

Correlation between HbA1c and Extent of Mucormycosis Disease

—A Prospective Observative Study

Siddharth Nirwan, Dharendra Tak, Pawan Singhal*, Anjali Bansal, Jitendra Kumar Jangir, Anshu Dev, Akshita Agarwal, Kailash Singh Jat, Anjani Kumar Sharma

Department of Otorhinolaryngology Head and Neck Surgery, SMS Medical College and Hospital, Jaipur, India
Email: *drps.ent@gmail.com

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Abstract

Background: Prognosis in Mucormycosis is poor, secondary to the nature of such opportunistic angioinvasive fungal infection that affects immuno-compromised patients with uncontrolled diabetes which is a common risk factors in most of the cases. **Objectives:** Patients with post-Covid Mucormycosis presenting to the ENT OPD were included and evaluated for HbA1c, extent of disease, and subsequently underwent the required modality of management. **Methods:** A prospective observational study was done in 154 patients of mucormycosis and according to the extent of disease such as sinonasal involvement, orbital extension or intracranial extension, the HbA1c values were compared among themselves. **Results:** In our study, out of 154 patients, 86 (55.8%) patients have only sinonasal involvement, 30 (19.4%) patients have extension into orbit and 38 (24.6%) patients have intracranial spread. In patients with sinonasal involvement, mean HbA1c was 9.8 ± 2.41 ; in orbital extension, mean HbA1c was 12.7 ± 2.31 and in intracranial extension, mean HbA1c was 13.4 ± 1.98 . **Conclusion:** In our study, elevated HbA1c is indicative of poor glycaemic control and positively correlated with increased invasiveness and aggressive fungal disease.

Keywords

Mucormycosis, Immune-Compromised Patients, HbA1c Values

1. Background

Mucormycosis, formerly known as zygomycosis, is a disease caused by the many fungi that belong to the family Mucorales. These includes *Mucor*, *Rhizopus*, *Absidia*, *Cunninghamella* and *Apophysomyces elegans*. Rhino-orbital cerebral

Mucormycosis (ROCM) is the most common form of Mucormycosis. The incidence of ROCM has been rising globally, particularly in India and Middle East. It has recently become a matter of immediate concern after second wave of COVID-19 in India in 2021 [1]. Commonly identifiable risk factors for Mucormycosis are diabetes mellitus, patients receiving immunosuppressive therapy, leukaemia, neutropenia, neutrophil dysfunction, hematopoietic stem cell transplantation, diabetic ketoacidosis, iron overload and human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) [2].

The humid environment of the nose and paranasal sinuses fosters the multiplication and invasion of fungi. Depending on the duration, host immunity, and severity of the disease, further invasion of the mucosa and bone may occur. COVID-19 itself induces increase in blood sugar levels by its action on pancreas. A higher death rate from severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is linked to diabetes. Angiotensin-converting enzyme 2 (ACE2), the primary entry factor for SARS-CoV-2 infection, was studied in relation to pancreatic expression in light of research indicating a possible link between SARS-CoV-2 infection and the development of diabetes [3]. Diabetes mellitus and COVID-19 share a bidirectional relationship with adverse outcomes.

Prognosis in Mucormycosis is poor secondary to the nature of such opportunistic angio-invasive fungal infection that affects immunocompromised patients with uncontrolled diabetes which is a common risk factors in most of the cases.

2. Aim and Objectives

The aim of this prospective observational study is to find out the Correlation between HbA1c values and the extent of mucormycosis disease.

3. Objectives

- To determine the HbA1c values in the mucormycosis patients.
- To determine the extent of disease by performing magnetic resonance imaging.
- To determine the correlation between HbA1c values and the extent of mucormycosis disease.

4. Methodology

4.1. Material and Methods

A prospective observational study was done at SMS Medical College & Hospital, Jaipur, India between April 2020 and May 2021. A total of 154 patients were included in the study. Routine workup of the patient of post covid mucormycosis was done such as complete relevant history, complete blood examination, general physical examination, Endoscopic examination of nasal findings followed by biopsy and KOH staining to confirm mucormycosis, Computed Tomography (CT) scans to see sinus mucosa thickening and early bone destruction, Magnetic Resonance Imaging (MRI) for assessing extension into the cavernous sinus and

identifying cerebral involvement, HbA1c to evaluate the diabetic history of patient. Patients subsequently underwent the required modality of management either medical management, or surgical debridement followed by medical management.

4.2. Inclusion Criteria

- All patients coming to ENT OPD with post covid mucormycosis picture.

4.3. Exclusion Criteria

- Patients with no history of Covid-19 were excluded.
- Patients with normal HbA1c values.

5. Results

In our study 92.85% of the patients had diabetes mellitus. Among them 60.80% of the patients had newly detected diabetes and 39.20% were known case of diabetes. The mean HbA1c was 10.89 gm/dl with standard deviation 3.07.

Out of 154 patients, 86 (55.8%) patients have only sinonasal involvement, 30 (19.4%) patients have extension into orbit and 38 (24.6%) patients have intracranial spread (**Figure 1**).

In our study, in patients with sinonasal involvement mean HbA1c was 9.8 ± 2.41 , in orbital extension mean HbA1c was 12.7 ± 2.31 and in intracranial extension mean HbA1c was 13.4 ± 1.98 (**Table 1** and **Figure 2**).

Table 1. Represents respective number of patients, mean HbA1c with extension of disease.

Extension of disease	No of patients	Mean HbA1c	Standard deviation
Sinonasal	86 (55.8%)	9.8	2.14
Orbital extension	30 (19.4%)	12.7	2.31
Intracranial extension	38 (24.6%)	13.4	1.98

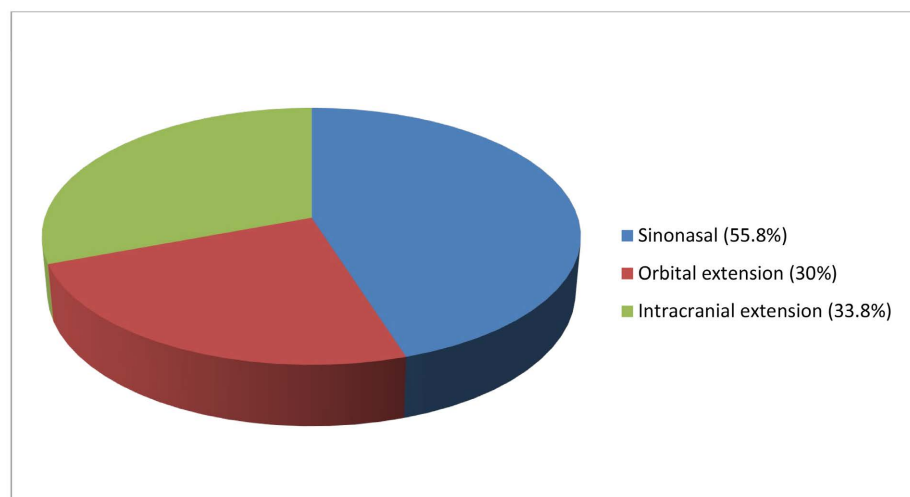


Figure 1. Percentage of patients with different extension of disease.

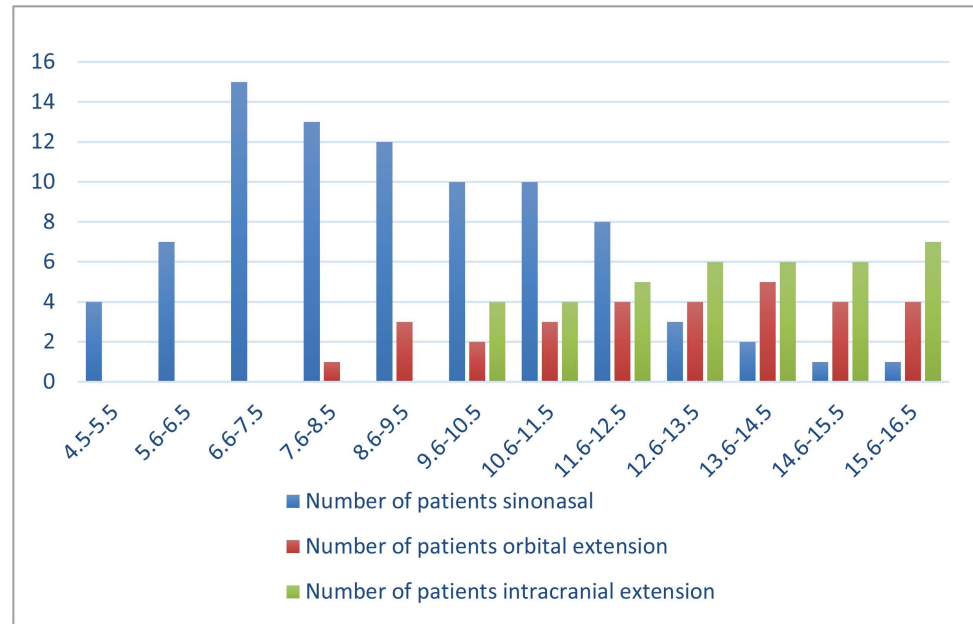


Figure 2. Number of patients along with their respective extension of disease and HbA1c values.

6. Discussion

Despite being relatively rare in healthy people, mucormycosis is predisposed by a number of vulnerable illnesses. This includes uncontrolled DM with or without DKA, haematological and other malignancies, organ transplantation, prolonged neutropenia, immunosuppressive and corticosteroid therapy, iron overload or hemochromatosis, deferoxamine or desferrioxamine therapy, voriconazole prophylaxis for transplant recipients, severe burns, acquired immunodeficiency syndrome (AIDS), intravenous drug abusers, malnutrition and open wound following trauma. Mucormycosis can involve nose, sinuses, orbit, central nervous system (CNS), lung (pulmonary), gastrointestinal tract (GIT), skin, jaw bones, joints, heart, kidney, and mediastinum (invasive type), but ROCM is the commonest variety seen in clinical practice world-wide. The term “ROCM” should be understood to encompass the full range of conditions, from restricted rhino-orbital illness (progression to orbits) to rhino-orbital-cerebral disease (involvement of the central nervous system). The area of involvement may differ due to underlying condition. The most common route of entry for fungi is through the respiratory tract. Sporangiospores travel through the nasal cavity and deposit in the sinus and turbinates. With the help of the complement pathway, phagocytic cells and neutrophils, they can be removed from healthy individuals by destroying the spores and preventing them from germinating. Once in the favourable condition, the spores swell, germinate, and progress to germ tube formation with hyphal extension. The hyphae invade the tissues and have a tendency to invade blood vessels where they cause thrombosis and tissue necrosis [4]. There is evidence that hyperglycaemia and acidosis impair the ability of phagocytes to kill the spores through their normal oxidative burst and non-oxidative mechanisms [5].

In our study 92.85% of the patients had diabetes mellitus. Similar results according to the study of Skiada *et al.* [6] diabetes was seen as a risk factor for Mucormycosis in 73.5% of cases in India and according to Patel *et al.* [7] 62.7% of Mucormycosis cases, diabetes mellitus was most common underlying disease.

In our study 60.80% of the patients had newly detected diabetes and 39.20% were known cases of diabetes. Similar results were obtained in study done by Singh *et al.* [8] in which pre-existing diabetes mellitus was seen in 80% of cases and among them 14.9% were in diabetic ketoacidosis. Goddanti N. *et al.* [9] and found that 36.66% had a history of recent onset diabetes mellitus and 59% had a history of chronic diabetes and 4% subjects were non-diabetic. Similar study done by Maddimani R *et al.* [10] they found that 84.5% patients had diabetes mellitus with Mean HbA1c level was 10.98. As compared to previous studies, diabetes mellitus remained most common risk factor for Mucormycosis. according to a study published in Nature, the virus may be causing new-onset diabetes by destroying pancreatic beta cells and aggravating diabetes that already exists [11]. By oxidative and non-oxidative pathways, hyperglycaemia caused phagocyte malfunction, decreased chemotaxis, and faulty intracellular killing [12].

In our study mean HbA1c was 10.89 gm/dl. FA Wani *et al.* [13] did a study in 2022 and found mean HbA1c value 11.07 and out of 11 rhino-orbital Mucormycosis cases and all the cases (4) of rhino-orbital-cerebral cases had HbA1c levels > 8 and thus Established Significant association between Hba1c > 8 and rhino-orbital and rhino-orbito-cerebral form of Mucormycosis.

In our study, out of 154 patients, 86 (55.8%) patients have only sinonasal involvement, 30 (19.4%) patients have extension into orbit and 38 (24.6%) patients have intracranial spread. Similarly, Agrawal A *et al.* [14] in 2022 did a study and found that out of 480 cases, 443 (92.29%) were found to suffering from diabetes mellitus and rhino Mucormycosis without extra sinus spread was present in 190 (39.58%) patients with mean Hba1c 7.01 ± 0.54 , with sinonasal-orbital involvement in 217 (45.21%) patients with mean Hba1c 8.46 ± 0.25 and with intracranial involvement in 73 (15.20%) patients with mean Hba1c 9.18 ± 0.24 . The extension of disease was strongly associated with increased serum Hba1c levels ($p < 0.001$) and results were similar to our study. Similarly, Yadav T *et al.* [15] found significant positive correlation between HbA1c level and disease stage. Mean HbA1c in sinonasal involvement, with sinonasal-orbital involvement, and with intracranial involvement were 8.8 ± 2.27 , 8.8 ± 2.18 , and 11.3 ± 2.44 respectively.

Diabetes is the “classic” risk factor for Mucormycosis and is associated with increased morbidity and mortality in COVID-19. There are many reasons why Mucormycosis occurs in COVID-19. Diabetes is a proinflammatory state which leads to deficient control of SARS-CoV-2 replication and severe COVID-19 infections [16]. COVID-19 infection itself causes impairment of cell-mediated immunity through immunomodulation which makes patients susceptible to fungal co-infections. SARS-CoV-2 infection leads to decreased insulin secretion due to direct pathogenic effect on pancreatic islet cells. It also induces insulin resistance

due to transient hyper-inflammatory state. Subsequently, a state of hyperglycaemia is produced leading to the growth of invasive Mucormycosis [17]. Hyperglycaemia inhibits NK cell degranulation, macrophage phagocytosis, and neutrophil activity and chemotaxis. Additionally, the fungal ligand spore coating homolog (CotH) protein and endothelial cell GRP 78 (Glucose Regulatory Protein 78) expression are also upregulated in this circumstance. This causes fungal angioinvasion and endothelial cell destruction [18].

7. Conclusion

One established risk factor for mucormycosis is diabetes mellitus. It's also crucial to remember that mucormycosis is more likely in people with ketoacidosis, even if individuals with poorly controlled diabetes do not usually have mucormycosis. For people with diabetes, the leading cause of morbidity and death is a delay in diagnosis. In our study, elevated HbA1c is indicative of poor glycaemic control and positively correlated with increased invasiveness and aggressive fungal disease. Strict monitoring of HbA1c and prompt correction of the blood sugar level helps in reducing the morbidity and mortality.

Conflicts of Interest

There was no conflict of interest.

Ethical Clearance

Ethical clearance was taken from institutional ethical committee.

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No funding was required in our study.

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