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Coronavirus: Role of zinc as an immune booster

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Abstract
The global pandemic coronavirus disease has created a chaotic situation all over the world. This is happened due to SARS-CoV-2 infection, which is spread through the human to human connection. Now different countries have discovered vaccines for coronavirus. At the same time our body needs its own immune system. For these reasons immune boosting substance are also required. This review paper indicates that zinc acts as an immune booster in our body against the coronavirus disease. In addition, it is also an immunomodulatory and immunosuppressive component. On other hand zinc has antioxidant properties, which can remove the free radicals from our body with increasing fluidity of the cell membrane. This may result, improve the lymphocyte's function. Depending on this information it is clear that zinc have the power of create resistance barrier against coronavirus infection.

Keywords: Antioxidant, coronavirus, free radicals, immunomodulator, immune boosting, immunosuppressive**,** SARS-CoV-2, zinc

Introduction

Coronavirus is the large group of single-stranded RNA virus which causes mostly respiratory and less frequently gastrointestinal diseases. In December 2019 the new coronavirus was identified in Wuhan China (Calder, 2021) [7]. The currently spread coronavirus is known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) progresses is rapidly there by urgently challenging the healthcare system worldwide (Mossink, 2020) [36]. The symptoms such as severe pneumonia, severe respiratory failure, common cold and acute respiratory distress syndrome (ARDS) etc. are observable in a patient affected by SARS-CoV-2 infection. This illness is called coronavirus disease discovered in 2019 or COVID-19 (Chinni *et al.*, 2021) [11].

The essential bio-metal zinc involved in various biological processes like proliferation, differentiation, cell cycle regulation protein and DNA-RNA synthesis and apoptosis (Chinni *et al.*, 2021) [11]. At its own functional role is to demonstrated for the immune system (Wessles *et al.*, 2017). Zinc is a component of nutritional immune booster (Haase and Rink, 2014). If zinc status alteration is happened significantly then immune response resulting in developed susceptibility to inflammatory and infectious diseases including malaria, measles, pneumonia, acquired immune deficiency syndrome (Gammoh and Rink, 2017) [15].

Various research studies have showing that zinc's have functional properties to inhibit the viral replication. This virus group include coronavirus (Hulist, 2004), respiratory syncytial virus infection (Suara *et al.*, 2004) [51], cytomegalovirus infection (Li *et al.*, 2005) etc. The zinc status of human is known as critical measure of immune response against viral infection (Read *et al.*, 2019). All human's immune response, which is protect our body from foreign pathogen that are affected by zinc. Natural killer cell activity, phagocytosis by macrophages and neutrophils and certain functions such as chemo-toxins and oxidative burst are impaired by the decreased level of zinc (Keen *et al.*, 1990) [26].

This is the acceptable discussion that is especially adult persons at risk of disturb zinc balance, which develops risk of COVID-19 (Mossink, 2020) [36]. In addition, nutritional, clinical and immunological study suggest that, the status of zinc may play a significant role in curing and controlling of COVID-19. To improving and antiviral immune response, zinc containing dietary preventive and nutritional intervention measure are mostly required.

Zinc and human immunity

Zinc is the most important essential trace elements for human. It involved in many physiological functions. The requirement of zinc of an adult is approximately 1 mg per day for adult men and 8 mg per day for adult women (Chasapis *et al.*, 2012) [10].

In human immune system, zinc affects multiple aspects (Shankar *et al*., 1998) [48]. Zinc is crucial for normal development and functioning of cell mediated innate immunity neutrophil and natural killer cells. Due to zinc deficiency macrophages are also affected.

Zinc are important elements for the maturation and functioning of self and also a factor for the thymus hormone thymulin (Calder *et al.,* 2011) [6]. This thymulin intrathymic and periferal immunoregulatory properties (Rink *et al.,* 2000; Bach *et al.,* 1998) [46]. Thymic atrophy is caused by the deficiency of zinc and it also effects on mature T cell. The evaluation of the high relative receptor for interleukin-2 are initiated by zinc (Kruse-jarres *et al.,* 1998; Dowd *et al.,* 1986) [28, 14]. B-cell produced antibody is also depend on zinc.

It was informed that zinc can stop the viral replication and reduce the excessive inflammatory reaction in human cell. Zinc reacts in the receptor ACE-2 (Angiotensin converting enzyme-2 receptor) of SARS-CoV-2 and block the integration with spike proteins of the virus (Suara *et al.,* 2004; Haase *et al.,* 2009) [51]. The clinical effects of zinc deficiency are a weaken defense against bacterial, fungal and viral infections.

Immunity and zinc

In intracellular environment of human cell zinc acts as protein and DNA synthesizer (Wu and Wu, 1987). This results immunoglobulin may produce. Various tress elements like zinc, selenium, copper reacts as an antioxidant (Prasad, 2014) [41]. The essential antioxidant zinc is crucial for the breakdown the harmful oxygen molecule in living cell (Bertolotto *et al.,* 2012) [5] by the antioxidant enzyme production (Machin *et al.,*1987). Various defensive activity of immune cell is reliant to the liquidity of the cell membrane. Due to various metabolism reactions, free radicals are produced. In example, when a fatty acid concentration is increased in the cell membrane, the membrane fat's peroxidation is occurred and free radicals' production also increases rapidly. Membrane liquidity decreases for increasing the fatty acids peroxidation. For these reasons immune response is damaged. This high free radical's concentration decreases the immune function of lymphocytes. Depend on this above discussion zinc as an antioxidant, have a active role in boost the immune responses in human beings (Bendich, 1990) [4].

Zinc as an antiviral immunity

The functional component zinc is involved in building innate immunity besides the acquired antiviral immunity (Maggini *et al.,* 2018) [32]. The previous study has shown that, accurate nutritional status is beneficial to create preventive way against viral infection (Calder *et al.,* 2020) [8]. Zinc is the antioxidant that increase the number of T cell, interleukin-2 (IL-2) production, natural killer cell (NK cell) activity, which enhance the response of lymphocytes to mitogen (Muscogiuri *et al.,* 2020) [37].

Zinc affects directly or by indirectly on the wide variety of viral species (Iddir *et al.,*2020) [23], specifically RNA virus such as respiratory syncytial virus, rhinovirus and SARS-CoV-2 (Adams *et al.,* 2020) [1]. These responses are achieved by various mechanisms include controlling virus entry, fusion, propagation and production of viral protein (Read *et al.,* 2019; Ishida *et al.,* 2020) [24]. Moreover, zinc probably prevents and protects cellular membrane by the blocking of virus entry into the cell (Kumar *et al.,* 2020; Hoang *et al.,* 2020) [29, 19]. Zinc has made its effective role in antiviral immunity through the control of tight junction protein, rendering in the mucosal membrane integrity conservation (Read *et al.,* 2019; Mossink *et al.,* 2020) [36].

Due to antiviral effects of zinc, inhibit the replication pathway of the virus (Hoang *et al.,* 2020; Razzaque, 2020) [19] through alteration of proteolytic treatment of RNA dependent RNA polymerase (RdRp) and polyprotein processing (Mayor-Ibarguren *et al.,* 2020; Carlucci *et al.,* 2020) [9]. Replication of SARS coronavirus are inhibited by using a mixture of Zn^{2+} ions and pyrithione at low concentration (2 μM Zn^{2+} and 2 μM pyrithione) in cell culture. In coronavirus Zn^{2+} ions have functional role for inhibiting both the proteolytic processing of replicase polyproteins and the RNA dependent RNA polymerase (RdRp) activity (Arnold *et al.,*1999) [2].

Preventive activity of zinc ionophores against coronavirus

The elements Zn have immunomodulatory effects as well as direct antiviral effects which are considered as the potential treatment in therapy of COVID-19 infection. Zn^{2+} ions and zinc ionophores are able to work in blocking the SARS coronavirus RNA polymerase activity by decrement its replication (Te *et al.,* 2010).

Two zinc ionophores is hinokitiol and pyrithione which engaged in the transfusion of zinc into the cytosol from extracellular region. They are increase zinc concentration in intracellular place. Hence, viral polyprotein will effectively weaken the replication of RNA virus for disturbance of proteolytic processing (Krenn *et al.,* 2009) [27]. The new study demonstrates that chloroquine is a zinc ionophore that increases the flow of zinc into the cell (Xue *et al.,* 2014) [55]. Hydroxychloroquine (HCQ) is one of the Zn ionophore which is preventive and therapeutic measure for covid-19 treatment.

Chloroquine and hydroxychloroquine trend to store in the lower pH environment like as swollen tissues and lysosomes (Pal *et al.,* 2020; Sehrezenmeirer *et al.,* 2020). They are increase pH of lysosomes and reduce the viral load through glycosylation of cellular receptor of SARS-CoV-2 (Pahan *et al.,* 2020; Maity *et al.,* 2020) [38]. SARS-CoV-2 infected patient highly risk of occurring thrombosis (Helms *et al.,* 2020) [18]. Chloroquine and hydroxychloroquine can abate the procoagulant state by obstacle of antiphospholipid antibody binding for resistance of platelet quantity (Jancinova *et al.,* 1994) [25]. In this way chloroquine and hydroxychloroquine combined zinc therapy may be more effective in COVID-19 treatment (Derwand *et al.,* 2020; Rahamaan *et al.,* 2020) [13].

Immunomodulatory activity of zinc

Coronavirus disease mainly affects respiratory system, this causes pneumonia and acute respiratory distress syndrome are occurred (Skalny *et al.,* 2020) [49]. In coronavirus disease patient, zinc plays an effective role as an immunomodulator. As an immune modulator function, zinc regulates proliferation, differentiation, maturation and function of leukocytes and lymphocytes (Hojyo *et al.,* 2016) [20].

Coronavirus infection imbalanced the immune response due to hyper information of lungs, and increase production of cytokines which are worked as promoting information. During inflammatory condition, zinc is distributed from the serum to tissue that's results serum hypozinconia occurred (Wessles *et al.,* 2017). Zinc deficiency decrease the immune response and disrupt innate immunity system. This causes the activity of impaired monocyte cytokines production, natural killer cell's function, chemotaxis and neutrophilic granulocytes oxidative explosion are reduced (Kumar *et al.,* 2020; Ibs *et al.,* 2003) [29].

Zinc deficiency can initiate thymus atrophy, including changes of thymic hormones production, decreases concentration of lymphocytes and activation of B-cell and secretion of antibody that develops infection severity and duration. Maximum immunogens are depending on T-cells and hence, due to zinc insufficiency antigen production is decreases drastically, and our body losses their responses in antibody production (Parry *et al.,*1997).

Zinc is the critical measure of COVID-19 treatment

- **Enhancing cell-mediated and adaptive immunity**

Zinc plays an effective role in cell mediated immunity against any pathogens like bacteria and virus. Zinc is the main regulator for controlling the function of proliferation of neutrophils, macrophages, natural killer cells, T and B lymphocytes and cytokines production by the immune cell. Intracellular Zn^{2+} is crucial for removal and killing of the pathogen from infection site by the neutrophil (Hasan *et al.*, 2006) [17].

- **Effects of chloroquine and zinc to reduce viral infection**

Chloroquine increases vascular p^H when stocked in acetous organelles, i.e.- lysosomes. These pH increasement break the acidification in lysosome conduct the deterioration of autophagosome fusion and autophagic degradation (Solomon *et al.*, 2009; Mizushima *et al.*, 2010) [50, 35].

- **Zinc can directly counteract SARS-CoV-2 replication**

Zn^{2+} plus directly resist the RdRp activity. Especially Zn^{2+} was found for interrupt the SARS-CoV-2 RdRp elongation and template binding (Te *et al.*, 2010).

- **Enhancing efficiency of antiviral drugs**

Some of antiviral medicine such as ribavirin, lopinavir, and antibiotics such as Azithromycin and doxycycline has been prescribed for the therapy of COVID-19. Zinc supplementation can favour COVID-19 treatment using of these antiviral medicine (Rahaman *et al.*, 2018).

Conclusion

Various epidemiological research data and the recent observational study reported that zinc is the essential amino boosting component of coronavirus disease. Zinc has an antioxidant, anti-inflammatory, immunosuppressive, immunomodulatory function. It improves innate immunity besides the acquired antiviral immunity. As an antioxidant property, zinc plays an important role in increasing the number of T- cells, interleukin-2 production, natural killer cell activity. This may result immunity against viral pathogenesis in the host cell being prevented. Recent studies have shown that zinc improves the protein synthesis in the cell and produces an antioxidant enzyme which is the main ingredient for the removal of free radicals from the cell and increases the activity of the lymphocytes against SARS-CoV-2. The replication of SARS-CoV-2 is diminished by the action of Zn2+ and zinc ionophores. Chloroquine and hydroxychloroquine are the type of zinc ionophores that enhance the flow of zinc into the lysosomal cell and by the increasement of the pH level, lysosomes decrease the viral load of SARS-CoV-2. Because of zinc deficiency, thymic hormone production, lymphocytes concentration, activation of B and T-cell are diminished. From this review study, we are known that zinc supplementation is most important and crucial for COVID-19 infection. The appropriate amount of zinc in a daily diet is considered to be suitable care for coronavirus disease patients.

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