



## Predisposing Factors for Mucormycosis in Patients with Diabetes Mellitus; An Experience of 21 Years in Southern Iran

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### ► ABSTRACT

**Objectives:** To determine the prevalence and predisposing factors of mucormycosis in patients with diabetes mellitus (DM) in a Shiraz referral centers.

**Methods:** This retrospective case control study, reviewed the medical records of 162 patients with pathologically confirmed diagnosis of mucormycosis hospitalized in two major Shiraz University hospitals during the last 21 years. For each diabetic patient, two patients with diabetic ketoacidosis (DKA) matched for age, sex and the date of admission was selected as control group. Age, type of diabetes mellitus (DM) and duration of involvement as well as paraclinical findings were compared between cases and controls.

**Results:** There were 162 patients with mucormycosis of which 30 (18.5%) had DM as predisposing factor. Diabetes was the second common predisposing disease next to leukemia. There were 19 (63.3%) women and 11 (36.7%) men among the patients. The overall mortality rate was 53.33% mortality rate. The mean age of the patients was  $45.3 \pm 17.6$  years. The mean duration of diabetes in case and control groups were  $5.75 \pm 5.43$  and  $7.2 \pm 7.85$  years respectively, without any statistical significance between them ( $p=0.063$ ). Blood sugar in patients was lower than control group ( $p=0.012$ ). Serum bicarbonate level in case group was higher than in control group ( $p<0.001$ ). Arterial pH in control group was more acidic than case group ( $p<0.001$ ). Insulin dependent DM was significantly more prevalent in control group compared to case group (73.4% vs. 36.6%;  $p=0.002$ ).

**Conclusion:** Our study showed that the number of hospitalized patients with mucormycosis over the last 7 years has been decreased which is due to better control of infection in diabetics. In addition to hyperglycemia and acidosis, several other unknown factors like immune defects may predispose diabetics to this fungal infection.

**Keywords:** Mucormycosis; Diabetes mellitus; Predisposing factors; Iran.

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### Introduction

Zygomycosis is an invasive fungal infection which is primarily caused by fungi belonging to the *Mucoraceae* family. As in other invasive fungal diseases, impairment of the immune system is the most important predisposing factor to these fungal infections. Patients at risk usually have compromised

defense mechanisms, mainly caused by diabetes mellitus (DM), hematological diseases like leukemia or lymphoma, intravenous drug abuse or cytotoxic therapy, although there are reports of zygomycosis in otherwise healthy patients [1]. Other studies have reported diabetes mellitus as a predisposing factor to mucormycosis in 36%–88% of cases [2-4]. DM

is a clinical syndrome associated with deficiency of insulin secretion or function. It is considered as one of the largest emerging threats to health in the 21<sup>st</sup> century. It is estimated that there will be 380 million cases of DM in 2025 [5]. Beside the classical complications of the disease, DM has been associated with reduced response in T cells, neutrophil function, and responsible for disorders of humeral immunity [6-8]. Consequently, DM increases the susceptibility to infections by most common microbial pathogens as well as fungal agents that cause mucormycosis only in subjects with DM [8]. Such infections, in addition to their associated repercussions, may trigger DM complications such as hypoglycemia and ketoacidosis. The number of people with DM is increasing worldwide [9]. Because of the rising prevalence of DM, the number of patients at risk for this deadly infection is dramatically increasing [10]. Unfortunately, despite disfiguring surgical debridement and additional antifungal therapy, the overall mortality rate for mucormycosis remains as high as 50%, and approaches 100% among patients with disseminated disease or those with persistent neutropenia [11,12]. Clearly, new approaches to prevent and treat mucormycosis are urgently needed, and such strategies can be facilitated by clear understanding of the pathogenesis of the disease. Predisposing factors to mucormycosis are not well known in patients with diabetes, due to its rarity. The aim of this study was to determine the prevalence and predisposing factors of mucormycosis in patients with DM admitted to referral centers in Southern Iran.

## Materials and Methods

### *Study population*

This was a retrospective case control study being performed in Nemazee, Shahid Faghihi and Khalili hospitals affiliated with Shiraz University hospitals, principal referral centers in southern Iran, over a period of 21 years from April 1990 through March 2011. We included all the patients who were pathologically diagnosed to have mucormycosis and DM who were admitted to our centers during the study period. We excluded those with underlying diseases other than DM and also those suffering from leukemia and malignancies. Of 162 mucormycosis cases 30 (18.5%) had diabetes as their underlying disease. For each diabetic patient, two age-, sex- and admission's date-matched patients with diabetes ketoacidosis (DKA) were selected as control group. Those with malignancies and autoimmune diseases were not included as the control group. The study protocol was approved by Shiraz University of Medical Sciences institutional review board (IRB) and medical research ethics committee. As this was a

retrospective analysis of medical charts, no informed written consents were obtained from the patients.

### *Study protocol*

Evaluation at presentation included a detailed history, and otorhinolaryngologic, ophthalmic and neurologic examinations to assess the extent of the disease. Laboratory investigations included complete blood counts, blood urea, serum creatinine, serum glucose, urine for ketone bodies and blood gas analysis. Diagnosis was made on histopathological examination and KOH preparation of biopsy specimens obtained from the nasal cavity and/or paranasal sinuses and the palate. An orbital fine needle aspiration cytological (FNAC) study was done in some patients when histopathological diagnosis from other sites was equivocal. Computerized tomographic scans of the paranasal sinuses, orbits and brain were obtained to assess the extent of disease. All these information were obtained from the medical charts by reviewing and entering into a standard data gathering form.

The treatment strategies were similar in all the patients. All the patients were treated with systemic Amphotericin B as soon as the diagnosis of mucor was established, along with treatment to stabilize the underlying metabolic derangement. After a test dose of 1 mg of amphotericin B in 100 ml of normal saline, 0.7 mg/kg/day of amphotericin B was given over 6 hours. All the patients underwent local resection of the lesions until a safe margin was reached. The outcome of treatment group was evaluated in terms of treatment success and treatment failure. Treatment success was defined as a disease-free, stable patient with controlled metabolic status. Treatment failure was defined as progression of disease to a more advanced stage, worsening general condition or mortality due to the infection. We also recorded epidemiological characteristics, the site of infection and type of DM and its duration.

### *Statistical analysis*

The statistical package for social science, SPSS for Windows, Version 15.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis. To determine the factors affecting patients' prognosis, paraclinical findings, type of DM and duration of the disease were compared between two groups. Chi-square and Mann-Whitney tests were used for statistical analysis. The independent t-test was used to compare the parametric data between two study groups. A *p*-values less than 0.05 was considered statistically significant.

## Results

A review of hospital records identified 162 cases of mucormycosis hospitalized in Shiraz University

hospitals during the last 21 years, from April 1990 to March 2011. The underlying diseases were leukemia in 95 (58.6%), DM in 30 (18.5%), aplastic anemia in 15 (9.25%), lymphoma in 6 (3.7%), myelodysplastic syndrome subsequent to liver transplantation in 4 (2.46%), gastric cancer in 1 (0.61%), breast cancer in 1 (0.61%), Fanconi anemia in 1 (0.61%), kidney transplant in 1 (0.61%), rheumatologic disorder in 1 (0.61%), midline granuloma in 1 (0.61%) repeated abortion 1 (0.61%) and chronic granulomatous disease in 1 (0.61%) patient. The diabetic mucormycotic patients aged from 6 years to 72 years with mean age of  $45.2 \pm 17.6$  years. With respect to gender, 19 (63.3%) of diabetics were females compared to 11 (36.7%) males. We also included 60 patients who were matched for age, sex and date of admission with DKA as control group. The mean age of the control group was  $43.6 \pm 13.6$  and there were 38 (63.3%) and 22 (36.7%) men and women among the controls respectively. The overall mortality rate was 53.3% (14 patients survived and 16 were expired). There was no significant difference between cases and controls regarding the baseline characteristics including age ( $p=0.163$ ) and gender ( $p=0.998$ ). The mean duration of diabetes in case group was  $5.75 \pm 5.43$  (1-16 years) and 7 patients have recently been diagnosed to have DM. In control group the mean duration of diabetes was  $7.2 \pm 7.85$  (1-25 years) and 10 patients have recently been diagnosed with DM. There was no significant difference between patients and controls regarding the duration of the DM ( $p=0.072$ ). The mean duration of presenting signs and symptoms in patients and treatment period was  $12.5 \pm 4.5$  days. The initial site of mucormycosis was rhinocerebral

in 25 (83.3%) patients, pulmonary involvement was recorded in 2 (6.66%) patients, hard palate was affected in 1 (3.33%), bladder in 1 (3.33%) and scalp mucormycosis found in 1 (3.33%) patient. A significant increase was noted in the number of hospitalized mucormycotic diabetic patients from 1998 to 2003 followed by diminishing trend in ensuing 7 years (Figure 1). Figure 2 demonstrates the age distribution of diabetic leukemic patients. The highest number of hospitalized patients was in the second and sixth decade of age and more than half of them aged more than 50 years.

Insulin-dependent DM (IDDM) and non-insulin dependent DM (NIDDM) were found in 11 (36.7%) and 19 (63.3%) of case group respectively. As for the control group, 44 (73.3%) patients had IDDM and 16 (26.7%) exhibited NIDDM. IDDM was significantly more prevalent in control group compared to case group ( $p=0.002$ ).

Table 1 compares the laboratory findings of patients with mucormycosis and controls. As demonstrated, blood sugar and serum bicarbonate levels were significantly lower in the case group when compared to control group. The serum of the patients in the control group was more acidic than the case group. Only 7 (23.3%) patients with mucormycosis in the case group were in diabetic ketoacidosis state. Other laboratory data showed no statistically significant differences.

## Discussion

Mucormycosis is a devastating acute invasive filamentous fungal infection occurring mostly in patients with uncontrolled diabetes mellitus [13] and

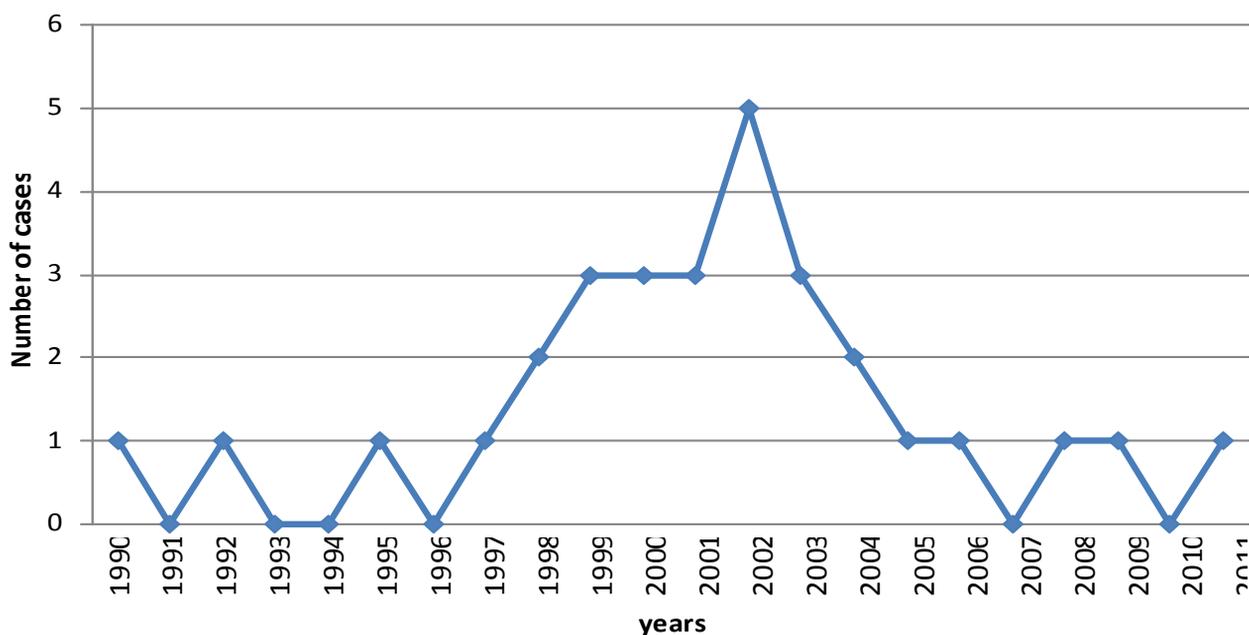
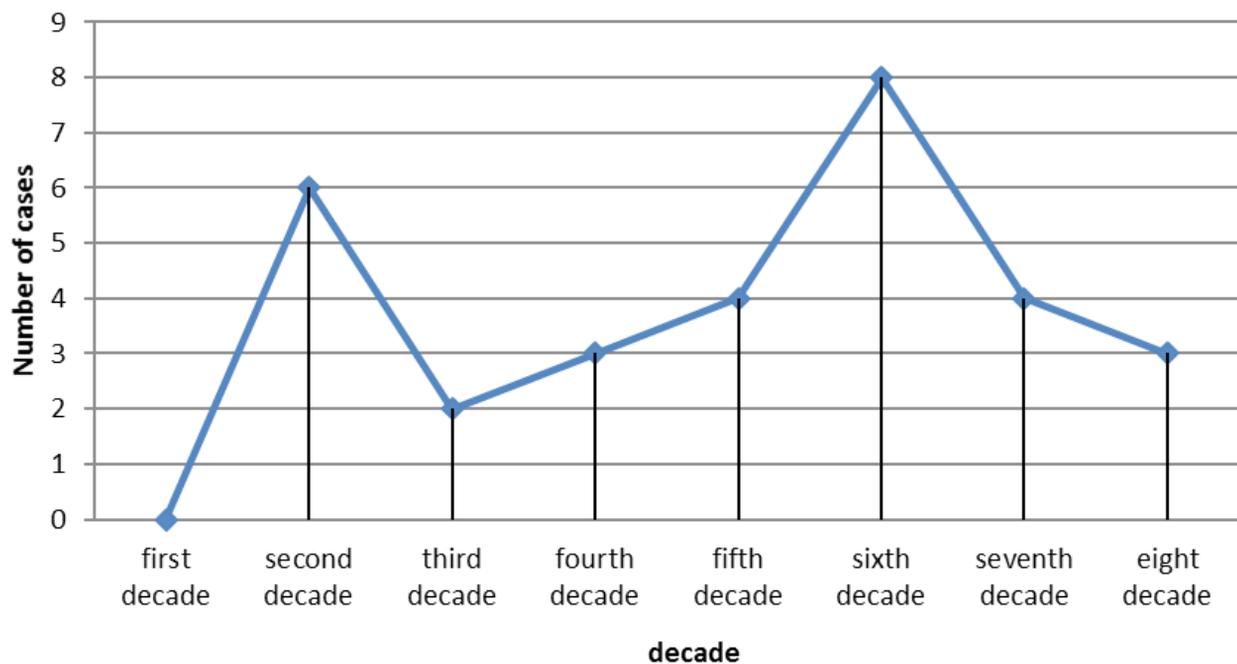


Fig. 1. Number of mucormycotic diabetic patients admitted to hospitals affiliated with Shiraz University of Medical Sciences from 1990 to 2011.



**Fig. 2.** Age distribution of 30 diabetic patients with mucormycosis hospitalized in hospitals affiliated with Shiraz University of Medical Sciences from 1990 to 2011.

in severely immunocompromised patients, such as those with hematological malignancy [14] or those who have undergone solid organ transplantation or hematopoietic stem cell transplantation (HSCT) [15]. Of note, are also several cases occurring following trauma in contact with contaminated soil [16].

The epidemiology of zygomycosis seems to be different between developed and developing countries. In developed countries, the disease is still a rarity, and at present is mostly seen in patients with haematological malignancies, those undergoing chemotherapy, in bone marrow transplant recipients, and as an emerging infection in patients receiving voriconazole therapy or prophylaxis. However, in developing countries, especially in India, the number of zygomycosis cases seems to be on the rise, occurring commonly in patients with uncontrolled diabetes [17]. In our study, like developed countries, haematologic malignancies are the most common predisposing factor in diabetes.

Despite the increasing number of diabetes worldwide

[9] and according to numerous reports, mucormycosis in patients with diabetes mellitus as underlying illness, has declined since 1990s [2]. This finding could be a consequence of better glycemic control and decreasing rates of diabetic ketoacidosis and of the widespread use of statins in patients with diabetes [18]. Consistent with other investigations, our study showed a diminishing trend of mucormycosis in diabetic patients, especially over the last 7 years.

Rhinocerebral mucormycosis is the most common form of mucormycosis in patients with diabetes mellitus [2,19]. It may also occur in patients with underlying malignancies, recipients of hematopoietic stem cell or solid organ transplants, and individuals with other risk factors [14]. The infection develops after inhalation of fungal sporangiospores into the paranasal sinuses and may then rapidly extend to adjacent tissues. Upon germination, the invading fungus may spread inferiorly to invade the palate, posteriorly infect the sphenoid sinus, laterally into the cavernous sinus to involve the orbits, or cranially to

**Table 1.** Laboratory findings in diabetic patients with mucormycosis and control group.

Laboratory data	Mucormycosis group (n=30)	Control group (n=60)	p-value
WBC <sup>a</sup> ( $\times 10^3/\mu\text{L}$ )	13.4 $\pm$ 2.7	12.54 $\pm$ 3.6	0.981
Hb (mg/dL)	10.47 $\pm$ 4.9	11.93 $\pm$ 4.1	0.182
BUN <sup>b</sup> (mg/dL)	34.25 $\pm$ 13.5	34.12 $\pm$ 16.3	0.998
Blood sugar (mg/dL)	363.7 $\pm$ 58.9	555.6 $\pm$ 101.3	0.015
Serum pH	7.35 $\pm$ 2.2	7.09 $\pm$ 1.8	<0.001
Serum bicarbonate (meq/L)	16.79 $\pm$ 5.9	7.39 $\pm$ 2.7	<0.001

<sup>a</sup>WBC: White blood cell count; <sup>b</sup>BUN: Blood urea nitrogen

invade the brain [20]. Like other studies rhinocerebral mucormycosis was a common form of involvement in our patients.

studies carried out in 1971, 1994 and 1999, and showed an unexplained propensity of males to zygomycosis, with the male to female ratio between 2.4:1 and 3:1 [21]. This finding was confirmed by the 2005 larger review study done by Roden and associates who showed that males constituted 65% of the reviewed cases [2], thus sex seems to increase the incidence of mucormycosis. A recent study carried out by Jagarlamundi *et al.*, on patients with acute leukemia, showed the predominance of mucormycosis in males (M/F=2.5:1) [13]. However, this was contrary to our study on diabetics where mucormycosis was more prevalent in males than in females.

The infection also seems to be age-related with respect to underlying disease, since contrary to leukemia it occurred more in diabetics in older age than in leukemic patients. In our study the mean age of diabetics was  $45 \pm 17.6$  years compared to 30.08 years in leukemic patients, although the mean age in previous review studies reported to vary from 30s to 40s [21]. Since deep mucormycosis encompasses many syndromes, the mortality rate varies greatly from 33.3% in a Korean report [22], to a deteriorated rate of 63% in an Italian study [23], and to a staggering 96% in disseminated form [2]. This diverse variation in mucormycosis mortality rate can be explained by many factors, including early diagnosis, site of the infection, patient's immune status, correction of other co-morbid factors, and the type of therapy. Diabetics may have a more favorable outcome than non-diabetics. An overall survival rate of 60-77% for rhino-orbito-cerebral mucormycosis has been reported in diabetics, compared to 20-34% in non-diabetics [24]. In our study the mortality rate was 53.33%. Although antifungal treatment and surgical debridement and controlling of underlying disease were done for all patients, the mortality rate, to some extent, can be attributed to delayed treatment. The mean duration of presenting signs and symptoms of this infection and treatment was  $12.5 \pm 4.5$  days.

In a study conducted by Barati *et al.*, [25] in a teaching hospital in Tehran, of 30 patients, 18 were diabetic of which 14 (77.77%) were NIDDM and 4 (23.23%) IDDM, with mean duration of diabetes  $6.7 \pm 6.6$  years. This was consistent with our study where most patients (63.33%) had NIDDM with duration of diabetes  $5.75 \pm 5.43$  years. However, in control group most patients (3.3%) had IDDM. It seems that type 2 diabetes is more susceptible to mucormycosis.

Clinical and experimental data clearly demonstrate that individuals who lack phagocytes or have impaired phagocytic function are at higher risk of

mucormycosis. For example, severely neutropenic patients are at increased risk for developing mucormycosis. In contrast, patients with AIDS do not seem to be at increasing risk for mucormycosis [26]. These findings suggest that neutrophils, but not necessarily T lymphocytes, are critical for inhibiting fungal spore germination. Furthermore, both mononuclear and polymorphonuclear phagocytes of normal hosts kill Mucorales by the generation of oxidative metabolites and the cationic peptides, defensins [27-29]. A recent study showed that exposure of neutrophils to *R. oryzae* hyphae results in upregulation in Toll-like receptor 2 expression and in a robust proinflammatory gene expression with rapid induction of NF- $\kappa$ B pathway-related genes [30]. In the presence of hyperglycemia and low pH, which is found in patients with diabetic ketoacidosis (DKA), phagocytes are dysfunctional and have impaired chemotaxis and defective intracellular killing by both oxidative and nonoxidative mechanisms [31]. The exact mechanisms by which phagocytes are impaired by ketoacidosis, diabetes mellitus, and corticosteroids are yet to be determined. Furthermore, phagocyte dysfunction alone cannot explain the high incidence of mucormycosis among patients with DKA, because the incidence of mucormycosis in these patients is increased more than that of infections caused by other pathogens [11,26,32]. In our study diabetic control group are more acidotic and hyperglycemic than case group and only 7 (23.3%) patients were in diabetic ketoacidosis state and Besides diabetic ketoacidosis, chronic metabolic acidosis due to other causes, such as chronic renal failure with uremia [33] chronic salicylate poisoning [34] and methylmalonic aciduria [35] has also been reported as a risk factor for mucormycosis. It seems that acidosis due to hyperglycemia merely cannot explain the exact mechanisms by which diabetics are susceptible to mucormycosis. Patients with diabetic ketoacidosis have elevated levels of available serum iron, likely due to the release of iron from binding proteins in the presence of low pH. Iron is then internalized by the zygomycetes with the help of copper oxidase (Cu-oxidase) and the high affinity iron permease rFTR1. Therefore, the increased susceptibility of patients with diabetic ketoacidosis to mucormycosis is likely due, at least in part, to an elevation in available serum iron during diabetic ketoacidosis following proton-mediated dissociation of iron from transferrin [36]. But it cannot explain the mechanism in non-ketoacidotic diabetic's involvement by mucormycosis. Other mechanisms suggested for this infection include greater availability of glucose to the pathogen causing mucormycosis, reduced serum inhibitory activity against the *Rhizopus* in lower pH, and the

increased expression of some host receptors that mediate the invasion and damage to human epithelial cells by *Rhizopus* [37-39].

Because of the rarity of mucormycosis, the data analysis about its management, predisposing conditions, mortality and factors affecting mortality and laboratory findings have not so far been delineated and clarified and conclusions drawn are based on the results of case series and case reports, animal model study and in vitro susceptibility data. Therefore, sufficient information is not available for comparison of our data and statistical conclusion. Further studies are thus warranted to determine

the exact predisposing factors involved in this lethal infection, confirm our results, and provide a definitive conclusion and to improve the outcome of infections in diabetics.

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**Conflict of Interest:** None declared.

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