REVIEW ARTICLE
PRACA POGLĄDOWA

POSSIBLE ROLE OF VITAMIN D IN PATHOGENESIS OF LICHENOID DERMATOSES (A REVIEW OF LITERATURE)

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ABSTRACT

The aim of the study was search and analysis of the data of review, experimental and clinical scientific and medical publications on the issues of the possible role of VD in pathogenesis of lichenoid dermatoses.

Materials and methods: An analysis of the studying of the scientific and medical literature was shown. Searching was carried out through the PubMed/MEDLINE portal from the databases of the National Center Biotechnology Information, Web of Science Core Collection, U. S. National Library of Medicine, National Institute for Health and Clinical Excellence, as well as the portals «Scientific Electronic Library eLIBRARY.RU», «Russian Science Citation Index (RSCI)» and «Index Copernicus».

Conclusions: The results of studies had convincingly demonstrated that deficiency of VD in the blood, decrease vitamin D receptors activity can lead to development of lichenoid dermatoses.

KEY WORDS: vitamin D, psoriasis, atopic dermatitis, lichen planus, pathogenesis

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INTRODUCTION

Today, more and more often known vitamin D is called "hormone D" in connection with its newly discovered functions. Traditionally, antirachitic vitamin in recent studies has shown properties to suppress cell proliferation, angiogenesis, renin production, stimulate insulin synthesis, macrophage production of cathelicidin, regulate immune responses [1]. These new properties significantly increase the importance of VD in various pathologies, including dermatological ones. Psoriasis (Ps), atopic dermatitis (AD) and lichen planus (LP) are content a group of lichenoid dermatoses due to common morphology and they are the most common dermatoses. These dermatoses are chronic and multifactorial, have a complex pathogenesis, including genetic, immunological, environmental, metabolic factors and other. A lot of publications of recent years have been demonstrated the deep violations of VD status in patients with lichenoid dermatoses. Along with this, an understanding of the pathogenic role of VD in the development of this chronic skin pathology opens up prospects for the rational and effective using of VD supplements for the correction of such diseases.

THE AIM

The aim of the work was search and analysis of the data of review, experimental and clinical scientific and medical publications on the issues of the possible role of VD in pathogenesis of lichenoid dermatoses.

MATERIALS AND METHODS

An analysis of the studying of the scientific and medical literature was shown. Searching was carried out through the PubMed/MEDLINE portal from the databases of the National Center Biotechnology Information, Web of Science Core Collection, U. S. National Library of Medicine, National Institute for Health and Clinical Excellence, as well as the portals «Scientific Electronic Library eLIBRARY.RU», «Russian Science Citation Index (RSCI) » and «Index Copernicus».

REVIEW AND DISCUSSION

VITAMIN D METABOLISM: APPLIED ASPECTS.

VD has a steroid structure and it is synthesized in the body endogenously in the skin under the influence of UV B. A precursor of vitamin D – 7-dehydrocholesterol, is found in the membranes of the keratinocytes of the basal and spinous layers of epidermis [2]. Under the influence of ultraviolet rays with a wavelength of 290 – 315 nm, cholecalciferol is formed by means of a photochemical reaction. Cholecalciferol binds to blood proteins, reaching the liver, undergoes hydroxylation, forming 25-hydroxyvitamin D or 25 (OH) D_3. In this form, VD is biologically inert, but it is precisely its level that corresponds to the amount of vitamin D that enters the body and is produced on the skin. That is why serum 25 (OH) D_3 is most commonly used to monitor VD the body's, whose serum levels below

20 ng / mL (50 nmol / L) are considered deficient, 21-29 ng / mL – failure. The final stage of the production of VD is its hydroxylation in the kidneys, where its biologically active form, calcitriol or 1.25 (OH) D_3, is synthesized [1].

VITAMIN D & CELL PROLIFERATION, DIFFERENTIATION AND APOPTOSIS.

From the point of view on the pathogenesis of psoriasis the properties of VD to suppress cell proliferation and stimulate cell differentiation are very interesting. In an in vitro experiment, a low concentration of 1.25 (OH) $2D_3$ (10^{-9} M or less) contributes to keratinocyte proliferation, while at high pharmacological doses (more than 10^{-8} M) a pronounced antiproliferative effect and stimulation of differentiation appear [3,4].

A recent study found that VD receptor (VDR) signaling has a protective effect on keratinocyte apoptosis in the oral cavity by regulating miRNA-802 and p53-positive apoptosis modulator (PUMA), which may be important when considering the pathogenesis of oral lichen planus (OLP) [5]. It was studied the molecular mechanisms of suppressing the expression of the in oral LP (OLP). A study on a human sample showed that the LPS (lipopolysaccharide) markedly reduced the expression of VDR mucosal keratinocytes, and the downregulation was accompanied by pronounced induction of miR-346 and tumor necrosis factor alpha (TNFα) compared with healthy tissues. In addition, vitamin D / VDR signaling inhibited the LPS-induced p53-activating apoptosis induction modulator (PUMA) in keratinocytes by inhibiting the activation of nuclear factor -κB (NF-κB), which reduced keratinocyte apoptosis [6]. At the same time, PUMA hyperactivity was found in the affected epithelium, which inversely correlated with VDR expression. Thus, this study indicates that LPS is responsible for the suppression of VDR in oral keratinocytes and this process is associated with the development of OLP.

VITAMIN D AND SKIN BARRIER.

Today, it is known that 1,25 (OH) D regulates cell proliferation in the basal layer and increases the synthesis of keratins (K1 and K10), involucrin, transglutaminase, loricrin and filagrin in the spinous layer of the epidermis. In addition, VD is involved in the regulation of the synthesis of glucosylceramides necessary for the integrity and permeability of the barrier in the stratum corneum. This is explained to the ability of VD to regulate intracellular calcium levels, due to the induction of the calcium receptor and phospholipase C enzymes. It was shown that the deficiency of calcipotriol, as well as the loss of its receptor function, violates the differentiation of the epidermis, reducing levels of involucrin and loricrin and, accordingly, keratogalin, which leads to hyperproliferation of cells of the basal layer [7]. The decreasing of VDR expression and a decreasing o tight junction proteins have been observed in psoriatic skin. Tight junctions are fundamental for the regulation of adhesion and permeability of keratinocytes, as well as for polarizing the differentiation of skin cells, for regulating the gradient of extracellular calcium, interacting with nuclear and cytoplasmic proteins, and influencing the regulation of specific genes involved in differentiation of keratinocyte [8].

VITAMIN D AND GENETICS.

Recently, a link between the vitamin D receptor polymorphism (VDR) and psoriasis susceptibility has been discovered. Richetta et al indicate that the A-1012G promoter polymorphism of the VDR gene is associated with the risk of developing psoriasis by inhibiting VDRmRNA expression, contributing to the disorder of the skin barrier and the development of psoriatic lesions [9]. A meta-analysis of 16 studies of VDR polymorphism and psoriasis, in which 2086 patients participated and 2182 controls showed that polymorphisms in VDR ApaI, BsmI and FokI were not associated with susceptibility to psoriasis in the general, Caucasian or Asian populations. However, the VDR TaqI polymorphism was associated with susceptibility to psoriasis in Caucasian populations [10].

Interesting facts have been revealed by studying the influence of vitamin D receptor polymorphism (VDR) genes and vitamin D metabolism genes on the development of AD. For example, VDR BsmI polymorphism increased the risk of AD in the Turkish population, and the specific haplotype of VDR BsmI, ApaI, and TaqI polymorphisms was overrepresented in patients with severe AD in the German population [11]. There is evidence that among the 6 common polymorphisms in CYP24A1 and CYP27B1, the CYP24A1rs2248359C allele and specific haplotype were associated with an increased risk of severe atopic dermatitis [12]. The authors of this study focused on genes that encode the synthesizing vitamin D enzyme Cyp27b1 and the inactivating vitamin D enzyme Cyp24a1. In 281 patients with AD, the SNP C allele of Cyp24a1 rs2248359 was overrepresented compared to 278 healthy controls. The gene halotype for Cyp27b1 and Cyp24a1 were also associated with AD. The authors concluded that in patients with AD and certain genotypes, VDR activity may be reduced, which may play a role in the development of AD.

Ex vivo 1.25 (OH) 2 D3 significantly reduced FcεRI expression on mDCs (myeloid dendritic cells) and surface-bound IgE on mDCs and pDCs (plasmacytoid dendritic cells). Using of oral VD reduced the expression of surface-bound IgE at pDC in children with AD. This demonstrates the ability of VD to suppress the allergic phenotype of circulating DCs in children with AD, which explains the potential mechanism of action on the pathogenesis of AD [13].

VITAMIN D &INFLAMMATION AND IMMUNITY.

Some studies have reported that VD is a key modulator of the inflammatory process [14, 15]. Both the innate and adaptive segments of the immune system play an important role in the pathogenesis of psoriasis. In particular, T cells play a major role in the development of psoriasis, namely T-helper (Th)

1, Th-17 and Th-22, which interact with various cell types through a number of cytokines, including tumor necrosis factor-α (TNF-α) IL-6 and IL-17 [16]. The activity of these cells is modulated by specific T-lymphocytes, called regulatory T-cells (Treg). Regulatory T cells (Tregs) are able to inhibit the immunological response and maintain cutaneous immunological homeostasis, preventing an autoimmune response to autoantigens. There is an opinion that the immunoregulatory properties of VD in patients with psoriasis can be partially mediated by the induction of Tregs [17]. It was shown by same authors that VD inhibits the proliferation of T-lymphocytes by inducing the generation of CD25 + / CD4 + -Tregs, which stimulate tolerance and suppress immunity after stimulation with antigen. The correlation between serum levels of VD and the T-reg population ($p<0.001$) and with the PASI score ($p = 0.04$) have been found in patients with psoriasis [17]. According to the authors of the study, a low level of VD can reduce the number of circulating T-regs, disrupting immunological homeostasis in patients with psoriasis and stimulating inflammatory activity. At the same time the AD is characterized by significant activation of the TH2 immune response in the skin of the lesion, with some contribution to the pathways of the cytokines TH22, TH17 / IL-23 and TH1[18].

The absence of VDR in the biopsy samples of the affected areas of patients with OLP was found, and was associated with inflammatory response to activated T-cells of type 1 (Th1) and also a reduced level of serum 25-hydroxyvitamin D in patients with OLP. The study showed that 1,25 (OH) 2 D3 plays an anti-inflammatory role in OLP, mediating the NF-κB signaling pathway, but not the AP-1 signaling pathway, in a VDR-dependent manner. Therefore, treatment with VD supplements may be a potential strategy for managing OLP [19].

An association of vitamin D3 deficiency with antimicrobial peptide LL-37 deficiency was found in a clinical study by Albenali et al., who noted a clinical improvement in patients with AD along with an increase in LL-37 levels after taking oral VD [20]. At the same time, another study did not reveal a significant correlation between the level of serum 25 [OH] D and the severity of AD in children and adults on the SCORAD scale or the level of serum cathelicidin (LL-37) [21]. VD deficiency in AD patients was associated with a higher blood eosinophil count as well. These results confirm the possible role of VD in the eosinophilic immune response [22].

In recent years, the role of vitamin D deficiency in the colonization of S. aureus in children with AD has been studied. A study of skin isolates in atopic children revealed that some virulence factors of S. aureus, including tsst-1, eta, cna, aur and sec, were associated with low levels of 25 [OH] D. The authors suggested that VD deficiency may be associated with more virulent properties of S. aureus in patients with AD [23]. This assumption was confirmed by a clinical study in which an oral intake of VD in a daily dose of 2000 IU for 28 days caused an improvement in the clinical symptoms of AD against a background of a decrease in S. Aureus skin colonization [24].

It have been found the active metabolite of VD had an anti-inflammatory effect on the inflammatory profile of human monocytes/macrophages, inhibiting the expression and production of several pro-inflammatory cytokines, including TNF-α, IL-1, IL-6 and IL-8 [25]. Moreover, the secretion of hydrogen peroxide in human monocytes is also activated by 1.25(OH) D, which induces oxidative stress [26].

It has recently been reported that 1,25 (OH) D reduces S100A7 levels (usually elevated in psoriatic skin) in IL-22-stimulated human epidermis, in IL-17-stimulated keratinocytes in psoriatic skin [3]. It has been found that using of VD and its analogues for psoriatic lesions significantly decreases the infiltration of skin by Th17 cells and inhibits their expansion ex vivo [27, 28].

A recent meta-analysis of randomized observational studies on the relationship of AD and VD showed a deficiency of 25 [OH] D in the blood serum of patients with AD, and, accordingly, the therapeutic strategy for using VD supplementation for the treatment of AD is promising [29]. An analyzing the content of 25 (OH) D3 in cord blood, followed by observation for 6 months, it was found that the level of VD is inversely proportional to the risk of infantile atopic dermatitis [30]. It is known that in children with a higher level of 25 [OH] D at birth, the production of IL-5 and IL-13 was reduced, which, in fact, reduced the chances of developing atopic inflammation [31].

As a cytokine regulator, 1,25 (OH) 2D3 inhibited HIF-1α (hypoxia-induced factor-1α), which in turn blocked the production of IFNγ (interferon gamma) and IL-1β (interleukin-1 beta) in human oral keratinocytes. Given that in VDR – / – mie, as well as in VDR-deficient human biopsies, the HIF-1α status of the oral epithelium is increased, which is accompanied by an increase in IFNγ and IL-1β, VD may play a role in the development of inflammation in OLP [5].

CONCLUSIONS

An analysis of the medical literature of recent years has shown the multi approach effect of VD on various processes involved in the pathogenesis of chronic lichenoid dermatoses. It controls the processes of cell proliferation, differentiation, apoptosis, and deep disturbances in these processes were associated with low concentrations of VD and low expression of VDR, which is important for the pathogenesis of Ps and LP. The stimulating effect of VD 3 on the synthesis of barrier and moisturizing substances of the epidermis is necessary for understanding the role of its deficiency in the development of AD and Ps.

It was found that VDR polymorphism and low activity were associated with development of Ps, AD and OLP. The anti-inflammatory activity of 1.25 (OH) 2D3 for OLP, the anti-infective effect of 25 OH D for the colonization in atopic skin by S. aureus, and the immunosuppressive effect of VD in psoriasis have been shown. Active VD metabolites have an anti-inflammatory effect, causing the expression and production of TNF-α, IL-1, IL-5, IL-6, IL-8, IL-13, IL-17, IL-22, which indicates a certain potential of VD supplements in immune correction of lichenoid dermatoses.

The results of studies had convincingly demonstrated that deficiency of VD in the blood, absence VD in the skin lesions and decrease VDR activity can lead to development of lichenoid dermatoses. The literature data showed the rationality of targeted studies of the pathogenic role of VD status of blood, healthy and affected skin in Ps, AD and LP, using new diagnostic technologies and methods. Scientists have been able to visualize VD and its metabolites in the skin and subcutaneous tissue using secondary ion mass spectrometry (ToF-SIMS) to analyze skin biopsies. Such studies should be promising and promising for studying the role of VD in dermatological pathology [32]. Every these results will help to work-up a new pathogenetic strategy for the treatment and prevention of lichenoid dermatoses by filling up VD deficiency and restoring low activity of the VDR.

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