Acta Scientific NUTRITIONAL HEALTH (ISSN:2582-1423)

Volume 7 Issue 3 March 2023

Review Article

Contribution of Micronutrients to Boost the Immunity: "We Contribute for Human's Healthy Life"

Srilatha Bashetti*

Associate Professor, Department of Biochemistry, Dr. Patnam Mahender Reddy Institute of Medical Sciences, India

***Corresponding Author:** Srilatha Bashetti, Associate Professor, Department of Biochemistry, Dr. Patnam Mahender Reddy Institute of Medical Sciences, India.

DOI: 10.31080/ASNH.2023.07.1202

Received: January 23, 2023

Published: February 06, 2023

Abstract

Worldwide the leading cause for mortality and morbidity is widespread of viral infections. Well established public health practice to reduce the spread and severity of infections is by regular and timely vaccination, proper hygene and sanitization, etc., however, proper and sufficient nutrition is highly recommended to build-up an optimal immune function to fight against the infections and reduce its effect on the health of an individual. The micro-nutrients like vitamins and minerals help in supporting the immune system, contributing increase resistance to infections caused by various viruses. The aim of the review article is to throw a light of knowledge regarding the role of micronutrients and stating its importance to maintain a good health and quality of life. COVID-19, had explaind the importance of micronutrients and their role in reducing the burgen of infectious diseases. The article tries to give a public note and recommend every individual to have sufficient/optimal nutrion with supplementation of omega -3 fatty acids and all the other micronutrients to establish a strong immune system against infections and lead a healthy and fit life.

Keywords: Micronutrients; Boost; Immunity

Introduction

The 21st century had witness major epidemics few of those further qualified as pandemics influenced by old diseases such as yellow fever, cholera and plague. It also includes certain emerging diseases like severe acute respiratory syndrome (SARS), Zika, Ebola, Influenza and the most recent pandemic with huge impact ever is COVID-19. Most of these viruses had its action on lungs and it is evident from the reports that tuberculosis is the upmost infectious disease wherein single organism lead to about 1.5 million deaths in 2018 [1]. The outbreak of COVID-19 had a serious impact on human life and had led the way for new challenges in the healthcare system across the world. The disastrous effect of the virus and its faster diffusion all the world was a serious concern which got declared as medical emergency by WHO (World Health Organization) [2]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has a multifaceted spread of clinical manifestations and the virus effects are reported from mild to severe life-threatening outcomes, few cases reported asymptomatic infections while many had experienced critical pneumonia, acidosis, acute respiratory syndrome, multi-organ failure and many more symptoms from cold, fever to serious complication finally led to death of millions of people across the world [3,4]. In such situation wherein there is no proper cure or vaccination only immune systems efficacy and functionality remained as a key factor as a defence mechanism or a protection shield against the viral infection [5]. This led to a huge realization about the importance of consuming nutritional food containing micronutrients and vitamins contributing towards stronger and healthier immune system. Studies had shown that the supplementation of vitamin D, A and high doses of Selenium after influenza Vaccination had improved the humoral immunity in paediatric patients [6,7]. Studies reported that stronger the immunity lesser were the effects of the virus on the individuals effected by the virus. Malnutrition was the primary reason led to increased mortality and morbidity leaving a remarkable influence on the healthcare system with an economic drift experienced by the entire world irrespective of developed, developing or underdeveloped countries [8]. Taking this scenario into consideration, the present review article tried to emphasize on the need of consuming nutritional diet

consisting various vitamins and other micronutrients which helps to build a strong immune system that is capable of fighting against deadly viral infections caused by many viruses. This review article will help to understand that balanced nutrition protects us from various viral infections. In short, the review is all about contribution of micronutrients to boost up the immunity, it emphasizes on the supplementation of vitamins and minerals and describes there contribution towards building up strong immunity.

Importance of micronutrients

The pandemic scenario of COVID-19 had presented the clinical evidence by correlating the complication with the recovery rate relating it to inadequate intake of micronutrients and stated that this may contribute to disease seriousness or impaired resistance to infections [9]. Malnutrition refers to incorrect and inadequate intake of nutritious diet that include energy giving food (like carbs, fat, protein) and immunity boosting food (like- Vitamins and minerals). Insufficient or inadequate intake of energy food fails to meet the requirements needed for an individual to lead a healthy life wherein, deficiency of micronutrients refers to lack of micronutrient intake those needed in minute amounts and contribute for healthy development and growth [10]. It is observed that individuals are overfed in myth of their visualization of consuming energy food may still found to be deficient of one or more micronutrients. Balanced nutrition is pivotal in maintaining well-regulated immune homeostasis. Hence, it is learnt that nutrition is the deciding factor in supporting immune system. Calder et.al; stated that the key to develop defense against the viral threats or infections is by maintaining adequate nutrition [10]. Drastic changes in our lifestyle and dietary habitsmay be due to huge social distancing in the present scenario might have significant contribution in developing impoverished nutritional staus, that of which could have been the reason for undermined immune functionality. As described before the contributing reasons for impaired immune responses, may be insufficient intake or minor deficiencies of few micronutrients [11,12]. This can be hopefully reversed by correcting the individual's nutritional staus. The highlights published by the scientific panel named European Food Safety Authority (EFSA) stated that Vitamin A (β-carotene), D, C, folate, B6, B12, iron, zinc, selenium and copper are the depended micronutrients contributes for healthy maintenance of immune system. There are various studies and updates on theses micronutrients enhasizing their importance inbuiding up strong immunity [13]. It is well established that deficiencies of micronutrients may affect both the adaptive and innate immunity, further leading to immunosuppression which further may add up to increase the susceptabilty to various infections. The leading cause for worldwide morbity and mortality is learnt to be by viral infections whether it is seasonal influenza or recent out break as COVID-19 [14]. Micronutrients play a fundamental role in innate immunity maintaining the physical barriers of functional and structural integrity like mucus membrane, skin, etc; micronutrient s also have a supporting role for chemotaxis and microbial proteins of innate cells. Minerals and vitamins possess killing and phagocytic activies of macrophages and neutrophils [15]. Hence, it is learnt that deficiency of micronutrients like essential minerals and vitamins deprives adaptive immunity particularly cell mediated immunityand antibody-mediated humoral response.Poor nutritional status elevates the susceptibility and seriousness of infections. The reverse of it like repeated infection or serious infections increases the risk of malnutrition, assumed cause may be by inducing anorexia which is associated with decrease in intake of nutrients leading to malabsorption, altered metabolism further increases the demand for nutrients [16].

Role of vitamin A against viral infections

- **Functions: Adaptive immune response:** Production of antibodies, growth, and differentiation of β-cells, immunoregulatory functions.
- **Innate immune and inflammatory response:** Differentiation and function of NC-cells, integrity of epithelial cells, inhibition of Th1/Th17 generation, phagocytic and oxidative burst activity of macrophages, secretion of the pro-inflammatory cytokines IL-2 and IL-23.

Vitamin A has a greater contribution to boost up the intergrity of epithelial tissues especially in undernuroished children suffering from serious infections. Infection- related mortality and morbidity due to vitamin A deficiency can be reduced by supplementation of Vitamin A [17-20]. Studies explained the association of vitamin A supplementation in children reducing incidence of measles and diarrhea with a low to moderate evidence [21-23]. Meta-analysis studies on 12,33,856 children had stated that administration of vitamin A reduces all-causes of infections related deaths in children by 12% [24,25], There are many such studies enhasized the need to administrate vitamin A as it supports effective functioning of immune system and can also be practiced in patients with associated fat malabsorption disorders [26].

Vitamin C

Ascorbic acid has a powerful antioxidant property, an elctron donor, plays a major role in various biological processes like, collagen synthesis, metabolism of neurotransmitters, cartinine synthesis facilitates fatthy acid transport, metabolism of cholesterol, acts as a co-factor of metalloenzymes, maintains the copper and iron atoms, required for absorption of iron, etc; Studies reported >80% low incidence of pneumonia in the groups administrated with Vitamin C, these studies support the role of ascorbic acid in reducing the risk of pneumonia particular in cases with low levels of plasma vitamin C. The studies also provided evidence of vitamin C role in decreasing the severity and incidents of common cold [27,28]. There are several studies in this area that stated vitamin

C supplementation helped in reduction of upper respiratory tract infections like common cold. Recent scenario of COVID-19 played a crucial role in treating and preventing severe respiratory SARS-CoV-2 viral infection. A randomised clinical trail in pateints with sepsis and ARDS had shown significant decrease in mortality rate and significant rise in ICU free days for about 28 days and about 60 hospital-free days this is on infusion of vitamin C for about 96 hours but it failed to improve the primary outcome scores related to organ dysfunction [29]. Recent retrospectively observed data by Diao., *et al.* describes the efficient role played by vitamin C in reducing affects of viral respiratory tract infections and facilitated the clearance mediated by T cells [30]. This encourages taking up further studies to learn the role of vitamin C in treating and preventing the complications of COVID-19 disease.

- **Adaptive immune response:** Immunoregulation of antibody production [IgM and IgG], differentiation and proliferation of β- and T-cells, T-cell mutation via epigenetic mechanism.
- **Innate immune and inflammatory response:** Scavengers of reactive oxygen species (ROS), barrier integrity, apoptosis process of neutrophils, anti-bacterial activity and chemotactic ability of neutrophils, reduction of formation of neutrophil extracellular traps.
- **Vitamin D:** 1,25 dihydroxycholicalciferol is the active form of vitamin D also known as vitamin D3. Vitamin D3 actions are carried out through ligation with nuclear Vitamin D receptor (VDR), these actions lead to the regulation of transcriptional process of over and about 1000 target genes. It is learnt that VDR is widely distributed in various cells and tissues, includes even the immune system [31,32]. Vitamin D has important role in maintaining calcium homeostasis, stimulate bone remodeling, involved in regulation of immunity, pulmonary function,fetal development [33], controls gastrointestinal infectionsand many dsmore biochemical processes [34]. In addition, Vitamin D had also established its beneficiary immunoregulatory effect of the host cell towards viral infections, the latest being SARS-CoV2. It has the inhibitory effect on the production of pro-inflammatory cytokines, appears to be counter productive. The pathogenicity of SARS-CoV2 virus or any other respiratory viruses can be linked to hypercytokinemia also known as 'cytokine strom' [35-39]. There are several studies, focused on the link between vitamin D and its role in lower respiratory tract infections (LRTI) especially in children below 5years of age due to increased susceptibility observed in this age group. Micronutrient deficiency and malnutrition is the most common reason for increases pneumonia cases in children with rickets and frequent treatment-failure in rachitic children [40-43]. This scenario is observed mostly in developing countries. Several studies had established the link between low Vitamin D levels and increased risk for acute respiratory tract infections [44-47], which may further lead to frequent and longtime illness [48], ventilation support [49], longer stay in intensive care unit (ICU) and hospital stay [50,51]. Latest studies regarding association of Vitanim D deficiency with frequency and severity in COVID-19 cases stated a correlation between vitamin D levels in COVID patients and deaths [52]. A cmparitive, small cohort study among 107 pateints in Switzerland in understanding the association of vitamin D levels with seriousness of COVID-19. It showed that the levels of vitamin D were significantly lower in naso-pharyngeal swab test positive patients when compared to the controls with negative swab test [53]. Yet another study in New Orleans, stated that the frequency of insufficiency of vitamin D if higher i.e about (84.6%) in COVID-19 patients, those admitted in ICU and showed a 100% frequency in patients above 75 years [54]. An informatory outcome from a recent pilot study enumerated that high dose administration of 25-hydroxyvitamin D had significant positive effect and had reduced the necessity for ICU treatment for hospitalized proven COVID -19 patients. This study urges for larger clinical trials to establish a proper match with definite answer. However, age, co-morbidies, etc., are the proven risk factors for increase in the severity of SARS-CoV2 infection, any valid and exact reason for its widespread and severe symptoms had been not known yet. With a knowledge referring the role of vitamin D in immune system modulation and by hypercytokemia action it states that vitamin D has a potential role and contributes to reduce the severity of the infection/disease especially in COVID-19 [55].
- **Adaptive immune response:** Th-1 to Th-2 shift, increases Th2 cytokines (IL-4, IL-10), limits over production of pro-inflammatory cytokines from T-cells, induces differentiation of T reg, reduceses excessive antibody production.
- **Innate immune and inflammatory response:** Modulation of macrophages/monocytes and functions of dendritic cells, limits over production of pro-inflammatory cytokines from macrophages, production of anti-microbial peptides likehuman beta-defensin and cathelicidin, neutrophils and macrophages from immune system and respiratory cellsepithelial cells.
- **Zinc:** Zinc acts as a co-factor for various transcriptional factors and enzymes, hence known as one of the essential micronutrient or trace element. It is involved in establishing a balance between anti-inflammatory and pro-inflammatory reactions through numerous different mechanisms. Zinc can either inhibit or enhance immune fuctions depending upon the requirement. Zinc plays a vital role in protecting the organism from pathogenic attacks by maintaining integrity of membrane barrier, essential for intestinal and pulmonary epithelia as first line of defence [55-57]. Oxidative stress can

also be proven to be reduced by zinc hence, used to treat cold symptoms [58] found in respiratory viral infections like dengue [59] and SARS-CoV viruses [60]. The combination of zinc-ionophores with Zn2+ (Pyrithione) increases intracellular Zn2+, inhibits replication of SARS-CoV (coronavirus) [61-69].

- **Adaptive immune response:** Enhance the number of T regulatory cells, limits excessive release of pro-inflammatory cytokines IL-2, IL-6 and TNF-alfa).
- **Innate immune and inflammatory response:** Direct antiviral effects, decreases oxidative stress, maintenance of membrane barrier integrity.
- **Omega 3 Fatty acids:** Omega-3 fatty acids are polyunsaturated fatty acids (PUFA), important phospholipid components of cell membrane structures. They have an important role in pulmonary, cardiovascular, endocrine and immune system functions [70] Omega-3 fatty acids had proven to resolve inflammation induced by infections and also reduces respirator tract infections [71]. Acute respiratory distress syndrome (ARDS) and lung injury is known to be improved by administration of omega-3 fatty acid [72-74]. Reports stated that the severe COVID-19 could be manifested as a hyperinflammatory syndrome,wherein it has caused ARDS and multi-organ failure in about 50% of cases as an effect of hypercytokinaemia (cytokine storm) [75]. Few studies conducted had determined the role of omega-3 fatty acids in modulating the systemic inflammatory resposes and also learnt that it affect the production of plasma cytokines. It explained the association of consumption of omega-3 fatty acids with reduced illness duration and lesser episodes of illness related to upper respiratory tract infections [76]. In a randomized clinical trial administration of omega-3 fattyacids in patients suffering with acute lung injury, had given a negative outcome i.e., it had not shown any improvement in patient condition neither it improved the pulmonary outcomes nor had any positive effect on systemic inflammatory responses [77,78]. A systematic review conducted by Dushianthan., *et al*. had reported a significant positive improvement in the duration of ventilator days by improvising the blood oxygenation levels and and length of ICU length stay in patients with ARDS those supplemented with nutrition rich in antioxidants like Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) enriched polyunsaturated fatty acids (PUFA), although the review stated very low quality of evidence [79]. However, supportive research studies are highly recommended to validate this hypothesis.
- **Adaptive immune response:** Specialised pro-resolving mediations (SPMs) like T-regulatory cells formation, B-cell activation, up regulatory expressions.
- **Innate immune and inflammatory response:** Inhibition of cytokine production, str uctures of cell membranes, clearance of polymorphonuclear leukocytes, inhibiting neutrophil migration.

Figure 1

Conclusion

It is the need of the time to learn the importance of incorporating proper nutrition with good amount of micronutrients in diet to build up a strong immunity there by building resistance against infections. Latest invitro, observational and clinical trials in the area of effects of COVID-19 infections studied, had proven the beneficiary role of micronutrients in reducing the severity of infections, prolonged hospital stay and even mortality. It is understood that micronutrients like minerals and vitamins work together to establish an effective immune system by various biochemical mechanisms. Further studies in this area are recommended to achieve in-depth knowledge about the synergistic effects of the micronutrients on immune responses against viral infections. It also explains that maintaining optimal nutrition within the recommended levels by nutritional societies, may reduce the burden of disease for instant like COVID-19, frequency of infections, etc., the article clearly emphasizes that nutritional supplementation or administration will ensure to reduce the symptoms and helps in recovery but will never contribute to prevent or cure the disease.

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