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Corresponding Author
Shashank Tyagi,
Department of Biochemistry, SRVS Government Medical College, Shivpuri, Madhya Pradesh, India
drshashanktyagi@yahoo.com

Author Designation
[1]Assistant Professor
[2]Lab Chemist
[3]Demonstrator
[4]Professor and Head

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Prevalence and Risk Factors of Fungal Infections among Diabetic and Non-Diabetic Individuals

[1]Vepada Ravi Kiran, [2]Narendra Rahaengdale, [3]Nandini Shukla and [4]Shashank Tyagi

[1]Department of Microbiology, SRVS Government Medical College, Shivpuri, Madhya Pradesh, India
[2,4]Department of Biochemistry, SRVS Government Medical College, Shivpuri, Madhya Pradesh, India
[3]Department of Community Medicine, Atal Bihari Vajpayee, Government Medical College, Vidisha, Madhya Pradesh, India

ABSTRACT
Diabetes mellitus is group of metabolic disorder characterised by the high blood glucose level over a prolonged period. Patients with diabetes are prone for fungal infection compared with general population. This study aimed to investigate the prevalence and risk factors of fungal infection in diabetic and non diabetic individuals. This prospective observational study was conducted in department of microbiology in a tertiary care center, India. A total of 600 participants (300 diabetics and 300 non diabetics) were enrolled in this study. All samples were collected from various sites and cultured on Sabouraud dextrose agar. Gram stain was used to observe yeast cells and lacto phenol cotton blue stain was used for hyphae. The prevalence of fungal infection was more in type II diabetes (26%) than non diabetics (11%). Majority of the participants were 61-70 years age group, predominantly female. Most of them was obese category and belong to middle socio-economic class. The duration of diabetes and insulin therapy was significantly associated with the fungal infection ($p<0.05$).*Candida* species were the most common isolates followed by Aspergillus. Fungal infection was more prevalent in type 2 Diabetes mellitus patients. Hyperglycaemic state and duration of diabetes was significantly associated with fungal infection.

INTRODUCTION

Diabetes mellitus (DM), a non-communicable metabolic condition, has been linked to a broad spectrum of opportunistic bacterial and fungal infections[1]. According to the American Diabetes Association (A.D.A.), diabetes mellitus (DM) can be classified into the following categories: (i) Type 1 diabetes mellitus (T1DM), characterized by the loss of pancreatic b-cells induced by an autoimmune response, (ii) Type 2 diabetes mellitus (T2DM), identified by the gradual loss of insulin secretion and/or the development of insulin resistance, (iii) Gestational DM, developed in some pregnant women; and (iv) Other types of DM that are due to miscellaneous causes[2,3]. Fungal infections are taken less seriously but these are present as silent killers. Globally, more than 300 million people are at extremely high risk and 25 million people are at high risk of dying due to fungal infections[4]. Diabetes patients are vulnerable to fungal infection. The risk of mycoses increases 1.38-fold in patients with diabetes 6 and diabetes is widely recognized as a risk factor for invasive pulmonary aspergillosis. Uncontrolled hyperglycemia contributes to a poor prognosis of type 2 diabetes patients with Cryptococcosis[5,6]. The main determinants of burden of fungal infections are linked to socio-economic, geographical characteristics and increasing number of at-risk populations. Individuals susceptible to fungal infections include those with immunosuppressive illnesses such as HIV/AIDS, tuberculosis, chronic pulmonary diseases (COPD), cancer and diabetes[7,8]. Uncontrolled hyperglycemic condition leads to infection due to dysfunction of the immune system by the reduction of T-lymphocyte, neutrophil activity, reduction of secretion of inflammatory cytokines, disorders of antibody mediated immunity along with angiopathy, neuropathy, glycosuria and increased apoptosis of polymorph nuclear leukocytes[9,10]. The diabetic patients, due to their condition, lack adequate immunity to defend the body system against invading pathogenic fungal organisms thus they can be exposed to these agents either by inhalation of the spores of these fungal agents from the environment or by close contacts.

Aims and objectives: The aim of this study was to determine the prevalence of systemic fungal infections in diabetic and non diabetic patients and also evaluated the risk factors and association of insulin therapy on outcome of systemic fungal infection.

MATERIALS AND METHODS

This is a cross-sectional survey carried out at department of microbiology in a tertiary care hospital, India. The participants were recruited during normal routine check-up (out-patients) or those admitted into the hospital wards (in-patients) during the study period. All suspected patients of fungal infections were enrolled and analysed.

Inclusion criteria:

- Patients aged 18 years and above
- Participants diagnosed type II diabetes mellitus and age matched control
- Participants who provides consent for the study

Exclusion criteria:

- Participants below 18 years of age
- The diabetic patients with co-infections of human immunodeficiency virus and pregnant women
- Patients who received antifungal therapy before or at the time of admission
- Participants who not willing for the study

All participants underwent a detailed history, age, gender, body mass index, socio-economic status, residential areas, education, duration of diabetes, clinical examination and investigations which included complete blood counts, Blood sugar fasting, Blood sugar post prandial, HbA1c, KOH mount, Urine R/M, LFT, RFT and Lipid Profile

The samples were collected from the all participants from various sites of each individual. The samples included oral wash, foot swab from inter digital space, midstream urine, hair shaft and nail scrapings.

All samples were inoculated in Sabouraud dextrose agar (SDA) containing chloramphenicol 50 mg L^{-1} concentration, incubated at 370°C and at 250°C for 7-14 days under aerobic conditions. Fungal colonies morphology was recorded. Each isolates were stained by Gram stain for the detection of yeast cells. Colony growth which showed hyphae spreading on the media was identi ed by using lactophenol cotton blue mount

Data analysis: Data was entered and analyzed by using SPSS software version 21. Independent t-test and linear regression analysis were applied and $p<0.05$ was taken as statistically significant

RESULTS

A total of 600 participants (300 were diagnosed diabetic patients and 300 non diabetic healthy persons) were enrolled for the study. Majority of the participants (59%) were females than male, although the difference was not statistically significant, most of them were 61-75 years age group, the mean age of the subjects was 55.29±9.35 (range of 18-80 years-old). 48.3% of diabetic patients was obese and 51.6% belongs to middle socio-economic class (Table 1).

Table 1: Distribution of socio-demographic characteristics among study participants

Characteristics	Diabetic group (n = 300)	Non diabetic group (n = 300)	p-value
Age in years			
18-30	35	45	0.444
31-45	65	55	
46-60	85	90	
61-75	105	95	
>75	10	15	
Gender			
Male	123	137	0.148
Female	177	163	
Body mass index (BMI)			
Underweight (<18.5)	25	30	0.252
Normal (18.5-24.9)	130	145	
Obese (>24.9)	145	125	
Socio-economic class			
Lower	52	56	0.333
Middle	142	155	
Upper	106	89	

Table 2: Prevalence of fungal infection among diabetic and non diabetic individual

	Diabetic individuals	Non diabetic individuals	p-value
Fungal infection present	78 (26%)	33 (11%)	<0.0001
Fungal infection absent	222	267	

Table 3: Association of fungal infection with diabetic therapy and complications

Variables	Total no.	Fungal infection	p-value
Duration of diabetes			
≤5 years	122	42	0.036
>5 years	178	36	
Insulin therapy			
Yes	138	50	0.001
No	153	21	
No response	9	7	
Family history of diabetes			
Present	80	22	0.785
Absent	220	56	
Previous antibiotic therapy			
Yes	67	20	0.526
No	233	58	
HbA1c level			
≤7	162	45	0.559
>7	138	33	

The prevalence of fungal infection among diabetic patients was 78 (26%) whereas among non diabetic individuals it was only 11%. Statistically significantly higher prevalence of fungal infection was observed in diabetic patients as compared to non diabetic participants (Table 2).

The risk factors that were assessed indicated that duration of diabetes and insulin therapy was statistically significant for systemic fungal infection in diabetics, with a $p<0.05$. The diabetic patients with less than 5 years duration had 53.8% fungal isolates than those with greater than 5-years, 46.2%. The other parameters assessed, like family history of diabetics, HbA1c level and previous antibiotic therapy were not statistically ($p>0.05$) (Table 3).

It was observed that there was no multiple fungal growths in each of the patients thus the colonization of the fungal isolates were specific for each participant. The frequency of the fungal isolates indicates that *Candida* species was 38 (48.7%) while *Aspergillus* species accounted for 36 (46.2%). The dimorphic fungi, *Blastomyces dermatitidis* and *Coccidioides immitis* were isolated 8.9 and 5.1%, respectively. Details shown in Fig. 1.

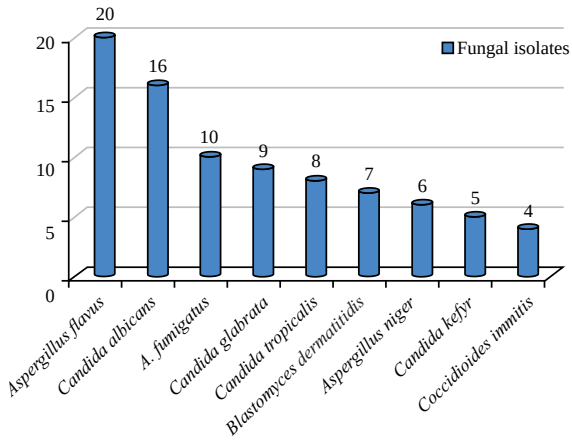

Fig. 1: Distribution of fungal isolates among diabetic patients

DISCUSSIONS

Diabetic patients are prone to suppressed immunity due to excessive accumulation of sugar resulting from decreased insulin secretion due to this the diabetic patients are exposed to opportunistic fungal infections[11]. Thus the goal of this study was to assess systemic fungal infections in diabetic patients.

This is important because in undiagnosed cases, pulmonary pneumonia may present a serious clinical problem in the affected diabetics.

The prevalence rate of fungal infection was significantly higher among diabetic patients as compared to healthy individuals. In a similar study in South Africa, Moore *et al*.[12] and Saud *et al*.[13] reported that fungal infections in diabetics are twice higher than non-diabetics. The key risk factor for this high prevalence is increase in blood sugar level. High blood sugar promotes the binding of fungus to the host cell surface and high glucose in salivary secretions with low pH, poor oral hygiene and very low salivary secretions also allow the growth of more than 50 *Candida* species colonies in the oral cavity[14].

In our study it has been reported that women are more infected with fungal infections, concordance finding reported by Kachi *et al*.[15].

Majority of the participants were older age group seen in current study, correlate with the Nigotia *et al*.[16]. Thus the age difference among the diabetic remains a factor in systemic fungal infections. This may be due to interaction between aging and suppressed immunity due to diabetes[17].

In this study the duration of diabetes and insulin therapy were significantly associated with the fungal infection, similar to other studies like: Santosh *et al*.[18], Stoeckle *et al*.[19] and Unnikrishnan *et al*.[20].

It was indicates that the patients that were newly diagnosed of diabetes had a greater prevalence of than those that were diagnosed of diabetes for more than 5 years. Patients before knowing their diabetic status blood sugar levels of the diabetic patients were higher and most of them cannot be controlled by the use of insulin therapy, hence higher prevalence of fungal infections among this group.

Another important risk factor for systemic fungal infection in diabetes is the family history of diabetes but in present study it was not significantly associated with the fungal infection, accordance to Khanam *et al*.[21].

The frequency of fungal infection indicates that *Candida* species was predominant isolates followed by Aspergillus species, our results comparable with the Luque *et al*.[22] and Rodrigues *et al*.[23].

Aspergillus flavus constitutes the majority 25.6% of the fungal isolates. In contrast Santhosh *et al*.[18] reported that Aspergillus fumigatus is the predominant species followed by *Aspergillus flavus* but it has been noticed that in certain locales and hospitals, *Aspergillus flavus* is more common in air than Aspergillus fumigates for unclear reasons Hedayati *et al*.[24]. Those with severe liver disease are at high risk for Aspergillus infection, which agreed with Panasiuk *et al*.[25] that suggested that invasive Aspergillosis is a potential fatal complication of severe liver disease.

In our study, the isolation of *Candida* species was higher than other fungal isolates which is in agreement in a review by Richardson and Lass-Flörl[26] and Lao *et al*.[1], reported the rising incidence of *Candida* species can attributed to several risk-factors that are prevalent in critically ill patients.

The occurrence of *Blastomyces dermatitidis* and *Coccidioides immitis* are of public concern because these dimorphic fungi are not common in this environment because of its weather and lack of soil salinity but can be as a result of occupational hazards or occupational exposure to endemic regions with archeology and high dust exposure[27,28].

CONCLUSION

Diabetics are more prone to fungal infections then non diabetics. Glycemic status and duration of the diabetes has a significant relationship with the prevalence of fungal infection and well controlled blood sugar is beneficial for avoiding fungal infection in such patient. Fungal agents like *Blastomyces dermatitidis* and *Coccidioides immitis* are of public health challenge due to high transmission rate. Early screening of the patients is important in the control and management of the infection

REFERENCES

1. Lao, M., C. Li, J. Li, D. Chen, M. Ding and Y. Gong, 2019. Opportunistic invasive fungal disease in patients with type 2 diabetes mellitus from southern China: Clinical features and associated factors. J. Diabetes Invest., 11: 731-744.
2. ADS., 2018. Classification and diagnosis of diabetes: Standards of medical care in diabetes-2018. Diabetes Care, 41: S13-S27.
3. ADA., 2019. Classification and diagnosis of diabetes: Standards of medical care in diabetes-2019. Diabetes Care, 42: S13-S28.
4. GAFFI, 2013. Our vision Is to reduce illness and death associated with fungal disease worldwide. Global Action Fund for Fungal Infectious (GAFFI), Hale, UK, https://www.hindawi.com/journals/ipid/2020/7949868/
5. Bassetti, M., J. Garnacho-Montero, T. Calandra, B. Kullberg and G. Dimopoulos *et al*., 2017. Intensive care medicine research agenda on invasive fungal infection in critically ill patients. Intensive Care Med., 43: 1225-1238
6. Li, Y., W. Fang, W. Jiang, F. Hagen and J. Liu *et al*., 2017. Cryptococcosis in patients with diabetes mellitus Ii in Mainland China: 1993 2015. Mycoses, 60: 706-713.
7. Upton, A. and K.A. Marr, 2006. Emergence of opportunistic mould infections in the hematopoietic stem cell transplant patient. Curr. Infect. Dis. Rep., 8: 434-441.

8. Armstrong-James, D., G. Meintjes and G.D. Brown, 2014. A neglected epidemic: Fungal infections in HIV/AIDS. Trends Microbiol., 22: 120-127.
9. Alves, C., J. Casqueiro and J. Casqueiro, 2012. Infections in patients with diabetes mellitus: A review of pathogenesis. Indian J. Endocrinol. Metab., 16: 27-36.
10. Baradkar, V., M. Mathur and S. Kumar, 2010. Hichrom candida agar for identification of candida species. Indian J. Pathol. Microbiol., 53: 93-95.
11. Muller, L.M.A.J., K.J. Gorter, E. Hak, W.L. Goudzwaard, F.G. Schellevis, A.I.M. Hoepelman and G.E.H.M. Rutten, 2005. Increased risk of common infections in patients with type 1 and type 2 diabetes mellitus. Clin. Infect. Dis., 41: 281-288.
12. Moore, P.A., J.C. Zgibor and A.P. Dasanayake, 2003. Diabetes: A growing epidemic of all ages. J. Am. Dent. Assoc., 134: 11-15.
13. Saud, B., P. Bajgain, G. Paudel, V. Shrestha and D. Bajracharya *et al*., 2020. Fungal infection among diabetic and nondiabetic individuals in Nepal. Interdiscip. Perspect. Infect. Dis., 2020: 1-7.
14. Mohammadi, F., M.R. Javaheri, S. Nekoeian and P. Dehghan, 2016. Identification of *Candida* species in the oral cavity of diabetic patients. Curr. Med. Mycol., 2: 1-7.
15. Kachi, U.T., A.V. Nneka and E. Uche, 2018. Assessment of systemic fungal infections among diabetic patients in Enugu, Nigeria. J. Infect. Dis. Epidemiol., Vol. 4. 10.23937/2474-3658/1510051
16. Nigotia, P., M. Subha, S. Jain, S.K. Jain, A Kansal and A. Garg, 2022. A study of fungal infections in diabetic patients in relation to glycemic status: A prospective study. J. Cardiovasc. Dis. Res., 13: 3328-3334.
17. Abu-Elteen, K.H., M.A. Hamad and S.A. Salah, 2006. Prevalence of oral Candida infections in diabetic patients. Bahrain Med. Bull., Vol. 28.
18. Santhosh, Y.L., K.V. Ramanath and M.R. Naveen, 2011. Fungal infections in diabetes mellitus: An overview. Int. J. Pharm. Sci. Rev. Res., 7: 221-225.
19. Stoeckle, M., C. Kaech, A. Trampuz and W. Zimmerli, 2008. The role of diabetes mellitus in patients with bloodstream infections. Swiss Med. Weekly, 138: 512-519.
20. Unnikrishnan, R., R.M. Anjana and V. Mohan, 2016. Diabetes mellitus and its complications in India. Nat. Rev. Endocrinol., 12: 357-370.
21. Khanam, A., G. Hithamani, J. Naveen, S.R. Pradeep, S. Barman and K. Srinivasan, 2023. Management of invasive infections in diabetes mellitus: A comprehensive review. Biologics, 3: 40-71.
22. Luque, A.G., M.S. Biasoli, M.E. Tosello, A. Binolfi, S. Lupo and H.M. Magaró, 2008. Oral yeast carriage in HIV infected and non infected populations in Rosario, Argentina. Mycoses, 52: 53-59.
23. Rodrigues, C., M. Rodrigues and M. Henriques, 2019. *Candida* sp. infections in patients with diabetes mellitus. J. Clin. Med., Vol. 8. 10.3390/jcm8010076
24. Hedayati, M.T., A.C. Pasqualotto, P.A. Warn, P. Bowyer and D.W. Denning, 2007. *Aspergillus flavus*: Human pathogen, allergen and mycotoxin producer. Microbiology, 153: 1677-1692.
25. Panasiuk, A., J. Wysocka, E. Maciorkowska, B. Panasiuk, D. Prokopowicz, J. Zak and K. Radomski, 2005. Phagocytic and oxidative burst activity of neutrophils in the end stage of liver cirrhosis. World J. Gastroenterol., 11: 7661-7665.
26. Richardson, M. and C. Lass-Flörl, 2008. Changing epidemiology of systemic fungal infections. Clin. Microbiol. Infec., 14: 5-24.
27. Reyes-Montes, M.D., M.A. Pérez-Huitrón, J.L. Ocaña-Monroy, M.G. Frías-De-León, E. Martínez-Herrera, R. Arenas and E. Duarte-Escalante, 2016. The habitat of *Coccidioides* spp. and the role of animals as reservoirs and disseminators in nature. BMC Infect. Dis., Vol. 16. 10.1186/s12879-016-1902-7
28. Crum, N., C. Lamb, G. Utz, D. Amundson and M. Wallace, 2002. Coccidioidomycosis outbreak among united states navy seals training in a *Coccidioides immitis*-Endemic area-coalinga, California. J. Infect. Dis., 186: 865-868.