Reply: Iron chelation may harm patients with COVID-19

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Dear Editor

A strikingly high level of ferritin has been reported in patients with the novel coronavirus disease 2019 (COVID-19) [1]. One of the possible explanations of this observation is inflammation induced by COVID-19 infection which increases the hepcidin level, the main regulator of tissue iron store, as discussed by Garrick and Ghio [2]. Moreover, the novel coronavirus (SARS-CoV-2) spike protein has hepcidin-like action, which means that the virus can directly increase ferritin level regardless of the inflammatory effect [1]. I agree with Garrick and Ghio that the release of free iron secondary to interaction between SARS-CoV-2 and haemoglobin molecule as an explanation of high ferritin level in COVID-19 remains a theoretical possibility, and it has not been practically confirmed as yet. It is believed that ferritin protein generated by inflammation has less iron content than normal ferritin [3]. Therefore, a test measuring serum ferritin iron content could differentiate between high ferritin secondary to inflammation or other causes, such as an iron overload state [3]. Although this test is useful in understanding the pathophysiology of SARS-CoV-2 infection, in my opinion, it has a limited value to ascertain the safety and effectiveness of iron chelation in management of COVID-19, and this is because of two reasons. First of all, a high ferritin level, regardless of the cause, has been linked with poor prognosis in COVID-19 [4]. The level of ferritin in COVID-19 non-survivors is higher than that of the survivors by twofold [5]. Intracellular iron generates reactive oxygen species in the lung by interacting with oxygen molecules which could predispose to the development of adult respiratory distress syndrome (ARDS) [5]. In addition, intracellular iron and hyperferritinemia increase the risk of coagulopathy and

oxidative stress and induce endothelial inflammation which could predispose to disseminated coagulation and multi-organ failure [1, 5]. Secondly, iron chelation drugs are not only able to bind free iron but they can also remove iron from iron-containing proteins, which means that iron chelation can have an anti-ferritin effect [6]. In fact, deferoxamine increases degradation of ferritin by lysosomes [4]. Other iron chelators, such as deferasirox, bind cytosolic iron released from ferritin [4]. In addition, deferoxamine decreases the production of free radicals generated by intracellular iron, which limits the chance of development of ARDS and subsequent tissue fibrosis [4]. Garrick and Ghio suggested that hepcidin antagonist could be a potential future possible approach in supportive management of COVID-19. Interestingly, it is stated that one of the additional pharmacological effects of deferoxamine is downregulation of hepcidin [1].

Iron-containing enzymes are required for viral replication, including coronavirus [6]. It is noticed that coronavirus replication was suboptimal in iron-depleted cells compared with iron replete cells [6]. A cellular protein, called aconitase, plays a role in coronavirus replication [7]. High intracellular iron level increases expression and enzymatic activity of aconitase protein [7]. This effect was enhanced with co-treatment with vitamin C and blocked by co-treatment with deferoxamine [8]. These findings contradict what was stated by Garrick and Ghio that iron is not required for coronavirus replication.

Garrick and Ghio suggested that iron chelation treatment might exacerbate cytokine storm. However, some evidence stated the opposite. H-chain of ferritin activates macrophages to produce inflammatory cytokines [4]. On the other hand, deferoxamine decreases the levels of IL-6, which is the main inflammatory mediator which precipitates cytokine storm [4]. In conclusion, multiple evidence support the possible beneficial effect of the use of iron chelation as a supportive treatment in COVID-19, and it seems that there is not enough evidence to suggest that this approach is harmful. However, as with any other drugs, iron chelation drugs have to pass through a series of clinical studies to confirm their safety and effectiveness.

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Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

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