Review Article

# Respiratory infections: Role of Vitamin D and surfactant proteins A and D

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## ABSTRACT

Respiratory tract infection is the common viral infection and the principal cause of death among children under 5 years of age. It damages lung epithelium and increases mucus production and inflammation, leading to dyspnea. The sunshine vitamin (Vitamin D) and surfactant protein (SP) A and D along with their usual function play an important role in host defense. This article reviews with immune role of Vitamin D and SP A and D which aids excessive cytokines production, boosts phagocytosis, hinders inflammatory activity, and thus acts as a first-line defense against lung pathogens.

**KEY WORDS:** Innate immunity, respiratory tract infection, surfactant protein, Vitamin D

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## INTRODUCTION

Respiratory tract infection (RTI) is the primary cause of death in children under 5 years of age. It is usually caused by various viruses; sometimes, <20% are caused by bacteria or both. Inhaled microbes damage the epithelial lining of the tract and increase the mucus production and inflammation, leading to breathing difficulty. It is the main reason for the financial burden on healthcare services and accounts for a huge proportion of daily consultations of physicians.[1]

Vitamin D and surfactant proteins (SPs) have recently been found to play an important role in preventing infections of the respiratory tract by increasing immunity. Therefore, it is necessary to enhance our current knowledge about the immunological functions of the Vitamin D and SP in the prevention of RTI. This review deals with the information on Vitamin D and SPs immune function.

## VITAMIN D

Vitamin D is usually referred as "sunlight hormone" or "sunshine vitamin" as it is derived mainly from sunlight. It is a secosteroid hormone that is vital to homeostasis of calcium and a pluripotent hormone with vast immunological function. Vitamin D is the only micronutrient which is synthesized by the skin and utilized as a hormone. Skin exposed to ultraviolet-B spectrum coverts 7-dehydrocholesterol in subcutaneous fat to produce an inactive form of Vitamin D. This inactive form is hydroxylated in the liver to form 25(OH) D and converted into the active form 1,25 dihydroxyvitamin D in the kidney.[2-4]

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Synthesis of Vitamin D is affected by latitude, lack of sun exposure, season, use of sunscreen, indoor lifestyle, clothing, air pollution, low intake of calcium, intestinal malabsorption, deficiency of maternal Vitamin D, and obesity (Vitamin D is hidden in adipose tissue).[3,5,6]

Recent studies show that Vitamin D deficiency and insufficiency have a potential role in developing respiratory infection, and ample level of Vitamin D in the body is linked with better lung function. The prevalence of respiratory infection during the winter season is probably due to decrease Vitamin D production resource from sun exposure. Infants with low Vitamin D level in cord blood and low Vitamin D content in breast milk are more prone to developing respiratory infection.[7]

### Immune function of Vitamin D in lungs

The antiricketic Vitamin D alongside with its role in skeletal health is now known for strengthening the immunity by increasing the production of natural antibodies.[8] The innate immunity will take action quickly against the entered pathogen according to the level of immune cells and proteins in the body. Vitamin D builds up the innate immune system by increasing the amount of good immune protein.[9,10] It also operates as immune system modulator, averts excessive production of inflammatory cytokines, and boosts the macrophages activity. Vitamin D that is mediated by Vitamin D receptor (VDR) has wide range of effects on different cells of immune system and expresses innate defense against viruses and bacteria.[6,7] Vitamin D and its receptor manipulate the three foremost immunity troupes of the lungs (airway epithelium, alveolar macrophages, and dendritic cells) in identifying the pathogen and encountering them.[4]

As mentioned earlier, the Vitamin D is converted to active form by two hydroxylation steps. The airway epithelium expresses high levels of 1α-hydroxylase which converts inactive Vitamin D to active form. The active form of Vitamin D kindles cathelicidin secretion and other peptides in the epithelial cell that guard against bacterial and viral infections. Thus, locally generated Vitamin D promotes innate immunity and controls inflammation and tissue damage in the respiratory tract.[4,11,12] It also promotes the adaptive immune response by initiating macrophages and triggering the cells responsible for antigen recognition, the T- and B-lymphocytes.[13] Alveolar macrophages generate active Vitamin D which plays a significant intracrine role in macrophage response to infection. The enzyme 1α-hydroxylase expressed by stimulation of macrophages has favorable effects on host defense.[4,14] Vitamin D has been found to have direct effect on T- and B-cells. Both T- and B-lymphocytes express VDR and 1α-hydroxylase. Vitamin D helps in producing cytokine interleukin (IL)-10 which plays a major role in anti-inflammation and immunosuppressant. Monocyte-derived dendritic cells boost up the function of 1α-hydroxylase and metabolize Vitamin D originator to active Vitamin D. Dendritic cells initiate and regulate the adaptive immunity against the inhaled microbes by maturation. This maturation is exemplified by controlling antigen uptake and activation of inhabitant T-cells. Vitamin D generated by dendritic cells hinders cell differentiation and maturation and increases IL-10 secretion. The inhibition dendritic cell maturation and T-cell hyperresponsiveness had immunosuppressive actions.[4] The enzyme matrix metalloproteinases (MMPs) in the lung is concerned with the inflammation and cell movement. Vitamin D is found to lessen the level of circulating MMPs and thus reduces the lung inflammation.[15] Thus, locally generated Vitamin D in theairways and lungs will minimize the tissue damage and inflammation by clearing the microbes.[4]

### Vitamin D and respiratory viruses

Inhaled respiratory viruses unite first to the nonspecific receptors such as glycolipids or glycoproteins on the respiratory epithelium and endocytosis occur which assists the virus for subsequent reproduction, transcription, and translation of new viruses to infect new cells. The infected cells are predicted by intracellular intrinsic pathogen recognition receptors in the lung epithelium and commence a brisk immune response against viral invasion.[16] At the same time, viral infection amplifies the activation of Vitamin D in the airway and boosts cathelicidin production in the form of LL-37. LL-37 disrupts viral membrane through electrostatic interactions and blocks the viral entry. Vitamin D also slows down proinflammatory cytokine release by macrophages and upregulates the antimicrobial peptides to exhibit antiviral activity.[17]

## VITAMIN D SUPPLEMENTATION

Adequate Vitamin D level lessens the risk of lower RTI.[18] Hence, it is necessary to modify the dietary habits (including oily fish, cod liver oil, organ meats, and egg yolks), exposure to sunlight, and Vitamin D supplementation for overcoming the deficiency. The recommended dose for Vitamin D supplementation is 400–1000 IU for children <1 year and 600–1000 IU for children >1–18 years of age. It is available in the form of drops for infants and chewable tablets for children and adolescence.[19,20]

## PULMONARY SURFACTANT

The surface tension between two media is decreased by a thin film of amphiphilic molecules are called surfactant or surface active agent. The surfactant present in the lung is called pulmonary surfactant which facilitates gas diffusion by reducing the surface tension at gaseous-aqueous interphase, maintains alveolar size, lung compliance, lung tissue elasticity, keeps alveolar dry, and also plays a host defense role.[21]

In humans, the pulmonary surfactant is discriminated between 24 and 34 weeks of gestation. It is a fusion of 70%–80% of phospholipids (dipalmitoylphosphatidylcholine) and phosphatidylglycerol, 10% of proteins (SP A, SP B, SP C, and SP D), and 10% of neutral lipids (mainly cholesterol).[22] The different compounds of surfactant are synthesized by multivesicular bodies from endoplasmic reticulum and Golgi apparatus. The synthesized surfactant is transferred to prelamellar bodies and gathered to form lamellar bodies. The lamellar bodies endure exocytosis form alveolar type II cells to secrete the surfactant into extracellular matrix.[23]

### Immune function of surfactant protein A and D in lungs

Among the four types SP A, B, C, and D, SP A and SP D are a huge glycosylated protein with hydrophilic property and they are the molecular factors of inherent host defense immune system.[21] These proteins contain collagen C-type lectin and belong to collectin family with carbohydrate-binding properties. They attach to the particular carbohydrates and lipid structure on the surface of pathogens (bacteria, virus, fungal, and protozoa) through calcium-dependent interaction and prevent them from penetrating the target cell. It also stimulates alveolar macrophages for opsonization of pathogens. These protein control inflammation and regulate the immune cell activity in lungs.[22] The SP A and SP D make the innate host defense by altering cytokine production, enhancing immune cell chemotaxis and function, and regulating cell proliferation and apoptosis.[24]

### Surfactant protein A and D and respiratory viruses

SP A and SP D in the mucus layer and alveolar surface bind to glycoproteins such as G protein and F protein of respiratory viruses, assist in pathogen elimination by neutralization and clumping, and boost phagocytosis.[25] The G protein is accountable for viral attachment, and the F protein is responsible for infiltration of the virus into the host cells and spreading from cell to cell.[26] SP A binds with oligosaccharides through sialic acid deposits and C-type lectin of SP D binds with carbohydrate structure on the viruses, which inactivates and inhibits hemagglutination activity, thus preventing inflammation, and enhances viral clearance. The immunologic environment of both SP A and SP D aids in host defense and at the same time hinders the inflammatory activities that injury the lung and impair gas exchange.[27]

## CONCLUSION

Vitamin D and SP A and D other than their traditional functions also play a vital role in lung innate immunity. They act as a first-line defense against respiratory viruses, both individually and dependently. They optimize the lung function by improving viral clearance, inhibit inflammation, and boost phagocytosis along with the reverse defense mechanism in the respiratory tract [Figure 1].

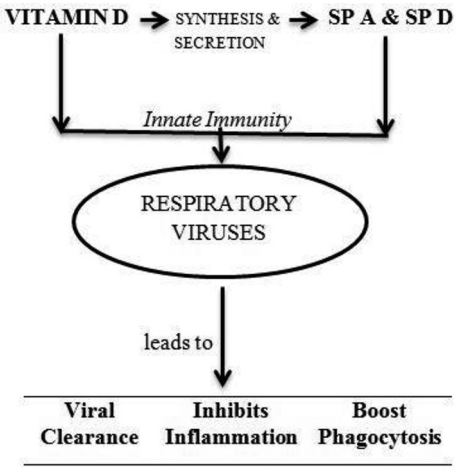


**Figure 1:** Immune function of Vitamin D and surfactant protein A and D

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