A Review on Mucormycosis in View Of COVID-19, Diabetes and The Role of Iron

By

Zarin Jumana
17326006

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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Student's Full Name & Signature:

____

Zarin Jumana
Student ID: 17326006

Approval

The thesis/project titled "A Review on Mucormycosis in View Of COVID-19, Diabetes and The Role of Iron" submitted by

1. [Zarin Jumana (17326006)]

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Examining Committee:

Supervisor:
(Member)

____

Akash Ahmed
Lecturer
Department of Mathematics and Natural Sciences
Brac University

Program Coordinator:
(Member)

____

Mahbubul Hasan Siddiqee, PhD
Assistant Professor
Department of Mathematics and Natural Sciences
Brac University

Departmental Head:
(Chair)

____

A F M Yusuf Haider, PhD
Professor
Department of Mathematics and Natural Sciences
Brac University

Abstract

COVID-19 has made people all over the world susceptible to other diseases caused by various microorganisms. One of them is caused by a fungus called mucormycosis or black fungus. Together with diabetes and COVID-19, it creates the perfect mechanism to make a person less immune to other diseases. This review concerns with how becoming infected with COVID-19 makes way for diabetes to either occur or worsen and for the fungi to be opportunistic and infect a person who is already immunocompromised. There are comparisons made from one country to another having all of the above diseases altogether. The role that iron plays in declining the condition of combination of diseases is also mentioned.

Keywords: COVID-19; diabetes type I and II; mucormycosis; black fungus; iron; risk factors

Dedicated to my loving parents

Johurul Alam and Parvin Sultana,

my sister Jehan and my brother Rayan

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Table of contents

Contents

List of tables

List of Acronyms

COVID-19	Coronavirus Disease 2019
WHO	World Health Organization
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
H1N1	Influenza type A virus
ICU	Intensive Care Unit
MERS-CoV	Middle East Respiratory Syndrome coronavirus
OR	Odds ratio
SARS-CoV-1	Severe Acute Respiratory Syndrome Coronavirus 1
ROCM	Rhino Orbital Cerebral Mucormycosis
CT	Computer Tomography
MCR	Mucormycosis
CKD	Chronic Kidney Disease
IHD	Ischemic Heart Disease
DKA	Diabetic Keto Acidosis
T2DM	Type 2 Diabetes Mellitus
DM	Diabetes Mellitus
T1DM	Type 1 Diabetes Mellitus
SOT	Solid organ transplant
CAPM	Coronavirus associated pulmonary mucormycosis
CAM	Coronavirus associated mucormycosis
GI	Gastrointestinal tract
CD4+ T cells	Helper T cells
ROC	Rhino Orbital Cerebral
ACE-2	Angiotensin Converting enzyme 2

Chapter 1

Introduction

COVID-19 was declared a pandemic by WHO on 11th March 2020. Coronavirus being the main culprit of the pandemic caused to affect lives of 216,845,841 people and caused death of 4,509,821 people as of 29th August 2021 (Source: Worldometer as of writing the report). Although 193,781,657 people recovered from COVID-19, people became weak and immunocompromised and are falling victims to diseases which are caused by bacteria, fungi etc. An order of fungi, Mucorales, is on the spotlight for causing mucormycosis (black fungus) infection (Hibbett et al., 2007). Among the organisms of the order Mucorales, *Rhizopus oryzae* was the most common organism isolated and was responsible for almost 70% of all mucormycosis cases (Ribes et al., 2000); (Spellberg et al., 2005); (Roden et al., 2005). With a high morbidity and mortality rate, Mucormycosis the third most common invasive fungal infection (Bouza et al., 2006); (Kontoyiannis et al., 2012). Patients who are immunocompromised because of diabetic ketoacidosis, organ transplantation, neutropenia, and/or increased levels of free iron in the serum are more susceptible to this life-threatening infection mucormycosis (Ibrahim et al., 2012). People who have poorly controlled diabetes mellitus and other co-morbidities as risk factors, in them the mucormycosis infection are emerging along with COVID-19 infection (D. Garg et al., 2021a). To treat severe or critical COVID-19, corticosteroids are used which is a well-known risk factor for mucormycosis (Lionakis & Kontoyiannis, 2003).

Viral pandemics which happened in the past were witnessed to have association with diabetes which increased morbidity and mortality. In the Severe Acute Respiratory Syndrome (SARS-CoV-1) outbreak which happened in the year 2002-2003, diabetes was considered as an independent risk factor for complication and even death (J. K. Yang et al., 2006). Then during the Influenza A (H1N1) infection outbreak in 2009, diabetes increased the risk of hospitalization by three times in the Intensive Care Unit (ICU) (Allard et al., 2010). Also, during the outbreak of Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV) which happened in the year 2012, in almost 50% of the population, diabetes was prevalent and the odds ratio (OR) for severe or critical infection of MERS-CoV ranged from 7.2-15.7 in diabetic cohort compared to the overall population (Badawi & Ryoo, 2016). 35% was the rate of mortality in patients who had diabetes (Al-Tawfiq et al., 2014), (Alraddadi et al., 2016).

There are several risk factors for patients who are infected with COVID-19 and who have diabetes. Patients who have severe or critical COVID-19 are used to treat with corticosteroids which help in fungal growth and thus predisposed patients with mucormycosis (Lionakis & Kontoyiannis, 2003). In a research it was evident that pancreatic islets were induced damage upon by SARS CoV-1 which resulted in acute diabetes and diabetic ketoacidosis (J.-K. Yang et al., 2010). In fact, having diabetes mellitus is said to be a “classic” risk factor and rate at which morbidity and mortality rate is associated is increased (A. K. Singh et al., 2020). This aim of this review paper is to discuss the clinical manifestations, the causative agents, the connection between COVID-19, mucormycosis and diabetes and to look at the role of iron.

Chapter 2

Method

Google Scholar and PubMed was searched using the terms “COVID-19”, “SARS-CoV-2”, “Coronavirus”, “Diabetes”, “Black Fungus”, “Mucormycosis”, “Mucor”, “ROCM”, “Pulmonary mucormycosis”, “Cutaneous mucormycosis”, “Gastrointestinal mucormycosis”, “Transferrin”, “Iron and mucormycosis” up to September 2021. Only Journal articles were used which contained adequate information about risk factors, predisposing factors, causative agents, clinical outcomes, prevalence, microbiology, diagnosis, treatment, and epidemiology. The role of iron in playing a major role in light of both diabetes and mucormycosis was included.

Chapter 3

Clinical manifestation

Clinical manifestations of Mucormycosis which had diabetes as risk factors

Mucormycosis infects patients who lacks the ability of protecting themselves such as immunocompromised patients. The disease is mainly diagnosed by doing a biopsy after isolating them from the site of infection. Other imaging tests like CT can also be done to diagnose (Prakash & Chakrabarti, 2019). Depending on the different anatomical sites in the body, mucormycosis can be classified into several types which are: rhino-orbital-cerebral (ROCM), pulmonary, gastrointestinal, cutaneous, disseminated, and other miscellaneous forms (Jeong et al., 2019). The most common mucormycosis is ROCM. The organism that mostly causes ROCM is Rhizopus, Cunninghamella was linked with pulmonary or disseminated mucormycosis and the organism that is linked with cutaneous mucormycosis is either Apophysomyces or Saksenaea (Jeong et al., 2019). Diabetes mellitus is associated with these forms of mucormycosis as a predisposing factor. The association of these clinical manifestations of mucormycosis with diabetes is explained.

3.1 Rhino-Orbital-Cerebral Mucormycosis

Rhino-Orbital-Cerebral-Mucormycosis generally affects the nose, sinuses, eyes and, brain (Ethiraj, G., 2021).

The most common underlying causes for ROCM is uncontrolled diabetes and diabetes ketoacidosis and it was also observed that patients with diabetes mellitus were more prone to ROCM than patients without diabetes mellitus (Jeong et al., 2019). It occurs mainly in immunocompromised patient with more than 70% cases having a complication called diabetic ketoacidosis (Fouad et al., 2021). In a study from the United States, it was reported that 83% of the patients had diabetes mellitus (Reed et al., 2008). In another case study conducted by (Fouad et al., 2021) it was observed that 10 patients out of 12 had diabetes and poorly controlled diabetes prior to their hospital admission and 6 out of 12 patients had SARS-CoV-2.

Table 1: ROCM cases all over the world

Country	**Patients with COVID-19 and MCR**	**Mean age**	**DM**	**Other Risk factor**	**Paper**
India	2818	51.9	2194 (78%)	Hypertension-690(80%) Renal disease-80(10%) Chronic sinusitis-18(2.1% Bronchial asthma-17(2) Cardiovascular disorder-16(1.9) Cerebrovascular disease-8(0.9)	(Sen et al., 2021)
Iran	8	52	13	HTN-7(46) Hematologic malignancies-2(13) Asthma-2(13) Cardiovascular disease-2(13)	(Pakdel et al., 2021)
UK	218	---	61-T2DM 6-T1DM 4-DKA	------	(Goldman et al., 2020)
USA	2	42	2-T2DM	Sinusitis-1 COVID-19 associated pneumonitis-1	(Dallalzadeh et al., 2021)
Egypt	6	51.25	6	CKD IHD, DKA	(Fouad et al., 2021)

A study was conducted by (Sen et al., 2021) in India with 2826 cases of rhino-cerebral mucormycosis out of which 2818 of the cases had both COVID and ROCM. Hospitalized cases were 2029, Home care cases were 735 and asymptomatic COVID cases were 54. Among the 2818 cases, 2194 of the patients had T2DM (Type II diabetes mellitus) and 690 of them had hypertension, 80 of them had renal disease, 18 of them had chronic sinusitis, 17 of them had bronchial asthma, 16 of them had cardiovascular disorder, and 8 of them had cerebrovascular disorder as the clinical manifestation. 2073 out of 2371 patients received corticosteroids as treatment.

A cross-sectional study was conducted in Iran by (Pakdel et al., 2021) of 58 patients out of which only 15 were confirmed to have both COVID-19 and mucormycosis. The median age of the patients were 52 years old with 66% male population. 13 out of 15 patients had DM and the rest had other risk factors such as hypertension, asthma, cardiovascular disease hypothyroidism, cirrhotic liver, tuberculosis, and hematological malignancies side by side with diabetes. 8 (53.33%) of the patients had severe COVID-19 infection, 5 (33.33%) of them were moderate and 2 (13.33%) of them were mild. It was observed that the mucormycosis associated risk factor varied from having uncontrolled diabetes to DKA, steroid therapy, chemotherapy, neutropenia, and hypertension.

A study in UK by (Goldman et al., 2020) conducted with 218 patients who were admitted to a hospital . They all had confirmed COVID-19 infection. Out of the 218 patients, 61 previously had T2DM, 6 previously had T1DM and 4 of the patients were diagnosed with DKA. The 4 patients who developed DKA were not known to have T1DM but three of them had pre-existing T2DM and they were prescribed with oral hypoglycemics. The 1 patient who did not have any pre-existing DM was observed to have high glycated hemoglobin. But all 4 patients were given intravenous insulin.

In a case report by (Dallalzadeh et al., 2021) in the USA, 2 patients with ROCM associated COVID-19 were subjected to secondary infections. Their mean age was 42 years old, and both had T2DM as their underlying disease. They both developed diabetic ketoacidosis but received different treatments. One received corticosteroid and antibiotics and the other patient was treated with remdesivir.

A case report conducted by (Fouad et al., 2021) in Ain Shams University Hospitals in Egypt with 12 cases in 6 months whose mean age was 51.25 years in which 6 cases had both COVID-19 and mucormycosis. All 6 of the cases had DM as comorbidities along with CKD (chronic kidney disease), IHD (ischemic heart disease), and DKA. 4 out of 12 cases had poorly controlled DM, 1 had well controlled DM and the rest 1 had DKA. In 3 out of 6 cases the patients were recovered, the rest 3 cases ended in fatality.

There is one thing worth mentioning which is the use of corticosteroid as a treatment of both diabetes and COVID-19. Corticosteroid helps to develop the growth of mucormycosis. Therefore, having either one of the two may expedite the process of development of mucormycosis. In a review done by (Reed et al., 2008) about the treatment of diabetes and mucormycosis it was observed that corticosteroid therapy was given to diabetic patients. Corticosteroid was also used to treat severe/ critical COVID-19 which is detected as a well-known risk factor for mucormycosis (John et al., 2021).

3.2 Pulmonary Mucormycosis

While RCOM is the most common type of mucormycosis that can occur anatomically, Pulmonary mucormycosis is the second most common site of involvement and can be observed mainly in patients who have hematological disorders and who are transplant recipients (Jeong et al., 2019). The major risk factor for Pulmonary mucormycosis is hematological malignancy (32%-40%), which is then followed by diabetes mellitus (32%), stem cell transplant (1%-9.8%) and solid organ transplant (6.5%-9%) (Tedder et al., 1994). In a review conducted by (Lee et al., 1999), it was analyzed that the 56% of people with pulmonary mucormycosis had diabetes and 20% were presented with diabetic ketoacidosis. So, patients with diabetes were presented with and without ketoacidosis. The polymorphonuclear leukocytes are able to detect but unable to contain the initial infection which makes diabetes prone to ROCM (Vaughan et al., 2018). The mortality rate associated with diabetes mellitus patients is 60% (Tedder et al., 1994). Steroid therapy was also used in the case of pulmonary mucormycosis which was concluded as a significant risk factor (Prakash et al., 2019). Patients with well-controlled diabetes mellitus followed by pulmonary mucormycosis received short courses of steroids which made chronic obstructive diseases worse (Hoang et al., 2020).

Table 2: COVID-19 associated Pulmonary mucormycosis all over the world

Country	Patients with COVID-19 and MCR	Mean age	DM	Other Risk factor	Paper
USA	1	44	T2DM	Pneumonia Acute Respiratory Distress Syndrome	(Khan et al., 2020)
Bangladesh	1	53	T2DM	Poor glycemic control Systemic hypertension Bronchial asthma	(Afroz et al., 2021)
India	187	53.4	113	Hematologic malignancies Renal transplantation	(Patel et al., 2021)
USA (3) UK (2) Netherlands (3) India (2) Italy (1) Austria (1) Chile (1) France (1)	14	----	5	Hematologic malignancies SOT and DM SOT	(M. Garg et al., 2021)

In the study supervised by (Khan et al., 2020), a 44 year old Hispanic woman was suspected of CAPM. She had DM and she was intubated upon admitting to the hospital. She also had COVID-19 associated pneumonia. Her blood glucose count, lung sounds, serum sodium level, serum creatinine level, serum bicarbonate levels were examined and recorded. In her ICU state, her metabolic status was observed to have been deranged and respiratory status also worsened gradually resulting in acute respiratory distress syndrome. Patients who are diabetic usually present with rhino-cerebral disease whereas people who are immunocompromised and are transplant recipients are mainly prone to pulmonary mucormycosis (Jeong et al., 2019).

(Afroz et al., 2021) in their study about the patient who is 53-year-old was referred to their center because of his fever and lung lesion. He had T2DM with poor glycemic control. As his underlying risk factors, he also had systemic hypertension and bronchial asthma. He was infected with COVID-19 about 2 months ago which was 39 days after taking his first dose of vaccine.

A retrospective observational study was conducted by (Patel et al., 2021) with 16 healthcare centers across India from September through December 2020. A total of 295 cases were diagnosed and reported but 8 cases were omitted as there was not enough data. Thus, out of 287 cases 187 (65.2%) patients had CAM. The mean age of all the cases was 53.4 years and 74.6% were male and 25.4% were female. All the cases had one or more underlying diseases. 113 (60.4%) of cases had DM as underlying disease, 2 (1.1%) had Hematological malignancies, 3 (1.6%) had renal transplantation. 61 (32.6%) of the patients were infected with COVID-19 and 48 (78.7%) out of them were treated with Glucocorticoids. But Glucocorticoid was given to a total of 146 (78.1%) patients out of the total cases. Pulmonary MCR was the site of involvement for 16 (8.6%) patients. Among the patients who had Pulmonary MCR, 8 (4.5%) survived.

In a retrospective study conducted by (M. Garg et al., 2021) the confirmed cases of CAPM were described. There were 14 cases of CAPM reported which were from USA (3), UK (2), Netherlands (3), India (2), Italy (1), Austria (1), Chile (1), France (1). It was not specified but among the 14 cases, 5 had DM. These patients were observed to have been on ventilation and underwent surgery. They also had a high mortality rate compared to CAM cases (conducted side by side with CAPM cases). They also had certain risk factors such as hematologic malignancies, SOT and DM side by side and SOT alone.

3.3 Cutaneous Mucormycosis

When mucormycosis involves the skin and subcutaneous tissue, it is termed as cutaneous mucormycosis (Chakrabarti et al., 2006). Patients who are incompetent and are victims of certain trauma such as breaching of skin are more susceptible to cutaneous mucormycosis. In a review conducted on cutaneous mucormycosis it was observed that 43%-67% of the patients were immunocompetent and only 10%-15% of the patient may occasionally develop cutaneous mucormycosis (Skiada et al., 2012). In a case analysis conducted by (Adam et al., 1994) it was observed that out of 25 patients, 11 had diabetes and out of those 11 patients, 7 had diabetic ketoacidosis (DKA) and all the patients had diabetes type II. The survival rate for those patients with cutaneous mucormycosis is comparatively higher (69.1%) than the other types of mucormycosis (Chakrabarti et al., 2006) this is also because of the early diagnosis and treatment of the infection.

Table 3: Cutaneous Mucormycosis cases

Cases	**Patients with COVID-19 and MCR**	**Mean age**	**DM**	**Other Risk factor**	**Paper**
Case 1	1	68	T2DM	Heart transplant Hypertension Chronic kidney disease Obstructive sleep apnea	(Khatri et al., 2021)
Case 2	1	67 (M)	DM	Hypertension Ischemic heart disease	(Shakir et al., 2021)

3.4 Gastrointestinal Mucormycosis

One of the most difficult form of mucormycosis which is difficult to diagnose is gastrointestinal mucormycosis and its number of cases is presently rising (Kaur et al., 2018). The predisposing factors of GI mucormycosis are observed in people transplant recipients and hematological malignancies but other than these, it can also develop in neonates, in patients with malnutrition and in patients undergoing peritoneal diagnosis (Kaur et al., 2018). There are two types of immunocompromised hosts: one is classical immunocompromised hosts in which patients with GI mucormycosis are observed to have solid organ transplant (52%), hematological malignancies (35%) and neutropenia (38%) as major risk factors (Kaur et al., 2018). The other type of incompetent host is non-classical immunocompetent hosts in which patients with GI mucormycosis are observed to have diabetes mellitus (12.2%), malnutrition (16.7%), peritoneal dialysis (8.5%) and the use of broad-spectrum antibiotics as major risk factors. For adult population, the main risk factors are diabetes mellitus and peritoneal dialysis and for children the main risk factors are usage of broad-spectrum antibiotics and malnutrition.

Table 4: GI mucormycosis cases worldwide

Cases	**Patients with COVID-19 and MCR**	**Mean age**	**DM**	**Other Risk factor**	**Paper**
Case 1	1	57	DM	Acute mesenteric ischemia	(Jain et al., 2021)
Case 2	1	86	DM	Arterial hypertension	(Monte Junior et al., 2020)
Case 3	1	48	No	No underlying illnesses	(R. P. Singh et al., 2021)
Case 4	1	38	No	Crohn's disease	(Morton et al., n.d.)

The fatality of gastrointestinal mucormycosis is 85% as said in the study of (Kaur et al., 2018) which is a review conducted in India about the global cases of GI mucormycosis. A total of 176 cases could be retrieved from the years 1948 through 2017. Among them, 89 cases were from Asia, 33 cases were from North America, 26 cases were from Africa, 16 cases were from Europe, 8 cases were from Australia and 4 cases were from South America. Among the 176 patients, 172 cases had record out of which 89 cases were adults and 21 of them had diabetes mellitus and the rest 83 were pediatric patients.

Chapter 4

Causative agents

Causative agents related to Mucormycosis in association with diabetes and COVID-19

In an attempt in classifying the fungi phylogenetically, (Hibbett et al., 2007) in their study they took into account 7 phyla, 10 subphyla, 35 subclasses, 12 subclasses and 129 orders from one kingdom and one subkingdom. They included *Chytridiomycota, Monoblepharidomycetes, Neocallimastigomycota, Neocallimastigomycetes, Dikarya, Acarosporales, Baeomycetales, Candelariales, Umbilicariales, Lecanoromycetidae, Eurotiomycetidae, Mycocaliciomycetidae, Melanosporales, Corticiales, Gloeophyllales, and Trechisporales.* The phylum *Zygomycota* was not accepted because it was distributed in the subphyla of the phylum *Glomeromycota* called Mucormycotina.

The *Mucorales* which are thought to cause zygomycosis in humans are from the species *Rhizopus* sp. and *Mucor* sp. Among the *Rhizopus* sp. the most common is *Rhizopus (oryzae) arrhizus* and can be identified in a number of countries such as India, Pakistan, New Guinea, Taiwan, Central and South America, Africa, Iraq, Somalia, Egypt, Libya, Israel, Turkey, Spain, Italy, Hungary, Czechoslovakia, Germany, Ukraine, the British Isles, and the United States (Ribes et al., 2000). From cultivated grassland to and different forest locations, it can also be found in volcanic mud. They can be isolated from hay, decaying grass, barley, wheat, corn, rice etc.

Members from the mucor species are ubiquitous in nature and can be found in environmental samples all around the world. Spores of this organism can be obtained from air or dust samples and from hospitals or home. They can also be found in dog fur. Many organisms from this species can cause disease such as *M. circinelloides*, *M. hiemalis*, *M. rouxianus*, *M. ramosissimus,* and *M. racemosus.*

Even though *Rhizopus arrhizus* is the most common agent for causing mucormycosis, the causative agent varies across different geographic locations. For example, in Asia the causative agent predominant is *Apophysomyces variabilis* (Prakash & Chakrabarti, 2019) which cannot be observed in Europe or Africa while in Europe it is *Lichtheimia* species. There are three isolates of *Saksenaea vasiformis* which were reported from North and South America and the other nine isolates were from India (4) and Spain (5). There were 4 cases of mucormycosis observed from Europe (2), Australia (1) and the USA (1), the causative agent of which was *Syncephalastrum racemosum* (Jeong et al., 2019).

In the review of (Jeong et al., 2019), the organism associated with the type of mucormycosis was analyzed. It was observed that *Rhizopus* spp. was isolated from patients with Rhino-Orbital-Cerebral-Mucormycosis patients, *Cunninghamella* spp. was isolated from pulmonary mucormycosis patients, Lichtheimia spp., Saksenaea spp., and Apophysomyces spp. was isolated from cutaneous mucormycosis.

The fact that *Rhizopus* sp. is the most common among all these can be proved with the help of (Prakash et al., 2019). They conducted a prospective multicenter study from 2013 to 2015 at 4 care centres in India. Institutional Ethics committee also approved all 4 centres individually.

Table 5: Number of cases according to site of infection

Site of infection	**Total number of cases**	**Cases in North India**	**Cases in South India**
Rhino-orbito-cerebral	248 (63.9%)	201	47
Pulmonary	50 (12.9%)	44	8
Cutaneous	37 (9.5%)	28	9
Gastrointestinal	25 (6.4%)	23	2

According to the table-5 it can be clearly observed that the number of cases for ROCM is comparatively higher than pulmonary, cutaneous and gastrointestinal type of mucormycosis. The total number of cases combined both from North India and South India are 248 whereas that of pulmonary, cutaneous and gastrointestinal are respectively 50, 37 and 25.

Chapter 5

Pathophysiology

<u>Pathophysiology between COVID-19, Diabetes mellitus, and Mucormycosis</u>

Not only are COVID-19 patients immunocompromised, they become susceptible to different diseases one of which is mucormycosis. Many patients also have diabetes as an underlying factor who become more prone to mucormycosis. One of the most common risk factor of COVID-19 is diabetes mellitus (Guan et al., 2020) and poorly controlled diabetes mellitus induces mucormycosis (D. Garg et al., 2021b). COVID-19 can also precede to initiate diabetes (Heaney et al., 2020). Diabetes mellitus conversely can impair the function of innate immune system by impairing phagocytic activity (Lecube et al., 2011). With acidosis and diabetes mellitus infection caused by mucormycosis worsens. Diabetic patients who are susceptible to mucormycosis are also observed to be on systemic corticoid use (Binder et al., 2014) which is also used in the treatment of sever or acute COVID-19 (Moorthy et al., 2021) which can be life-threatening for some patients in association with mucormycosis. The use of steroids can weaken the immune system and make one susceptible to mucormycosis. The blood sugar level may also rise with the use of steroids which is a challenge for those patients who have uncontrolled diabetes (Mahalaxmi et al., 2021). Even the physicians who are documenting the mucormycosis cases observed that the patients with diabetes who are treated with steroids both for diabetes and SARS-CoV-2 have become prone to fungal attack.

Mucormycosis in patients with COVID-19 can increase in many ways. At first, the immune system becomes compromised with the infection of COVID-19 which may lead to the reduction of immune cells such as CD4 + T and CD8 + T cells and T lymphocytes which enables a patient to become prone to any secondary fungal infections (Lionakis & Kontoyiannis, 2003). Finally, the use of glucocorticoid is beneficial because it reduces the length of hospital stay and helps with getting well from COVID-19 but glucocorticoids are known to develop mucormycosis and help with their growth.

<u>The mechanism which induces patients with diabetes mellitus and COVID-19 to develop MCR</u>

In (Moorthy et al., 2021) study about retrospective, multi-centric analysis of 18 cases of mucormycosis, it can be observed that the use of steroid and having diabetes mellitus as underlying disease, leads to a patient becoming prone to infection caused by mucormycosis.

Table 6: 18 cases with history of DM, COVID-19 infection and steroid uptake

Case No.	**Age + Sex**	**Diabetes**	**Steroid uptake**	**COVID-19 status**	**Diagnosis (MCR)**
1	58 (M)	Yes, and poorly controlled	YES	POSITIVE	Mucormycosis
2	56 (M)	Yes, and poorly controlled	YES	POSITIVE	Mucormycosis
3	35 (M)	Yes, and poorly controlled	YES	POSITIVE	Mucormycosis
4	73 (M)	Yes, and poorly controlled	YES	POSITIVE	Mucormycosis
5	53 (M)	Yes, and poorly controlled	YES	POSITIVE	Mucormycosis
6	55 (M)	Yes, and poorly controlled	YES	POSITIVE	Mucormycosis
7	63 (M)	Yes, and poorly controlled	YES	POSITIVE	Mucormycosis
8	52 (F)	Yes, and poorly controlled	YES	POSITIVE	Aspergillosis
9	37 (M)	Yes, and poorly controlled	YES	POSITIVE	Mucormycosis
10	45 (M)	NO	NO	POSITIVE	Mucormycosis + Aspergillosis
11	53 (F)	Yes, and poorly controlled	YES	POSITIVE	Mucormycosis
12	68 (M)	Yes, and poorly controlled	YES	POSITIVE	Mucormycosis
13	67 (M)	NO	YES	POSITIVE	Mucormycosis
14	61 (M)	Yes, and poorly controlled	YES	POSITIVE	Mucormycosis
15	49 (M)	Yes, and poorly controlled	YES	POSITIVE	Mucormycosis

16	63 (F)	Yes, and poorly controlled	YES	POSITIVE	Mucormycosis
17	57 (M)	Yes, and poorly controlled	YES	POSITIVE	Mucormycosis
18	39 (M)	Yes, and poorly controlled	NO	POSITIVE	Mucormycosis
	M-15 F-3	Non-diabetic=2 Diabetic=16			

It can be observed from table-6 that all the cases which resulted in mucormycosis has COVID-19, steroid uptake and diabetes in common between the cases. Although there were 2 cases where the patients were not diabetic, they also resulted in mucormycosis and they were observed to have COVID-19 positive and diabetic. Only one case which was exceptional is the case No. 10 which was non-diabetic as well as did not uptake steroid but was only COVID-19 positive.

5.1 Relation of diabetes mellitus with MCR

When a person develops diabetes, two things can happen: 1. Pancreas fails to transport insulin to the required body cells and 2. Cells become resistant to insulin.

In type I diabetes, blood glucose levels become high because the body fails to produce enough insulin (which helps to reduce the glucose level of the blood by transporting them into the cells which use glucose to transform into energy). The accumulation of glucose in the blood becomes dangerous because then the free fatty acid breaks down into ketone bodies (Azzam & Prentice, 2019) by a process called lipolysis. These ketone bodies are Acetoacetic acid and B-hydroxybutyric acid, and the acetoacetic acid is a ketoacid which lowers the pH of the blood making it an ideal environment for fungal growth. This is also called diabetic ketoacidosis which normally takes place in type I diabetes but now-a-days can also be observed in patients with type II diabetes. This is where organisms which cause mucormycosis swoops in and takes advantage of the environment because the acidic pH of the blood facilitates their growth and survival. That is why patients who have diabetes or poorly controlled diabetes are prone to being attacked by mucormycosis.

Table 7: Zygomycosis observed in patients with diabetes

Type of zygomycosis	Number and percentage	Diabetes as underlying factor
ROC	97 (54.5%)	Uncontrolled diabetes 131 (73.6%)
Cutaneous	26 (14.6%)	
Disseminated	16 (9.0%)	
Gastrointestinal	15 (8.4%)	

In a period of 5 year, a study was conducted by (Chakrabarti et al., 2006) with 178 cases of zygomycosis, in which it was observed that males suffered more from the infection than females. The type of zygomycosis that was found among the patients were ROC, Cutaneous, Disseminated and Gastrointestinal of which majority of the cases were from ROC zygomycosis (97). Uncontrolled diabetes was found in all of them which covered 73.6% (131 cases). But it was observed that diabetes occurred for the first time in among 56 of the patients. For the rest of the 75 cases, T1DM was found in among 10 patients and the rest were T2DM. Among the patients who had Rhino Orbito Cerebral type of zygomycosis, 6 were diagnosed with confirmed case of ketoacidosis. In cutaneous zygomycosis, diabetes was observed among 46.2% of patients. The most common isolate that was found from this investigation was *Rhizopus oryzae* which was isolated from 61.5% of the patients. The second most common was *Apophysomyces elegans* which was isolated from 27% of the cultures.

5.2 Relation of COVID-19 with MCR

COVID-19 is an infectious disease caused by virus SARS-CoV-2 that is known to cause mild or acute respiratory distress from which people can recover with no treatment to special treatment when becomes severe or acute. One kind of steroid known as the glucocorticoid is used to treat severe or acute COVID-19 (D. Garg et al., 2021b) which can help to develop secondary infections for example, mucormycosis. The organism which usually cause mucormycosis which is associated with COVID-19 were primarily *R. arrhizus*, *Rhizopus* spp. and *Rhizopus microsporus* (Muthu et al., 2021) and these organisms cause mucormycosis according to different anatomic locations such as ROCM, Pulmonary mucormycosis, cutaneous mucormycosis, gastrointestinal mucormycosis etc. (Jeong et al., 2019). Steroids in heavy doses can also weaken the immune system which can make the patient susceptible to mucormycosis. On the other hand COVID-19 impairs the immune system which prevents the polymorphonuclear phagocytes from attacking the fungal spores (Mahalaxmi et al., 2021). The corticosteroids and immunosuppressants which are used to treat COVID-19 patients has the ability to suppress macrophage and neutrophils (Mcnulty, 1982) making the occurring of mucormycosis facile (Khatri et al., 2021) and the immune system failing from protecting the patient.

5.3 Relation of COVID-19 with diabetes

In a study conducted by (Li et al., 2020), it was reported that ketosis, ketoacidosis and diabetic induced ketoacidosis (DKA) can be caused by COVID-19 mainly in patients who are victims of diabetes. Both ketosis and diabetes increase the length of hospital stay of a patient which makes a patient prone to acquiring mucormycosis from hospital instruments and hospital environment. When the consumption of ketone decreases, blood concentration of ketone bodies increase which results in ketosis (Kovács et al., 2019). It should also be remembered that severe COVID-19 can increase the resistance of insulin (Affinati et al., 2021) which can worsen the situation of a diabetes patient. SARS-CoV-1 was observed to have induced the pancreatic islet cells which resulted in acute diabetes and diabetic ketoacidosis (J.-K. Yang et al., 2010). Similarly in case of SARS-CoV-2 there is a diabetogenic state due to ACE-2 receptors high expression and insulin resistance (Kothandaraman et al., 2021).

Chapter 6

Role of Iron

Microbial pathogens need iron for their growth and virulence (Howard, 1999). But iron can be found bound to proteins such as transferrin in mammalian hosts so the amount of free iron available in the serum is very less (Artis et al., 1982) which acts as a defense mechanism for the host against fungi in particular. In fact, it is evident that the iron-binding protein transferrin is an active substance of the serum. Patients who have diabetic ketoacidosis along with diabetes (either type I or II) have higher levels of free iron in the serum which happens due to the release of iron from binding proteins in presence of acidosis (Artis et al., 1982). In acidotic condition, the capability of iron binding to its protein decreases. These patients who have elevated levels of free iron are susceptible to infections caused by fungi and in this case mucormycosis (Ibrahim et al., 2003). This way iron accumulates and the overload of iron helps in the pathogenesis of mucormycosis (Prakash & Chakrabarti, 2019). There are times when severe COVID-19 can result in a syndrome called the hyper-ferritinemic syndrome (John et al., 2021) in which genetic mutations, underlying diseases and infections play a role and makes it complex and variable (Perricone et al., 2020). The hyper-ferritinemic syndrome results in tissue damage which then further cause the free iron to get released (Edeas et al., 2020) and in the acidic serum the condition worsens which benefits the growth and development of mucormycosis (Ibrahim et al., 2012).

Siderophores secreted by other organisms can be used by fungi such as Rhizopus as xenosiderophores and can search for iron. Fungi themselves can produce siderophores and can supply it to the cell. Siderophores can supply iron to the cells by one of the three mechanisms (Ibrahim et al., 2008), such as:

1. Siderophore can directly supply iron to the host cell by crossing the plasma membrane but without entering into the cell. Here, the mechanism that takes place between the siderophore and storage compound is exchange (Carrano et al., 1976)
2. Then, chelated Fe^{3+} reduces to Fe^{2+} that helps transfer the iron directly without the siderophore entering the cell.
3. Another mechanism that exists is called a shuttle mechanism which helps to take in the entire siderophore into the cell. When the siderophore is into the cell, the enzyme reductase releases iron which makes siderophore a compound for storage.

There is also another way fungi can get access to iron which is by making the environment acidic (Ibrahim et al., 2008). Because under acidic condition they can gather iron from the cell surface. Fungi can also use the excreted hydroxy acids (for e.g., citric acid) and mobilize the iron so that the iron can be transported intracellularly.

Chapter 7

Discussion

COVID-19, Diabetes and Mucormycosis (also known as the black fungus) has made so many people the victim of serious illness and death. However dangerous they may be, the mechanism which connected these three is shockingly astounding. They are interconnected in such a way which makes people call it the perfect storm. Both COVID-19 and Diabetes make an individual susceptible to other diseases be it bacterial, viral, or fungal. They weaken the immune system of a healthy person and makes them vulnerable towards other menacing diseases. Mucormycosis has become that menacing diseases amidst the pandemic which is caused when the underlying diseases are diseases which weaken the immune system and make one prone towards it.

Mucormycosis is an infection caused by fungi mainly of the genera *Rhizopus* and *Mucor* which is a rapid infection and can be fatal at times without treatment (Artis et al., 1982). It is an invasive fungal infection which has high morbidity and mortality rate and it is mainly observed in patients with uncontrolled diabetes than hematological malignancies and transplant recipients in countries which are developing (Prakash et al., 2019). In the past, during viral pandemics, the association of diabetes increased the morbidity and mortality rate which is why diabetes alone is a risk factor which may lead to further complications and even death (A. K. Singh et al., 2020). This is because during the outbreak of SARS-CoV-1 in 2002-2003, diabetes was considered to be one of the most independent risk factor which led to complication and death (J. K. Yang et al., 2006). Similarly during the Influenza A (H1N1) infection outbreak in the year 2009, the patients who were diabetic, the risk of them getting hospitalized increased by 4 times the risk of ICU patients (Allard et al., 2010).

Diabetes and Diabetic Ketoacidosis, both play an important part in initiating and exacerbating the state of a mucormycosis infected patient. Ketoacidosis is a metabolic disorder which accumulates the ketone bodies and acidosis (Li et al., 2020) making the serum pH low thus facilitating the growth and development of fungi. Uncontrollable blood glucose can lead to this fatal metabolic condition called DKA which is mostly observed in patients with T1DM, but it can also occur in patients with T2DM. Ferritin is a protein present in blood which contains iron. In COVID-19 infected patients, high ferritin level is observed which has the ability to release reactive oxygen that damages the tissue nearby (John et al., 2021).

Conclusion

Mucormycosis is said to be a rare fungal infection, but this pandemic had all the people know about black fungus and so many of the people has seen the dark side of it, faced it, survived it, and generally just grasped the idea of what mucormycosis can do. It is rare but with the right underlying diseases and circumstances it is common to the point where millions of people can be affected by it. This overview is about the interconnections of mucormycosis with diabetes and COVID-19 and how one is helping the other develop it. During the pandemic, the patients who were infected with COVID-19 were susceptible to secondary infections caused by microorganisms. One of them was mucormycosis. Patients with diabetes and COVID-19 were specially associated with people becoming infected by mucormycosis. COVID-19 is an infectious disease caused by SARS-CoV-2. People infected by the virus may face mild to severe respiratory illness where the severe cases must be treated, or it may get worse. People who are immunocompromised and have various underlying diseases tend to be susceptible towards COVID-19. If the strain is a mutated one then even a healthy person can become sick if comes within its perimeter. People with acute or severe COVID-19 can develop mucormycosis also because of its association with glucocorticoid. Countries which had the most population and the least amount of precaution during the pandemic, were observed to have the most cases of both COVID-19 and mucormycosis. Patients with COVID-19 were also observed to have new onset of diabetes. All these information altogether make people to conclude it as the perfect storm, as one is observed to influence the other two and vice versa.

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