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UVB and Vitamin D in Psoriasis

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1. Introduction

Psoriasis is a chronic, inflammatory disease affecting the skin and potentially the joints. Both genetic and environmental factors are important in the etiology of the disease. Psoriasis is characterized by keratinocyte hyperproliferation, abnormal keratinocyte differentiation, and immune-cell infiltration into the epidermis and dermis.

Disease management is dependent on severity, psychosocial effects and the patient's lifestyle. Currently, psoriasis may be treated with phototherapy or by using various topical, systemic, and biologic drug treatments. Topical treatments include creams and ointments containing tar, dithranol, corticosteroids, salicylic acid or vitamin D-related compounds.

Vitamin D3 analogs inhibit proliferation, induce terminal differentiation of human keratinocytes and exhibit immunomodulating properties. Several studies have shown vitamin D analogs to be a safe, efficacious and long-term treatment option for psoriasis. Vitamin D3 analogs are also used in combination with phototherapy.

Phototherapy (broadband UVB, narrowband UVB (NBUVB) and heliotherapy – treatment with natural sunlight) is a commonly used treatment modality for widespread psoriasis. A similar wavelength spectrum of UVB (280-315 nm) is responsible for vitamin D synthesis in the skin. Vitamin D3, or cholecalciferol, is produced from 7-dehydrocholesterol in the basal epidermis when exposed to UVB, and is then hydroxylated in the liver into 25-hydroxyvitamin D [25(OH)D], which is the major circulating metabolite. Further hydroxylation into 1,25-dihydroxyvitamin D [1,25(OH)2D] occurs primarily in the kidneys. Hydroxylation in the kidneys is stimulated by parathyroid hormone (PTH) and suppressed by phosphate. Homeostatic mechanisms include parathyroid activity, serum calcium and serum 1,25(OH)2D3 itself. Vitamin D is an essential steroid not only for calcium homeostasis and skeletal health, but also for regulation of cellular growth, cell proliferation and cell differentiation. Vitamin D is obtained by skin production in response to UVB or by intake of vitamin D rich food or supplements. Vitamin D status is measured by serum/blood concentration of its metabolite 25(OH)D.

The wavelength spectrum of UVB responsible for vitamin D synthesis (broadband UVB, 290-320 nm) has been used successfully for years to treat psoriasis and other chronic inflammatory skin disorders. This chapter aims to increase knowledge about the effects of UVB on vitamin D production during treatment with phototherapy in patients with psoriasis and to investigate the impact of UVB-induced vitamin D on psoriasis, bone, lipid

and carbohydrate status in psoriasis patients. A review of the published studies will be used to accomplish this task. In our previously published studies, the serum concentrations of 25(OH)D, 1,25(OH)2D, PTH, calcium and creatinine were measured before and after phototherapy in Caucasian patients with moderate to severe active plaque psoriasis. Bone mineral density (BMD) was examined using dual-energy X-ray absorptiometry (DEXA) at the hip and lumbar spine in a group of postmenopausal women with psoriasis. Lipid and carbohydrate status were assessed in patients treated with heliotherapy.

We found that UVB/heliotherapy improved the psoriasis score and lipid and carbohydrate status of the patients, increased serum 25(OH)D synthesis and reduced serum PTH concentrations. Vitamin D production in psoriasis patients increased less with narrowband UVB than with broadband UVB phototherapy. There was no correlation between the dose of UVB and the increase in 25(OH)D. The ratio of low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol decreased, and the levels of glycosylated hemoglobin A1c (HbA1c) also decreased in psoriasis patients during heliotherapy. Postmenopausal women with psoriasis had higher BMD than age-matched controls, a finding that could be related to their higher body weight, levels of physical activity and UVB exposure.

The changes in serum concentrations of vitamin D metabolite 25(OH)D were not related to the degree of improvement in psoriasis severity. This can be explained by the fact that 25(OH)D is biologically inert. It is unclear if the serum 25(OH)D level is linked to the level of the active form of vitamin D3 (1,25(OH)2D) present in the skin. It has been suggested that cutaneous conversion of 25(OH)D to 1,25(OH)2D does not play a role because the amount of free 25(OH)D3 that penetrates the cell membrane of epidermal keratinocytes is too small to produce sufficient amounts of 1,25(OH)2D. Therefore, of great interest will be the study of UVB induced local effects on vitamin D synthesis and metabolism in psoriatic skin.

2. Content

2.1 Vitamin D, skin production and metabolism

Vitamin D or calciferol refers to cholecalciferol or vitamin D3 and ergocalciferol or vitamin D2. D3 is produced in the skin as a result of ultraviolet irradiation of 7-dehydrocholesterol (7-DHC) and D2 is produced by ultraviolet irradiation of the plant sterol ergosterol(1).

Vitamin D was discovered in the 1900's as a result of research efforts geared towards the treatment of the disease, rickets. Within the last decade, vitamin D has become a popular topic in medical research as investigators aim to elucidate the role it plays in both maintaining health and contributing to the onset of disease.

Most people obtain their vitamin D requirement from sunlight exposure (2) in addition to smaller amounts obtained through the diet since very few foods naturally contain vitamin D.

7-DHC absorbs ultraviolet B (UVB) radiation and optimum wavelengths for vitamin D3 production are between 295 nm and 300 nm with a peak at 297 nm(3). Levels of 7-DHC have been observed to decline with age, which might negatively impact vitamin D3 synthesis in the skin (2). Vitamin D3 produced in the skin or ingested from the diet can be stored in body fat and later released into circulation. Vitamin D3 is sequestered deep into body fat, making it less bioavailable in obese individuals(4). Vitamin D is biologically inert and must be hydroxylated in the liver to form 25-hydroxyvitamin D [25(OH)D or calcidiol], which is the

major circulating metabolite. Further hydroxylation into 1,25-dihydroxyvitamin D [1,25(OH)2D or calcitriol] occurs primarily in the kidneys (Figure 1). Hydroxylation in the kidneys is stimulated by parathyroid hormone (PTH) and suppressed by phosphate. Homeostatic mechanisms include parathyroid activity, serum calcium and serum 1,25(OH)2D itself. Conversion of vitamin D to 25(OH)D is mediated by the enzyme vitamin D-25-hydroxylase (CYP27A1). The synthesis and degradation of calcitriol are regulated by the enzymes 25(OH)D-1-α-hydroxylase (CYP27B1) and 25(OH)2D-24-hydroxylase (CYP24A1), respectively. The combined activity of these enzymes is an important factor in determining the circulating concentrations of 25(OH)D, and 1,25(OH)2D(1). In addition to the kidney, other tissues and cells, including keratinocytes and immune cells, contain these enzymes and are able to convert 25(OH)D to active 1,25(OH)2D(5).

Besides being an essential steroid for calcium homeostasis and skeletal health, vitamin D also plays a role in regulation of cellular growth, cell proliferation and cell differentiation. Vitamin D also regulates the immune system, controls cancer cell growth and plays a role in the regulation of blood pressure(6). These effects are mediated through the intracellularly located vitamin D receptor (VDR). VDR is a member of the steroid, estrogen and retinoid receptor gene family of proteins that mediate transcriptional activities of the respective ligands. The VDR complex interacts with vitamin D responsive elements on the target gene. Alterations in calcitriol levels and polymorphisms of the VDR gene have been shown to be associated with several malignant and autoimmune diseases including psoriasis vulgaris(7).

25(OH)D is used clinically to measure vitamin D status. The cut-off level for serum 25(OH)D, which is used as a diagnostic marker for vitamin D deficiency, has varied over the years(8-10). The early biochemical changes in vitamin D insufficiency include a rise in serum PTH, which begins to increase as serum 25(OH)D levels fall below 30 ng/ml or 75 nmol/l(9). This level of 25(OH)D has become the suggested cut-off point for vitamin D deficiency or inadequacy(9, 11-13). At the present time, there is no clear consensus regarding levels of 25(OH)D for optimal health but levels of > 50 nmol/l (20 ng/ml)(14) and > 75 nmol/l (30 ng/ml) have been based on considering the outcomes of bone health, fracture prevention and colorectal cancer(15,16). Sun exposure is the strongest factor influencing 25(OH)D. The serum concentrations of 25(OH)D vary seasonally, with maximum and minimum values in the late summer and winter respectively(17). The extent of this seasonal variation depends on factors such as latitude, skin pigmentation, clothing, and the use of sunscreen(18).

Currently, limited data is available on the role of vitamin D deficiency in the pathogenesis or outcomes of psoriasis. The lack of conclusive data combined with vitamin D's immunomodulatory role, warrants further research investigating the role of vitamin D insufficiency in chronic diseases as well as monitoring 25(OH)D levels in children and adults of all ages as a part of routine physical examinations.

2.2 The effects of vitamin D in psoriasis

Vitamin D has pleotropic functions; it acts as a hormone by controlling calcium homeostasis as well as exerting autocrine/paracrine effects on tissues that express CYP27B1 and VDR. Besides its local effects, calcitriol may also act in psoriasis through its immunomodulatory properties by inhibiting T-cell proliferation and Th1 development, modulating antigen-presenting cell (APCs) function, inducing hyporesponsiveness to antigens, inhibiting

production of IL-2, IL-17, IL-8 and interferon-γ, increasing the production of IL-10 and regulatory T cells(19, 20). Calcitriol has also been suggested to reduce production of interferon-α in some cells(21). Calcitriol is involved in the regulation of antimicrobial peptides cathelicidin and human β-defensin 2 (HBD2), which both participate in the pathogenesis of psoriasis (22). Vitamin D's role in psoriasis is further supported by studies that confirm the link between VDR polymorphism and psoriasis (23, 24). An association between VDR genotypes (Apa1) and the mean age at onset of psoriasis were previously observed (25). Since VDR gene polymorphisms show ethnic variability, concern arises on how to treat psoriasis patients of different populations according to their potentially varied treatment response (26). Moreover, it has been demonstrated that VDR gene polymorphisms may also play a role in partial resistance to calcipotriol therapy (24).

There are few studies on high-dose vitamin D3 in the treatment of psoriasis while systemic administration of 1,25(OH)2D for the treatment of psoriasis might be limited by its toxicity. A number of small trials show the efficacy and safety of vitamin D metabolites in the treatment of psoriasis and psoriatic arthritis (27-29). Systemic calcitriol treatment had an immunomodulatory effect manifested by a short-term temporary decrease in type 1 immune responses and a decrease in disease activity in patients with psoriatic arthropathy (27). Administration of vitamin D3 could be a better option than calcitriol or alphacalcidol since it is safer and less expensive, although more studies are needed to assess its efficacy (21). However, the use of calcitiol in dermatology is hampered by its hypercalcemic activity. There is limited information on the role of vitamin D deficiency in the pathogenesis of psoriasis or the role of vitamin D deficiency in response to treatments with topical or systemic drugs. There is a report of resolution of anti-TNFα-induced psoriasiform lesions by high doses of vitamin D3, in a patient with rheumatoid arthritis and vitamin D deficiency (21). More studies are needed to assess the possible usefulness of high-dose vitamin D3 in the treatment of psoriasis.

2.3 Effects of vitamin D3 analogues in psoriasis

The observation that keratinocytes and T cells express VDR and that 1,25(OH)2D is a potent stimulator of keratinocyte differentiation provides a potential basis for the clinical use of VDR ligands for the treatment of psoriasis (30, 31). Clinical data that first supported the use of vitamin D analogs was obtained when a patient treated orally with 1-hydroxyvitamin D3 for osteoporosis showed remarkable remission of psoriatic lesions(32). In addition, promising clinical results were obtained in studies using oral 1-hydroxyvitamin D3, oral and topical calcitriol which led to improvement of psoriatic lesions in approximately 70-80% of patients (33). Vitamin D3 analogs (calcipotriol (Dovonex), calcitriol (Silkis) or tacalcitol (Curatoderm)) inhibit proliferation, induce terminal differentiation of human keratinocytes and exhibit immunomodulating properties (33). Differentiation of keratinocytes results in the formation of a cornified envelope (CE) that provides the barrier function of the skin. The expression of involucrin, a component of the CE, and transglutaminase I (TGase I), the enzyme that cross-links the components of CE, was increased by calcitriol and other VDR ligands(35). Treatment of keratinocytes with a medium containing high calcium also stimulated keratinocyte differentiation by increasing the expression of involucrin and TGase I. 1,25(OH)2D also promoted keratinocyte differentiation, at least in part by increasing intracellular calcium and by increased expression of calcium receptors in keratinocytes(36). Calcitriol indirectly induces the expression of keratin 1, involucrin, TGase I, loricrin, and

filaggrin, which are required for CE formation. VDR ligands decreased the expression of proinflammatory cytokines IL-2, IFN-γ, IL-6, IL-8 (37-40) and proliferation of T lymphocytes and keratinocytes. Furthermore, topical calcipotriol increased anti-inflammatory cytokine IL-10 in psoriatic lesions(41), and increased the expression of IL-10 receptor in keratinocytes(42).

Antigen presenting cells (APCs), which play an important role in psoriasis, are one of the major targets of calcitriol-mediated immunosuppressive action (43). VDR ligands prevent the activation, differentiation, maturation and survival of APCs, leading to T cell hyporesponsiveness(44). Calcitriol also increased the expression of IL-10 and decreased the expression of IL-12, two major cytokines that are involved in Th1-Th2 balance(45).

Several studies have shown that calcipotriol as well as calcitriol and tacalcitol are efficacious, safe and can be used on a long-term basis for psoriasis (43, 46-49). Vitamin D3 analogs can be used in combination with phototherapy(50).

2.4 Vitamin D status in patients with psoriasis

Few studies on vitamin D status and its role in psoriasis have been performed or published. Low vitamin D status is associated with an increased risk of cancer, autoimmune, infectious, and inflammatory diseases, although the role of vitamin D status in the pathogenesis of psoriasis is unknown.

3. The effects of phototherapy on vitamin D status in patients with psoriasis

A similar wavelength spectrum of UVB is responsible for vitamin D synthesis (280-315 nm), which has been successfully used for years to treat psoriasis and other chronic inflammatory skin disorders.

Phototherapy (broadband UVB, narrowband UVB and heliotherapy - treatment with natural sunlight) is an effective treatment, commonly used for widespread psoriasis. Therefore, phototherapy is an excellent option for patients with generalized psoriasis because of its superior systemic safety profile in comparison to systemic and biologic agents (51).

In addition to standard broadband ultraviolet radiation B (BUVB), (280-315 nm), narrowband phototherapy (NBUVB) (monochromatic UV between 311-312 nm) and heliotherapy (treatment with natural sunlight) have become important treatment modalities for psoriasis. Research suggests that NBUVB is more effective than broadband UVB for reducing PASI scores, as well as being a safer and better tolerated option for patients in comparison to PUVA when taken at suberythemogenic doses (52). Furthermore, these advantages along with the handling ease of the NBUVB lamp led to a reduction in the usage of broadband UVB. However, one drawback of the new lamp is that the radiation times have almost doubled (54). Additionally, several studies indicate that combination therapy using both calcipotriol and UVB radiation illustrate more rapid healing of psoriasis when compared to monotherapy of either treatment (50,55).

Serum levels of 25(OH)D increased during treatment with artificial UV (BUVB and NBUVB) and during heliotherapy(56-59). The increase in 25(OH)D was higher in the BUVB treated patients when compared to the NBUVB ($p=0.008$) and heliotherapy ($p=0.017$) treated groups. Low-dose NBUVB treatment significantly increased vitamin D status in

patients with psoriasis, atopic eczema and other skin disorders with low initial levels of 25(OH)D(60, 61). Within the following intervention studies, age showed no correlation with the observed increase in 25(OH)D levels (57, 58, 62). This indicates the skin's capacity to produce vitamin D3 during phototherapy of psoriasis is independent of the patient's age or psoriasis severity. Phototherapy of psoriasis is the time-consuming procedure long enough to provide adequate cutaneous production of vitamin D even in elderly patients. The ability of the skin to produce vitamin D declines with age (63) due to insufficient sunlight exposure (11, 64) and a reduction in the functional production capacity of the skin(63, 65, 66). The increase in 25(OH)D3 was enhanced in patients with low baseline levels of vitamin D.

Vitamin D production in patients with psoriasis increased less with NBUVB than with BUVB phototherapy(58). One explanation might be that the optimal wavelength for initiation of the vitamin D3 pathway was 300±5 nm in vitro and in vivo(67, 68) which is in the BUVB range (280-315 nm). The synthesis of vitamin D was stimulated by wavelengths between 290-315 nm, but not for wavelengths longer than 315 nm. One study (58) reported that a wavelength of 311 nm effectively induced vitamin D synthesis, but not to the same extent as wavelengths in the BUVB range. UVB treatment including NBUVB treatment of psoriasis was a sufficiently time-consuming procedure to increase vitamin D. The time required for NBUVB to have an effect can reduce the difference in the potential of vitamin D production between the two lamps. The treatment time correlated strongly with the type of lamp (patients treated with NBUVB required 4 times the exposure patients treated with BUVB needed). This is consistent with other studies demonstrating that the dose response of the erythemal spectra of NBUVB should be about 4.2 times that of BUVB(69). The dose of UVB also correlated with the type of lamp, but no correlation between the dose of UVB and the increase of 25(OH)D3 levels was found (58). This might be due to the fact that serum concentrations of 25(OH)D3 were measured at different time points and a plateau level was reached after three weeks, which was also seen in a previous study(70). An *in vitro* study demonstrated that the dose-response relationship of UV exposure and cholecalciferol synthesis was nonlinear. It was hypothesized that exposure to additional UV did not result in a proportional increase in vitamin D levels(71). This might be explained by autoregulation of the skin synthesis, storage, and slow, steady release of vitamin D3 from the skin into the circulation(3). Non-linear vitamin D synthesis is easily explained by the photo equilibrium that is set up as a result of continued exposure to ultraviolet radiation as reported by Holick et al(72). Vitamin D production is a unique, autoregulated mechanism which occurs at two levels. Excessive sun exposure does not lead to overdosing of vitamin D3 due to conversion of previtamin D3 to inactive photoproducts (lumisterol 3 and tachisterol 3) as well as conversion of vitamin D3 to its isomers in the skin (5,6-trans vitamin D3, suprasterol I, suprasterol II) which are thought to have a low calcemic effect at physiological concentrations. The synthesis of previtamin D3 reached a plateau at about 10 to 15 percent of the original 7-dehydrocholesterol content(72). Vitamin D3 is synthesized in the skin and released steadily and slowly from the skin into the circulation(3).

In a study by Ryan, the number of exposures to NBUVB was the sole predictor of an increase in serum 25(OH)D level, whereas prior phototherapy was the only predictor of baseline serum 25(OH)D levels in the group of psoriasis patients treated with phototherapy(73).

Patients with lower 25(OH)D levels at baseline responded better to sunlight and phototherapy which is consistent with other studies(3, 6, 57). All patients reached serum levels of 30 ng/ml (75 nmol/l) after two weeks of sun exposure(62). A circulating level of 25(OH)D of >30 ng/ml, or >75 nmol/L, appears to be necessary to maximize the health benefits of vitamin D(6).

Sun exposure is the major source of vitamin D for most humans(6). During the winter months vitamin D production is insufficient to meet the optimal requirements in both younger and older adults at Northern latitudes(74). Psoriasis lesions usually worsen during winter, and many patients are therefore given repeated UVB treatment during this season. In addition to healing psoriatic lesions, UVB therapy also provides these patients with vitamin D during the winter months, when levels of 25(OH)D in Northern countries are generally low. UVB therapy even increased serum 25(OH)D levels in patients taking vitamin D supplements. This is in line with previous studies, which reported that UV-induced vitamin D synthesis had a greater influence on the serum levels of circulating calcidiol than the per oral intake of supplements(75, 76).

Skin pigment, sunscreen use, aging, time of day, season, and latitude all affect previtamin D3 synthesis(18). There was no difference in the increase of 25(OH)D between the different skin types in the present studies(59). This was most likely due to subjects being exposed to individually adjusted doses of UVB depending on skin phototype and erythemal response to therapy. All patients had previously experienced UVB therapy for their psoriasis disease. As expected, fair-skinned patients required lower doses of UVB (broadband and narrowband) than patients with skin type III and IV. This finding is consistent with other studies examining the effect of skin pigmentation on vitamin D synthesis(77). Melanin pigment in human skin competes with, and absorbs UVB photons responsible for the vitamin D synthesis(77).

The increase in 25(OH)D during the first two weeks of heliotherapy was very similar to the increase in 25(OH)D during treatment with BUVB and NBUVB for two to three months. The correlation between sunlight measures and serum 25(OH)D is evidently weak(78). Patients reached their plateau of daily sun exposure after the first week. It is likely that vitamin D production was most prominent during the first week, when the patients experienced redness and some of them even got sunburned(56).

The increase in 25(OH)D during 15 days of climate therapy was significant even though patients used sunscreen on body sites susceptible to sunburn, and though the skin was affected by psoriasis lesions(56, 62). This indicates that short-term therapeutic UVB exposures are sufficient to increase vitamin D synthesis in psoriasis patients. SPF-8 sunscreen has been observed to reduce the skin's production of vitamin D3 by 95%(79). Clothing also completely blocks all solar UVB radiation and thereby prevents vitamin D3 production(79).

Psoriasis improved in all patients, with a reduction in the PASI score of about 75% on all regimens(59, 73). Improvement in psoriasis correlated positively with the increase in 25(OH)D3 levels in one (58) ($p=0.047$; the group of patients treated with BUVB and NBUVB) but not in the other studies (57, 61, 62, 73). There was no correlation between change in serum 25(OH)D levels and change in PASI or change in DLQI in the study of psoriasis patients treated with NBUVB in Ireland(73). No relationship was found between

levels of 25(OH)D and psoriasis but a negative correlation was found between the severity of psoriasis and the basal serum level of 1,25(OH)2D(80).

The skin is the only tissue yet known in which the complete UVB-induced pathway from 7-DHC via intermediates (previtamin D3, vitamin D3, 25(OH)D) to the final product 1,25(OH)2D, takes place under physiological conditions(81), (Figure 1). Levels of 1,25(OH)2D tended to increase during phototherapy, but significant increases were noticed only during heliotherapy, and only in women with 25(OH)D3 below 30 ng/ml, and in ages ≥ 70 years. One explanation might be that these patients had lower serum concentrations of 25(OH)D at the start of the treatment.

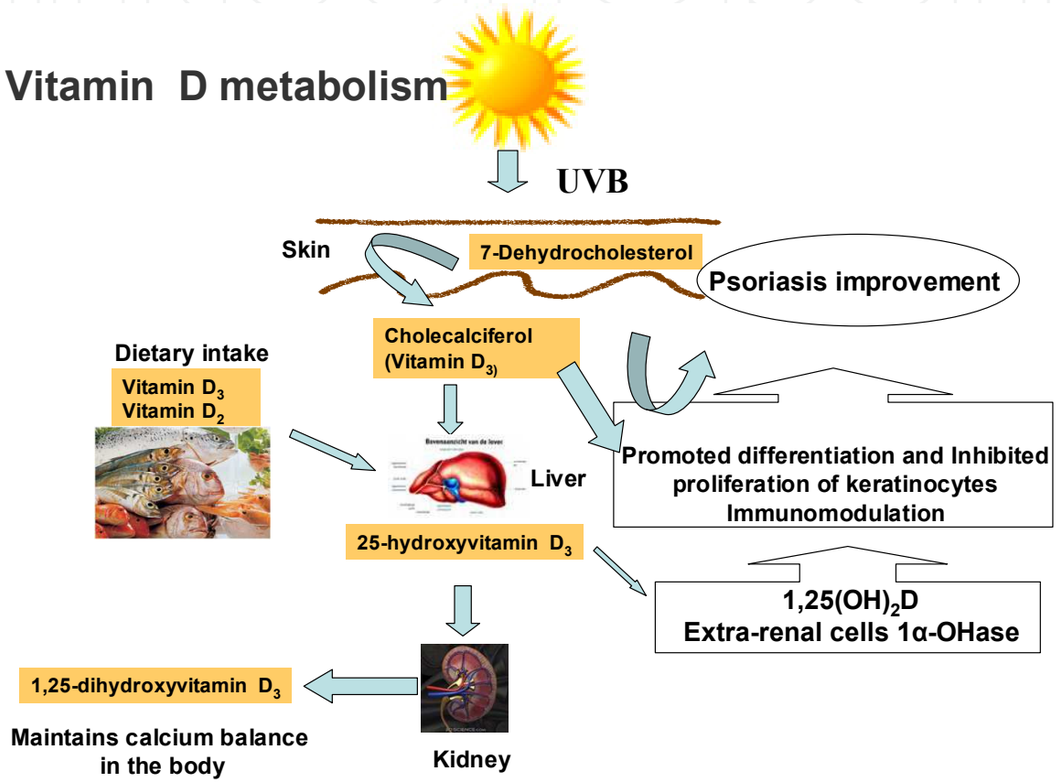

Fig. 1. Schematic outline of vitamin D metabolism and mechanism of action in psoriasis.

It has been postulated that the synthesis of 1,25(OH)2D is tightly regulated, and that increases in 25(OH)D concentrations due to exposure to sunlight have no effect on serum 1,25(OH)2D levels(6, 82). The observation that both 25(OH)D and 1,25(OH)2D increased in vitamin D deficient subjects following UVB exposure(83) or after vitamin D supplementation(84) has been reported previously. The increase of 1,25(OH)2D levels between patients treated with heliotherapy and patients treated with NBUVB differed ($p=0.02$). This might be explained by lower values of 25(OH)D at baseline in patients treated with heliotherapy(59).

Keratinocytes are capable of producing a variety of vitamin D metabolites, including 1,25(OH)2D, 24,25(OH)2D, 1,24,25(OH)3D(85) from exogenous and endogenous sources of 25(OH)D. Thus, the local UVB-triggered production of calcitriol may primarily regulate

epidermal cellular functions in an auto- and paracrine manner, but this should not be crucial for systemic vitamin D effects (5) and systemic vitamin D deficiency does not stimulate epidermal synthesis of 1,25(OH)2D(86).

Cutaneous production of 1,25(OH)2D3 may regulate growth, differentiation, apoptosis and other biological processes in the skin(87, 88). Therefore, topical vitamin D analogs have been used as a safe and effective treatment for psoriasis vulgaris(89, 90). The NBUVB has been shown to have less capacity to induce a local skin production of 1,25(OH)2D3 at 44% of the monochromatic irradiation at 300 ±2.5 nm(68). Nevertheless, the known therapeutic effect of UVB light therapy for the treatment of psoriasis may be mediated via UVB-induced production of 1,25(OH)2D(81). In vitro studies have shown that the substrate concentration of cholecalciferol in keratinocytes mainly determines the synthesis rate of 1,25(OH)2D in these cells(91). Thus, higher synthesis rates of cholecalciferol should result in a faster and more pronounced release of 1,25(OH)2D into the extracellular fluid. UVB-induced membrane damage to epidermal keratinocytes may also increase the outflow of newly synthesized calcitriol(92).

It is not clear if the serum 25(OH)D level is linked to the level of the active form of vitamin D3 present in the skin. It has been suggested that cutaneous conversion of 25(OH)D to 1,25(OH)2D does not play a role because the amount of free 25(OH)D3 that penetrates the cell membrane of epidermal keratinocytes is too small to produce sufficient amounts of 1,25(OH)2D(88). The main form of circulating 25(OH)D is presented in a complex with vitamin D-binding protein (DBP) with only a very small amount (0.03%) available as the free form. Furthermore, the deeper layers of the epidermis are not vascularized, which further impairs the passage of the 25(OH)D3-DBP complex from blood to epidermal keratinocytes(88).

The receptor for calcitriol and the production of 1,25(OH)2D vary with the differentiation in a manner suggesting feedback regulation, and both are reduced in the later stages of differentiation(93). 1,25(OH)2D increases involucrin, transglutaminase activity, and cornified envelope formation in preconfluent keratinocytes(94). NBUVB treatment increases cathelicidin and decreases HBD2 levels in healing skin lesions of psoriasis and atopic dermatitis(61). It has been shown that HBD2 and cathelicidin expression in psoriatic skin are higher in serum vitamin D sufficient patients than in serum vitamin D deficient psoriasis patients(95).

The 1,25(OH)2D molecule and its analogs, as well as UVB phototherapy, exert antiproliferative, prodifferentiative, and immune-modulatory effects on keratinocytes that are of particular importance for the therapy of hyperproliferative skin diseases such as psoriasis vulgaris(5, 96). However, the full range of UVB and vitamin D3 effects is not completely understood.

4. Serum PTH in psoriasis patients during treatment with phototherapy

PTH decreased after the treatment with phototherapy(57). 25(OH)D concentrations below 30 ng/ml (75 nmol/l) resulted in secondary hyperparathyroidism and a decrease in BMD(97). PTH increases with increasing age, possibly due to less sunlight exposure and/or reduced calcium/vitamin D intake(98). The clear concomitant decrease in serum PTH after UVB exposure indicates that the skin's capacity to synthesize vitamin D is maintained even at

older ages and with part of the skin covered by psoriatic lesions. Serum concentrations of calcium and creatinine were unaltered after phototherapy(58).

5. Bone status in patients with psoriasis treated with UVB phototherapy

Multiple risk factors that contribute to low serum 25(OH)D and osteoporosis have been identified. They include inadequate sun exposure(99), insufficient intake of fortified foods or vitamin D supplements(100), low body mass index, white ethnicity, lack of exercise, use of medications that accelerate vitamin D metabolism, diseases that alter vitamin D metabolism such as malabsorption syndromes, and chronic liver disease(9, 13, 101).

Information regarding the prevalence of osteoporosis in addition to the epidemiological study of risk factors for developing osteoporosis among psoriasis patients has been sparse and controversial. Psoriasis patients with or without arthritis may suffer from osteoporosis(102). However, a previous study showed that patients with chronic plaque psoriasis had a low BMD despite risk factors, although the subgroup with joint involvement appeared to be at a higher risk of developing osteoporosis and therefore required prevention therapy(103). Reduced BMD has been linked to palmoplantar pustular psoriasis(104). The existence of less severe periarticular osteoporosis has also been reported(105). Psoriasis patients with peripheral arthritis with longer duration of joint disease(106) and patients with a greater number of affected joints are at a higher risk of developing osteoporosis(102).In a study by Pedreira, patients with psoriasis and psoriatic arthritis did not present with a lower BMD, but they had a higher prevalence of osteoporotic fractures and were at a higher risk of developing metabolic syndrome(107).

Postmenopausal women with psoriasis treated with phototherapy had higher BMD of both the hip and lumbar spine compared with age-matched controls (57, 108). In the same study(108), patients with 25(OH)D levels below 30 ng/ml and secondary hyperparathyroidism had lower BMD in terms of both T and Z scores of the hip and the lumbar spine compared with those with higher vitamin D levels, consistent with another study(109). No relationship between psoriasis onset and bone status was found. Higher body weight and BMI are factors, which may have contributed to the higher BMD in patients(108) compared with controls

In general, bone loss increases with age. BMD has been shown to be a predictive indicator for bone fractures in healthy subjects and in patients with osteoporosis(111).

A family history of fractures, physical activity, smoking and estrogen substitution are important factors influencing bone mass(112-114). Low body weight is related to low skeletal muscle mass and an increased risk of fractures(114, 115). Muscle tissue and strength are important for body balance and the prevention of falls(116). Previous studies confirm the protective effect of weight gain against fractures(17).

Physical activity correlated positively with BMD in psoriasis patients(108). Physical activity has been claimed to be beneficial for bone mass and protective against fractures(117). Regular walking in middle-aged and elderly women is associated with a reduced risk of vertebral deformity(118). Subjects who took a daily walk of at least 30 min had a significantly better climbing capacity, higher BMD and lower concentration of serum triglycerides than subjects who walked less(119). Lifetime exercise was also positively associated with BMD of the hip(120).

Vitamin D is important for bone metabolism(121). Vitamin D deficiency thus contributes to the pathogenesis of osteoporosis and hip fractures(122). Supplementation strategies involving calcium and vitamin D supplements are cost-effective for preventing osteoporotic fractures(123).

The same range of UVB (290–315 nm) that induces vitamin D synthesis also improves psoriasis. Treatment with UVB in patients with psoriasis is most common during winter months when UVB is lacking, and levels of vitamin D are low in Northern countries(123). Furthermore, UVB therapy heals psoriasis and supplies these patients with vitamin D at levels similar to those of the general population(123), which might have positive effects on bone status as well.

6. Blood glucose and lipid status in psoriasis patients during treatment with heliotherapy

Psoriasis is considered a chronic and debilitating inflammatory disease associated with serious comorbidities (124, 125). Large epidemiological studies have shown that psoriasis and psoriatic arthritis are associated with metabolic diseases including obesity, dyslipidemia and diabetes(126). The chronic inflammation in psoriasis can predispose patients to other inflammatory conditions. The proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), and other factors that are overproduced in patients with psoriasis likely contribute to the increased risk for the development of metabolic syndrome(127, 128).

Inflammatory factors have also been associated with insulin resistance and β-cell failure, both of which are key features of type 2 diabetes mellitus (129). There is evidence that vitamin D may stimulate pancreatic insulin secretion directly through nuclear receptors that are found in a wide variety of tissues, including T and B lymphocytes, skeletal muscle, and the pancreatic islet β-cells(130). There is some evidence that suggests increased PTH activity is associated with, and possibly causes, reduced insulin sensitivity(130). The prevalence of impaired glucose tolerance and diabetes mellitus is increased in patients with primary hyperparathyroidism (131, 132).

Vitamin D has a wide range of effects on the immune system: it promotes the differentiation of monocytes into macrophages thus increasing their cytotoxic activity; reduces the antigen-presenting activity of macrophages to lymphocytes; prevents dendritic cell maturation; inhibits T lymphocyte-mediated immunoglobulin synthesis in B cells and inhibits delayed-type hypersensitivity reactions(8, 133, 134). Furthermore vitamin D has been reported to down-regulate the production of several cytokines: IL-2, IL-6 and IL-12, interferon-γ, TNF-α, and TNF-β (134, 135). Alternations in vitamin D status and/or action may affect insulin sensitivity, β-cell function or both. Therefore, vitamin D may be involved in the pathogenesis of type 2 diabetes mellitus at both environmental and genetic levels(129). Psoriasis patients are more likely to be insulin resistant and to have impaired glucose tolerance, higher fasting insulin levels, and impaired β-cell function than non-psoriatic subjects(136).

Heliotherapy improves lipid and carbohydrate status of psoriasis patients(56). Increases in high-density lipoprotein (HDL)-cholesterol and decreases in HbA1c during climate therapy could be explained by several factors. One possible mechanism could be a direct effect of vitamin D on insulin sensitivity(130). Another is that sun exposure usually implies greater outdoor physical activity, leading to beneficial effects on lipids and insulin sensitivity,

unrelated to serum 25(OH)D concentrations(130). Diet might also influence glucose and lipid metabolism. Although climate therapy did not change the basal glucose levels of the patients, the HbA1c levels decreased about 10 %, indicating improved insulin sensitivity (56). The observed associations between vitamin D, insulin, and glucose metabolism in humans have not yet been confirmed by intervention studies and, hence, a causal association has not been established(130).

A high prevalence of atherosclerosis is also reported in psoriasis patients. High serum lipid levels have been suggested in the pathogenesis of atherosclerosis. High serum lipid levels are more common in psoriasis and may be responsible for an elevated prevalence of cardiovascular accidents in this group of patients(137). Patients with psoriasis exhibit a dyslipidemic profile, including increased levels of plasma cholesterol, triglycerides (TG), LDL, very low-density lipoprotein (VLDL) cholesterol and decreased levels of HDL cholesterol. Lipid abnormalities in psoriasis patients may be genetically determined(138). The ratio of low-density lipoprotein cholesterol (LDL) and high-density lipoprotein cholesterol (HDL) decreased, and the levels of hemoglobin A1c (HbA1c) also decreased in psoriasis patients during heliotherapy(56). Serum concentrations of 25(OH)D at baseline in psoriasis patients treated with heliotherapy correlated positively with serum HDL at baseline(56), consistent with a previously published study(139).

Psoriasis is associated with obesity, which is a component of metabolic syndrome. Obesity has been shown to be an independent risk factor for the development of psoriasis, and is also associated with more severe psoriasis (140). Abdominal obesity is a proinflammatory state with the visceral adipose tissue providing a rich source of inflammatory molecules known as adipocytokines including leptin, adiponectin, visfatin and resistin. This may explain an important association between obesity, insulin resistance and related inflammatory disorders.

Inflammation plays a key role in the pathogenesis of psoriasis and a number of chronic inflammatory systemic diseases listed above. Activated inflammatory cells and pro-inflammatory cytokines, such as TNF-α and IL-1β, contribute to the development of psoriatic lesions and play an important role in atherosclerosis (141).

7. Conclusion

Recent literature has provided plenty of information concerning the preventive and therapeutic role of vitamin D in many inflammatory diseases including psoriasis. Vitamin D inhibits proinflammatory processes by suppressing the enhanced activity of immune cells that take part in the autoimmune reaction. Phototherapy (UVB and heliotherapy) improved psoriasis and lipid and carbohydrate status of the patients, increased serum 25(OH)D synthesis and reduced serum PTH concentrations. UVB therapy heals psoriasis and supplies these patients with vitamin D, which might have positive effects on bone status as well.

The beneficial role of vitamin D for psoriasis might be due to both a skin and systemic increase in vitamin D metabolism. Cutaneous 1,25(OH)2D generated in psoriatic skin after UVB exposure develops a growth-inhibitory effect on proliferating epidermal keratinocytes similar to topically applicated calcitriol. It is unknown if skin affected by diseases such as psoriasis or eczema differ in vitamin D production compared to normal skin. Further research is needed to achieve a more comprehensive understanding of the synthesis of vitamin D in psoriatic skin and the role of vitamin D status in the prevention and treatment of psoriasis.

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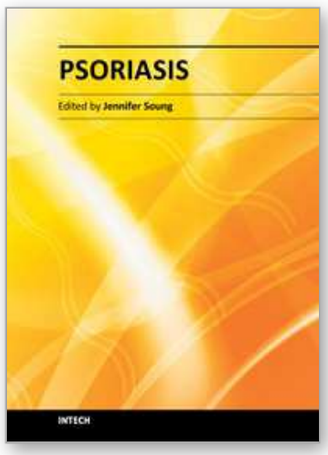

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We hope you enjoy and find the information provided in this book useful in your research or practice. We urge that you continue to keep abreast of the new developments in psoriasis and share your knowledge so that we may advance treatment and cures of psoriasis.

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