Immunomodulatory Effects of Vitamin D in Influenza Infection

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Abstract: Background: Vitamin D has mainly been described in the literature beyond its skeletal functions, including an influence on the immune responses against infections. Observational and interventional studies have represented evidence that Vitamin D deficiency may cause increased risk of seasonal influenza and pulmonary tract infection.

Methods: A structured search of EMBASE, Medline, and Web of Science databases was fulfilled to extract all eligible articles published prior to September 2017.

Results: In this review, our goal is to define the possible mechanisms that link influenza-mediated immune responses to Vitamin D. Herein, we first briefly describe the role of Vitamin D in the immune responses and then elucidate three immunological processes that connect Vitamin D to influenza infection. Finally, we describe randomized controlled trials and observational studies exploring the effect of Vitamin D supplementation on seasonal influenza infections and vaccinations.

Conclusion: Our literature review suggests that treatment of influenza-infected individuals with Vitamin D supplements or cathelicidin-derived agents may provide appreciable protection against natural influenza infection. Moreover, Vitamin D given at appropriate doses may facilitate protection against seasonal flu.

Keywords: Vitamin D, influenza virus, infection, immune response, infection, immunomodulatory effect.

1. INTRODUCTION

Vitamin D or 1,25-dihydroxyvitamin D (1,25(OH)2D) is increasingly being identified as a pluripotent hormone that can regulate immune responses with roles that expand beyond its classical function in calcium homeostasis [1, 2]. Previous studies have demonstrated that effector immune cells, mostly peripheral blood mononuclear cells (PBMCs), express Vitamin D receptor (VDR) that mediates all known Vitamin D associated biological effects, and are able to metabolize the 1,25-dihydroxyvitamin D, the active form of Vitamin D [3, 4]. This implies that Vitamin D could be a substantial element in the immune response circumstance against infection [5]. Moreover, the role of Vitamin D in immune modulation has been demonstrated in many studies [6]. In vitro activated T- and B-cells can transform the 25-hydroxy Vitamin D, the inactive form of Vitamin D, to 1,25-dihydroxy Vitamin D in human cells [7]. Therefore, the regionally produced 1,25-dihydroxy Vitamin D has an effect on immune cells in an autocrine or paracrine pattern. Previous studies have demonstrated that Vitamin D plays critical roles in adaptive or innate immune responses against viral and bacterial infections. It has been reported that there was a considerable association between Vitamin D deficiency and respiratory diseases such as respiratory syncytial virus infection [8-11], tuberculosis [12], influenza [13], and other pulmonary disorders [14, 15]. Epidemiologic evidence also has proposed a significant correlation between Vitamin D concentrations and the outbreak of pulmonary infections [16] like influenza [10, 17]. Also, seasonal variations in serum Vitamin D concentrations have been observed [8]. The winter incidence of influenza negatively correlates with seasonal serum Vitamin D levels [18, 19].

In this review, we discuss the role of Vitamin D in the modulation of innate and adaptive immune responses to influenza virus infection. We will also mention observational and randomized controlled trials of Vitamin D supplementation in humans and the association of Vitamin D deficiency with increased risk of influenza infection. Finally, we will note the latest therapeutic approaches with regard to the relationship between Vitamin D supplementation and recovering from influenza infection.
1.1. The Role of Vitamin D in Immunity and Barrier Function

Vitamin D is a secosteroid hormone, generated from 7-dehydrocholesterol in the skin after exposure to ultraviolet B (UVB) light and is also stored in and supplied from certain nutrients [20]. When investigating the role of Vitamin D in immunity to influenza viruses, it is worth highlighting some of the key mechanisms involved in the host defense against infectious agents. Epithelial cells covering the skin and the outer layer of the respiratory, gastrointestinal, and genitourinary tract, constitute the first level of defense, which maintains tissue integrity against invasion by infectious agents [21]. In addition, Vitamin D induces the expression of genes, which are involved in the gap junctions (e.g. connexin 43), tight junctions (e.g. occludin) and adherens junctions (e.g. E-cadherin) [22]. The capacity of Vitamin D to boost antimicrobial responses to a pathogenic challenge has been shown to be highly associated with tissue-specific synthesis of 1,25-dihydroxy Vitamin D [23]. These effects of Vitamin D are mediated by its binding to VDR, also known as nuclear receptor subfamily 1, group I, member 1 (NR1I1). VDR is a nuclear receptor that is dimerized with an isoform of the Retinoid X Receptor (RXR) upon binding to its ligand [24, 25]. These heterodimers of VDR-RXR then bind to Vitamin D response elements (VDRE), which exist on target genes [26]. Furthermore, the heterodimers of VDR-RXR can be replaced by the nuclear factors of activated T cells that eventually lead to repression of cytokine-related genes like interleukin (IL)-2 [27] (Fig. 1).

It has been reported that 1,25(OH)2D could inhibit Th1 cell proliferation, resulting in decreased production of interferon (IFN)-γ and IL-2 [28]. Decreased production of IFN-γ can lead to impaired antigen presentation by dendritic cells (DCs), resulting in reduced proliferation and recruitment of lymphocytes [29]. Unlike Th helper 1 (Th1) cells, Vitamin D increases the expression of Th2 associated cytokines such as IL-4, which polarize the cellular immune response towards the Th2 phenotype [30, 31].

Furthermore, it has been reported that the active form of Vitamin D could modulate innate immune responses [23, 32]. Toll-like receptors (TLRs) are key components of innate immune responses that recognize Pathogen Associated Molecular Patterns (PAMPs) such as viral proteins and nucleic acids. Following ligation, stimulated TLRs induce the production of cytokines, antimicrobial peptides [33], and reactive oxygen species (ROS) [34].

Interestingly, the expression of several TLRs can be affected by VDR induction. For instance, the expression of CD14, the co-receptor of TLR4, is stimulated by Vitamin D in epidermal keratinocytes and monocytes [35, 36]. Stimulation of TLR2 in macrophages leads to the upregulation of cytochrome P450 family 27 subfamily B member 1 (CYP27B1, 1α-hydroxylase) that facilitates the conversion of Vitamin D to its active form [37, 38]. There is a significant correlation between 1,25(OH)2D levels and expression of TLR related anti-microbial peptides [39, 40]. Human beta defensin 2 (HBD2), a potential chemoattractant for polymorphonuclear cells and monocytes, is up-regulated by 1,25-dihydroxy Vitamin D [23, 41]. However, vitamin D is inadequate for effective activation of monocytes [42]. Human cathelicidin, an endogenous antibacterial peptide also known as cationic host defense peptides, is another

Fig. (1). Metabolism and biological effect of 1α;25(OH)2D3. Vitamin D is either supplied from dietary sources or skin surface production following UVR. The 25 hydroxylation in the liver leads to production of 25(OH)2D3 (low activity), which is converted to 1,25(OH)2D3 in kidney. The active form of Vitamin D (1α;25(OH)2D3) then attaches to nuclear VDRs; which induces the heterodimerization of VDR with RXR in nucleus and binds to VDRE in the promoter regions of target genes. The 1,25(OH)2D3 act as a key intermediate molecule between innate and adaptive immune responses. Vitamin D3 modulates adaptive immune response through inhibition of maturation and antigen presentation of DCs and macrophages.
antimicrobial peptide induced by TLR1/2 stimulation in many immune cells [43].

In humans, the cleavage of propeptide hCAP18 can lead to the production of active antimicrobial cathelicidin peptide LL-37 [44]. In addition to the polymorphonuclear cells, other types of immune cells including natural killer (NK) cells, B cells, and monocytes express the hCAP18, revealing that this propeptide is a substantial element in the immune response to infections [45]. Considering this, several types of immune cells highly express cathelicidin in response to 1,25(OH)2D because of VDR response element [46]. At the cellular level, the expression of 1α-hydroxylase by keratinocytes and macrophages induces cathelicidin expression [47]. Recently, it has been demonstrated that the ability of macrophages and keratinocytes to produce cathelicidin is considerably impaired in the absence of 1,25(OH)2D, VDR, or 1-alpha-hydroxylase [48]. The peptide LL-37 of cathelicidin, also has anti-viral effects on a wide range of respiratory viruses [49]. Altogether, the production of cathelicidin LL-37 in human alveolar macrophages, which has anti-viral effects in influenza infection, is increased by VDR overexpression [50].

1.2. Role of Vitamin D in Influenza Infection

The upregulating role of Vitamin D on cathelicidin expression could be one of the mechanisms explaining the anti-viral activity of Vitamin D in influenza infection [51, 52]. Decreased production of pro-inflammatory cytokines by the vitamin D metabolite, 1,25(OH)2D, could be another mechanism [53]. Interestingly, an amazing observation made after the H1N1 influenza pandemic (1918–19) was that the mortality rate was higher in young people compared to infants and the elderly [54, 55]. The reason for this difference might be that young adults have a more robust immune system, making them prone to develop overt inflammatory immune responses to infection. It has been demonstrated that both H1N1 and H5N1 serotypes of influenza viruses induce a Th1 type cell-mediated immune response [56-58]. This type of immune response produces proinflammatory cytokines such as IL-6 and tumor necrosis factor (TNF)-α, which may aggravate disease severity [33]. Studies show that 1,25-dihydroxy vitamin D could modulate influenza associated inflammatory responses [52]. Moreover, 1,25(OH)2D inhibits the differentiation of Th1 cells, thus, skewing the Th1/Th2 balance towards a Th2 response, leading to the suppression of inflammatory responses caused by influenza (Fig. 2) [59, 60].

1.3. Promoting Innate Immune Responses by Production of Antimicrobial Peptides

The established function of Vitamin D in inducing overexpression of cathelicidin could directly link influenza

**Fig. (2).** The ability of Vitamin D to promote anti-influenza responses. Macrophages and epithelial cells of the pulmonary tract are the main targets of influenza A virus invasion. In response to influenza infection; epithelial cells and macrophages produce a large number of cytokines and chemokines; including antiviral IFN-α/β, MCP-1; RANTES; MIP-1α CXCL-8; and etc. Anti-viral responses to a pathogenic challenge seems to be mainly dependent on tissue specific synthesis of 1; 25(OH) 2D.
infection and vitamin D [51, 61]. Cathelicidin LL-37 has been reported to have both direct microbicidal effect and a wide range of immunomodulatory properties, including modulation of neutrophil activity, death of infected epithelial and neutrophils, stimulation of autophagy in infected macrophages, and promoting the proliferation and function of DCs [43, 62, 63]. Most of these innate immunity processes can profoundly impact the outcome of influenza infection in both humans and mice [50, 64].

The potent anti-influenza activity of human and mouse cathelicidin has been shown in vitro and in vivo. For instance, the administration of this anti-microbial peptide protects mice against influenza virus infection [20, 42, 51]. Barlow et al. also observed that anti-viral activity of murine and human cathelicidin (mCRAMP and LL-37, respectively) was comparable to zanamivir, an influenza virus-specific drug, in decreasing disease severity and viral load [65]. In vitro and in vivo experiments have proposed that LL-37 may act directly on the influenza virus instead of receptor-based mechanisms [50, 65]. Treatment of influenza-infected mice with cathelicidin LL-37 decreases pro-inflammatory cytokines levels in the lungs compared to the infected mice without cathelicidin treatment [65].

Overexpression of LL-37 by leukotriene B4 (LTB4) is correlated with amelioration of influenza A infection in mice [66]. Cathelicidins are able to modulate influenza associated inflammatory responses and increase responses to IL-1β [67]. Interestingly, IL-1β has been reported to be an essential component of host immunity in murine respiratory influenza infection [68]. Study conducted by Shweta et al. also supported the idea that the ability of LL-37 to inhibit influenza A virus strains mainly resulted from the direct effects on the virus [51]. Unlike human neutrophil defensins (HNPs) and collectins, LL-37 did not induce viral aggregation and it was revealed that cathelicidin directly targeted the lipid envelope of virus for disruption. It has been shown that LL-37 and defensins did not inhibit hemagglutinin (HA) activity of the Phil82 or PR-8 strains of influenza A virus as determined by the HA inhibition assay [69, 70].

1.4. Negative Regulation of NF-κB and Anti-Influenza Activity

Cells lacking VDRs are more prone to generate proinflammatory cytokines and chemokines due to intrinsic higher nuclear factor (NF)-κB signaling activity. This indicates that VDR signaling pathway potentially inhibits NF-κB activation [71]. The ability of VDR agonists to suppress NF-κB activation has been demonstrated in various cell types [72, 73]. For instance, Elocalcitol as an agonist of vitamin D, inhibits IL-8 production, which leads to downregulation of cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2) expression and inhibition of NF-κB p65 nuclear translocation [74].

Activation of NF-κB is the main feature of most viral infections [33]. Induction of NF-κB by influenza virus requires activation of inhibitor of NF-κB (IκB) kinase (IKK) [75]. Isolated structures of the influenza virus such as overexpressed viral HA, nucleoprotein [9] or matrix-protein-1 (M1), and double-strand RNA (dsRNA) can also activate IKK [76]. Expression of various pro-inflammatory and antiviral cytokines such as TNF-α and IFN-β is also induced by NF-κB. In addition, the influenza virus-induced activity of the IFN-β promoter is significantly impaired in cells overexpressing the transdominant negative mutants of IκBα or IκK2 [77].

It has been reported that an active NF-κB signaling pathway is a common prerequisite for influenza virus infection in the cells of the pulmonary system [78]. Cells with low NF-κB activity are resistant to influenza infection, whereas upregulation of NF-κB leads to vulnerability to influenza infection. Furthermore, blocking of NF-κB signaling pathway prevents influenza virus infection [78]. Treatment of the human lung A549 epithelial cells with 30 and 100 nM of calcitriol 1,25(OH)2D3 before and/or after H1N1 exposure has been shown to have no considerable effect on the viral load but significantly decreased autophagy and recovered apoptosis in H1N1 infection back to its prior levels [79]. Moreover, calcitriol has significantly reduced the levels of H1N1-induced IFN-stimulated gene-15 (ISG15), TNF-α, and IFN-β [79]. Vitamin D treatment prior and/or post-H1N1 infection downregulated the mRNA levels of IL-6 and IL-8. In epithelial cells, vitamin D inhibited the H1N1-induced transcription of the inflammatory chemokines including regulated on activation, normal T cell expressed and secreted (RANTES) and IL-8 [79]. Type-1 IFNs are antiviral cytokines that particularly regulate gene expression via several signaling pathways like NF-κB [77]. In the study of Lai Wei et al., several immunomodulatory and antiviral genes were strongly induced by IFN in NF-κB deficient embryonic fibroblasts. Chromatin immunoprecipitation (ChIP) analyses demonstrated that NF-κB was directly bound to the promoters of IFNs genes while the treatment of cells with IFN led to binding of STAT1 and STAT2 to IFNs promoters. However, in NF-κB deficient cells, IFNs induced binding of IFN regulatory factor-1 (IRF1) to the promoters of interferon-stimulated gene (ISG). Moreover, it has been shown that NF-κB inhibits both antiviral and immunomodulatory functions of IFNs against influenza virus [80, 81]. Taken together, these findings provide a potential molecular mechanism whereby the action of 1, 25(OH)2D on NF-κB pathway may affect influenza virus infection.

1.5. Th1/Th2 Polarization

Previous studies have demonstrated that 1,25(OH)2D affects the Th cell polarization by inhibiting the development of Th1 cells, suppressing the inflammatory and IFN-producing cells, promoting Th2 cells development, and induction of anti-inflammatory responses through IL-4, IL-5, and IL-10 [45, 82]. These effects of vitamin D indicate that CD4+ T cells can be direct targets for this nutrient [31]. Considerably, higher serum levels of TNF-α, IL-17, IL-8, and also IL-6 were detected in patients hospitalized with pandemic influenza A virus [83].

Primary cytokine response including IFN-α, TNF-α, and IL-1 is initiated by infected cells at the site of infection and they are responsible for local and systemic inflammatory responses [84]. These cytokines are quickly followed by increased levels of IL-6 and several chemotactic cytokines including monocyte chemoattractant proteins (MCPs), macrophage inflammatory proteins (MIPs) and IL-8, a
Subsequent studies have confirmed the involvement of inflammation and influenza infection [87]. Furthermore, there are many other studies that have examined the therapeutic effect of Vitamin D on influenza infection. Vitamin D could decrease influenza pathogenesis and shift the inflammatory response away from Th1 towards Th2 anti-inflammatory response [97]. The severe mortality and morbidity of influenza infection is mainly related to upregulation of inflammatory cytokines. Associations of various metabolic pathways with inflammatory cytokines have been established [98]. In addition, IL-10 is associated with a cluster of 94 metabolites including carboxychromanol, calcitriol, and acylcarnitine. This indicates the potential immunomodulatory roles of Vitamin D3 in influenza infection (Fig. 3). These new findings imply that targeted inhibition of metabolic pathways and/or supplementation of Vitamin D in response to cytokine profiles may stabilize metabolic pathways and protect against adverse outcomes of influenza infection [97].

1.7. Intervention and Therapeutic Approaches

The number of studies that have examined the therapeutic effect of Vitamin D on influenza is not adequate. However, there are studies that have evaluated the therapeutic effect of Vitamin D for influenza and some of them have shown a
significant association between Vitamin D status and the persistence of the influenza infection [13]. A recent cohort study showed that serum Vitamin D concentrations were not correlated with a significantly lower risk of influenza infection, whereas, in retrospective subgroup analyses, Vitamin D sufficiency was significantly correlated with a lower risk of influenza infection in non-vaccinated subjects [99, 100]. In another study, it was demonstrated that maintenance of a serum concentration of 1,25(OH)2D at least 38 ng/ml could significantly decrease the severity of acute viral pulmonary tract infection and the burden of influenza disease during the cold seasons in temperate regions influenza (Sabetta et al, 2010). Furthermore, individuals with lower serum concentrations of Vitamin D, had a twice as high risk of developing severe flu infection compared to individuals with high serum levels of Vitamin D [17].

Ultraviolet radiation (UVR) has both Vitamin D-dependent and independent consequences on influenza infection. Primarily, Vitamin D and UVR participate in common pathways of innate immune activation via induction of antimicrobial peptide synthesis and inhibition of adaptive immune responses. While UVR can initiate Vitamin D independent effects in the skin, such as induction of IFN signaling pathways via photoproducts, 1,25(OH)2D has broader systemic effects due to its paracrine and autocrine modulation of cellular responses in a variety of tissues [101]. William et al. analyzed the death rate of individuals suffering from pneumonia with regard to estimation of wintertime and summertime solar Ultraviolet-B (UVB) doses as an index of people's mean Vitamin D level status. In that study which explored the deaths related to the large 1918-1919 influenza virus pandemic, they revealed that the lowest influenza-related case fatality rates in the United States were found in regions with the highest exposure to solar UVB light, leading to increased Vitamin D synthesis. In contrast, the highest influenza case fatality rates were found in region with lowest exposure to solar UVB [102].

People with sufficient Vitamin D could recover from influenza infection sooner than people with low levels of Vitamin D. It has been revealed that people with serum Vitamin D concentrations above 38 ng/mL recovered from influenza within an average of 2 days; on the other hand, people with Vitamin D levels lower than 38 ng/mL took an average of 9 days to recover from influenza infection [17, 103]. In a 3 year placebo-controlled longitudinal study conducted in the United States, one group of old African-American women given 800 IU of 1,25(OH)2D per day for 2 years, then 2,000 IU Vitamin D per day for the third year experiences significantly fewer influenza-like illness symptoms compared to the placebo group. Interestingly, when the dose of Vitamin D was at 2,000 IU per day, only one person in the Vitamin D group had influenza infection. Compared to 30 out of 110 women in the placebo group. Moreover, the placebo group showed influenza-like symptoms mainly during the winter, whereas who got influenza infection in the Vitamin D group manifested symptoms regardless of the season [104].

In addition, a Japanese study investigating the preventive effects of Vitamin D supplementation on influenza infection risk in school children, showed that pupils given vitamin D (1200 IU) during the winter season for 12 weeks experienced markedly lower rates of influenza A infection than placebo-treated children, although such differences were not found for influenza B. [8]. A UK study showed that for each 4 ng/ml rise in serum Vitamin D levels, there was a 7% lower risk of contracting influenza infection. Also, the seasonal pattern of Vitamin D levels was similar to that of influenza infection [14]. Nevertheless, a meta-analysis of studies conducted on acute respiratory infections in healthy children did not show any significant prophylactic effects on the routine use of Vitamin D supplementation. The authors proposed that such supplementation might be effective in children with previously diagnosis of asthma [105]. It has been reported that human blood levels of Vitamin D correlates with IgM and IgG isotypes and ratios [106, 107]. However, Vitamin D failed to enhance seasonal influenza vaccine humoral immunogenicity. For instance, vitamin D levels did not correlate with seroprotection (HAI ≥40 and 4-fold increased between pre- and post- vaccination) to seasonal influenza vaccine in people aged 50 and over [108]. In contrast, another study reported that Vitamin D deficiency was associated with a higher rate of seroprotection with a pandemic influenza vaccine [79]. A prospective cohort study of children (3-15 years) showed that serum Vitamin D levels were not correlated to influenza vaccine immunogenicity in healthy children and adolescents [109].

Furthermore, the impact of Vitamin D on influenza vaccine immunogenicity in HIV-positive patients was also evaluated using data from a phase 3 randomized trial during the 2008–2009 pandemic influenza season. Approximately 33% of the subjects were on supplementation with Vitamin D at the initiation phase of the study. Cooper et al. showed that there was no evidence of augmented influenza vaccine immunogenicity with 1,25(OH)2D supplementation in the HIV-infected adults [110]. In agreement with this study, the study of Nancy et al. showed the same results [111] (for summary see Table 1).

In agreement with other studies, Sadarngani et al. did not find any significant correlation between baseline Vitamin D levels and seroprotection. However, they found a marginal positive correlation between baseline Vitamin D levels and alteration in influenza-associated Granzyme B cellular responses. The serine protease Granzyme B generated by DCs, NK cells, and cytotoxic T cells induces cytotoxic T cell-mediated apoptosis of influenza infected cells. Moreover, Granzyme B has been assigned a prominent role in cell mediated immunity to influenza vaccine [112]. Also, influenza-associated Granzyme B responses have been shown to negatively correlate with aging [113]. Overall, no obvious association was shown between Vitamin D levels and humoral immune responses to influenza vaccination in elderly people. In children as well as in elderly people, Vitamin D doesn’t appear to have a significant effect on of influenza vaccine immunogenicity.

CONCLUSION

The regulatory activity of Vitamin D on cathelicidin expression and on production of pro-inflammatory cytokines appear to be the main elements explaining the effects of Vitamin D on influenza infection. Evidence for a correlation between Vitamin D deficiency and risk of influenza infection exists, although it is mainly derived from in vitro and animal
Table 1. Different studies that investigated the association between Vitamin D supplementation and effectiveness of vaccination and treatment of influenza.

<table>
<thead>
<tr>
<th>Type</th>
<th>Author</th>
<th>Year</th>
<th>Sample size</th>
<th>Dose/concentration</th>
<th>Outcome</th>
<th>Intervention</th>
<th>Location</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccination</td>
<td>Krisel</td>
<td>1999</td>
<td>175 adults</td>
<td>1.0 μg/ml of IM calcitriol</td>
<td>Co-administration of 1,25(OH)2 at a site adjacent to influenza vaccination does not increase Ab responses.</td>
<td>RCT</td>
<td>USA</td>
<td>P=0.009</td>
</tr>
<tr>
<td>Treatment</td>
<td>Aloia and Li-Ng</td>
<td>2007</td>
<td>208 postmenopausal</td>
<td>800 IU/d</td>
<td>Decrease the Risk of self-reported cold or influenza</td>
<td>RCT</td>
<td>USA</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Vaccination</td>
<td>Sundaram</td>
<td>2008-2010</td>
<td>1103 adult</td>
<td>Vitamin D deficiency (&lt;10 ng/mL)</td>
<td>No association was found between Vitamin D deficiency and serologic response to influenza vaccination.</td>
<td>Cohort</td>
<td>Marshfield</td>
<td>P=0.05</td>
</tr>
<tr>
<td>Treatment</td>
<td>Urashima</td>
<td>2009</td>
<td>247 children</td>
<td>2000 IU/day</td>
<td>Decrease incidence of influenza A</td>
<td>RCT</td>
<td>Japan</td>
<td>P=0.009</td>
</tr>
<tr>
<td>Treatment</td>
<td>Urashima</td>
<td>2010</td>
<td>167 adults Vit D G</td>
<td>1200 IU/d</td>
<td>Vit D during the winter reduce the incidence of influenza A</td>
<td>RCT</td>
<td>Japan</td>
<td>P=0.006</td>
</tr>
<tr>
<td>Treatment</td>
<td>Jorde</td>
<td>2011</td>
<td>569 adults</td>
<td>1111–6800 IU/d</td>
<td>Decrease the Risk of influenza-like illness;</td>
<td>RCT</td>
<td>Norway; Austria; USA; Scotland; Denmark; and Belgium</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Vaccination</td>
<td>Principi</td>
<td>2012</td>
<td>116 children</td>
<td>1,000 IU/d (&gt;20 ng/ml (deficiency) highest (&gt;30 ng/mL) and lowest (&lt;20 ng/mL)) Administration of Vit D doesn’t evoke antibody responses to flu vaccine There was no association between Vit D and antibody responses to vaccine. In sub group; Vit D sufficiency was associated with lower risk of influenza</td>
<td>RCT</td>
<td>Milan</td>
<td>P=0.5</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Nancy</td>
<td>2016</td>
<td>179 case and 353 control</td>
<td>164 HIV infected and 64 HIV uninfected adults</td>
<td>Decrease the Risk of self-reported cold or influenza</td>
<td>RCT</td>
<td>USA</td>
<td>P=0.39</td>
</tr>
<tr>
<td>Treatment</td>
<td>Nunnii</td>
<td>2016</td>
<td>116 children</td>
<td>1,000 IU/d (&gt;20 ng/ml (deficiency) highest (&gt;30 ng/mL) and lowest (&lt;20 ng/mL)) Administration of Vit D doesn’t evoke antibody responses to flu vaccine There was no association between Vit D and antibody responses to vaccine. In sub group; Vit D sufficiency was associated with lower risk of influenza</td>
<td>RCT</td>
<td>Japan</td>
<td>P=0.05</td>
<td></td>
</tr>
</tbody>
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RCT: randomized controlled trial; Vit D G: Vitamin D group; PL G: Placebo group; IM: intramuscular.

studies. Randomized controlled trials and observational human studies of supplementing various forms of Vitamin D have yielded promising but also conflicting results. Studies conducted on influenza vaccines, Vitamin D failed to augment vaccine immunogenicity. Our literature review suggests that treatment of influenza-infected individuals with Vitamin D supplements or cathelicidin-derived agents may however provide appreciable protection against natural influenza infection. Moreover, Vitamin D given at appropriate doses may facilitate protection against seasonal flu. However, further clinical studies are needed to evaluate the potential benefit of 25(OH) D supplementation in preventing seasonal influenza infection.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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