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Review Article

Potential role of adjuvant micronutrient therapy in the management of respiratory tract infections: a narrative review

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ABSTRACT

Respiratory tract infections (RTIs) are highly prevalent and variable in nature, and are accountable for considerable morbidity and mortality. Acute respiratory tract infections (ARIs) are the third leading cause of death worldwide and the most common cause of antibiotic prescription among adults. It is common knowledge that inappropriate or overuse of antibiotics for RTIs is a crucial contributing factor with respect to the emergence of microbes that are resistant to the drug's effects. Overuse of antibiotics and antibiotic resistance is a global issue that is becoming a serious concern. There is a growing need for novel approaches and adjuvant therapies for such infections, particularly in the setting of worsening antibacterial resistance. The strategy of supporting the immune system of the host in advance of infection exposure would decrease the number and severity of infections and thus decrease antibiotic use. Micronutrients have varied roles throughout every stage of the immune system and help in strengthening and maintaining immune function. Deficiencies of micronutrients are associated with varied health outcomes and can impact both innate and adaptive immunity profoundly, causing immunosuppression and thus leading to increased susceptibility to infections. Moreover, in view of the COVID-19 pandemic situation, the factors that help the proper functioning of the immune system have garnered much interest and hence the maintenance of an optimal status of certain micronutrients could be particularly beneficial.

Keywords: Micronutrients, Respiratory tract infections, Vitamins, Zinc, COVID-19

INTRODUCTION

Respiratory tract infections (RTIs) are the commonest, and potentially most severe, of infectious diseases managed by clinicians.¹ Acute respiratory tract infections (ARTIs) were accounted for approximately 2.38 million deaths in 2016 worldwide.² Furthermore, they are a major cause of morbidity and mortality in children and are responsible for about 20-40% of outpatient and 12-35% of inpatient attendance.³ It has been documented that on an average, children experience 3 to 6 episodes and adults about 2.5 episodes of RTIs annually.⁴ Antibiotics are among the most frequently prescribed drugs for RTIs in both adults and children, despite the data from trials showing that antibiotics have limited efficacy in the management of a large proportion of these infections.⁵ Although most of the

respiratory infections are viral in nature, a high percentage of these are often managed with antibiotics.⁶ Almost 55% of patients suffering from acute RTIs are inappropriately administered antibiotics in the US ambulatory physician practices.⁷ Inappropriate antibiotic usage may result in antibiotic resistance, increased cost, and higher adverse effects incidence, including anaphylaxis.⁶ It has long been established that antimicrobial resistance is a worldwide public health issue, which has been accelerated due to antibiotics overuse. Increased antimicrobial resistance has resulted in severe forms of infections, complications, longer hospital stays, higher medical expenses and mortality.⁸ Given the rising rates of anti-microbial resistance coupled with the identification of inflammatory and immune factors as vital components underlying the symptoms, novel approaches that target them have

garnered much interest.^{2,9} Micronutrients are shown to be fundamental in all stages of the human immune response.^{2,10} These supplements may help prevent (vitamin D and C) and treat (vitamin D, C and zinc) acute respiratory tract infections.¹¹ Moreover, multiple micronutrient supplementation may also help decrease antibiotic usage.¹⁰ Supplementation with micronutrients appears to be a safe and effective way to support optimal functioning of the immune system, with the potential to decrease the risk and consequences of infections. Supplementation of micronutrients should always be in conjunction with a balanced diet and conform to the recommended upper safety limits established by expert regulatory bodies.¹² The aim of this narrative literature review is to discuss the pivotal micronutrients related to the immune system with a special focus on vitamin C, D and zinc and their potential role in supporting immunity, particularly against respiratory infections.

Impact of RTIs on asthma and COPD exacerbations

Asthma and Chronic obstructive pulmonary disease (COPD) patients have an increased risk of RTIs.^{13,14} Most COPD exacerbations are triggered by RTIs.¹⁵ Around 50-70% of exacerbations are caused by RTIs.¹⁶ In a study of hospitalized patients with severe exacerbations, 78% of them had either viral or bacterial infection.¹⁷ Upper respiratory tract infections are responsible for 50% of COPD exacerbations and infection due to rhinovirus, respiratory syncytial virus and influenza have been linked to exacerbations.¹⁷ Identification of respiratory viruses has been recorded in 80-85% of asthma exacerbations that led to reduced peak expiratory flow and wheezing in school-aged children. While respiratory viruses have been identified in 45-80% of adults experiencing exacerbations, with the most common pathogen being Rhinoviruses (RVs).¹⁸ Studies using Reverse transcription polymerase chain reaction (RT-PCR) show that almost 60% of acute asthma exacerbations in adults and about 85% in children, were related to Upper respiratory tract infections (URTIs).¹⁹

The trinity: respiratory infections, immunity and micronutrients

RTIs are characterized by both airway and systemic inflammation and immunity defines the outcomes of such infections.^{20,21} Optimal function of the immune system is crucial to decrease the risk of infections.¹² The human immune system is regarded as a complex and integrated network of specialized organs, tissues, cells, chemicals, and proteins, which has undergone evolution for protecting the host from an array of pathogens, like viruses, bacteria, fungi, as well as parasites. It could be compartmentalized into epithelial surface, and cellular and humoral components of either innate and acquired immunity.²²

It is common knowledge that both the innate and adaptive immune responses to the pulmonary pathogens are important for the maintenance of a healthy respiratory

system and prevention of pulmonary diseases.²¹ It is well-established and documented in the past clinical literature that the micronutrients have beneficial effects on the immune system. Owing to the micronutrients' impact on cellular immunity, antibody production and epithelial barriers, they have a key role to play in the maintenance and strengthening of the immune system.²³ Figure 1 lists the role of micronutrients like vitamin C, D and zinc in immune defense.^{12,22}

Role of Vitamin C	Role of Vitamin D	Role of Zinc
<ul style="list-style-type: none"> • Barrier integrity maintenance • ROS scavenger • Microbial killing enhancement • Enhancement of differentiation and proliferation of B and T cells • Antibody levels enhancement 	<ul style="list-style-type: none"> • Antimicrobial peptides production • Reduces excessive antibody production • Modulation of cytokine production • Inducing differentiation of T reg • Modulation of macrophages and dendritic cells functions 	<ul style="list-style-type: none"> • Barrier integrity maintenance • Antiviral action • Reduction of oxidative stress • Modulation of cytokine levels • T reg enhancement

Figure 1: Micronutrients linked with immunomodulatory activities and their role in immune defense.^{12,22}

Vitamin D which is a fat-soluble entity, derivative of sterols, is regarded as one of the essential nutrients. While it has an essential role to play in various physiological processes such as immunity, cellular growth, and cellular differentiation, its most significant role is the maintenance of calcium and phosphate homeostasis.^{24,25} The role of vitamin D in the immune response is well-documented.²⁴ It plays a significant and key role in controlling innate and adaptive immunity. The proliferation and differentiation of B-cells is suppressed via induction of apoptosis in activated B-cells.²⁵

Cathelicidin, an antimicrobial protein produced by vitamin D stimulated expression, has activity against a variety of pathogens like bacteria, fungi and enveloped viruses. Furthermore, vitamin D inhibits the production of proinflammatory cytokines whereas it increases the production of anti-inflammatory cytokines.^{26,27} Thus, with regards to Toll like receptor (TLR) signaling, vitamin D reduces the expression of various TLRs such as TLR2, 4, and 9, and decrease the production of proinflammatory cytokines such as IL-6, IL-23, TNF- α , inducible nitric

oxide synthase, IL-1, and several T cell-recruiting chemokines present in monocytes/macrophages. It has been shown that vitamin D causes the inhibition of LPS-induced cytokine production via the Mitogen-activated protein kinase phosphatase-1 (MKP-1) signaling activation in macrophages and monocytes.²⁷ An important antioxidant and a cofactor for many biosynthetic and gene regulatory enzymes, vitamin C, helps in the immune defense by supporting multiple cellular functions related to components of the immune system.²² It mounts up in phagocytic cells and augments activities such as chemotaxis, phagocytosis, and eventually microbial killing.²² It has critical antioxidant properties, and acts directly by scavenging reactive oxygen and nitrogen species, thereby controlling inflammation and improving recovery.^{11,28}

Vitamin C plays a pivotal role in the maintenance of epithelial barriers in skin and lungs owing to its involvement in synthesis of collagen, healing of wound and protective action against Reactive oxygen species (ROS)-induced damage. It also helps regulate the cytoskeletal rearrangements in alveolar epithelial cells and gene expression of tight junction proteins.²⁸ Past published data demonstrated that high levels of serum vitamin C are linked to improved antibody response, neutrophil function, and mitogenic response of lymphocytes.⁴ With regards to the lymphocytosis, the role of vitamin C may be ambiguous; however, it has been shown to augment differentiation and proliferation of B- and T-cells. Deficiency of vitamin C leads to impairment in immunity and increased susceptibility to infections. Consequently, infections have a significant influence on vitamin C levels owing to the increased inflammation and metabolic requirements.²² According to Hemila et al the decreased levels of vitamin C reported during infection indicates that use of vitamin C supplements may impact preventing and treating infections positively.⁴ Zinc is an essential and determinant trace element that is part of multiple biological processes owing to its function as a cofactor, signaling molecule and structural element.²⁹ It plays a critical role in the maintenance of both innate and adaptive immune functions.²⁴ Zinc deficiency may lead to an increased susceptibility to several pathogens.³⁰ Right from the barrier of the skin to gene regulation within lymphocytes, the past clinical literature has shown that zinc has a prominent impact on various aspects of the immune system. Its influence on the normal development and functioning of cells mediating nonspecific immunity cannot be denied.

Thus, its deficiency has an impact on acquired immunity via prevention of both the outgrowth and certain T lymphocyte functions namely activation, and Th1 cytokine production.³⁰ Although the exact mechanism is uncertain, zinc exhibits antiviral activity through modulation of viral particle entry, fusion, replication and viral protein translation.²⁹ Past *in vitro* studies have shown that zinc salts were found to inhibit rhinovirus replication, possibly via interference with rhinovirus cleavage.³¹

Micronutrients and respiratory infections: clinical overview

Few studies have shown the link between the zinc levels and Respiratory syncytial virus (RSV) infection. Particularly, it has been shown that whole blood zinc was significantly reduced in pediatric population with RSV pneumonia. About 80% of children with severe pneumonia had low zinc levels. Similarly, a 2-fold lower zinc serum level was reported in pediatric acute lower respiratory infection patients.²⁹ A total of 100 individuals who developed common cold symptoms within 24 hours before enrollment were included in a randomized, double-blind, placebo-controlled study conducted by Mossad et al. It was observed that the time to complete resolution of symptoms was significantly longer in the placebo group as compared to the zinc group. A significant reduction in the number of days with symptoms like coughing, headache, hoarseness, nasal congestion, nasal drainage, and sore throat was seen in the zinc group.³² According to a 2021 meta-analysis by Abioye et al a total of nine studies assessed the impact of zinc supplements with respect to the shortening of the duration of common cold among 1038 individuals, and all studies reported significant effects.¹¹ In their randomized, placebo-controlled trial, Prasad et al. established that zinc lozenges consumption was linked to reduced severity and duration of cold symptoms, particularly cough. It was further hypothesized that the improvement in clinical symptoms post zinc treatment may be associated with a reduction in pro-inflammatory cytokine levels.³³ A meta-analysis published in 2016 by Lassi et al. showed that supplementation with zinc significantly decreased the incidence and prevalence of pneumonia in children aged 2-59 months by 13 and 41% respectively.²⁹

Similarly, the effects of zinc supplementation related to upper respiratory tract infections was also adequately validated. In particular, in a 12-month, triple-blind, randomized controlled trial conducted by Martinez-Estevéz et al the number of URTI episodes in children on daily zinc supplementation decreased by 73%.²⁹ Per a recent systematic review and meta-analysis by Abioye et al fourteen studies of vitamin C and common cold risk reported significant protective effects.¹¹ In a randomized controlled trial conducted by Johnston et al it was found to play a protective role against common cold in men with marginal vitamin C status.³⁴ In the systematic review by Hemila et al identification of seven trials with military workforces, three trials consisting of students accommodated in closed quarters, and two trials that included marathon runners was done. A statistically significant 45 to 91% decrease in the incidence of common cold in the vitamin C group was observed in 5 of the included trials. Moreover, a statistically significant 80 to 100% decrease in the pneumonia incidence was found in the vitamin C group in three trials.³⁵ In a randomized double-blind clinical trial conducted on elderly patients, it was found that patients supplemented with vitamin C did significantly better than those in the placebo group in a

clinical scoring system centered on major symptoms of the acute respiratory infections.³⁶ In a double blind randomized controlled trial conducted by Sasazuki et al among 305 participants in a community with high gastric cancer mortality in Japan, use of vitamin C resulted in 64% lower risk of common cold over a period of 5 years.³⁷ Although few studies have shown that regular supplementation with vitamin C may not reduce the incidence of common cold in the general population, it was halved in patients facing short periods of great physical stress. It should however be noted that vitamin C supplementation proved beneficial with respect to the duration of colds, especially in children.²⁸

The protective role of vitamin D as an adjunctive therapy against respiratory tract infections has been well-demonstrated in individuals susceptible to these infections.²³ Wang et al in their systematic review, showed that vitamin D deficiency may be related to a longer duration of ARI.²³ Nnoaham et al in their meta-analysis showed links between low serum vitamin D levels and an increased risk of active tuberculosis in healthy individuals.²³ Charan et al included five clinical trials in their meta-analysis with the defined outcome of episodes of respiratory tract infections in vitamin D versus placebo groups. Beneficial effects of vitamin D supplementation with respect to the rate of respiratory tract infections was observed in both adult and pediatric groups.³⁸

Perspectives for COVID-19

Some of the epidemiological factors known until now that are related to COVID-19 have underlying link with the nutritional status and micronutrients that are identified to contribute to the normal functioning of the immune system.³⁹ Thus, in view of the COVID-19 pandemic, potential protective effects of micronutrients have garnered much interest. The premise that vitamin C supplementation may be helpful in the COVID-19 management is supported by the past studies demonstrating its well-established role as a vital medicament against viral infections.²⁸ It is believed that vitamin C supports immune function via modulation of cytokine storms due to COVID-19 infection.⁴⁰

This was confirmed in a study that evaluated IL-6 and tumor necrosis factor alpha levels in hospitalized patients with pneumonia.²⁸ A high dose of vitamin C is used to manage Acute respiratory distress syndrome (ARDS). Fowler et al reported a case of virus-induced ARDS managed with high-dose, intravenous vitamin C and found that there was a rapid resolution of lung injuries with no evidence of post-ARDS fibro-proliferative sequelae. Another study demonstrated that timely administration of high-dose, intravenous vitamin C improves the COVID-19 outcomes.⁴⁰ Although oral dose of vitamin C is not beneficial in the critical COVID-19 infection, it has been proposed that oral vitamin C supplementation may reduce the progression from mild to critical COVID-19 cases.²⁸ An in vitro study showed that zinc may have antiviral

activity against SARS-CoV RNA polymerase.⁴¹ In the COVID A to Z trial, Thomas et al. concluded that interventions like high doses of zinc gluconate, ascorbic acid, or a combination of both did not significantly shorten the duration of symptoms in ambulatory patients diagnosed with SARS-CoV-2.

However, there were multiple limitations in the study with the main limitation being the absence of placebo control group; open label study design, and the lack of masking. Furthermore, participants were recruited in a single health system, and hence, the current study's outcomes may not be representative of the outcomes of patients from other health care settings. There is a possibility that certain groups with higher susceptibility such as older patients were underrepresented in the study and the study results may not be generalized broadly. Few studies have shown that deficiency of vitamin D is related to increased risk of SARS-CoV-2 infection and related hospitalization.⁴²

Vitamin D plays a vital role in the reduction of the cytokine storm by increasing the expression of anti-inflammatory cytokines and downregulation of the pro-inflammatory cytokines in severe COVID-19 patients.^{39,40} It also stimulates the development of T regulatory cells.⁴⁰ Other micronutrients such as vitamin B, selenium and magnesium are also vital in the proper functioning of the immune system.⁴³ In a study conducted in South Korea, it was observed that 76% of the COVID-19 patients were deficient in vitamin D whereas 42% of them were deficient in selenium, with higher deficiency in those with severe form of disease. The study also reported pyridoxine and folate deficiency in 6.1%, and 4.0% of the patients respectively. Selenium decreases oxidative stress and inflammation and helps boost the immune system.⁴⁴ An observational study from Singapore demonstrated that hospitalized patients with COVID-19 who were administered vitamin B12, vitamin D and magnesium supplementation had decreased COVID-19 symptom severity and these supplements significantly decreased the requirement for oxygen and intensive care support.⁴⁵ Magnesium may help in the protection of tissues from damage via multiple mechanisms such as anti-inflammation, anti-oxidation and immune-regulation.⁴⁶

The information about COVID-19 is still evolving and the role of certain crucial micronutrients in supporting the immune function needs to be further explored. Further research regarding the potential nutritional risk factors could help understand the susceptibility of some individuals to COVID-19.³⁹

CONCLUSION

Current findings state that micronutrients have an impact on the incidence and severity outcomes of RTIs and provide promising evidence for their potential protective role. Nevertheless, further studies are needed to assess the synergistic effects of multiple micronutrients in the immune response against infections. Integrating

micronutrients into the prevention and therapeutic management of RTI may complement pharmacological interventions and help reduce the disease burden globally. It is noteworthy that micronutrient supplementation should be in addition to a nutritious and wholesome diet and placed within recommended upper safety limits set up by regulatory expert bodies. Furthermore, it is vital to recognize that in some cases, micronutrient supplementation may not essentially prevent infections, or cure it, but may help reduce symptoms and facilitate recovery. The role of micronutrients in COVID-19 is an interesting area of research and further studies are the need of the hour to develop a better understanding regarding their benefits against COVID-19.

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