

Role of Vitamin D in Treatment of Warts: Review Article

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Abstract:

Viral warts are common cutaneous lesions associated with human papillomavirus (HPV) infection and may be difficult to treat, particularly when lesions are multiple, large, or recalcitrant. Conventional destructive treatment modalities may be painful, may cause scarring, and usually target only treated lesions without affecting distant warts. Vitamin D has emerged as a promising therapeutic option because of its effects on keratinocyte proliferation and differentiation as well as its immunomodulatory activity. Vitamin D may enhance cell-mediated immune responses against HPV through activation of toll-like receptor pathways, induction of antimicrobial peptides, and regulation of several inflammatory cytokines. Both topical vitamin D analogues and intralesional vitamin D3 have shown encouraging results in the treatment of different types of warts, with previous studies reporting high clearance rates, limited adverse effects, and low recurrence. These findings support further evaluation of vitamin D as an effective and relatively safe therapeutic approach for viral warts. Vitamin D has attracted increasing attention in the management of viral warts because of its combined antiproliferative and immunomodulatory effects. In the skin, active vitamin D interacts with vitamin D receptors in keratinocytes, helping to regulate epidermal proliferation and differentiation, while also influencing local immune responses. Its role in enhancing antimicrobial peptide production and modulating cytokines such as interleukin-6, interleukin-8, tumor necrosis factor- α , and interferon-gamma may contribute to improved immune recognition and clearance of HPV-infected cells. This immunologic effect is particularly relevant in patients with multiple or recalcitrant warts, where conventional destructive therapies may be less practical or associated with pain, scarring, and recurrence. Previous studies of intralesional vitamin D3 have demonstrated encouraging therapeutic responses with relatively low recurrence rates, supporting its potential role as an alternative immunotherapeutic modality for resistant warts.

Keywords: Vitamin D; Viral warts; Human papillomavirus; Intralesional immunotherapy; Calcipotriol; Immunomodulation; Dermatology.

Introduction:

A synthetic vitamin D3 derivative (calcipotriol) was first approved by the FDA in 1993 for the treatment of psoriasis. In addition, it is a safe and effective treatment for a wide variety of diseases (1).

Keratinocytes produce vitamin D and can enzymatically metabolize vitamin D by 25-hydroxylation (CYP27A1) and 1 α -hydroxylation (CYP27B1) to the active metabolite, 1,25-dihydroxyvitamin D (1,25(OH)2D). The 1,25(OH)2D metabolite binds to nuclear vitamin D receptors to regulate gene expression, which can have intracrine effects in the keratinocyte or paracrine effects on immune cellular responses in the skin (2).

Activation of toll-like receptors by vitamin D in macrophages induce an antimicrobial peptide, which may augment immune recognition of HPV of other viruses (3).

Topical vitamin D

Topical application of an analog of 1,25(OH)2D, calcipotriol, suppresses proliferation and stimulates terminal differentiation of epidermal keratinocytes and has been used successfully for skin conditions like psoriasis (4) and ichthyosis (5).

Topical vitamin D has been tried as a potential therapeutic cure for warts with promising results (6,7).

Intralesional vitamin D

Intralesional immunotherapy with skin test antigens and vaccines has been effective in the management of such warts without scarring and decreased recurrences (8).

Nofal and Nofal (9) and Shaheen et., (10) reported that immunotherapy is being tried widely for the treatment of warts over the last few years. Immunotherapy is based on enhancing cell-mediated immunity to achieve an HPV-targeted immune response. Various immunotherapeutic approaches have been attempted which lead to the release of different cytokines and its tumor necrosis factor (TNF- α) that stimulate a strong immune response against HPV. Various antigens have been tried including measles, mumps, rubella (MMR), tuberculin purified protein derivative (PPD), *Mycobacterium* vaccine, and *Candida* antigen.

Immunotherapy antigens such as measles, mumps, rubella (MMR) vaccine, tuberculin (purified protein derivative), and vitamin D3 have been tried. Although not well elucidated, vitamin D3 employs the ability of the immune system to recognize the antigens that induce a delayed-type hypersensitivity reaction not only to the antigen yet also against HPV. The stimulated immune response clears all lesions on other body sites along with the treated lesions (11).

All these treatment modalities may be painful and have been known to cause scarring (10).

In addition, destructive modalities are not suitable for the treatment of multiple and refractory warts as they clear only treated lesions and not distant ones. Therefore, to overcome these disadvantages, immunotherapy has been widely used for the management of warts over the last couple of years. It acts on the basic principle of enhancing cell-mediated immunity for the clearance of warts (12).

Al-Sabak et al, (13) reported that No definite mechanism of action has been elucidated until now. However, with intralesional injection of vitamin D3, it is plausible that a toll-like receptor can activate human macrophages and upregulate the expression of vitamin D receptor (VDR) and vitamin D-1-hydroxylase genes, leading to the induction of the antimicrobial peptide and elimination of warts .

There is no longer any need to treat each wart individually thanks to a delayed form of hypersensitive reaction created toward the injected antigen. This can boost the immune system's ability to recognize and eradicate the human papillomavirus (HPV) in different sections of the body. Intra-lesional immunotherapy, as opposed to physically ablative treatments, is suggested as a first-line therapy for many stubborn, and big warts due to its low relapse rate and low risk of adverse effects (14).

Essayed Ghaly et al., (15) reported that the likely mechanism of action of intralesional vitamin D involves the regulation of keratinocyte proliferation and, at the same time, the inhibition of the production of certain cytokines such as interleukin-6 (IL-6), IL-8, and tumor necrosis factor (TNF)- α and the stimulation of the production of IFN gamma. A study of patients with common warts showed higher efficacy of intralesional vitamin D than intralesional BCG

Samta et al., (16) reported that it has immunomodulatory effects by inhibiting the expression of interleukin-6, interleukin-8, tumor necrosis factor (TNF)- , and TNF-c mediated through the VDR-dependent pathway. Topical vitamin D3 regulates epidermal cell proliferation and is involved in the formation of antimicrobial peptides.

Vitamin D inhibits the proliferation of cells, triggers apoptosis and cell differentiation, regulates cytokines production, induces antibacterial peptides in the skin, and can be used as an immunotherapeutic agent when injected into lesions (16, 17).

The lower level of vitamin D in patients with viral warts suggested the association between the role of vitamin D and the treatment of viral warts (18).

According to a study containing 64 patients with recalcitrant warts, the injection of 0.2- to 0.5-mL vitamin D3 solution led to a complete response in 90% of the patients. In this study, patients were followed up for 6 months to detect a possible recurrence, but only 3.33% of patients showed recurrence (19).

In another study, in patients who suffered from plantar warts, after the injection of 0.2 mL of 7.5 mg/mL D3, 16 out of 20 patients experienced complete resolution of warts without major adverse effects (20).

In a study conducted in 2020, vitamin D3 injection led to an appropriate improvement in the treatment of warts. A higher dosage was associated with a better response to treatment in this study, but the need for further evaluation was also mentioned in this study (21).

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