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Vitamin D is closely linked to the clinical courses of herpes zoster: From pathogenesis to complications

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ABSTRACT

Vitamin D is renowned for its pleiotropic effects, including but not limited to bone integrity, and it has assumed an important role in the current research era. As vitamin D receptors are present in a variety of human tissues, particularly immune cells, the immunomodulatory potential of vitamin D cannot be overemphasized. Herpes zoster, which presents as grouped cutaneous vesicles over dermatomes or visceral/central nervous system infection in its severe form, has a higher incidence in immune-suppressed patients. Considering the importance of vitamin D in host immunity, we hypothesize that vitamin D acts as an effect-modifier for the entire herpes zoster spectrum with regard to disease susceptibility, manifestation, efficacy of pharmacologic management, and emergent complications during treatment. Moreover, the possibility exists that vitamin D might affect the course of postherpetic neuralgia. In line with this theory, we comprehensively searched the existing herpes zoster literature and provided important insight into the relationship between the disease courses of herpes zoster and vitamin D.

Introduction

Vitamin D is an essential micronutrient for human health. Although it is synthesized in skin tissues from 7-dehydrocholesterol after ultraviolet exposure, vitamin D can also be obtained through the consumption of certain fatty fish, fish liver oils, eggs, milk, cheese, and related products. Vitamin D comes in two forms, D_2 from ergosterol after ultraviolet irradiation and D_3 from skin or certain foods. Although vitamin D-fortified commercial foods are available in most developed countries, the prevalence of vitamin D deficiency still varies according to geographical areas with different sunlight exposure levels.

Physiologic functions of vitamin D comprise the promotion of intestinal calcium and phosphate absorption as well as structural bone integrity. Traditionally, vitamin D deficiency is defined as a serum 25-hydroxyvitamin D (25-OH-D) level less than 20 ng/ml according to the Institute of Medicine recommendations [1]. With the discovery of more phenotypes associated with suboptimal 25-OH-D levels, a vitamin D "insufficiency" status defined as between 20 and 30 ng/ml is now recognized by researchers to be clinically significant and warrant attention. Continuously insufficient vitamin D levels could predict the long-term risk of osteoporotic fracture and even the development of abnormal glycated hemoglobin (a defining feature of diabetes mellitus [DM]) [2,3]. It is estimated that 20–80% of North American and European community-dwelling elderly people are vitamin D-deficient, whereas younger adults or children are similarly at risk for hypovitaminosis D [1,4].

Another important feature that characterizes the importance of vitamin D deficiency/insufficiency is the emerging role of low vitamin D levels in target organs besides the bone as well as calcemic regulation. These so-called non-classical actions of vitamin D include impacts on the metabolic, neoplastic, inflammatory, and immune systems. The most commonly cited effects of low vitamin D levels involve DM and atherosclerosis [5]. A meta-analysis concluded that vitamin D insufficiency could negatively influence glycemic control, predisposing patients to subsequent DM [6]. Low 25-OH-D and even 1,25-dihydroxyvitamin D ($1,25\text{-}(OH)_2\text{-}D$) levels reportedly predict significantly higher all-cause and cardiovascular mortality rates among at-risk populations [7].

Among these pleiotropic effects, immune regulation appears to be the most unique. The initial evidence for this effect emerged from studies conducted in the early 1980s, all of which identified elevated $1,25\text{-}(OH)_2\text{-}D$ levels to be synthesized by macrophages in patients with granulomatous diseases [8]. This triggered the subsequent outpouring of studies focusing on vitamin D related

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immunoregulation, as the vitamin D receptor (VDR) was demonstrated to be expressed on many immune cells. Localized 25-OH-D metabolism in effector cells could influence the proliferation of other VDR-expressing targets and potentially participate in the coordination of innate and adaptive immune systems [9].

The hypothesis

Rare studies attempt to address the possibility that vitamin D, whether its body reserve or therapeutic usage, play an important role in the entire clinical spectrum of herpes zoster (HZ) disease courses. Judging from the above arguments, variations in serum vitamin D levels could potentially affect the incidence of various immunity-dependent infections, among which herpes zoster (HZ) from varicella-zoster virus (VZV) reactivation is typical. Moreover, therapeutic use of vitamin D, whether nutritional or activated forms, is expectedly capable of reducing herpes zoster risk or at least ameliorating its adverse impact on patient-level outcomes.

Basis for the hypothesis

Vitamin D modulates both innate and adaptive immunity against viral infections

Vitamin D in the form of 1,25-$(OH)_2$-D binds to the VDR, thus transcriptionally regulating target genes via VDR and retinoid X receptor dimerization and nuclear translocation. By displacing nuclear factors for cytokine-related gene expression, vitamin D could reduce the production of inflammatory mediators [10]. Vitamin D serves as an important modulator of innate immunity. Through VDR activation, vitamin D can upregulate CD14, a co-receptor of toll-like receptor 4 (TLR-4), in monocytes and keratinocytes [11]. TLRs—important mediators of innate immunity—recognize pathogen-associated molecular patterns, including both bacteria-derived lipopolysaccharides and viral proteins [12,13]. Vitamin D demonstrably affects the secretion of several TLR-associated antimicrobial peptides that possess antiviral effects [14]. For example, 1,25-$(OH)_2$-D was found to directly upregulate defensin β2 secretion from human keratinocytes, monocytes, and neutrophils, for which defensin β2 serves as a chemoattractant and exhibits potential antiviral effects [15]. Similarly, 1,25-$(OH)_2$-D potently stimulated human cathelicidin release from neutrophils and possibly monocytes and natural killer cells [16]. Human cathelicidin is induced upon TLR1/2 activation and contributes to mucosal immunity as well as confers antiviral effects. In its peptide form LL-37, cathelicidin effectively inhibits vaccinia virus, herpes simplex virus type 1, and retrovirus replication [17]. However, in adaptive immunity, 1,25-$(OH)_2$-D was found to suppress T helper cell type 1 (Th-1) proliferation and reduce interleukin-2 and interferon γ release while increasing the level of interleukin-4 level, a Th-2-associated cytokine [18]. Therefore, 1,25-$(OH)_2$-D shifts the adaptive immune response from a Th-1 towards a Th-2 response, but whether this phenomenon assists in or impairs antiviral immunity remains controversial. Nonetheless, vitamin D deficiency has been repeatedly found to correlate with macrophage dysfunction and bacterial infection [19]. In addition, severe 1,25-$(OH)_2$-D deficiency has been associated with clinically advanced human immunodeficiency virus (HIV) infection, and vitamin D supplementation remarkably inhibits hepatitis C virus (HCV) proliferation [20,21].

Virus survival: manipulation of the vitamin D status

As described above, immune cells such as neutrophils and monocytes/macrophages, frequently harness vitamin D for the control and elimination of pathogens, including viruses. In contrast, microbes have also developed measures to dodge host immune attacks. One of these successful strategies lies in the exogenous regulation of the host's vitamin D status by influencing the VDR and enzymes involved in vitamin D metabolism. Indeed, VDR and *CYP27B1* gene polymorphisms have been found to associate with disease progression in HIV-infected patients [22]. A direct pathogen-driven effect could be exemplified by the finding that *Aspergillus fumigatus* downregulates VDR activity via gliotoxin secretion in macrophages and the airway epithelium [23]. Similar scenarios occur during viral infections. Epstein–Barr virus (EBV)-infected B cells display significantly lower levels of VDR expression, compared with uninfected cells [24]. HIV infection also prominently attenuates VDR activity [20]. Reduction in the VDR expression or activity levels leads to impaired innate and potentially adaptive immunity, thus permitting intracellular pathogens such as viruses to persist without eradication. Furthermore, anecdotal evidence suggests that several types of viral infection alter vitamin D metabolism and potentially dysregulate host immunity [21].

Evaluation of the hypothesis

Vitamin D and zoster virus infection: preliminary epidemiologic evidence

Previous literature addressing the influence of vitamin D on HZ incidence is scarce. Potential reasons for the lack of study of this issue include the comparatively lower incidence of HZ relative to other viral infections, perceived lower public health importance of HZ, prominent recall bias resulting in difficulty ascertaining cases, and modest effects gained from aggressive therapy against HZ. With a gradual recognition of the impact of HZ on patients' quality of life and the introduction of highly effective zoster vaccination for HZ prevention [25], research groups have placed more interest on HZ prophylaxis as well as potential adjunctive measures to enhance vaccination efficacy.

The first study to address the effect of vitamin D on HZ incidence came from a pilot attempt in chronic dialysis patients [26]. The incidence of HZ in the general population ranges from 1 to 7 episodes per 1000 patient-years, depending on the country and survey origin [27]. As renal failure exerts a significant negative impact on host immunity in a dose-dependent manner and patients with end-stage renal disease have a higher risk of developing HZ [28], the authors enrolled patients under chronic dialysis to study the risk factors of HZ. They identified an HZ incidence of 20–30 episodes per 1000 person-years among chronic dialysis patients [26]. More importantly, the authors identified that the use of active vitamin D was associated with a significantly lower risk of developing HZ (odds ratio [OR] 0.06, $p = 0.005$). This biologic relationship was further consolidated by the fact that a lower active vitamin D dosage and duration existed in the HZ group. These findings could serve as an empirical evidence supporting the hypothesis that active vitamin D exerts an immunomodulatory role in patients (especially immunocompromised ones), rendering the recipient less likely to develop HZ. A summarized figure illustrating current evidence for our vitamin D and HZ susceptibility theory is provided as Fig. 1.

Multi-dimensional impact of vitamin D on the clinical courses of patients with HZ

Vitamin D deficiency has been found to be highly prevalent among several types of virus-infected patients, to serve as an important risk factor of viral respiratory tract infections, and to modify immune responses to viruses (manifesting as antibody

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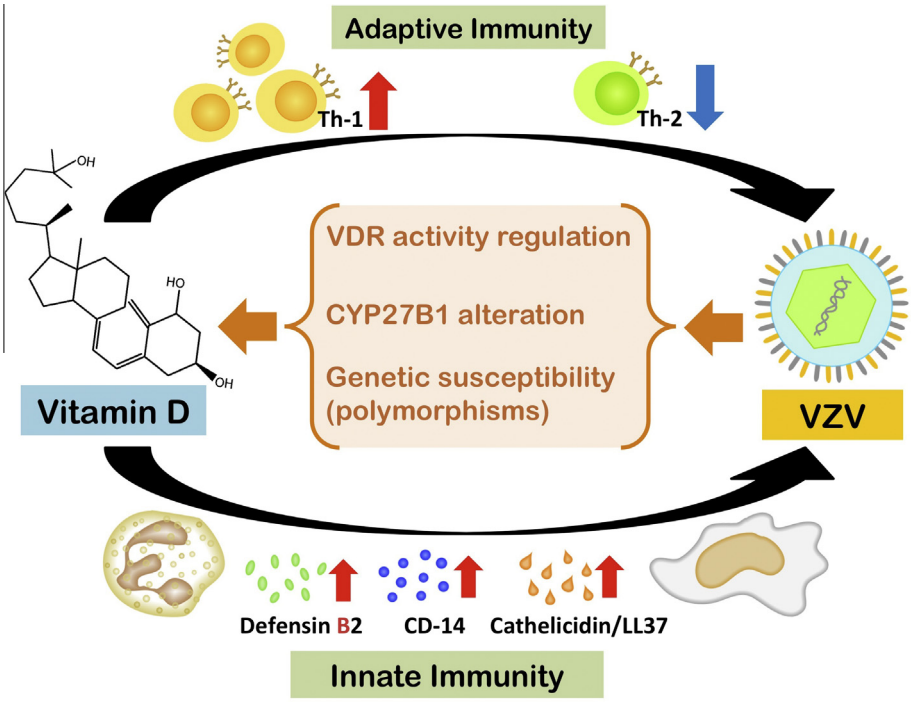

Fig. 1. Diagram illustrating the reciprocal relationship between vitamin D status and VZV activity/survival.

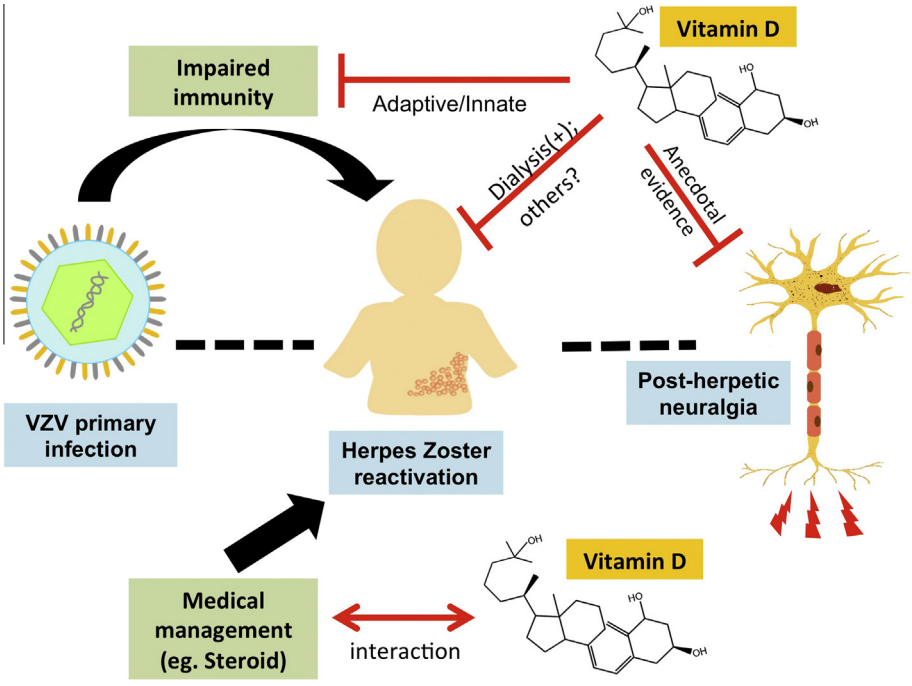

Fig. 2. Vitamin D influences the entire spectrum of VZV/zoster related illness.

titers) [29–31]. Similar phenomena have been demonstrated in HIV-, EBV-, and HCV-infected patients; however, very few reports have specifically addressed these issues in patients with VZV infection or HZ. The available reports only indicated that an advanced age, past experiences of repeated VZV exposure, and receipt of cell immune-suppressive therapies could increase the risk of subsequent HZ [27,32], but very few mentioned vitamin D. We provided important observations for the potentially close vitamin D–HZ relationship, as summarized in Fig. 2.

Predisposition to infection/reactivation

Vitamin D deficiency predisposes the host to immune deficiency and potentially facilitates HZ development. Low levels of vitamin D were found to impair innate and adaptive immunity, whereas vitamin D per se exhibits antiviral effects in vitro [19,21]. VZVs, which belong to the *Herpesviridae* family, manifest a natural course similar to other herpesviruses. Primary VZV infection occurs during an early stage of human life and is

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asymptomatic or with mild symptoms only, after which VZVs establish a long-term or latent relationship with the host. However, the prevalence of vitamin D deficiency/insufficiency has apparently increased according to a temporal trend [33,34], and thus it is likely that the influence of vitamin D on the susceptibility to primary VZV infection gradually becomes important. In addition, during the reactivation phase, the quality of immune surveillance might also be compromised if the vitamin D levels decrease, thus contributing to a higher risk of HZ development. One group of researchers tested this theory by assaying the VZV glycoprotein-related IgG titers and investigating their relationship with vitamin D status in patients under dialysis [35]. They found that both serum total and bioavailable vitamin D levels were significantly associated with zoster antibody levels in a positive fashion, after confounder adjustment. These findings are indirectly in line with clinical observations that a close relationship exists between vitamin D levels and immunity against VZV.

Other plausible pathways that potentially link vitamin D deficiency and HZ development are listed below. First, vitamin D deficiency/insufficiency was recently found to correlate with mental stress accumulation [36]. Mental stress could influence the activity of CD8+ T cells through the induction of neuroendocrine factors, thus regulating the switch between viral latency and reactivation in neurons [37]. In addition, vitamin D deficiency increases the susceptibility of children to gastrointestinal and otologic infections [38]. Fever and fatigue resulting from these infections also serve as physical stressors and are closely associated with the occurrence of herpes cold sores [39]. Finally, vitamin D deficiency might represent a dietary state of nutritional inadequacy, among which micronutrient deficiencies (vitamins A, B6, C, and E, folic acid, zinc, and iron) have an inverse dose–response relationship with the risk of HZ [40]. However, that study did not determine which specific micronutrient deficiencies conferred an elevated risk of HZ. Another study indicated hyporetinolemia as an important link between nutritional inadequacy and HZ [41], but further mechanistic study is required to confirm this relationship.

Predisposition to treatment complications

Treatment of HZ consists mainly of topical or systemic antiviral therapies, including acyclovir, brivudin, famciclovir, and valacyclovir, although the topical forms have been frequently reported to lack efficacy. Systemic agents constitute the first-line treatment for immunocompromised patients and immunocompetent patients of advanced age and with moderate to severe pain/rash within 72 h of onset [42]. In addition, adjunct treatments include analgesics, among which corticosteroids are widely used by practitioners to ameliorate acute pain, accelerate recovery, and improve the quality of life [43]. As prolonged corticosteroid use is detrimental to bone health through osteoporosis induction whereas vitamin D is capable of restoring the bone mass, vitamin D deficiency likely plays a role in the development of complications during treatment for HZ.

Predisposition to drug futility

A growing body of evidence has affirmed that the vitamin D status might affect pharmacologic efficacy in patients with viral infections. Vitamin D deficiency/insufficiency is associated with a 2.4-fold higher risk of virologic failure in HIV patients after initiating combinatorial anti-retroviral therapy [44]. Similarly, low vitamin D levels correlated with an impaired response to anti-HCV therapy and lower rate of sustained virologic response in HCV-infected patients [45]. In addition, VDR gene polymorphism might play a role in the rate of treatment failure (peg-interferon/ribavirin) in HCV-infected patients, and polymorphisms in vitamin D activating enzymes (*CYP27B1*) also affect the responses of hepatitis B virus-infected patients to interferon-based regimens [46,47]. As the control of most viral infection episodes depends on cell-based immunity and related cytokines (including interferon), we propose that vitamin D might also play a role in controlling VZV replication during HZ management. Further studies, including virologic in vitro assay or vitamin D-induced T cell activity assay specific for VZV, are expected to better characterize the influence of vitamin D status on the HZ treatment response and potential synergistic effect with anti-viral pharmaceuticals.

Vitamin D and postherpetic neuralgia

Postherpetic neuralgia (PHN) is a syndrome that follows the recurrence of HZ, and it is characterized by a constant, deep/sharp pain or brief, piercing-like pain that persists despite rash resolution. The pathophysiology of PHN might involve both central and peripheral mechanisms [48]. The central mechanism suggests that degeneration of the spinal nerves and neurons following VZV reactivation could result in hyperexcitability of the cord neurons and culminate in dorsal horn atrophy, a histopathologic characteristic of PHN [49]. In addition, the peripheral mechanism refers to the findings of reduced skin innervation density and impaired C-fiber function in patients with PHN [50,51]. However, a unifying theory to explain the occurrence of PHN remains controversial.

Previous studies confirmed that VDRs are located within microglial cells. By attenuating inducible nitric oxide synthase expression in microglial cells, vitamin D could limit the inflammatory status of the central nervous system, thus potentially reducing the sequelae of neuronal atrophy or axonal demyelination [52]. Vitamin D has also been found to reduce Schwann cell inflammation and improve myelination and neural recovery after nerve injuries [48,53]. Furthermore, the D_2 form of vitamin D enhances axonal regeneration by increasing axonogenesis and improving neuronal responses to metabolites [54]. One report stated that vitamin D could induce nerve growth factor expression, thereby reducing the possibility of injured spinal nerve non-recovery [55]. Others have suggested that inadequate micronutrient levels accompanied by low vitamin D stores might impair antiviral immunity, thus permitting prolonged viral replication in dorsal root ganglia and predisposing patients to PHN development through persistent neuroinflammation [56]. The phenomenon by which vitamin D could ameliorate neuropathic pain has been exemplified by studies mainly involving diabetic neuropathy [57]. Nonetheless, despite circumstantial evidence that vitamin D levels could modify or even retard the course of PHN, currently there is only indirect evidence supporting that vitamin D supplementation could reduce the occurrence of PHN.

Consequences of the hypothesis

In addition to its traditional roles of calcium regulation and healthy bone turnover maintenance, vitamin D exerts pleiotropic effects such as metabolic and immune modulation. Vitamin D is capable of enhancing innate immunity and modifying adaptive immunity directly or indirectly, thus contributing to its antiviral efficacy. Through its immunotropic effects, vitamin D potentially plays a role in the incidence of immunity-dependent infections, including VZV reactivation. Our hypothesis that vitamin D not only affects host susceptibility to VZV but also modifies the clinical course of patients with HZ, including therapeutic efficacy and complications, is important and necessitates more investigation, since the overall global burden conferred by HZ is heavy but ameliorable. Our current hypothesis could be confirmed by both experimental

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and epidemiologic means. First, VZV-specific T-cell stimulation response or alternatively, antibody response to VZV under different vitamin D treatment conditions (nutritional/activated forms, active analogs; stepwise dosage) would be important. Nationwide or region-specific survey for HZ events could be conducted alongside serum 25-OH-D and 1,25-$(OH)_2$-D levels measurement for analyzing their correlations. Finally, interventional studies aiming at elucidating the effect of therapeutic vitamin D use on the combined outcomes of HZ and PHN reduction in high-risk population, or even general population would be definitive and informative. We expect that vitamin D could serve as an important tool with potential pharmacologic utility for adults with HZ.

Conflict of interest

The authors have no relevant competing interests to declare in relation to this manuscript.

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