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Research Article

The Potential Role of Arginine/Glutamine/Zinc/Copper as a Supplemental Immuno-Enhancing Nutrients In Suspected/Infected Sars-Cov-2 Patients

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Abstract: When considering different treatment modalities for the recent COVID-19 outbreak we need to think of inclusive and well-rounded strategies that tackle more than one aspect of the infection. As COVID-19 has become the recent major concern all over the world; as this virus was able to paralyze most of the human beings' activities, took away many lives and left governments and people helpless, an urgent solution to eradicate and control the spread of this disease is needed. Specific nutrients with immunological and pharmacological effects, when consumed in amounts above the daily requirement, are referred to as immune-enhancing nutrients. In this review, we'll go over the possible advantages of supplementing patients with immune-enhancing micronutrients like arginine, glutamine, zinc, copper, and vitamin C. Such nutrients could foster an enhanced immune response by modulating both innate and adaptive mechanisms. Deficiency states are common and further compromise the ability of the body to rid itself of an infectious challenge.

Keywords: Arginine; Ascorbic acid; Copper; COVID-19; Glutamine; Immuno-Nutrients; Zinc.

INTRODUCTION

The outbreak COVID-19 that has spread all over the world with 924,668 cases and 46,368 deaths as of 1 April 2020. The clinical presentation varies from asymptomatic or mild respiratory symptoms to critical ARDS. Worst outcomes are seen in patients of older age having comorbidities such as cardiovascular, diabetes mellitus, cerebrovascular, and kidney diseases. The reports says that most patients needed intensive care units (ICU) are in the age group 63-66 years, while age group 46-51 years did not require ICU admission (Singhal, T. 2020). The search for treatment regimens has taken the world by storm. While there has been a great attempt at finding a definitive treatment, much of the care provided to patients is supportive (Yi, Y. *et al.*, 2020). Up to date, there is no effective antiviral therapy available for COVID-19. Yet there is another aspect, that hasn't been formally regarded as a modifiable tool in the fight against COVID-19 which is: the inherent strength of a patient's immune system (Goh, K. J. *et al.*, 2020).

The immune system responds to invading foreign bodies in an innate (fast, non-antigen specific) and adaptive (slow, antigen specific) manner. The innate immune system is comprised of physical barriers, complement system, and a variety of phagocytic. The adaptive response includes antigen-specific cells, e.g. T lymphocytes and B lymphocytes, which can be activated to secrete antibodies specific to the infecting pathogen. While slower to respond than the innate system, the adaptive system is responsible for generating immunological "memory", where a repeated infection with the same pathogen will generate a vigorous, fast antigen-specific response. The state of one's immune system is greatly affected by many confounding factors like concomitant disease, nutritional status, and age (Murphy, K. *et al.*, 2008).

Generally, high percentage of hospitalized patients is malnourished and this affects the immunity negatively. So, it is rational to suggest immunonutrition in clinical practice. Immunonutrition is the specific nutrients and micronutrients in amounts higher than the amounts taken in diet which have modulatory effect on immune system activities, and the effects on the patient immunity activation. Glutamine, arginine, anti-oxidants, ω-3 poly unsaturated fatty acids (ω3-PUFAs) and nucleotides are considered as immunonutrients.[5] To understand the role of immunonutrition, first we need to

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review the immune response. Once invading organism enters the body, it starts powerful biological processes, the main three of them are first creation of hostile environment for the pathogen. Second, supply immune system with nutrients from endogenous sources. Third, immune response may damage the healthy tissues so body strengthens the protective and control systems. When the primary goal has been achieved, competing the pathogen, inhibitory systems start working to terminate the response. So nutritional factor is important in the pathway (Grimble, R.F. 2001). Hyper-inflammatory status is seen in many patients with COVID-19, and cytokine storm thus complicating the infection and increasing the risk of mortality (Li, H. *et al.,* 2020). Taking into consideration, the lymphodepleting nature of the COVID-19 infection and the stress it further puts on the body by creating a pro-inflammatory state, all measure should be taken to contain such an infection. Subsequently, we propose the use of an immunoenhancing nutrient concoction composed of arginine, glutamine, zinc, copper, and vitamin C as a supportive measure in possible treatment strategies (Guo, Y. R. *et al.,* 2020).

DISCUSSION

Glutamine can be classified as a conditionally essential amino acid in case of sepsis and major surgery, because glutamine muscle stores are depleted under these severe metabolic stress conditions. A study in 2011 reported that ICU patients at the time of admission had low plasma glutamine level, less than 0.42 mmol/L (Kim, H. 2011). Critically ill patients have shown lower levels of circulating glutamine and this has been associated with worse ICU outcomes. This could increase the risk of secondary infection, as well as, recovery time. In one systematic review of 22 meta-analyses conducted on glutamine supplementation, in critically ill or surgical patients, through parenteral or enteral routes showed reduced rates of hospital acquired infectious complications and shortened lengths of stay in hospital. Similarly, another Cochrane meta-analysis concluded there was moderate evidence that glutamine supplementation could reduce the infection rate and days on mechanical ventilation in critically ill or surgical patients (McRae, M. P. 2017; & Casaer, M., & Ziegler, T. 2020).

In addition, glutamine improves gut barrier function by maintain enterocyte and colonocyte integrities, and it is considered as precursor of glutathione (the major in-vivo anti-oxidant). Immunonutrients that have anti-oxidant activity or substances that increase glutathione synthesis seems to be beneficial (Tao, K. M. *et al.,* 2014). Glutamine requirements seem to surpass the synthesis capacity of glutamine of mammalian body thus leading to lower plasma and intracellular glutamine concentration and this is the reason behind exogenous supplementation of glutamine in critically ill patients. Viral or bacterial pneumonia are direct offending agent and the most common cause to ARDS. Dysregulated inflammation, inappropriate accumulation of leukocytes and platelets, improper activation of coagulation pathways, and changed permeability of alveolar endothelial and epithelial barrier are features of ARDS (Oliverira, G. P. *et al.,* 2016).

Arginine, like glutamine, is depleted in many medical problems like infection, critical illness, sepsis, trauma, gastrointestinal disorders and cancer. Similarly, arginine is considered also as conditionally essential amino acid. Sufficient arginine levels in the body have an essential role in maintaining normal host defense mechanisms and immunologic function (Ma, X. *et al.,* 2019). T cells are highly sensitive to nutritional state and T cell dysfunction is related to acute nutritional deficiencies. Arginine is an important amino acid for the activation of naïve T cells (Li, P. *et al.,* 2007). Interestingly, many pulmonary diseases are associated with increased arginase activity and an arginine deficiency. The arginine deficiency of sepsis is believed to be the result of reduced arginine intake and impaired endogenous de novo arginine synthesis. More high quality studies are needed to examine the arginine replacement therapy in septic critically ill patients (Davis, J. S., & Anstey, N. M. 2011). As for the coronavirus, the elderly and those with underlying disorders (e.g. hypertension, chronic obstructive pulmonary disease, diabetes, and cardiovascular disease) are more likely to experience the detrimental effects of this virus and become critically ill. They could rapidly develop acute respiratory distress syndrome, septic shock, metabolic acidosis, and coagulation dysfunction, possibly leading to death (Huang, C. *et al.,* 2020). Arginine supplementation can come into play in such a scenario considering the likelihood of being in a state of deficiency. Essentially, arginine levels could be 41% less than normal non-ICU controls (Morris, C. R. *et al.,* 2017).

Arginine has been reported to have beneficial effects in both humans and experimental animals because of its anti-inflammatory properties and antiapoptotic effects. In one study conducted on mice that experienced lipopolysaccharide (LPS) induced lung damage, arginine treatment effectively decreased neutrophil accumulation, which aids its functional role in regulating leukocyte accumulation (Nieves Jr, C., & Langkamp-Henken, B. 2002). Additionally, when the mice were pre-treated with arginine, they presented with less expression of TNFα, IL-1β, and IL-6 in lung tissues (proinflammatory cytokines). When it comes to human subjects, arginine has shown to play a significant role in both innate and acquired immunity. It's important for lymphocyte proliferation and development, as well as, building the right type of immune response to an immunological challenge (Efron, D. T., & Barbul, A. 1998). Arginine depletion causes inhibition of interferon- gamma and interleukin 2, reduction of T cell proliferation, weakening of T cell

functions and rising susceptibility to infections. There is a relation between poor clinical outcomes and nutrition deficiency; amino acid therapeutic replacement can be beneficial (Peranzoni, E. *et al.,* 2008).

Moving to micronutrient role in infections and particularly viral infections. Strong immune responses needs adequate level of micronutrients. Zinc, copper, vitamin A, vitamin D, vitamin C, vitamin E and other trace elements and vitamins, all of them are described as micronutrient. Liver is the one of the organs responsible for micronutrient metabolism and storage. Many of them are important to derive an effective immune response. Zinc, a transition metal and an essential micronutrient, is required to control key biological processes like cellular development, metabolism, repair, and maintenance (Wu, D. *et al.,* 2019). Innate immune defenses, including phagocytosis, natural killer cell activity, cytokine production and complement pathway activation, require adequate zinc levels (Gupta, S. *et al.,* 2019). It is reported that administration of zinc in common cold viral infection reduces the severity and the duration of infection (Mousa, H. A. L. 2017). As for the immune system, it works on multiple levels of innate and acquired immunity. Essentially, it helps maintain the integrity of skin and mucosal membranes. With regards to innate immunity, it maintains natural killer (NK) cells cytotoxic activity and has a central role in cellular growth and differentiation of immune cells that have a rapid differentiation and turnover. Whereas for acquired immunity, it's involved in T-helper 1 (Th1) cytokine production and thus supports Th1 response. Additionally, it induces the development of regulatory T-cells (T_{reg}) which is important for maintaining immune tolerance (Gombart, A. F. *et al.,* 2020).

Apart from being required to maintain cellular harmony, zinc has also proven to have anti-oxidative properties by inhibiting the oxidative degradation of macromolecules like DNA and RNA by down regulating the reactive oxygen species (ROS) production and accumulation (Prasad, A. S., & Bao, B. 2019). Additionally, intracellular zinc levels have been associated with the degree of phagocytosis capacity of macrophages. However, the exact mechanism that zinc affects macrophage function has yet to be fully understood (Gao, H. *et al.,* 2018). Low zinc levels are often reported in elderly individuals, which may increase their susceptibility to infectious pathogens and increase the risk of pneumonia and mortality (Santos, H. *et al.,* 2019). Several controlled trials have investigated whether zinc supplementation is protective against infection in the elderly population. In one study, supplementation with 20mg zinc and 100 µg selenium for 2 years was associated with a significant decrease in the event of respiratory infections in the institutionalized elderly. Another study showed that 29% of nursing home residents (>65 y) had low serum zinc levels (<70 µg/dL) even after receiving multi-vitamins/minerals including 7mg zinc/d for 1 year. When compared to individuals whose serum zinc levels >70 µg/dL, they had higher pneumonia incidence, greater total antibiotic use, and longer duration of pneumonia and antibiotic use. This poses the possibility that zinc deficiency correction, in the elderly, may require a more rigorous route of supplementation than orally alone (Meydani, S. N. *et al.,* 2007).

Corona virus replication can be inhibited by increasing intracellular zinc levels was the main conclusion in a study, in 2010. Zinc ions are essential for cellular enzymes' proper folding and activation, and for transcription factors. Cell culture studies found that increased levels of zinc ions intracellularly inhibits replication of RNA-viruses involving respiratory syncytial virus RSV and influenza virus. This study tested the effect of zinc ions on SARS CoV replication and the result was, zinc inhibits the SARS CoV at the elongation phase of RNA synthesis (Te Velthuis, A. J. *et al.,* 2010). The most susceptible patients for COVID-19 and its complications are elderly. In elderly, zinc supplementation has reduced stress biomarkers and inflammatory cytokines and decreased infection incidents by approximately 66%. An estimation by World Health Organization (WHO) of 2 billion individuals in the developing countries might have nutritional zinc deficiency. Zinc deficiency causes oxidative stress, immune system dysfunction, and higher formation of inflammatory cytokines. Zinc has anti-inflammatory and antioxidant effect (Prasad, A. S. 2014).

Copper is a trace element which is required for the functioning of variety cellular enzymes. Once it is absorbed from digestive tract it is transported to liver. It is very essential for erythrocyte production, copper deficiency may cause anemia. It's also an important catalytic cofactor in the oxidation and reduction of proteins that carry out fundamental biological functions that are required for growth and development (Tapiero, H. *et al.,* 2003). Deficient states of copper are usually also associated with deficiencies in other important trace elements like zinc. Such a deficiency can manifest as reduced IL-2 and decreased T-cell proliferation. As a result, this can lead to ineffective immune response to infections, as well as, increased viral virulence which is concerning during a time of a viral pandemic (Alpert, P. 2017). Copper is an essential part of the copper/zinc-superoxide dismutase, a key enzyme in defense mechanism against ROS which allows it to act as a free-radical scavenger. Such anti-oxidative properties can prove as crucial necessities at times of high stress (Calder, P. C. *et al.,* 2020).

Vitamin C has roles in multiple aspects of immunity, including supporting epithelial barrier function, growth and function of both innate and adaptive immune cells, chemotaxis of white blood cell to sites of infection, phagocytosis and microbial killing,

and antibody production (Mikirova, N. A., & Hunninghake, R. 2014). Literature had always focused on vitamin C role in viral respiratory tract infection especially influenza and common cold. Systematic review study concluded that vitamin C has a role in prevention of common cold viral infection. It is suggested in treatment and prevention. In large meta-analysis of 30 randomized clinical trials, vitamin C has revealed benefits in prevention of viral respiratory tract infections such as common cold especially in cold stress subjected patients. Vitamin C strengthens the neutrophil and monocytes activity. Plus, it has antioxidant effects and increase glutathione production (Nahas, R., & Balla, A. 2011). Another recent study summarized that vitamin C, zinc, Echinacea preparations and garlic had moderate effect on prevention of upper respiratory tract infections (Voß, S. *et al.,* 2018). In infections phagocytes are activated to either kill the bacterial invader or deactivate the viral invader. This process includes reactive oxygen species (ROS) formation. On the other hand, these ROS have harmful effects on the normal host cells and it appears to play a role in infection pathogenesis. Vitamin C is efficient in protecting the host cells from ROS released by macrophages. After viral infections it is justified to suppose a decreased vitamin C levels and need for replacement therapy. Vitamin C levels in white blood cells are ten folds higher than in plasma, this correlates with immune system requirement of vitamin C for phagocytic function, interferon production and suppressing viral replication and T cell maturation (Hemilä, H. 2017). One meta-analysis reported a significant reduction in the risk of pneumonia with vitamin C supplementation, particularly in individuals with low dietary intakes. Likewise, it was shown that disease severity and risk of death, in older patients, were reduced with supplementation (Hemilä, H., & Louhiala, P. 2013).

According to SCMM/ A.S.P.E.N guidelines immune-modulating nutrients should be used in critically ill patients requiring mechanical ventilation and used with caution in patients of severe sepsis. This guideline gives grade B recommendation for using immune-modulating nutrient for ICU patients. Unfortunately, this category of patients is seen in pandemic COVID-19. COVID-19 is reported to cause ARDS and acute lung injury requiring mechanical ventilation. The inappropriate use of immunonutrients may cause harmful effect. Health care team must check the content for the nutritional formula since it differs between manufacturing companies and choose the most appropriate one for the patient depending on health status and patient preferences (Brown, B. *et al.,* 2015). To date, there is no approved coronavirus vaccine. Potential treatment of COVID-19 includes antivirals, CoV entry inhibitors, Cov replication inhibitors and neutralizing antibodies of CoV-S protein. We suggest approaching all treatment options pharmacological, nutritional and non-pharmacological to increase the survival and reduce the severity of suspected or infected COVID-19 patients.

CONCLUSION

In summary, the effects of all the aforementioned micronutrients on the immune system may vary, but the main goal is to enhance the immune response in controlling a viral infection. Once again, this treatment strategy is only meant to supplement current therapies for COVID-19. Combining different immunonutrients may have synergistic effect of more than the individual immunity and physiological effect of each nutrient. Since there is shortage in ventilators, any potentially beneficial intervention should be made for COVID-19 patients. Even though immunonutrition has not been fully understood, immune enhancing nutrients may exert beneficial effects on several patients' population. Further experimental and large randomized clinical trials focusing on the development and progression of respiratory diseases are necessary to understand the effects and possible therapeutic role of glutamine, arginine, zinc, and vitamin C in COVID-19.

Clinical Relevancy Statement

COVID-19 or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the novel viral infection that has emerged in Wuhan, China in December 2019. Therapeutic approaches are mainly supportive and symptomatic. These patients are under huge stress and nutritional function should be assessed. Supplementation of immune-nutrients is important especially for patients with immunodeficiency, virus or overwhelming infections accompanied by a state of malnutrition. Many drugs have been tried by various clinical sectors with minor effects or no benefits. So, using immune-enhancing nutrients as adjuvant therapy can boost the recovery and reduce the mortality in a safe way using naturally existed nutritional elements.

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