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Vitamin D effects on immune response against Covid-19 and influenza infection: A review

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ABSTRACT

Vitamin D could decrease the risk of viral infections with regulation of the immune system response against viral activity. Proper level of 25(OH)D decreases the risk of chronic respiratory tract infections (RTIs), malignancies, hypertension, cardiovascular disease, and diabetes mellitus. Vitamin D can decrease risk of RTIs through some mechanisms. Adequate levels of vitamin D can decrease the level of pro-inflammatory cytokines which predominantly release from innate immune cells. It also can preserve tight junctions in the base membrane. Vitamin D may eliminate enveloped viruses by activating cathelicidin (a protein in the membrane of neutrophils, macrophages, and epithelial cells). These processes can reduce the risk of a cytokine storm and severe pneumonia. Clinical trials have shown the beneficial influences of vitamin D in decreasing the risk of viral pneumonia, dengue fever, hepatitis B, hepatitis C, and herpes infections.

Keywords: Vitamin D, influenza, covid-19, innate immune cells, infections

INTRODUCTION: Viral acute respiratory infections are a prominent cause of disease and global mortality. The viral pathogens which cause acute respiratory infections are picornaviruses, orthomyxoviruses (influenza C, influenza A and influenza B), paramyxoviruses (parainfluenza viruses 1, 2, 3, and 4), human metapneumovirus (hMPV) and respiratory syncytial virus (RSV), adenoviruses, human bocavirus (HBoV), and coronaviruses [1, 2]. The seasonal influenza vaccine is the only viral vaccine which is administered for the viral respiratory pathogen in the United Kingdom. This vaccine is not 100% efficient and may require repetitive administrations in order to achieve proper levels of protection against influenza infection, especially in older individuals [1]. Effective antiviral drugs (such as Oseltamivir) for treatment of influenza are not available in many countries [2]. Vitamin D exerts an immunologic role in plasma levels around 50 nmol/liter. Several studies have been performed to characterize the connection between the severity of acute viral infections of respiratory systems and plasma levels of vitamin D. Clinical trials for vitamin D supplementation for the inhibition of acute respiratory infections have controversial results [4]. Moreover, several in vitro studies have examined the effects of vitamin D and its metabolites on immune responses against respiratory viruses without significant results [5]. Thus, we reviewed studies about respiratory infections (such as SARS-CoV-2 and influenza), immune system reactions against them, and the role of vitamin D in the process of infections.

Innate Immune Response with Vitamin D: Respiratory viruses can spread via airborne transmission of droplets and aerosols among humans. Some of these viruses bind to non-specific receptors, such as glycolipids and glycoproteins, in the epithelium of the respiratory tract of the respiratory system. For example, they bind to intercellular adhesion molecule 1 (ICAM-1) [6]. After binding to epithelial cells, viruses can enter into the cells by endocytosis or membrane fusion. Then, the viruses perform reproductive activity (transcription and translation of genome, respectively) through intracellular enzymes of the infected host cells. During the infection of host cells, the innate immune system can recognize the pathogen-associated molecular patterns (PAMPs) of the virus. This occurs by using various intracellular innate pathogen recognition receptors (PRRs) such as the nucleotide binding-oligomerization domain (NOD)-like receptors (NLRs), toll-like receptors (TLRs) and retinoic-acid-inducible gene-I (RIG-I)-like receptors (RLRs) [7]. Epithelial cells of the pulmonary system show a wide variety of molecular expression of all human RLRs and TLRs. RLRs and TLRs identify viruses and ligand to the PRRs of epithelial cells in order to initiate a quick immune response against viral multiplication [8, 9]. In addition, SARS-CoV-2 may infect dendritic cells and tissue-resident macrophages of the respiratory epithelium. Aside from mentioned mechanisms, stimulation of PRRs could also initiate the innate immune response [10].

The intracellular toll-like receptors including TLR 9, 8, 7 and 3 (relative to UNC93B1 structure) are mostly sited on the endoplasmic reticulum (ER) membrane [11]. These nucleic acid-sensing TLRs identify unmethylated CpG double-stranded DNA motifs (TLR 9), intermediary double-stranded RNA (TLR 3), or single-stranded RNA (TLR 8/7) of the viral genome [12]. After detection of genetic components of viruses through noted TLRs, these receptors send molecular signals to UNC93B1 in order to signal the release of inflammatory cytokines such as IL-1B, IL-6, IL-18, and TNF-α from the cells of the innate immune

system. Simultaneously, in order to eliminate foreign molecules, the component of the nucleic acid of virus and TLR are transmitted into the lysosome. Besides TLRs, other innate immunity receptors like RLRs (a receptor similar to RIG-I) in the cytosol play a crucial role in the immune response against several RNA viruses [13]. Another innate immunity receptor is MDA5 (melanoma differentiation-associated gene 5) which plays an important role in detecting picornaviruses [14]. Furthermore, the cytosolic NOD2-NLRS also have the capability to detect ssRNA related to RSV. IRF (Interferon Regulatory Factor), a protein related to innate immunity in the cytoplasm, can detect the genome of viruses which leads to release of INF- I (IFN- β and IFN- α) from the cell. INF-I stimulates MAPK (mitogen-activated protein kinase) and NF-κB (nuclear factor kappa B) signaling pathways which cause production of various inflammatory cytokines [15].

Triggering of the IFN- I receptor induces expression of ISGs (interferon-stimulated genes) which results in antiviral responses of the host tissue. These genes induce apoptosis in infected host cells that leads to macrophages scavenging them. These genes also provoke up-regulation of HLA class I in infected cells, which promotes activation of cytotoxic T cells. These mechanisms lead to the restriction of a viral infection [16, 17].

Inflammatory cytokines such as IL-6, TNF-α, IL-12, IL-1β cause infiltration of neutrophils, macrophages, and NK cells into the lung tissue. TNF-α and IL-1β can also cause stimulation of MAPK and NF-κB pathways

[18]. Activation of PRR (pattern recognition receptor) signaling in viral infections causes the release of IL-15 and CXCL10, CXCL8, CXCL9. These chemokines accelerate the infiltration of neutrophils and NK cells into the respiratory system [19]. Antiviral functions of macrophages and neutrophils in respiratory infections are relatively unknown [20]. It seems that the antigen presenting capacity of macrophages is limited in viral infections of the respiratory system. However, antiviral activity of LL-37 in macrophages and neutrophils have been investigated [21]. Due to lower levels of CD11b, a phagocytic receptor of macrophages, they have less phagocytic activity than their counterparts in other tissues [22]. In addition, alveolar macrophages have an essential role in the phagocytosis of infected cells and cleaning of apoptotic cellular debris in lung tissue. They also release pro-inflammatory chemokines such as CXCL10, CXCL9, TNF-α, IL-6, and IL-8 which cause increased infiltration of inflammatory cells into the lung tissue. In the absence of alveolar macrophages (or decreased function of macrophages), viral infection of lung tissue can lead to accumulation of inflammatory cells, serum proteins, and apoptotic debris in airways (as well as airway obstruction) [23, 24].

Adaptive Immune Response with Vitamin D: PRR signaling accelerates attraction of dendritic cells towards infected cells via over-expression of CCR7 and CCL20 in the membrane of epithelial cells of the respiratory tract [25]. In the beginning of a viral infection, dendritic cells interact with CD4+ and CD8+ naïve T cells which differentiate them into effector T cells in lymph nodes. Effector cells of T helper 1 can produce IFN-γ, IL-2 and TNF-α which cause stimulation of NK cells in order to secrete cytoplasmic granules. These cytokines can also activate CD8+ effector T cells which induce apoptosis of infected cells through Fas ligand and Fas receptor interaction

[26]. B cells have an essential role in immune activity against viral infection through production of antibodies. After the immune system is exposed to a foreign protein (an antigen), the antigen is recognized

by the BCR (B Cell Receptor) and transported into the B cells through receptor-mediated-endocytosis. After degradation of the antigen in B cells, it can be present in the membranes of these cells with the complex of HLA-II [27, 28]. The follicular T helper binds to the peptide complex with TCR (T Cell Receptor) and then CD40L appears in the membrane of the T cell [29]. The interaction between CD40L and the CD40 receptor of B cells, in addition to the release of cytokines like IL-4 and IL-21, results in B cell stimulation and antibody switching. The majority of the production of antibodies from B cells is dependent on the noted T cell-B cell interaction process [30].These antibodies develop humoral immunity against viral infections and facilitate the eradication of viral components from the blood. In the opsonization process, the Fc part of IgG binds to Fcγ receptor (CD16) of NK cells which causes activation of these cells against infected cells [31]. Activation of NK cells through the Fc part of antibody, called antibody-dependent cellular toxicity, causes death of infected cells by releasing perforin and granzyme [32].

Special Effects of Vitamin D on the Innate Immune Response:

1. Cathelicidins are a group of antimicrobial polypeptides which are primarily stored in lysosomes of macrophages and polymorphonuclear cells. LL-37 and defensin are members of this subset which are produced by various immune and immune-related cells such as epithelial cells, B cells, monocytes, γδ T-cells and NK cells [33]. Primary defense against viruses and bacteria is built through the accumulation of polypeptides from the respiratory epithelium. LL-37 can also induce infiltration of different immune cells into lung tissue after exposure to RSV. Hence, proper levels of vitamin D can upregulate the expression of LL-37 and defensin which can potentially prevent the entrance of micro-organisms into the respiratory epithelium [34].
2. Vitamin D inhibits the transformation of monocytes into macrophages. Additionally, the impairment of M1 (inflammatory) type of macrophages can modulate inflammation of respiratory tissue [6].
3. Vitamin D signaling can have decreased NF-κB activity. It also may decrease autophagy through activation of NF-κB, TNF-α, and IFN-γ [35]. Simultaneously, vitamin D signaling can have increased autophagy through elevated cytosolic calcium, Beclin-1, cathelicidin, PI3KC3, lysosomal protease activity, NOD-2. Increased level of autophagy is essential for controlling inflammation in the immune system. However, development of RSV infection has been demonstrated in decreased levels of autophagy [36].
4. Effects of high levels of vitamin D on oxidative stress have also been investigated. The PI3KC3 (class III phosphatidylinositol 3-kinase complex) pathway, which is regulated by vitamin D and vitamin D receptor signaling, can increase the generation of Reactive Oxygen Species (ROS) and Inducible Nitic Oxide Synthase (iNOS) in monocytes and macrophages. This molecular setting may lead to a beneficial response against viral infection [37].
5. Vitamin D can boost expression of TLR2 and TLR4 in monocytes which can help in detecting a viral genome [38].
6. Higher levels of vitamin D also can reduce expression of CD86 in antigen presenting cells, such as macrophages and dendritic cells [39]. CD86 is a receptor with an important role in

antigen presentation to T cells. Vitamin D can also decrease expression of CD80, CD40, and HLA- II, which have a co-stimulatory role in antigen presentation to T cells in macrophages and dendritic cells [40]. Mentioned molecular changes in the membrane of APCs (Antigen Presenting Cells) may have modulatory effects on T cells [41]. This molecular pattern, along with decreased expression of CD1a in dendritic cell membranes, can prevent maturation of these cells and induce differentiation of tolerogenic dendritic cells [42]. Tolerogenic dendritic cells inhibit production of IL-12 from T helper 1 and IL-23 from T helper 17 [43, 44]. These cells can induce differentiation of regulatory T cells from naïve T cells. Tolerogenic dendritic cells can also decrease the number of T helper 17 cells in the blood stream. Due to stimulatory role of IL-17 in neutrophils, this process can potentially reduce inflammatory activity of neutrophils [45, 46]. Tolerogenic dendritic cells can also produce IL-10 and TGF-β. These cytokines act as immunoregulatory agents with several biologic pathways [47, 48].

7. Vitamin D can also decrease the expression of pro-inflammatory chemokines such as CCL11, CCL 19, CXCL1, CX3CL1, and CXCL10 in infiltrated macrophages [49].

Effects of Vitamin D on the Adaptive Immune Response: Vitamin D can regulate the interaction among innate and adaptive immune cells with modulation of dendritic cells activity, as explained previously [50]. LPS stimulated PBMCs (Peripheral Blood Mononuclear Cells) can be affected by vitamin D signaling in terms of down regulating of NF-Kb and TNF-α [51]. Moreover, differentiation of T helper 2 cells is related to vitamin D signaling through increasing the gene expression of c-Maf and GATA3. T helper 2 cells can produce IL-4, IL-10 and IL-5β which have different effects on immune cells [52]. Effects of vitamin D on CD8+ (cytotoxic) T cells are not yet understood. However, in patients with Multiple Sclerosis, vitamin D can inhibit the production of INF-γ, TNF-α and increase the level of TGF-β and IL-5β in cytotoxic T cells [53, 54].

Effects of Vitamin D on the Immune Response to Influenza Virus and Coronavirus

Influenza Virus: Influenza, commonly known as "the flu", is an infectious disease caused by an influenza virus. The subtypes of this virus that involve the respiratory system of human are influenza A, B and C. Influenza A is a common seasonal virus. It is subdivided into different serotypes based on the antibody response of the immune system against this group of viruses. H1N1, informally called the Spanish flu, caused a great pandemic which infected about 500 million of people in the world in 1918. Another subtype of influenza A is H5N1, which caused bird flu in 2004. Type B influenza virus cannot cause rapid outbreaks due to a lower rate of infection among humans. Influenza C is less common than other types of this disease and usually causes mild illness in children [55].

Vitamin D supplementation may have promising results in respiratory infection with influenza as shown in a clinical trial of vitamin D supplementation in Japanese students. Another study has shown that vitamin D supplementation decreased genes expression of CXCL8, IFN-β, RANTES (CCL5), TNF-α, IL-6, and ISG15 [34]. Noted regulatory function of vitamin D on immune response is important due to limiting excessive inflammation which may cause injury, such as pulmonary edema or cytokine storm, to host tissue. These pathologic processes are capable

of developing the infection and raising the mortality rate of influenza.

LL-37 has antiviral properties against influenza in terms of inhibition of viral replication and prevention of the virus from entrance into the epithelium. Due to the rise in LL-37 polypeptide expression with higher levels of vitamin D, this molecular pathway is important in influenza infections [56-58]. However, more clinical studies should occur for assessment of correlation between higher levels of vitamin D and severity of influenza infections.

SARS-CoV-2 (COVID-19): Vitamin D has great potential to decrease the risk of viral pandemics and epidemics. Higher levels of 25(OH)D can decrease the risk of several chronic diseases such as chronic respiratory tract infections (RTIs), cancers, hypertension, cardiovascular disease, and diabetes mellitus [59-63]. Patients with chronic diseases have a greater risk of death from RTIs than healthy individuals. Vitamin D decreases the risk of RTIs through a few mechanisms: reducing the release of pro-inflammatory cytokines which are produced by the innate immune system, preserving tight junctions, killing enveloped viruses through cathelicidin and its components, and reducing the risk of a cytokine storm which may lead to pneumonia [59, 64-66]. Clinical trials have shown that higher levels of 25(OH)D are related to decreased risk of pneumonia, dengue fever, hepatitis B and C viruses, herpesvirus, human immunodeficiency virus, and RSV (respiratory syncytial virus) infections [67-69].

Conclusion: Some effects of vitamin D on the immune system such as increasing the level of IL-1β may not help with modulating the immune response versus viral infections of respiratory system. However, it seems that sufficient levels of plasma containing vitamin D (around 50 ngr/mL) are crucial for proper immune response for respiratory infections with different viruses. An effective primary immune reaction against viral infections would help the respiratory system to restrict the replication of the virus without serious damage of host cells. Therefore, proper levels of vitamin D may have regulatory effects on immune system and improve the clinical outcome of patients with COVID-19. However, understanding the precise role of vitamin D in SARS-CoV-2 infection requires more clinical studies.

Abbreviations: RTIs: chronic respiratory tract infections; hMPV: human metapneumovirus; RSV: respiratory syncytial virus; HBoV: human bocavirus; ICAM-1: intercellular adhesion molecule; PAMPs: pathogen-associated molecular patterns; PRRs: pathogen recognition receptors; TLRs: toll-like receptors; NOD: nucleotide binding-oligomerization domain; RIG-I: retinoic-acid-inducible gene-I; ER: endoplasmic reticulum; MDA5: melanoma differentiation-associated gene 5; IRF: Interferon Regulatory Factor; MAPK: mitogen-activated protein kinase; NF-κB: nuclear factor kappa B; ISGs: interferon-stimulated genes; BCR: B Cell Receptor; PI3KC3: phosphatidylinositol 3-kinase complex class III; ROS: Reactive Oxygen Species; NOS: Nitic Oxide Synthase; APCs: Antigen Presenting Cells; PBMCs: Peripheral Blood Mononuclear Cells; *25-OH D3*: *25-Hydroxyvitamin D3*

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