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Health Sciences Review 1 (2021) 100005

Contents lists available at ScienceDirect

Health Sciences Review

journal homepage: www.elsevier.com/locate/hsr

Mucormycosis: A triple burden in patients with diabetes during COVID-19 Pandemic

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ARTICLE INFO

Keywords:
Mucormycosis
Diabetes
COVID-19
Triple burden

ABSTRACT

With the upsurge in the cases of COVID-19 around the world, plenty of potential COVID-19 complications are becoming more prevalent, including a higher risk of secondary bacterial and fungal infections. Mucormycosis is one such condition which has high prevalence among individuals with diabetes who were infected with COVID-19.The usage of steroids in the treatment further inflates the risk of infection and exacerbation of disease in pre-existent mucormycosis patients. Generally, Corticosteroid-induced diabetes can arise on long-term steroid medication, increasing the likelihood of mucormycosis. In patients with COVID-19, the indications and dose of corticosteroids should be properly regulated, and persons with diabetes who take insulin or oral anti-diabetic medicines should be cautious. To avoid poor outcomes, strategies to improve glycemic management should be emphasized. This narrative review elucidates different disciplines on rampant use of steroids, iron and zinc supplements as well as the methods utilized as primary or adjunctive treatment of this fatal condition. This article may help to pave the way for robust research that needs to be done to tackle the deadly triple burden of the disease.

1. Introduction

Mucormycosis is a life-threatening infection caused by fungus in the Mucorales order [1]. Absidia, Mucor, and Rhizopus are all members of the mucoraceal family, which causes mucormycosis [2]. The filamentous molds trigger fungal mucormycosis which is 80 times more common in India with approximately 0.14 cases per 1000 people where consumption of contaminated food, inhaling spores into nasal passages or lungs, or inoculating the disrupted skin or wounds are the usual causes [3,4]. Mucormycosis can be classified into six clinical groups based on the anatomical locations involved: rhino cerebral, pulmonary, cutaneous, gastrointestinal, and miscellaneous or disseminated infection depending on the underlying conditions. These underlying conditions are withdrawal or reduction of corticosteroids, hematological malignancies, hematopoietic stem cell transplantation, adequate control of glycemia in cases of diabetes [5]. Those experiencing the underlying conditions, such as diabetes mellitus (DM), diabetic ketoacidosis, or those on steroids, have shown a spike in incidence of COVID-19 associated Mucormycosis (CAM). Rhino-orbital mucormycosis is the most common clinical manifestation in the immunocompromised patients, followed by rhino-orbital-cerebral mucormycosis, both of which appear as secondary infections post SARS CoV-2 exposure. The hallmark of the rhinocerebral mucormycosis is tissue necrosis caused by angioinvasion as well as subsequent thrombosis. This manifests as eschars that are notoriously dark and necrotic. The fungi enter the paranasal sinuses via inhalation and thus can spread to the sphenoid sinus, as well as cavernous sinus. Patients may experience blurred vision, sinusitis, facial pain or numbness, ophthalmoplegia, or periorbital cellulitis as a result of the swelling around the orbit [6].

COVID-19 has become a worldwide pandemic and infected many countries, posing challenges to the mankind. Extensive usage of corticosteroids during COVID-19 treatment, poorly managed diabetes mellitus (DM), hematological malignancy, solid organ transplant and immunosuppression are the major risk factors. In addition to this, hypoxia, insulin deficiency, metabolic acidosis, diabetic ketoacidosis, increased Fe^{+2} levels, and reduced phagocytic nature of white blood cells due to immunodeficiency appears to be aiding mucorales spore germination in COVID-19 infected population [7]. DM has been linked to impaired T cell response, neutrophil function, and humoral immune abnormalities. As a result, DM makes people more susceptible to infections. Immunosuppression was most common in COVID-19 patients, which was evidenced by a reduction in CD4 and CD8 cells along with the T cells, as

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https://doi.org/10.1016/j.hsr.2021.100005
Received 18 September 2021; Received in revised form 18 November 2021; Accepted 30 November 2021

well as significant alveolar damage, inflammatory exudation, and coagulopathy [3].

The risk for COVID-19 infected individuals having mucormycosis increases with the usage of steroids in their treatment. Furthermore, the exacerbation of this condition is more likely in pre-existent mucormycosis in diabetic patients who are infected with COVID-19 and under steroid medication. The different disciplines on rampant use of steroids,iron and zinc supplements as well as the methods utilised as primary or adjunctive treatment of this fatal condition, will be discussed in this review.

2. Epidemiology

The pervasiveness of mucormycosis ranged from 0.005 to 1.7 per million people worldwide, with India's prevalence approximately 80 times higher (0.14 per 1000) than developed countries [7]. Mucormycosis is a high public health burden in India due to the enormous proportion of diabetic individuals (almost 62 million). Diabetes mellitus was shown to be the underlying condition in 54–76 percent of mucormycosis cases, with 8–22%. Furthermore, there was a geographic variation in the rate of diabetes mellitus among mucormycosis patients in India. Diabetes mellitus was already a prominent risk factor prior to COVID-19, with regional disparities ranging from 67 percent in North India to 22 percent in individuals from the South [8].

3. Materials & methods

This narrative review uses vocables like mucormycosis, diabetes, COVID-19, polymononuclear, prophylaxis, cytokines, and inflammatory responses to pull together information from bibliographic databases like Google Scholar, PubMed, and Scopus. The linguistic filters were employed as a criterion for selecting publications, and only articles published in the English language were assessed. Scientific work, meta-analysis, systematic reviews, and peer reviews were among the primary and secondary research sources. Unpublished, incomplete, or only partially available data, as well as publications in different languages, were omitted from the study. This narration contains a substantial amount of current information. However, if it is relevant and required, previous information dating back to 1992 is presented. There was no sponsorship from any groups, and all of the data was freely available to download.

3.1. The, physiological, pathological and immunological aspects of mucormycosis and diabetes

The epithelial cells which are encountered at the early infection sites, like alveoli and skin epithelia, are the first line of defense towards Mucorales. Injury to the epithelium advances to the basement membrane in patients at risk of invasive mucormycosis, exposing extracellular matrix proteins. The basement membrane proteins laminin and type IV collagen have been demonstrated to attach to R. oryzae resting spores. Mucorales spores germinate and penetrate host cells after adhering to basement membrane proteins. In people with invasive mucormycosis, R. oryzae-specific genes encoding lytic enzymes are produced, which could indicate Mucorales' method of tissue invasion [9]. Mucorales spores act as they would in their native environment once within the organism: they expand, germinate, advance to germ-tube production along with hyphal appendage (Fig. 1). The tissue-invasive form of these organisms, known as hyphae, has a preference for blood vessels, causing tissue necrosis and thrombosis. In vitro, hyphae have also been shown to harm endothelial cells in a time-dependent and dose-dependent manner [10]. Fig. 3 explains the mucorales invasion is caused by altered cellular pathways in diabetes. A. Inhalation, cutaneous inoculation, or ingestion are all the ways for spores to enter the body. B. In the presence of a healthy immune system, macrophages (black triangles) consume spores and prevent them from sprouting through the alternative complement pathway. C. Diabetes inhibits phagocytosis and polymorphonuclear (PMN) chemotaxis, preventing macrophages from phagocytozing spores, culminating in liberated independent spores (1) in cells. (2) Spores enlarge and convert into buds (3), which eventually extended into hyphae. Although polymorphic mononuclear cells are employed, oxidative burst failure is related to the growth of vascular invasion, and eventually dissemination hematogenous due to fungal growth and finally leads to Mucormycosis [7].

3.1.1. Phagocytic cells

PMN is an important component for the defense of anti-Mucorales[11]. Innate defense inhibits germination of spores and hyphal growth and promotes hyphal destruction in mucormycosis. The function of adaptive immunity isn't completely known [12]. The collaboration between Mucorales and individuals with diabetes has been studied using several in vitro and in vivo models. When spores infiltrate tissues, the immune reaction kicks in quickly. When Mucorales contact a healthy immune host, the phagocytic cells use the alternative complement pathway to engulf the spores. The spores are unable to germinate once within the phagocytic cell [13]. In the animal model, the leukocytic penetration of tissue was less than twenty minutes following intradermal injection of R. oryzae spores. An increase in macrophages and proliferating fibroblasts 24 h after inoculation was the most noticeable alteration. In a diabetic animal model of rabbits, PMN margination was late, and substantial fungal growth was linked to the takeover of tissues deeply and major blood vessels after 24 h [14].

Hyperglycemia and acidosis have also been shown to impede phagocytes' capability to destroy the spores by oxidative and non-oxidative processes [15]. Both human and murine tests have confirmed these findings. Diabetic mice's bronchoalveolar macrophages had a diminished capacity to block germination of spores and adhere to Rhizopus hyphae [11] *in vitro*, whereas non-diabetic mice's bronchoalveolar macrophages were able to damage spores of R. oryzae and hyphae. Diabetic mice's serum assisted the sprouting of spores while limiting macrophage adherence to the spores [11]. In this scenario, the total of accessible serum iron in diabetic mice and healthy controls did not differ. When bronchoalveolar macrophages were grown with blood samples from diabetic rats and DM patients, they were shown to be less efficient in inhibiting spore germination [13].

The impaired function of PMN cells in a mouse model of diabetes, along with intracerebral mucormycosis, led to 90% of the animals died after 11 days after receiving R. oryzae intra-sinus injection [16]. In histopathological lesions of diabetic mice, the spores were preceded by the inflammation including infiltration of macrophages and PMN [11]. Reactions with the production of PMN boosted IL-8 and TNF after hyphae had grown, which may be amplified by granulocyte–macrophage-colony boosting factor activation (GM-CSF) and IFN. When hyphae became really extensive for mononuclear cells to phagocytoze, PMN's oxidative burst activity caused the majority of the injury [17]. However, this capacity varies per filamentous fungus: for example, when compared *to Aspergillus fumigatus*, PMN's ability to generate oxidative damage is reduced against *R. oryzae*[18]. Oxidative burst activity and phagocytosis cell involvement were reported in a Drosophila model *in vivo* [19]. In this circumstance, D. melanogaster S2 phagocytic cells internalized a small number of spores and generated Rhizopus spp. less hyphal damage than Aspergillus spp. [19]. Toll- like receptors-2 (TLR-2) and proinflammatory gene expression were also triggered by R. oryzae hyphae (TNF, IL-1B) [18].

3.1.2. Role of iron and pH

Due to iron sequestration by iron-binding proteins, R. oryzae is the commonly found Mucorales in diabetes-related mucormycosis. It a parasitic fungus that cannot grow in human serum *in vitro* [20]. *R. oryzae*, on the other hand, obtains iron in iron-depleted conditions owing to a high-affinity iron permease that promotes development. Infected ketoacidotic mice express the gene that supports this permease, known as "FTR1"[21]. In Diabetes, platelet function is affected by

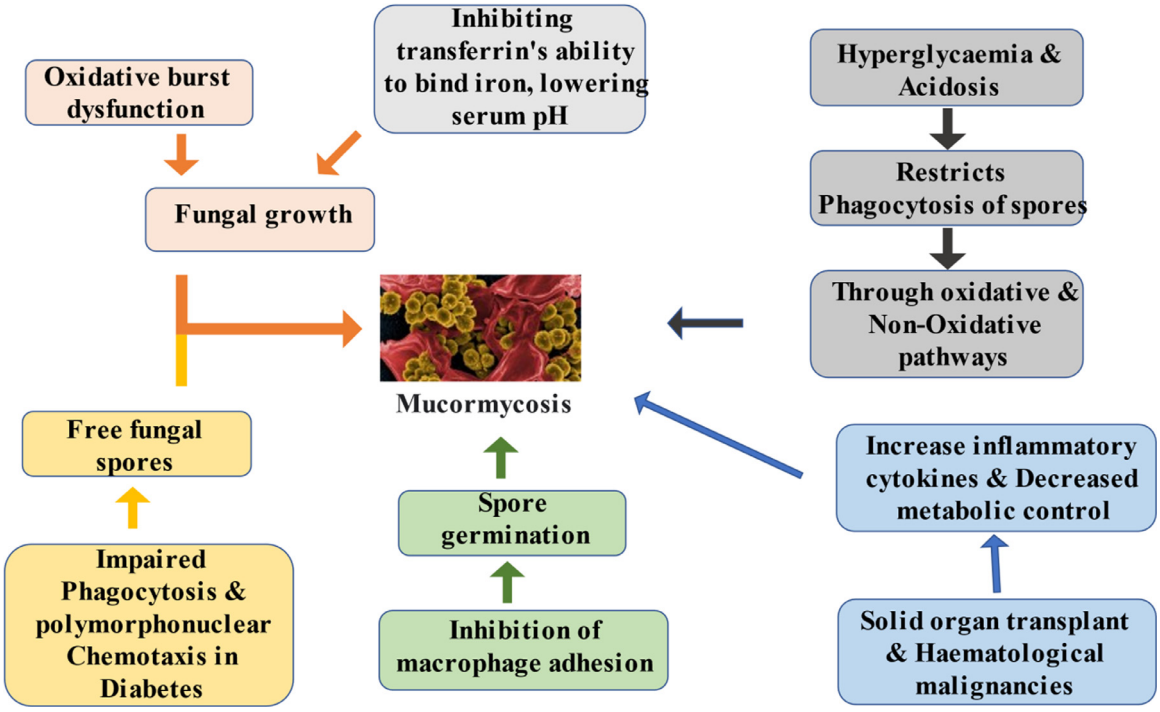

Fig. 1. Major causative pathways of Mucormycosis in persons with diabetes.

structural and functional alterations in platelet membrane properties, as well as changes in nitric-oxide metabolism. During the Mucorales invasion's early stages, there is a connection between innate immune suppression induced by diabetes and changes in metabolic pathways of iron /pH. Mucorales hyphae are eliminated by platelets in a time-dependent fashion and restricting the growth of fungus by inhibiting germination and hyphal development, in addition to innate immunity [22].

In ketoacidosis animals, GRP-78 expression is higher in the brain, lungs and sinuses than in normal mice [23]. As seen in ketoacidotic circumstances, decreasing blood pH favors the growth of fungus by reducing transferrin's capacity to bind iron (Fig. 3). In ketoacidotic mice, lowering the amount of FTR1 gene copies also affects *R. oryzae* pathogenicity [21]. Thus, Mucorales pathogenicity is dependent on iron metabolism, which is known to be affected in diabetes, notably in *R. oryzae*. Endocytosis of *R. oryzae* spores happens in vitro when they come into contact with endothelial cells. Endocytosis is inhibited by the iron chelator phenanthroline. The efficacy of the iron chelator is reduced by Ketoacidosis, and it also promotes spore endocytosis. Attack and destruction of human endothelial cells by *R. oryzae* are also mediated by 78 kDa glucose-regulated proteins, a new host receptor (GRP-78), which was recently found [23]. The abundance of zinc and iron in the body creates an ideal habitat for the fungi that cause Black Fungus to flourish. When the Covid pandemic hit India in March 2020, zinc, along with a variety of other vitamins, became popular as a supplement to enhance immunity and combat the Coronavirus. However, several recent researches have suggested that zinc may be one of the primary causes of Black Fungus in humans [24].

3.1.3. The role and usage of corticosteroids in mucormycosis in covid-19 infected individuals having diabetes patients

Despite the effectiveness of corticosteroid all patients should be thoroughly evaluated for immunosuppressive side effects. Because of the worrisome trio of COVID-19 infection where usage of steroids, existence of diabetes and severity are indicators of a bad prognosis, making glycemic control and early detection critical for a positive outcome [3].

4. Factors affecting the severity of mucormycosis infection

4.1. Age

COVID-19 is more likely to affect the aged, particularly in those receiving long-term care facilities, and persons of any age group with substantial underlying health issues, according to current data and clinical expertise. The elderly with long term medical disorders like diabetes, cardiac or pulmonary diseases, are at a greater risk of not just getting severe sickness, but also of dying if they become ill [25].

4.2. Co- morbidities associated with COVID-19

The primary causes for immunosuppressant patients include extensive usage of steroids and other medicines provided in the guise of COVID-19 therapy. COVID-19 infection is more likely in people who have uncontrolled medical diseases like diabetes, hypertension, pulmonary, hepatic, and renal illness; cancer patients who are on chemotherapy; smokers; transplant patients; and patients who are on steroid therapy on a long-term basis. The mask, if worn on a daily basis without being changed or washed, could be hazardous to one's health and contribute to the onset of mucormycosis in the body. Moisture exposure to COVID-19 patients' unaltered masks or oxygen therapy in hospitals could lead to a fungal infection like mucormycosis [26].

4.3. COVID-19 treatment

In both CAM and non-CAM groups, liposomal AmB (LAmB) was the most commonly utilized antifungal agent. However, when compared to the non-CAM group, the utilization of liposomal AmB was much reduced in the CAM group. In CAM patients, Posaconazole and Isavuconazole were utilised more frequently than in non-CAM patients. Antifungal medication, such as Amphotericin B (AmB) plus triazoles, was utilized substantially more frequently in CAM patients than in non-CAM patients, either concurrently or sequentially. In both groups, combined medical and surgical care was used [27].

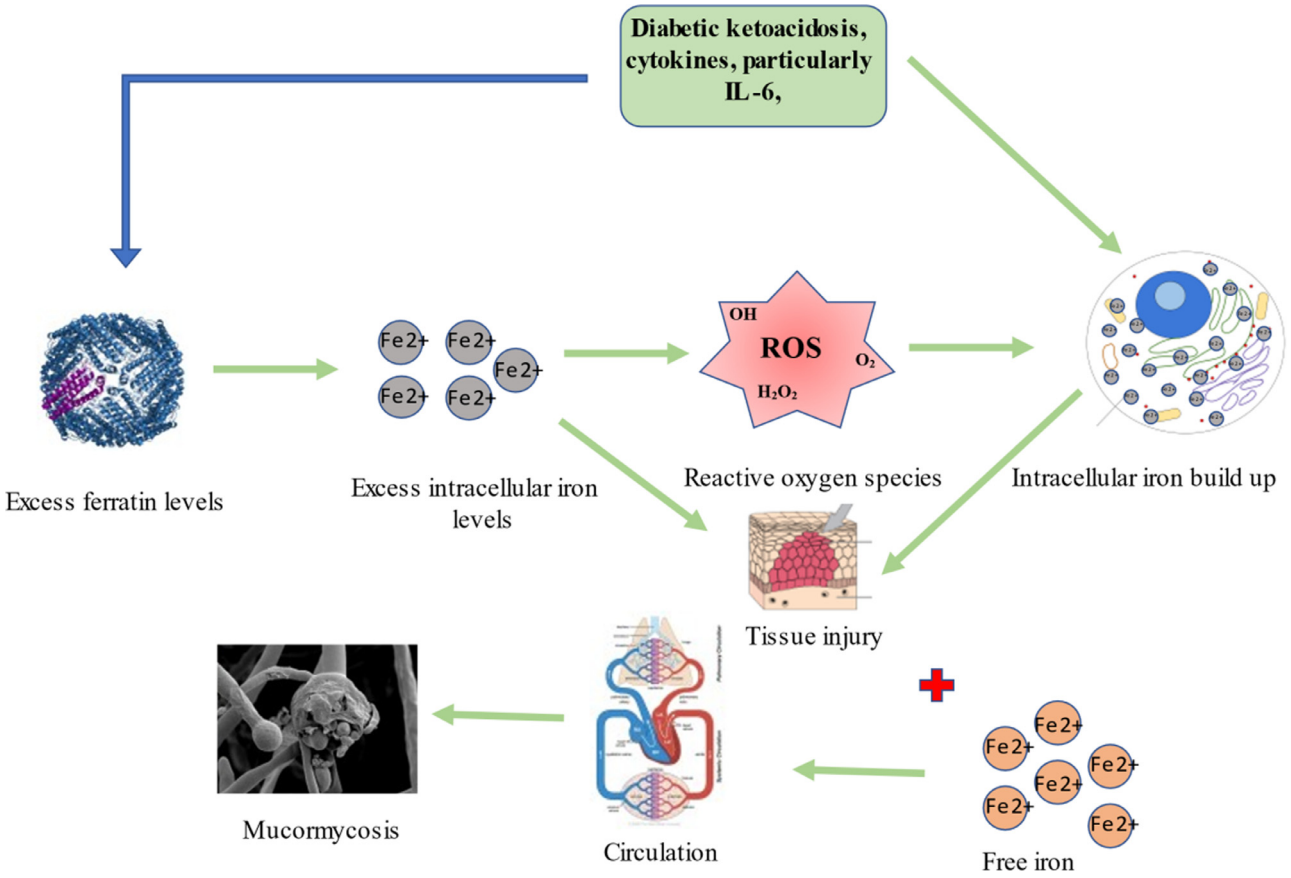

Fig. 2. Excess ferritin levels leading to fungal growth and Mucormycosis.

4.4. Site involved for mucormycosis

Mucormycosis could affect the nose, sinuses, orbit, CNS, lungs, GIT, skin, jaws, joints, heart, renal, and mediastinum but Rhino-Orbital-Cerebral mucormycosis (ROCM) is the commonest type globally. It's worth noting that the phrase "rhino-orbital-cerebral illness" encompasses the complete array of illnesses ranging from limited sino-nasal disease, limited rhino-orbital illness (advancement to orbits), and rhino-orbital-cerebral illness (CNS involvement) [28]. Yet, for both the CAM and non-CAM groups, the site of involvement was identical. Several CAM patients had toothache, tooth loosening, and radiologic jaw involvement [27]. In India, ROM and ROCM accounted for 89 percent of instances, but they only accounted for 64 percent overall. In India, pulmonary, disseminated, and other locations were reported less frequently [27] Sinuses (39%), pulmonary (24 percent), disseminated (23 percent), skin and soft tissue infection (19%) are the most prevalent sites of mucorycosis infection [29].

COVID-19 infection occurs in critically ill patients with inflammatory cytokine storms, such as IL-1β, IL-6, IL-8, IL-10, and TNF-α. In order to manage this, corticosteroids are popularly used in clinical practice to reduce the inflammation of the lungs [32]. Glucocorticoids have been widely utilized to minimize hospitalization and death in COVID-19 infected people. In most COVID-19 infection procedures, Dexamethasone and Methylprednisolone have been included, especially in moderate to severe instances. Patients are more susceptible to secondary infections due to the immunosuppressive nature of glucocorticoids [31]. For a long time, the efficacy of corticosteroids, particularly in virus-related sickness, has been questioned. An Expert Consensus on the use of corticosteroids in Patients with 2019-nCoV Pneumonia in China discussed the debate and controversy surrounding corticosteroid use in COVID-19 patients and recommended that glucocorticoids be used with caution [30].

The systemic corticosteroids were used to treat 75% COVID-19 patients with mucormycosis, with systemic corticosteroids being started in 80% of them before the diagnosis of mucormycosis, which validates our findings. In healthy patients taking long-term steroid therapy, corticosteroid-induced diabetes can develop, increasing the risk of mucormycosis in a vulnerable person [32].

According to evidence, SARS CoV-1 causes pancreatic islet destruction, culminating in acute hyperglycemia and diabetic ketoacidosis along with euglycemic diabetic ketoacidosis [33,34]. The raised expression levels of ACE2 receptors present in pancreatic islets, as well as enhanced insulin sensitivity due to cytokine storm, could describe the 'diabetogenic state' in SARS CoV-2 infection [36]. Susceptibility to opportunistic mycoses such as mucormycosis increase due to overuse of corticosteroids, which disrupts glucose homeostasis [34].

In patients with COVID-19, the indications and dose (Methylprednisolone 40 mg to 160 mg/day for 6 days depending on the weight and condition of the patients) should be properly regulated, and patients with diabetes who take insulin or oral anti-diabetic medicines should be cautious [35].

The recent increase in mucormycosis instances in both recovered and new COVID-19 cases are certainly linked to corticosteroid treatment. This significant rise is thought to be the result of infection, with COVID-19 playing a role in multiple ways. To begin with, immunological dysregulation, as demonstrated by the reduction in the numbers of CD8 + T cells, T lymphocytes and CD4 + T cells and, may affect innate immunity, resulting in an increase in fungal infections risk[36,3]. Consecutively, COVID-19 shares an etiology with thrombotic microangiopathies (TMA), which produce angioinvasion and endothelial dysfunction in the similar way that mucormycosis does, aggravating the disease [37].

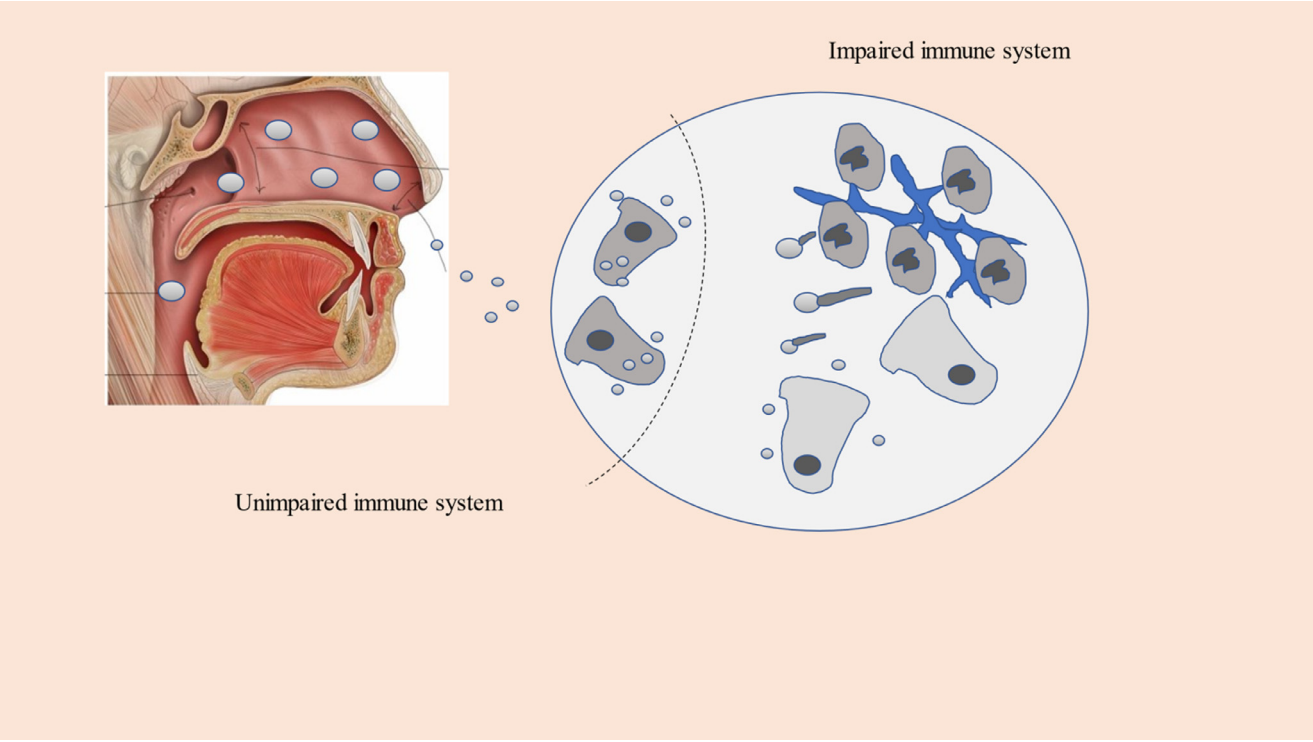

Fig. 3. Impaired immune system
Figure 2 The impaired cellular pathways responsible for Mucorales invasion in diabetes. A. Spores enter the organism by inhalation, cutaneous inoculation or ingestion. B. In cases of a competent immune system, macrophages mediated by the alternative complement pathway (black triangles) engulf spores and prevent their germination. C. Phagocytosis and polymorphonuclear (PMN) chemotaxis are impaired in diabetes, and macrophages are unable to phagocytose spores, resulting in free spores (1) in tissues. (2) The spores swell and form buds (germ-tube growth; 3) which elongate into hyphae (4). PMN are recruited, however oxidative burst dysfunction is linked to fungal growth, vascular invasion, and eventual haematogenous dissemination.
(Adapted from Rammaert et al.) [45].

4.5. Challenges in mucormycosis diagnosis

Initial and precise diagnosis of mucormycosis is critical, and diagnosis will rely on early detection of risk factors, clinical symptoms, and radiological abnormalities until improved molecular diagnostic methods and biomarkers come available, as well as culture and biopsy confirmation. The foundations of diagnosing mucormycosis are direct inspection, culture, and histopathology, although they are time-consuming and insensitive. New molecular diagnostic techniques such as in-situ hybridization and polymerase chain reaction (PCR) offer an alternative which could result in the early diagnosis and onset of therapy [38].

In patients with diabetes and COVID-19, rhino-cerebral or rhino-orbital symptoms are highly common whereas cranial distress without inflammation can be a neuropathic pain without necrosis or facial asymmetry, and it should not be regarded as an indicator of mucormycosis. Most cases of rhino cerebral mucormycosis appear acutely, with symptoms similar to sinusitis or periorbital cellulitis. Mucormycosis pleiotropic clinical symptoms and cryptic presentation sometimes delay diagnosis, resulting in poor results [30]. Although the effectiveness of pre-emptive antifungal medication has yet to be demonstrated, hyperglycemia control appears to be critical for MCR prevention and management [39].

Diplopia, pleuritic pain, necrotic naso-sinus eschars, and cutaneous necrotic lesions are some of the clinical afflictions in the vulnerable host that have a significant predictive value [40,7]. However, these signs are vague, and the differential diagnosis involves a variety of infections induced by angioinvasive pathogens like Fusarium spp., Aspergillus spp., Pseudomonas aeruginosa and Scedosporium spp.; thus, early detection of mucormycosis requires a high index of skepticism as well as quick recognition of host predisposing factors [7].

Detection and characterization of fungi down to the genus or family level is important for prognostic, therapeutic and epidemiological purposes [5,6]. Recovering Mucorales from clinical microbiology specimens is difficult. Invasive approaches to obtain the necessary material can be challenging and dangerous, especially in critically ill individuals with coagulopathy or thrombocytopenia. It may be challenging to find Mucorales hyphae on wet mounts and require special chitin-binding stains which can be observed using a fluorescence microscope, or they may be very less in number to notice. Furthermore, it has been demonstrated that tissue processing procedures such as homogenization or strong tissue grinding destroy the coenocytic hyphae [40]. While filamentous fungi are generally different from other Mucorales, morphological features may be atypical in certain circumstances when antifungal therapy is started before biopsy, making Mucorales difficult to distinguish from other filamentous fungi [40].

A definite diagnosis is difficult due to several reasons, along with the clinical picture which is not specific to mucormycosis and the numerous disadvantages of recently available diagnostic methods. Many presumed mucormycosis confirmed following a postmortem investigation [40].

For identifying mucormycosis early and accurately, molecular identification is a promising alternative. A great deal of research has centered on ribosomal targets (18S, 28S, and ITS) as well as other DNA targets (the high-affinity iron permease I gene FTRI or cytochrome b) for identifying Zygomycetes from cultures [32]. A major issue for the initial detection of mucormycosis is the establishment of molecular tools for detecting amplicon from serum/ plasma or Broncho Alveolar Lavage (BAL) fluid in individuals with early-stage lung mucormycosis. Sensitivities of 67% and 100% were discovered with a significant level of specificity in one of the initial animal research investigations to create

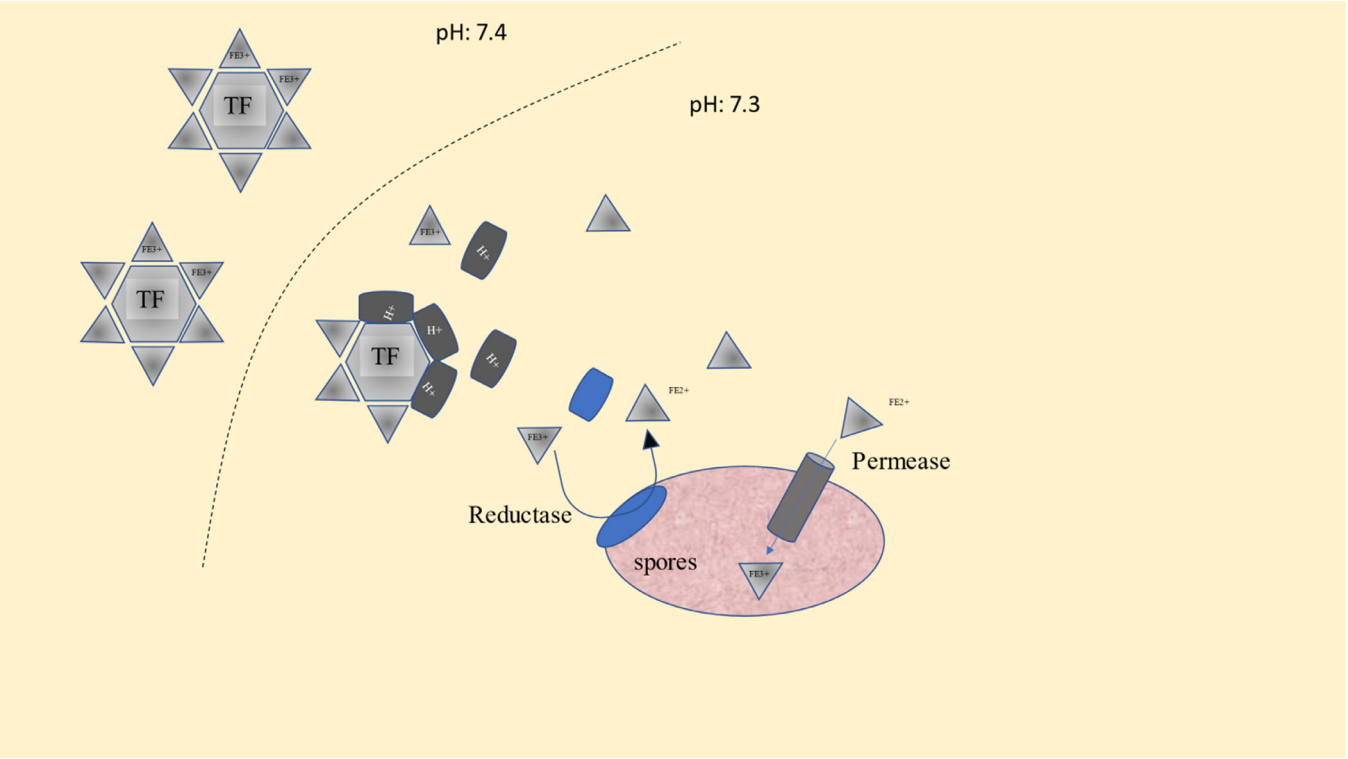

Fig. 4. Role of iron in pathogenesis of Mucormycosis
Fig. 4: The pathogenesis of Mucormycosis is connected to changes in iron metabolism in diabetes. The binding protein transferrin transports ferric iron (Fe^{3+}) (TF). TF iron-binding capacity is reduced by proton (H+) efflux in low pH situations, such as ketoacidosis, and free iron is released into the bloodstream (explained in Fig. 4).This accessible iron is reduced to ferrous iron (Fe^{2+}) by a Mucorales spore membrane reductase enzyme, which solubilizes free iron to allow it to penetrate spores through the high-affinity permease FTR1, resulting in a ferric form that aids the growth of Mucorales spore [20].

organism-specific amplicon from the bloodstream and BAL fluid in experimentally invasive lung mucormycosis [33].

A likely diagnosis of mucormycosis involves the presence of conditions (diabetes mellites is a risk factor for the mucormycosis), radiological or clinical symptoms consistent with mucormycosis, and physical observation or a positive culture recovered from pathological site of the sample. Tissue biopsies and/or positive cultures retrieved from aseptic areas are essential to formulate a diagnosis of confirmed mucormycosis.CT scans revealed mucosal thickening of the sinuses and bone resorption in rhinocerebral lesions, while MRI is required to detect expansion into the cavernous sinus and detect invasion in rhinocerebral nodules in the brain. An MRI can show cavernous sinus thrombosis, orthrombosis, or aneurysm of the internal carotid artery, as well as orbital and intradural enlargement [43].

Unlike invasive aspergillosis, mucormycosis diagnosis is not aided by the identification of circulating antigens such as galactomannan and D-1, 3-glucan [44]. Mold in damaged tissue is used to make a diagnosis, which is usually validated by a fungal culture, which reveals the presence and type of fungal infection. However, despite the presence of infectious fungi, a fungal culture may not identify a fungal infection. The polymerase chain reaction (PCR) can be useful in the detection of causative species. AmB, isavuconazonium sulfate, posaconazole, or their combination are among the few therapies available for mucormycosis. A few anti-mucormycosis drugs are currently under clinical trials. L-AmB or AmB lipid complex (ABLC) is the first-line antifungal drug indicated. The effectiveness of L-Amb and ABLC is dose-dependent, with 10 mg/kg yielding excellent results in mice [45].

The discovery of a *R. oryzae* specific 23 kDa protein employing signal sequence trap retrovirus-mediated expression (SST-REX) was another advancement in improving the diagnosis of mucormycosis. An ELISA approach was used in an animal model for the assessment of the presence of the serum antigen and lung homogenates [3]. In the *Rhizopus-soryzae* genome, the chitin deacetylases and their protein families are abundant and involved in chitosan or chitin synthesis of the fungal cell wall. However, still there is no antifungal for this target. The failure of null mutant retrieval of *R. oryzae*, which was recently been resolved using certain methods like genome editing utilizing clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9),resulted in a point mutation in R. oryzae. Although RNA interference and CRISPR/Cas9 are being used quite extensively in other fungal species, this initial alteration in Rhizopus will lead to new viral infection pathways being discovered in the coming years. Host immunologic and metabolomic profiling, tailored immunotherapy, and tissue hypoxia reversal may indeed develop into better alternative treatments in the long run [46].

4.6. *Management principles of mucormycosis*

Mucormycosis' invasive nature results in a mortality rate of more than 50%, but antifungal therapy alone is seldom effective, resulting in a 100% fatality rate, especially in patients with disseminated disease [40,41]. Mucormycosis is treated with AmB (AmB) as a first-line treatment. However, there are still several issues to work out, such as the best dosage and time to start therapy. In comparison to aspergillosis, animal studies have shown that greater AmB tissue content may be preferred for the effective therapy of mucormycosis. To manage the infection, many doctors who treat mucormycosis utilize maximal tolerance dosages of liposomal AmB, which can cause nephrotoxicity [41].

According to a retrospective research looked at the influence of rapid AmB-based treatment on mucormycosis patients, delayed AmB-based therapy has led to the enhancement of mortality risk by two-fold in patients with hematological malignancy and mucormycosis in comparison

to early therapy (83% vs. 49%). Delay in treating invasive mucormycosis was also revealed to be an independent predictive factor of poor outcome in multivariate analysis [47].

The risk of fungal infections is increased not only by the unique SARS-CoV-2 infection but also by the use of anti-inflammatory and immunosuppressive medicines which should be reduced or stopped if possible once the diagnosis is suspected, and antifungal drugs should be started [48]. Mucormycosis has necrotic and inflammatory consequences due to the lack of selected methods for diagnosing, culture, and treatment of fungal infections. Due to delays in seeking medical assistance and detecting the condition, as well as difficulty in controlling the advanced stage of infection, mucormycosis-related mortality is quite high in India [44].

Isavuconazole(ISZ) a novel anti-mucorales medication, which shows efficacy comparable to AmB. It is a broad-spectrum antifungal with good oral bioavailability, and linear pharmacokinetics. After oral or intravenous injection, Isavuconazonium sulfate is rapidly hydrolyzed to the Triazole isavuconazole (ISZ). It appears to give a higher likelihood of survival than earlier therapies. Although it was just recently introduced in the Indian market, its efficacy is still being determined [49]. Although Posaconazole has been demonstrated to be efficient against Mucorales *in-vitro* and *in-vivo* studies, there is no evidence that it should be used as a first-line treatment. As a result, Posaconazole has a position in the therapeutic arsenal as a prophylactic or consolidating medication after L-AmB induction [45]. Posaconazole's safety and efficacy in patients with ROCM were studied in South India. The study found no deaths, with 66.6% of patients experiencing complete disease clearance and the rest seeing considerable disease reduction. In moderate doses, intravenous ISZ and intravenous or delayed-release tablet Posaconazole are indicated. Both the triazoles are frequently suggested as rescue therapies. AmB deoxycholate is not advised due to its severe toxicity. Echinocandins exhibit less activity at larger doses than at lower doses, which could be due to the amplification of homeostatic fungal cell-wall reactionsthat help the fungal organisms from the consequences of Echinocandins by enhancing the synthesis of chitin [50].

Adjuvant immunological treatment with recombinant granulocyte colony-stimulating factor (G-CSF) and GM-CSF, or recombinant IFN-α, have been used effectively in the mucormycosis management in combination with LAmB. It's unknown whether recombinant cytokines can help immune-compromised mucormycosis sufferers [51]. Fluconazole should be used to treat mucormycosis in individuals with neutropenia or graft-versus-host disease, while Itraconazole and Voriconazole should be used as prophylactic medications [52].

Deferiprone and Deferasirox can reduce *R. oryzae* cell proliferation in vitro, although Deferoxamine can't. Deferasirox is utilised in combination with other antifungals in mouse models. It has increased the diabetic ketoacidotic mice mortality when combined with LAmB compared to a placebo and when used alone. Furthermore, when compared to mono- and bitherapy, triple therapy utilizing LAmB, micafungin, and Deferasirox enhanced survival and decreased the tissue fungal load in the same mouse model. Deferasirox may have the same positive effects in people. Unfortunately, Deferasirox therapy worsened outcomes; higher mortality was also was concluded in the "Deferasirox-AmBisome Therapy for Mucormycosis (DEFEAT Mucor study) which is a randomized, double-blinded, placebo-controlled trial" in 2011. In this scenario, patients with DKA having hemodialysis and Deferoxamine chelation therapy having increased concentration of free serum iron, hence they are more prone to mucormycosis [42].

4.7. Prophylaxis of mucormycosis with COVID- 19

Mucormycosis may be most frequent in the patients who have been given antifungal prophylaxis or who have used Itraconazole or Voriconazole inappropriately. These patients usually have disseminated mucormycosis, which is the deadliest form of the disease. Breakthrough mucormycosis has been reported in patients on Posaconazole or echinocandin prophylaxis [53].

A failure of prophylaxis leads to the emergence of new fungal infections. They're uncommon, but they do happen, and they're usually associated with a bad outcome. Breakthrough fungal infections under triazoles, particularly Posaconazole, have been observed to be less than 5% in patients with hematological malignancies [50].

Antifungal prophylaxis is correlated with a high risk of rhino-orbito-cerebral mucormycosis in individuals diagnosed with COVID-19 and who require corticosteroids is considered necessary [49]. However, no study has been undertaken about how to define groups of hematology individuals who are at "high risk for Invasive Fungal Infection (IFI)" either on a low IFI estimated incidence or the proportion of hospitals who must be treated and for which primary antifungal prophylaxis may be preferable to alternative intervention. Hematopoietic Cell Transplant patients (HCT) may require prophylactic therapy for at least 6 months following the transplant. The degree of immunosuppression displayed by biological indicators (e.g., levels of CD4 T cells) during this time may impact the efficacy of antifungal prophylaxis [54]. AmB and AmB lipid complex are suggested as monotherapy for first-line treatment. When AmB lipid formulations are unavailable, Posaconazole and ISZ are suggested for salvage therapy, especially in situations of refractory or intolerant AmB resistant fungal infections. In case of remission induction chemotherapy for acute myeloid leukemia or myelodysplastic syndrome, Posaconazole delayed-release tablets should be used as a prophylaxis. Posaconazole has assumed a greater role in these indications than AmB. In neutropenic patients, patients with graft-versus-host disease, or patients with a high-risk factor, primary prophylaxis with Posaconazole may be recommended [55]. Posaconazole has limited action against certain Mucorales species, and only limited cases of breakthrough mucormycosis infection in hematologic malignancy patients have been documented while on Posaconazole prophylaxis. If IFD arises while on Posaconazole prophylaxis, mucormycosis should be suspected and diagnosed as early as possible. Given the high prevalence of breakthrough mucormycosis in people using Posaconazole prophylaxis, empirical antifungal treatment with L-AmB or ISZ might be a viable option for a wide variety of aspergillosis and mucormycosis in those patients [20,46,45]. ISZ is a drug that has been approved to treat invasive aspergillosis and mucormycosis. ISZ and Posaconazole infusions can be administered in the case of preexisting renal impairment. The gastroenteric and hepatic side effects of ISZ are well-known, though it is generally well tolerated. Although ISZ has been used as a prophylactic, it is an unapproved and off-label treatment. No randomized clinical trials are comparing it against Posaconazole or Voriconazole as a prophylactic [46]. Voriconazole, which is commonly used as an antifungal prophylactic to avoid opportunistic systemic fungal infections, is inefficient against Mucorales and has been linked to outbreaks of mucormycosis [56]. Voriconazole's broad spectrum suggests that it could be useful as a preventive medication. Voriconazole's in vitro coverage and clinical efficacy against the majority of fungal pathogens may make it particularly effective for IFI prophylaxis in the hematology setting, where invasive mound infections are common. Serious side effects such as persistent visual abnormalities, QT-interval prolongation, and liver toxicity are possible. These are very common in patients with relevant underlying disorders, necessitating careful monitoring of visual and hepatic function [49]. Neutropenia, broad-spectrum antibiotics, uncontrolled hyperglycemia,corticosteroids, and Voriconazole prophylaxis are all linked to increased vulnerability to ROCM. Despite the fact that the patient was administered high-dose systemic corticosteroids for an extended length of time as part of the induction therapy, had severe neutropenia, and was given broad-spectrum antibiotics prior to acquiring ROCM, Fluconazole was given as an antifungal preventive in this case. Unfortunately, prospective research on antifungal prophylaxis in emerging targeted medicines like Blinatumomab is limited. Clinicians must examine opportunistic and difficult-to-treat illnesses like mucormycosis to increase the chances of patient's survival [57,34].

5. Discussion

Extensive usage of steroids during COVID-19 treatment, poorly managed diabetes mellitus (DM), hematological malignancy, solid organ transplant, immunosuppression being the major risk factors followed by hypertension, and other co-morbidities [3]. Innate defense inhibits germination of spores and hyphal growth and promotes hyphal destruction in mucormycosis. Hyperglycemia and acidosis have also been shown to impede phagocytes' capability to destroy the spores by oxidative and non-oxidative processes [15]. PMN generates oxidative damage against *R. oryzae* ketoacidotic [14] circumstances, decreasing blood pH favors the growth of fungus by reducing transferrin's capacity to bind iron [21]. Mucormycosis symptoms include sinus pain, one sided congestion of the nostrils, headache, inflammation, loss of sensation, toothache. Mucormycosis is characterized by nasal discoloration or reddening, hazy vision, chest discomfort, bloody cough, and difficulty in breathing are significant burdens for COVID-19 patients [58]. The "endothelialitis" and increased ferritin levels are most commonly presented in COVID-19 patients, coincidentally they too are major risk factors [58,59]. A major issue for the initial detection of mucormycosis is the establishment of molecular tools for detecting amplicon from serum/ plasma or BAL fluid in individuals suffering from early-stage lung mucormycosis [42]. Regardless of its function, elevated ferritin levels result in an excess of intracellular iron, which produces reactive oxygen species and damages tissue. COVID-19 is a disease that causes hyperferritinemia, along with changes in iron metabolism and hyperglycemia. It's uncertain whether increased ferritin levels are a sign of serious clinical symptoms or a pathophysiological modulator. Due to severe infection and diabetic ketoacidosis, cytokines, particularly IL-6, Increase ferritin production while inhibiting iron export, leading to intracellular iron buildup, which worsens the problem [60]. Free iron is released into the blood as a consequence of tissue damage. Overload of iron and excess free iron are two of the most essential and different risk factors for mucormycosis, as evidenced in the circumstances [1]. This narrative review focuses to give an overview of the major pressing issues to cover the knowledge gap and to pave the way to new robust research on the topic. So that similar problems can be tackled easily.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author declarations

All the authors did not present any conflict of interest.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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