

A comprehensive review on the relationship between serum vitamin D levels and cutaneous warts, molluscum contagiosum, and recurrent herpes simplex

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Viral skin diseases range from simple superficial exanthems to complex systemic diseases, affecting people of all ages. Careful assessment of infectious contacts and immunization status is of considerable importance along with a thorough physical examination. Recent research has linked a deficiency of vitamin D to an increased risk of autoimmune, infectious, and atopic disorders. Intralesional vitamin D3 may be an effective treatment option for warts. Vitamin D3 derivatives are effective for various skin conditions, including psoriasis, transient acantholytic dermatosis, actinic porokeratosis, and keratosis palmaris et plantaris. Vitamin D3 treatment has been shown to decrease chemokine synthesis and monocyte trafficking, as well as to downregulate toll-like receptors (TLRs) 2 and 4 of monocytes. This suggests an association between TLRs and vitamin-D-mediated innate immunity. The effect of vitamin D derivatives was speculated to be derived from its potential to regulate epidermal cell proliferation and differentiation and to modulate cytokine production. According to some studies gathered here, not only we can use different forms of vitamin D as therapy for viral skin disease, but also there is an important relationship between them. Therefore, we should consider the serum level of vitamin D for better management of these disorders. Also, keeping vitamin D levels within the normal range may be a preventative healthcare strategy.

Keywords: molluscum contagiosum, recurrent herpes, skin, vitamin D, warts

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INTRODUCTION

Viral skin diseases range from simple superficial exanthems to complex systemic diseases that can affect individuals of all ages. The characteristic morphology, distribution, configuration, and course of the cutaneous eruptions are of great importance in the classification and diagnosis of viral exanthems. Precise evaluations of infection contacts and immunization status, as well as a detailed physical examination, are all-important ¹.

It seems that, more than previously thought, a complex interaction exists between vitamin D and viral infections. This interaction is shown as the induction of an anti-viral state and immunoregulation with the involvement of both cellular and viral factors, inducing autophagy, apoptosis, and genetic and epigenetic alterations ². While crosstalk between vitamin D and intracellular signaling pathways may provide an essential modulatory effect on viral gene transcription, the immunomodulatory effect of vitamin D on viral infections appears to be transient ³.

Vitamin D

In the skin, vitamin D shows potent immunomodulating and antimicrobial activity. It reduces systemic and local inflammation by affecting T cell activation and promoting the activation of macrophages. Recent research has linked the deficiency of vitamin D to an increased risk of autoimmune, infectious, and atopic disorders ⁴.

There is an interaction between vitamin D and cells of the immune system. These cells express the vitamin D receptor and are capable of metabolizing circulating 25-hydroxyvitamin D into its active form, 1, 25-dihydroxy vitamin D, which has revolutionized the field and suggested a regulatory role on both the innate and adaptive immune systems ⁵.

Moreover, therapy with vitamin D3 can result in reduced chemokine synthesis and monocyte trafficking, as well as the down-regulation of toll-like receptors (TLRs) 2 and 4 of monocytes. The immunomodulatory effect of 1, 25(OH)₂D₃ in T cell subsets has also been shown to induce a significant decrease in IFN γ and TNF α cytokines in single-cell expression. It is well known that 1, 25(OH)₂D₃ modulates lymphocyte and macrophage functions ⁶.

The vitamin D system has multiple physiological and pharmacological effects mediated by the action of the vitamin D receptors (VDRs). Recently, VDR activators (VDRAs) have been shown to inhibit cell replication and to have immunomodulatory properties ⁷.

Following the TLR activation of human macrophages, the expression of VDR and vitamin D-1-hydroxylase genes is upregulated and the antimicrobial peptide is induced. This indicates that there is a relationship between TLRs and vitamin-D-mediated innate immunity. The potential of vitamin D derivatives in regulating epidermal cell proliferation and differentiation and modulating cytokine production can justify their effect.

Vitamin D3 can be obtained from 7-dehydrocholesterol in the skin and also from the diet. Vitamin D3 gets hydroxylated to 25-hydroxyvitamin D3 (25D3) by 25-hydroxylase (cytochrome P450 family 2 subfamily R member 1 [CYP2R1]). Further, hydroxylation by 1, α -hydroxylase (cytochrome P450 family 27 subfamily B member 1 [CYP27B1]) converts 25D3

to 1, 25-dihydroxyvitamin D3 (1, 25D3). Both 25D3 and 1, 25D3 are the agonists of the VDR and could independently regulate the expression of various genes ^{7,8}.

Vitamin D3 derivatives are effective for various skin conditions, including psoriasis, transient acantholytic dermatosis, actinic porokeratosis, and keratosis palmaris et plantaris (KPP) ⁹. Besides, there is a correlation between the infection of the skin and vitamin D levels. This infection is important because of its link to the development of certain skin cancers, particularly squamous cell carcinoma ¹⁰.

Cutaneous warts and vitamin D

Cutaneous and genital warts are common dermatological conditions caused by the human papillomavirus (HPV), of which there are over 100 types. HPV probably infects the skin via areas of minimal trauma. Risk factors include the use of communal showers, the occupational handling of meat, and immunosuppression. In immunocompetent people, warts are harmless and resolve as a result of natural immunity within months or years ¹¹.

Common, plantar, and flat warts are placed in the primary classes of non-growing warts. While warts are generally self-limited, they should be treated because of the possibility of spreading. Common warts often develop in the periungual region of the fingers. In general, cryotherapy, topical application of salicylic acid, or occlusive taping can remove this type of warts. Plantar warts are often located in the heel or metatarsal heads on the pressure points. Flat warts are commonly seen on the dorsum of the hands or the face ¹².

Despite their benign nature, warts spoil the appearance and may trigger the Koebner response; transmission to others can also occur. Hence, adequate and timely treatment is important. There are several conventional treatments available with variable responses ¹³.

Plantar warts are typically resistant to treatment. In recent years, treatments have included the administration of intralesional tuberculin, the measles, mumps, and rubella vaccine, and *Candida albicans* antigen immunotherapy ¹⁴.

Common therapies for warts involve destructive methods such as cryotherapy with liquid nitrogen,

local injection of bleomycin, electrocoagulation, topical application of glutaraldehyde, and local and systemic interferon- β therapy.

These treatment modalities often cause pain and sometimes scarring or pigmentation after treatment¹⁰. Low levels of serum vitamin D in patients with viral warts explain the role of vitamin D in topical and intralesional therapy¹⁵.

As a supplementary treatment, the local use of activated vitamin D can be a good choice for the treatment of the recalcitrant wart. In fact, patients are more satisfied with this therapy and can tolerate it well. Recently, researchers have focused on the levels of activated vitamin D to be reached, especially in consideration of local cellular growth regulation.

These levels may explain the striking effect of activated vitamin D and the minimal effect of its simple application¹⁰.

The effectiveness of a topical vitamin D3 derivative (1 α , 25-dihydroxy-22-oxacalcitriol) was investigated in patients with refractory warts. Simple local applications of maxacalcitol ointment (25 μ g/g) and calcipotriol have been reported as treatments in individual cases⁹.

With these treatments, all warts safely and successfully disappeared without pain or other side effects within 2 weeks to 6 months¹⁴.

Aktas *et al.* included twenty patients with single or multiple plantar warts in their study. Vitamin D3 (0.2 mL, 7.5 mg/mL) was injected into the base of the warts after prilocaine (0.1 mL, 20 mg/mL) injection. A maximum of five warts were treated in one session, with a maximum of two injections performed at four-week intervals. In total, 16 of 20 patients (80%) showed complete resolution of warts, and one patient showed partial resolution. Three patients failed to show any response. No recurrence or serious adverse effects were observed. Intralesional vitamin D3 may be an effective treatment option for warts¹⁴.

Recurrent herpes and vitamin D

The herpes simplex virus (HSV) is one of the most common infectious pathogens responsible for various diseases, including encephalitis, keratitis, uveitis, fever blisters, and genital infections¹⁶. HSV has two distinct types, type 1 and type 2, and belongs to the *Herpesviridae* family¹. HSV-1

remains the primary cause of cold sores, also known as herpes labialis, and HSV-2 is the primary cause of genital herpes. HSV-1 accounts for about 20% of current cases of genital herpes in the United States¹⁷.

Recurrence is caused by immune-suppression, sunlight, menses, stress, trauma, trigeminal nerve manipulation, dental extractions, or genital irritation. Although the frequency and severity vary, episodes of recurrence are usually shorter and milder. Genital HSV-1 recurs less frequently than HSV-2¹.

The recognition of the viral glycoproteins and DNA through TLRs results in the induction of the innate immune response through the production of type I interferons and proinflammatory cytokines. Previous studies have shown that the activation of TLR2 and TLR9 subsequent to HSV infection leads to the production of proinflammatory cytokines. Both 25D3 and 1, 25D3 are the agonists of VDRs and could independently regulate the expression of various genes⁷.

Vitamin D supplementation to the HeLa cells before HSV-1 infection significantly downregulated TLR2 as well as HSV-1 mRNA expression⁸.

Molluscum contagiosum (MC) and vitamin D

The pediatric molluscum contagiosum virus (MCV) is among the most prevalent *Poxviridae*, representing a common public health issue. The spread of the virus among children is rapid and easy. The virus produces some substances that block the immune response formation in the infected host¹⁸.

Molluscum contagiosum is an epidermotropic pox virus infection commonly affecting children. The virus can be spread to others by direct skin contact. In patients with regular immune function, the virus induces an effective antiviral response that prevents the manifestation of MC or leads to complete remission. As contact with the virus and mounting of a virus-specific immune response usually occur during childhood, MC infections are rarely found in adults¹⁹.

Strong evidence to support many of the treatments in common use for warts or MC has been lacking, but there is currently more reason to endorse the use of salicylic acid, cryotherapy, and both topical and intralesional immunotherapy

for warts. The commonly used treatments for MC, namely cantharidin and imiquimod, now have evidence to suggest less efficacy than previously thought²⁰.

Both warts and MC are likely to resolve spontaneously, but as clearance can take months or years, treatment is usually sought for cosmetic reasons and pain, particularly for warts. MC lesions are often asymptomatic but can become inflamed and pustular, and lesions may number over a hundred²⁰.

CONCLUSION

According to some studies gathered here, not only we can use different forms of vitamin D as therapy for viral skin disease, but also there is an important relationship between them. Therefore, we should consider the serum level of vitamin D for better management of these disorders. Also, keeping vitamin D levels within the normal range may be a preventative healthcare strategy.

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