Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Clinical Nutrition ESPEN 40 (2020) 90–91

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Opinion Paper

Copper as a potential adjunct therapy for critically ill COVID-19 patients

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ARTICLE INFO

Article history:
Received 29 June 2020
Accepted 18 September 2020

Keywords:
COVID-19
Copper
Critically ill
Treatment

SUMMARY

COVID-19 is a major health problem affecting all people worldwide and has a high mortality rate especially in critically ill patients. Although much is known about its different clinical symptoms, there are significant knowledge gaps about its pathology and cellular responses to the virus. Copper plays an essential role in respiration, immune function and free-radical defense. Despite its important action in physiochemical properties, only small amount of copper is presented in biological fluid, none of which presents as free ion form that readily affirms its depletion in critically ill patients. Recent studies confirmed its anti-viral capacity. Closer understanding of copper signaling, its vulnerability, method of assessment and interpretation, administration rout and dosage opens up new perspectives regarding therapeutic copper administration against critically ill COVID-19 patients. So, it seems that physicians should consider copper insufficiency in their critically ill COVID-19 patients. However, an attention should be paid to copper toxicity and estimating the adverse responses depending on copper dose or severity of copper limitation, as well as the duration of copper misbalance.

COVID-19 is a major health problem affecting all people worldwide and has a high mortality rate especially in critically ill patients. Although much is known about its different clinical symptoms, there are significant knowledge gaps about its pathology and cellular responses to the virus [1]. A huge number of studies with different therapeutic interventions are being performed for COVID-19 management. But there is not any fundamental therapeutic intervention till now and currently the aim of treatments is decreasing viral load and spread with supportive care. Cardiopulmonary system involvement and COVID-19 associated respiratory distress syndrome are the leading causes of mortality from this disease. As currently there is not any vaccine or targeted drug, one of the most important available therapeutic options is enhancing immune system capacity against SARS-CoV-2.

Copper plays an essential role in respiration, immune function and free-radical defense. Despite its important action in physiochemical properties, only small amount of copper is presented in biological fluid, none of which presents as free ion form that readily affirms its depletion in critically ill patients [2]. Copper containing enzymes perform essential functions like O_2 transportation, metabolism and production of signaling molecules responsible in oxidative stress [3]. Copper is required for enzymes such as CuZn-superoxide dismutase which is the main part of defense against oxidative stress. Copper is required for normal immune response against infection and for oxidative phosphorylation, for collagen and elastin synthesis which are all essentials in ARDS pathogenesis [4]. Lee et al. assessed the serum concentration of trace elements and evaluated their clinical significance in 167 critically ill patients. They showed that lower levels of copper concentrations was seen at ICU admission and increased level of copper with its substitution during ICU stay was associated with a significantly lower mortality compared to lower concentration of copper (5.6 vs. 50.0%, $p = 0.013$) [5]. Copper deficiency symptoms include immune malfunction, mostly pronounced in older patients, and damage in host pathogen response. On the other hand the contact killing of viruses on metallic copper surfaces is explained in previous studies [6]. Copper supplementation has been shown to have an important role in regulation of IL_2 which is critical in T helper cell proliferation, the balance between Th_1 and Th_2 cells, and NK cell cytotoxicity which is also important in management of immune dysregulation in critically ill COVID-19 patients [7]. Copper antiviral characteristics

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https://doi.org/10.1016/j.clnesp.2020.09.022

include inactivation of single or double-stranded DNA or RNA viruses, destroying the viral genomes and block papain-like protease-2 which is crucial for SARS-CoV-1 replication [8]. It has been demonstrated that copper induces autophagy and apoptosis which is correlated with the formation of autophagic vacuoles maintaining the cell's anti-viral defense.

It has recently been shown that diffuse intravascular thrombosis is one of the major reasons found in postmortem analysis of critically ill COVID-19 patients. Lynch et al. in their study on rats showed that although the mechanism of the development of thrombotic lesions in Cu-deficient females during this study is unclear, results clearly demonstrate that hemostatic function is impaired in copper deficiency [9].

Copper toxicity is associated with severe multi-organ injury and gastrointestinal and urinary tract hemorrhage. Very little is known concerning the nature of copper induced coagulopathy; however, the mechanisms responsible for the compromised coagulation kinetics can be via oxidation of key fibrinogen disulfide bridges, copper induced glutathione dysfunction and increased plasminogen activator inhibitor type 1 [10]. As patients with inflammatory situations exhibit higher mean serum copper concentrations related to disease activity, the increase in copper levels can be related to the body's physiological reaction to fight inflammation. Moreover, the inflammation may be the result of insufficient hepatic copper repositories that cannot support an anti-inflammatory response. During infection, the intracellular levels of metals are mediated by tightly controlled acquisition and efflux systems. Loss of the copper exporter encoded by copA has shown to lead to decreased virulence in infection in different organs. Deletion of copA results in enhanced macrophage-mediated bacterial clearance, underscoring the importance of copper efflux in evading immune defenses [11]. These findings, linking copper with autophagy and vacuoles formation, support further studies of copper as a candidate for the treatment of viral infections.

Based on the mentioned sentences, therapeutic supplementation of copper and correction of its deficit may be beneficial for critically ill COVID-19 patients. This is also important in critically ill COVID-19 patients who receive zinc supplement as copper and zinc are competitively absorbed from the small intestine and high doses of zinc administration can result in copper deficiency in these patients. It seems that surge of copper is an essential response for counteracting the infection and balancing the immune dysfunction in human bodies. So, assessment of serum levels of copper may lead to misinterpretation of data leading to inappropriateness of copper supplementation. Intracellular copper assessment and its metalloproteinase is a critical step in monitoring the copper level and function. Previous studies showed that ceruloplasmin may have a role in iron trafficking across the enterocyte during inflammation, participating in host defence and balancing of ferritin levels [12]. In considering the high level of ferritin in severe COVID-19 cases copper role seems to be significant.

Finally, closer understanding of copper signaling, its vulnerability, method of assessment and interpretation, administration rout and dosage opens up new perspectives regarding therapeutic copper administration against critically ill COVID-19 patients. So, it seems that physicians should consider copper insufficiency in their critically ill COVID-19 patients. However, an attention should be paid to copper toxicity and estimating the adverse responses depending on copper dose or severity of copper limitation, as well as the duration of copper misbalance. However, repletion of a micronutrient during a critically ill patients does not mean clinical outcomes are improved. There have been numerous instances where a low level of something has been associated with a bad outcome, however, randomized controlled trials comparing efficacy of repletion against placebo have not shown benefit (e.g., vitamin D, vitamin C). Given above, it is important that physician walk away thinking copper is a magic bullet for COVID-19.

Funding

None.

Authors contribution

Sh.F: Study hypothesis, manuscript drafting.
S.M: Study hypothesis, manuscript editing.
A.M: Literature review, manuscript drafting, final edition.
All authors read and approved the final version of manuscript.

Declaration of competing interest

The authors declare no conflict of interest.

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