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Vitamin D status in psoriasis patients during different treatments with phototherapy ☆

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ABSTRACT

Background: Phototherapy (broadband UVB (BUVB), narrowband UVB (NBUVB) and heliotherapy) is commonly used treatment modalities for widespread psoriasis. Vitamin D3, cholecalciferol, is produced in the epidermis by ultraviolet radiation (290–315 nm) of 7-dehydrocholesterol. 25-hydroxyvitamin D [25(OH)D], and 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] are the major circulating metabolites. Sun exposure is the strongest factor influencing 25(OH)D. The similar wavelength spectrum of UVB responsible for D vitamin synthesis (BUVB, 280–315 nm) has been successfully used for years to treat psoriasis.
Purpose: The aim was: (1) To increase the knowledge about the effects of phototherapy on vitamin D production during treatment of psoriasis. (2) To examine if there were differences between the effect of BUVB, NBUVB and heliotherapy on vitamin D synthesis in psoriasis patients.
Methods: Serum concentrations of 25(OH)D, 1,25$(OH)_2$D, PTH, calcium and creatinine, measured before and after phototherapy in white Caucasian patients with moderate to severe active plaque psoriasis, were aggregated from three studies.
Results: Psoriasis improved in all patients, with a reduction in PASI ((Psoriasis Area and Severity Index) score of about 75% on all regimes. Serum 25(OH)D increased and PTH decreased after the phototherapy. The increase in 25(OH)D was higher in the BUVB treated patients compared with NBUVB. There was no correlation between the dose of UVB and the increase of 25(OH)D.
Conclusion: UVB and heliotherapy improved the psoriasis score, increased the serum 25(OH)D levels and reduced the serum PTH concentrations. Vitamin D production in psoriasis patients increased less with NBUVB than with BUVB phototherapy.

1. Introduction

Psoriasis is a common chronic inflammatory disease affecting the skin and potentially the joints. Phototherapy (broadband UVB, narrowband UVB and heliotherapy) is an effective treatment, commonly used for widespread psoriasis.

In addition to standard broadband ultraviolet radiation B (BUVB), (280–315 nm), narrowband phototherapy (NBUVB) (monochromatic UV between 311 and 312 nm) and heliotherapy (treatment with natural sunlight) have become important treatment modalities for psoriasis.

Vitamin D3, or cholecalciferol, is produced in the epidermis and dermis by ultraviolet radiation (290–315 nm) of 7-dehydrocholesterol 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$(OH)_2$D] 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$(OH)_2$D itself. Vitamin D is an essential steroid for calcium homeostasis and skeletal health but even for regulation of cellular growth, cell proliferation and cell differentiation.

Sun exposure is the strongest factor influencing 25(OH)D. The similar wavelength spectrum of UVB responsible for D vitamin synthesis (BUVB, 280–315 nm) has been successfully used for years to treat psoriasis and other chronic inflammatory skin disorders.

Few studies on vitamin D status and its role in psoriasis have been performed or published.

Abbreviations: 25(OH)D or calcidiol, 25-hydroxyvitamin D; 1,25$(OH)_2$D or calcitriol, 1,25-dihydroxyvitamin D; BUVB, Broadband ultraviolet radiation B; NBUVB, Narrowband ultraviolet radiation B.

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In this report, we attempt to compare the effects of different types of phototherapies on vitamin D status in psoriasis patients, assembling data from three different studies in which values for both 25(OH)D and $1,25(OH)_2D$ were measured.

2. Material and methods

2.1. Design

The studies providing data for this analysis are listed in Table 1, and pertinent descriptive information from each study is provided. Clinical characteristics, UVB doses, number of treatments, frequency and amount of UVB irradiated body of the subjects included in the different studies, are presented in Table 1.

Further details on the three published studies [1–3], including identification of the principal investigators and institution, are contained in their respective reports [1–3]. Treatment duration ranged from 8 to 12 weeks, and the serum concentrations of 25(OH)D, $1,25(OH)_2D$ and PTH were measured before and after treatment. The third study was performed at Gran Canaria [3], where psoriasis patients were treated with heliotherapy and the serum concentrations of 25(OH)D, $1,25(OH)_2D$ and PTH were measured before the start, after 1 day and after 15 days of sun exposures, respectively.

For all studies, participants gave written informed consent. Declaration of Helsinki protocols was followed. All studies have been approved by the respective Ethics Committee and institutional review boards.

2.2. Analytic methods

The analytic methods were described in detail in the primary reports of the studies concerned [1–3]. The serum concentrations of 25(OH)D and $1,25(OH)_2D$ were measured by radioimmunoassay (DiaSorin, Stillwater, MN, USA). Serum PTH was measured using the immunochemical luminescence method (mass concentration), serum calcium by photometry, 600 nm and serum creatinine by using an enzymatic method (μmol/l).

2.3. Statistical analyses

Data are given as mean ± SD or median (min–max) if not otherwise stated. Simple descriptive statistics and univariate correlations were performed using the statistics routines of software (Excel, Microsoft Inc, SPSS, Version 15).

Student's paired *t* test was used for comparisons of the blood test results before and after sun exposure. Associations between variables were tested by Pearson correlation analysis. Probability values (2-sided) were considered significant at values of <0.05.

3. Theory

For most people sun exposure is the main vitamin D source while dietary intake is of minor importance [4]. During the last decade vitamin D has become a hot topic in medical research and the knowledge about its vital role in health and disease is constantly increasing. Vitamin D is an essential steroid for calcium homeostasis and skeletal health, for regulation of cellular growth, cell proliferation and cell differentiation [5]. Vitamin D regulates the immune system, controls cancer cell growth and plays a role in the regulation of blood pressure [4]. 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 binds in the nucleus to the vitamin D responsive element on the gene. Alterations in $1,25(OH)_2D$ levels and polymorphisms of VDR gene have been shown to be associated with several malignant or autoimmune diseases including psoriasis vulgaris. [6].

Therefore, vitamin D insufficiency may cause many chronic diseases that affect both children and adults [7].

25(OH)D is used clinically to measure vitamin D status. Sun exposure is the strongest factor influencing 25(OH)D. The serum concentrations of the 25(OH)D shows clear seasonal variation, with maximum in late summer and minimum at the end of winter [8]. The extent of this seasonal variation depends on the latitude, skin pigmentation, clothing and the application of a sunscreen [9]. The latitude of Sweden (Gothenburg) is 57°42‘ north of the equator and in this geographic area UVB is not present in sunlight from October to March. It is known that the risk of morbidity or mortality from colon, prostate, breast, ovarian, oesophageal, non-Hodgkin's lymphoma, and a variety of other aggressive cancers is related to living at higher latitudes and thereby a higher risk of vitamin D deficiency [10] Thus, the vitamin D has such important health implications that measurement of 25(OH)D should be part of a routine physical examination for children and adults of all ages.

Information about vitamin D status in patients with psoriasis and the effect of phototherapy on vitamin D status in this group is sparse. Phototherapy is an excellent option for patients with generalized psoriasis because of its superior systemic safety profile in comparison to systemic or biological agents [11]. Low-dose NBUVB treatment gives a significant increase of the vitamin D

Table 1
Clinical characteristics, UVB doses, number of treatments, frequency and amount of UVB irradiated body of the psoriatic subjects included in three studies [1–3] with different phototherapies.

Type of therapy	BUVB (post-menopausal women) [1]	BUVB and NBUVB [2]	Heliotherapy [3]
Number of subjects	24	68	20
Sex: male/female	0/24	51/17	14/6
Age (year) (mean ± SD)	69 ± 5.9	54.1 ± 16.0	47.2 ± 10.7
PASI score before	6–12 (range)	9.0 ± 4.7	9.8 ± 4.5
PASI score after	1–4 (range)	2.6 ± 1.6	2.4 ± 1.7
Age at onset of psoriasis (year) (mean ± SD)	34.0 ± 23	26.3 ± 14.2	
UVB dose (J/cm^2) (mean ± SD)	1.6 ± 1.48	16.1 ± 12.4 BUVB 50.4 ± 39.6 NBUVB	11.8 ± 1.69
Number of treatments (mean ± SD)	23.3 ± 5.5 (mean ± SD)	24.9 ± 3.2 (mean ± SD)BUVB 26.4 ± 4.3 (mean ± SD)NBUVB	15 days
Frequency	2–3 times/week for 8–12 weeks	2–3 times/week for 8–12 weeks	15 days in a row
Amount of irradiated body	Whole body	Whole body	Whole body

PASI (psoriasis area and severity index).
BUVB (broadband ultraviolet radiation B).
NBUVB (narrowband ultraviolet radiation B).

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status in patients with psoriasis, atopic eczema and other skin disorders with low initial levels of 25(OH)D [12].

The aim of the article was to contribute to increase the knowledge regarding vitamin D status in psoriasis patients during treatment with phototherapy. It is not known whether 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 the skin. More studies are needed to develop safe recommendations for sun exposure to obtain appropriate vitamin D levels especially in the Scandinavian population. It is also necessary to establish new recommendations for daily vitamin D supplements in different patient groups.

4. Results

Phototherapy induced vitamin D production in patients with psoriasis. Serum levels of 25(OH)D increased during the treatment with artificial UV (BUVB ($p < 0.00001$), NBUVB ($p < 0.0001$)) and during the heliotherapy ($p < 0.0001$) (Table 2, Figs. 1 and 2).

The increase in 25(OH)D was higher in the BUVB treated patients compared to NBUVB treated group ($p = 0.008$) and compared to patients treated with heliotherapy ($p = 0.017$). The increase in 25(OH)D during 2 weeks of climatotherapy was similar to the increase in 25(OH)D during the treatment with NBUVB.

There was no difference in the percentual increase from baseline of 25(OH)D between older women or younger patients treated with BUVB, NBUVB, or heliotherapy, respectively.

Patients treated with BUVB during winter months increased their serum levels of 25(OH)D from 28.5 ± 8.8 to 64.6 ± 24.1 ng/ml ($p < 0.001$) and patients treated with NBUVB increased their 25(OH)D from 28.3 ± 6.8 to 47.2 ± 15.5 ng/ml ($p < 0.001$); ($p = 0.012$ between lamps). Patients treated with 2 weeks heliotherapy increased 25(OH)D from 22.9 ± 6.0 to 41.8 ± 6.3 ng/ml ($p < 0.001$), respectively, ($p < 0.015$ between BUVB treated patients during winter and patients treated with heliotherapy).

Serum concentration of 25(OH)D at the start in the NBUVB and BUVB studies was however, higher than in patients treated with heliotherapy ($p = 0.0001$). The mean serum concentration of 25(OH)D after UV therapy was also higher in patients treated with artificial lamps ($p < 0.0001$) compared with heliotherapy. The increase in 25(OH)D was enhanced in patients with low baseline levels of vitamin D.

PTH decreased after the treatment with BUVB and after heliotherapy (Table 2). The decrease in PTH was most prominent in the group of post-menopausal women treated with BUVB, study I. The suppression of PTH in post-menopausal women treated with BUVB was higher than in patients treated with NBUVB ($p = 0.005$), and in patients treated with heliotherapy ($p = 0.026$), respectively (Table 2, Figs. 3 and 4).

$1,25(OH)_2D$ increased more during the heliotherapy than with NBUVB ($p = 0.02$) (Table 2).

There was no correlation between the dose of UVB and the increase of 25(OH)D, or $1,25(OH)_2D$ respectively. No correlation was found between serum 25(OH)D and BMI.

Serum concentrations of calcium and creatinine were unaltered after the phototherapy.

Psoriasis improved in all patients, with a reduction in PASI score of about 75% on all regimens. PASI at start was similar in all groups and improved similarly on all regimens.

Improvement in psoriasis correlated positively with the increase in 25(OH)D levels in study II [2] ($p = 0.047$; the group of patients treated with BUVB and NBUVB) but not in the other studies (I [1] and III [3]).

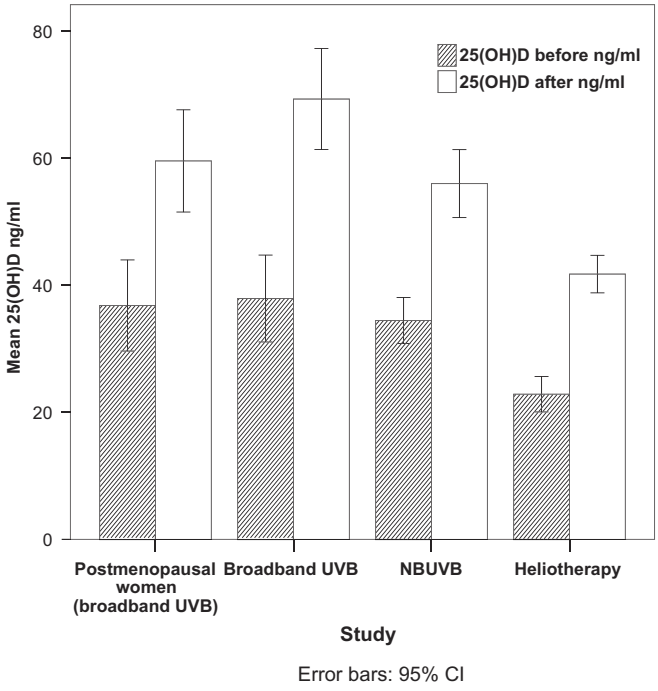

Fig. 1. The mean 25(OH)D serum concentrations before and after the treatment with broadband UVB (BUVB) lamp [1,2], narrowband (NBUVB) lamp [2] and heliotherapy [3], respectively. Error bars: 95% CI.

Table 2
Changes in serum concentrations of 25(OH)D, $1,25(OH)_2D$ and PTH in psoriasis patients treated with BUVB, NBUVB and heliotherapy [1–3] (mean ± SD).

	Post-menopausal women treated with broadband UVB [1]	Broadband [2]	Narrowband [2]	Heliotherapy [3]
$1,25(OH)_2D$ (pg/ml)				
25(OH)D (ng/ml)				
Before	36.8 ± 17.0	37.9 ± 16.9	34.8 ± 11.9	22.9 ± 6.0
After	59.6 ± 18.7	69.4 ± 19.7	55.3 ± 17.6	41.8 ± 6.3
Before	53.2 ± 17.0	59.4 ± 16.8	62.1 ± 25.6	58.6 ± 16.8
After	61.7 ± 11.0	66.5 ± 19.3	62.0 ± 19.1	73.1 ± 23.7
PTH (ng/l)				
Before	63.3 ± 26.2	31.6 ± 17.2	33.7 ± 17.7	41.8 ± 17.3
After	48.4 ± 17.3	23.3 ± 12.8	29.2 ± 14.1	38.6 ± 12.9

BUVB (broadband ultraviolet radiation B).
NBUVB (narrowband ultraviolet radiation B).
PTH (parathyroid hormone).

5. Discussion

Serum 25(OH)D levels increased in psoriasis patients following treatment with BUVB, NBUVB phototherapy and heliotherapy. Psoriasis improved in all patients, with a reduction in PASI score of about 75% on all regimens. UVB and sun exposure are the strongest factors influencing 25(OH)D [7,8,13–15]. The same wavelength of the UVB spectrum (280–315 nm) that is responsible for D vitamin synthesis in the skin also improves psoriasis lesions, and has therefore been used in psoriasis therapy.

Vitamin D production in patients with psoriasis increased less with NBUVB than with BUVB phototherapy. One explanation might be that the optimal wavelength for initiation of the vitamin D pathway was 300 ± 5 nm in vitro and in vivo [16,17], which is in the BUVB range (280–315 nm). The synthesis of vitamin D was stimulated by wavelengths between 290 and 315 nm, but not longer than 315 nm. The present results from the second study [2] showed that a wavelength of 311 nm was effective for inducing

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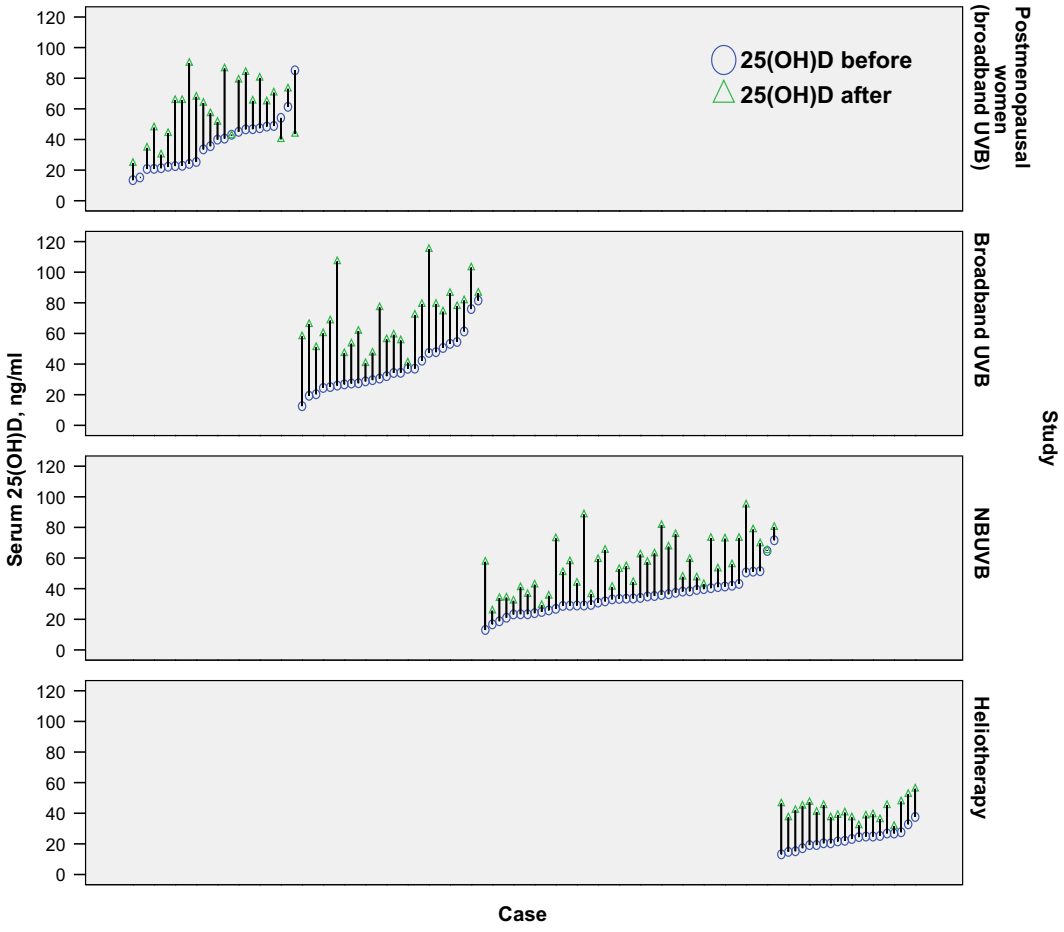

Fig. 2. Changes in serum concentrations of 25(OH)D induced by broadband (BUVB), narrowband (NBUVB) and heliotherapy in each psoriatic patient.

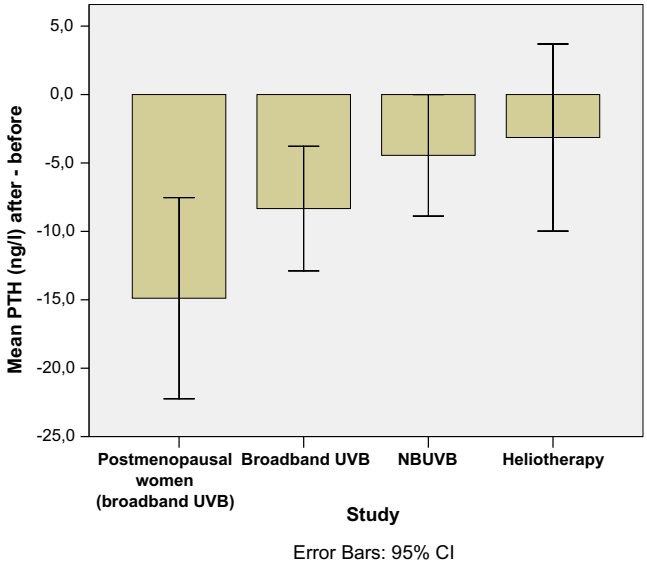

Fig. 3. Changes in serum parathyroid hormone (PTH) after different phototherapies in psoriatic patients.

vitamin D synthesis, but not to the same extent as wavelengths in the BUVB range. UVB treatment of psoriasis was a sufficiently time-consuming procedure to increase vitamin D also with NBUVB. The time required for NBUVB to have an effect can reduce the difference in the potential for vitamin D production between the two lamps. The treatment time correlated strongly with the type of lamp (patients treated with NBUVB required four times longer exposure times than patients treated with BUVB). 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 [18]. The dose of UVB also correlated with the type of lamp, but we could not find any correlation between the dose of UVB and the increase of 25(OH)D levels. This might be explained by autoregulation of the skin synthesis, storage, and slow, steady release of vitamin D from the skin into the circulation [7]. 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. [19].

The vitamin D production is a unique, autoregulated mechanism which occurs at two levels. Excessive sun exposure does not lead to overdosing of vitamin D due to conversion of previtamin D to inactive photoproducts (lumisterol 3 and tachisterol 3) as well as conversion of vitamin D to its isomers in the skin (5,6-trans vitamin D, suprasterol I, suprasterol II) which are thought to have a low calcemic effect at physiological concentrations. The synthesis of previtamin D reached a plateau at about 10–15% of the original 7-dehydrocholesterol content [19]. Vitamin D is synthesized in the skin and released steadily and slowly from the skin into the circulation [7].

The serum concentrations of 25(OH)D almost doubled during 15 days of climate therapy [3]. Patients with lower 25(OH)D levels at baseline responded better to sunlight and phototherapy which is consistent with other studies [1,4,7]. All patients reached serum

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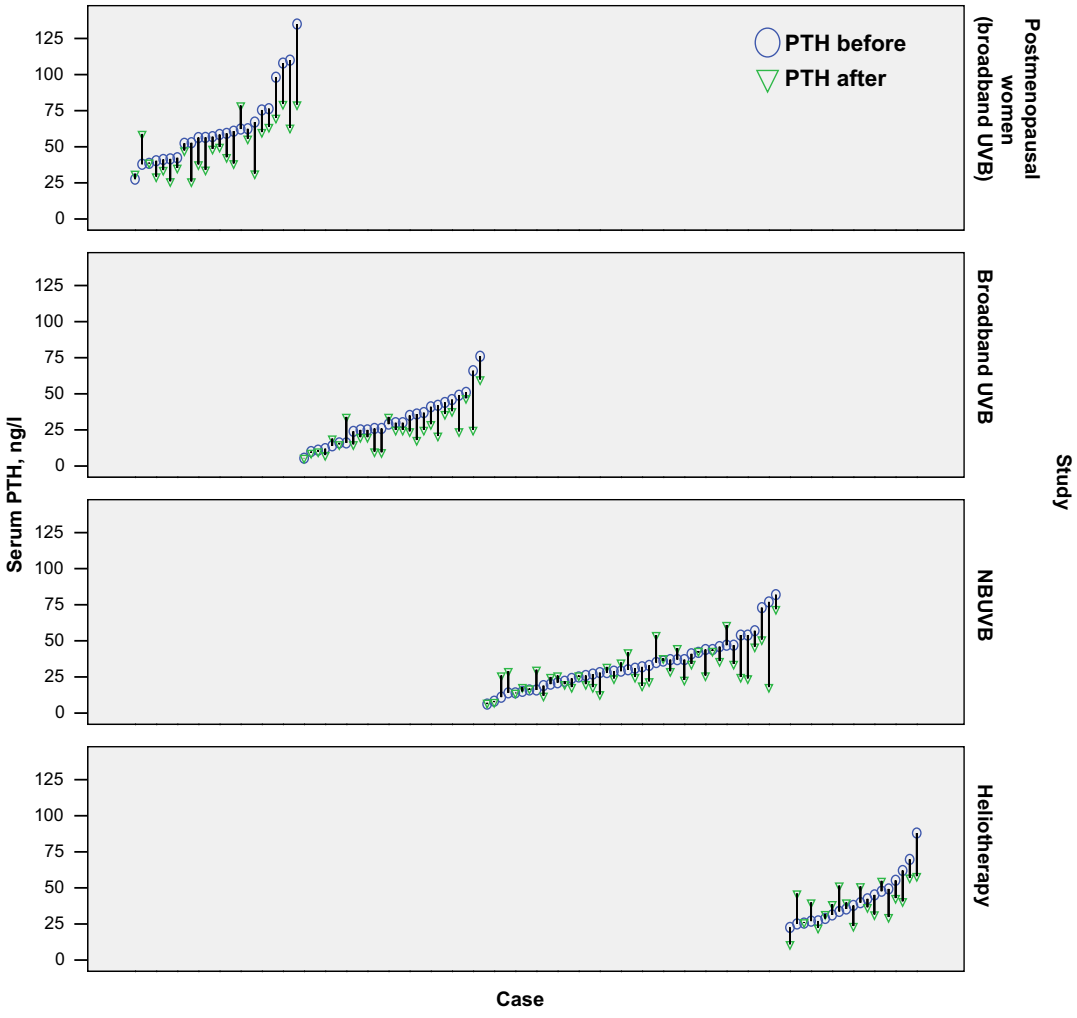

Fig. 4. Changes in serum concentrations of parathyroid hormone (PTH) induced by broadband (BUVB), narrowband (NBUVB) and heliotherapy in each psoriatic patient.

levels of 30 ng/ml (75 nmol/l) after 2 weeks of sun exposure. 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 [4].

The ability of the skin to produce vitamin D declines with age [20] due to insufficient sunlight exposure [21,22] and a reduction in the functional production capacity of the skin [20,23,24]. All women in the first study [1] were post-menopausal and we were unable to see any negative correlation between age and vitamin D synthesis in line with a previous population study carried out at the same location [8]. Age did not correlate with the increase in 25(OH)D in our intervention studies [1–3].

The increase in 25(OH)D during 2 weeks of heliotherapy was very similar to the increase in 25(OH)D during treatment with BUVB and NBUVB for 2–3 months.

There was no difference in the increase of 25(OH)D between the different skin types in the present studies. The reason could be that the subjects were 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 types III and IV. This finding is consistent with other studies examining the effect of skin pigmentation on vitamin D synthesis [25]. Melanin pigment in human skin competes with, and absorbs the UVB photons responsible for the vitamin D synthesis [25].

We found no correlation between the increase of the dose of UVB and the increase of serum 25(OH)D levels within the groups. This might be due to the fact that serum concentrations of 25(OH)D were measured at different time points and a plateau level was reached after 3 weeks, which was also seen in a previous study [26]. A recent in vitro study demonstrated that the dose–response relationship of UV exposure and cholecalciferol synthesis was non-linear. It was hypothesized that exposure to additional UV did not result in a proportional increase in vitamin D levels [27].

The correlation between sunlight measures and serum 25(OH)D has been shown to be weak [28]. Patients reached their plateau of daily sun exposure after the 1 week. It might be that the vitamin D production was most prominent during the 1 week, when the patients had experienced redness and some of them even got sunburned.

The increase of 25(OH)D during 15 days of climate therapy was significant even though the patients used sunscreens on body sites susceptible to sunburn, and even though the skin was affected by psoriasis lesions [3]. SPF-8 sunscreen seemed to reduce the skin's production of vitamin D3 by 95% [29]. Clothing completely blocked all solar UVB radiation and thereby prevented vitamin D production [29].

Serum concentration of 25(OH)D at baseline was lower in patients treated with heliotherapy ($p = 0.0001$) than in patients

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treated with BUVB and NBUVB, and in post-menopausal women with psoriasis treated with BUVB. This might be explained by that the group of psoriasis patients started their heliotherapy in the end of the winter just when serum levels of vitamin D were lowest in the northern countries [3]. Serum 25(OH)D levels in the post-menopausal psoriatic women before UVB therapy [1] were similar to those in age- and location-matched control women [8].

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 [15,30,31]. 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 [31]. This level of 25(OH)D has become the suggested cut-off point for vitamin D deficiency or inadequacy [22,31–33].

The skin is the only tissue yet known in which the complete UVB-induced pathway from 7-DHC via intermediates (previtamin D, vitamin D, 25(OH)D) to the final product $1,25(OH)_2D$, takes place under physiological conditions [34]. 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)D below 30 ng/ml, and in ages $\geqslant$70 years. One explanation might be that these patients had lower serum concentrations of 25(OH)D at the start of the treatment.

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 [4,35]. The observation that both 25(OH)D and $1,25(OH)_2D$ increased in vitamin D deficient subjects following UVB exposure [36] or after vitamin D supplementation [37] 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.

Keratinocytes are capable of producing a variety of vitamin D metabolites, including $1,25(OH)_2D$, $24,25(OH)_2D$, $1,24,25(OH)_3D$ [38] from exogenous and endogenous sorces 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 [39] and systemic vitamin D deficiency does not stimulate epidermal synthesis of $1,25(OH)_2D$ [40].

Cutaneous production of $1,25(OH)_2D$ may regulate growth, differentiation, apoptosis and other biological processes in the skin [41,42]. Topical vitamin D analogs have been also used as a safe and effective treatment for psoriasis vulgaris [43,44]. The NBUVB has been shown to have less capacity to induce a local skin production of $1,25(OH)_2D$ at 44% of the monochromatic irradiation at 300 ± 2.5 nm [17].

PASI score correlated positively to the increase in 25(OH)D after BUVB and NBUVB but not after heliotherapy. We do not have a good explanation for this. It might be that a larger population of psoriasis patients is needed to clarify this finding.

We found no correlation between reduction in PASI score and serum concentrations $1,25(OH)_2D$. Nevertheless, the known therapeutic effect of UVB light therapy for the treatment of psoriasis may be mediated via UVB-induced production of $1,25(OH)_2D$ [34]. 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 [45]. 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 [46].

From the three respective studies [1–3], it is not possible to draw conclusions about the ability of psoriasis skin to produce vitamin D. A larger study is needed to examine the correlation between PASI and the capacity of psoriasis skin to produce vitamin D during UVB exposure. The beneficial role of vitamin D for psoriasis might be due to both a surface and a 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 topical applicated calcitriol [47].

In conclusion, UVB and heliotherapy improved the PASI score, increased the serum 25(OH)D levels and reduced the serum PTH concentrations. Vitamin D production in psoriasis patients increased less with NBUVB than with BUVB phototherapy. The increase in 25(OH)D after 15 days of heliotherapy corresponded to the increase in 25(OH)D after treatment of psoriasis with UVB lamps for 2–3 months.

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