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EFFECT OF VITAMIN D, ZINC AND COPPER SUPPLEMENTS TO ENHANCE TREATMENT OF COVID-19 PATIENTS

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ABSTRACT

The 2019 Coronavirus diseased caused by the severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) is one of the greatest global health challenges of recent times. To date, no known vaccine has been approved for its prevention and therapeutic interventions involve supportive care. Current preventive measures involve physical distancing, the use of face mask, regular hand washing, or the use of alcohol-based sanitizers. Several previous studies have reported potential antiviral properties of Vitamin D, Zinc, and Copper. Supplementation of these immunomodulators has the potentials to enhance the innate and adaptive immune response in immunocompromised and critically ill patients by the restoration of the depleted immune cell functioning or improvement in normal immune cell functions. Vitamin D administration protected against acute lung injury. Zinc is effective against hepatitis C viral replication and exposure to copper resulted in the loss of coronavirus 229E viral genome. In this review, we present evidence for the potential benefits of Vitamin D, Zinc, and Copper supplementation which may assist critically ill COVID-19 patients.

KEYWORDS: Coronavirus, COVID-19, Innate Immunity, Adaptive Immunity, Supplements

The novel Coronavirus disease 2019 code-named (COVID-19) caused by the SARS-CoV-2 virus originated from Wuhan province in China and became a global health pandemic affecting the lives and livelihood of all earth's human inhabitant. In the light of the economic and global health challenge posed by the virus, any initiative geared at improving the health condition of hospitalized patients to increase recovery rate and reduce the death rate would be taken as being medically and economically important (Ebadi and Montano-Loza, 2020).

Critical ill COVID-19 patients suffer from severe immune suppression which involves virus-mediated damage and a host autoimmune response resulting in acute respiratory distress syndrome (Patel *et al.*, 2019), acute lung injury, and multiple organ failure (Shi *et al.*, 2020). In patients infected with the SARS-CoV-2 virus, this virus enters the host's cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptors situated at the respiratory tract (Hoffmann *et al.*, 2020). To nip the virus in the bud will require a strong protective immune response. When this fails to happen, the disease then progresses resulting in the activated macrophages induced release of interleukin (IL)-1B and IL-18 and type 1 T helper (Th1) immune cells leading to lung inflammation and fibrosis (Conti *et al.*, 2020).

Mammals have evolved a complex immune network through which it integrates and coordinates the adaptive and innate immune responses to the threat of pathogens. The innate immune system is the first line of defense and consist of physical barriers such as the skin acting as a shield to prevent the entry of pathogen. The innate immune system also consists of antimicrobial peptides, macrophages, neutrophils, natural killer cells, and phagocytes that move swiftly to destroy invading pathogens through the initiation of inflammatory response cascade (Murphy and Weaver, 2016). The adaptive response, however, consists of antigen-specific cells such as the T lymphocytes which kill the infected cells and B lymphocytes which functions to secrete specific antibodies to target the infecting pathogen. Although slower than the innate immune system, the adaptive system functions to retain the history of attacks by a specific pathogen ensuring that a fast antigen is generated to target such a pathogen (Murphy and Weaver, 2016).

Since no known scientifically proven drugs exist for the cure of this virus, currently available preventive measures against COVID-19 involves the use of face mask, physical distancing, hand washing with soap, or the use of an alcohol-based hand sanitizer. However, a healthy immune system proves to be an important weapon to combat this virus. Several vitamins and trace elements exist which have been proven to be important for normal immune function (Wintergerst *et al.*, 2007). These micronutrients play an important role in counteracting the damaging potential of oxidative agents to the cells (Evans and Halliwell, 2001). For example, while supplementation with vitamin D increases humoral immunity in children after influenza vaccination (Patel *et al.*, 2019), supplementation with a high dose of zinc on the other hand enhances immunity in patients with torquetenovirus (TTV) (Iovino *et al.*, 2018). However, a deficiency of these micronutrients leads to immune suppression and increases an individual's susceptibility of an invading pathogen creating a continuous cycle of

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deficiency and disease susceptibility (Maggini *et al.*, 2007).

Given the current global pandemic arising from the spread of COVID-19, with no available vaccine for the prevention of this disease, we present arguments for vitamin D, Zinc and copper supplementation as immunity enhancers to attenuate the pro-inflammatory and immune compromised state rising from SARS-CoV-2 infection in critical and non-critical ill patients.

Potential Role of Vitamin D Supplementation Against Sars-Cov-2

Vitamin D is a steroid human produced in the skin through a series of reactions catalyzed by the ultraviolet radiation from the sun. In the liver, vitamin D3 or the oral vitamin D counterpart is converted to 25-hydroxyvitamin D, 25(OH)D and finally converted in the kidney into 1,25(OH)2D (calcitriol), the main hormonal metabolite (Pike and Christakos, 2017). Vitamin D possesses a broad spectrum of anti-inflammatory, antioxidant, antifibrotic, and immunomodulatory actions (Hughes and Norton, 2009). Its immunomodulatory action on the innate and adaptive immune systems occurs via its receptor, the Vitamin D Receptor (VDR) and an enzyme, CYP27B1, expressed in respiratory epithelial cells and immune cells such as B cell, T cell, macrophages, and monocytes and responsible for its conversion into its active metabolite form, calcitriol (Pfeffer and Hawrylowicz, 2012) (Tay *et al.*, 2020).

Vitamin D protective effect against acute lung injury involves the modulation of the expression angiotensin-converting enzyme 2 (ACE2) receptors situated at the respiratory tract in lung tissue (Xu *et al.*, 2017). Vitamin D functions to maintain tight junctions, preventing the entry of unwanted substances. It decreases the release of pro-inflammatory cytokines (responsible for inducing inflammation-related pneumonia) through the induction of T regulatory cells and enhances the innate immune system through the induction of antimicrobial peptides such as defensins and cathelicidins which can decrease the replication of the virus (Aranow, 2011) (Grant *et al.*, 2020) (Jeffery *et al.*, 2009).

According to epidemiological studies, vitamin D deficiency is linked to viruses induced-respiratory tract infections and acute lung injury (Hansdottir and Monick, 2011). Several lines of evidence point to the importance of vitamin D at reducing the risk of contracting COVID-19, including the fact that the first outbreak of the virus happened in winter when vitamin D concentration is low, and that vitamin D deficiency is implicated in acute respiratory distress syndrome and other evidence revealed that towards the end of summer, the number of COVID-19 cases in the Southern Hemisphere was rather low (Grant *et al.*, 2020).

According to the Endocrine Society, a daily vitamin D supplementation of 1000–4000 IU and a serum 25(OH)D concentration of 30 ng/mL or more is recommended for hospitalized patients (Holick *et al.*, 2011). Besides, according to the U.S. Institute of Medicine, no adverse effects were reported for a daily vitamin D supplementation of <10,000 IU (Ross *et al.*, 2011). Furthermore, for the critically ill patient on ventilators in the intensive care unit, previous clinical trials revealed that a vitamin D dose of 250,000–500,000 IU to be safe for these patients and this supplementation was associated with improved blood oxygen-carrying capacity and elevated hemoglobin levels in addition to a decrease in hospitalization duration of the patients (Han *et al.*, 2016) (Smith *et al.*, 2018).

Potential Role of Zinc Supplementation Against Sars-Cov-2

Zinc is the second most abundant trace element in the body coming immediately after iron. As a result of its binding capacity with proteins to form metalloproteins, only a little fraction exists in the free form. The main source of zinc in the body is usually from a diet rich in red meat, fish, eggs, and other dairy products. Due to its limited storage in the body, to achieve and maintain balance, zinc as to be constantly supplemented (Cummings and Kovacic, 2009). It is an essential micronutrient needed to combat an invading virus (Read *et al.*, 2019).

The role of zinc in immunity and the viral response has been previously noted. For example, it has been shown that zinc oxide and zinc salt inhibited the replication of the hepatitis C virus, the H1N1 influenza virus, and other nidovirus groups of viruses such as SARS-coronavirus (Razzaque, 2020). It also blocks the replication of the hepatitis E virus (Kaushik *et al.*, 2017). It is noteworthy that SARS-CoV-2 responsible for COVID-19 belongs to the nidoviruses group and its RNA-dependent- RNA-polymerase and 3CLpro protease share more than 95% of sequence similarity SARS-CoV (Lu *et al.*, 2020). Because of this, it is thus safe to hypothesize that the anti-viral effect of zinc seen in other nidoviruses could be replicated with the SARS-CoV-2.

Although the anti-viral mechanism of zinc is not fully understood, it is thought to achieve this through the production of antiviral interferon, preventing the binding of the virus to the mucosa, suppression of inflammatory response and inhibition of key enzymes such as RNA-dependent- RNA-polymerase (RdRp) needed for viral replication (Razzaque, 2020). The deficiency of zinc has been observed in several viral infections including common cold, hepatitis C virus, herpes simplex virus, and the human immunodeficiency virus (HIV) (Read *et al.*, 2019), implying that the deficiency of zinc leads to impaired immunity against viral infections. In severe COVID-19 patients with underlying medical conditions such as hypertension and cardiovascular disease, zinc deficiency becomes a medical concern since these patients are treated with diuretics like

hydrochlorothiazide, angiotensin 2 receptor antagonists and angiotensin-converting-enzyme inhibitors which can lead to the excessive passage of zinc in the urine and ultimately leading to zinc deficiency (Braun and Rosenfeldt, 2013).

Zinc supplements and zinc lozenges are two known remedies employed against colds and respiratory illnesses. Previous reports showed that zinc lozenges are effective against upper respiratory infections in children and may also be effective at reducing the duration of cold for 24 hours (Johnstone *et al.*, 2012). As a supplement, zinc could be prescribed in the different forms of zinc salt such as zinc-sulfate, zinc-gluconate, and other forms of zinc salt with great consideration for the composition of elemental zinc in these salts. The daily recommended allowance of zinc for a healthy adult is between 15–30 mg of elemental Zn (Saper and Rash, 2009). Since this daily allowance of zinc differs amongst individuals concerning the health status, age, weight, and sex, great care should be taken to ensure that the right dose is administered. This is because the administration of a high dose of zinc for a long duration could lead to anemia, a decrease in the blood levels of high-density lipoprotein cholesterol, and a deficiency of copper (Saper and Rash, 2009).

Zinc supplementation must, therefore, be assessed on a case by case basis taking into concern low dietary intake, zinc deficiency, and other related diseases. A previous study found daily intake of 20-40 mg to be safe and efficacious (Gammoh and Rink, 2017). Another study reported than a daily intake of zinc at a dose of 30–50 mg might be useful in mitigating against RNA viruses like influenza and coronaviruses (McCarty and DiNicolantonio, 2020). Furthermore, the US Food and Nutrition Board recommended daily intake of zinc of 11 mg and 8mg for adult males and females respectively (Gammoh and Rink, 2017). It thus shows that the recommended daily intake of zinc differs from study to study and also in different countries. Health authorities need to determine the daily allowance of zinc in their country and make an appropriate recommendation.

Potential Role of Copper Supplementation Against Sars-Cov-2

Copper is an essential trace element found in nuts, cereals, and fruits (Bost *et al.*, 2016). It is a dietary mineral essential for the maintenance of the structure of DNA (Uriu-Adams and Keen, 2005). Its absorption takes place in the small intestine and it is readily available in circulation. Copper is important for the proper functioning and maintenance of the immune system. It plays a role in the functioning of neutrophils, T helpers, natural killer cells, macrophages, and B cells which are involved in cell-mediated immunity, killing of infectious microorganisms, and generation of specific antibodies (Percival, 1998). A considerable high amount of copper is present in the eggs and eggshells of domestic birds such as the pigeon and quail. For example, the quail egg has about 4.67 ± 1.08 μg/g and the eggshell of pigeon has (4 ± 0.29 μg/g) of copper respectively and this may be effective in fighting viral infections (Nisianakis *et al.*, 2009). A high copper concentration appears to be harmful to invading pathogens and is one strategy used by macrophages as a defense system (Besold *et al.*, 2016), and this could be important in taming secondary infections after primary viral infection.

Copper deficiency has been reported to be linked to dysfunctional immune response and increased infection rate (Bonham *et al.*, 2002) and it is also related to the deficiency in white blood cells and abnormal connective tissues (Percival, 1998). Mechanistically, copper deficiency arises due to sustained TNF-α-induced inflammation of the lungs in mice which could be attenuated following copper supplementation (Liu *et al.*, 2016). Copper is effective at neutralizing viral infections arising from single- or double-stranded DNA and RNA viruses, poliovirus, bronchitis virus, and human immunodeficiency virus type 1(HIV-1) virus (Sagripanti *et al.*, 1993). Upon exposure to copper, the human coronavirus 229E lost its viral genome, shape, and undergoes destructions in its envelope including its surface spikes dispersion (Warnes *et al.*, 2015). Cu is also effective at inhibiting the replication of influenza A virus through the damage to the negative-sense of its RNA genome (Noyce *et al.*, 2007).

Although there is no recommended dose for the intake of copper against COVID-19, a previous study revealed that a daily intake of 7.8mg of copper reduces oxidative stress and improves immune response in a cross-sectional study of the British population (Pearson *et al.*, 2005).

CONCLUSION

The current global COVID-19 pandemic has ravaged global health and economy with no approved vaccines for its prevention. The effect of individual immunity as a protective shield against the contraction of the virus cannot be overemphasized. For immunosuppressed patients and the elderly, food supplements and micronutrients with proven antiviral property could be helpful as immunity enhancers against COVID-19. It is therefore important to determine the serum concentration of these micronutrients and vitamin before supplementation. Health authorities should follow the recommended daily allowance of these nutrients which are applicable in their territories since these daily allowances vary from country to country.

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