Literature Review

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Fungal infection characteristic in type 2 diabetic mellitus: Narrative review

Karakteristik infeksi jamur pada penderita diabetes mellitus tipe 2: Telaah naratif

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Abstract

Background: Individuals diagnosed with type 2 diabetes mellitus demonstrate a weakened immune system compared to those in a state of excellent health, rendering them more vulnerable to viral, bacterial, and fungal infections. **Objective:** This study aimed to examine the characteristics of fungal infections in individuals diagnosed with type 2 diabetes mellitus (DM).
Methods: This study is a narrative review that conducted a comprehensive search of literature worldwide using the e-library PubMed. The journals that fulfilled the inclusion criteria were further examined and interpreted in the form of narratives.
Fungal infections include genitourinary fungal infections, oral fungal infections, invasive fungal diseases, and fungal infections in diabetic foot ulcers. Some studies have found that the use of sodium-glucose co-transporter 2 (SGLT2) inhibitors may be associated with fungal infections. In addition, studies have discussed the types of fungal infections in diabetic patients, as well as their association with SGLT2 inhibitor use. In addition, one study examined the association between IL-23R polymorphisms and fungal infections.
Conclusion: Patients with type 2 diabetes are prone to a range of diseases including fungal infections. In addition to immunocompromised conditions, patients with type 2 DM are susceptible to fungal infections due to factors such as the administration of SGLT2 inhibitor medications and the influence of the IL-23R gene polymorphism**.**

Keywords
Characteristic of fungal infection, diabetes mellitus type 2, fungal infection, infection

Abstrak

Latar Belakang : Pasien dengan diabetes tipe 2 memiliki sistem kekebalan tubuh yang lemah, membuat mereka lebih rentan terhadap infeksi seperti virus, bakteri, dan jamur.
Tujuan: Untuk menilai karakteristik infeksi jamur pada individu yang didiagnosis dengan diabetes melitus (DM) tipe 2.
Metode: Penelitian ini merupakan tinjauan naratif yang melakukan pencarian literatur secara komprehensif di dengan menggunakan Pubmed. Setelah jurnal-jurnal yang ada memenuhi kriteria inklusi dan eksklusi, jurnal-jurnal tersebut diperiksa lebih lanjut dan diinterpretasikan dalam bentuk narasi.
Hasil: Infeksi jamur meliputi infeksi jamur genito-urinaria, infeksi jamur oral, penyakit jamur invasif, dan infeksi jamur pada ulkus kaki diabetes. Dalam beberapa penelitian, ditemukan bahwa penggunaan inhibitor Sodium-Glucose-Co-Transporter 2 (SGLT2) dapat berhubungan dengan infeksi jamur. Selain itu, terdapat studi yang mendiskusikan jenis-jenis infeksi jamur pada pasien diabetes, serta hubungannya dengan penggunaan inhibitor SGLT2. Selain itu, satu penelitian juga mencari hubungan antara polimorfisme gen IL-23R dengan infeksi jamur.
Kesimpulan: Penderita diabetes melitus tipe 2 rentan terhadap berbagai penyakit, termasuk infeksi jamur. Selain karena kondisi menurunnya sistem imun, pasien DM tipe 2 rentan terhadap infeksi jamur karena faktor-faktor seperti pemberian obat penghambat SGLT2 dan pengaruh polimorfisme gen IL-23R.

Kata Kunci
Karakteristik infeksi jamur, diabetes mellitus tipe 2, infeksi jamur, infeksi

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Introduction

Diabetes mellitus (DM) is a metabolic illness that presents a substantial global health burden as its prevalence continues to increase on a yearly basis. Diabetes mellitus is a collection of complex metabolic disorders that can be distinguished by chronic hyperglycemia. This can be ascribed to either compromised secretion of insulin, a compromised effect of insulin, or a combination of both (Petersmann et al., 2019). There are two primary classifications of diabetes: type 1 diabetes (T1D) and type 2 diabetes (T2D). Diabetes type 2 is prevalent type of diabetes, accounting for over 90% of all diabetes cases worldwide (Webber, 2013). Approximately 462 million people worldwide are affected by type 2 diabetes, accounting for 6,28% of the global population (Laakso, 2016).

Typically, the human body employs remarkable processes to defend itself against infiltration by bacteria, viruses, fungi, poisons, and parasites. Diabetes disturbs the immunological response of individuals. Furthermore, T2D can impair cellular immunity in addition to the potential risk of neuropathy-induced damage to natural barriers. This is caused by the lack of insulin and high blood sugar levels (Berbudi et al., 2019).

Patients diagnosed with diabetes mellitus are prone to a wide range of viral, bacterial, parasitic, and fungal infections. Individuals diagnosed with diabetes are prone to infection and typically have longer hospital stays than those in the general population (Lao et al. 2020). In developing nations, infection ranks among the top three primary causes of death among those with diabetes, contributing to a four-fold increase in the likelihood of fatality (Lao et al., 2020). Although fungal infections are frequently undervalued, they may be fatal. The clinical range of fungal infections includes a continuum, from minimal or asymptomatic skin infections to more severe invasive infections (Saud et al., 2020). An uncontrolled hyperglycemic condition can result in infection due to impaired functioning of the immune system. A study revealed that oral wash exhibited the highest fungal growth, followed by toe, urine, hair, and nail samples (Saud et al., 2020).

A study conducted in Nepal demonstrated a notable disparity in the prevalence of fungal infections between individuals with diabetes (34,0%) and those without diabetes (4,7%) (Saud et al., 2020). In a study conducted by Lao et al., the prevalence of invasive fungal disease (IFD) among individuals diagnosed with type 2 diabetes who were admitted to hospitals was 0,4%. Of 30,984 patients, 120 were identified. In contrast, the prevalence of invasive fungal disease (IFD) among non-diabetic patients admitted to the same institution was 0,2%, with 249 cases out of the overall population of 119,255 (Lao et al., 2020). Kandregula et al. conducted a study that showed that the prevalence of fungal infections among individuals diagnosed with foot ulcers was 31,7% (Kandregula et al., 2022).

Many factors influence the incidence of fungal infections in patients with type 2 diabetes mellitus, including blood sugar levels, medications taken, and other comorbidities. Glucose and fructose are the primary pathophysiological and nutritionally crucial sugars in individuals with diabetes mellitus (DM). Nevertheless, it is worth noting that other simple carbon sources significantly contribute to the proliferation of Candida spp. in DM patients (Rodrigues et al., 2019). Man et al. studied the growth rate of Candida albicans in the presence of varying concentrations of glucose and fructose. This study aimed to gain a more comprehensive understanding of the nutrient acquisition method utilized by this bacterium and its potential association with the hyperglycemic condition observed among those with diabetes (Man et al., 2017). Researchers have discovered a direct correlation between glucose levels and C. albicans growth, which could indicate a connection between the prevalence of yeast infections and poorly controlled diabetes (Man et al., 2017). In addition, fungal infections vary; therefore, it is necessary to study the characteristics of fungal infections in people with type 2 diabetes mellitus.

Methods

Research Design

This research is a narrative literature review that presents the findings of earlier researchers and will be discussed in narrative form. The process of doing a literature review involved several key processes. These included determining the research topic and formulating the research problem, conducting a literature search in PubMed, evaluating the data obtained, and conducting data analysis and interpretation (see Figure 1. Research design)

Inclusion and Exclusion Criteria

To ensure that the journal is suitable for use in this research, there are several inclusion criteria: the journal discusses the characteristics of fungal infection in type 2 Diabetes Mellitus, and the population of the study was adult diabetes mellitus (>18 years old). Moreover, the exclusion criteria were as follows: the journal was not published within the last five years (2018-2023), the journal was not available in free full text, and the journal was not published in English.

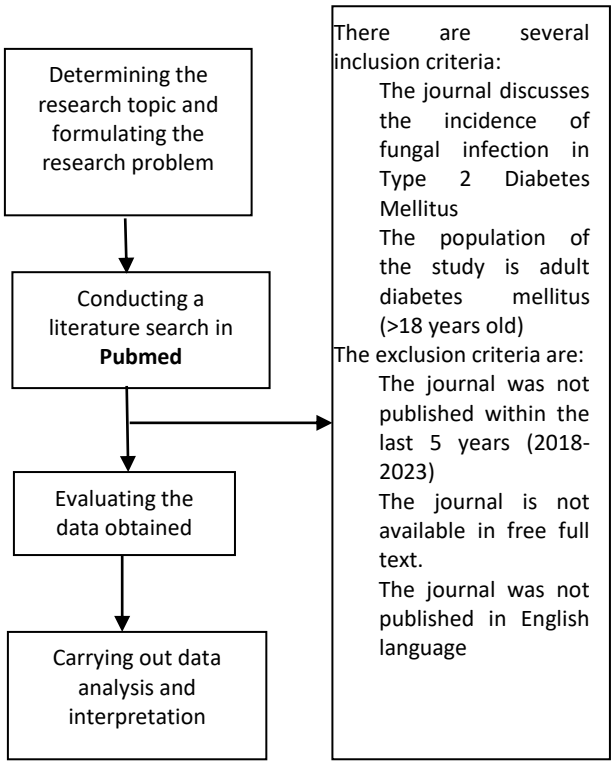

Figure 1. Research design

Data Searching

Researchers used search terms to make it easier to include appropriate journals. The search terms using Medical Subject Headings (MeSH) were ("Incidence" AND "Fungal Infection in Type 2 Diabetes Mellitus" OR " Fungal Infection in Type 2 DM"). These sources were retrieved from the PubMed database.

Data Selection and Collection

After searching for the data, a screening was carried out in the Abstract and Results section. After obtaining suitable journals, they were collected, analyzed, and interpreted.

Data Analysis and Interpretation

The data obtained from the journals were analyzed. The data will be collected, and the statistical results from the journal will be collected and interpreted in a narrative form.

Results

Articles that are found in Pubmed using Medical Subject Headings (MeSH) ("Incidence" AND "Fungal Infection in Type 2 Diabetes Mellitus" OR " Fungal Infection in Type 2 DM") are 143 articles. After excluding some criteria (the journal was not published within the last five years, the journal was not available in free full text, and the journal was not published in English), 31 articles remained. Twenty-three articles did not meet our inclusion criteria. Eight articles specifically addressed fungal infections in patients diagnosed with type 2 diabetes mellitus (Figure 2. Data selection).

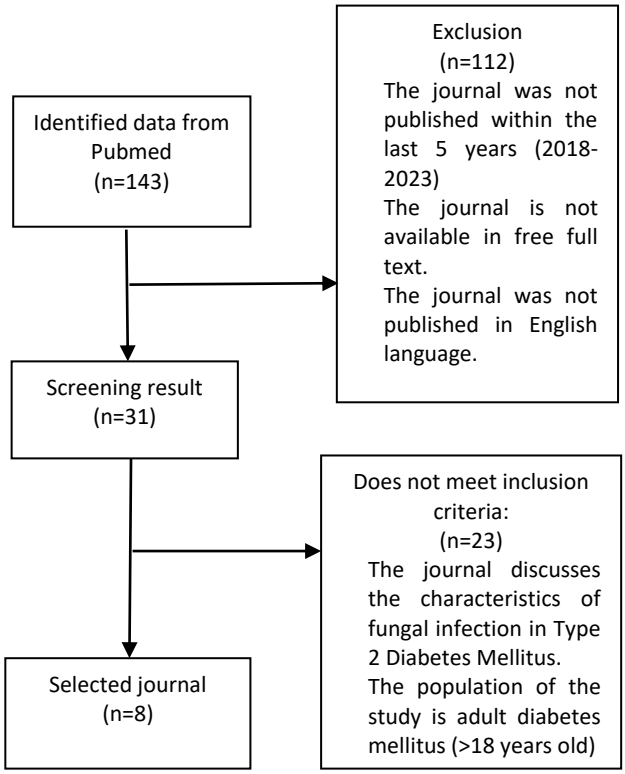

Figure 2. Data selection

Aamir et al. compared two groups of Pakistani Muslim individuals with type 2 diabetes: group A received empagliflozin (a sodium-glucose-co-transporter 2 inhibitor), and group B received normal therapy. The study findings showed that group B had two instances of fungal vaginal infections, whereas group A did not report any cases (p = 0,142) (Aamir et al., 2022). A study conducted by Al Badri et al. showed a high incidence of oral fungal infections among those

with diabetes, which has been linked to the consequences of variation in IL-23R genes. For IL23R rs (1884444 G/T), the starting point exhibited three genotypes (GG, GT, and TT). Notably, the GT genotype was significantly associated with oral fungal infection in patients with type 2 diabetes mellitus (T2DM), with a positive count of 17,0 and a negative count of 5.0 (X2=38,4, p<0,001). In contrast, statistical analysis showed that the impact on GG genotypes was insignificant (Al-Badri et al., 2022).

A study conducted by Lao et al. found that 0.4% of 120 patients diagnosed with type 2 diabetes mellitus had invasive fungal illness. Of the total sample size of 56 individuals, 46,7% were found to have yeast infection. Among these patients, 55,4% had candidiasis and 44,6% developed cryptococcosis. The clinical signs of candidiasis typically occur in the urinary tract (38,7%), abdominal cavity (32,3%), esophagus (9,7%), bloodstream (6,5%), biliary tract (3,2%), lung (3,2%), abdominal cavity + bloodstream (3,2%), and bloodstream + renal pelvis (3,2%). Cryptococcosis has an incidence rate of 64% in the lungs, 16% in the meninges, 4% in the bloodstream, 4% in the soft tissue, 4% in the bloodstream and meninges, 4% in the lungs and meninges, and 4% in the abdominal cavity, lung, and meninges (Lao et al., 2020).

Petrovic *et al's* revealed that *Candida spp*. were present on the tongues of 27,4% of participants. The prevalence of this condition was higher in diabetic patients with inadequate glycemic control (47,5%) than in healthy individuals without periodontitis (22,2%), healthy individuals with chronic periodontitis (16,7%), and type 2 diabetes patients with good glycol regulation and chronic periodontitis (21,5%). Patients diagnosed with type 2 diabetes (group C+D = 25) exhibited a notably greater occurrence of Candida spp. detection (37,3%) than healthy patients (group A + B = 15 (19,5%)) (*p-value* = 0,013) (Petrovic et al., 2019).

The research conducted by Yokoyama et al. found that patients diagnosed with type 2 diabetes mellitus also had vaginitis. Before inclusion in the trial, the participants received therapy with other antidiabetic medications or insulin. A total of 147 female patients diagnosed with type 2 diabetes were initiated on SGLT2 inhibitor use throughout the specified time frame. Of these, 33 patients refused to undergo vaginal swabs, whereas the remaining 114 patients underwent the test. They used luseogliflozin (2,5 mg, *n* = 23), empagliflozin (10 mg, *n* = 22), tofogliflozin (20 mg, *n* = 20), canagliflozin (100 mg, *n* = 18), ipragliflozin (50 mg, *n* = 18), dapagliflozin (2,5 mg, n = 23), empagliflozin (10 mg, n = 22), tofogliflozin (20 mg, n = 20), canagliflozin (100 mg, n = 18), dapagliflozin (50 mg, n = 18), and dapagliflozin (5 mg, n = 13) (Yokoyama et al., 2019).

The participants who tested positive for Candida culture revealed a higher level of HbA1c (8,3 ± 1,8 mmol/mol) compared to those who tested negative for Candida culture (7,4 ± 1,0 mmol/mol); the p-value was found to be 0,01. At the onset of SGLT2 inhibitor treatment, 9 patients had a positive Candida culture, while 65 patients had a negative Candida culture. After 6 months of SGLT2 inhibitor use, all nine patients who initially showed Candida growth continued to exhibit positive cultures. Furthermore, of the 65 patients who did not have Candida growth at the beginning, 24 (36,9) fungal infections affected the skin. They achieved this by providing a concise overview of their 11-year experience at a specialized medical referral facility in Southern Taiwan. According to the study, 46% of individuals who underwent mycosis implantation were diagnosed with type 2 diabetes mellitus. A significant number of the remaining patients were immunocompromised (26%), engaged in gardening (23%), and had a documented history of local plant-related injuries (9%). The incidence of invasive fungal infections with skin involvement is 60% among individuals with weakened immune systems and 40% among those diagnosed with type 2 diabetes mellitus (Hsu & Lee, 2023).

The aim of a study conducted by Musyoki et al. was to provide a description of the Candida species that infect diabetic foot ulcers in patients receiving clinical care at Kenyatta National Hospital and to evaluate their susceptibility to antifungal treatments. Among the 152 samples obtained from the foot ulcers, 31 exhibited yeast cells, which were verified by the germ tube test (GTT) and further confirmed using the VITEK - 2 System and MALDI-TOF MS (Musyoki et al., 2022).

Of the 31 samples that contained yeast cells, 36 Candida species were effectively isolated and differentiated. Candida albicans was the most frequently observed species, accounting for 75% of cases (n=27). On the other hand, Candida lusitaniae was the leading non-albicans Candida

isolate, comprising 8% (n=3), followed by Candida dubliniensis at 5% (n=2). Additional Candida species, excluding albicans, that were identified include C. glabrata, C. tropicalis, C. famata, and C. parapsilosis (each accounting for 2% of the total, n=1). The predominant Candida isolates were obtained from male individuals (24%, n=22), patients aged ≥ 40 years (20%, n=23), acute wounds (21%, n=20), and ulcers classified as Wagner grades I and II (20%, n=26). However, the observed correlation was not statistically significant (p>0,05). Additionally, molds were collected from eight culture plates during a period–7-14 days of aerobic incubation at a temperature range of 19-25°C. The molds were recognized and distinguished as Penicillium spp. (38%, n=3), Aspergillus spp. (25%, n=2), Microsporum spp. (25%, n=2), and Trichophyton mentagrophytes (12%, n=1) based on the colonial morphology observed using the SDA and Lactophenol Cotton Blue (LPCB) staining procedure (Musyoki et al., 2022).

Table 1. Narrative review study result

Author	Study Design	Location of Study	Fungal Infection	Glucose Lowering Agent
Aamir AH, *et al.* (2022)	Randomized clinical trial	Pakistan	Genital fungal infection	Sodium–glucose co-transporter 2 (SGLT2) inhibitors (Empagliflozin)
Al Badri AS, *et al.* (2022)	Case-control study	Baghdad	Oral fungal infection, Genito-urinary Fungal Infections (GFIs)	Not stated
Lao M, *et al.* (2020)	Retrospective cohort study	China	Invasive fungal disease (candidiasis, cryptococcosis, pulmonary fungal infection)	Oral antidiabetic drugs and combined therapy (insulin and oral antidiabetic drugs)
Petrovic SM, *et al.* (2019)	Cross-sectional observational study	Serbia	Oral candidiasis	Not stated
Yokoyama H, *et al.* (2019)	Cross-sectional observational study	Japan	Vaginal candidiasis	Sodium–glucose co-transporter 2 (SGLT2) inhibitors
Hsu TJ, *et al.* (2023)	Retrospective cohort study	Taiwan	Implantation mycosis, invasive fungal infections	Oral antidiabetic drugs and insulin
Musyoki VM, *et al.* (2022)	Cross sectional observational study	Kenya	Fungal infection of diabetic foot ulcer	Not stated
Adimadhyam S, *et al.* (2019)	Retrospective cohort study	USA	Genital mycotic infections	Sodium–glucose co-transporter 2 (SGLT2) inhibitors

In general, 35 Candida species were susceptible to voriconazole, flucytosine, micafungin, caspofungin, amphotericin B, and fluconazole, with susceptibility rates ranging from 77% to 77%. Susceptibility to flucytosine and amphotericin B was the highest among the six antifungal drugs, but caspofungin exhibited the highest level of resistance. Candida albicans exhibited resistance to caspofungin, fluconazole, micafungin, and voriconazole at a rate of 26%. However, it was susceptible to amphotericin B and flucytosine at rates ranging from 81% to 96%. Candida species that were not C. albicans showed susceptibility (90-100%) to the majority of the antifungal drugs that were tested (Musyoki et al., 2022).

The study carried out by Adimadhyam et al. discovered that a cohort of 23,276 patients received freshly prescribed sodium-glucose co-transporter-2 inhibitors (SGLT2i) and antifungal drugs within the specified study period. Canagliflozin was the most frequently initiated index medication, accounting for 68,9% of cases, followed by dapagliflozin at 22,4%. Fluconazole

was the most commonly prescribed treatment (58,3%), followed by nystatin (15,6%) and clotrimazole (15,3%). An increased vulnerability to fungal infections was observed across all periods, with the largest significant effect observed during the 90-day period [Average Susceptibility Ratio (ASR) 1.53 (confidence interval, CI 1.43-1.60)] (Adimadhyam et al., 2019).

Type 2 Diabetes Mellitus (T2DM) is a prevalent metabolic condition on a global scale, principally resulting from the confluence of two key factors: dysfunctional insulin production by pancreatic β-cells and impaired responsiveness of insulin-sensitive tissues to insulin (Galicia-Garcia et al., 2020). Hyperglycemia in diabetes is believed to impair the immunological response, resulting in an inability to effectively regulate the proliferation of invading microorganisms in individuals with diabetes. Uncontrolled hyperglycemia can result in infection due to immune system dysfunction. This imbalance is represented by a decrease in T-lymphocyte and neutrophil activity, a reduction in the release of inflammatory cytokines, disruptions in antibody-mediated immunity, the development of angiopathy, neuropathy, glycosuria, and a high rate of apoptosis in polymorphonuclear leukocytes (Chávez-Reyes et al., 2021).

Table 2. The diagnostic criteria for diabetes and prediabetes according to the american diabetes association

Parameter	Prediabetes	Diabetes
HbA1c	5,7-6,4% (39-47mmol/mol)	≥ 6.5% (48 mmol/mol)
Fasting plasma glucose	100-125 mg/dL (5,6-6,9 mmol/L)	≥ 126 mg/dL (7 mmol/L)
2-hour plasma glucose during 75 gr OGTT	140-199 mg/dL (7,8-11,0 mmol/L)	≥ 200 mg/dL (11,1 mmol/L)

A study by Saud *et al* The incidence of fungal infection was significantly greater in those with diabetes (34,0%) compared to those without diabetes (4,7%) (Saud et al., 2020). Diabetes mellitus type 2 has been found to be correlated with various infections, specifically those affecting the skin, mucous membranes, soft tissues, urinary system, and respiratory tract, as well as those established subsequent to surgical procedures or hospitalization (Akash et al., 2020; Berbudi et al., 2019).

Based on this review, fungal infections include genito-urinary fungal infections, oral fungal infections, invasive fungal diseases (candidiasis, cryptococcosis, and pulmonary fungal infection), and fungal infections of diabetic foot ulcers. The causative pathogens are Candida spp., Cryptococcus spp., Aspergillus spp., Trichophyton spp., Mucor spp., and Rhizopus sp. The outcomes of this study align closely with the research carried out by Bansal et al., which showed that the incidence of fungi in individuals with diabetes varied between 7,0% and 17,38%. The most commonly found fungal species in this population include Candida, Aspergillus, Fusarium, Rhodotorula, and Trichosporon spp. (Bansal et al., 2008).

The glucose-lowering agents used in these studies included SGLT2 inhibitors, oral antidiabetic drugs, and insulin. SGLT2 inhibitors have been reported to cause frequent fungal infections as side effects (Yokoyama et al., 2019). Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a class of pharmaceutical agents that are used to manage diabetes. These agents effectively reduce blood glucose levels by inhibiting glucose reabsorption in the proximal tubules. (Rodrigues et al., 2019; Sweatt,S.K, Gower, B.A, Chieh, A.Y, Liu, Y, Li, 2016).

The administration of these drugs is usually well tolerated; nevertheless, the presence of glucose in urine, which is normally pharmacologically produced, increases the risk of genital mycotic infections and urinary tract infections (UTIs). This phenomenon arises because of the establishment of a suitable milieu for proliferation of typically benign genital microorganisms. (Rodrigues et al., 2019). In another study by Li *et al.,*the precise mechanism by which SGLT2 inhibitor treatment leads to genital mycotic infections is not fully understood (Li et al., 2017).

Fungal infections are also associated with genetic polymorphisms. Badri *et al.* suggested that there is a positive association between IL-23R rs (1884444 G/T) and disease (Al-Badri et al., 2022). In contrast, the GG genotype had an opposite relationship with the disease and can be regarded as a beneficial factor, as indicated by an odds ratio (OR) value of 0,31 and a statistically significant

disparity (p=0,03). Conversely, the TT genotype showed a direct relationship with increased vulnerability to the condition, as indicated by an odds ratio (OR) of 4,2 and a statistically significant disparity (P0,001) (Al-Badri et al., 2022). However, the results of previous research contradict the findings reported by Li and Yue, who posited that there are no substantial variations in the genotype and allele frequencies of polymorphisms between individuals diagnosed with systemic lupus erythematosus and a control group consisting of healthy individuals (M. Li et al., 2019; Y. Li et al., 2017). Li and Yue conducted a study on a Korean population and found that IL23R rs1884444 had a noteworthy impact on esophageal cancer (M. Li et al., 2019).

In accordance with research conducted by Badri et al., it is evident that genetic diversity exerts an impact on immune pathways. The implications of this phenomenon include the modulation of mucosal defense and systemic host immunity against commonly encountered fungal infections in humans, such as Candida, Aspergillus, and Cryptococcus. Additionally, these findings revealed a significant impact on the diversity of bacteria present in the oral cavity of individuals diagnosed with type 2 diabetes mellitus (T2DM). Polymorphisms in cytokine genes directly affect the number of cytokines, resulting in a modified flora environment and an elevated likelihood of their conversion to microbial pathogens. This finding is unprecedented in the Iraqi population. (Al-Badri et al., 2022).

Conclusion

Patients with type 2 diabetes mellitus are prone to a range of diseases, including fungal infections. Patients diagnosed with type 2 diabetes mellitus exhibit distinct characteristics with respect to the prevalence of fungal infections.

In addition to immunocompromised conditions, patients with type 2 DM are susceptible to fungal infections due to factors such as the administration of SGLT2 inhibitor medications and the influence of the IL-23R gene polymorphism. With the results of this study, it is hoped that people will be more aware of controlling their blood sugar levels, so that they do not suffer from diabetes mellitus.

Conflict of Interest

The authors declare no conflicts of interest.

Reference

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