Review paper

Vitamin D and its receptor – role and activity in the human body. Anomalies of metabolism and structure associated with psoriasis

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Abstract

Psoriasis is a common, chronic and recurrent inflammatory dermatosis with abnormally exaggerated epidermal cellular turnover, which affects about 2.5% of the world's population. One of the therapeutic modalities for the treatment of moderate skin lesions is phototherapy with NB-UVB radiation (311 nm). The 290-315 nm UV radiation produces in the epidermis vitamin D of 7-dehydrocholesterol which is then hydroxylated into 25(OH)D and 1,25(OH)$_2$D. Active metabolites of vitamin D, apart from regulating calcium-phosphorus homeostasis, have been shown to inhibit hyperproliferation and to induce terminal differentiation of cultured human keratinocytes through their action on the genome by the nuclear receptor VDR (vitamin D receptor). The literature includes many studies on VDR gene polymorphism and abnormal vitamin D metabolism in some patients with psoriasis. These anomalies could be possibly connected to adverse reactions to NB-UVB and treatment with vitamin D analogues.

Key words: psoriasis, vitamin D metabolism, VDR polymorphism.

Introduction

Psoriasis is a common, chronic and recurrent inflammatory dermatosis characterized by abnormally exaggerated epidermal cellular turnover and erythematous lesions with silvery scales, affecting about 2.5% of the world's population. The etiology of the disease is affected by genetic, immunological and environmental factors. Psoriasis constitutes a significant clinical problem due to its high frequency, chronic course and no possibility of an ultimate cure. Although this condition is rarely fatal, it significantly influences the everyday life of the patients due to their stigmatisation, resulting in psychological and psycho-sociological problems.

Phototherapy appears to inhibit DNA synthesis, to influence the epidermal cytokine system and to modulate the antigen-processing cells. The most effective part of the UVB spectrum against psoriasis is between 304 nm and 314 nm. One of the treatment modalities of psoriasis is narrow-band UVB phototherapy (NB-UVB, with maximum emission at 311 nm), which is used in patients with moderate to severe skin lesions. The 290-315 nm UV radiation produces in the epidermis vitamin D, which is then hydroxylated into 25-hydroxyvitamin D (25(OH)D) and 1,25-dihydroxyvitamin D (1,25(OH)$_2$D, calcitriol). 1,25(OH)$_2$D is the ligand of the vitamin D receptor (VDR), which is a candidate modifying gene, having immunosuppressive effects and being involved in anti-proliferative and pro-differentiation pathways in keratinocytes [1-4].

Vitamin D is a group of secosteroid derivatives, discovered in 1919-1924 with several identified forms. Traditionally, it was believed to take part only in homeostasis of calcium and phosphates, but its total functions are still unknown and difficult to define, due to its ability to influence various additional metabolic processes. The properties of this molecule reflect the definition of a vitamin (a chemical compound necessary to control the course of life processes, which cannot be synthesized in sufficient quantities by an organism, and deficiency of which leads to development of diseases), a steroid hormone (regulates calcium metabolism via the endocrine pathway) and of a cytokine for macrophages (it can be produced in macrophages, independently from calcium-phosphate regulation) [5-8].

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Vitamin D metabolism

Vitamin D is obtained in human beings in two ways: by photoconversion of 7-dehydrocholesterol (7-DHC; this is its main source: 90-100%) or from food (about 10%). Photosynthesis of cholecalciferol in the human skin is mediated by UVB radiation (290-315 nm), in a two-step process (vitamin D is synthesized by the photoconversion of 7-DHC to previtamin D, which thermally isomerizes to vitamin D_3).

In the blood, vitamin D is bound to a specific α-globulin, vitamin D binding protein (DBP), then it is retained by the liver, where it undergoes a preliminary activation step by hydroxylation at position 25 (C25), catalysed by the enzyme 25-hydroxycatalase D. 25-hydroxycholecalciferol (25(OH)D, calcidiol) is released into the blood stream and transported with DBP. Calcidiol consists of a basic form of vitamin D present in the blood with a biological half-time of 19 days (it can be stored in the liver and fat tissue for longer times).

Part of the 25-hydroxycholecalciferol synthesised in the liver is transported by α-globulin to the tissues. The tissues take up 25(OH)D as a result of a decrease in Ca^{2+} concentration in the extracellular matrix, mainly in renal tubes but also in bones, placenta, prostate, keratinocytes, macrophages, T lymphocytes and in some cancer cells. Next, calcidiol is hydroxylated at position C1 by the mitochondrial enzyme 1α-hydroxylase-25(OH)D (CYP-27B1). This reaction produces 1α,25-dihydroxycholecalciferol (1α,25(OH)$_2$D, calcitriol), being the most effective metabolite of vitamin D.

Since the level of calcitriol decreases to undetectable levels upon disturbances in renal functioning, it indicates the local role of the vitamin D form produced by other tissues and organs. However, the fact that antigen-presenting cells can constitute a source of 1α,25-dihydroxycholecalciferol means that its concentration is several times higher in sites of inflammation than in plasma [5, 7, 9-11].

The role of vitamin D in the human body

The main physiological role of vitamin D is to maintain the appropriate calcium levels in serum by influencing the calcium absorption in small bowels, by re-capture of calcium and phosphates in the kidneys and by mobilisation of calcium stored in bones. Its deficiency causes rickets, osteomalacia and osteoporosis. Many studies indicate the existence of a relation between vitamin D deficiency and a decrease in white muscle fibres and with an increased risk of metabolic syndrome, additionally leading to development of diabetes type 2 and myocardial infarction.

Furthermore, there have been many studies on the relation between vitamin D levels and telomere length in leucocytes (possible relationship with slowing down the ageing processes) and on its role in innate immunity (activation of anti-bacterial proteins in monocytes and ker-

atinocytes as a result of binding with Toll-like receptor 2) and in adaptive immunity (inhibition of Th1 and B cell proliferation, inhibition of IL-2, IL-6, IL-12, IFN-γ, TNF-α production and stimulation of IL-4, IL-5 and IL-10 production), morbidity from respiratory diseases, modification of the course of diseases (including atopic dermatitis and inflammatory bowel diseases), and decreasing the risk of disease development (sclerosis multiplex, lupus erythematosus, rheumatoid arthritis). Other studies have also included vitamin D levels as an indicator of the general health condition.

At the moment, 1α,25-dihydroxycholecalciferol is believed to play a role as one of the basic regulators of cell life. It has been shown to influence apoptosis induction, to inhibit proliferation (it inhibits the cell cycle in the G0/G1 phase) and to stimulate cell differentiation. Therefore, it helps to maintain proper activity of the immune and haematopoietic systems and it regulates production of melanin and differentiation of keratinocytes. Multiple epidemiological studies have shown that a low level of vitamin D (< 30 ng/ml plasma) may be related to a higher risk of cancer development, such as breast cancer, bowel and anus cancer, ovarian and uterine cancer, prostate cancer and leukaemia. It was also observed that the incidence of cancer is higher in areas with less sunlight and among persons with black skin [12-23].

Structure and mechanism of action of the vitamin D receptor

The VDR was discovered in 1969, and on the basis of its DNA binding domain, it was classified as a member of the steroid receptor superfamily (class II nuclear receptors); the latter also includes receptors for triiodothyronine (TR), all-trans retinoic acid (RAR), 9-cis retinoic acid (retinoid X receptor, RXR) and peroxisome proliferator-activated receptor (PPAR).

The VDR gene is located on chromosome 12q. It consists of 11 exons, and it possesses many known polymorphisms related to primary hyperthyroidism, bone density, tuberculosis morbidity and body height. Similarly to other molecules of nuclear receptors, VDR possesses the following domains: A/B domain at the N-terminus (short, built from 21 amino acids, probably responsible for ligand-independent transcription activation), C domain (containing two so-called "zinc fingers", responsible for interaction of VDR with DNA), linking D domain and E/F domain (binds the ligand and participates in dimerisation with other receptors and in transcription activation). Receptors of group II migrate to the nucleus independently from its ligand presence. Upon lack of its ligand (calcitriol), VDR binds with VDRE (vitamin D response elements) as a monomer (VDR-DNA) or homodimer (VDR/VDR-DNA), less frequently as a heterodimer with RXR. The presence of calcitriol destabilises VDR/VDR homodimers, facilitating formation of VDR monomers, interacting with RXR,

and it induces heterodimerisation. Formation and binding of a VDR/RXR heterodimer with DNA is additionally stimulated or inhibited by the RXR receptor ligand. The type of interaction depends on the mutual proportion of VDR and RXR, and the conducted research showed that the limited expression of RXR reduces the number of VDR/RXR heterodimers, while high expression of RXR stabilises and co-activates them. Within the heterodimer, VDR is responsible for the specificity of the complex binding with VDRE, while RXR increases its affinity and the strength of binding with DNA.

1,25(OH)$_2$D induces phosphorylation of vitamin D receptor within the DNA binding domain by kinase C at serine residues 51, 119 and 125. This process starts approximately 30 min after calcitriol action, and it reaches a maximum after 2-3 h. The structural changes induced at the C-terminus domain, binding vitamin D ligand, and also those in the gene encoding receptor protein can produce the effect of resistance to this hormone [7-10, 24-26].

On the basis of the restriction end analysis of the DNA extracted from blood leucocytes, using PCR, A, B, T and F VDR alleles were identified (indicating the lack of restriction sites for the *ApaI*, *BsmI*, *TaqI* and *FokI* restriction enzymes) as well as a, b, t and f VDR alleles (indicating the lack of restriction sites for the above-mentioned enzymes). Part of the preliminary study showed that division into BB and bb genotypes shows the highest clinical implications (for example, more frequent allele b is related to higher bone density). However, there are also many studies showing no relationship between VDR polymorphism and the incidence of osteoporosis. The discrepancies in the published studies could have been caused by the fact that no molecular consequences of VDR polymorphism have been detected so far, and more frequent incidence of a particular variant in the population does not always show any cause-effect relationship with any pathological condition or disease [24, 26-28].

After the 1α,25(OH)$_2$D-VDR complex is formed and it binds to a receptor of retinoid X, the formed heterodimer interacts via N-terminal regions of the "zinc finger" with the specific DNA sequences in the promoters of regulatory genes. The formed complex further binds transcription factors, causing a change of transcription of about 200 genes, including the genes for cytokines, calcium-binding proteins (CaBP), 24-hydroxylases, prostate-specific antigen (PSA), parathormone (PTH), osteocalcin and collagen.

Vitamin D receptor can modulate VDRE expression in three ways: it can positively regulate expression of certain genes by binding to VDRE present in promoter regions; it can negatively regulate expression of other genes by binding to negative VDRE; or it can inhibit expression of certain genes antagonising the action of certain transcription factors, such as NF-κB. Using the above-mentioned mechanisms, vitamin D may negatively regulate expression of the genes important for the outcome of psoriasis. Through the first pathway, it affects the substances with anti-proliferative activities (p21 and IGFBP-3) and those having an influence on proliferation (involucrin and PLCγ1). The third pathway influences both anti-inflammatory substances (IL-2, IL-12, TNF-α, IFN-γ), and anti-proliferative substances (EGF-R and c-myc present in keratinocytes and K16, present within the psoriatic lesions) [9, 10, 21, 22, 29, 30].

Metabolic pathway of vitamin D in the skin

The skin supports multiple vitamin D metabolic processes. The epidermis is the main site of its photosynthesis from 7-dehydrocholesterol, but keratinocytes also support production of 25-hydroxylase and 1α-hydroxylase enzymes. These facts were confirmed by the studies carried out recently on epidermal cells, both *in vitro* and *in vivo*. These studies showed that keratinocytes possess an autonomic metabolic pathway for vitamin D and they are the only cells in our body in which the whole pathway of UVB-induced metabolic processes takes place, from 7-DHC to 1α,25(OH)$_2$D. It was also confirmed that calcitriol produced in the skin may have an endo- and autocrine effect within keratinocytes themselves, but also a paracrine effect within the neighbouring cells, mainly by regulating their growth, differentiation and apoptosis, which also explains the efficiency of UVB therapy in psoriasis.

Several clinical studies have suggested that concentrations of both the free calcitriol and its DBP-bound form present in serum (10^{-11} M to 10^{-10} M) are too low to induce a hormonal VDR-dependent effect. The inhibitory effect of 1α,25-dihydroxycholecalciferol on keratinocyte differentiation *in vitro* and cytokine production was observed only at a total concentration above 10^{-6} M. Additionally, some researchers have shown that the conversion in the skin of the blood-present 25(OH)D to 1α,25(OH)$_2$D plays no significant role *in vivo*, due to formation of very small amounts of the active metabolite. There is not enough of the substrate due to the fact that almost all 25(OH)D in serum is practically bound to DBP (only about 0.03% is present in its free form) and this complex has less ability to penetrate from blood to epidermal keratinocytes and to reach appropriate concentrations in comparison to the free form. This was confirmed in part by clinical observations showing the lack of any clinical effect of phototherapy performed on covered psoriatic skin, while healthy skin simultaneously irradiated with UVB produced a detectable increase in 25(OH)D levels in blood.

Recently, *in vitro* studies of other skin cells (fibroblasts) showed expression of 25-hydroxylase and attracted attention to their role in providing vitamin D and calcidiol to keratinocytes but also to the blood stream [5, 9, 10, 26, 31-34].

Multiple *in vitro* and *in vivo* studies proved a dose-dependent influence of 1α,25(OH)$_2$D on proliferation and differentiation of skin cells. At low concentrations, calcitriol stimulates keratinocyte proliferation *in vitro*, while in higher, pharmacological doses ($\geq 10^{-8}$ M) it inhibits this

process. In practice, it has been used for local treatment of psoriasis; synthesised analogues of vitamin D (calcipotriol and tacalcitol) inhibit proliferation of keratinocytes and stimulate them to differentiate. The mechanism responsible for differentiation is not directly dependent on VDR, but many studies have shown an increase in mRNA for the VDR after analogues of vitamin D had been applied topically on psoriatic areas, and this increase correlated with a visible clinical improvement of the skin appearance.

The last decade has confirmed a strong immunosuppressive influence of calcitriol, when provided at the organism level, and its ability to improve the clinical outcome of many diseases in which Th1 lymphocytes play a role, especially in psoriasis. It was also shown that $1\alpha,25(OH)_2D$ directly influences differentiation of Th2, increasing production of interleukin IL-4, IL-5 and IL-10, and decreasing synthesis of IL-2 and INF-γ. Calcitriol also removed pathogenetic activity of autoreactive Th1 lymphocytes.

Another way of calcitriol activity is induction of apoptosis in keratinocytes by its ability to initiate transformation of sphingomyelin to ceramide. This process does not take place at physiological concentrations of the molecule but only when its concentration is significantly increased.

The in vitro studies on keratinocytes showed the photoprotective effect of $1\alpha,25(OH)_2D$. It was found that calcitriol induces synthesis of metallothionein, which is a known anti-oxidant. Probably, it is a protection mechanism directed at synthesis of harmful oxygen radicals, initiated by UVB irradiation.

Psoriatic patients differ in their response to treatment with active vitamin D metabolites. An increase in mRNA for VDR within psoriatic lesions after topical treatment was observed only in those patients who reacted with a significant improvement of the clinical condition. The studies performed in keratinocyte and fibroblast cultures prepared from psoriatic patients showed partial resistance to antiproliferative action of calcipotriol. No decrease in VDR expression in keratinocytes and fibroblasts was found if the vitamin D analogues were used on the psoriatic lesions after earlier application of corticosteroids, as shown by observations during subsequent application of the combined treatment [10, 35-38].

VDR gene polymorphism in psoriatic patients

In relation to the above-mentioned differences in the reaction to treatment with vitamin D analogues, subsequent analyses of VDR genotype in psoriasis were performed. The studies of psoriatic patients from Turkish and Japanese populations showed a relationship between TaqI polymorphism and development of the disease (statistically significantly more T alleles than in the control group), while a South-Korean and another Turkish study showed the ApaI allele to be more frequent (in the first, more frequent presence of allele A, and in the second, allele a). Studies in an Italian population showed no relationship between BsmI

VDR gene polymorphism and development of psoriasis. No relationships between particular VDR genotypes and PASI indicator, family history of psoriasis or involvement of nails in the tested persons were found.

Different results concerning VDR gene polymorphism obtained in different ethnic groups have been presented several times. This suggests that it may be related to racial differences or environmental factors, or it just shows that VDR polymorphism is not the cause of psoriasis, although it may be connected with a so far unknown locus, located nearby. Analysis of VDR gene polymorphism has not proved so far to be helpful in prediction of a good clinical response to topical treatment with vitamin D analogues, despite its relationships with AA, Bb and TT genotypes indicated by some researchers.

Analyses of the levels of vitamin D receptor levels in the skin have also brought contradictory results. Some studies showed no significant differences in VDR and RXR levels between healthy and psoriatic skin, while other studies showed significant differences in VDR expression levels, with an increase found within skin with psoriatic lesions [10, 39-46].

Conclusions

Despite the fact that the knowledge on vitamin D metabolism has significantly developed, the contradictory results concerning VDR gene polymorphism and its expression obtained in the studies on psoriatic patients still prevent clear definition of a relationship between particular VDR genotypes (BsmI, FokI or ApaI) and the presence of skin lesions or the expected efficacy of treatment. It is also difficult to define, with a high probability, which patients will not respond to SUP 311 nm irradiation or topical treatment with vitamin D analogues, before any treatment starts.

Therefore, it is necessary to perform further studies on the mechanisms of action of the traditional therapeutic regimens, such as NB-UVB phototherapy, in order to further optimise them.

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