Chapter

Viral Infections, Including Influenza and Corona Virus Disease 2019, and Vitamin D: A Mini-Review

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Abstract

Recent research about the influence of vitamin D (VD) deficiency on the occurrence of viral infections suggests that children with VD deficiency have attenuated immune response. This, in turn, increases the severity of viral infections, especially those of the respiratory tract, that show a typical seasonality pattern during the winter months. Despite the immunization of children at the global level, outbreaks of influenza do frequently occur. Over the past months, we have witnessed that the explosive pandemic of the corona virus disease 2019 (COVID-19) has caused significant mortality in some countries. Numerous studies have shown that VD deficiency is increasingly prevalent worldwide, and that it is potentially associated with the onset of viral infections. Persons with hypovitaminosis D and subsequent secondary immunodeficiencies ought to be identified and treated, while preventive supplementation of VD should be recommended to the general population to avoid VD deficiency during the winter. In this way, the burden of viral infections on population health and economy could be reduced. This paper also reviews the influence of VD on infections caused by hepatitis B and C viruses, human papillomavirus, Epstein–Barr virus, Human herpes virus 6, herpes simplex virus, and human immunodeficiency virus.

Keywords: viral infections, vitamin D, hypovitaminosis, influence

1. Introduction

The non-skeletal effect of vitamin D (VD) has been a hot topic of research for almost 20 years, and benefits have been found for many health conditions, including cancer, diabetes, autoimmune diseases, cardiovascular diseases [1, 2]. The increase in global VD deficiency is most likely due to poor sun exposure and poor diet [3].

The dietary sources of VD cannot fulfill the body's requirements [4]. Sun exposure accounts for >90% of VD production in humans. Most people are now spending more time indoors, therefore, their exposure to sunlight is often limited. In the summer, due to fear of malignant skin diseases, use of creams with high ultraviolet (UV) protection is common, which further contributes to VD deficiency [5]. Air pollution in large urban industrial agglomerations with insufficient insolation also predisposes

to VD deficiency [6, 7]. Taken together, hypovitaminosis D has become a pandemic in itself, identified across ethnicities and age groups worldwide [8–10]. Diekmann investigated the VD status of residents in a German nursing home in Nurnberg, and found VD deficiency (<50 nmol/L) in 93.9% of the residents [11]. Hypovitaminosis D is common in elderly people [12].

VD was classified as a vitamin for historical reasons, although it is actually a hormone in the group of secosteroids (steroids with an open B ring). Until recently, scientists focused on how VD affects the maintenance of plasma calcium and phosphate regulation, particularly in children who have rickets, and in adults, and older people with osteopenia and osteoporosis [13]. New research indicates that this vitamin/hormone plays a significant role in the functioning of the immune system, in fact, it is essential for its optimal functioning [14].

Why is VD so important? Firstly, VD functions as a natural steroid. It is the secosteroid vitamin/hormone, which regulates the immune system function as an immunomodulator. This means that their end-targets are lymphocyte activation and proliferation, and differentiation of promyelocytes and monocytes. Secondly, the VD receptor (VDR) has been identified in most tissues. VD influences the innate and adaptive immune responses. This immunomodulator also targets dendritic cells (DCs), as well as B-lymphocytes, modulating both innate and adaptive immune responses [15].

Thirdly, VD influences the cytokine network through inhibition of secretion of several cytokines by T cells. This immunomodulatory effect may be very important in treatment of viral infections and autoimmune diseases. Different reports have demonstrated the ability of VD to reduce the synthesis of interferon-γ (IFN-γ) and interleukin-2 (IL-2) in peripheral blood lymphocytes (PBL) and T-cell lines [16–18]. VD inhibits IFN-γ production and increased IL-10 production by peripheral blood mononuclear cells (PBMCs) [19]. Initial plasma IFN-γ and IL-10 are higher in COVID-19 Intensive Care Unit (ICU) patients and cytokine storm can occur [20–22].

Furthermore, VD can suppress cytokine storm by reducing the severity of influenza A. It significantly decreases the levels of tumor necrosis factor-alpha (TNF-α), interferon-beta (IFN-β), and IFN-stimulated gene-15 [23]. This is very important in case of severe clinical presentations of viral infection, especially those of the respiratory system [6]. VD also influences the acquired immunity and regenerate endothelial function and lining [24]. This effect is also important in order to minimize the alveolar damage in acute respiratory distress syndrome (ARDS) which can appear after viral acute respiratory infections (ARI) [25].

The condition of the average person's immune system worsens in winter. To explain this, one hypothesis has focused on VD levels, which depend in part on UV light exposure (higher in summer) that positively modulates the immune system. The best evidence is that VD supplementation reduces the incidence of ARI, according to a meta-analysis of randomized trials. VD supplementation is safe protecting against ARI and very deficient patients experience the most benefit [26]. This effect can explain the variation in influenza incidence in summer and in winter. Epidemiologic evidence links poor VD status to high susceptibility to viral infections and autoimmune diseases. Generally, hypovitaminosis D has been linked to the increased susceptibility to viral infections. It is an area of growing interest in scientific community [27–30].

The latest research indicates an interesting interaction between VD and the viruses, focusing on its antiviral and immunoregulatory activity such as the induction of autophagy and apoptosis [31]. This mini review is focused on the influence of VD on morbidity from viral infections including influenza and corona virus disease 2019 (COVID-19), which have been of special interest in the recent months.

The optimal level of VD in serum is recommended at >75 nmol/L [32, 33]. The reference ranges of VD are inconsistent according to different recommendation [34]. The simplest and most acceptable differentiation is that VD insufficiency is considered when VD levels are between 50 and 75 nmol/L, while levels ≤50 nmol/L are considered inadequate and suggest VD deficiency [8]. Deficiency can be strong (30 – 49.9 nmol/L), significant (20 – 29.9 nmol/L) or extreme (< 20 nmol/L) [32].

1.1 Epstein–Barr virus, human herpes virus-6

Alvarez-Lafuente revealed that low levels of VD have been described as one of the possible factors involved in the etiopathogenesis of multiple sclerosis (MS) [35]. Epstein–Barr virus (EBV) and human herpes virus 6 (HHV-6) infections have also been proposed as MS triggers [36, 37]. Possible effect of VD levels on viral load have been suggested [35]. VD levels could be involved in the regulation of the replication/reactivation of EBV in peripheral blood cells of MS patients; moreover, viral load seems to be higher when VD levels in serum are low [35]. Maghzi revealed that levels of VD in patients with infectious mononucleosis were significantly lower at the time of infection than in the control group and concluded that it could be a risk factor for the onset of autoimmune disease in general [38].

Hypovitaminosis D, Epstein–Barr virus (EBV) and human herpes virus 6 (HHV-6) infections have been described as possible MS triggers, but the pathogenesis of MS associated with HHV-6 infection remains unknown [39]. The presence of EBV in the CNS and demonstration of the underlying mechanism (s) linking EBV to the pathogenesis of MS remain to be elucidated. Astrocytes and microglia, in addition to B-cells can also be infected [40]. EBV is present and transcriptionally active in the brain of most cases of MS and supports a role for the virus in MS pathogenesis [40].

Pérez-Pérez analyzes the association between VD and viruses EBV and HHV-6 in 482 patients with multiple sclerosis [41]. The VD levels were significantly higher in the first school semester of the year than in the second and EBV viral load was significantly higher when VD levels were low [41]. Elevated EBV antibody levels and hypovitaminosis D may have impact on the relapsing–remitting form of MS [42]. High-dose oral VD supplementation can help the humoral immune responses against the latent EBV antigen, Ebstein-Barr nuclear antigen (EBNA)1 by decreasing the antibody levels from baseline to week 48 [42].

1.2 Human papillomavirus

There are a few clinical studies about the influence of VD deficiency on occurrence of human papillomavirus (HPV) infection, but two authors are particularly worth mentioning because they revealed that VD deficiency enhance severity of HPV cervical infection. Özgü E et al. investigated whether VD deficiency could be a reason for the HPV infection persistence in cervical premalignant lesions [43]. They concluded that, the deficiency of VD and its metabolites could be a possible reason for HPV DNA persistence and related cervical intraepithelial neoplasia [43].

Another group of authors headed by Shim studied the association of sufficient level of VD with cervical-vaginal HPV infection due to high-risk HPV (cancer-causing) or vaccine-type HPV and revealed that infections were increased in women with VD levels that were severely deficient [44].

These studies are a good guide to some new research into finding evidence of the benefits of VD in the fight against HPV. It is particularly important that supplementation of VD could possibly be considered in therapy of infections caused by HPV.

1.3 Herpes simplex virus

Investigations of VD potential to prevent herpes virus infection or reactivation are limited. Kumar has investigated the herpes labialis cells supplementation with VD before herpes simplex virus (HSV)-1 infection and studied the effect after 6, 12, and 24 h post-infections [45]. The supplementation of VD downregulate the viral load and Toll-like receptors (TLR) 2 mRNA during the initial phase of the infection [45]. The influence of VD was examined by Choi in vivo mouse model and observed that VD improved herpes simplex virus-induced Behçet's disease-like inflammation by down-regulating the expression of TLR and pro-inflammatory cytokines [46].

Öztekin A and authors have studied the association between VD and recurrent herpes labialis (RHL) in a population with RHL. They compared VD levels in healthy volunteers with and without RHL [47]. The individuals with RHL had significant VD deficiency, with VD levels below the recommended levels in more than 96% of the population. Most importantly, the study established a significant association between low serum VD levels and presence of RHL [47].

1.4 Human immunodeficiency virus

VD deficiency is also prevalent among patients with human immunodeficiency virus (HIV) infection. High levels of VD and VDR expression are also associated with natural resistance to HIV-1 infection [48]. VD deficiency is linked to a stronger inflammatory response and immune activation, low peripheral blood CD4+ T-cells, faster progression of HIV disease, and shorter survival time in HIV-infected patients [48]. VD supplementation and restoration of VD level to the recommended serum values in HIV-infected patients may improve immunologic recovery in combination with the antiretroviral therapy by reducing the level of inflammation and immune activation, and by increasing the immune response to viral pathogens [48]. Jiménez-Sousa suggests that VD deficiency may contribute to the pathogenesis of HIV infection and VD supplementation can reverse alterations of the immune system. Author supports VD supplementation as prophylaxis, especially in individuals with more severe VD deficiency [48].

People diagnosed with HIV are vulnerable to VD insufficiency and deficiency. The supplementation acts against HIV disease progression by boosting the immune response [49]. In vitro findings suggest that the VD treatment may reduce HIV-1 transmission modulating levels and function of T cells, and the production of antiviral factors [50].

1.5 Hepatitis B and C virus

VD deficiency is involved in the pathogenesis of chronic liver diseases caused by hepatitis B (HBV), and C viruses (HCV). High prevalence of VD deficiency with serum levels below 20 mg/mL in patients with HBV and HCV infections has been reported. Current literature was reviewed in order to understand the effects of VD supplementation in combination with IFN-based therapy on the virologic response in HBV and HCV infected patients. Hoan revealed that is important to know the significance of VD hypovitaminosis in the outcome of HBV- and HCV-related chronic liver diseases [51].

VD signaling is involved in infectious and non-infectious liver diseases. It is very important to understand the risk factors for the development of HBV. Probably there is relationship between VDR polymorphisms and the risk of HBV infection. Another group of authors headed by He Q in meta-analysis indicates that VDR

polymorphisms FokI genotype FF, Ff and allele F increase the risk of HBV infection and possibly has a role in the HBV susceptibility [52].

Low serum levels of VD are associated with increased HBV replication. HBV-transfected cells, inhibit VD impact [53]. The analysis of the immunological response of VD supplementation in chronic HCV patients by Kondo revealed that VD could improve the sensitivity of Peg-IFN/RBV therapy on HCV-infected hepatocytes by reducing the cytokine IP-10 production from PBMCs and expression of IFN-stimulated genes expression in the liver. Th1 responses in subjects treated with VD3/Peg-IFN/RBV were significantly higher than in those treated with Peg-IFN/RBV at 12 weeks after Peg-IFN/RBV therapy ($p < 0.05$) [54].

A recent study shows that supplementation of VD significantly improves sustained viral response via IFN-based therapy. VD reduces the extra- and intracellular levels of HCV core antigen in a concentration-dependent manner. This finding confirmed the improved efficacy of anti-HCV treatment via the combination of VD and IFN [55]. Calcitriol and VD_3, both remarkably inhibit HCV production in a VDR-independent mechanism [56]. A group of authors led by Murayama using an HCV cell culture system identified several compounds with anti-HCV activity by screening VD derivatives, which reduce HCV production by suppressing the expression of apolipoprotein in host cells [57].

2. Respiratory viruses

Acute respiratory viral infections (ARVI) remain the leading cause of morbidity and mortality worldwide, and a major global health problem because the availability of the effective antiviral drugs is limited. Such epidemics have significant negative economic consequences worldwide because of the increased absence from work and school resulting in long lasting economic crises. This can also lead to an overall collapse of the health care system. A number of observational studies revealed that VD deficiency is associated with increased risk of ARVI. Meta-analysis of trials revealed that there is protective effect of VD supplementations on the prevention on ARVI [58]. VD and its metabolites have immunomodulatory effect on respiratory epithelial cells surface markers infected with respiratory viruses (RV) modulating secretion of interferon 1, TNF and IL-6 [58]. VD mediates viral entry in epithelial cells and stimulates the expression of potent antimicrobial peptides in the respiratory tract epithelial cells protecting the lung from infection [58, 59].

Esposito and colleagues reviewed all of the studies published in PubMed over 15 years concerning VD deficiency and supplementations in children with respiratory tract infections. They concluded that VD seems to be very important because of its part of immune system. However, further studies are needed to evaluate the impact of VD deficiency in terms of the epidemiology and the outcome of pediatric respiratory tract infections [25, 60].

Brockman-Schneider and colleagues hypothesized that VD could directly reduce rhinovirus (RV) replication in airway epithelium but they found that VD does not directly affect RV replication in airway epithelial cells, but can instead influence chemokine synthesis and alters the growth and differentiation of airway epithelial cells [61].

2.1 Influenza virus

Influenza appears in a seasonal cycles [62, 63]. Seasonality to influenza correlates with a seasonal drop in VD serum levels and is associated with solar radiation,

which triggers seasonal VD skin production. Common winter VD deficiency has negative effects on innate and acquired immunity. UV radiation from artificial sources or from sunlight reduces the incidence of viral respiratory infections [64].

VD supplementation is associated with reduced incidence and severity during influenza A virus (IAV) infection restoring the autophagic flux inhibited by IAV by upregulating the expression of Syntax in-17 (STX17) and V-type proton ATPase subunit (ATP6V0A2). It causes a concomitant decrease in cellular apoptosis via a VDR. VD is useful for limiting IAV-induced cellular injury via its pro-autophagic action [65].

Zhou and colleagues studied the clinical efficacy of VD for preventing influenza A in 400 infants. They revealed that a high-dose VD (1200 IU) is suitable and safe for the prevention of seasonal influenza because of rapid relief from symptoms, rapid decrease in viral loads and quick recovery [66]. This study suggests that VD supplementation during the winter may reduce the incidence of influenza A in infants [66]. Urashima investigated the effect of VD supplementation (1200 IU/d) during the winter on the incidence of seasonal influenza A in schoolchildren and proved that it can reduce it [67].

Very cheap prophylaxis with use of VD as a prophylactic therapy for influenza starting at the end of October till the end of April is very useful; Would be crucial to prove it from a potential easy and cheap prophylaxis or therapy support perspective as far as influenza infections are concerned. Gruber-Bzura **e**xplore the preventive effect of VD supplementation on viral influenza infections also [68].

In people diagnosed with hypovitaminosis D at the beginning of the autumn **s**upplementation with 2000 IU of VD helps to bring levels to normal, but if extremely low serum VD values are proven, the reimbursement doses may be even higher.

2.2 Novel beta-coronavirus SARS-CoV-2

Coronaviruses are seasonal, with little transmission in the summer. Coronavirus disease (COVID-19) is caused by a novel beta-corona virus, renamed by the WHO to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to destigmatize the association of the virus with any geographic location or nationality. COVID-19 is a potentially fatal disease and has been declared as a global pandemic nowadays.

A number of additional preprints and publications regarding VD on COVID-19 have appeared. Some reviews tried to explain the involvement of micronutrient VD in COVID19 treatment and prophylaxis. Vitamin D supplementation could possibly improve clinical outcomes of patients infected with COVID-19 [69].

Lau revealed that VD insufficiency prevalence in ICU patients was 84.6%, vs. 57.1% in floor patients and concluded that may be an underlying driver of COVID-19 severity [70]. Rharusun in his retrospective Indonesian cohort study revealed that majority of the death cases were older male with pre-existing condition and hypovitaminosis D. Majority of the COVID-19 cases with insufficient and deficient VD status died [71]. Bloukh conclude that adequate serum vitamin D levels are needed for the prevention of severe cases of COVID-19 [72, 73]. The elderly have lower levels of vitamin D due to a variety of biological and behavioral factors [74, 75].

VD deficiency has been found to contribute to ARDS and case-fatality rates increase with age and with chronic disease comorbidity, both of which are associated with hypovitaminosis D. This supports the view that VD deficiency may also favor the emergence of more severe forms of the disease. It is also well known that older people, especially those housed in homes, have a high percentage of VD deficiency. Unfortunately, today we are witnessing an explosive rate of infections

in nursing homes with poor outcomes. VD prevention and treatment for deficiency worldwide would greatly help to overcome this pandemic. VD is known to regenerate endothelial lining, which may be beneficial in minimizing the alveolar damage caused in ARDS. In animal model VD reduce lung permeability by modulation of renin-angiotensin system activity and ACE2 expression [76]. Grant recommends that raising serum VD concentrations to 100 – 150 nmol/l should be able to reduce the risk of COVID-19 infection and death [77].

McCullough recommends reaching those concentrations rapidly by taking large doses of VD for a few weeks, followed by several thousand IU/d VD for the duration of the COVID-19 pandemic. Such doses have been found not to have adverse health effects. Randomized controlled trials and large population studies should be conducted to evaluate these recommendations [78].

There have been a few investigations of VD effect on interstitial pneumonia. Tsujino and his colleagues used human pulmonary fibroblast cell lines (HPFCs) and a mouse model of Bleomycin-induced pulmonary fibrosis. They evaluated whether VD was activated in the lungs and had a preventive effect against interstitial pneumonia [79]. Expression of the VDR gene and genes for enzymes metabolizing VD were evaluated in two HPFCs, as well as the suppressive effect of VD on induction of inflammatory cytokines [79]. Symptoms of Bleomycin-induced pulmonary fibrosis were improved and expression of fibrosis markers/fibrosis inducers was decreased by a high VD diet, so they concluded that VD is activated locally in lung tissues and high dietary intake may have a preventive effect against interstitial pneumonia [79]. Martineau concluded that VD supplementation is safe and protects against acute respiratory tract infection overall. Patients who were very VD deficient experienced the most benefit [80].

Daneshkhah investigates if there is a link between severe cases of COVID-19 expressing cytokine storm and VD deficiency [81]. Age-specific case fatality (CFR) was investigated for the elderly (age ≥ 70 yr), Italy and Spain present the highest CFR (>1.7 times that of other countries). A more severe deficiency of VD lower than 25 nmol/L is reported in Italy and Spain compared to other countries. His investigation suggests that elimination of severe VD deficiency reduces the risk of high CRP levels, which may be used as a surrogate marker of cytokine storm expected to reduce in severe COVID-19 cases of up to 15% [81].

Kakodkar in his review points out that VD regenerates endothelial lining and is beneficial in lowering the alveolar damage and ARDS [82]. This protective effect is 19% better on those on a daily bolus compared to those on a monthly one while in those with deficiency protective effect is 70% better. The author and his colleagues consider this vitamin very important in the prevention and treatment of COVID-19 [82].

Recent study of COVID-19 and VD indicate that the severity of the clinical picture of COVID-19 depends of VD deficiency that is more prevalent in patients with severe COVID-19 disease. The inflammatory response is higher with increased chances of mortality [83]. Antiviral and anti-inflammatory action of VD is high and supplementation can have preventive effect on the development of severe COVID-19 forms [84].

A clinical trial on the severity of COVID-19 clinical imaging and VD deficiency should be performed and useful. Caccialanza R. and other authors propose a pragmatic protocol for early nutritional supplementation of non-critically ill patients hospitalized for COVID-19, explaining that most patients present at admission have severe inflammation and anorexia leading to a drastic reduction of food intake [85]. Many published data revealed that VD has immunomodulatory effect. Prevention by supplementation is recommended [86]. There is a link between immunodeficiency in individuals with obesity and greater viral pathogenicity because of VD

deficiency/insufficiency in this population [87]. Among patients with COVID-19 in intensive care units (ICU) the prevalence of obesity was 47.5% (49/103). In a multivariate analysis, severe obesity (BMI ≥35 kg/m2) was associated with ICU admission [88].

The first preliminary data collected by Giancarlo Isaia in Turin indicate that patients hospitalized for COVID-19 have a very high prevalence of hypovitaminosis D. Italy is currently the country with the third highest number of Coronavirus cases after the United States and Spain. If we compare the data of southern and northern Italy, published on-line by Statista Research Department, we can see that in southern Italy, which is also poorer, there are significantly fewer infected with SARS-Cov-2 [89].

Vitamin D levels are severely low in the aging population especially in Spain, Italy, and Switzerland. This is also the most vulnerable group of the population in relation to COVID-19 [90–92]. There is a variation in mortality of COVID-19 between different countries and countries in southern hemisphere have a relatively low mortality. For instance, there is a big difference between Australia's 2 per million in 10th the UK's 68 per million by April 3rd 2020., which may support the hypothesis that VD is a factor that determines the severity of the disease [93].

3. Discussion

The viruses that have already been circulating among the population earlier are less severe than the new ones, which have an advantage because the population was not previously immunized to them. Many respiratory viruses are winter-seasonal in temperate regions. For influenza, it has been shown in the lab that absolute humidity strongly affects flu transmission, where drier conditions are more favorable.

There is a significant correlation between VD deficiency in children and the incidence and severity of lower respiratory tract infection (LTRI). Children with LRTI have significantly lower mean VD levels as compared to controls and their disease manifestation was severe [94].

The hypothesis that hypovitaminosis D can influence severity of influenza or COVID-19 has to be confirmed by future research.

Analyzing the immune mechanisms might help us to understand why some people show severe complications while others can be asymptomatic. We have to discover the influence of VD on specific targets in immune system immunomodulating the response on virus influenzas and SARS-CoV-2.

This knowledge can be useful for preventive therapeutic purposes when VD can be used as an immune-protector and antiviral factor. Increasingly, there is a growing awareness that this secosteroid hormone/vitamin is a very important factor in the proper functioning of the immune system in response to various viral infections and consequent complications such as autoimmune or malignant diseases.

In recent years, we have witnessed explosive flu epidemics, generally respiratory infections including this year pandemic of COVID-19 that we can associate with the worldwide epidemic of hypovitaminosis D. It would be necessary that organizations, societies, and country government institutional bodies be lobbied to recommend VD in winter time and adopt guidelines for the prevention of hypovitaminosis D, in order to prevent or at least minimize the outcome of this pandemic with is causing grave and tragic consequences on the health of mankind and of course the economy.

Interventional and observational epidemiological studies provide evidence that VD deficiency may confer increased risk of influenza and respiratory tract infection. Cell culture experiments support the thesis that VD has direct anti-viral effects particularly against enveloped viruses [95].

3.1 Recommendations

For optimal functioning of the immune system and protection against infections caused by viruses, serum VD concentration has to be between 75 and 150 nmol/L. Preventive doses for adults in risk of hypovitaminosis D have to be from 1200-2000 IU and for children at risk for hypovitaminosis D have to be from 800-1200 IU.

For proven VD deficiency for adults, 4000 IU have to be prescribed for the first 8 weeks and then maintained at 1200-2000 IU and for children 2000 IU 8 weeks and maintained 1200-1400 IU depending on the severity of the deficit.

Considering the recommendations presented in **Table 1**, a personalized approach to the treatment and prevention of VD deficiency is extremely important. It is important to identify in the population individuals with secondary immune deficiency caused by hypovitaminosis VD. Such persons have to be treated with higher doses.

In children and adults, we have to bring serum VD levels to >75 nmol/L and maintain them between 90 and 120 nmol / L especially in epidemic conditions to 150 nmol/L After VD replacement therapy, a rechecking of the serum VD concentration is recommended after two months. In period of maintenance therapy rechecking has to be every two months. As can be seen in the preprints and publications on severity of COVID-19 infections those with concentrations >75 nmol/L still have symptomatic infections. Thus, going to 100 to 150 nmol/L would result in reduced risk of symptoms better than just >75 nmol/L.

It is known that VD concentrations decrease with age because the skin is old and has reduced capacity to produce VD and the intestines absorb VD more slowly from food. Elderly Europeans, are thus at risk of hypovitaminosis D during winter [96, 97].

The same is happening worldwide, especially among the older population living in the northern hemisphere. They have to be tested for levels of VD in serum at the beginning of November and at the end of February. The elderly population is the most susceptible to influenza and COVID-19 and has the most frequently fatal complications. It is the same population that is most likely to suffer from hypovitaminosis D, which significantly worsens the condition of the aging immune system [98].

A serum VD lower than 25 nmol/L was found in 2 to 30% of adults, while this percentage may increase to 75% or more in older persons in institutions [90, 91].

The Institute of Medicine (IOM) finds doses <4000 IU/day are safe for old people. Boucher suggest that ≥1000–2000 IU of VD daily is necessary in this

	Therapy for hipovitaminosis D	**Prevention of hipovitaminosis D**
Children	1. 2000 IU 8 weeks, then VD serum levels control 2. Maintenance 1200-1400 IU, VD serum levels control every two months	1. 800 IU – 1200 IU VD serum levels control every two months
Adults	1. 4000 IU 8 weeks, then VD serum levels control 2. Maintenance 1200-2000 IU, VD serum levels control every two months	1. 1200 IU – 2000 IU VD serum levels control every two months
Elderly	1. 5000 IU 8 weeks, then VD serum levels control 2. Maintenance 2000 - 3000 IU VD serum levels control every two months	1. 2000 - 3000 IU VD serum levels control every two months

Table 1.
Recomandations for daily VD administration.

population with numerous clinical problems related to the indicated age, especially when independence is lost, when hypovitaminosis D is also present worsening the patient's clinical condition. Much higher doses than these are needed for the treatment of the established deficiency [99].

A preventative strategy should be established and endorsed by the organizations, societies, and country governments be lobbied to recommend VD in winter, which is extremely important for maintaining the good health of the world's population. Preventive administration of VD or replacement therapy in the early winter months to early spring could reduce the severity of clinical symptoms in patients with COVID-19 infection. It is necessary to optimize VD status to enhance every one's immunity for protection against SARS-CoV-2 infection. Prevention of influenza outbreaks and COVID-19 must begin as early as the first days of November so that the population enters a season of respiratory infections with a prepared and strengthened immune system. Jakovac in his letter to the editor recommends intensive supplementation as possible prophylaxis with VD with even higher doses [100]. Maintenance of adequate VD status may be an effective and inexpensive prophylactic method against viral infections, but the optimal supplementation regimen has to be defined.

The latest literature by Paul Marik and East Virginia Medical School (EVMS) medical group published on line a protocol explaining prevention and treatment COVID-19 with instructions for applying VD 1000-4000 IU (unknown optimal dose) in prevention and therapy in mildly symptomatic patients [101].

4. Conclusion

Persons with VD deficiency have attenuated immune responses with secondary immunodeficiency. This condition increases the severity of viral infections especially those of respiratory tract that show typical seasonality pattern during the winter months. Children, adults, especially older population have to take supplementation of VD for reason to cure and deficiency prevention. By the general acceptance of the fact that VD supplementation has a positive effect on immunity we can reduce the risk and severity of viral infections with important public health benefits.

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