Comparison of serum glycosylated hemoglobin levels in patients with different stages of orbital mucormycosis

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Abstract

Background: The Indian subcontinent saw a sudden, sharp rise in the cases of mucormycosis during the second wave of COVID-19 pandemic. The most common presentation was Rhino-orbital-cerebral mucormycosis (ROCM).

Aim: To compare the levels of glycosylated hemoglobin in patients with different stages of orbital mucormycosis

Methods: 116 clinically diagnosed cases of orbital mucormycosis were included in the study. The study design was a retrospective, observational study of case records. Each patient was staged according to the proposed staging of ROCM by Honavar SG. Only patients with stage 3 were included in the study. The level of glycosylated hemoglobin (HbA1c), levels of random blood sugar (RBS) and presence or absence of diabetic ketoacidosis on presentation to the hospital was noted. Statistical analysis was done by one way ANOVA test.

Results: Out of 116 patients, 15 cases (12.9%) had diabetic ketoacidosis on presentation. The mean HbA1c levels in stage 3a was 5.02±0.73%, in stage 3b was 6.73±0.88%, stage 3c was 8.4±0.97% and in stage 3d was 10.54±0.85%. One way ANOVA test showed a significant difference ($p<0.005$) in mean HbA1c levels in all the stages of the disease involving the orbit.

Conclusion: There have been several risk factors for acquiring mucormycosis amongst which diabetes mellitus has an important significance in the disease presentation and progression. In our study it was found that there is a direct relation between the glycemic status of the study subjects and the severity of orbital mucormycosis.

Key words: Mucormycosis, HbA1c levels, diabetes mellitus

Introduction

Mucormycosis or zygomycosis is a rare fungal disease caused by filamentous molds of the order Mucorales[1]. The nose, paranasal sinuses, orbit and brain are the most common areas involved. It is an opportunistic infection that flourishes in individuals who have impaired immune system[2]. Diabetes mellitus (DM) is one of the most important risk factors for developing mucormycosis. The most frequent presentation in patients with DM is rhino-orbital-cerebral mucormycosis[3]. Hyperglycemia and acidosis, seen in DM have been shown to impede the immune system's capability to destroy the Mucorales spores by oxidative and non-oxidative processes through phagocytosis. The endothelialitis and raised ferritin levels that are commonly present in COVID patients, coincidentally are also the major risk factors[4]. These factors would have probably led to a rise in cases of mucormycosis during the second wave of Covid globally.

This retrospective study was undertaken with an aim to determine the correlation between the stage of orbital disease in ROCM and the level of glycemic control in each case by obtaining their glycosylated hemoglobin (HbA1c) and random blood sugar (RBS) levels on their presentation to the tertiary care center.

Material and Methods:

This study was conducted at a medical college hospital in South India, after the approval from the Institutional Ethics Committee. The study design was a retrospective, observational study of case records which included clinically diagnosed cases of orbital mucormycosis, irrespective of Covid history who presented to the tertiary center during the second wave of Covid 19 pandemic that is from April 2021 to

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September 2021. A patient with ocular symptoms and signs of the disease with or without associated sino-nasal or cerebral manifestations was considered as a case of orbital mucormycosis in this study.

Patients of any age who were clinically diagnosed with orbital mucormycosis irrespective of cerebral involvement, Covid status or history of DM were included in the study. Patients with prior history of immunocompromised status, or on immunosuppressive therapy and patients with presence of only sino-nasal mucormycosis without ocular manifestations were excluded from the study.

The demographic details, past history of diabetes mellitus and treatment history of diabetes were obtained from each case. Glycosylated hemoglobin (HbA1c) levels and random blood sugar (RBS) levels of each patient on presentation to the hospital were noted. Presence or absence of diabetic ketoacidosis (DKA) on presentation as diagnosed by the physician was also noted. RBS levels of ≥250mg/dl with presence of urine ketone bodies and metabolic acidosis on arterial blood gas analysis was the criteria to diagnose DKA. Each patient was staged according to the proposed staging of ROCM by HonavarSG[5]. [Table 1]

Patients with involvement of the nasal mucosa were graded as stage 1, with involvement of paranasal sinuses as stage 2, with involvement of orbit as stage 3, and with involvement of the central nervous system (CNS) as stage 4. Only patients with stage 3 were included in the study as per the inclusion criteria. Stage 3 ROCM with involvement of the medial orbit, nasolacrimal duct without affecting vision was graded as 3a and that with diffuse orbital involvement without affecting vision was graded as 3b. Central retinal artery occlusion or involvement of orbital apex, superior orbital fissure, inferior orbital fissure with loss of vision was graded as stage 3c. Bilateral orbital involvement with loss of vision was graded as stage 3d[5]. In each case, correlation between severity of orbital disease and the glycemic status on presentation was assessed.

Table 1: Stages of ROCM involving the orbit as proposed by Honavar SG

Stage of ROCM	Involved structures
3a	the medial orbit, nasolacrimal duct without affecting vision
3b	diffuse orbital involvement without affecting vision
3c	Central retinal artery occlusion or involvement of orbital apex, superior orbital fissure, inferior orbital fissure with loss of vision
3d	Bilateral orbital involvement with loss of vision

Statistical analysis: The data was analyzed using Microsoft Excel (version 16.0). Chi-square test and one way ANOVA test were used to compare the outcomes. For all tests, p values ≤ 0.05 was defined as statistically significant.

Results:

This Study included 116 patients of ROCM, blood samples were collected and analyzed.

Table 2: Demographic data and systemic comorbidities of ROCM patients

Features	Patients (%), n=116
Age	
Mean(years)	51.81
Median(range), years	52(43.5-60)
Gender	
Male	85(73.3)
Female	31(26.7)
Diabetes status	
Not diagnosed/absent	49(42.2)
Diagnosed	67(57.8)
Diabetes treatment	
Oral hypoglycemic agents (OHA)	39(33.6)
Insulin	28(24.01)
None	49(42.2)
Ketoacidosis (DKA)	
Absent	101(87.1)
Present	15(12.9)
Stage of ROCM	
3a	37(31.9)
3b	24(20.7)
3c	38(32.8)
3d	17(14.7)

Patients who were diagnosed with diabetes were 67 in number. 39 patients were on OHA, 28 patients were on insulin. Patients with DKA were 15 in number. The number of patients in stage 3c were 38 which was found to be maximum.

Table 3: HbA1c and RBS levels in subjects with different ROCM stages

Stage of ROCM	Count	HbA1c (%)		RBS (mg/dl)	
		Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
3a	37	5.02 (0.73)	5 (4.3 - 5.42)	156.54 (30.49)	147 (134-187)
3b	24	6.73 (0.88)	6.5 (6.31 - 6.95)	230.63 (56.15)	214 (209-237)
3c	38	8.4 (0.97)	8.37 (8 - 9)	315.74 (82.98)	272 (260 -367)
3d	17	10.54 (0.85)	10.7 (10 - 11)	351.29 (94.29)	367 (300-431)

The mean HbA1c levels including all stages was 7.29±2.1 % and mean RBS levels was 252.56±101 mg/dl.

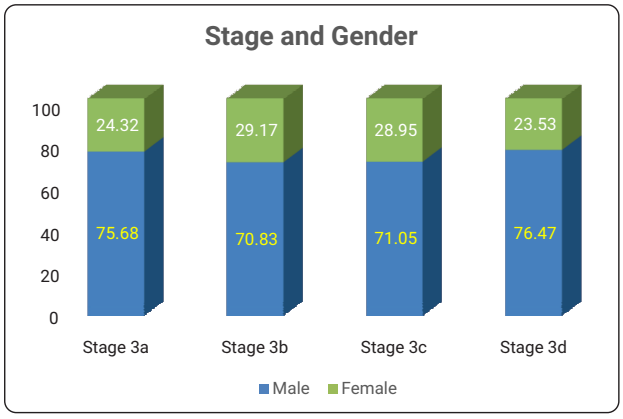

Figure 1 shows the distribution of study subjects with gender and stage of ROCM

Distribution of study subjects with gender and Stage of ROCM, which showed male preponderance in all the stages

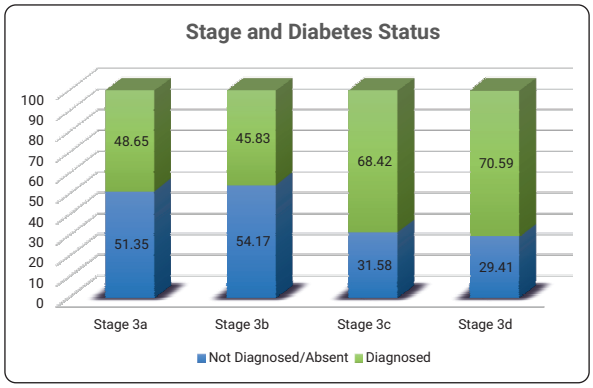

Figure 2 shows the distribution of study subjects with diabetes status and stage of ROCM.

A total of 67 patients had a past history of DM and 49 cases were not known cases of DM. In comparison to the stages 3a and 3b, stages 3c and 3d had higher proportions of patients with past history of DM

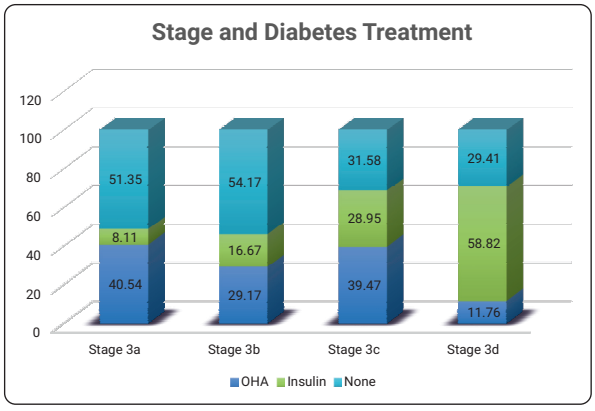

Figure 3 shows the distribution of study subjects with DM treatment status and the stage of ROCM

High proportion of cases were on insulin as compared to OHA as the stage progressed with a p value of 0.002 which was statistically significant.

Table 4: Distribution of study subjects with Ketoacidosis and Stage of ROCM

	Stage of ROCM					
Ketoacidosis	Stage3a n (%)	Stage3b n (%)	Stage3c n (%)	Stage3d n (%)	Total n (%)	Chi square test
Absent	37 (100)	23 (95.83)	28 (73.68)	13 (76.47)	101 (87.07)	p<0.005 (Sig.)
Present	0 (0)	1 (4.17)	10 (26.32)	4 (23.53)	15 (12.93)	

More number of Study subjects were seen to have developed diabetic ketoacidosis in stage 3c of ROCM (10 subjects) with statistical significance of p<0.005

Table 5: Comparison of Mean HbA1c (%) in subjects with different Stages of ROCM

Stage of ROCM	n	HbA1c (%)		One way ANOVA
		Mean	SD	
3a	37	5.02	0.73	F = 190.3 p<0.005 (Sig.)
3b	24	6.73	0.88	
3c	38	8.40	0.97	
3d	17	10.54	0.85	

The mean HbA1c was seen to be higher as the stage advanced with a statistically significant difference (p< 0.005) between the values in each stage.

Table 6: Comparison of Mean RBS (%) in subjects with different Stages of ROCM

Stage of ROCM	n	RBS (mg/dl)		One way ANOVA
		Mean	SD	
3a	37	156.54	30.49	
3b	24	230.63	56.15	F = 49.7
3c	38	315.74	82.98	**p<0.005 (Sig.)**
3d	17	351.29	94.29	

The mean RBS values was seen to be higher as the stage advanced with a statistically significant difference (p< 0.005) between the values in each stage.

Discussion:

Mucormycosis is a life-threatening fungal disease caused by Rhizopus, Mucor, and Rhizomucor organisms. It typically affects individuals with immunocompromised state like diabetes mellitus (DM), those with hematological malignancies like leukemia and lymphoma, renal failure, long-term corticosteroid and immunosuppressive therapy, cirrhosis, burns, protein-energy malnutrition, acquired immune deficiency syndrome (AIDS) renal transplant and stem cell transplant recipients[6].

The devastating pandemic of COVID-19 led to a sharp rise in mucormycosis cases worldwide. India had the highest burden of mucormycosis with an estimated prevalence of 140 cases per million population[7]. India, a country with already prevailing burden of diabetes mellitus also was faced an epidemic of mucormycosis, strongly suggesting a probable interplay between the two diseases. The frequent use of corticosteroids that exacerbated glucose homeostasis, may have predisposed patients to mucormycosis[8]. The most common presentation of the disease noticed was that of rhino-orbital-cerebral mucormycosis[9].

The mucormycosis pathogen produces branching aseptate hyphae and reproduce by formation of asexual spores. Contact with the microorganism occurs through spore inhalation, which land on nasal and oral mucosa. In immunocompromised host germination of the spores occur thus leading top invasion of the hyphae into the bloodstream resulting in Thrombosis, Ischemia and Infarction with Necrosis of the affected tissues[10]. In Diabetes Mellitus the immunological response of the body to any pathogen changes in several ways. Hyperglycemia decreases chemotactic and phagocytic efficiency thus facilitating the organisms to survive in acid rich environment. This further stimulated fungal proliferation resulting in various clinical presentation which includes Rhino-orbital-cerebral, pulmonary and cutaneous forms of mucormycosis[11].

In patients with DKA there is increased risk of mucormycosis due to following pathogenesis. Firstly, the ability of the Transferrin to bind to Iron is disrupted temporarily by Ketoacidosis thus eliminating the host-defense mechanism. Also, the ketone bodies produced during DKA is utilized by the enzyme Ketoreductase produced by the Rhizopus organism. These mechanisms permit the growth and proliferation of the mucormycosis pathogen[6,12,13].

Previously, there have been studies on association between DM and mucormycosis. In a study by Mishra et al., in patients with CAM (COVID associated mucormycosis), 87.5% had Diabetes Mellitus as the most common co-morbidity. The majority of the patients had poor glycemic control with a mean HbA1c of 9.06%[14]. Serris et al., in their study found that uncontrolled DM is the most common underlying disorder in patients with ROCM[15].

In our study, our focus is to study the correlation between the glycemic status of the individuals and the stage of orbital disease of ROCM in ophthalmologist's point of interest. Thus, we have restricted our research only to the orbital stages of the disease which has already been considered as the advanced form of the disease[5].

In our study we found that the mean HbA1c and mean RBS values were seen to be higher as the stage of ROCM advanced with a statistically significant difference between the values in each stage.

Conclusion:

Mucormycosis is an opportunistic invasive fungal infection which occurs in immune-suppressed individuals. The second wave of COVID gave rise to a dreadful endemic inside an already devastating pandemic in most of the parts of the world by rapidly rising cases of mucormycosis. Ophthalmologists had a major role in tackling the orbital manifestations. There have been several risk factors for the development of mucormycosis amongst which diabetes mellitus has an important significance in the disease presentation and progression. In our study it was found that there is a direct relation between the glycemic status of the study subjects and the severity of orbital mucormycosis. Hence prolonged hyperglycemia must be brought under control as it may significantly increase the risk of progression of the disease.

References

1. *Reid G, Lynch III JP, Fishbein MC, Clark NM. Mucormycosis. InSeminars in respiratory and critical care medicine 2020 Feb (Vol. 41, No. 01, pp. 099-114). Thieme Medical Publishers.*
2. *Kumar A, Verma M, Hakim A, Sharma S, Meena R, Bhansali S. Epidemiology of mucormycosis cases during the second wave of COVID-19 in a tertiary care institute in western Rajasthan, India. Cureus. 2022 Mar 8;14(3).*

3. *Cuffare, Benedette.Diabetes and mucormycosis, 2021 July 12. [Url: https://www.news-medical.net/health/Diabetes-and-Mucormycosis.aspx, Date of acces: 2/7/24, 16;08].*
4. *Fathima AS, Mounika VL, Kumar VU, Gupta AK, Garapati P, Ravichandiran V, Dhingra S, Murti K. Mucormycosis: A triple burden in patients with diabetes during COVID-19 Pandemic. Health Sci Rev 2021 Jan 1;1:100005.*
5. *Honavar SG. Code mucor: guidelines for the diagnosis, staging and management of rhino-orbito-cerebral mucormycosis in the setting of COVID-19. Indian J Ophthalmol 2021 Jun 1;69(6):1361-5*
6. *Artis WM, Fountain JA, Delcher HK, Jones HE. A mechanism of susceptibility to mucormycosis in diabetic ketoacidosis transferrin and iron availability. Diabetes. 1982 Dec 1;31(12):1109-14.*
7. *John TM, Jacob CN, Kontoyiannis DP. When uncontrolled diabetes mellitus and severe COVID-19 converge: the perfect storm for mucormycosis. Journal of fungi. 2021 Apr 15;7(4):298.*
8. *Lionakis MS, Kontoyiannis DP. Glucocorticoids and invasive fungal infections. The Lancet. 2003 Nov 29;362(9398):1828-38.*
9. *Bhattacharyya A, Sarma P, Sharma DJ, Das KK, Kaur H, Prajapat M, Kumar S, Bansal S, Prakash A, Avti P, Thota P. Rhino-orbital-cerebral-mucormycosis in COVID-19: A systematic review. Indian J Pharmacol 2021 Jul 1;53(4):317-27.*
10. *Kajs-Wyllie M. Hyperbaric oxygen therapy for rhinocerebral fungal infection. J Neurosurg Nurs 1995 Jun 1;27(3):174-81.*
11. *Marx RE, Stern D. Inflammatory, reactive and infectious diseases in oral and maxillofacial pathology. Carol Stream III. 2003:104-6.*
12. *Afroze SN, Korlepara R, Rao GV, Madala J. Mucormycosis in a diabetic patient: a case report with an insight into its pathophysiology. Contemp Clin Dent 2017 Oct 1;8(4):662-6.*
13. *Spellberg B, Edwards Jr J, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. Clin Microbiol Rev 2005 Jul;18(3):556-69.*
14. *Mishra Y, Prashar M, Sharma D, Kumar VP, Tilak TV. Diabetes, COVID 19 and mucormycosis: clinical spectrum and outcome in a tertiary care medical center in Western India. Diabetes & Metabolic Syndrome: Clinical Research & Reviews 2021 Jul 1;15(4):102196.*
15. *Serris A, Danion F, Lanternier F. Disease entities in mucormycosis. Journal of Fungi 2019 Mar 14;5(1):23.*

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