DOI: https://doi.org/10.61841/mc2acz58 Publication URL: https://nnpub.org/index.php/MHS/article/view/2216

ASSOCIATION OF TYPE 2 DIABETES MELLITUS AND CANDIDIASIS : A TEN YEARS SYSTEMATIC REVIEW

[1*]Ronald Yulianto, [1]Ellen Aristika Gunawan

[1]*Faculty of Medicine, Tarumanagara University, Special Region of Jakarta, Indonesia*

Correspondence Author:
ronald.y.chung@gmail.com

ABSTRACT

Background: *Diabetes mellitus is a chronic disease that may reduce resistance to microbial infection of tissues and decrease tissue repair capacity. It is both an endocrine and a metabolic dysfunction involving the control of blood glucose levels, resulting in hyperglycemia.*

The aim: *The aim of this study to show about association of type 2 diabetes mellitus and candidiasis.*

Methods: *By the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. This search approach, publications that came out between 2014 and 2024 were taken into account. Several different online reference sources, like Pubmed, SagePub, and Sciencedirect were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.*

Result: *Five publications were found to be directly related to our ongoing systematic examination after a rigorous three-level screening approach. Subsequently, a comprehensive analysis of the complete text was conducted, and additional scrutiny was given to these articles.*

Conclusion: *Diabetic patients had a higher candidal carriage rate and a variety of candidal species that were resistant to azole antifungal agents.*

Keyword: *Candidiasis, type 2 diabetes mellitus, fungal, infection.*

INTRODUCTION

Diabetes mellitus is a group of metabolic disorders characterized by high blood glucose levels over a prolonged period. Patients with diabetes are susceptible to infection and usually require more hospitalization, compared with the general population. With the productive management of diabetic complications, the proportional mortality due to vasculopathy has declined, offset by non-vascular causes, including infection, during the past three decades. In developing countries, infection is one of the three leading causes of deaths in patients with diabetes, and increases the excess risk to fourfold.[1]

Diabetes mellitus is a predisposing factor to the fungal infections, especially those caused by *Candida* species is well-established. Patients with diabetes are prone to infection; and oral candidiasis has been found to be more prevalent among patient with diabetes compared with nondiabetic controls. In the majority, *Candida* is the part of the normal flora and is in the normal state kept under control by means of specific and nonspecific defense mechanisms and by the competition of the microbes in the normal flora.[2]

DM can also lead to a compromise in cellular immunity. A series of inflammatory reactions occur because of insulin resistance, as insulin signaling stoppage causes aggravation to the pre-existing inflammatory milieu due to metabolic disturbances in DM. In accordance with the American Diabetes Association, diabetic patients suffer from a major problem of a weak immune system that hampers their capability to fight intrusive microorganisms, rendering them a higher predisposition to infections. The recovery time from infections or injuries in individuals with DM is significantly prolonged in comparison to the healthy population. The diseases that Candida species can cause with greater incidences in diabetics.[3]

Diabetes mellitus has many oral manifestations, complication, and infections such as dry mouth, burning mouth syndrome (BMS), taste disorders, oral candidiasis, rhinocerebral zygomycosis (mucormycosis), aspergillosis, geographic tongue, oral lichen planus, delayed wound healing, periodontal disease, gingivitis, and increased incidence of infection.[4]

Yeast infections in diabetic patients are common. *Candida* spp. is frequently found in patients with poor glycemic control, and it was already shown that increased oral *Candida* carriage is related to increasing levels of glucose in saliva. Oral candidiasis is commonly caused by *C. albicans* species and presents many clinical forms (pseudomembranous candidiasis, cheilitis, and stomatitis).[4]

Taking into account such considerable global prevalence of these two frequently coexistent clinical conditions, it is of no wonder that diabetic patients with genitourinary candidiasis are currently pervasive not only in primary practice but also in secondary and tertiary care facilities. In addition, a relatively new group of anti-hyperglycemic drugs known as sodium glucose cotransporter 2 (SGLT2) inhibitors made both females and males more prone to *Candida* colonization of the urogenital region as well as for subsequent infection. All of this means urogenital *Candida* infections may become even more ubiquitous among diabetic patients in the future. Therefore, given the scarcity of recent and comprehensive sources that provide an integrative and critical overview of the available literature on this topic, in this review we aimed to summarize microbiological, pathophysiological, and clinical facets of urogenital infections with *Candida* species in both females and males with diabetes.[5]

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this literature review, we compare and contrast association of type 2 diabetes mellitus and candidiasis. It is possible to accomplish this by researching or association of type 2 diabetes mellitus and candidiasis. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it needs to determine about association of type 2 diabetes mellitus and candidiasis. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2014, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used " association of type 2 diabetes mellitus and candidiasis." as keywords. The search for studies to be included in the systematic review was carried out using the PubMed, SagePub, and Sciencedirect databases by inputting the words: *(("Candidiasis"[MeSH Subheading] OR "fungal infection"[All Fields] OR "Diabetes mellitus" [All Fields]) AND ("Type 2 Diabetes Mellitus"[All Fields] OR " Risk factor"[All Fields]) AND ("Complication"[All Fields]) OR ("Management" [All Fields]))*used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and cannot have been seen anywhere else.

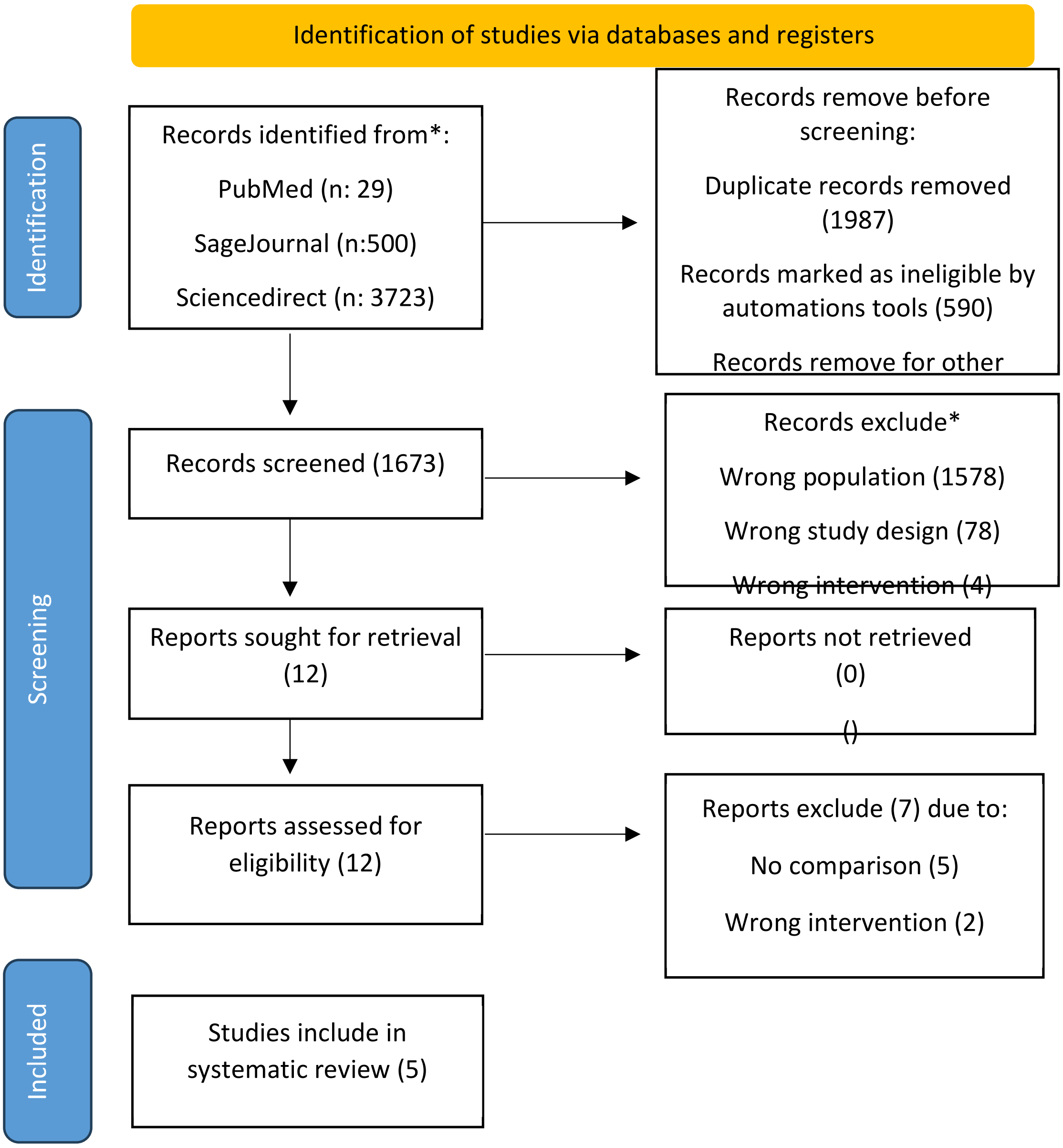

Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. in order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

Using reputable resources like Science Direct, PubMed, and SagePub, our research team first gathered 4252 publications. A thorough three-level screening strategy was used to identify only five papers as directly relevant to our ongoing systematic evaluation. Next, a thorough study of the entire text and further examination of these articles were selected. Table 1 compiles the literature that was analyzed for this analysis in order to make it easier to view.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Gomes, CC et al., 2017[6]	Brazil	A case-control study was conducted on 15 patients with type 2 diabetes mellitus (G1) and 15 non-diabetics (G2) with periodontal endodontic lesions.	30	*C. albicans* was identified in 79.2% and 20.8% of the 60 samples collected from diabetic and normoglycemic patients, respectively. Of the 30 samples collected from periodontal pockets, 13 showed a positive culture for *C. albicans*, with 77% belonging to G1 and 23% to G2. Of the 11 positive samples from root canals, 82% were from G1 and 18% from G2. Production of proteinase presented a precipitation zone Pz<0.63 of 100% in G1 and 72% in G2, in redox and negative (Pz=1), under anaerobic conditions in both groups. Hydrophobicity of the strains from G1 indicated 16.4% with low, 19.3% with moderate, and 64.3% with high hydrophobicity in redox. In G2, 42.2% had low, 39.8% had moderate, 18% had high hydrophobicity in redox. In anaerobic conditions, G1 showed 15.2% with low, 12.8% with moderate, and 72% with high hydrophobicity; in G2, 33.6% had low, 28.8% had moderate, and 37.6% had high hydrophobicity. There was statistical difference in the number of positive cultures between G1 and G2 (p<0.05) with predominance in G1. There was statistical difference for all virulence factors, except hemolysis (p=0.001).
Kumar, S et al., 2014[7]	India	The study population	90	The salivary glucose levels were significantly higher in

		consisted of three groups: Group 1 consisted of 30 controlled diabetics and Group 2 consisted of 30 uncontrolled diabetics based on their random nonfasting plasma glucose levels. Group 3 consisted of 30 healthy controls.		controlled and uncontrolled diabetics when compared with controls. The salivary candidal carriage was also significantly higher in uncontrolled diabetics when compared with controlled diabetics and nondiabetic controls. The salivary glucose levels showed a significant correlation with blood glucose levels, suggesting that salivary glucose levels can be used as a monitoring tool for predicting glycemic control in diabetic patients. In controlled diabetics, the salivary glucose levels showed a very large correlation coefficient ($r = 0.841$) and statistically strong significant association ($P < 0.001$) with blood glucose levels. A large correlation coefficient (r-value = 0.629) and statistically strong significant association ($P < 0.001$) was seen between salivary glucose levels and glycosylated hemoglobin. The correlation coefficient between salivary glucose levels and candidal counts showed a large correlation ($r = 0.539$) in controlled diabetics. A statistically significantly strong association was seen between salivary glucose levels and candidal counts ($P < 0.001$) in the same.
Vijayalakshmi, L et al., 2020[8]	India	The samples included in the study were divided into two groups: group A, comprises 50 patients with type 2 DM, and group B, comprises 30 subjects who were nondiabetic. A nonrandom consecutive sampling technique was used to enroll the subjects for the study. The $\chi 2$ test was used to examine the characteristics of the samples.	80	The results found that there is a significant difference in saliva and swab for *Candida* growth between patients with type 2 DM and normal healthy individuals. Swab had shown slightly more *Candida* growth than saliva in group A (type 2 DM). No significant variation in Candida growth was found. *Candida krusei* was seen in normal healthy individuals alone. In antifungal susceptibility pattern to various antifungal agents, *Candida tropicalis* has shown a significant result for various antifungal agents whereas *Candida albicans* and *Candida dubliniensis* did not show any significant result for various antifungal agents used in group A (patients with type 2 DM).

Bhuyan, L et al., 2018[9]	India	Study group comprised of well-controlled, moderately-controlled and poorly controlled Type II diabetic patients grouped according to the level of glycated hemoglobin concentration with 50 patients in each group and 50 healthy individuals.	100	There was a significant difference in frequency of *Candida* in poorly controlled diabetes when compared to moderately controlled diabetes, well controlled diabetes and normal patients (*P* = 0.045). A higher number of colony count was seen among poorly controlled diabetes than well controlled, moderately controlled and non diabetic subjects. A comparatively low number of non-albicans were seen in healthy individuals. *C. albicans* showed an increased resistance to fluconazole in DM patients in comparison to control group (*P* = 0.001). Other species showed a variable sensitivity pattern.
Shenoy, MP et al., 2014[10]	India	The study design comprised of previously diagnosed 30 patients each with type 1 diabetes mellitus (Group A) and type 2 diabetes mellitus (Group B) and 30 age-, sex- and dental status-matched healthy non-diabetic individuals as controls (Group C).	90	Data analysis showed statistically significant higher positive candidal growth in Group A and Group B when compared to Group C. The CFU/ml values were significantly higher in Groups A and B as compared with Group C. Significant positive correlation of CFU/ml with fasting blood sugar level and HbA1c% in both Groups A and B was seen. Oral signs and symptoms observed in diabetics were dry mouth, burning sensation, fissuring and atrophic changes of tongue and erythematous areas, which positively correlated with candidal load. Oral signs and symptoms in diabetes like erythematous areas in oral cavity, fissured tongue, atrophic changes in tongue and burning sensation were seen to be higher in Group B patients when compared to Group A, except for 83% of Group A patients presented with complications of dry mouth when compared to 67% in Group B

Gomes, CC et al (2017)[6] showed the prevalence of *Candida albicans* was higher in patients with diabetes mellitus in samples collected from periodontal pockets and root canals. Strains of *Candida albicans* showed increased virulence in diabetic patients compared to normoglycemic patients. The production of proteinase and phospholipase activity were higher in diabetic patients when analyzed in redox. Hydrophobicity of the strains were higher in diabetic patients under anaerobic conditions. However, hemolytic activity was positive for both groups in both atmospheres.

Kum
ar, S et al (2014)[7] showed the detection of diabetes can be performed by measuring the salivary glucose levels. This study can be taken as a stepping stone to establishing accepted reference values for salivary glucose, whereby, in the future,

saliva may serve as a non-invasive specimen for the detection of diabetes. Oral diagnosticians are advised to screen the diabetic patients for any oral fungal infections at the earliest and further institute the management for the same.

Vijayalakshmi, L et al (2020)[8] showed diabetic individuals are prone to a hyperglycemic state, which in turn favors the growth and establishment of *Candida* species. Although a smaller percentage of multidrug-resistant *Candida* species has been observed in the saliva of patients with type 2 DM, it is prudent to consider prophylactic measures in such patients. We suggest extensive and elaborative studies in the future to either support or refute our results.

Bhuyan, L et al (2018)[9] showed a higher proportion of strains different from *C. albicans* species isolated from unstimulated saliva and their variable susceptibility to the commonly prescribed antifungals in diabetes indicate the necessity of the special mode of diagnostic and therapeutic management. This highlights the importance of routine candidal speciation and appropriate selection of prophylactic antifungal regimen after susceptibility testing, especially during intermittent visits. This might prevent systemic dissemination of this opportunistic yeast in such patients. Failure of host defense in patients with diabetes necessitates an effective oral health regime. Dental health practitioners should make the patients aware of possible risk factors associated with poor oral health and should provide guidance for effective oral care.

Shenoy, MP et al (2014)[10] showed both type 1 and 2 DM patients are more predisposed to candidal carriage density. The glycemic control status i.e. HbA1c% of these individuals may directly influence candidal colonization and various oral manifestations and hence their symptomatology. The assessment of long-term glycemic status of diabetics is more reliable than estimating the fasting and postprandial blood glucose levels for establishing the disease status in these patients having predisposing factors for development of candidal infection. The quantitative and biochemical characterization allow better insight in studying the association of DM and candida. The diagnosis and management of increased candidal colonization and clinical candidiasis may be achieved considering both local and systemic factors. Underlying DM may be identified by the presence of oral candidiasis, which serves as a clinical marker. Further studies involving both candidal characteristics (culture and biochemical) and salivary profile of patients with DM may aid in better understanding of the association of this group of mycotic organisms and DM.

DISCUSSION

Diabetes mellitus (DM) is a chronic metabolic and degenerative disorder that is characterized by chronic hyperglycemia and causes long-term complications like retinopathy, neuropathy, and nephropathy, generally accelerating macro- and micro-vascular changes. It is becoming one of the largest emerging threats to public health in the 21st century. Several immune alterations have been described in diabetes with cellular immunity being more compromised and with changes in polymorphonuclear cells, monocytes, and lymphocytes. DM individuals have higher glucose serum concentrations than healthy individuals (between 4.0 to 5.4 mmol/L or 72 to 99 mg/dL when fasting and up to 7.8 mmol/L or 140 mg/dL two hours after eating; hemoglobin A1c (glycohemoglobin) ≤5.7%). In type 1 DM, the pathogenesis is multifactorial because of antibody-mediated autoimmunity, environmental toxins exposure, and major histocompatibility complex (MHC) Class II histocompatibility complex HLA-DR/DQ genetic polymorphisms.[11,12]

Type 2 diabetes is the most common type of diabetes, accounting for about 90% of the cases. The prevalence of type 2 diabetes is constantly increasing. It is estimated that there are currently about 1.5 million diabetic patients in Iran. In some people, infection with *C. albicans* is not recognized as the first symptom of diabetes. In a study in Pakistan, of 100 diabetic patients hospitalized for other causes, 27 showed symptoms of infection with Candida.[13]

Type 2 DM is principally a disease of middle age and elderly. It has both micro vascular and macro vascular complications. In micro vascular complications, cutaneous manifestations are very common and in this group, infections especially fungal are most frequent. Oral candidiasis is a common fungal infection in type 2 diabetics that presents as discrete and confluent white plaques on the buccal mucosa, tongue, and sometimes the palate, gingivae, and floor of the mouth; these plaques may be wipeable.[9]

Many studies have reported that Candida species are the most common yeast isolated from diabetic foot ulcers. However, few studies have reported *C. albicans* as the most common species. Increased prevalence of fungal infections in the spaces between the fingers and nails in the diabetic foot leads to severe and profound inflammatory processes in the foot. Fungal infections among immunocompromised patients, especially diabetic patients, are one of the most important health concerns in the world today.[13,14]

Diabetes mellitus has numerous complications on the oral cavity represented by the increased pathogenic activity of the oral microbiota to cause diseases such as dental caries, periodontal diseases (PD), and oral candidiasis or cause physiological disorders such as dry mouth (xerostomia and decreased salivary flow rate), lesions in oral mucosa, altered taste, geographic tongue, oral cancer, burning mouth syndrome, and temporomandibular disorders.[15]

Diabetes mellitus may also encourage different fungal species like *Candida* to become pathogenic due to many DM-related factors such as xerostomia, low salivary flow, higher salivary glucose level, and microvascular degeneration. *Candida albicans* is the most frequent species of *Candida* in diabetic patients compared to non-diabetic individuals.[15]

Fungal infections of oral mucosal surfaces and removable prostheses are more commonly found in diabetics and higher salivary glucose concentration may be associated with increased oral candidal carriage in diabetics. It is becoming increasingly apparent to investigators and clinicians that saliva has many diagnostic uses and is valuable in the young, the old and infirm, and in large-scale screening and epidemiological studies. Salivary glucose concentrations may also be used as a non invasive tool to monitor glycemic control in diabetics. The aim of this study was to assess the correlation between blood glucose levels and salivary glucose levels in order to determine if salivary glucose levels could be used as a noninvasive tool for monitoring glycemic status in diabetics and also to explore the correlation between salivary glucose levels and oral candidal carriage.[16]

CONCLUSION

In conclusion, diabetic patients had a higher candidal carriage rate and a variety of candidal species that were resistant to azole antifungal agents. Oral candidal colonization was significantly associated with glycemic control, type of diabetes, and pH of saliva. Although *Candida albicans* was the predominant isolate, a variety of other candidal species, with less susceptibility to azole antifungal agents, were identified in diabetics.

REFERENCES

[1] Lao M, Li C, Li J, Chen D, Ding M, Gong Y. Opportunistic invasive fungal disease in patients with type 2 diabetes mellitus from Southern China: Clinical features and associated factors. J Diabetes Investig. 2020;11(3):731–44.
[2] Chouhan S, Kallianpur S, Prabhu Kt, Tijare M, Kasetty S, Gupta S. Candidal prevalence in diabetics and its species identification. Int J Appl Basic Med Res [Internet]. 2019;9(1):49. Available from: https://journals.lww.com/10.4103/ijabmr.IJABMR_259_18
[3] Mohammed L, Jha G, Malasevskaia I, Goud HK, Hassan A. The Interplay Between Sugar and Yeast Infections: Do Diabetics Have a Greater Predisposition to Develop Oral and Vulvovaginal Candidiasis? Cureus. 2021;13(2).
[4] Nouraei H, Jahromi MG, Jahromi LR, Zomorodian K, Pakshir K. Potential Pathogenicity of Candida Species Isolated from Oral Cavity of Patients with Diabetes Mellitus. Biomed Res Int. 2021;2021(type 1):1–6.
[5] Talapko J, Meštrović T, Škrlec I. Growing importance of urogenital candidiasis in individuals with diabetes: A narrative review. World J Diabetes. 2022;13(10):809–21.
[6] Gomes CC, Guimarães LS, Pinto LCC, Camargo GADCG, Valente MIB, Sarquis MIDM. Investigations of the prevalence and virulence of candida albicans in periodontal and endodontic lesions in diabetic and normoglycemic patients. J Appl Oral Sci. 2017;25(3):274–81.
[7] Kumar S, Padmashree S, Jayalekshmi R. Correlation of salivary glucose, blood glucose and oral candidal carriage in the saliva of type 2 diabetics: A case-control study. Contemp Clin Dent. 2014;5(3):312–7.
[8] Vijayalakshmi L, Raj JS, Kavitha J, Krishnaraj S, Manovijay B, Manikandan D. A case–control study to evaluate candidal parameters in the oral cavity of patients with type 2 diabetes mellitus. J Pharm Bioallied Sci [Internet]. 2020;12(5):389. Available from: https://journals.lww.com/10.4103/jpbs.JPBS_115_20
[9] Bhuyan L, Hassan S, Dash K, Panda A, Behura S, Ramachandra S. Candida species diversity in oral cavity of type 2 diabetic patients and their In vitro antifungal susceptibility. Contemp Clin Dent [Internet]. 2018;9(5):83. Available from: https://journals.lww.com/10.4103/ccd.ccd_70_18
[10] Shenoy MP, Puranik RS, Vanaki SS, Puranik SR, Shetty P, Shenoy R. A comparative study of oral candidal species carriage in patients with type1 and type2 diabetes mellitus. J Oral Maxillofac Pathol. 2014;18(5):60–5.
[11] Rodrigues CF, Rodrigues ME, Henriques M. Candida sp. Infections in patients with diabetes mellitus. J Clin Med. 2019;8(1).
[12] Pérez-Vielma NM, Gómez-López M, Martínez-Godínez M de los Á, Luna-Torres AL, Domínguez López A, Miliar-García Á. Candida Variety in the Oral Cavity of Mexican Subjects with Type 2 Diabetes Mellitus and TLR2 Gene Expression. Clin Pract. 2024;14(2):417–25.
[13] Rasoulpoor S, Shohaimi S, Salari N, Vaisi-Raygani A, Rasoulpoor S, Shabani S, et al. Candida albicans skin infection in patients with type 2 diabetes: a systematic review and meta-analysis. J Diabetes Metab Disord. 2021;20(1):665–72.
[14] Zarei N, Roudbary M, Mohammadi SR, Santos ALS Dos, Nikoomanesh F, Mohammadi R, et al. Prevalence, molecular identification, and genotyping of Candida species recovered from oral cavity among patients with diabetes mellitus from Tehran, Iran. Adv Biomed Res. 2022;11(1):29.
[15] Al-Janabi AAHS. A Positive or Negative Connection of Diabetes Mellitus to the Oral Microbiota. Eurasian J Med. 2023;55(1):83–9.
[16] Bhattacharyya A, Chandra S, Singh A, Raj V, Gupta B. Salivary glucose levels and oral candidal carriage in Type 2 diabetics. J Oral Biol Craniofacial Res [Internet]. 2018;8(3):158–64. Available from: http://dx.doi.org/10.1016/j.jobcr.2016.11.004