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# Is Ferritin One of The Missing Link in Putting Together the Pieces of Covid-19 and Mucormycosis?

**Abstract:**

**Purpose of review :**The exact cause of increased incidence of mucormycosis in covid-19 patient is an enigma. Cause cannot be attributed to a single factor, although many theories are doing the rounds. Predisposing factors include an immune-compromised host (both due to viral infectionas well as systemic corticosteroid therapy), diabetic ketoacidosis, zinc medications etc.Medical professionals are at a loss of words in explaining the exact cause of this phenomenon. The purpose of this review is to hypothesise if increased availability of iron in the host has any adjunctive role in increased incidence of mucormycosis in covid-19 patients.

**Recent findings :** Hyperferritenemia has been detected in covid-19 patients with increase levels in tune with high morbidity, mortality and severity of covid 19. Dual role has been attributed to this iron containing protein acting both as a product of inflammation (released by various inflammatory cells) as well as mediator of inflammatory responses. There has been a sudden surge in zygomycetes infection particularly of the order mucorales. Mucormycosis caused by Rhizopus oryzaes is a life threatening infection seen in covid-19 patients. A novel mechanism in pathogenesis of mucormycosis is iron acquisition.

**Summary :** This review will try and explore whether increased in serum ferritin in covid 19 patients and iron acquisition as a novel perspective on mucormycosis pathogenesis and treatment are both inter-related in any ways.

**Key words :** ferritin, covid-19, mucormycosis.

## Introduction:

Ferritin is a nhemoprotein and regulates many biological functions ranging from angiogenesis, iron storage, to immune-modulation. It consists of two types of polypeptide chains (light chains and heavy chains). This acute phase reactant is secreted extracellularly as well as intracellularly during infection. The functions of both these in a single molecule of ferritin differ drastically for the same reasons. At individual level elevated serum ferritin is seen in those exposed to high pathogen load [1].Cytokines regulate ferritin levels in various cells like hepatocytes, mesenchymal cells, monocytes, macrophages at both translation and transcription levels [2].It is secreted by hepatocytes, kupffer cells, proximal tubules, renal cells and macrophages as by in-vivo and in-vitro studies[3,4,5,6].Serum ferritin is an acute phase reactant in a multitude of diseases like infectious, rheumatologic, hematologic and malignant diseases.

Novel coronavirus disease first identified in Wuhan(China) has continued to spread unabated across the world. It has even been detected in remote icy regions of Antarctica. Since it is an inflammatory viral disease, the rise in levels of inflammatory markers such as C- reactive protein, erythrocyte sedimentation rate, serum amyloid A and ferritin is well documented. Ferritin has been known to be associated with dengue related complications as well [6].Various studies have correlated hyperferritenemia with severe covid 19 diseases. Also correlation has been found between hyper ferritenemia and covid-19 non-survivors.

Mucormycosis, a life threatening zygomycetes infection caused by Rhizopus oryzae is increasingly witnessed in covid-19 patients. Iron has found a significant role in the pathogenesis of mucormycosis due to iron acquisition mechanisms unique to this fungus.

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This review hopes to shed light whether surge of ferritin in covid 19 patients and increased incidence of mucormycocis in such patients is in any way related. Whether it could give answers to unanswered questions posed by triple whammy of pandemic, host related factors as well as surge in consumption of zinc, iron supplements and antimicrobials.

## Overview of ferritin and inflammation:

Iron, inflammation and mechanisms of redox biology are explicably linked. Many schools of thought exist to abjugate exact role of ferritin in inflammation which are as follows [7].

1. First school of thought says that hyperferritenemia is only an "innocuous onlooker"; simply an acute phase reactant released during imflammation is only an “innocuous onlooker” acute-phase reactant.
2. Second school of thought proposes that hyperferritenemia has a protective role to play in making iron unavailable for bacterial growth a protective role to play in making iron unavailable for bacterial growth.
3. Third school of thought postulates that ferritin is a key immunomodulator having dual roles of activation and suppression of inflammatory responses.

Looking at these three possibilities with an unbiased view, evidence still supports the fact that serum ferritin levels have been directly correlated with increase in severity, morbidity of many systemic diseases. Vice versa, decreased, decreased ferritin levels correlates with resolution of inflammatory state as well as severity of infection.

## Immunomodulation role of ferritin:

Ferritin plays a role as a local cytokine in rat hepatic cells, activating NF-KB cascade, independent of iron [7]. This further activates array of inflammatory mediators like IL-1 beta, NO synthase (iNOS) [8]. Search for specific receptors in humans is a work under progress.

## Immunosuppressive role of ferritin:

Some unknown receptors propagate binding of T and B lymphocytes to FTH.This binding brings about charade of affects like T cell multiplication decreases, B cell maturation lessens and immunoglobulin production is hampered [9,10].These are largely mediated by IL-10 [7].TLR-9 stimulation by CpGDNA could trigger hyperferretenemia independent of lymphocyte activation [11].

## Overview of covid-19 and ferritin

Cytokine storm has been the major cause of mortality in covid-19 patients. There has been increase in various inflammatory markers like CRP, D dimer, ferritin, amyloid in covid 19 sufferers. Various studies have implicated serum ferritin with increased severity of covid 19 and decreased ferritin leads to improvement in covid 19 disease.

Macrophages in particular and cytokines may cause ferritin production and secretion which in turn may promote several pro-inflammatory (interleukin 1-beta) as well as anti-inflammatory cytokines. Patients with certain inflammatory conditions like viral/bacterial sepsis, immunological pathologies, rheumatological diseases can present with MAS(macrophage activation syndrome) with leads to multiple organ failure post cytokine storm [7].

## Overview of iron and mucormycosis:

Increased levels of available iron in serum makes patient uniquely susceptible to infection by class Zygomycetes (Rhizopusoryzae causing mucormycosis) not to other pathogenic fungi. In a logical sense iron chelators should decrease growth of fungus (exception deferoxime) [12].

## Some of the pathogenic mechanisms related to iron:

1. Fungi have special ability to obtain iron for its growth as well as for virulence requirements by producing siderophores. Zygomycetes secrete a siderophore called Rhizoferrin[13]. However iron obtained from rhizoferrin is insufficient in sufficing its requirements.
2. They can also utilize siderophores by other organisms/mechanisms (xenosiderophores) [14]. They obtain iron from xenosiderophoretic mechanisms example bacterial siderophore deferoxime (iron chelator) [14].Deferoxime caused dissemination of rhizopus infection. Other iron chelators had no effect.
3. Homologues of haemoxygenase gene CaHMX1

[12]:Genome project undertaken for rhizopus revealed 2 homologues of haemoxygenase gene. They may provide means of obtaining iron (mainly from human blood )

## Potential link between viral etiology, ferritin and fungal dissemination??

The sudden rise in cases of this deadly fungus concomitant with covid 19 virus serves as a food for thought for healthcare professionals who deal with such patients on a day to day basis. This review proposes a link between this viral etiology(novel coronavirus), haeme containing biomarker (ferritin), and fungal pathogenesis(mucormycosis) in the presence of confounding variable such as certain medications and immune status of the host. More epidemiological studies of longitudinal nature are desired to find exact answers to this perplexing phenomenon to prevent many tragedies unfolding during this pandemic.

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