Review article

Iron Chelation Therapy in COVID-19 Infection: A Review Article

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Abstract

The recent outbreak of corona virus and coronavirus disease (COVID-19) caused by the SARS-CoV-2 virus is a global concern. Despite efforts to clarify the physiology and potential therapy, specific guidelines for the treatment of COVID-19 disease have yet to be established, and many therapeutic options are under investigation. Accumulating evidence suggests that dysregulation of iron homeostasis contributes significantly to the pathogenesis of COVID-19 through its toxic effects by the formation of reactive oxygen species (ROS). This review focuses on summarizing the available literature and relevant studies conducted to date on the possible therapeutic effects of iron chelation therapy in the treatment of COVID-19 disease. Scientific databases (PubMed, Scopus, Google Scholar) were searched for relevant articles using the following keywords: COVID-19, SARS-CoV-2, coronavirus, clinical management, iron chelators/chelation. Research articles, reviews, research letters, case reports, and commentaries were considered. Although there is ample evidence of the potential beneficial effects of using iron chelators as adjuvant treatment in COVID-19, further research on this topic is needed.

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The novel disease

In December 2019, a new virus from the coronavirus group (initially 2019-nCov) emerged and caused the appearance of unusual viral pneumonia in China. The disease is called coronavirus disease (COVID-19) and in March 2020, the World Health Organization declared COVID-19 a pandemic. The 2019nCov was later named SARS-CoV-2 due to its structural similarity to the SARS-CoV virus that caused the 2003 SARS outbreak (1). Vaccination campaigns against the SARS-CoV-2 virus are currently underway worldwide, but the COVID-19 pandemic is still out of control and continues to cause high mortality. Unfortunately, there is still no specific therapy for COVID -19 and patients rely on general and supportive therapies. Although drugs (antiviral drugs, monoclonal antibodies, corticosteroids, immunosuppressants) included in the recommended guidelines for the treatment of the infection show promising results, given the rising number of COVID-19 cases, additional therapeutic choices should be identified and thoroughly evaluated (2-4). The goal of therapy is to prevent the occurrence of a cytokine storm and to avoid significant damage to body tissues resulting in multiorgan failure and death. Most cases have a milder clinical course, but up to 14% of cases can be severe, and present with moderate to severe pneumonia requiring hospitalization. Severe cases are characterized by dyspnea, tachypnea (RR ≥ 30/min), hypoxemia (SpO2 ≤ 93%), PaO2/FiO2 ratio < 300, and/or pulmonary infiltrates involving more than 50% of the lung parenchyma. All of this can lead to severe disease requiring intensive care unit (ICU) treatment and can be life-threatening in 5% of cases characterized by respiratory failure that can provoke the development of acute distress syndrome (ARDS), septic shock, multiple organ dysfunction and death (5). Risk factors for fatal outcome include age, underlying comorbidities (hypertension, diabetes mellitus, obesity, heart failure, coronary artery disease), and disease severity, which increases by up to 49% in critically ill patients (6,7). In addition, coronavirus also affects numerous other organ systems, such as the cardiovascular system (e.g., myocardial damage, cardiomyopathy, and cardiac arrhythmia (8-11), the neurological system, and can also cause acute kidney injury and liver damage (12,13). Inflammation-induced coagulopathy, which causes an elevated coagulation state, is a consequence of damage to the endothelium and the action of pro-inflammatory cytokines (especially IL-6) (14-16). Endothelial cells are potential targets for SARS-CoV-2 due to the highly expressed ACE 2 receptors, which are thought to be the major (but not the only) port of entry into a cell for the virus (17). The virus also recognizes porphyrin in hemoglobin, with higher binding affinity than that to hACE2, resulting in oxygen deprivation (17). In addition to endothelial cells and porphyrin, transferrin receptors (TfR) are also considered as a possible target of viral action(18, 19). TfR is found on numerous tissues and cells, including cells of the respiratory system. Transferrin, a circulating glycoprotein that transports iron, delivers iron to cells when it binds to TfR. Studies in animal models have shown that viral infection did not occur when connection between virus and TfR was affected (18).

Iron and ferritin in inflammation

Iron metabolism is very important for the functioning of the whole body and ferritin plays a crucial role in this process. Ferritin is a protein that binds iron and is found in the bloodstream, cytosol and mitochondria. It is involved in crucial cellular activities, including immune regulation by making iron available and protecting cells from the toxic performance of free iron (20). By measuring serum ferritin levels, one can get an insight into iron status. During inflammation, there is often an increase in serum ferritin concentration with hypoferremia. Oral iron supplementation drugs have been shown to increase mortality in humans when taken during infection (20). Serum ferritin synthesis, apart from iron availability, is also regulated by inflammatory cytokines such as IL-1β and IL-6 (pro-inflammatory cytokine in COVID-19 infection) and increased hepcidin production, which in turn is stimulated by pro-inflammatory cytokines, especially IL-6 (21). To survive and

replicate in host cells, microbes require iron and to limit viral replication, the innate immune system takes control of iron metabolism by reducing iron bioavailability (2). To protect the host during active infection, ferritin reduces iron bioavailability to the pathogen. As a result, serum iron concentration decreases and serum ferritin concentration increases, limiting the availability of iron for erythropoiesis and leading to further exacerbation of anemia, which is called anemia of inflammation (AI) (22). Ferritin also plays a role in inflecting the immune response by inducing anti-inflammatory cytokines and limiting free radical-induced damage (23). Inflammation and infection produce large amounts of oxygen radicals (ROS) that leak into the fluids and tissues in the area of inflammation, causing cellular damage that can lead to endothelial dysregulation of the immune response, resulting in hyperinflammation and cytokine storms and multiple organ failure (24). When the concentration of non-transferrin bound iron in plasma is too high, it converts to its redox-active form called labile plasma iron. This further contributes to the production of ROS, leading to tissue lesion and, over time, fibrosis (5). These toxic free radicals are formed by the Fenton reaction, in which, in the presence of a harmful byproduct of aerobic metabolism hydrogen peroxide, ferrous iron (Fe^{2+}) is oxidized to ferric iron (Fe^{3+}), producing a hydroxyl radical and hydroxide ion.

In addition to ferritin, transferrin and its effect on iron must also be mentioned, as it has been shown that the concentration of transferrin changes during COVID-19 disease. Transferrin is a glycoprotein synthesized by the liver. It is found in the bloodstream, where it transports iron to TfR receptors on cells. When there is iron deficiency in the body and hypoxia, transferrin concentration increases, while it decreases during inflammation (18). Transferrin saturation with iron (TSAT) indicates how much iron is bound to transferrin and is an important marker for iron availability and the amount of systemic iron (18).

The role of iron in COVID-19 infection

Dysregulation of iron homeostasis, including iron overload, has also recently been recognized as an important element in the pathogenesis of COVID-19, along with high levels of proinflammatory CD4 and CD8 T cells, extensive cytokine release, and an increased coagulation state. As mentioned earlier, elevated ferritin levels not only indicate an acute phase response, but also play an important role in inflammation by contributing to the progression of cytokine storm (20). During cytokine storm there is an enormous and uncontrolled release of pro-inflammatory cytokines (IL-6, IL-10, TNF-α, IL-1β, IFN-γ, IL-2, IL-7 and IL-10, G-CSF, MIP-1 alpha, and others), which is especially prominent in more severe clinical forms of COVID-19 disease. As a result of the cytokine storm and the damaging cytopathic effect of the virus, there is destruction of the lungs and other organs and, at the same time, a further increase in cytokine levels. Besides the cytokine storm, high levels of intracellular iron generate ROS interaction with oxygen molecules and increases the risk of coagulopathy, oxidative stress and endothelial inflammation, all of which together can lead to disseminated coagulopathy and multiorgan failure (25). According to current clinical and experimental data, it is possible that significant oxidative stress may cause the progression of ARDS characterized by damage to the lung parenchyma, decreased lung capacity, endothelial and capillary membrane damage resulting in protein leakage (24). During this tissue damage and lysis, there is an additional increase in the level of ferritin, the synthesis of which is already elevated due to ongoing inflammation (26). Moreover, analysis of lavage fluid from patients with ARDS shows increased levels of iron and increased cellular levels of transferrin, ferritin, and lactoferrin, implying interruption of pulmonary iron homeostasis in ARDS (4).

As mentioned earlier, during COVID-19 infection, there is an iron overload and little attention is paid to this finding. Several studies suggest that patients with high ferritin levels have a much more severe form of COVID-19 disease, clinical deterioration of the patient's condition, a higher

mortality rate, and worse outcome in patients treated in the ICU (23,24). Hyperferritinemia is linked with considerably elevated mortality in septic patients, which has also been shown in patients with severe COVID-19 infection in ICU% (5). Patients with COVID-19 disease and ferritin levels above 300 μ g/l had a 9-fold higher risk of death4. Although little is well-known about the management of iron balance in SARS-CoV-2 patients, some conclusions can be drawn from other viral infections such as hepatitis B, hepatitis C, and HIV, in which iron overload leads to a worse prognosis (5,27). In HIV infection, for example, HIV 1 replication is dependent on host cell enzymes that require iron, and iron supplementation has been shown to lead to increased mortality in HIV-infected patients, indicating the importance of iron excess in HIV infection (2).

The level of transferrin and TSAT, mentioned earlier in the text, proved useful in assessing the severity of COVID-19 disease and survival. In patients hospitalized for COVID-19 disease, the serum concentration of transferrin decreases, although at the same time a low serum iron level is present (19, 28-31). It is possible that COVID-19 inflammation regulates the action of transferrin and prevents its increase when low iron levels are present (19). A very low concentration of transferrin was observed in patients who required oxygen therapy, and a continuous decrease in concentration was observed in patients who died (19, 28-31). In patients who survive, serum transferrin levels recover after some time. The TSAT decreases in COVID-19 patients, especially in patients who have a severe form of the disease and are in the ICU (19, 30). The drop in TSAT level is explained by the fact that at the beginning of the infection, the availability of iron for the pathogen is limited. After a few days, the TSAT level recovers and returns to normal range. It is interesting to note that TSAT levels were higher in intubated patients than in non-intubated patients, which may be explained by changes in the regulation of metabolism at different stages of the disease or by the effect of the tube on iron metabolism (19).

Overexpression of IL-6, IL-1 β , and IFN- γ during inflammation also leads to an increase in hepcidin levels (5). Hepcidin is an iron-regulating peptide hormone produced in the liver and released into the bloodstream in response to inflammation and increased iron levels in the body. The production of hepcidin in the liver is stimulated by IL-6 (32). It is a negative regulator of iron by sequestering iron in enterocytes and macrophages, increasing intracellular ferritin levels, and preventing iron efflux from storage cells by inhibiting ferroportin (33). It is possible that SARS-CoV-2 virus has a hepcidin-like effect because of the identical amino acid sequence between hepcidin and the coronavirus spike glycoprotein. By mimicking the action of hepcidin, SARSCoV-2 could remarkably increase circulating and tissue ferritin (especially in liver, spleen, bone marrow, and muscle) independent of inflammation, while causing serum iron deficiency and hemoglobin deficiency (4, 32). It is also possible that coronaviruses enter cells through complex mechanism by a mimic effect using their spike proteins and cleave their spike polypeptides using host furins and proteases, which promotes cell entry (32).

COVID-19 infection resembles hyperferritinemic syndromes due to high blood ferritin levels and inflammation triggered by the cytokine storm, as well as lymphopenia, decreased NK count and activity, abnormal liver function tests, coagulopathy, pleurisy, pericarditis, lung consolidation, pulmonary edema, and myocarditis (34,35). Because iron chelation is the basis for treating iron overload, as it is in other hyperferritinemic syndromes, and because impaired iron metabolism has been observed in COVID-19 infection, iron chelator therapy may be beneficial.

There are several theories about how increases in ferritin and free iron may occur during COVID-19 infection. An in-silico model suggests and considers direct interaction between several viral proteins and hemoglobin, but side effects on inflammation or tissue damage are not considered (36, 37). The viral proteins (ORF1ab, ORF10, ORF3a) originate from infected plasma cells and together remove heme from the b-

chain of hemoglobin, remove iron from heme, and consequently sequester iron-free protoporphyrin IX (PPIX). As a result, a toxic amount of iron is released, functional hemoglobin levels are impaired and hemoglobin metabolism is disturbed. Another theory, as addressed previously in the text, is that AI may be the cause of the decreased hemoglobin level (2, 22).

Iron chelator therapy

Iron chelators have several beneficial properties such as chelating iron, inhibiting the redox properties of free iron, and preventing the involvement of iron in Fenton reactions. They inhibit the production of hydroxyl radicals and the production of other ROS which lead to oxidative damage and ferroptosis (38). Another useful mechanism of iron chelators is the downregulation of hepcidin and the removal of iron from iron-binding proteins, showing their anti-ferritin effect (2,39). FDA-approved iron chelators such as deferoxamine (DFO), deferiprone, and deferasirox have so far been used as iron overload therapy in a number of pathogens in vivo and in vitro, particularly (DFO) (17). Each of the iron chelators has different efficacy in iron overload therapy. DFO could be effective against SARS-CoV-2 because it forms a stable complex with iron, scavenging iron-mediated hydroxyl radical formation and acting as an antiviral (4). What is more, iron chelators can reduce the availability of cellular iron involved in the replication of RNA viruses such as West Nile virus, HIV, and hepatitis C virus, a property that could be used in the treatment of COVID -19 infections (17). The chelator deferasirox has a different effect, binding cytosolic iron discharged from ferritin (5).

Lactoferrin, a glycoprotein that is part of the body's natural immunity, is one of the potential naturally occurring iron chelators. It is produced by exocrine glands and neutrophils and found in human milk and all secretions. It has a variety of therapeutic effects. Apart from iron binding and effect on the immune system, it also diminishes inflammation by affecting the formation of cytokines and ROS, thus reducing iron overload. It also inhibits the joining of heparan sulfate proteoglycans, which prevents viruses from cell entry (40).

Iron chelation therapy in COVID-19

As more research indicates that endothelial inflammation is an important pathophysiological mechanism responsible for the multiorgan involvement and organ failure in SARS-CoV-2 infection, many researchers believe that iron chelators may prove useful in improving the systemic manifestations of COVID-19 (41). Experimental studies in animals with bleomycin-induced pulmonary fibrosis, in which fibrosis and worsening lung function are associated with increased iron aggregation in the lungs, have shown that iron chelator therapy is beneficial (42).

Due to the lack of adequate therapy, an increasing number of investigators are suggesting that targeted iron therapy may help treat the more severe forms of COVID-19, as iron is likely required for viral replication and functions of SARS-CoV-2 (5). Previous research and findings have shown that iron chelation may have an effect on proinflammatory cytokines and free radicals, which are closely related with severe COVID-19 disease and may lead to tissue destruction, with acute lung injury and ARDS being the most severe outcomes. Because of all these factors, iron chelators represent a potential COVID-19 treatment (5). Iron chelators could alleviate ARDS and contribute to the control of SARS-CoV-2 through several mechanisms: reduction of iron attainability, inhibition of viral multiplication, increase in the titer of neutralizing antiviral antibodies and B cells, prevention of endothelial inflammation, and inhibition of pulmonary fibrosis and lung decay by reducing pulmonary iron accumulation (41). As mentioned before, iron chelator DFO could be useful as a potential therapy for COVID-19 infection because it reduces the replication of some RNA viruses, as shown by in vitro studies, and also reduces the availability of iron in serum and body tissues, which could prevent pulmonary fibrosis after COVID-19 infection (39). In vitro, it also lowers levels of IL-6

and endothelial inflammation, which could reduce the severity of COVID-19 infection and multi-organ damage and failure (39). In a mouse model, preconditioning with DFO was shown to protect the lungs from mechanical ventilation damage by reducing ROS formation in mitochondria and macrophages (43).

There is only one study of 25 patients that evaluated the effect of tocilizumab and an adjuvant iron chelator in severe COVID-19 pneumonia and whether the prescribed therapy would reduce mortality (44). Eleven patients received therapy with tocilizumab and the adjuvant iron chelator deferasirox and over 80% had a favorable outcome. The therapy proved to be a good option for patients with significant hyperferritinemia and severe COVID-19 disease. Two trials are currently underway to check the efficacy and safety of DFO compared to the standard of care or tocilizumab in patients with COVID-19 (NCT04333550, NCT04361032), the results of which are eagerly awaited (5).

Vlahakos et al have proposed possible therapeutic guidelines for iron chelator therapy (45) Several parameters indicative of patient deterioration would be monitored (e.g., oxygen demand ≥60%, ferritin levels ≥ 1000 ng/ml and CRP level > 10-fold above baseline, platelets < 100 000 × 109/L and lymphocyte counts < 1000 × 109/l) and their deterioration would indicate progressive severity of COVID-19 infection and predict the need for more aggressive critical treatment. It has been suggested that oral iron chelator therapy could be administered 10-14 days after the onset of severe COVID-19 infection. Iron chelators have been successfully used for half a century to treat diseases with excessive iron accumulation (45). It is possible that intravenous iron chelator therapy may provide sufficient and rapid lowering of plasma iron levels to relieve cytokine storm in patients with severe COVID-19 infection in ICU. In moderate cases, oral chelators can prevent the development of a severe inflammatory response. Scientists all over the world agree that treatment of patients with COVID-19 infection should begin as soon as possible and at the appropriate dose. However, it is essential to conduct adequately powered randomized trials before using iron chelators in patients with severe COVID-19 infection (45).

In addition to iron chelators, hepcidin antagonists could be used as a potential therapy to lower iron levels instead of iron chelators in the supportive care of COVID-19 in the future, since all infections trigger inflammation that increases hepcidin levels as the main regulator of iron, causing anemia. It is also known that ferritin formed during inflammation contains less iron than normal ferritin (39,46,47). In addition, cytokines are overexpressed during COVID-19, leading to an increase in hepcidin levels (17). DFO decreases the level of IL-6, an important inflammatory mediator that triggers a cytokine storm. In addition, there is evidence that the other pharmacological benefit of DFO is the downregulation of hepcidin (39). It has been observed that replication of coronaviruses in iron-deficient cells is suboptimal compared to iron-rich cells (2).

Some encouraging in vitro studies on the effects of the naturally occurring iron chelator lactoferrin on SARS-CoV and on SARS-CoV-2 viruses have shown that lactoferrin inhibits the initial phase of viral infection (40,42,48).

Iron chelator therapy and its beneficial effects on pneumonia and secondary fibrogenesis suggest that iron chelators should be taken into account to improve the long-term outcome and survival of patients with COVID-19, especially those with severe COVID-19 infection (5). Some of the known iron chelators, such as DFO, deferasirox, and deferiprone, as well as the natural iron chelator lactoferrin, may be efficient in the therapy of COVID-19 (4).

Conclusion

According to the literature, iron chelator therapy could have a number of beneficial effects in patients with COVID -19 infection, especially in severe forms of the disease, without causing harm in severe COVID-19 patients. Unfortunately, there are currently not enough adequate randomized prospective trials to confirm the benefits of iron chelator treatment, and the current evidence base is poor. Several

clinical trials need to be conducted first to prove the efficacy and safety of iron chelator use, and further research is needed in order to establish new therapeutic guidelines that may include iron chelators as supportive treatment for COVID -19 disease.

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