary at rates ranging from 8.5% to33% (10). Kung et al. analyzed 3280 HIV-negative, non-transplant (NHNT) patients with cryptococcosis, comparing the results between patients withT2D (30%)and those without T2D (70%)(23). The NHNT patients with T2D had higher rates of obesity, hyperlipidemia, hypertensive diseases, heart failure, chronic kidney disease, cirrhosis, and bone marrow failure compared to the NHNT patients without T2D. Furthermore, the rate of cognitive dysfunction was higher among NHNT patients with T2D, with cognitive dysfunction being a risk factor for cryptococcosis. Incidence and prevalence were similar among male and female patients. There was no difference between the groups for mortality, hospitalization, or ICU admission outcomes following cryptococcal infections (23).

Association between diabetes and vaginal infections

In the normal vaginal microbiota, *Lactobacillus* species and *Candida* species are balanced. When that balance changes, vulvovaginal candidiasis (VVC) develops. VVC is an opportunistic fungal infection and the most frequently isolated species in such cases is *Candida albicans* (27). Complicated VVC, in contrast to uncomplicated VVC, is caused by non-albicans *Candida* (NAC) species in women with

adverse conditions such as diabetes and immunodeficiency, as well as during pregnancy. It is a recurring infection and cannot be easily treated with short-term antifungal drugs (28). VVC affects millions of women. Various predisposing factors, such as broad-spectrum antibiotic therapy, decreased cellular immunity, high levels of vaginal glycogen and estrogen levels (in pregnancy), uncontrolled diabetes, and stress, facilitate the development of VVC (27). The prevalence rates of VVC worldwide vary between 12% and 57%. *C. albicans* is more common in healthy premenopausal women, as well as in pregnancy, with asymptomatic colonization and acute episodes of VVC, whereas NAC species, and particularly *C. glabrata*, are more frequently the causative agents of VVC in postmenopausal, diabetic, and immunocompromised women (27). It is suggested that pregnant women with GDM are more prone to vaginal *Candida* infections (4).

Association between diabetes and invasive pulmonary aspergillosis

Aspergillus is a ubiquitous filamentous saprophytic fungus commonly isolated from construction sites, soil, and hospital dust. Repeated inhalation of the spores is common and tends to trigger symptoms only in susceptible individuals with underlying lung diseases or immune system dysfunction (29). Nevertheless, it can also be observed in immunocompetent populations; patients with malnutrition, diabetes, or other underlying chronic diseases have a 27% higher risk of developing invasive pulmonary aspergillosis (IPA) than the general population. Common risk factors include prolonged and severe neutropenia, cancer, and the chronic use of corticosteroids, immunosuppressants, or biologic medications (29). *Aspergillus* taxa are among the most common opportunistic pathogens associated with morbidity and mortality in immunosuppressed patients worldwide (30). Early diagnosis of IPA is crucial to prevent progression to a disseminated form of the disease and thus improve the likelihood of the patient's survival (29).

Association between diabetes and fungal keratitis

Fungal keratitis is a common sight-threatening infectious disease of the cornea. Corneal trauma is the predominant risk factor for fungal keratitis. Patients with diabetes also have an increased risk of fungal infection. HbA1c levels and diabetes duration influence the severity of various diabetic complications. In a study conducted with 851 fungal keratitis patients, including 111 diabetic and 740 non-diabetic patients, the patients with diabetes were significantly older than those without diabetes and the male sex ratio was significantly higher in the diabetic group. There was no difference in pathogen types between the two groups, with *Fusarium* being the most commonly isolated pathogenic genus, followed by *Alternaria* and *Aspergillus* (31). Ocular trauma, ocular surface disease, and the use of contact lenses are widely recognized risk factors for fungal keratitis. In addition, diabetes mellitus is a risk factor for fungal keratitis. Corneal re-epithelialization is significantly delayed in diabetic patients. Among diabetic changes in the cornea, impaired epithelial regeneration caused by the long-term effects of hyperglycemia is reported to be the most important variable. Penetrating keratoplasty is the only treatment option if the fungal infection reaches the endothelium (31).

Association between diabetes and mucormycosis

Mucormycosis is a serious but rare fungal infection caused by fungi that belong to the order Mucorales of the subphylum Mucoromycotina. *Mucor* mold is commonly found in soil, manure, plants, decaying fruits and vegetables, air, and even the mucus of healthy individuals (32). The symptoms of mucormycosis vary from person to person but generally include headache, fever, facial and nasal pain, blackish nasal discharge, loss of vision, and toothache. Left untreated, this infection can cross the central nervous system and become a life-threatening disease (33). Mucormycosis can be life-threatening in diabetic and severely immunocompromised individuals (32). The main mode of infection of mucormycosis is through the inhalation of spores, consumption of contaminated food, and inoculation of fungi in abrasions or cuts on the skin (34). In developed countries, malignancy has been recognized as the

main risk factor for mucormycosis, whereas in developing countries, uncontrolled diabetes mellitus is the main factor related to the development of this disease (11,13). The incidence of mucormycosis has increased over the last two decades and the mortality rate remains high despite antifungal therapy and surgical operation. Mucormycosis can be classified into six forms based on the location of its occurrence, including rhino-orbito-cerebral mucormycosis (ROCM); pulmonary, cutaneous, gastrointestinal, and disseminated forms; and mucormycosis of uncommon sites. Among these forms, ROCM is the most commonly occurring form in patients with diabetes mellitus and hyperglycemia (13,33). ROCM is particularly common in patients with diabetic ketoacidosis (DKA) (11). The most common sites of infection are the sinuses (39%), lungs (24%), disseminated sites (23%), and skin and soft tissues (19%) (33–35). Cerebral mucormycosis begins with the inhalation of spores, which is the most efficient way for the fungus to penetrate the respiratory tract and colonize the nasal mucosa (11). Fungal tropism in vascular blood vessels creates arteriole thrombosis, which leads to orbital involvement and affects the orbital wall. Furthermore, oculomotor and optical nerves are responsible for blindness in such cases with or without thrombosis of the ophthalmic artery. Black eschar indicates necrosis and is a worrying sign of local extension (11). While most human infections are caused by *Rhizopus* spp. (59%), *Mucor* spp. (28%), and *Rhizomucor* spp. (4%), other clinically relevant organisms within the order Mucorales include the taxa of *Apophysomyces*, *Cunninghamella*, *Lichtheimia*, *Saksenaea*, and *Syncephalastrum* (13). Among the species that cause mucormycosis, *Rhizopus* species are associated with ROCM. *Cunninghamella* may befound in pulmonary or disseminated forms. Although rare, *Lichtheimia* and *Apophysomyces* species have been reported to cause infections in diabetic patients (11). Karat et al. stated that all ROCM patients included in their study had extremely high glycemic levels, but 24.63% of these patients were newly diagnosed with diabetes for the first time during the study (35). Mucormycosis has been associated with various underlying conditions that predispose an individual to the infection. Diabetes, neutropenia, organ transplantation, trauma and burns, hematological disorders, steroid use, metabolic acidosis, renal insufficiency, increased iron, and medications such as voriconazole and broad-spectrum antibiotics are known to predispose individuals to mucormycosis (16,33).

1. Pathogenesis

Hyperglycemia and acidosis induce the excessive glycosylation of carrier proteins such as transferrin and ferritin, resulting in an increase in serum free iron (35). Mucorales taxa use free iron for their developmental processes. Patients with DKA have higher levels of serum free iron; thus, in this context, they have a higher risk of developing mucormycosis (5). The novel host receptor glucose-regulated protein 78 (GRP78) mediates the invasion and damage of human endothelial cells by fungi of the order Mucorales. The spore coat (CotH) protein is present on the spore surfaces of Mucorales taxa and inhibits the host's immune defenses. CotH is a fungal ligand that mediates attachment to GRP78 during host cell invasion, constituting an important step in the pathogenesis of mucormycosis (35). High glucose, iron, and ketone concentrations are linked to increased GRP78 expression in DKA patients. This situation is associated with the hypersensitivity of DKA patients to mucormycosis via the invasion and damage of endothelial cells by *R. oryzae* (11,13). An important virulence factor involved in the pathogenesis of Mucorales taxa is the high-affinity iron permease (FTR1) enzyme. This enzyme allows pathogen survival in iron-poor environments (13). Respiratory inhalation of these fungal spores from the environment is the mode of exposure. The spores proliferate in the nasal mucosa and spread to the paranasal sinus, eventually reaching the orbits and brain in cases of pathogenic mucormycosis (36). Hematological or other malignancies, previous organ transplantation, acquired immunodeficiency syndrome, intravenous drug use, immunosuppressive medications, iron overload, deferoxamine therapy, blood transfusions, trauma, and malnutrition are additional conditions that predispose patients to ROCM. In patients with these features, the mortality rate of ROCM is high, varying between 40% and 80% depending

on the patient's characteristics and risk factors. Rapid diagnosis, antifungal drug therapy, and surgical debridement are critical to prevent mortality (36).

2. Management

Suspected and confirmed cases of mucormycosis should be considered emergencies due to the high risk of death and treatment should be initiated immediately (36). To obtain successful results from combined medical treatment and surgical interventions, it is necessary to correct the underlying predisposing factors (13). Antifungal treatment includes the lipid formulation of amphotericin B, posaconazole, and isavuconazole. Mucorales taxa are intrinsically resistant to fluconazole, itraconazole, voriconazole, and echinocandins. In the treatment of cases of mucormycosis, high-pressure oxygen is additionally used (13,37).

3. Prognosis

The overall prognosis of ROM is poor despite the existence of treatment options. Mortality rates vary between 40% and 80% (33). Correction of the underlying risk factors, early initiation of antifungal treatment and surgical debridement, and the degree of anatomical involvement play roles in determining morbidity and mortality in patients with ROCM. Neutrophils are an important part of the innate immune system and are involved in the initial defense against fungi. In diabetic patients with ketoacidosis or hyperglycemic states, chemotactic factors released by neutrophils are reduced and fungal cells readily increase (33). The CotH protein found on the spore surfaces of Mucorales taxa is responsible for penetrating, lysing, and damaging immune cells. Once Mucorales spores enter a host cell, IL-4, IL-10, IL-17, and IFN-γ are produced by Mucorales-specific T cells. These pro-inflammatory cytokines damage the host cell (33).

Microbiological examination

Pathogen identification and antifungal susceptibility are critical in determining appropriate antifungal therapies. The joint clinical guidelines of the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) and the European Confederation of Medical Mycology (ECMM) strongly recommend the combined use of direct microscopy, histopathology, and culture for diagnosis. Increasing the diagnostic accuracy is of great importance. The area to be sampled is cleaned with 70% alcohol and skin scrapings and/or nail clippings are collected and sent to the microbiology laboratory in sterile containers for mycological examination. Direct microscopic study of samples is an important diagnostic tool that distinguishes between the pathogen and contaminants. Mucorales hyphae are broad and ribbon-like multinucleated cells with no septation or rare septation (13). Mucorales taxa are rapidly growing fungi but the yield of cultures is often low. This may be attributed to careless processing of the specimen or the prior administration of antifungal therapy. Superficial samples are inoculated on Sabouraud dextrose agar plates with and without cycloheximide. These plates are incubated at 25 °C and 30 °C for up to 4 weeks before being discarded as negative. Filamentous fungal isolates are identified based on colony morphology, microscopic appearance, and biochemical tests. Yeast isolates are identified using systems based on germ tube production, microscopic morphology on cornmeal agar, and the assimilation of carbohydrates. Samples taken from the nasal cavity and/or paranasal sinuses are first sent to the microbiology laboratory for potassium hydroxide/calcofluor white staining and then for fungal culturing. The definitive diagnosis of mucormycosis is made according to the presence of tissue invasion with broad, non-septate, branching fungal elements in histopathology as well as culture positivity (35,36).

CONCLUSION

Diabetes constitutes a serious public health problem. It is one of the most common metabolic disorders and an important determinant of morbidity and mortality in patients with fungal infections. Early detection of hyperglycemia and tight glycemic control coupled with early isolation of the causative agent and early diagnosis will contribute to better control of the disease and its consequences. Antifungal therapy and surgery should be used together to prevent mortality. Elimination of predisposing factors is critical for effective treatment. Diabetes, with the dysregulation and impairment of functions of immune system cells, negatively impacts phagocytic activity, which is necessary for controlling and killing pathogens and processing them for antigen presentation. Thus, diabetes is a risk factor for fungal infections.

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