

“GLYCEMIC CONTROL VARIATIONS IN COVID-19 ASSOCIATED MUCORMYCOSIS”

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ABSTRACT

Background: Mucormycosis is opportunistic invasive fungal infection characterised by angioinvasion, thrombosis and necrosis of the tissues. Diabetes mellitus being the commonest immunocompromised state predisposing to mucormycosis in India, a study about glycemic control in CAM (covid-19 associated mucormycosis) patients and the severity of mucormycosis was necessary so as to reduce the morbidity and mortality in CAM patients.

METHODS

A retrospective descriptive study was conducted between May 2021 and July 2021 at Bowring & Lady Curzon hospital. 315 patients with post-covid ROCM (rhino-orbito-cerebral mucormycosis) were included in the study. Glycemic control of the patients was monitored with FBS, PPBS, HBA1C values. The extent and severity of CAM was studied in patients with good and poor glycemic control.

RESULTS

243 (77.14%) patients were male and 72 (22.86%) were female. 296 (93.97%) patients had prior history of diabetes mellitus and 19 (6.03%) patients had newly detected diabetes mellitus. 275 (87.30%) patients had poor glycemic control. 17 (6.18%) patients out of 275 presented with diabetic ketoacidosis (DKA). 40 (12.70%) patients had good glycemic control.

CONCLUSIONS

Diabetes mellitus has emerged as important risk factor associated with development of mucormycosis. In covid-19, poorly controlled diabetes, steroid induced hyperglycemia, covid induced insulin resistance act as fertile land for the development of mucormycosis. Hence monitoring glycemic status, judicious use of steroids, control of sugars may help in reducing the severity or occurrence of mucormycosis.

KEYWORDS

Mucormycosis, Diabetes mellitus, Covid-19 associated mucormycosis, Hyperglycemia.

INTRODUCTION

Mucormycosis is an acute invasive fungal infection caused by saprophytic fungi of Class Phycomycetes, Order Mucorales, and Family Mucoraceae, characterized by angio-invasion leading to host tissue infarction and necrosis.[1]

In India most common risk factor used to be uncontrolled diabetes mellitus, followed by hematological malignancy, patients receiving chemotherapy, solid-organ transplant recipients on immunosuppressive therapy, patients on prolonged high dose of corticosteroids or immunosuppressive drugs.[2]

Predisposing factors for mucorales spores to germinate in covid-19 affected patients include a fertile host environment of hypoxia,

hyperglycemia (diabetes, new onset hyperglycemia, steroid-induced hyperglycemia), acidosis (metabolic or diabetic ketoacidosis), high free iron levels, impaired phagocytic activity of white blood cells, ciliary dysfunction, cytokine storm (associated with insulin resistance and hyperglycemia), thromboinflammation (SARS-CoV-2 mediated, steroid-mediated or comorbidities), along with additional risk factors like prolonged hospitalization with or without mechanical ventilators.[3]

Albert Lecube et al conducted a study to evaluate whether peripheral blood mononuclear cells (PBMCs) from type 2 diabetes mellitus patients present an impairment of phagocytic activity and whether eventual impairment in phagocytic activity is related to glycemic control. They concluded that chronic diabetic state result in impaired host innate immunity, especially the phagocytic activity of PBMCs. Reduced PBMCs activity (such as impaired chemotaxis, bacterial phagocytosis, superoxide production, leukotriene release, lysosomal-enzyme secretion and endoplasmic reticulum stress) and impaired baseline intracellular calcium and superoxide in diabetes predispose them to infections including mucormycosis.[4]

As covid-19 associated mucormycosis (CAM) was declared as epidemic in India[5] with alarmingly increasing number of cases, and diabetes mellitus being the commonest immunocompromised state predisposing to mucormycosis in India, a study about glycemic control in CAM patients and the severity of mucormycosis was necessary so as to reduce the morbidity and mortality in CAM patients.

MATERIALS & METHODS

A retrospective descriptive (record based) study was conducted between May 2021 and July 2021 at Bowring & Lady Curzon hospital, Shri Atal Bihari Vajpayee Medical College and Research Institute, Karnataka, India. 315 patients with post-covid ROCM were included in the study.

Inclusion Criteria

1. Post Covid RTPCR negative CAM who were histopathologically and/or radiologically proven mucormycosis [European Organization for Research and Treatment of Cancer / Mycoses Study Group (EORTC/MSG group) criteria].[6]

Exclusion criteria

1. Patients with no history of RTPCR positive COVID 19 infection.
2. RTPCR positive CAM.

After obtaining approval from the institutional ethics committee, the patients fulfilling the inclusion criteria were enrolled for the study. Patient's demographic details, clinical features, laboratory test results, radiological reports and details of medical and surgical interventions performed were collected using a detailed proforma. FBS (fasting blood sugar), PPBS (postprandial blood sugar), HbA1C (glycated haemoglobin) levels was sent for all patients at the time of admission to monitor glycaemic control.

Extent and severity of CAM was based on staging of rhino-orbito-cerebral mucormycosis (ROCM) by Honavar SG et al[7]

- Stage 1 – Involvement of the nasal mucosa.
- Stage 2 – Involvement of the paranasal sinuses, perisinus inflammation.
- Stage 3 – Involvement of the orbit.
- Stage 4 – Involvement of the central nervous system.

Patients were divided into 2 categories based on FBS, PPBS and HbA1C values according to American Diabetic Association.[8]

- a. Good glycemic control – HbA1C < 7% (53mmol/mol), FBS < 130mg/dL (7.2 mmol/L), PPBS < 180mg/dL (10.0 mmol/L).
- b. Poor glycemic control – HbA1C > 7% (53mmol/mol), FBS > 130mg/dL (7.2 mmol/L), PPBS > 180mg/dL (10.0 mmol/L).

The extent and severity of CAM was studied in both the categories. Patients were managed in

consultation with physician and were started on injection insulin (regular) according to sliding scale during their hospital stay. Surgical debridement and systemic antifungals formed the crux of the treatment along with glycemic control. FBS, PPBS, HBA1C was repeated after 1 month of initiation of treatment.

Statistical tool for analysis: Data collected in the proforma was collated in MS Excel and analysed statistically using SPSS software version 24. Mean was calculated for FBS, PPBS and HBA1C values data was presented in tables and bar chart.

RESULTS

315 patients were included in the study. 243 (77.14%) patients were male and 72 (22.86%) were female. 296 (93.97%) patients had prior history of diabetes mellitus and 19 (6.03%) patients had newly detected diabetes mellitus

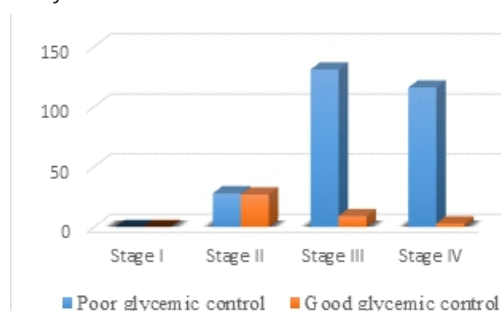


Figure 1 Glycemic control and extent/severity of ROCM

Patients with poor glycemic control :

275(87.30%) patients had poor glycemic control as per criteria.[8] 217 patients were male and 58 were female (ratio 3.7:1). 262 (95.27%) patients were on oral hypoglycemic agent (OHA) and 13 (4.73%) were on insulin. Mean FBS, PPBS, HBA1C values at the time of admission were 226.84 mg/dl, 252.32 mg/dl, 8.68 +/- 1.08%. 28 (10.18%), 131 (47.64%), 116 (42.18%) patients presented with stage II, III, IV ROCM respectively (Figure 1). Mean HBA1C levels in these patients were 7.36+/- 0.25%, 8.53+/-0.91%, 9.14+/-1.08% in stage II, III, IV disease respectively. Patients were started on injection insulin (regular) according to sliding

scale along with GRBS (General Random Blood Sugar) monitoring three times a day.

Patients with Diabetic ketoacidosis (DKA) :17 (6.18%) patients out of 275 presented with diabetic ketoacidosis (DKA). 5 (29.41%), 12 (70.59%) DKA patients presented with stage III, IV ROCM respectively. Mean HBA1C levels in these patients were 11.95%, 12.16% in stage III, IV disease respectively (Figure 2).

Management of DKA included correction of hyperglycemia with insulin infusion, correction of fluid loss and electrolyte imbalances, acid-base balance

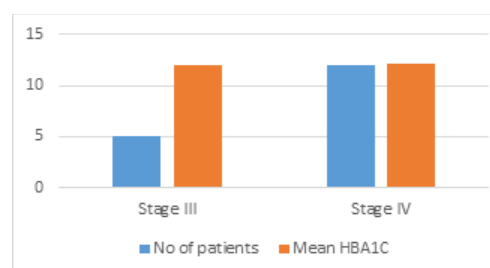
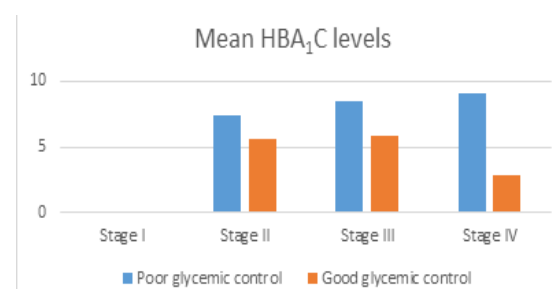


Figure 2: No. of patients, Mean HBA₁C levels in Stage III, IV patients with DKA



Patients with good glycemic control : 40 (12.70%)

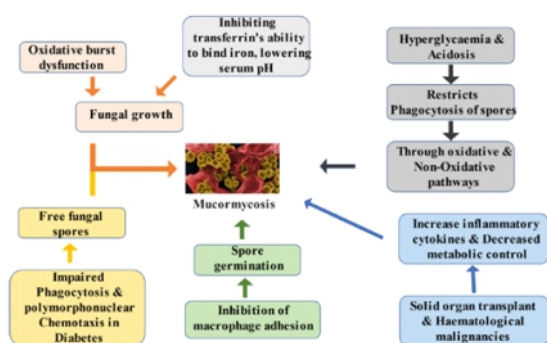
patients had good glycemic control as per criteria.[8] 31 patients were male and 9 were female (ratio 3.4:1). 37 (92.5%) patients were on OHA and 3 (7.5%) were on insulin. Mean FBS, PPBS, HBA₁C values at the time of admission were 116.1 mg/dl, 154.57 mg/dl, 5.74%. 27 (67.5%), 9 (22.5%), 4 (10%) patients presented with stage II, III, IV ROCM respectively (Figure 1 & 3). Mean HBA₁C levels in these patients were 5.6+/-0.56, 5.88+/-0.78, 6.4+/-0.62 in stage II, III, IV disease respectively.

Figure 3 Glycemic control and mean HBA_{1c} Levels

DISCUSSION

Mucormycosis is opportunistic invasive fungal infection characterised by angioinvasion, thrombosis and necrosis of the tissues. Mucormycosis is not unfamiliar to India; the disease prevalence in India in 2019 was estimated to be 140 cases per million population which was about 80 times higher than in developed countries.^[10] In a retrospective multicenter study conducted in India between September to December 2020, it was found that prevalence of CAM in hospitalised patients was 0.27%.^[11] A recent systematic review conducted by Musuza JS et al observed that CAM constitutes 0.3% of COVID-19 coinfections.^[12]

According to the IDF in 2019, the top three countries with the highest number of individuals with diabetes are China (116.4 million), India (77.0 million), and the United States of America (31.0 million). The prevalence of diabetes in India has risen from 7.1% in 2009 to 8.9% in 2019. It is also estimated that nearly 57% of adults with diabetes are undiagnosed in India, which is approximately 43.9 million.^[13]



SARS-CoV-2 infection causes endothelial dysfunction due to direct viral invasion and host inflammatory response causing apoptosis and pyroptosis of endothelial cells. Diabetes is a chronic inflammatory state associated with endothelial dysfunction Endothelial adhesion and

angioinvasion are critical for invasion of mucorales. Thus, patients with diabetes with covid-19 infection are at high risk for invasive mucormycosis. Overall, hyperglycemia in patients with diabetes and covid-19 on steroids contributes to risk of mucormycosis by following mechanism: a) Induction of defect in neutrophil-macrophage phagocytotic system; b) Upregulation and increased expression of GRP78 receptor in humans and mucorales specific protein Coth; c) Hyperglycation of iron sequestering proteins leading to disruption in iron sequestration and increased delivering of iron to mucorales.^[14] (Figure 4)

In our study, 275 patients had uncontrolled diabetes mellitus at the time of admission with male predominance (77.14%). Mean HBA_{1c} levels in these patients were 7.36%, 8.53%, 9.14% in stage II, III, IV disease respectively which indicated severity of ROCM increased with increase in mean HBA_{1c} levels.

Figure 4 Probable pathogenesis of mucormycosis in patients with diabetes mellitus^[9] 17 (6.18%) patients out of 275 presented with diabetic ketoacidosis (DKA). Hyperglycemia increases glucose-regulated 78 kDa protein (GRP78) expression on the human endothelial cells, the essential receptor for vascular invasion by mucorales through its spore coat protein (Coth). Rhizopus also interacts with GRP78 on nasal epithelial cells via Coth3 to invade and damage the nasal epithelial cells. The expression of GRP78 and Coth3 is significantly enhanced by high glucose, iron, and ketones (the hallmark of DKA), potentially causing ROCM.^[15,16] 40 (12.70%) patients had good glycemic control as per criteria.^[8] 27 (67.5%), 9 (22.5%), 4 (10%) patients presented with stage II, III, IV ROCM respectively and mean HBA_{1c} levels was < 7% indicating lesser severity of ROCM as compared to patients with poor glycemic control.

In a multicentric collaborative study conducted by Sen M et al 2194 patients (78%) had diabetes mellitus, 972 (44%) were uncontrolled or had

diabetic ketoacidosis (DKA).^[7] The prevalence of diabetes in CAM was higher than historical cohorts of mucormycosis not associated with covid (92% vs 76%) in a study conducted by Binder U et al.^[17]

Diabetes mellitus has emerged as important risk factor associated with development of mucormycosis in both CAM and non covid mucormycosis patients. In covid-19, poorly controlled diabetes, steroid induced hyperglycemia, covid induced insulin resistance act as fertile land for the development of mucormycosis. Hence monitoring glycemic status, judicious use of steroids, control of sugars may help in reducing the severity or occurrence of ROCM.

CONCLUSION

High prevalence of mucormycosis in India, undiagnosed or poorly controlled diabetes (high HBA_{1c} levels), covid-19-induced immune system dysregulation, and therapies such as injudicious use of steroids, which cause immune suppression help in development of mucormycosis. Preventive measures may need to focus on identification, optimal management of these risk factors for CAM, including aggressive glycemic control and avoidance of steroid overuse.

DECLARATIONS

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Conflict of interest: Nil

Ethical approval: Taken

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