WWJMRD 2021; 7(7): 6-13
www.wwjmrd.com
International Journal
Peer Reviewed Journal
Refereed Journal
Indexed Journal
Impact Factor SJIF 2017: 5.182 2018: 5.51, (ISI) 2020-2021: 1.361
E-ISSN: 2454-6615
DOI:10.17605/OSF.IO/MQUWN

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Coincidence of uncontrolled diabetes mellitus and COVID-19 Is a serious threat to Mucormycosis: a systematic review

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Abstract
Mucormycosis is an angioinvasive life-threatening fungal infection caused by mold of fungi having Class Zygomycetes and the order Mucorales. It is characterized by vascular invasion by the fungal hyphae which leads to thrombosis and necrosis. Mucormycosis cases increases gradually in people with active COVID-19 as well as those recovered from COVID-19 particularly in India. *Indian Government now declared mucormycosis as notifiable disease.* Diabetes mellitus (DM) augments severity of COVID-19 and risk factor for mucormycosis. The aim of this systemic review of literature is to find out correlation between COVID-19 along with comorbid DM and mucormycosis. We searched PubMed and Google Scholar up to 20th May, 2021 using key words. Subsequently we analyzed collected data and characterized event of mucormycosis in people with COVID-19 along with or without comorbid DM. Mucormycosis was predominant among male patients with active COVID-19 or recovered from COVID-19. COVID-19 patients with comorbid DM are maximally affected. Rhinocerebral mucormycosis or craniofacial mucormycosis is most prominent type of mucormycosis in India. Uncontrolled blood sugar in DM and vamped use of corticosteroids in a back ground of COVID-19 increase risk of mucormycosis. Germination of Mucorales spores is enhanced in hyperglycemic-COVID patients due to hypoxia, increase serum iron load, metabolic acidosis, decrease phagocytic activity of leukocytes and immunosuppression. Steroid therapy in severe COVID-19 cases creates ideal environment like immunosuppression and hyperglycemia to increase chance of mucormycosis. Maintenance of optimal blood sugar level and judicious use of corticosteroids in COVID-19 patients may be suggested to prevent infection from mucormycosis.

Keywords: COVID-19, Diabetes mellitus, Steroid therapy. Mucormycosis.

Introduction
Corona virus disease 2019 (COVID-19) is a global crisis at present. The pathogen responsible for such disease is enveloped RNA virus called severe acute respiratory syndrome coronavirus-2 (SARS CoV-2). The first case of COVID-19 was detected in Wuhan, China in December 2019 and since then spread globally. WHO declared the 2019-2020 coronavirus outbreak as a pandemic on 11th March, 2020. It is highly transmissible from person to person through respiratory droplets. More than 250 countries of the world now suffer in COVID-19 (1). At present (1st June, 2020) more than 171 million confirmed cases and more than 3.6 million people died in COVID-19 worldwide. Death from COVID-19 is due to viral pneumonia, intravascular coagulation and multi-organ failure (2). COVID-19 is common in diabetic patients. Diabetes mellitus (DM) is a most common metabolic disorder associated with chronic hyperglycemia due to defects in insulin secretion, insulin resistance or both. COVID-19 has been associated with opportunistic bacterial and fungal infections.

Mucormycosis is a life-threatening fungal infection, Invasion of fungal hyphae into blood vessels induces thrombosis and necrosis (3). Pathogen of mucormycosis is mold of fungi having class Zygomecetes and the order Mucorales. Mold of five genus of Zygomycetes viz. *Rhizopus, Mucor, Rhizomucor, Cunninghamella and Absidia* are involved in mucormycosis *(4)*. Most of mucormycosis in human is due to inhalation of mold of Rhizopus oryzae (5). Mucormycosis is previously known as phycomycosis or zygomycosis (6) and later as

mucormycosis by American pathologist (7). Globally 0.005 to 1.7 per million population are suffering in mucormycosis. India has the highest prevalence rate (140 per million) (8, 9). Prevalence of mortality from mucormycosis is high from cavernous sinus thrombosis, disseminated infection, osteomyelitis and death (10). In recent time prevalence of mucormycosis in COVID-19 patients have been increasing throughout the world particularly in India (11). Patients with COVID-19 are susceptible for fungal infection (12). Song et al (13) reported that patients with COVID-19 or those recovered from COVID-19 are at increased risk of developing mucormycosis. DM is independent risk factor of both COVID-19 and mucormycosis (14, 15). India with largest number of diabetic population is now considered as diabetic capital of the world due to (16), suggesting greater risk of mucormycosis among Indian. Corticosteroids are now widely use as anti-inflammatory agents in severe inflammation. Excessive use of corticosteroids is well known risk factors for mucormycosis (17). Nationalwide multi-center-study on mucormycosis suggested that more than 50% cases of mucormycosis in Indian had uncontrolled DM (18). COVID-19 patients with DM are not only increase severity of illness but are also more susceptible to fungal infection (19).

The purpose of this systemic review of literature was to find out possible mechanism of mucormycosis in COVID-19 infected subjects with or without hyperglycemia and to evaluate the impact of steroid treatment on mucormycosis in SARS-CoV-2 infected patients.

Mucormycosis:

Mucormycosis, a life-threatening fungal disease occur in immunosuppression patients caused by mold of Class Zygomycetes fungi having the order Mucorales. Mucorales enter into susceptible host through inhalation, ingestion of food contaminated with fungal mold and through damaged skin. It often coexists other conditions that induce immunosuppression (20). After entering the body it progresses rapidly due its blood vessel invasive characteristic (21). Invasion into blood vessels is followed by thrombosis and subsequent death of surrounding tissues from obstruction of blood supply (22). Depending on the site of infection it is classified as rhinocerebral or craniofacial, pulmonary, cutaneous, gastro-intestinal and disseminated type (23).

*Rhinocerebral or craniofacial mucormycosis***:** One-third to one-half of all mucormycosis are rhinocerebral type (24). 70% of this category is associated with DM (25). Rhinocerebral mucormycosis mainly occurs from inhalation of fungal mold and its deposition into nasal cavity. It is also common in patients who received a solid organ transplantation, prolonged suffering in neutropenia (26), and patients with hemopoeitic stem cell transplantation (27). Rhinocerebral mucormycosis is due to formation of hyphae in nose, paranasal sinus and brain. High blood glucose level, metabolic acidosis and more free iron in blood favors fungal invasion. Primary symptoms of Rhinocerebral mucormycosis include one-sided facial swelling, nasal congestion, black lesions on nasal bridge and inside of mouth and fever. In severe cases there is conjunctival suffusion, blurry vision (28, 29), loss of extra ocular muscle function, proptosis, vision loss and opthalmoplegia.

*Pulmonary mucormycosis***:** Inhalation of zygomycetes spores produces pulmonary mucormycosis. This type of mucormycosis is found in neutropenic and stem cell-transplant patients (27). It is associated with fever, dyspnea, cough, and chest pain (30).

*Cutaneous mucormycosis***:** Disruption of skin due to burns or traumatic disruption from accident and penetrating injury with plant material like thorn enables zygomycetes spores to penetrate into deeper tissues (20) and produces cutaneous mucormycosis. Cutaneous lesion was also noted in diabetic patients at insulin injection site or catheter insertion sites (28). Contaminated surgical dressing and contaminated tape (use during ventilation) also induces cutaneous mucormycosis. Ulcer in skin which turn black, excessive swelling around the wound and pain are the common symptoms of cutaneous mucormycosis.

*Gastrointestinal mucormycosis***:** Mucormycosis in gastrointestinal tract is rare and mainly occurs in malnourished patients and arises from ingestion of fungal spores. The stomach. Ileum and colon are mainly affected. Nonspecific abdominal pain, nausea and vomiting are the most common symptoms.

*Disseminated mucormycosis***:** The spread of fungal infection through the blood stream from primary infection site to affect another part of the body is referred to as disseminated mucormycosis. Pulmonary mucormycosis is the highest incidence of dissemination. Dissemination also occurs from gastrointestinal tract and skin lesion from burn injury.

Pathophysiology of mucormycosis:

Angioinvasion is a hall mark of mucormycosis. Epithelial cell damage (from DM or chemotherapy) allows fungal spore to come in contact with endothelium and binds with glucose regulator protein-78 (GRP78) via its spore coating protein known as CotH (31). Thus spore recognition is followed by endocytosis and cellular death. Anti GRP78 antibodies protect diabetic ketosis mice from mucormycosis (31). Penetration of fungal hyphae the endothelial lining of vasculature causes thrombosis and tissue necrosis (32).

Hyperglycemia, Diabetic ketoacidosis (DKA) and deferoxamine treatment are the risk factors of mucormycosis. Hyperglycemia-induce glycosylation of iron binding proteins viz. transferrin and ferritin diminishes their affinity to iron (33). Low pH in blood due to diabetic ketosis impairs iron chelation ability of transferrin (34). Glucose, free iron and metabolic acidosis enhance the fungal growth (35) and also augment fungal invasion by enhancing expression of GRP78 and CotH (36).

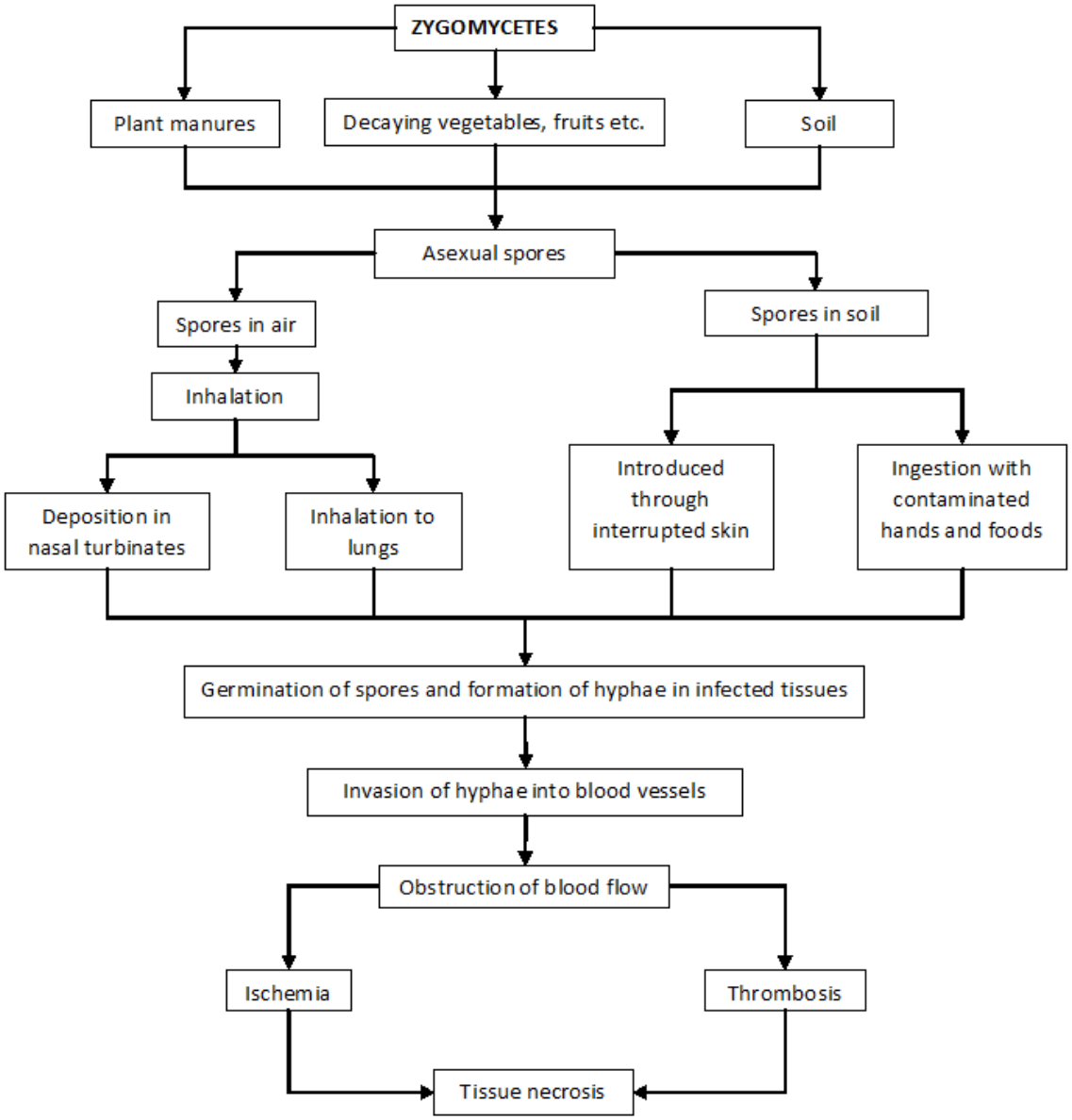

Fig.1: Pathophysiology of Mucormycosis.

Diabetes mellitus and mucormycosis:

DM is a most common metabolic disorder associated with hyperglycemia that result from decrease in insulin secretion, insulin insensitivity of tissues or both along with increase in glucose production and decrease glucose utilization. Serum free iron is increased in hyperglycemia (37). DM induces glycosylation of hemoglobin to release free iron (38). Serum ferritin stores iron in such a form that iron gets shielded from body fluid and unable to cause oxidative damage (39). Glycosylation of transferrin induces release of iron which leads to increased oxidative stress, endothelial and tissue damage (40). Hyperglycemia in DM increases osmolality of blood which may cause hemolysis to increase serum free iron (41). Free iron is a potent pro-oxidant and increases oxidative stress by participating in Harber Weiss & Fenton reaction to generate ROS like hydroxyl radical and hydroperoxy radical that induce lipid peroxidation (42) and tissue damage (43) Serum free iron was significantly raised in type-2 diabetic patients in compared to healthy individual (44). Iron Induces oxidative stress and insulin resistance. Oxidative stress increases release of iron from ferritin (45).

Iron is required for growth and virulence of fungal pathogen (46). Iron deprivation causes apoptosis of fungus (47). In mammalian host iron is sequestered by carrier protein like transferrin which leads to suppression of fungal growth. Acquisition of iron by fungal pathogen is essential for growth and induced pathogenesis (34). Serum free iron concentration was higher in poor glycemic control type-2 diabetes patients in respect to well glycemic control diabetes patients (48). Diabetes induced ketoacidosis causes proton mediated displacement of ferric from transferrin. Ferric is to reduce ferrous on fungal cell membrane by reductase. Such ferrous is reoxidized and transported to cytosol by membrane bound copper oxidase and permease respectively (49).

Hyperglycemia causes neutrophil dysfunction including defects in ROS production (50), impairment of neutrophil degranulation (51), inhibition of immunoglobulin mediated opsonization [52] and decreased neutrophil extracellular trap formation (53).

Hyperglycemia decreases phagocytic activity of monocytes (54) as well as peritoneal macrophages (55).

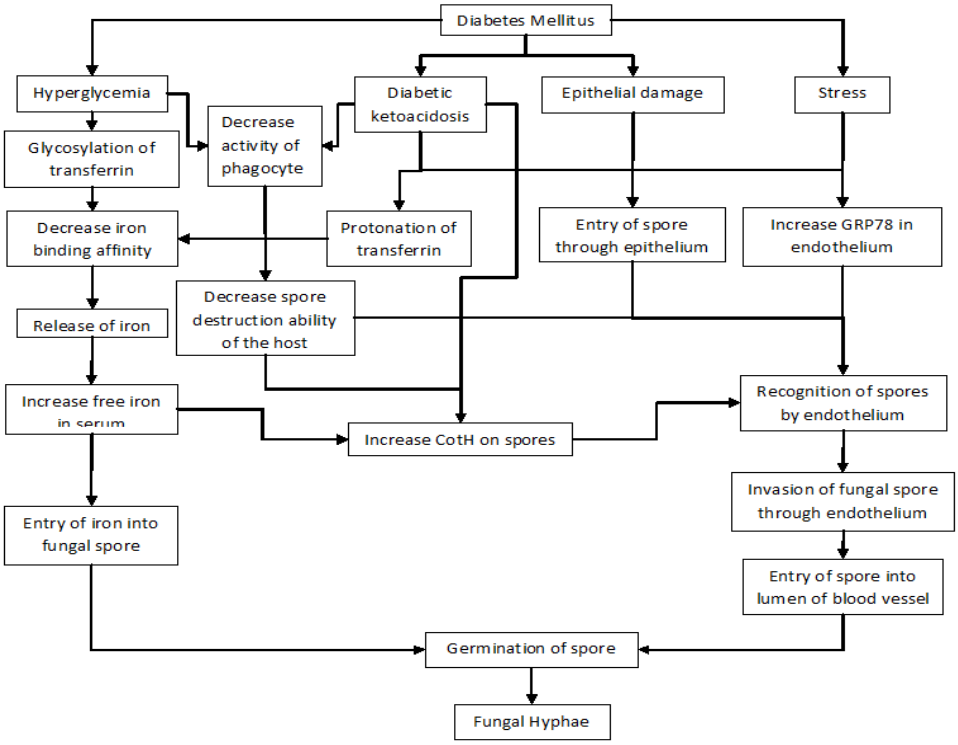

Fig.2: Mechanism of diabetes mellitus induced Mucormycosis.

Glucocorticoids and mucormycosis:

Glucocorticoid **(**Gc) increases susceptibility to invasive fungal infections by affecting various cells involved in immune and inflammatory response. It induces reversible lymphocytopenia by depleting circulating CD4T lymphocyte and lesser extent to circulating CD8 T lymphocytes (56). It inhibits activation and proliferation of T lymphocytes (57). It causes Th2 predominant cytokine response which leads to suppression of phagocytic cell activity (58) Decreases secretion of IL-2. IL-12, TNF-alpha and IFN-gamma whereas increases secretion of IL-4, IL-5 and IL-10 (59).

Glucocorticoids suppress several functions of neutrophil including adhesion, extravasation, phagocytosis, free radical formation, degranulation, chemotaxis and migration (60) via suppression of NF-kB (61). GCs impair phagocytic activities of monocyte and macrophages by suppressing ROS formation, migration and oxidative killing (62).

Natural killer cells exert cytotoxic effect directly or via liberation of cytokines and destroy hyphae of mucorales (63). Glucocorticoid impairs Natural killer cell induced cytotoxicity (64).

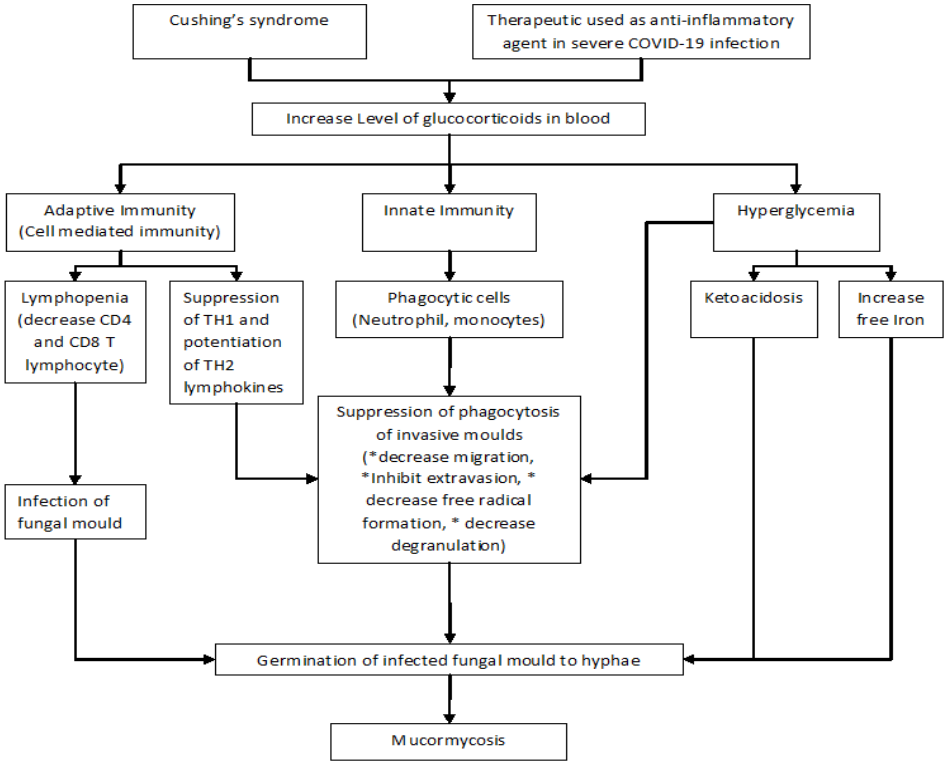

Fig.3: Mechanism of corticosteroid induced Mucormycosis.

COVID-19 and mucormycosis:

COVID-19 infection is associated with storm of inflammatory cytokines and decreased CD4 T cell and CD8 T cell count. Such environment induces fungal co-infection (13).Patients admitted to intensive care unit and those required for ventilation and had longer duration of hospital stay were more likely to develop mucormycosis (65).

Corticosteroids therapy has proven benefit against COVID-19-induced cytokine storm. The WHO recommended systemic corticosteroid for severe critical COVID-19 and not for non-severe cases. The current guide line in India recommended dexamethasone 0.1-0.2 mg/kg/day for 3 days for moderate cases and 0.2-0.4 mg/kg/day for severe cases. COVID-19 patients with progressive deterioration of oxygen indicators and excessive activation of body's inflammatory response can be treated with glucocorticoids for 3-5 days with dose 0.2-0.4 mg/kg/day (66). The NIH recommends the use of intravenous dexamethasone 6 mg per day for a maximum of 10 days for patients who are ventilated or require oxygen supplement (67). Extensive steroid treatment in COVID-19 management enhances the chance of fungal infection by suppressing immunity. Thus COVID-19 patients can be co-infected with mucorales during the middle or latter stage of this disease especially patients with uncontrolled blood glucose level. COVID-19 patients always have immunosuppression with a decrease in CD4 T cell and CD8 T cells (68) COVID -19 infection produces hyper-ferritinemic syndrome (69). COVID-19 – induced increase IL-6 stimulates ferritin synthesis and down-regulates iron export resulting in intracellular iron overload (69).

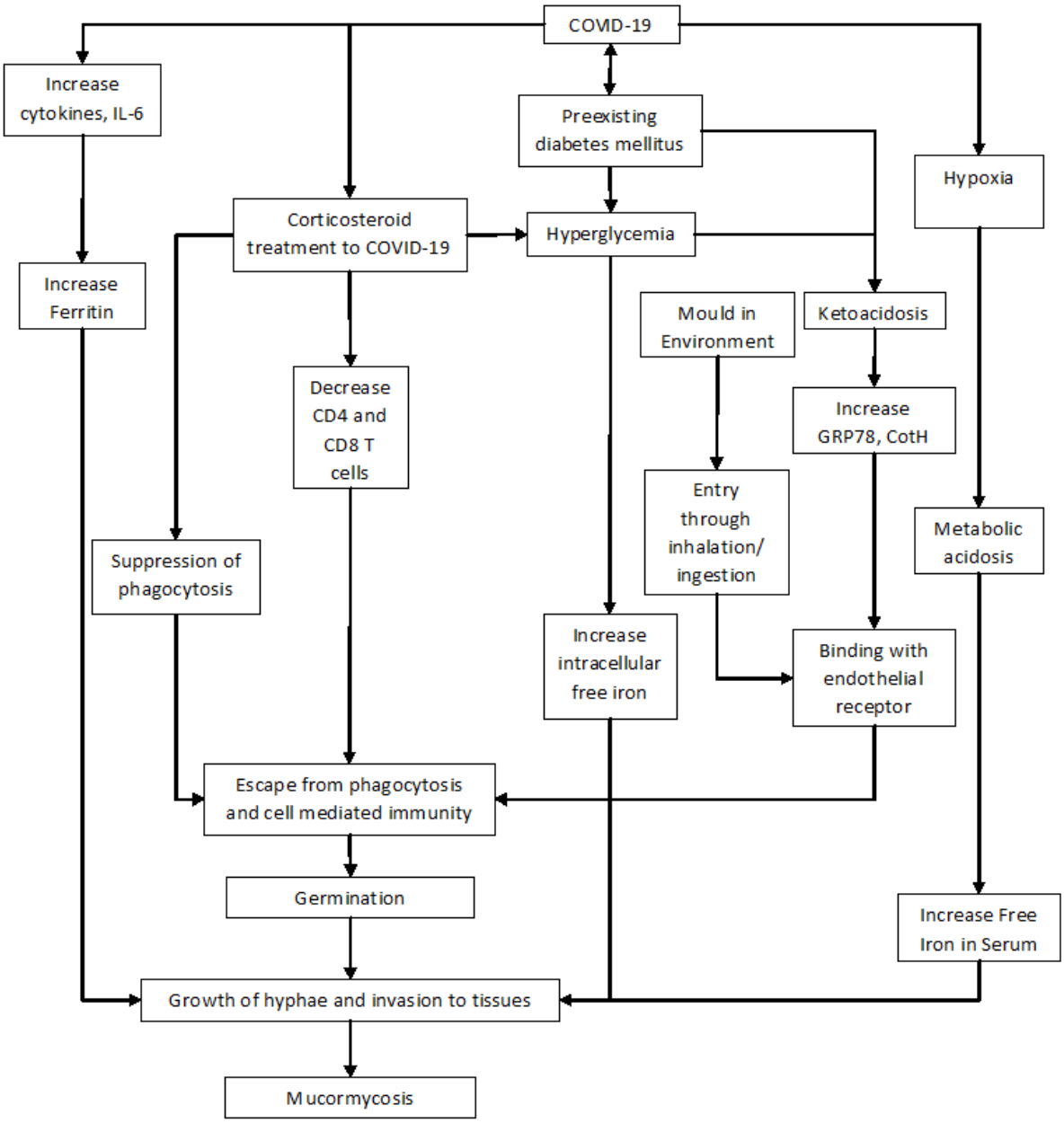

Fig.4: Mechanism of mucormycosis in patients with coincidence of diabetes mellitus and severe SARS-CoV-2 infection.

Conclusion

Mucormycosis is an angioinvasive life-threatening infection caused by mold fungi having the order Mucorales. Invasion of fungal hyphae into blood vessels can result in thrombosis and tissue necrosis. Invasion of fungal mold into blood vessels is due to interaction between Mucorales CotH and endothelium GRP78. Diabetes mellitus (Hyperglycemia, ketosis and elevated serum iron levels) enhance the expression of GRP78 and CotH to augment angioinvasion and fungal growth. SARS-CoV-2 infection is

associated with elevated cytokines particularly IL6 which increases ferritin levels to enhance fungal growth. Lymphopenia in COVID-19 patients suppress immunity against fungal infection. Main defense mechanism against fungal infection is phagocytic destruction of fungal spore by neutrophil and monocytes. Phagocytosis of fungal spore is hampered in diabetic patients and severe COVID-19 infection undergoing steroid therapy. Thus, severe COVID-19 patients with uncontrolled blood glucose treated with corticosteroids are exceptionally vulnerable to the development of mucormycosis. Emergency medical attention should be given to COVID 19 or COVID-19 recovered patients those begin to suffer in facial or orbital pain, headache, periocular swelling and double vision.

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