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PREVENTIVE ROLE OF MICRONUTRIENTS (VITAMIN D, ZINK AND SELENIUM) AGAINST COVID-19 INFECTION

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ABSTRACT

The novel coronavirus SARS-CoV-2 (Severe Acute Respiratory Syndrome-coronavirus-2), causing COVID-19 disease, is the most dangerous coronavirus ever identified, capable of infecting animals as well as humans across the globe. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects pulmonary epithelial cells. In severe cases, COVID-19 is accompanied by excessive activation of the innate immune system with progressive inflammation and a cytokine storm from activated cells, particularly in the airways, leading to the acute respiratory distress syndrome (ARDS). WHO has declared COVID-19 as a global pandemic. Though very little information about the potential protective factors of this infection are known. There is an urgent need for public health measures, not only to limit the spread of the virus, but also to implement preventive approaches to control severe COVID-19, e.g., by reduction of the excessive inflammation. Aged people are very much prone to severe respiratory infection than young people, probably due to the relation between old age and deficient nutrition and immunity. Clinical and subclinical micronutrient deficiencies common in older adults are known to contribute to decreased immune function and age-related diseases, implying that nutritional management is essential to reduce the risk of severe infection. There are lack of clinical data on preventive and/or therapeutic role of micronutrients like vitamin D, zinc and selenium in COVID-19 disease. In this review, recent clinical data on the role of these micronutrients in the protection against COVID-19 has been discussed.

KEYWORDS: Micronutrients, Vitamin D, Zink, Selenium, Covid 19 infection, Nutritional supplements.

INTRODUCTION

The outbreak and fast spreading of SARS-CoV-2 are a global health threat with an unstable outcome worldwide. The severity of the COVID-19 pandemic has dramatically surpassed the prevalence of acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), which were distributed to more limited regions in 2003 and 2012, respectively. The genomic structure of SARS-CoV-2 is comprised of a single-stranded RNA.[1] Severe COVID-19 infection is accompanied by excessive activation of the innate immune system with progressive inflammation and a cytokine storm from activated cells, particularly in the airways[2], leading to the cytokine release syndrome.[3] Unfortunately, in spite of their anti-inflammatory effects, corticosteroids have been observed to worsen the clinical status of patients with SARS or related virus infections.[4] Use of convalescent plasma has been tried as a possible approach, but the experiences with this strategy are limited.[5] Therefore, it is an urgent need for public health measures, not only to limit the spread of the virus, but also to implement preventive approaches to alleviate severe COVID-19, e.g., by reduction of the excessive inflammation. In case of severe COVID-19 patients, coexisting diseases include type 2 diabetes, hypertension, and heart disease. The elderly are more prone to severe respiratory infection than young people, apparently due to connections between old age and deficient nutrition and immunity. Clinical and subclinical micronutrient deficiencies common in older adults are known to contribute to decreased immune function and age-related diseases[6], implying that nutritional management is essential to reduce the risk of severe infection.[7] There are lack of clinical data on preventive and/or therapeutic role of micronutrients like vitamin D, zinc and selenium in COVID-19 disease. In this review, recent clinical data on the role of these micronutrients in the protection against COVID-19 has been discussed.

Preventive role of micronutrients like Vitamin D, zink and selenium against Covid-19 infection

Micronutrient deficiencies like deficiencies of vitamin D, zinc and selenium, which frequently occur in old age groups, contribute to age-related diseases including diabetes, hypertension, and coronary heart disease. These diseases, which in a substantial fraction of the cases are related to the metabolic syndrome, are characterized by

signs of low-grade inflammation, which may also result from ageing. Signs of inflammation like elevated values for CRP (C-reactive protein), represent a common aggravating factor in COVID-19. Adequacy of vitamin D, zinc and selenium, is essential for adequate immunocompetence, which to some extent may counteract an inflammatory aggravation. Dietary advice alone may not be sufficient to secure adequacy for these micronutrients in certain conditions, including in elderly subjects[8], involving the need for supplements in susceptible segments of populations.

Role of Vitamin D

Vitamin D is a steroid hormone, produced endogenously with the effect of ultraviolet radiation on the skin or available from exogenous food sources or dietary supplements. Vitamin D deficiency is a major public health problem affecting over a billion people across all life stages worldwide.[9] In the past decade, several studies demonstrated a potential link between vitamin D deficiency and various diseases, including systemic infection.[10] Vitamin D insufficiency affects the immune functions as vitamin D exerts an immunomodulation role[11], increasing innate immunity by secretion of antiviral peptides[12], which improves mucosal defenses.

Some recent reviews demonstrated some pathways by which vitamin D decreases the risk of microbial infections.[13] Vitamin D acts via different mechanisms in reducing the risk of viral infection and mortality. For reducing the risk of common cold, vitamin D uses three pathways: physical barrier, cellular natural immunity, and adaptive immunity. A recent review also supported the possible role of vitamin D in decreasing the risk of COVID-19 infections and mortality.[14] These comprise maintaining of cell junctions, and gap junctions, increasing cellular immunity by decreasing the cytokine storm with influence on interferon γ and tumor necrosis factor α and regulating acquired immunity by inhibiting T helper cell type 1 responses and stimulating of T cells induction . Vitamin D supplementation was also found to enhance CD4+ T cell count in HIV infection.[15]

Low levels of serum vitamin D were observed in acute respiratory tract infections including epidemic influenza. Some recent reviews hypothesized that vitamin D insufficiency may compromise respiratory immune function, increasing the risk of COVID-19 severity and mortality. There are some studies that determined the correlation of vitamin D levels with COVID-19 disease severity and mortality. Some clinical and epidemiological studies support to outline the hypothesis regarding COVID-19 and its relationship with vitamin D status. Some recent studies have indicated that COVID-19 is associated with the increased generation of pro-inflammatory cytokines, C-reactive protein (CRP), ARDS, pneumonia, and heart failure. There is a small cohort study demonstrated the protective effects of combined vitamin D, Mg and vitamin B12 against clinical deterioration of COVID-19[16].A recent review also suggested magnesium supplementation with vitamin D supplements as magnesium helps in regulating phosphate and calcium homeostasis. The enzymes involved in vitamin D metabolism seem to need magnesium which plays an important role as a cofactor in enzymatic reactions especially in the kidney and liver.[17]

Role of Zinc

Being an essential component of numerous enzymes, such as superoxide dismutase 1 and 3 , the trace metal zinc is important for the development and maintenance of immune and other cells.[18] Zinc deficiency is known to result in dysfunctional humoral and cell-mediated immunity.[19] In some aged person, low Zn status (serum Zn values <0.7 mg/L) has been found to represent a risk factor for pneumonia.[20] Long-term zinc deficiency is known to increase inflammations and inflammatory biomarkers.[21] Most facets of the immune system are affected by zinc deficiency, particularly the T-cell function. Zinc deficiency also drives a Th17 response, which is associated with increased inflammation. In elderly subjects, reduced concentrations of circulating zinc correlated with increased levels of the cytokines IL-6 (interleukine-6), IL-8, and TNF-α (Tumour necrosis factor-α).

Zinc also plays a role in acute respiratory infections.[22] A positive effect of zinc supplementation was observed in several studies on hepatitis C, which is induced by infection with a single-stranded RNA virus.[23] In this context, it is of interest that raising the intracellular concentration of zinc with zinc-ionophores like pyrithione or chloroquin could directly reduce the replication of a variety of RNA viruses in cells in vitro through inhibition of their RNA polymerase activity.[24] Combined administration of zinc and pyrithione, even at low concentrations, inhibited the replication of SARS coronavirus (SARS-CoV) in vitro. Consequently, zinc supplement may have effects, not only on the COVID-19-associated over-active inflammation, but presumably also on the SARS-CoV-2 agent itself.[25]

Role of Selenium

Selenium is an essential trace element for mammalian redox biology by occurring as selenocysteine in catalytical centers of many selenoproteins. An adequate supply of the amino acid serine is required for the synthesis of selenocysteine, which is incorporated into selenoproteins. Nutritional deficiencies of selenium may impact, not only the immune response, but also the pathogenicity of a virus.[26]

Of particular interest is the finding that a main protease of SARS-CoV-2 responsible for the viral replication, interacts with the essential seleno-enzyme glutathione peroxidase1 (GPX1)[27], which is strongly dependent on adequate selenium supply. It is notable that the GPX mimic ebselen (a synthetic selenium compound) is a potent inhibitor of the SARS-CoV-2 main protease.[28]

Dietary selenium deficiency, together with increased oxidative stress in the host, can alter a viral genome from a normally mildly pathogenic virus into a highly virulent agent after its entrance into the host, which occurred with the Coxsackie 3B virus in Keshan disease in a selenium-deficient area in China.[29] It was proposed that Se deficiency could play a substantial role in the genesis of SARS-CoV. The potential protective effect of selenium is explained by its role as an essential cofactor in a group of enzymes that, in concert with vitamin E, works to reduce the formation of reactive oxygen species (ROS). ROS in excess may trigger oxidative changes both in invading microorganisms and in the cells in the host.

Other selenoproteins, i.a., selenoprotein K (SELENOK) and selenoprotein S (SELENOS), also appear to play a role in the regulation of immune responses.

In a variety of infectious diseases selenium appears to play a significant role in protecting the respiratory system, in particular toward viral infections.[30] In older adult humans, Se treatment was shown to modulate response to the influenza vaccination, being accompanied by increased IFN-γ levels after vaccination.[31] Therefore, selenium supplementation to populations with suboptimal status has been considered a safe adjuvant therapy in preventive measures against viral infections.[32] The selenium status varies widely between different areas in the world. Compared with levels in Northern America[33], selenium levels in populations in large parts of Europe are well below a threshold of about 100 µg/L required for adequate expression of selenoproteins. The insufficient selenium intake is caused by low selenium content in soil and, consequently, in cereals and other food plants, as well as in fodder for grazing farm animals.[34]

CONCLUSION

Immune dysregulation is a key feature of severe COVID-19 disease. Therefore, the restoration of immune balance to prevent the hyper-inflammatory cytokine storm is a reasonable strategy to combat disease severity in COVID-19. The elderly are more prone to severe respiratory infection than young people, apparently due to connections between old age and deficient nutrition and immunity. Clinical and subclinical micronutrient deficiencies common in older adults are known to contribute to decreased immune function and age-related diseases, implying that nutritional management is essential to reduce the risk of severe infection. The micronutrients vitamin D, zinc and selenium, might be involved in the prevention of the COVID-19 disease. Based on experiences from treatments of SARS and other viral infections, it can be concluded that nutritive supplements of the micronutrients vitamin D, zinc and selenium administered at an early stage of the infection were important for enhancing host resistance against RNA viral infections, which might also include severe COVID-19.

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