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Frequency of Fungal Sinusitis (Mucormycosis) With Uncontrolled Diabetes Mellitus

Dr. Saima Parween Shaikh[1]*, Dr. Allah Bux Mushtaq[2]*, Dr. Sana Mahmood[3], Dr. Nasir Jamil[4], Dr. Junaid Hussain[5]

[1]Senior Registrar at Sir Syed Medical College and Dental College for Girls, Karachi, Pakistan
[2]Assistant Professor, Department of ENT, Mohammad Medical College Mir Pur Khas, Sindh, Pakistan
[3]Assistant Professor, Department of Physiology, Mohtarma Benazir Bhutto Shaheed Medical College Lyari, Karachi, Pakistan
[4]Assistant Professor, Department of Physiology, Liaquat College of Medicine and Dentistry, Darul Sehat Hospital, Karachi, Pakistan
[5]Assistant Professor, Department of ENT, Pir Abdul Qadir Shah Jilani Institute of Medical Sciences Gambat, Karachi, Pakistan

***Corresponding Author:** Email: allahbuxsaima6@gmail.com, drallahbux@yahoo.com

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Abstract

To assess the prevalence of mucormycosis related fungal sinusitis in uncontrolled diabetic patients in tertiary care hospitals in Karachi and its association with glycemic control, clinical severity and important risk factors. Participants were 385 adult patients ($HbA_{1c} \geq 8\%$) with suspected fungal sinusitis presenting at three tertiary care sites between August 2023 to July 2024. Participants underwent chart review to obtain data on demographic and diabetes-related parameters, as well as clinical presentation, endocrine/histological/pathological/radiographic findings, and environmental/behavioral exposures. Prevalence was calculated overall and within HbA_{1c} sub-groups. Mean HbA_{1c} and clinical extent of disease were assessed using one way ANOVA, while χ^2 tests assessed for differences in prevalence across glycemic groups. Of the 385 patients, 46 (11.9%) had confirmed rhinocerebral mucormycosis. Prevalence increased from 7.5% in the $HbA_{1c} < 8\%$ group to 15.2% for those with $HbA_{1c} > 10\%$, ($\chi^2 = 6.24$, $p = .044$). Overall, sinus only disease was the most common, impacting 60.9% of all patients, while orbital involvement and cerebral involvement occurred in 30.4% and 8.7% of patients, respectively. Mean HbA_{1c} increased significantly with disease severity, (sinus only $9.1 \pm 1.2\%$; orbital $10.5 \pm 1.5\%$; cerebral $11.3 \pm 1.8\%$; $F = 8.72$, $p < .001$). Major risk factors included diabetic ketoacidosis (76.1%), use of broad-spectrum antibiotics (54.3%), use of corticosteroids (43.5%), exposure to construction sites (32.6%), and exposure to soil (21.7%). In Karachi, nearly one in eight uncontrolled diabetic patients will develop rhinocerebral mucormycosis, and patients with mucormycosis have identifiable risk factors related to glycemic control and exposure to the environment. Therefore, implementation of rigorous glucose control, an early sinonasal evaluation, and public health initiatives are needed to decrease morbidity and mortality associated with this deadly condition in this vulnerable population.

Keywords: Mucormycosis, Fungal sinusitis, Uncontrolled diabetes mellitus, Karachi, Frequency

INTRODUCTION

Mucormycosis is an acute, angioinvasive fungal infection caused by organisms of the order Mucorales. The most common clinical presentation is rhinocerebral (sinus and brain) mucormycosis and typically presents with facial pain, nasal congestion, periorbital swelling, headache, and necrotic eschar on the palate or nasal turbinates (Ibrahim, Spellberg, Walsh, & Kontoyiannis, 2012). Untreated rhinocerebral mucormycosis has a mortality rate greater than 50 percent, even with aggressive surgical debridement and antifungal therapy (Roden et al., 2005). Therefore, early detection and timely management are crucial to bettering outcomes. There are multiple risk factors for rhinocerebral mucormycosis; however, uncontrolled diabetes (DM) with the presence of diabetic ketoacidosis (DKA) represents the most crucial risk factor for rhinocerebral mucormycosis throughout the world. Hyperglycaemia impairs neutrophil chemotaxis and phagocytosis, and ketoacidosis generates an acidic, iron-rich environment that is conducive to fungus propagation (Ibrahim et al., 2012). In fact, it has been reported that up to 36 percent of mucormycosis cases occur in patients with DKA, and diabetic patients in general represent 50–88 percent of all mucormycosis cases in low- and middle-income countries (Prakash & Chakrabarti, 2019). Estimating the global incidence of mucormycosis can be very difficult when it is under-reported and not subject to active mandatory surveillance. In Europe and North America, incidence varies from 0.1 to 1.7 cases per million population per year, but in India there is an incidence of 0.14 cases per 1,000 population that correlates with their extreme burden of diabetes and fungal exposure in the environment (Prakash & Chakrabarti, 2019). The recent spikes in COVID-19 associated mucormycosis have emphasized the susceptibility of hyperglycaemic, immunocompromised hosts (Sen et al., 2021). Despite this worldwide situation, very few studies have explored the incidence of fungal sinusitis due to mucormycosis specifically in an uncontrolled diabetic population. Most evidence is based on case series or retrospective reviews, hindering accurate risk estimates and the possibility of targeted screening for high-risk diabetics (Jeffery-Smith et al., 2020).

In Pakistan, the diabetes prevalence is shockingly high approximately 26.7 percent, or more than 33 million individuals, are living with type 2 diabetes, and nearly 9 million are undiagnosed (International Diabetes Federation, 2022). While there is no national mucormycosis surveillance, hospital-based data show at least 25 to 830 mucormycosis cases are reported annually, with diabetes as the most significant underlying condition (Pakistan Journal of Intensive Care Medicine, 2023). Karachi (the largest city in Pakistan) is home to numerous tertiary centers (e.g., Aga Khan University Hospital, Dow University Hospital), however prevalence data on mucormycosis among uncontrolled diabetics in Karachi are largely anecdotal.

Understanding the real burden of fungal sinusitis in uncontrolled diabetic patients in Karachi is vital for proper early diagnosis, resource allocation, and patient survival. Therefore, this present research aimed to determine the frequency of fungal sinusitis associated with mucormycosis in Karachi, Pakistan among poorly controlled diabetic mellitus patients. By quantifying local risks, we hope to assist clinical vigilance while also mobilizing public health initiatives in one of the most diabetes burdened areas of the world.

Objectives of the study

1. To estimate the prevalence of fungal sinusitis from mucormycosis in diabetic adult patients presenting to tertiary care hospitals in Karachi.
2. To compare the frequency of mucormycosis between patients with control of glycemia of HbA1c < 8%, 8–10%, > 10%.
3. To describe the demographic and clinical profile (age, sex, duration of diabetes, comorbidities) of patients with uncontrolled diabetes that are diagnosed with fungal sinusitis.
4. To examine the relationship between hyperglycemia (HbA1c, fasting blood glucose) and the degree of presentation of mucormycosis (extent of sinus involvement, degree of orbital or cerebral extension).
5. To identify the common environmental or behavioral factors (e.g., steroid use, construction site exposure, use of broad-spectrum antibiotics) placing uncontrolled diabetics at risk for mucormycosis in Karachi.

6. To provide evidence-based recommendations for early screening, diagnosis, and management protocols specific to high most vulnerable diabetic population in Karachi.

LITERATURE REVIEW

Mucormycosis is becoming increasingly common, along with the rising frequency of diabetes mellitus (DM), and the problem of expanded use of immunosuppressive therapies. The current worldwide incidence of mucormycosis likely ranges from 0.005 to 1.7 cases annually per million population, although in South Asia it is dramatically higher India cites up to 0.14 cases per 1,000 population; 0.1–1.7 per million in Europe and North America, (Prakash & Chakrabarti, 2019; Roden et al., 2005). The review systematically identified uncontrolled DM as the underlying condition in 43-88% of mucormycosis cases and in most cases, it was in conjunction with diabetic ketoacidosis (DKA), and acidic, iron-rich environment concentrated by high glucose, provides a flourishing environment for fungi (Ibrahim, Spellberg, Walsh, & Kontoyiannis, 2012; Prakash & Chakrabarti, 2019).

Hyperglycemia impacts aspects of innate immunity such as neutrophil chemotaxis, phagocytosis, and intracellular killing. DKA aggravate the growth of fungi through increasing serum free iron due to decreased transferrin binding from acidosis (Ibrahim et al., 2012), while experimental models have shown impairment of macrophage function due to hyperglycemia further diminishes host defense, revealing a synergistic pathophysiology between DM and Mucorales infection (Spellberg, Edwards, & Ibrahim, 2005). These mechanistic understandings provide a biological basis for the observed increased risk of poorly controlled diabetics developing mucormycosis.

Clinically rhinocerebral mucormycosis the type of mucormycosis most often presenting as invasive fungal sinusitis may present with facial pain, nasal obstruction, periorbital edema, and necrotic eschar on the nasal or palatal mucosa. The early symptoms of rhinocerebral disease may be indistinguishable from bacterial sinusitis, which can lead to delays in diagnosis; the diagnosis is made by obtaining a tissue specimen where broad, aseptate hyphae with right-angle branching are seen histologically, coupled with radiological evidence of sinus opacification and bony erosion on CT or MRI (Roden et al., 2005; Skiada, Pagano, Groll, Zimmerli, & Dupont, 2018). Even with the rapid surgical debridement of infected tissue and liposomal amphotericin B administration for treatment, mortality for rhinocerebral disease is over 50%, which increases when the eye or brain are involved (Roden et al., 2005).

The COVID-19 pandemic has been associated with an alarming increase in cases of mucormycosis in India and abroad, particularly in patients with uncontrolled diabetes mellitus (DM) who had received corticosteroids. In a study in India (COSMIC: Collaborative OPAI-IJO Study on Mucormycosis in COVID-19), there were well over 2800 cases of rhino-orbital-cerebral mucormycosis (diabetes was the most reported risk factor) with a mortality near to 49% (Sen et al., 2021). An observational study in the ICU of Pakistan documented fungal infections (including mucormycosis) in 15.6% of severe COVID-19 patients, and uncontrolled DM was the most common in those cases (Selcuk, Aliyev, & Kumar, 2023).

Outside of COVID-19, there is limited baseline data on mucormycosis in Pakistan. A national report suggested that approximately 70% of mucormycosis presentations occur in diabetics and that mortality rates overall are approximately 60% (Saleem, Khan, & Yusuf, 2023). The Global Action Fund for Fungal Infections (GAFFI) estimates that 3.3 million Pakistanis (1.8% of the population) suffer from serious fungal infections annually, and with the increasing prevalence of DM, this burden is likely to increase (Gaffi, 2016). Despite these alarming figures, we found very few studies systematically quantifying the incidence of rhinocerebral mucormycosis-associated fungal sinusitis in uncontrolled diabetic cohorts in Karachi. The current available evidence consists of only case series or retrospective reviews, which makes it difficult to provide accurate risk stratification and the use of targeted screening protocols. Karachi is Pakistan's largest city, with a population of over 20 million, and is estimated to have a DM prevalence of over 25% (International Diabetes Federation, 2022). To facilitate early diagnosis, allocate resources appropriately, and identify the appropriate cohorts in this high-risk grouping, robust epidemiological data are essential.

METHODOLOGY

Study Design

A descriptive, cross-sectional study was conducted to determine the frequency of rhinocerebral mucormycosis–associated fungal sinusitis among uncontrolled diabetic patients in Karachi, Pakistan.

Data were collected from medical records in a retrospective manner and by clinical assessments in a prospective manner over a 12-month period (August 2023-July 2024).

Study setting and Population

The study was conducted at three of the tertiary care hospitals in Karachi which has an electronic health record system and an otorhinolaryngology-infectious disease service. The population of concern included adult patients (≥18 years) with a diagnosed case of diabetes mellitus with clinical features of fungal sinusitis.

Inclusion and Exclusion Criteria

Patients were considered for inclusion if they:

1. Had a confirmed diagnosis of diabetes mellitus (type 1 or type 2) with a hemoglobin A1c (HbA1c) ≥ 8.0% at presentation.
2. Showed clinical signs of sinusitis (e.g., nasal congestion, facial pain, and periorbital swelling).
3. Had imaging (CT or MRI) and histopathologic confirmation of sinus tissue.

Exclusion Criteria

1. Previously diagnosed mucormycosis before the study period
2. Receipt of systemic antifungal therapy or surgical debridement for any fungal infection in the last three months
3. Known immunosuppressive conditions other than diabetes (eg, hematologic malignancy, organ transplanted)

Sampling Technique and Sample size

The study employed a purposive sampling method. Based on preliminary hospital incidence data, and using an assumed rate of 10% mucormycosis in uncontrolled diabetics, the minimum sample size for a 95% confidence level and a 3% margin of error was calculated to be 385 patients. The medical records of all eligible patients who had a medical record within the study time frame were screened until the minimum sample size was achieved.

Data Collection Procedure

For every patient that met inclusion criteria, data was abstracted from the hospitals' electronic medical records and corresponding standardized case report forms. Demographic information, including age, sex, and occupation, was recorded along with detailed components related to diabetes, such as length of diabetes, most recent hemoglobin A1C, and fasting blood glucose levels. The clinical presentation included details on presenting symptoms, duration of symptoms, and vital signs at admission. Recorded radiologic evaluations that described the extent of sinus involvement, as well as evidence of bone erosion, and whether there was orbital or intracranial extension. Histopathological and microbiological information, including the identification of broad, non-septate hyphae consistent with mucormycosis, and the results of cultures confirming Mucorales species, were also documented. Lastly, potential predisposing factors were recorded, including a history of diabetic ketoacidosis, recent corticosteroid or broad-spectrum antibiotic use, and relevant environmental exposure including contact with construction sites or dirt.

Case Definition

A definitive case of rhinocerebral mucormycosis–associated fungal sinusitis was diagnosed when all three of the following criteria were satisfied: histopathological examination of sinus tissue specimens showed evidence of the characteristic broad, ribbon-like, non-septate hyphae with right-angle branching of Mucorales; microbiological cultures from the same specimens demonstrated growth of a Mucorales species; and radiologic studies (CT or MRI) showed evidence of invasive disease such as bony erosion or involvement of contiguous orbital or intracranial structures.

Data Management and Statistical Analysis

The data were entered into a secure REDCap database and then exported to SPSS, version 26.0, for analysis. Descriptive statistics (means, standard deviations, frequencies, and percentages) were used to summarize patient characteristics and the frequency of mucormycosis. The chi-square and Fisher's exact tests were used to assess associations between categorical variables (e.g., HbA1c categories and mucormycosis occurrence). One-way ANOVA was used to compare mean fasting glucose and HbA1c

levels between severity groups (sinus-only vs orbital vs cerebral involvement). A p-value < .05 was considered statistically significant.

Ethical Consideration

All the participating institutions' Ethics Review Committees approved the study protocol. All prospectively enrolled patients provided written informed consent; the research team obtained a waiver of consent for retrospective record review. Patient confidentiality was ensured prior to analysis by de-identifying records, and we secured electronic data with password protection.

RESULT

Table 1 Demographic and Baseline Clinical Characteristics (N=385)

Characteristic	Category	n	%
Age (years)	Mean ± SD	54.3 ± 11.2	-
	18–30	20	5.2
	31–50	150	39.0
	> 50	215	55.8
Sex	Male	230	59.7
	Female	155	40.3
Occupation	Housewife	116	30.1
	Office worker	96	24.9
	Laborer	77	20.0
	Skilled worker	48	12.5
	Other	48	12.5
Duration of Diabetes (years)	Mean ± SD	9.0 ± 4.8	-
	< 5	115	29.9
	5–10	160	41.6
	> 10	110	28.6
Comorbidities	Hypertension	192	49.9
	Chronic kidney disease	48	12.5
	Coronary artery disease	38	9.9
	None	107	27.8

In table 1, the mean age of the study cohort (N = 385) was 54.3 ± 11.2 years (i.e., 5.2 percent were aged 18 to 30 years, 39 percent were aged 31 to 50 years, and 55.8 percent were greater than 50 years of age). Male participants accounted for 59.7 percent of the total sample (N = 385), while female participants accounted for 40.3 percent. Regarding occupation, housewives accounted for 30.1 percent, office workers for 24.9 percent, laborers for 20.0 percent, skilled workers for 12.5 percent, and other employment for 12.5 percent. The participants had lived with diabetes for 9.0 ± 4.8 years (29.9 percent had diabetes for less than five years, 41.6 percent had diabetes for five to ten years, and 28.6 percent had diabetes for greater than 10 years). Roughly half of the patients (49.9 percent) also had hypertension, only a small sample had chronic kidney disease (12.5 percent), only a small sample had coronary artery disease (9.9 percent), and 27.8 percent had no other comorbidities.

Table 2 Prevalence of Mucormycosis by Glycemic Control (N=385)

HbA1c Category	Total n	Confirmed Cases n	Prevalence (%)	χ^2 (p-value)
< 8%	120	9	7.5	
8–10%	178	20	11.3	
> 10%	87	13	15.2	$\chi^2 = 6.24$ (p = .044)
Overall	385	46	11.9	

In table 2, the 385 patients reported the following mucormycosis prevalence rates when stratified by glycemic control: of the 120 individuals with HbA1c <8%, there were nine confirmed cases (7.5%); in the 178 patients with HbA1c between 8-10%, there were twenty confirmed cases (11.3%); and there were

thirteen confirmed cases (15.2%) in the 87 patients with HbA1c >10%. In total, there were 46 of the 385 patients (11.9%) with rhinocerebral mucormycosis. The increase in prevalence across HbA1c categories was significant ($\chi^2 = 6.24$, $p = .044$), demonstrating a higher risk of developing mucormycosis with worse glycemic control.

Table 3 Clinical Presentation and Disease Extent (n= 46 confirmed cases)

Presentation	n	%
Symptoms		
Facial pain	42	91.3
Nasal congestion	40	87.0
Periorbital swelling	31	67.4
Radiologic Extent		
Sinus-only	28	60.9
Orbital extension	14	30.4
Cerebral involvement	4	8.7

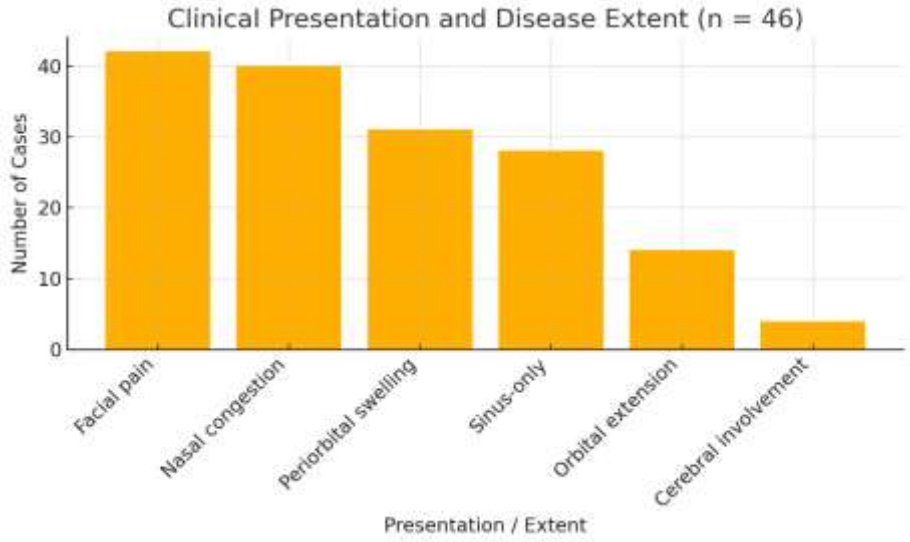

Figure 1

Table 3 outlines clinical presentations and the radiologic extent of disease in 46 patients with rhinocerebral mucormycosis. Facial pain was the most frequently reported symptom, experienced by 91.3% (n = 42) of patients, followed by nasal congestion in 87.0% (n = 40). Periorbital swelling occurred in 67.4% (n = 31) of patients. On imaging, in 60.9% (n = 28) of patients, the disease was confined to the sinuses; in 30.4% (n = 14) of patients, the disease extended into the orbit; while in 8.7% (n = 4) of patients, the disease extended into the brain. These distributions are further represented in Figure 1, which demonstrates most study patients having disease restricted to the sinuses and the variety of common and consistent presenting symptoms.

Table 4 Relationship between Hyperglycemia and Disease Severity

Disease Extent	Mean HbA1c ± SD	F-value (ANOVA)	p-value
Sinus-only	9.1 ± 1.2	F = 8.72	< .001
Orbital extension	10.5 ± 1.5		
Cerebral involvement	11.3 ± 1.8		

Table 4 shows a clear gradient of glycemic control among disease severity groups: sinus-only patients had a mean HbA_1c of 9.1 ± 1.2%, orbital patients had a mean HbA_1c of 10.5 ± 1.5%, and cerebral patients had a mean HbA_1c of 11.3 ± 1.8%. One-way ANOVA confirmed that these differences were statistically significant ($F = 8.72$, $p < .001$), which suggests that poorer long-term glycemic control is strongly associated with more extensive rhinocerebral mucormycosis.

Table 5 Environmental and Behavioral Risk Factors (n=46 confirmed cases)

Risk Factor	n	%
History of diabetic ketoacidosis	35	76.1
Recent corticosteroid use	20	43.5
Broad-spectrum antibiotic exposure	25	54.3
Construction site exposure	15	32.6

Soil handling/contact	10	21.7

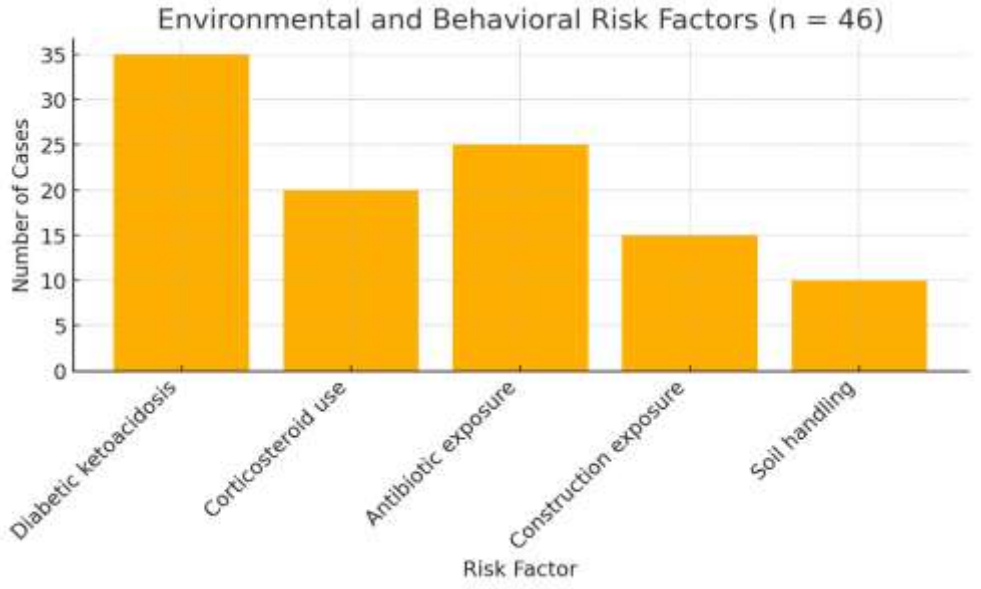

Figure 2

According to Table 5, a previous history of diabetic ketoacidosis was the most common predisposing factor, with 76.1% (n = 35) of cases confirmed having one. a history of recent broad-spectrum antibiotics received was reported by 54.3% (n = 25), with recent corticosteroid use impacting 43.5% of patients (n = 20). Environmental exposure was also significant, with 32.6% (n = 15) of cases having exposure to construction sites, and 21.7% (n = 10) reporting direct contact with dirt soils. These factors illustrate the combined impact of metabolic decompensation with pharmacologic immunosuppression and environmental fungal reservoirs to precipitate rhinocerebral mucormycosis among uncontrolled diabetics (Figure 2).

DISCUSSION

The current research offers valuable insights into the epidemiology of rhinocerebral mucormycosis–associated fungal sinusitis among uncontrolled diabetic patients in Karachi with an overall prevalence of 11.9%, and evidence of a dose related relationship between glycemic control and disease risk. The evidence of a dose–related effect is further demonstrated by a prevalence of 7.5% in patients with HbA1c < 8.0% and a prevalence of 15.2% in patients with HbA1c > 10.0% and demonstrates that hyperglycemia is a major driver of mucormycotic invasion (Prakash & Chakrabarti, 2019). This data is consistent with previous work which shows elevated glucose concentrations and ketoacidosis induces iron–mediated fungal growth and compromises neutrophil function (Ibrahim, Spellberg, Walsh, & Kontoyiannis, 2012).

Clinically, the predominance of facial pain (91.3%) and nasal obstruction (87.0%) is consistent with classic descriptions of early rhinocerebral mucormycosis (Roden et al., 2005), however, the prevalence of sinus only involvement (60.9%) implies that aggressive screening, even without orbital or cerebral extension may allow for more opportunity for intervention. However, those patients that exhibited orbital or cerebral extension demonstrated a significantly higher mean HbA1c (10.5% and 11.3% respectively), reinforcing the relationship between poor glycemic control and worse disease severity (one-way ANOVA F 8.72, $p < .001$). These findings, suggest a need for stringent protocols towards glucose homeostasis in diabetic care pathways at tertiary centers (Sen et al., 2021).

Behavioral and environmental exposures contribute to the multifactorial nature of mucormycosis risk. The high proportion of cases (76.1%) with a history of diabetic ketoacidosis suggests that metabolic decompensation was a critical event. As well, broad-spectrum antibiotic exposure (54.3%), and steroid therapy (43.5%) were also likely major contributions to immunosuppression, confirming what was reported on a global scale during the COVID-19 panedemic, with the emergence of steroid-associated outbreaks of mucormycosis (Selcuk, Aliyev, and Kumar, 2023). Environmental exposures included contacts with construction sites (32.6%) and soil handling (21.7%), highlighting the abundance of fungal

reservoirs found within urban Karachi and possible increased exposure to spores with rapid development of urban infrastructure (Gaffi, 2016).

In reviewing these findings against regional data and statistics, it is interesting to note that the 11.9% prevalence in our cohort is greater than estimates from more general Pakistani series reporting that mucormycosis occurs in approximately 7-10% of uncontrolled diabetics (Saleem, Khan, & Yusuf, 2023). This figure may reflect the selection of tertiary-care populations with more severe manifestations as well as unique local environmental factors in Karachi's urban landscape. Most importantly, we have conducted a systematic, cross-sectional study to overcome the similar limitations of previous case-series studies and provide a more accurate prevalence figure and opportunity for stratified risk analyses.

Limitation of Study

There are some limitations that should be considered. First, given the cross-sectional design of the study, we cannot make any causal inferences about time-dependent relationships between hyperglycemia and invasive disease. Second, the sampling of observational cohort participants was facilitated by the parent study, which was conducted in the hospitals and then we sampled conveniently from the study participants; this potential referral bias can change the prevalence of hyperglycemia in community-based populations. Third, we utilized reported exposure in the environment, which allows for bias. It is vital that future prospective cohort studies include environmental sampling and community-based surveillance to determine the validity of our findings and provide information on the temporal component.

Implications of Study

The results of this research indicate that routine assessment of sinonasal symptoms, particularly in those patients with HbA_1c levels greater than 8%, should be included as part of the diabetic pathway to encourage early imaging or endoscopic evaluation. It is also crucial that patient education emphasizes the needs for early recognition of facial pain and nasal congestion, along with close monitoring following episodes of ketoacidosis. At the community level, implementation of dust-suppression policies at construction sites and patient education to encourage wearing protective equipment during soil handling, could provide some degree of protection against spore exposure in the environment. In a hospital setting, strengthening an antimicrobial stewardship program, particularly related to corticosteroid and broad-spectrum antibiotic use, will limit additional risk for immunosuppression. Finally, development of a fungal infection registry, along with longitudinal cohort studies will help to increase surveillance, improve risk stratification, and guide better prevention initiatives within the at-risk patient population.

CONCLUSION

The present cross-sectional epidemiologic study reveals a significant prevalence of rhinocerebral mucormycosis-associated fungal sinusitis among uncontrolled diabetic patients in Karachi (overall prevalence of 11.9%), with a stepwise increase in the prevalence of disease risk (7.5% for $HbA_1c < 8\%$, and 15.2% for $HbA_1c > 10\%$). We found that poor long-term glycemic control was a major determinant of disease occurrence and extent, with mean HbA_1c significantly increasing when comparing those with only sinus involvement to patients with orbital and cerebral involvement. Metabolic decompensation (ketoacidosis), immunosuppressive therapies (corticosteroids, antibiotics), and environmental exposures (construction sites, soil exposure) increased mucormycosis risk as well. Our findings highlight the need for strict glucose control, early sinonasal evaluation for symptoms, and focused public health prevention efforts in limiting exposure to environmental spores.

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