8

UVB and Vitamin D in Psoriasis

A. Osmancevic

Dept of Dermatology, Sahlgrenska University Hospital, Gothenburg,
Sweden

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.
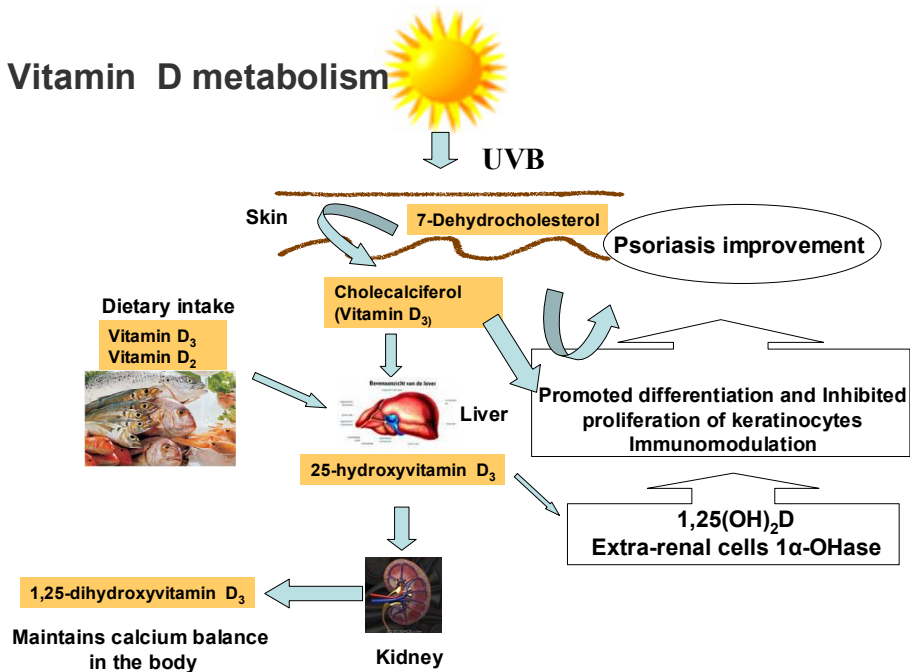

Fig. 1. Schematic outline of vitamin D metabolism and mechanism of action in psoriasis.

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 applied 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.

8. References

[1] Bikle DD. Vitamin D: Production, metabolism, and mechanisms of action. Diseases of Bone and Calcium Metabolism, Hyperparathyroidism: Endotex.com, 2004. p. 1-27.

[2] Holick MF. McCollum Award Lecture, 1994: vitamin D--new horizons for the 21st century. Am J Clin Nutr. 1994 Oct;60(4):619-30.

[3] Holick MF. The cutaneous photosynthesis of previtamin D3: a unique photoendocrine system. J Invest Dermatol. 1981 Jul;77(1):51-8.

[4] Holick MF. The vitamin D epidemic and its health consequences. J Nutr. 2005 Nov;135(11):2739S-48S.

[5] Bar M, Domaschke D, Meye A, Lehmann B, Meurer M. Wavelength-dependent induction of CYP24A1-mRNA after UVB-triggered calcitriol synthesis in cultured human keratinocytes. J Invest Dermatol. 2007 Jan;127(1):206-13.

[6] Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. Am J Clin Nutr. 2008 Apr;87(4):1080S-6S.

[7] Rucevic I, Barisic-Drusko V, Glavas-Obrovac L, Stefanic M. Vitamin D endocrine system and psoriasis vulgaris--review of the literature. Acta Dermatovenerol Croat. 2009;17(3):187-92.

[8] Zittermann A. Vitamin D in preventive medicine: are we ignoring the evidence? Br J Nutr. 2003 May;89(5):552-72.

[9] Favus MJ. Postmenopausal osteoporosis and the detection of so-called secondary causes of low bone density. J Clin Endocrinol Metab. 2005 Jun;90(6):3800-1.

[10] Grant WB, Holick MF. Benefits and requirements of vitamin D for optimal health: a review. Altern Med Rev. 2005 Jun;10(2):94-111.

[11] Chapuy MC, Preziosi P, Maamer M, Arnaud S, Galan P, Hercberg S, et al. Prevalence of vitamin D insufficiency in an adult normal population. Osteoporos Int. 1997;7(5):439-43.

[12] Holick MF, Siris ES, Binkley N, Beard MK, Khan A, Katzer JT, et al. Prevalence of Vitamin D Inadequacy Among Postmenopausal North American Women Receiving Osteoporosis Therapy. Obstet Gynecol Surv. 2005 Oct;60(10):658-9.

[13] Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. Endocr Rev. 2001 Aug;22(4):477-501.

[14] Lips P. Which circulating level of 25-hydroxyvitamin D is appropriate? J Steroid Biochem Mol Biol. 2004 May;89-90(1-5):611-4.

[15] Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. Am J Clin Nutr. 2006 Jul;84(1):18-28.

[16] Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr. 2004 Dec;80(6 Suppl):1678S-88S.

[17] Landin-Wilhelmsen K, Wilhelmsen L, Wilske J, Lappas G, Rosen T, Lindstedt G, et al. Sunlight increases serum 25(OH) vitamin D concentration whereas 1,25(OH)2D3 is unaffected. Results from a general population study in Goteborg, Sweden (The WHO MONICA Project). Eur J Clin Nutr. 1995 Jun;49(6):400-7.

[18] Holick MF. Sunlight, UV-radiation, vitamin D and skin cancer: how much sunlight do we need? Adv Exp Med Biol. 2008;624:1-15.

[19] Arnson Y, Amital H, Shoenfeld Y. Vitamin D and autoimmunity: new aetiological and therapeutic considerations. Ann Rheum Dis. 2007 Sep;66(9):1137-42.

[20] Adams JS, Hewison M. Update in vitamin D. J Clin Endocrinol Metab. Feb;95(2):471-8.

[21] Werner de Castro GR, Neves FS, Pereira IA, Fialho SC, Ribeiro G, Zimmermann AF. Resolution of adalimumab-induced psoriasis after vitamin D deficiency treatment. Rheumatol Int. Feb 3.

[22] Hollox EJ, Huffmeier U, Zeeuwen PL, Palla R, Lascorz J, Rodijk-Olthuis D, et al. Psoriasis is associated with increased beta-defensin genomic copy number. Nat Genet. 2008 Jan;40(1):23-5.

[23] Okita H, Ohtsuka T, Yamakage A, Yamazaki S. Polymorphism of the vitamin D(3) receptor in patients with psoriasis. Arch Dermatol Res. 2002 Jul;294(4):159-62.

[24] Dayangac-Erden D, Karaduman A, Erdem-Yurter H. Polymorphisms of vitamin D receptor gene in Turkish familial psoriasis patients. Arch Dermatol Res. 2007 Dec;299(10):487-91.

[25] Park BS, Park JS, Lee DY, Youn JI, Kim IG. Vitamin D receptor polymorphism is associated with psoriasis. J Invest Dermatol. 1999 Jan;112(1):113-6.

[26] Zuel-Fakkar NM, Kamel MM, Asaad MK, Mahran MZ, Shehab AA. A study of ApaI and TaqI genotypes of the vitamin D receptor in Egyptian patients with psoriasis. Clin Exp Dermatol. Jun;36(4):355-9.

[27] Gaal J, Lakos G, Szodoray P, Kiss J, Horvath I, Horkay E, et al. Immunological and clinical effects of alphacalcidol in patients with psoriatic arthropathy: results of an open, follow-up pilot study. Acta Derm Venereol. 2009;89(2):140-4.

[28] Perez A, Raab R, Chen TC, Turner A, Holick MF. Safety and efficacy of oral calcitriol (1,25-dihydroxyvitamin D3) for the treatment of psoriasis. Br J Dermatol. 1996 Jun;134(6):1070-8.

[29] Huckins D, Felson DT, Holick M. Treatment of psoriatic arthritis with oral 1,25-dihydroxyvitamin D3: a pilot study. Arthritis Rheum. 1990 Nov;33(11):1723-7.

[30] Feldman D, Chen T, Hirst M, Colston K, Karasek M, Cone C. Demonstration of 1,25-dihydroxyvitamin D3 receptors in human skin biopsies. J Clin Endocrinol Metab. 1980 Dec;51(6):1463-5.

[31] Provvedini DM, Tsoukas CD, Deftos LJ, Manolagas SC. 1,25-dihydroxyvitamin D3 receptors in human leukocytes. Science. 1983 Sep 16;221(4616):1181-3.

[32] Morimoto S, Kumahara Y. A patient with psoriasis cured by 1 alpha-hydroxyvitamin D3. Med J Osaka Univ. 1985 Mar;35(3-4):51-4.

[33] Nagpal S, Lu J, Boehm MF. Vitamin D analogs: mechanism of action and therapeutic applications. Curr Med Chem. 2001 Nov;8(13):1661-79.

[34] van der Vleuten CJ, Gerritsen MJ, Steijlen PM, de Jong EM, van de Kerkhof PC. A therapeutic approach to erythrodermic psoriasis: report of a case and a discussion of therapeutic options. Acta Derm Venereol. 1996 Jan;76(1):65-7.

[35] Pillai S, Bikle DD. Role of intracellular-free calcium in the cornified envelope formation of keratinocytes: differences in the mode of action of extracellular calcium and 1,25 dihydroxyvitamin D3. J Cell Physiol. 1991 Jan;146(1):94-100.

[36] Ratnam AV, Bikle DD, Cho JK. 1,25 dihydroxyvitamin D3 enhances the calcium response of keratinocytes. J Cell Physiol. 1999 Feb;178(2):188-96.

[37] Manolagas SC, Provvedini DM, Tsoukas CD. Interactions of 1,25-dihydroxyvitamin D3 and the immune system. Mol Cell Endocrinol. 1985 Dec;43(2-3):113-22.

[38] Muller K, Bendtzen K. 1,25-Dihydroxyvitamin D3 as a natural regulator of human immune functions. J Investig Dermatol Symp Proc. 1996 Apr;1(1):68-71.

[39] Pinette KV, Yee YK, Amegadzie BY, Nagpal S. Vitamin D receptor as a drug discovery target. Mini Rev Med Chem. 2003 May;3(3):193-204.

[40] Tobler A, Gasson J, Reichel H, Norman AW, Koeffler HP. Granulocyte-macrophage colony-stimulating factor. Sensitive and receptor-mediated regulation by 1,25-dihydroxyvitamin D3 in normal human peripheral blood lymphocytes. J Clin Invest. 1987 Jun;79(6):1700-5.

[41] Kang S, Yi S, Griffiths CE, Fancher L, Hamilton TA, Choi JH. Calcipotriene-induced improvement in psoriasis is associated with reduced interleukin-8 and increased interleukin-10 levels within lesions. Br J Dermatol. 1998 Jan;138(1):77-83.

[42] Michel G, Gailis A, Jarzebska-Deussen B, Muschen A, Mirmohammadsadegh A, Ruzicka T. 1,25-(OH)2-vitamin D3 and calcipotriol induce IL-10 receptor gene expression in human epidermal cells. Inflamm Res. 1997 Jan;46(1):32-4.

[43] Nagpal S, Na S, Rathnachalam R. Noncalcemic actions of vitamin D receptor ligands. Endocr Rev. 2005 Aug;26(5):662-87.

[44] Penna G, Adorini L. 1 Alpha,25-dihydroxyvitamin D3 inhibits differentiation, maturation, activation, and survival of dendritic cells leading to impaired alloreactive T cell activation. J Immunol. 2000 Mar 1;164(5):2405-11.

[45] Adorini L, Penna G, Giarratana N, Uskokovic M. Tolerogenic dendritic cells induced by vitamin D receptor ligands enhance regulatory T cells inhibiting allograft rejection and autoimmune diseases. J Cell Biochem. 2003 Feb 1;88(2):227-33.

[46] Bourke JF, Iqbal SJ, Hutchinson PE. The effects of UVB plus calcipotriol on systemic calcium homeostasis in patients with chronic plaque psoriasis. Clin Exp Dermatol. 1997 Nov;22(6):259-61.

[47] Fogh K, Kragballe K. Recent developments in vitamin D analogs. Curr Pharm Des. 2000 Jun;6(9):961-72.

[48] Langner A, Ashton P, Van De Kerkhof PC, Verjans H. A long-term multicentre assessment of the safety and tolerability of calcitriol ointment in the treatment of chronic plaque psoriasis. Br J Dermatol. 1996 Sep;135(3):385-9.

[49] van de Kerkhof PC, Berth-Jones J, Griffiths CE, Harrison PV, Honigsmann H, Marks R, et al. Long-term efficacy and safety of tacalcitol ointment in patients with chronic plaque psoriasis. Br J Dermatol. 2002 Mar;146(3):414-22.

[50] Kragballe K. Vitamin D and UVB radiation therapy. Cutis. 2002 Nov;70(5 Suppl):9-12.

[51] Nguyen T, Gattu S, Pugashetti R, Koo J. Practice of phototherapy in the treatment of moderate-to-severe psoriasis. Curr Probl Dermatol. 2009;38:59-78.

[52] Barbagallo J, Spann CT, Tutrone WD, Weinberg JM. Narrowband UVB phototherapy for the treatment of psoriasis: a review and update. Cutis. 2001 Nov;68(5):345-7.

[53] Storbeck K, Holzle E, Schurer N, Lehmann P, Plewig G. Narrow-band UVB (311 nm) versus conventional broad-band UVB with and without dithranol in phototherapy for psoriasis. J Am Acad Dermatol. 1993 Feb;28(2 Pt 1):227-31.

[54] Larko O. Treatment of psoriasis with a new UVB-lamp. Acta Derm Venereol. 1989;69(4):357-9.

[55] Schiener R, Behrens-Williams SC, Pillekamp H, Kaskel P, Peter RU, Kerscher M. Calcipotriol vs. tazarotene as combination therapy with narrowband ultraviolet B (311 nm): efficacy in patients with severe psoriasis. Br J Dermatol. 2000 Dec;143(6):1275-8.

[56] Osmancevic A, Nilsen LT, Landin-Wilhelmsen K, Soyland E, Abusdal Torjesen P, Hagve TA, et al. Effect of climate therapy at Gran Canaria on vitamin D production, blood glucose and lipids in patients with psoriasis. J Eur Acad Dermatol Venereol. 2009 Oct;23(10):1133-40.

[57] Osmancevic A, Landin-Wilhelmsen K, Larko O, Mellstrom D, Wennberg AM, Hulthen L, et al. UVB therapy increases 25(OH) vitamin D syntheses in postmenopausal women with psoriasis. Photodermatol Photoimmunol Photomed. 2007 Oct;23(5):172-8.

[58] Osmancevic A, Landin-Wilhelmsen K, Larko O, Wennberg AM, Krogstad AL. Vitamin D production in psoriasis patients increases less with narrowband than with broadband ultraviolet B phototherapy. Photodermatol Photoimmunol Photomed. 2009 Jun;25(3):119-23.

[59] Osmancevic A, Landin-Wilhelmsen K, Larko O, Krogstad AL. Vitamin D status in psoriasis patients during different treatments with phototherapy. J Photochem Photobiol B. Nov 3;101(2):117-23.

[60] Cicarma E, Mork C, Porojnicu AC, Juzeniene A, Tam TT, Dahlback A, et al. Influence of narrowband UVB phototherapy on vitamin D and folate status. Exp Dermatol. 2009 Oct 22.

[61] Vahavihu K, Ala-Houhala M, Peric M, Karisola P, Kautiainen H, Hasan T, et al. Narrowband ultraviolet B treatment improves vitamin D balance and alters antimicrobial peptide expression in skin lesions of psoriasis and atopic dermatitis. Br J Dermatol. Aug;163(2):321-8.

[62] Osmancevic A, Nilsen LT, Landin-Wilhelmsen K, Soyland E, Abusdal Torjesen P, Hagve TA, et al. Effect of climate therapy at Gran Canaria on vitamin D production, blood glucose and lipids in patients with psoriasis. J Eur Acad Dermatol Venereol. 2009 Apr 24.

[63] MacLaughlin J, Holick MF. Aging decreases the capacity of human skin to produce vitamin D3. J Clin Invest. 1985 Oct;76(4):1536-8.

[64] Barth J, Gerlach B, Knuschke P, Lehmann B. Serum 25(OH)D3 and ultraviolet exposure of residents in an old people's home in Germany. Photodermatol Photoimmunol Photomed. 1992 Oct;9(5):229-31.

[65] Holick MF, Matsuoka LY, Wortsman J. Age, vitamin D, and solar ultraviolet. Lancet. 1989 Nov 4;2(8671):1104-5.

[66] Need AG, Morris HA, Horowitz M, Nordin C. Effects of skin thickness, age, body fat, and sunlight on serum 25-hydroxyvitamin D. Am J Clin Nutr. 1993 Dec;58(6):882-5.

[67] MacLaughlin JA, Anderson RR, Holick MF. Spectral character of sunlight modulates photosynthesis of previtamin D3 and its photoisomers in human skin. Science. 1982 May 28;216(4549):1001-3.

[68] Lehmann B, Knuschke P, Meurer M. The UVB-induced synthesis of vitamin D3 and 1alpha,25-dihydroxyvitamin D3 (calcitriol) in organotypic cultures of keratinocytes: effectiveness of the narrowband Philips TL-01 lamp (311 nm). J Steroid Biochem Mol Biol. 2007 Mar;103(3-5):682-5.

[69] Leenutaphong V, Sudtim S. A comparison of erythema efficacy of ultraviolet B irradiation from Philips TL12 and TL01 lamps. Photodermatol Photoimmunol Photomed. 1998 Jun-Aug;14(3-4):112-5.

[70] Porojnicu AC, Bruland OS, Aksnes L, Grant WB, Moan J. Sun beds and cod liver oil as vitamin D sources. J Photochem Photobiol B. 2008 May 29;91(2-3):125-31.
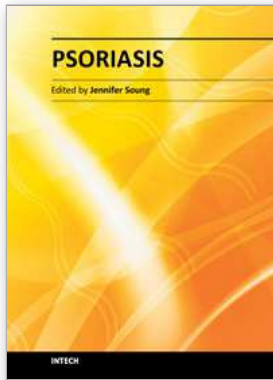
[71] Olds WJ, McKinley AR, Moore MR, Kimlin MG. In vitro model of vitamin D(3) (Cholecalciferol) synthesis by UV radiation: Dose-response relationships. J Photochem Photobiol B. 2008 Nov 13;93(2):88-93.

[72] Holick MF, MacLaughlin JA, Doppelt SH. Regulation of cutaneous previtamin D3 photosynthesis in man: skin pigment is not an essential regulator. Science. 1981 Feb 6;211(4482):590-3.

[73] Ryan C, Moran B, McKenna MJ, Murray BF, Brady J, Collins P, et al. The effect of narrowband UV-B treatment for psoriasis on vitamin D status during wintertime in Ireland. Arch Dermatol. Aug;146(8):836-42.

[74] Devgun MS, Paterson CR, Johnson BE, Cohen C. Vitamin D nutrition in relation to season and occupation. Am J Clin Nutr. 1981 Aug;34(8):1501-4.

[75] Armas LA, Hollis BW, Heaney RP. Vitamin D2 is much less effective than vitamin D3 in humans. J Clin Endocrinol Metab. 2004 Nov;89(11):5387-91.

[76] Holick MF. Vitamin D: A millenium perspective. J Cell Biochem. 2003 Feb 1;88(2):296-307.

[77] Chen TC, Chimeh F, Lu Z, Mathieu J, Person KS, Zhang A, et al. Factors that influence the cutaneous synthesis and dietary sources of vitamin D. Arch Biochem Biophys. 2007 Apr 15;460(2):213-7.

[78] McCarty CA. Sunlight exposure assessment: can we accurately assess vitamin D exposure from sunlight questionnaires? Am J Clin Nutr. 2008 Apr;87(4):1097S-101S.

[79] Matsuoka LY, Wortsman J, Hollis BW. Use of topical sunscreen for the evaluation of regional synthesis of vitamin D3. J Am Acad Dermatol. 1990 May;22(5 Pt 1):772-5.

[80] Morimoto S, Yoshikawa K. Psoriasis and vitamin D3. A review of our experience. Arch Dermatol. 1989 Feb;125(2):231-4.

[81] Lehmann B, Querings K, Reichrath J. Vitamin D and skin: new aspects for dermatology. Exp Dermatol. 2004;13 Suppl 4:11-5.

[82] Chesney RW, Rosen JF, Hamstra AJ, Smith C, Mahaffey K, DeLuca HF. Absence of seasonal variation in serum concentrations of 1,25-dihydroxyvitamin D despite a rise in 25-hydroxyvitamin D in summer. J Clin Endocrinol Metab. 1981 Jul;53(1):139-42.

[83] Adams JS, Clemens TL, Parrish JA, Holick MF. Vitamin-D synthesis and metabolism after ultraviolet irradiation of normal and vitamin-D-deficient subjects. N Engl J Med. 1982 Mar 25;306(12):722-5.

[84] Lips P, Wiersinga A, van Ginkel FC, Jongen MJ, Netelenbos JC, Hackeng WH, et al. The effect of vitamin D supplementation on vitamin D status and parathyroid function in elderly subjects. J Clin Endocrinol Metab. 1988 Oct;67(4):644-50.

[85] Bikle DD, Nemanic MK, Gee E, Elias P. 1,25-Dihydroxyvitamin D3 production by human keratinocytes. Kinetics and regulation. J Clin Invest. 1986 Aug;78(2):557-66.

[86] Vanhooke JL, Prahl JM, Kimmel-Jehan C, Mendelsohn M, Danielson EW, Healy KD, et al. CYP27B1 null mice with LacZreporter gene display no 25-hydroxyvitamin D3-1alpha-hydroxylase promoter activity in the skin. Proc Natl Acad Sci U S A. 2006 Jan 3;103(1):75-80.

[87] Reichrath J. Vitamin D and the skin: an ancient friend, revisited. Exp Dermatol. 2007 Jul;16(7):618-25.

[88] Lehmann B. The vitamin D3 pathway in human skin and its role for regulation of biological processes. Photochem Photobiol. 2005 Nov-Dec;81(6):1246-51.

[89] Sigmon JR, Yentzer BA, Feldman SR. Calcitriol ointment: a review of a topical vitamin D analog for psoriasis. J Dermatolog Treat. 2009;20(4):208-12.

[90] Tanghetti EA. The role of topical vitamin D modulators in psoriasis therapy. J Drugs Dermatol. 2009 Aug;8(8 Suppl):s4-8.

[91] Lehmann B, Knuschke P, Meurer M. UVB-induced conversion of 7-dehydrocholesterol to 1 alpha,25-dihydroxyvitamin D3 (calcitriol) in the human keratinocyte line HaCaT. Photochem Photobiol. 2000 Dec;72(6):803-9.

[92] Lehmann B, Sauter W, Knuschke P, Dressler S, Meurer M. Demonstration of UVB-induced synthesis of 1 alpha,25-dihydroxyvitamin D3 (calcitriol) in human skin by microdialysis. Arch Dermatol Res. 2003 Apr;295(1):24-8.

[93] Merke J, Schwittay D, Furstenberger G, Gross M, Marks F, Ritz E. Demonstration and characterization of 1,25-dihydroxyvitamin D3 receptors in basal cells of epidermis of neonatal and adult mice. Calcif Tissue Int. 1985 May;37(3):257-67.

[94] Hosomi J, Hosoi J, Abe E, Suda T, Kuroki T. Regulation of terminal differentiation of cultured mouse epidermal cells by 1 alpha,25-dihydroxyvitamin D3. Endocrinology. 1983 Dec;113(6):1950-7.

[95] Kim SK, Park S, Lee ES. Toll-like receptors and antimicrobial peptides expressions of psoriasis: correlation with serum vitamin D level. J Korean Med Sci. Oct;25(10):1506-12.

[96] van de Kerkhof PC. Biological activity of vitamin D analogues in the skin, with special reference to antipsoriatic mechanisms. Br J Dermatol. 1995 May;132(5):675-82.

[97] Sahota O, Mundey MK, San P, Godber IM, Lawson N, Hosking DJ. The relationship between vitamin D and parathyroid hormone: calcium homeostasis, bone turnover, and bone mineral density in postmenopausal women with established osteoporosis. Bone. 2004 Jul;35(1):312-9.

[98] Landin-Wilhelmsen K, Wilhelmsen L, Lappas G, Rosen T, Lindstedt G, Lundberg PA, et al. Serum intact parathyroid hormone in a random population sample of men and women: relationship to anthropometry, life-style factors, blood pressure, and vitamin D. Calcif Tissue Int. 1995 Feb;56(2):104-8.

[99] Webb AR, Kline L, Holick MF. Influence of season and latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. J Clin Endocrinol Metab. 1988 Aug;67(2):373-8.

[100] Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. Am J Clin Nutr. 1999 May;69(5):842-56.

[101] Landin-Wilhelmsen K, Wilhelmsen L, Bengtsson BA. Postmenopausal osteoporosis is more related to hormonal aberrations than to lifestyle factors. Clin Endocrinol (Oxf). 1999 Oct;51(4):387-94.

[102] Attia EA, Khafagy A, Abdel-Raheem S, Fathi S, Saad AA. Assessment of osteoporosis in psoriasis with and without arthritis: correlation with disease severity. Int J Dermatol. Jan;50(1):30-5.

[103] Millard TP, Antoniades L, Evans AV, Smith HR, Spector TD, Barker JN. Bone mineral density of patients with chronic plaque psoriasis. Clin Exp Dermatol. 2001 Jul;26(5):446-8.

[104] Nymann P, Kollerup G, Jemec GB, Grossmann E. Decreased bone mineral density in patients with pustulosis palmaris et plantaris. Dermatology. 1996;192(4):307-11.

[105] Frediani B, Allegri A, Falsetti P, Storri L, Bisogno S, Baldi F, et al. Bone mineral density in patients with psoriatic arthritis. J Rheumatol. 2001 Jan;28(1):138-43.

[106] Borman P, Babaoglu S, Gur G, Bingol S, Bodur H. Bone mineral density and bone turnover in patients with psoriatic arthritis. Clin Rheumatol. 2008 Apr;27(4):443-7.

[107] Pedreira PG, Pinheiro MM, Szejnfeld VL. Bone mineral density and body composition in postmenopausal women with psoriasis and psoriatic arthritis. Arthritis Res Ther. Feb 7;13(1):R16.

[108] Osmancevic A, Landin-Wilhelmsen K, Larko O, Mellstrom D, Wennberg AM, Hulthen L, et al. Risk factors for osteoporosis and bone status in postmenopausal women with psoriasis treated with UVB therapy. Acta Derm Venereol. 2008;88(3):240-6.

[109] Tangpricha V, Turner A, Spina C, Decastro S, Chen TC, Holick MF. Tanning is associated with optimal vitamin D status (serum 25-hydroxyvitamin D concentration) and higher bone mineral density. Am J Clin Nutr. 2004 Dec;80(6):1645-9.

[110] Naldi L, Chatenoud L, Linder D, Belloni Fortina A, Peserico A, Virgili AR, et al. Cigarette smoking, body mass index, and stressful life events as risk factors for psoriasis: results from an Italian case-control study. J Invest Dermatol. 2005 Jul;125(1):61-7.

[111] Fogelman I, Blake GM. Different approaches to bone densitometry. J Nucl Med. 2000 Dec;41(12):2015-25.

[112] Riggs BL. Pathogenesis of osteoporosis. Am J Obstet Gynecol. 1987 May;156(5):1342-6.

[113] Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, et al. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. N Engl J Med. 1995 Mar 23;332(12):767-73.

[114] Johnell O, Gullberg B, Kanis JA, Allander E, Elffors L, Dequeker J, et al. Risk factors for hip fracture in European women: the MEDOS Study. Mediterranean Osteoporosis Study. J Bone Miner Res. 1995 Nov;10(11):1802-15.

[115] Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. Lancet. 2002 May 18;359(9319):1761-7.

[116] Aniansson A, Zetterberg C, Hedberg M, Henriksson KG. Impaired muscle function with aging. A background factor in the incidence of fractures of the proximal end of the femur. Clin Orthop Relat Res. 1984 Dec(191):193-201.

[117] Cooper C, Barker DJ, Wickham C. Physical activity, muscle strength, and calcium intake in fracture of the proximal femur in Britain. Bmj. 1988 Dec 3;297(6661):1443-6.

[118] Silman AJ, O'Neill TW, Cooper C, Kanis J, Felsenberg D. Influence of physical activity on vertebral deformity in men and women: results from the European Vertebral Osteoporosis Study. J Bone Miner Res. 1997 May;12(5):813-9.

[119] Frandin K, Grimby G, Mellstrom D, Svanborg A. Walking habits and health-related factors in a 70-year-old population. Gerontology. 1991;37(5):281-8.

[120] Greendale GA, Barrett-Connor E, Edelstein S, Ingles S, Haile R. Lifetime leisure exercise and osteoporosis. The Rancho Bernardo study. Am J Epidemiol. 1995 May 15;141(10):951-9.

[121] Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, et al. Vitamin D3 and calcium to prevent hip fractures in the elderly women. N Engl J Med. 1992 Dec 3;327(23):1637-42.

[122] Chel VG, Ooms ME, Popp-Snijders C, Pavel S, Schothorst AA, Meulemans CC, et al. Ultraviolet irradiation corrects vitamin D deficiency and suppresses secondary hyperparathyroidism in the elderly. J Bone Miner Res. 1998 Aug;13(8):1238-42.

[123] Lilliu H, Pamphile R, Chapuy MC, Schulten J, Arlot M, Meunier PJ. Calcium-vitamin D3 supplementation is cost-effective in hip fractures prevention. Maturitas. 2003 Apr 25;44(4):299-305.

[124] Gottlieb AB, Chao C, Dann F. Psoriasis comorbidities. J Dermatolog Treat. 2008;19(1):5-21.

[125] Christophers E. Comorbidities in psoriasis. Clin Dermatol. 2007 Nov-Dec;25(6):529-34.

[126] Girolomoni G, Gisondi P. Psoriasis and metabolic comorbidities: the importance of well-designed prospective studies. Commentary. Dermatology. 2008;217(3):222-4.

[127] Gottlieb AB, Dann F, Menter A. Psoriasis and the metabolic syndrome. J Drugs Dermatol. 2008 Jun;7(6):563-72.

[128] Sommer DM, Jenisch S, Suchan M, Christophers E, Weichenthal M. Increased prevalence of the metabolic syndrome in patients with moderate to severe psoriasis. Arch Dermatol Res. 2006 Dec;298(7):321-8.

[129] Palomer X, Gonzalez-Clemente JM, Blanco-Vaca F, Mauricio D. Role of vitamin D in the pathogenesis of type 2 diabetes mellitus. Diabetes Obes Metab. 2008 Mar;10(3):185-97.

[130] Tai K, Need AG, Horowitz M, Chapman IM. Vitamin D, glucose, insulin, and insulin sensitivity. Nutrition. 2008 Mar;24(3):279-85.

[131] Procopio M, Magro G, Cesario F, Piovesan A, Pia A, Molineri N, et al. The oral glucose tolerance test reveals a high frequency of both impaired glucose tolerance and undiagnosed Type 2 diabetes mellitus in primary hyperparathyroidism. Diabet Med. 2002 Nov;19(11):958-61.

[132] Taylor WH, Khaleeli AA. Prevalence of primary hyperparathyroidism in patients with diabetes mellitus. Diabet Med. 1997 May;14(5):386-9.

[133] Luong K, Nguyen LT, Nguyen DN. The role of vitamin D in protecting type 1 diabetes mellitus. Diabetes Metab Res Rev. 2005 Jul-Aug;21(4):338-46.

[134] Mauricio D, Mandrup-Poulsen T, Nerup J. Vitamin D analogues in insulin-dependent diabetes mellitus and other autoimmune diseases: a therapeutic perspective. Diabetes Metab Rev. 1996 Apr;12(1):57-68.

[135] Lemire JM. Immunomodulatory actions of 1,25-dihydroxyvitamin D3. J Steroid Biochem Mol Biol. 1995 Jun;53(1-6):599-602.

[136] Ucak S, Ekmekci TR, Basat O, Koslu A, Altuntas Y. Comparison of various insulin sensitivity indices in psoriatic patients and their relationship with type of psoriasis. J Eur Acad Dermatol Venereol. 2006 May;20(5):517-22.

[137] Akhyani M, Ehsani AH, Robati RM, Robati AM. The lipid profile in psoriasis: a controlled study. J Eur Acad Dermatol Venereol. 2007 Nov;21(10):1330-2.

[138] Mallbris L, Granath F, Hamsten A, Stahle M. Psoriasis is associated with lipid abnormalities at the onset of skin disease. J Am Acad Dermatol. 2006 Apr;54(4):614-21.

[139] Carbone LD, Rosenberg EW, Tolley EA, Holick MF, Hughes TA, Watsky MA, et al. 25-Hydroxyvitamin D, cholesterol, and ultraviolet irradiation. Metabolism. 2008 Jun;57(6):741-8.

[140] Azfar RS, Gelfand JM. Psoriasis and metabolic disease: epidemiology and pathophysiology. Curr Opin Rheumatol. 2008 Jul;20(4):416-22.

[141] Libby P. Inflammation and cardiovascular disease mechanisms. Am J Clin Nutr. 2006 Feb;83(2):456S-60S.

Psoriasis

Edited by Dr. Jennifer Soung

ISBN 978-953-307-878-6

Hard cover, 372 pages

Publisher InTech

Published online 15, February, 2012

Published in print edition February, 2012

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.