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Review Article

Ferritin in COVID-19 infection and its diagnostic significance

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ABSTRACT

COVID-19 caused by SARS-CoV-2 (severe acute respiratory syndrome corona virus-2) is the major health issue facing the entire world at present. There are several pathological mechanism associated with the infection which aggravates to significant morbidity and mortality among the population. Of the several complications, hypercoagulation due to fibrin clot formation is one of the complications often seen in patients suffering from COVID-19 infection. The link of iron with hypercoagulation and related events are always a matter of discussion in the scientific world. Yet another cause of disseminated intravascular coagulation seen in these patients is cytokine storm, which occurs due to release of pro inflammatory signaling molecules as a result of increased inflammation due to depletion of iron stores. The viral attack can destroy the hemoglobin; release the iron content by separating it from the heme. This free iron in the blood will be able to produce free radicals which can convert fibrinogen into fibrin clots. More over iron could elicit oxidative stress which can subsequently lead to increased erythrocyte viscosity and thrombosis. Further ferritin, the iron storing protein will actively get released and can lose its inner iron content leading to increased free iron in circulation. It was evident that iron overload was one of the critical factor which determines the immunological processes leading to a type of cell death referred as ferroptosis. This review discussed with the mechanism involved in the release of iron and cytokine storm along with the diagnostic significance of ferritin in COVID-19 infection.

Keywords: COVID-19, SARS-CoV-2, Hypercoagulation, Ferritin, Cytokine storm, Ferroptosis

INTRODUCTION

Irrespective of the control measures, the infectivity of Covid-19 is continuing all over the world. There are several complications associated with the infection as the virus starts multiplying in the host cell. The dissociation of the porphyrins from iron of hemoglobin is one of the early pathogenic events of SARS Cov-2 infection leading to the release of free iron into the circulatory system. The hemoglobin then becomes distorted and may not be in a position to carry oxygen effectively to the tissues leading to tissue hypoxia and subsequently organ failure and remains the reason for multi organ involvement in Covid-19 infection. The released iron may accumulate in the circulation leading to iron overload and is a cause for oxidative damage to tissues and cells through free radical formation.[1] This increased iron load can result in aberrant immune function leading to cytokine production by the T-cells. Increased free iron can lead to hyperferritinemia due to dysregulation of iron homeostasis which can further lead to ferroptosis also, which induces a series of immune response which ends up in life threatening systemic inflammatory syndromes like cytokine storm.[2] Hence the increased level of ferritin is a key indicator of the inflammatory status in patients suffering from Covid-19 infection. This review highlights the possible

mechanism associated with iron overload and how hyperferritinemia can contribute to the complications of SARS Cov-2 infection and making it even fatal.

Cytokine storm

Cytokine storm and cytokine release syndrome are life threatening systemic inflammatory syndromes involving an uncontrolled and excessive release of pro inflammatory signaling molecules called cytokines and immune cell hyper activation that can be triggered by various therapies, pathogens, cancers, autoimmune condition and monogenic disorders. Symptoms of cytokine storm include fever, rash, fatigue, headache, myalgia, arthralgia, diarrhoea and so on.[3] Cytokine storm can also lead to life threatening complications including disseminated intravascular coagulation. The combination of hyper inflammation, coagulopathy and low platelet counts places the patients with disseminated intravascular coagulation complicating cytokine storm at high risk for both hypercoagulability and thrombosis as well as spontaneous hemorrhage, shock and death.[4] Cytokine storm can also lead to Acute Respiratoy Distress Syndrome causing dyspnoea, tachypnoea and hypoxia requiring mechanical ventilation and multi organ dysfunction causing renal failure, acute liver failure, encephalopathy and myocarditis. Laboratory profile of patients with cytokine storm shows leukocytosis or leukopenia, anemia, thrombocytopenia, hypertriglyceridemia, elevated ferritin, C Reactive Peptide and D dimer levels.[5] Prominent elevations in serum inflammatory cytokine levels such as interferon gamma, interleukin 6, interleukin 10 andsoluble interleukin2 receptor alpha are also usually present. Measurements of inflammatory acute phase biomarkers such as CRP and ferritin should be obtained since they have a strong predilection for disease severity. The cytokines are the body's natural response to defend against pathological processes; therefore, the cytokines have both protective and harmful effects on the body of the host. Cytokine storm occurs when there is an exaggerated response in the production of cytokines causing collateral damage, more than the immediate benefit of the immune response.[6]

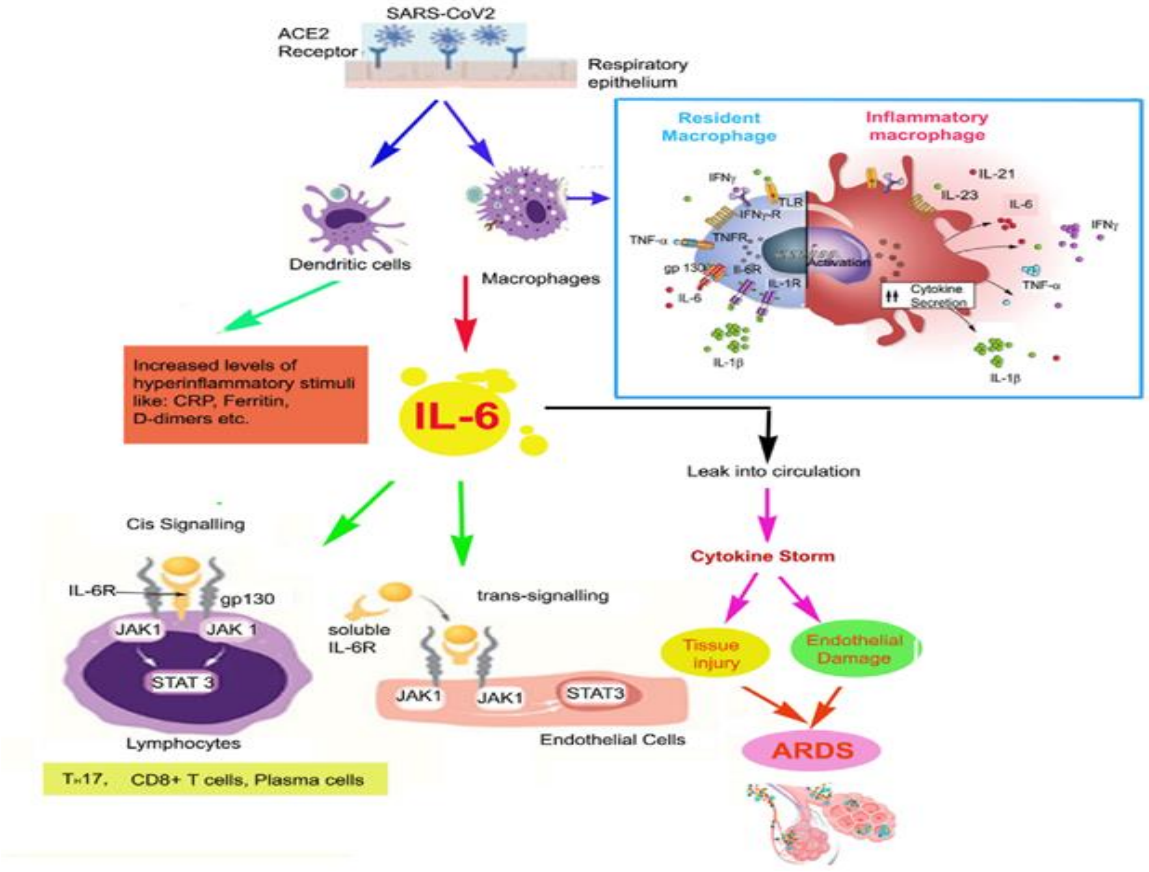

Figure 1: Cytokine storm in COVID-19 infection.

Cytokine storm and COVID-19

SARS-CoV-2 is the pathogen that causes coronavirus disease 2019 (COVID-19). The disease course of COVID-19 infection varies. It is asymptomatic or causes mild symptoms such as fatigue in some patients, while serious immunologic complications such as macrophage activation syndrome also known as secondary

hemophagocytic lymphohistiocytosis, which causes fatal cytokine storm syndrome and acute respiratory distress syndrome in others.[7] Patients who had a severe infection with COVID-19 showed a higher incidence of hemophagocytosis and elevated cytokine levels suggesting that cytokine storm plays a major role in the pathogenesis of the COVID-19 infection. The beneficial effects of the immunosuppressant agents in such patients further supports it.[8,9] Serum cytokine levels that are elevated in COVID-19 associated cytokine storm include interleukin 1 beta, interleukin 6, TNF, interferon gamma, macrophage inflammatory protein/(MIP) 1 alpha and 1 beta and VEGF.[10,11] Higher interleukin 6 levels are found to be strongly associated with shorter survival.[12] Other laboratory abnormalities include leukocytosis, elevated CRP, procalcitonin and D dimer levels (Figure 1).

Although immunologic dysregulation has been observed in severe cases of COVID-19, it is not known whether immune hyperactivity or a failure to resolve the inflammatory response because of ongoing viral replication or immune dysregulation underlies severe cases.[6] Co-morbid conditions associated with more severe cases of COVID-19, possibly because of the pre-existing chronic inflammatory state or a lower threshold for the development of organ dysfunction from the immune response. Early recognition and appropriate treatment of immunologic complications will decrease the morbidity and mortality in COVID-19 infection.

Ferritin in COVID-19 infection

Ferritin is a representative of the total body iron status. It is also one of the positive acute phase reactants. Ferritin is a key mediator of immune dysregulation, especially under extreme hyperferritinemia via direct immune suppressive and pro inflammatory effects, contributing to the cytokine storm.[13] Hyperferritinemia, thereby being a key component of the heightened inflammatory state identifies patients with increased mortality risk. Patients diagnosed with diabetes mellitus showed elevated serum ferritin levels, and it is known that they face a higher probability to experience serious complications from COVID-19.[14]

However, newer studies suggest that in spite of its strong association with mortality, it is not clear if the hyperferritinemia in COVID-19 patients is merely a systemic marker of disease progression or a key modulator in disease pathogenesis.[15] This could be revealed only if ferritin was estimated in these patients on regular basis as part of routine investigations along with other parameters. Recent studies have shown that Hepcidin, a key regulator of iron metabolism also played a significant role in inflammatory reactions and was also linked with the mobilization of iron in to the circulation.[16]

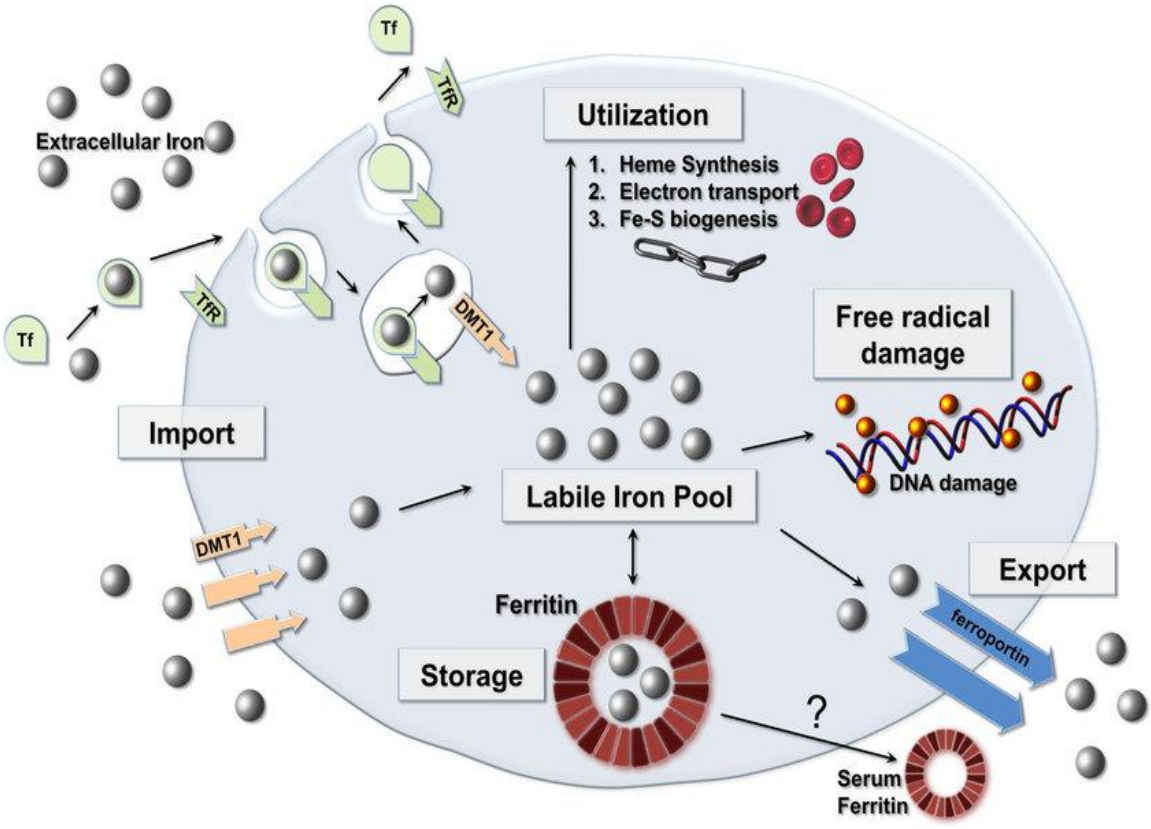

Figure 2: Iron uptake and storage.

Iron receptors and defects in iron uptake mechanism

The iron metabolism in the human body is quite complex as it involves a set of chemical reactions at the systemic and cellular level. While iron plays an integral role in the optimum functioning of the human body any defect in the homeostasis may lead to iron toxicity which can even be fatal. In industrialized countries, humans have 4 to 5 grams of iron in their bodies (~38 mg iron/kg body weight for women and ~50 mg iron/kg body for men).[17] The majority of the iron absorbed from digested food or supplements is absorbed in the duodenum by enterocytes.[18] Dietary iron must be in the form of ferrous state Fe^{2+} in order to get absorbed. A ferric reductase enzyme on the brush border of enterocytes, duodenal cytochrome B (D_{cytb}), reduces ferric Fe^{3+} to Fe^{2+}. A protein called divalent metal transporter 1 (DVT 1), which can transport several divalent metals across the plasma membrane, then transports iron across the enterocyte's cell membrane into the cell.[19] These enterocytes either store the iron as ferritin, which is accomplished by Fe^{2+} binding to apoferritin (in which case the iron will leave the body when the cell dies and is sloughed off into feces) or release it into the body via the only known iron exporter, ferroportin. Hephaestin, a ferroxidase that can oxidize Fe^{2+} to Fe^{3+} and is found mainly in the small intestine, helps ferroportin transfer iron across the basolateral end of the intestine cells. In contrast, ferroportin is post-translationally repressed by hepcidin.[20]

The iron is then transferred by various proteins in blood mainly by transferrin. Iron from transferrin is then transferred to the reticuloendothelial cells by the ferroportin receptor. Most of the iron is recycled by the reticuloendothelial system which breaks down aged red blood cells. In contrast to iron uptake and recycling, there is no physiologic regulatory mechanism for iron excretion. At a cellular level, the import of iron and uptake take place through a receptor mediated endocytosis with the help of transferrin receptor (TFR 1), transferrin receptor (TFR 2) and GAPDH.[21] The ferric ion bound with transferrin are recognized by these receptors which then lead to a conformational change to elicit endocytosis. Iron then enters the cytoplasm from the endosome via importer DMT1 after being reduced to its ferrous state by a STEAP family reductase. The labile iron pool found in the cytoplasm, ferrous iron is present in a soluble, chelatable state which constitutes the labile iron pool (~0.001 mM). The labile iron pool is potentially toxic due to iron's ability to generate reactive oxygen species.[22] In the storage iron pool, iron can be stored as ferritin with ferric iron due to the ferroxidase activity of the ferritin heavy chain (Figure 2). Dysfunctional ferritin may accumulate as hemosiderin which can be problematic in cases of iron overload. The ferritin storage iron pool is much larger than the labile iron pool, ranging in concentration from 0.7 mM to 3.6 mM.

The export of iron occurs to a wide variety of cells like red blood cells, macrophages, neurons as well as enterocytes. There is only one known iron exporter, ferroportin which transports ferrous iron out of the cell, generally aided by ceruloplasmin and hephaestin (mostly in enterocytes), which oxidize iron to its ferric state so it can bind ferritin in the extracellular medium.[23]

Hepcidin causes the internalization of ferroportin, decreasing iron export. Through an unknown mechanism, hepcidin down regulates the activities of both transferrin receptor 1 and the importer DMT1. However it is to be noted that the expression of hepcidin occurs only in certain cells like hepatocytes with tight controlled transcriptional process linked with iron metabolism and homeostasis. In this process hepcidin act as a gatekeeper of iron release from enterocytes into the rest of the body.[24] The body regulates iron levels by regulating each of these steps as is evident in the case of iron deficiency anemia, in which enterocytes could synthesize more D_{cytb}, DMT1 and ferroportin.[25] While in anemia of chronic disease, there was a upregulation of hepcidin, which inhibited the ferroportinpresent on the enterocytes and macrophages thereby inhibiting the iron absorption and the iron release from macrophages in the body.

Any defect in the iron uptake by the enterocytes or macrophages resulting in increased iron absorption and hyperferritinemia led to devastating complications. Downregulation of hepcidin or upregulation of ferroportin causes increased iron absorption and increased iron storage in the form of ferritin thereby altering the haemostasis of iron transport.[20] Since there were no major ways for iron excretion in the body, the elevated iron level was harmful to the body by the mechanism of free radical damage. Hemochromatosis (defect of the HFE gene) is atypical example of this state.

Diagnostic significance of iron and ferritin

There were studies conducted and proved that increased concentrations of iron in the lung tissues are associated with increased lung injury and subsequent respiratory complications in COVID-19 patients.[26] Similarly recent studies revealed that the serum level of ferritin was directly proportional to the severity of the disease in patients suffering from COVID-19 infection.[27] It should be understood from the mechanism discussed, that the iron homeostasis might be totally disturbed in acute and chronic infections of COVID-19 leading to increased depletion of iron stores and free iron overload. This free iron could elicit the response for the formation of free radicals and thus aggravating the tissue injury. The generated free radicals like hydroxyl radical could trigger the fibrin clot formation. Elevated free iron further enhances the production of ferritin and also parafibrin.[28] Parafibrin could trigger inflammatory reactions in the blood vessels and can cause clot formation very easily. The levels of ferritin can be very easily detected and

estimated in COVID-19 patients as a routine investigation.

CONCLUSION

Increased free iron in the circulation can cause hypercoagulation which is very common among COVID-19 infection. Iron is able to generate free radicals which can oxidatively damage the tissues. It became highly evident now, the depletion of ferritin from iron stores and release of iron into the circulation is a major causative factor of hypercoagulation in patients suffering from the infection due to the formation of the fibrin clots. Hence it will be always beneficial for the patient to estimate the serum ferritin levels to understand the extent of inflammatory process in the cell. It will be an indicator for hypercoagulation and subsequent organ damage in acute conditions of medical emergency.

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