

# Role of Vitamin A Supplementation in Prevention and Control of Coronavirus Disease-19: A Narrative Review

## Abstract

Coronavirus disease-19 (COVID-19) caused by SARS-CoV-2 is a novel viral infectious disease, which broke out in the end of winter season 2019 in China and soon became a pandemic. Characteristically there was severe local and systemic immune-inflammatory response to the virus, damaging the respiratory system and other organ systems. The morbidity and mortality caused by the disease are producing tremendous impact on health. The understanding about pathogenesis and manifestations of the disease was obscure. To date, no classic treatment or preventive measure was available for COVID-19 other than symptomatic and supportive care or few drugs under trial. A possibility exists that maintaining vitamin A adequate levels can protect the affected respiratory mucosa, increase antimicrobial activity, produce better antibody response, and have anti-inflammatory effects, thereby promoting repair and healing as well. It has been discussed in the review that by various mechanisms, immune regulation through vitamin A supplementation is beneficial to boost immunity in the current outbreak situation when the population is susceptible to the disease. There is a high possibility that vitamin A supplementation to cases as well as population at risk of COVID-19 has a key role in prevention and control. Hence, it is believed that along with other therapeutic and preventive measures, maintaining vitamin A sufficiency during and prior to the development of active disease may act as an adjuvant in population at risk and cases to prevent and control COVID-19.

**Keywords:** *Anti-inflammatory, COVID-19, immunomodulation, SARS-CoV-2, vitamin A supplementation*

## Introduction

Coronavirus disease-19 (COVID-19) is a novel viral disease and World Health Organization (WHO) has declared it a public health emergency of international concern.<sup>[1]</sup> The disease is contagious and, in affected individuals, has the risk of spreading rapidly from upper to lower respiratory tract, and has high morbidity and mortality.<sup>[1]</sup>

There was an urgent need to take appropriate preventive and control measures for the emerging disease. Also not much was known about the natural history of the novel viral disease.

Animal studies have shown that low levels of vitamin A are likely to increase the susceptibility to COVID-19 as in case of other infections including acute respiratory infections.<sup>[2-5]</sup> In an experiment conducted in 35-day-old hamsters, the findings

had shown that vitamin A deprivation decreased the replication of basal cells and mucous cells in tracheal epithelium, which showed minimal morphologic change with the manifold reduction of the mitotic rates.<sup>[2]</sup> Similarly, findings of the experiments conducted in rats had shown that vitamin A was important for the maintenance and functional integrity of mucus-secreting goblet cells in the small intestine.<sup>[4]</sup> Moreover, in view of the findings of a review article published in 2018, vitamin A supplementation in its deficiency state has been shown to improve immune response in infectious diseases.<sup>[6]</sup>

Vitamin A also has a role in host defense and has been suggested to have potential importance in the prevention of respiratory tract infections by regulating and promoting local and systemic immune responses.<sup>[6]</sup> Thus, the immune-regulatory mechanisms with adequate vitamin A required extensive review of available literature. In this article, we attempted to explore different

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mechanisms by which vitamin A can improve immune function to combat microbial infections and how the knowledge be applied in the prevention and control of COVID-19.

Hence, the authors made an attempt to review the available studies on various infectious/inflammatory diseases in order to explore the potential role of vitamin A supplementation in the prevention and control of COVID-19.

## Methods

The current paper is a narrative review whereon a search was done for various relevant studies on PubMed, Medline, EMBASE, Google Scholar, and other databases. The search areas were mainly vitamin A deficiency, infectious diseases, infections, microbes, virus, immune cells, coronavirus respiratory infections, COVID-19, and SARS-CoV-2. The relevant studies in English were selected and reviewed while others were excluded. The findings were interpreted to explore whether or not and how vitamin A supplementation can be beneficial in efforts to control COVID-19.

## Results and Discussion

### Pathogenesis of COVID-19

According to an observational prospective study conducted in Wuhan, China and published in a reputed journal, the upper respiratory system including the nasal and oropharyngeal mucosae are the first to be affected by SARS-CoV-2. Thereafter the virus affects the lower respiratory tract producing symptoms like fever, dry cough, dyspnea, etc.<sup>[7]</sup> In another descriptive study conducted in Wuhan, the findings, however, also showed that presentations of respiratory symptoms in COVID-19 could be a bit varied,<sup>[8]</sup> which could confuse further the management of cases. The peculiarity of the disease was that it was fatal in elderly and those with comorbid conditions.<sup>[8]</sup>

In a study conducted in Texas, the cellular and molecular bases of the increased inflammatory responses and severe tissue destruction within the lungs of SARS patients were studied.<sup>[9]</sup> As stated in the paper findings, SARS coronavirus bound to host cell angiotensin-converting enzyme 2 receptors for the virus spike protein to enter the respiratory epithelial cells and thereafter multiplied inside the host cell. As the virus entered the host, cell innate immunity comprising mucus layer along with underneath macrophages and dendritic cell fought against to eliminate the virus till adaptive immunity was made to respond for further handling of the infective agent.<sup>[9]</sup> In a literature review, earlier coronaviruses had been shown to activate the adaptive immune system through T-cell mediated secretion of inflammatory chemicals, proteins, and antiinflammatory chemicals/proteins.<sup>[10]</sup> Observational and other study evidences to support the role of T-cells for clearing the infection indicated lymphopenia in patients with severe COVID-19.<sup>[11,12]</sup> A noteworthy finding

published in a paper was that activated innate and adaptive immune systems produced inflammatory cytokines including IL-6, monocyte chemoattractant protein-1, tumor necrosis factor (TNF)-alpha, and macrophage inflammatory protein 1 alpha.<sup>[7,11,12]</sup> According to the findings of another molecular level study, though the activated cytotoxic T-cells, the CD8+ T-cells derived from CD4+ T-cells, contributed to killing the virus, this also contributed to lung tissue destruction.<sup>[13]</sup> The highly expressed inflammatory cytokines were likely to accelerate progression to cytokines storm. Most patients with COVID-19 predominantly had respiratory tract infections inoculated with SARS-CoV-2 infection, which was a milder form of the disease. However, a small proportion of cases could progress to more severe systemic disease characterized by acute respiratory distress syndrome, sepsis and shock, and multi-organ failure including kidney injury and cardiac injury. Autopsy findings in China and European countries showed endothelial damage of pulmonary vasculature and microvascular thrombosis in the findings of a review.<sup>[14]</sup>

The role of vitamin A in immunity is classified into action on the innate immune system and adaptive immune system, and its antiinflammatory effects.

Immunomodulatory effects of vitamin A on the innate and adaptive immune system:

In view of the findings of a comprehensive review article,<sup>[15]</sup> an effective immunity is critical to remove the pathogen and to limit the extent of injury. Humans have an elaborate innate and adaptive immune system, which play a vital role in eliminating injurious stimuli and promoting repair of the tissue.<sup>[15]</sup>

Host immune response to the pathogen also determines the severity of tissue damage, while immune deficiency is known to predispose to infectious diseases. It is recognized that the interplay of the immune system components in response to the pathogen is responsible for the pathophysiological effects and symptoms of the disease.

Recently, in the studies published in a reputed journal, vitamin A was reported as a nutrient having pleiotropic effects in the immune system through the molecular effects of its metabolites.<sup>[16,17]</sup> Vitamin A was required for optimum mucosal barrier function, appropriate functioning of neutrophils, macrophages, and natural killer (NK) cells, and also for the components of the adaptive immune system including T cells and B cells.<sup>[18]</sup>

Way back to 1925, researchers reported that in vitamin A deficiency states, various epithelia were changed to stratified squamous keratinizing epithelium.<sup>[19]</sup> Later in 1929–1930, before the advent of antibiotics, vitamin A was reported as an antiinfective agent.<sup>[20]</sup>

Findings of several randomized clinical trials of vitamin A supplementation suggested that maintaining vitamin A

sufficiency in the at-risk population decreased disease severity and reduced morbidity and mortality in many infectious diseases.<sup>[21,22]</sup> Also recent research showed that vitamin A supplementation had potential use in decreasing severity in measles, lower respiratory tract infections, and meningitis.<sup>[1]</sup> It was then reported that vitamin A deficiency caused epithelial cell shrinkage and predisposed to squamous keratinization in skin, digestive tract, respiratory tract, genitourinary tract, cornea, and surrounding soft tissue responsible for the symptoms of dry skin, diarrhea, coughing, keratomalacia, corneal opacity, dry eye, and urinary lithiasis.<sup>[23-26]</sup> Symptoms were relieved because of the key role of vitamin A in synthesis and maintenance of the integrity of the glycoprotein layer of the epithelium for its adequate function. Further, it was reported that keratinized epithelial tissue was not able to stop the foreign pathogen in its attack on the epithelial layer of the organ systems, promoting various infections.<sup>[27]</sup> The ability of vitamin A to regenerate damaged mucosa and at the same time promote phagocytosis by neutrophils and macrophages could reduce the incidence and duration of invasive disease like *Shigella* dysentery.<sup>[28,29]</sup> The protective effects of vitamin A were suggested due to the restoration of intestinal IgA secretion and T helper-2 cells (Th2) cytokine production. It is explained that the increase in IgA, which is a pathogen-specific antibody in the gut, improves recovery from primary infection and increases the ability to fight off secondary infection.<sup>[30]</sup>

Early evidence reported that vitamin A deficiency affected neutrophil development and compromised bacterial phagocytosis and microbial killing capacity.<sup>[31]</sup> Also as per the findings of some studies, vitamin A deficiency causes neutrophilia in rats in peripheral blood smear.<sup>[32,33]</sup> However, the development of neutrophilia was not seen in all mice strains during vitamin A deficiency.<sup>[34]</sup>

These studies indicate derangement of neutrophil function in vitamin A deficiency.

Vitamin A deficiency is also known to increase the transcription of interleukin-12 (IL-12) in macrophages.<sup>[35]</sup> However, retinoic acid inhibits IL-12 production by primary macrophages. Kim *et al.* demonstrated that the innate immune system through the transcellular metabolism activated dendritic cells and macrophages, and the immunomodulatory nutrient vitamin A produced antimicrobial response in tuberculosis.<sup>[36]</sup> Also low levels of serum vitamin A concentrations were found to be correlated with susceptibility to tuberculosis.<sup>[37-39]</sup> In another study, vitamin A deficiency was strongly suggested to have a role in viral disease—measles and diarrhea.<sup>[40]</sup>

In an extensive review, the antiviral responses of NK cells were demonstrated to be decreased in vitamin A deficiency.<sup>[41]</sup> Additionally in another study protective role of NK cells in the early stages of viral infections was notably decreased in cases with vitamin A insufficient levels.<sup>[42]</sup>

Researches have been conducted where in the effect of high dietary intake of vitamin A on recovery from influenza A viral pneumonia in mice was studied.<sup>[43]</sup> It has been seen in animal studies that vitamin A deficiency was found to cause alteration in T helper-1/T helper-2 (Th1/Th2) cytokine production. In vitamin A deficiency, secretion of Th2 cytokines was decreased while that of Th1 cytokines was increased. However, recently it was shown that high dietary vitamin A significantly increased antiinflammatory cytokines and improved secretory antibody IgA levels and decreased interferon (IFN)-gamma levels.<sup>[43]</sup>

Thus, the evidences discussed above irrefutably pointed to the immune-modulatory role of vitamin A, particularly in infectious disorders.

### Antiinflammatory effects of vitamin A

Inflammatory reaction is part of immune response and is comprised of immune cells and chemicals at the local site of injury and in the systemic circulation. Literature exists in which vitamin A had been reported to be a physiological antiinflammatory agent.<sup>[44]</sup> Moreover, a supportive observational study suggested that vitamin A deficiency induced exaggerated inflammation to injurious stimuli which might result in severe tissue injury so that children with low levels of vitamin A during acute illness with viral respiratory pathogen were associated with increased severity of the illness.<sup>[45]</sup>

The increased severity of illness was attributed to increased rate of vitamin A consumption by the injured epithelial tissue suggesting adequate levels of vitamin A promoted epithelial regeneration and decreased severity of the symptoms,<sup>[45]</sup> and it was hypothesized that vitamin A supplementation may have a role in the management of infection with respiratory syncytial virus, an RNA virus.<sup>[45]</sup>

Evidences were available which showed that adequate vitamin A levels reduced proinflammatory cytokines secreted by macrophages and at the same time promoted antiinflammatory cytokine.<sup>[46]</sup> In addition, as per findings of some molecular level studies in animals, vitamin A was also suggested to induce macrophages toward antiinflammatory lineage.<sup>[47,48]</sup> Furthermore, in an available research, the effect of retinoic acid on human dendritic cells was studied, and findings showed that vitamin A metabolite retinoic acid also promoted antiinflammatory cytokine secretion IL-10 by dendritic cells thus favoring T-cell differentiation toward antiinflammatory effects.<sup>[49]</sup> Further in a trial conducted on mice, it was shown that retinoic acid treatment inhibited IL-12 production in lipopolysaccharide activated macrophages by inhibition of nuclear factor-kappa B-DNA interaction and competition between NF-KB and retinoic acid X receptor.<sup>[50]</sup> In an inquiry, researchers examined the effects of metabolites of vitamin A on different proinflammatory and immune-modulating cytokines produced by monocytes to

understand the mechanisms by which retinoids affect the immune response.

The findings of the study showed that retinoic acid inhibited the production of TNF-alpha and IL-12, the proinflammatory cytokines and at the same time potentiate IL-10 production in monocyte/macrophage cell lines and human cord blood mononuclear cells.<sup>[51]</sup> In an investigation on the molecular mechanisms, it was suggested that plasma factors such as transforming growth factor- $\beta$  and prostaglandin E2 in presence of retinoic acid, acted synergistically to form IL-6 by basophils so that sensitivity of macrophages to IL-6 increased which resulted in M2 macrophage polarization thereby regulating inflammatory process in mice.<sup>[52]</sup>

As published in a review article, it had also been observed that macrophages in the tissue were highly adaptive in terms of their function to different microenvironments.<sup>[53]</sup> In addition to the role of vitamin A in the inflammatory phase, retinoic acid was witnessed to enhance wound healing primarily through promoting extracellular matrix components and decreasing levels of degrading matrix metalloproteinases.<sup>[54]</sup> This shows the role of vitamin A in multiple stages in the natural history of infectious disorders. In some surveys, vitamin A deficiency has been found to be highly prevalent in India.<sup>[55,56]</sup>

In an exhaustive literature review, vitamin A supplementation was substantiated to reduce morbidity and mortality in several randomized controlled trials in various infectious diseases.<sup>[6]</sup> In an observational study, lower levels of beta-carotene, which is a naturally occurring precursor of retinol (vitamin A), were also found to be related to tuberculosis morbidity and mortality.<sup>[57]</sup>

A spectrum of infections in which vitamin A supplementation has been presented/evidenced to have a role is shown in Table 1. Though the spectrum of these infections is large, a noteworthy finding is that many of the infections discussed above are acute respiratory infections. Similar to these instances, vitamin A supplementation was believed to benefit COVID-19 patients. This justifies at large for supplementation of vitamin A in SARS-CoV-2 as a preventive and control measure. Hence, the review

has broadened knowledge regarding role of vitamin A in prevention and control of COVID-19.

## Conclusion and Recommendation

Pathological/cellular changes in COVID-19 resemble those of other infectious respiratory disorders. Vitamin A has a role in the prevention of infectious disorders particularly respiratory disorders including prevention of the complications by modulating immune response to favor antimicrobial actions as well as restoring epithelial mucosa thereby promoting healing as well. It is concluded and hypothesized that vitamin A may have a preventive role in COVID-19 similar to other infectious disorders. Hence, ensuring vitamin A sufficiency through vitamin A supplementation may be one of the key strategies in the prevention and control of the pandemic of a novel infectious respiratory disease, COVID-19.

It is recommended that for effective control of COVID-19, efforts to eliminate vitamin A deficiency should remain one of the priorities as a public health measure. It is, however, suggested that as a good public health practice, while the introduction of vitamin A supplementation as a prevention and control measure for COVID-19, prior opinion/consent of the custodians of the communities may be sought so that the intervention is informed and acceptability is maximum among the populations.

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## Conflicts of interest

There are no conflicts of interest.

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**Table 1: List of microbial infections showing improvement with vitamin A supplementation**

Name of Infectious disease
Tuberculosis <sup>[57,58]</sup>
HIV/AIDS <sup>[18,54,59-61]</sup>
Upper respiratory infections <sup>[18,62]</sup>
Lower respiratory infections <sup>[18,62-65]</sup>
Diarrheal diseases <sup>[18,66,67]</sup>
Measles <sup>[18,68]</sup>
Mumps <sup>[69]</sup>
Malaria <sup>[18,70]</sup>

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