Acta Derm Venereol 2014; 94: 146–151

INVESTIGATIVE REPORT

Narrow-band Ultraviolet B Treatment Boosts Serum 25-hydroxyvitamin D in Patients with Psoriasis on Oral Vitamin D Supplementation

Meri J. ALA-HOUHALA[1,2], Toni T. KARPPINEN[3], Katja VÄHÄVIHU[4], Hannu KAUTIAINEN[5], Yvonne DOMBROWSKI[6], Erna SNELLMAN[3], Jürgen SCHAUBER[6] and Timo REUNALA[1,2]

[1]Department of Dermatology, Tampere University Hospital, [2]Medical School, University of Tampere, Tampere, Departments of Dermatology, [3]Päijät-Häme Central Hospital, Lahti,[4]Kanta-Häme Central Hospital, Hämeenlinna, [5]Units of Primary Health Care, Helsinki and Turku University Hospitals, and Department of General Practice, University of Helsinki, Finland, and [6]Department of Dermatology and Allergy, Ludwig-Maximilian-University, Munich, Germany

A course of treatment with narrow-band ultraviolet B (NB-UVB) improves psoriasis and increases serum 25-hydroxyvitamin D (25(OH)D). In this study 12 patients with psoriasis who were supplemented with oral cholecalciferol, 20 µg daily, were given a course of NB-UVB and their response measured. At baseline, serum 25(OH)D was 74.14 ± 22.9 nmol/l. At the 9th exposure to NB-UVB 25(OH)D had increased by 13.2 nmol/l (95% confidence interval (95% CI) 7.2–18.4) and at the 18th exposure by 49.4 nmol/l (95% CI 35.9–64.6) above baseline. Psoriasis Area Severity Index score improved from 8.7 ± 3.5 to 4.5 ± 2.0 ($p < 0.001$). At baseline, psoriasis lesions showed low vitamin D metabolizing enzyme (CYP27A1, CYP27B1) and high human β-defensin-2 mRNA expression levels compared with those of the healthy subjects. In conclusion, NB-UVB treatment significantly increases serum 25(OH)D in patients with psoriasis who are taking oral vitamin D supplementation, and the concentrations remain far from the toxicity level. Healing psoriasis lesions show similar mRNA expression of vitamin D metabolizing enzymes, but higher antimicrobial peptide levels than NB-UVB-treated skin in healthy subjects. ***Key words: psoriasis; ultraviolet B radiation; vitamin D; CYP27A1; CYP27B1; cathelicidin; human β-defensin.***

Accepted Apr 29, 2013; Epub ahead of print Aug 27, 2013

Acta Derm Venereol 2014; 94: 146–151.

Timo Reunala, Department of Dermatology, Tampere University Hospital, PO Box 2000, FIN-33521, Tampere, Finland. E-mail: timo.reunala@uta.fi

Vitamin D insufficiency is common in Europe and North America, especially during the winter when vitamin D synthesis induced by sunlight is zero (1, 2). The desirable concentration of serum 25-hydroxyvitamin D (25(OH)D), which is the best indicator of vitamin D status, is still under debate. A concentration below 75 nmol/l (30 ng/ml) is considered to be insufficient for bone fracture prevention (3). In addition to osteoporosis, low serum 25(OH)D concentration has recently been associated with risk of colorectal cancer and cardiovascular disease (4, 5). Vitamin D is also known to affect skin inflammation and innate or adaptive immune responses (6, 7).

Recent studies suggest that vitamin D insufficiency is also common in patients with psoriasis (8–10). Gisondi et al. (8) found that, in Italy in winter, serum 25(OH)D was below 50 nmol/l in 81% of patients with psoriasis compared with 30% of healthy controls. They also showed that vitamin D insufficiency was associated with psoriasis independently of age, sex and body mass index (BMI). Romaní et al. (10) concluded that the insufficiency was also common in patients with psoriasis and controls in Spain, but in their study carefully matched controls had a higher insufficiency rate than patients with psoriasis.

Narrow-band UVB (NB-UVB) phototherapy, a widely used effective treatment for psoriasis (11), suppresses interferon-gamma (IFN-γ) and interleukin (IL)-17 signalling pathways to resolve psoriatic inflammation (12). NB-UVB light emitting at 311–313 nm is also capable of activating vitamin D synthesis in cultured keratinocytes (13). Moreover, several studies have shown that, in addition to healing of psoriasis, NB-UVB treatment significantly increases serum 25(OH)D (14–17), and this increase correlates with the activation of circulating regulatory T cells (18).

Interestingly, the expression of cathelicidin, which is one of the most important antimicrobial peptides in human skin, is dependent on 1,25-dihydroxyvitamin D (1,25$(OH)_2$D) and is triggered by UVB-induced vitamin D metabolism (6, 19). Cathelidicin and another inducible cutaneous antimicrobial peptide, human β-defensin-2 (HBD2), can act as immune-regulating effectors or "alarmins" and link adaptive and innate immune responses (20). In addition, these antimicrobial peptides seem to have a role in the control of skin inflammation in psoriasis (21, 22).

The present study examined whether NB-UVB treatment can increase serum 25(OH)D in patients with psoriasis who are already supplemented with oral vitamin D. In addition, we investigated the effects of NB-UVB exposure on cutaneous mRNA expression of vitamin D-metabolizing enzymes and antimicrobial peptides.

 doi: 10.2340/00015555-1685
 ISSN 0001-5555

METHODS

Patients with psoriasis and healthy subjects

A total of 12 patients with psoriasis (mean age 42.8 years; Table I) participated in the study. Four patients had also psoriatic arthritis, but none of them received any systemic drug treatment because their arthritis was not active during the study. Inclusion criteria were no phototherapy, solarium or sunny holidays during the 2 preceding months. Before the NB-UVB course the patients had used cholecalciferol 20 μg (800 IU) daily for a mean of 3.3 months (Table I). Fifteen nurses and other hospital employees (mean age 46.1 years; Table I) volunteered as controls in the study. These subjects had used oral cholecalciferol for a mean of 3.4 months (Table I). The patients with psoriasis and the healthy subjects continued to use oral cholecalciferol during the NB-UVB course and subsequent to it.

The study protocol was approved by the ethics committee of Tampere University Hospital and all subjects gave their informed consent to participate. The study protocol followed the principles of the Declaration of Helsinki.

Narrow-band UVB exposure

The study was performed in winter from December 2011 to April 2012 in order to exclude the effect of the sun. The study subjects received NB-UVB exposure 3 times a week on the whole body area with a Waldmann UV 7001 cabin equipped with 40 TL01 tubes (Schulze & Böhm, Brühl, Germany). The first NB-UVB dose was 0.19 J/cm^2 (1.11 standard erythema dose (SED)) and it was gradually increased each time, according to a fixed protocol, up to 9 exposures, i.e. to 0.97 J/cm^2 (5.70 SED). If the subjects experienced mild itching or erythema, the next NB-UVB dose was either not increased or was reduced. This was the case in 6 patients with psoriasis and 8 healthy subjects. Thereafter, the NB-UVB treatment was given only to patients with psoriasis until the rash was almost or totally cleared. This took a mean of 20.5 (range 11–31) NB-UVB exposures. Clinical improvement was measured with the Psoriasis Area Severity Index (PASI) score.

The mean cumulative dose of NB-UVB given to the 12 patients with psoriasis during 9 exposures was 4.49 ± 0.44 J/cm^2 and to the 9 patients during 18 exposures 15.63 ± 1.67 J/cm^2. These doses are equivalent to 26.4 ± 2.6 SED and to 91.9 ± 9.8 SED, respectively. One SED is equivalent to 10 mJ/cm^2 Commission Internationale de l'Eclairage (CIE) erythema-weighted irradiance. In the 15 healthy subjects the mean cumulative dose of 9 NB-UVB exposures was 4.37 ± 0.55 J/cm^2, which is equivalent to 25.7 ± 3.2 SED. The cumulative NB-UVB doses given up to 9 exposures to the patients with psoriasis and healthy subjects did not differ ($p = 0.57$).

Measurement of serum 25-hydroxyvitamin D concentrations

Blood samples for serum 25(OH)D measurements were taken at baseline, and at 9th and 18th NB-UVB exposures. Follow-up samples were taken one month after the NB-UVB course. The samples were protected from light, centrifuged and then stored at –70ºC. Serum 25(OH)D concentration was analysed in duplicates using radioimmunoassay (Immunodiagnostic Systems, Boldon, UK), as described previously (23).

Table I. *Demography and use of oral cholecalciferol before narrow-band ultraviolet B (NB-UVB) course in 12 patients with psoriasis and 15 healthy subjects*

	Psoriasis patients	Healthy subjects	*p*-value
Male/female, *n*	7/5	1/14	0.008
Age, years, mean ± SD	42.8 ± 14	46.1 ± 11	0.47
Body mass index, kg/m^2, mean ± SD	29.6 ± 5.4	23.4 ± 3.8	0.002
Fitzpatrick skin type II/III/IV, *n*	3/6/3	3/10/2	0.66
Oral cholecalciferol, 20 μg daily before NB-UVB course, months, mean (range)	3.3 (1–24)	3.4 (1–24)	0.75

SD: standard deviation.

Skin biopsies and quantitative real-time PCR

Punch biopsies were taken from skin lesions of 12 patients with psoriasis (8 from the buttocks, 2 from elbows, and 2 from lower back) and from the buttocks of 13 healthy subjects at baseline and at the 9th NB-UVB exposure. The biopsies were immediately frozen and stored at –70ºC. Total RNA from biopsies was isolated using TRIsure Reagent (Bioline, Luckenwalde, Germany) and 1 μg of RNA was reverse-transcribed with High Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Foster City, CA, USA) to cDNA. The mRNA expression levels of CYP27A1 and CYP27B1 enzymes, and antimicrobial peptides cathelicidin and HBD2 were evaluated using a LightCycler® 2.0 system and the corresponding human Universal Probe Library Set (Roche), as described previously (15).

Statistical analysis

Statistical comparison between the groups was performed by Student's *t*-test, permutation test or χ^2 test, when appropriate. The changes within patients with psoriasis and healthy subjects were analysed by applying a permutation test to related samples. Repeated measures were analysed using generalizing estimating equation models with the unstructured correlation structure using bootstrap-type standard error.

RESULTS

Serum 25(OH)D concentrations at baseline, during and after NB-UVB course

At baseline, serum 25(OH)D concentration was 74.14 ± 22.9 nmol/l (mean ± SD) in the 12 patients with psoriasis and 74.30 ± 14.8 nmol/ in the 15 healthy subjects. At 9th NB-UVB exposure serum 25(OH)D had increased by 13.2 nmol/l (95% CI 7.2–24.9, $p = 0.0029$) in the patients with psoriasis and by 17.0 nmol/l (95% CI 6.7–21.0, $p < 0.001$) in the healthy subjects (Fig. 1, Table II).

At 18th NB-UVB exposure 25(OH)D had increased by 49.4 nmol/l (95% CI 35.9–64.6, $p = 0.0039$) in the 9 patients with psoriasis (Table II). PASI score improved in the patients with psoriasis from 8.7 (range 4.0–16.2) at baseline to 6.4 (range 2.1–12.8) at 9th and to 4.5 (range 1.1–8.2) at 18th exposure ($p < 0.001$; Table II).

One month after NB-UVB exposure, serum 25(OH)D was still increased from baseline by 29.9 nmol/l (95% CI 13.6–49.0; $p = 0.0078$) in the 8 patients with psoriasis and by 17.5 nmol/l (95% CI 10.1–24.9; $p < 0.001$) in the 15 healthy subjects (Table II).

Antimicrobial peptide and enzyme mRNA expression in skin biopsy specimens

At baseline, the mRNA expression levels of CYP27A1 and CYP27B1 were significantly lower ($p < 0.001$) in

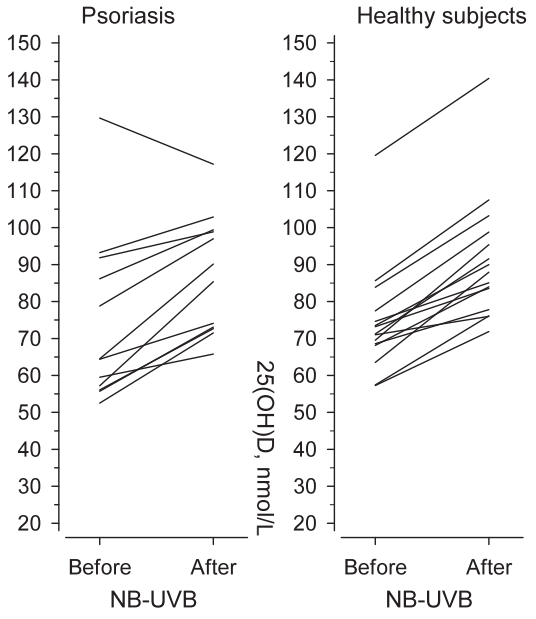

Fig. 1. Serum 25-hydroxyvitamin D (25(OH)D) concentrations before and at 9th (after) narrow-band ultraviolet B (NB-UVB) exposure in 12 patients with psoriasis and 15 healthy subjects. The patients with psoriasis and healthy subjects received oral cholecalciferol, 20 μg daily. The increase is significant in the patients with psoriasis ($p = 0.003$) and healthy subjects ($p < 0.001$).

the patients with psoriasis than in healthy subjects (Fig. 2A and B, Table III). At baseline cathelicidin mRNA expression levels were similar in the psoriasis lesions and in the normal skin of healthy subjects, whereas HBD2 mRNA levels were significantly ($p < 0.001$) higher in the psoriasis lesions (Fig. 2C, Table III).

NB-UVB exposure did not change CYP27A1, CYP27B1 and cathelidicin mRNA expression levels in the patients with psoriasis, but a significant ($p = 0.002$) decrease was seen in the HBD2 mRNA expression level (Fig. 2 and Table III). In the healthy subjects NB-UVB exposure significantly decreased CYP27A1, CYP27B1 and cathelidicin mRNA expression levels, while HBD2 increased slightly (Fig. 2, Table III).

DISCUSSION

Several recent studies have demonstrated that NB-UVB, a widely used treatment for psoriasis (11), significantly improves serum 25(OH)D concentrations, especially during the winter (10, 14–17). The number of NB-UVB exposures given in these psoriasis studies varied from 15 to 27 and the increase in serum 25(OH)D ranged from 66% to 163% (Table IV). In contrast to these previous studies, the present patients with psoriasis were additionally supplemented with oral 20 μg of cholecalciferol daily for a mean of 3.3 months before entry into the trial. Due to this pre-treatment their mean serum 25(OH)D was 74 nmol/l at baseline, which is twice as high as in our previous study (14). Nevertheless, UVB treatment further increased serum 25(OH)D, by 17% at the 9th and by 58% at the 18th NB-UVB exposure. Although the BMI was significantly lower in the healthy subjects than in the patients with psoriasis, the baseline 25(OH)D concentration and the increase at 9th NB-UVB exposure was of approximately the same magnitude. This finding is somewhat unexpected because obese subjects are more prone to vitamin D insufficiency due to the deposition of vitamin D precursors in fat tissue (2, 24). In a recent study (25) in which subjects were supplemented with 15 μg oral cholecalciferol daily, BMI in older, but not in younger, adults was shown to be negatively associated with the change in serum 25(OH)D. These results indicate that BMI is important when performing vitamin D studies, and vitamin D insufficiency reported in some psoriasis studies could be attributed to obesity and comorbidities associated with severe psoriasis. The limitation of the present study is that the patients with psoriasis and the healthy subjects were not matched for BMI. However, the similar and significant increases in serum 25(OH) D levels in both groups who were continuously supplemented with a rather high dose of oral vitamin D indicate that NB-UVB exposure is an efficient way to improve vitamin D balance. In agreement with this, 2 recent studies in healthy subjects have documented the superiority of NB-UVB exposure over oral supplementation of cholecalciferol, 20 μg and 40 μg daily, to improve serum 25(OH)D concentration (23, 26).

In the present study the mean increase in serum 25(OH)D at the 18th NB-UVB exposure was 58% and the highest individual concentration measured 155 nmol/l. Overall, the increase observed was not as marked as in previous psoriasis studies (Table IV). This is not unexpected, because it appears to be evident that the lower the starting 25(OH)D concentration the higher

Table II. *Narrow-band UVB (NB-UVB) doses, serum 25-hydroxyvitamin D (25(OH)D) concentrations and Psoriasis Area Severity Index (PASI) scores in 12 patients with psoriasis and 15 healthy subjects*

	At baseline	At 9th NB-UVB exposure	At 18th NB-UVB exposure	1 month after NB-UVB course
Patients with psoriasis, *n*	12	12	9	8
Total NB-UVB dose, J/cm^2, mean ± SD	–	4.5 ± 0.4	15.6 ± 1.7	–
25(OH)D; nmol/l, mean ± SD	74.1 ± 22.9	87.3 ± ± 16.0	117.3 ± 28.9	115.0 ± 26.5
PASI score, mean ± SD	8.7 ± ±3.5	6.4 ± 3.1	4.5 ± 2.0	–
Healthy subjects, *n*	15	15	–	15
Total NB-UVB dose, J/cm^2	–	4.37 ± 0.6		–
25(OH)D, nmol/l, mean ± SD	74.3 ± 14.8	91.3 ± 17.1		88.3 ± 19.9

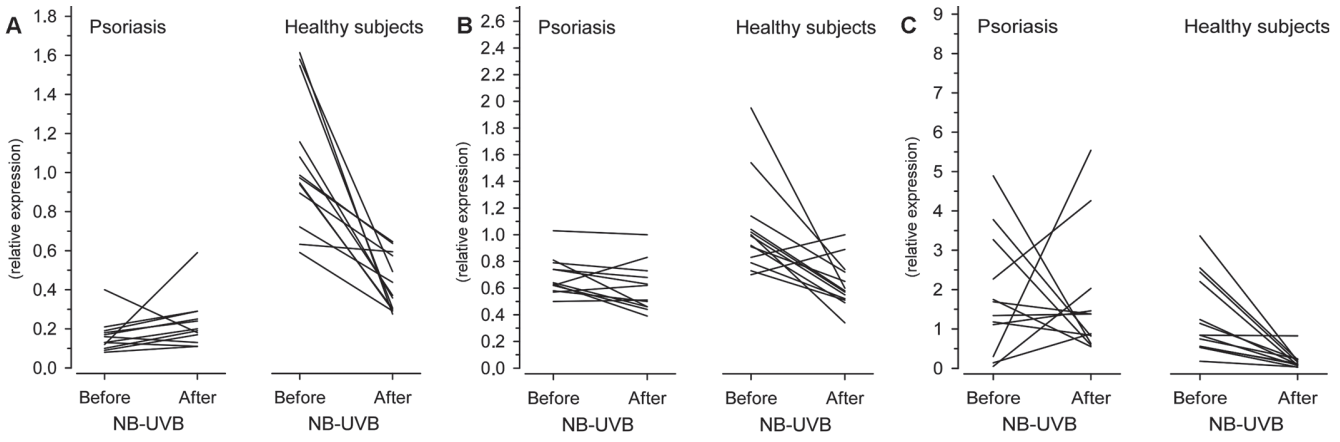

Fig. 2. (A) CYP27A1 mRNA, (B) CYP27B1 mRNA and (C) cathelicidin mRNA expression levels in skin lesions of patients with psoriasis ($n=12$) and normal skin of healthy subjects ($n=13$) before and at 9th (after) narrow-band ultraviolet B (NB-UVB) exposure. Before NB-UVB course the CYP27A1 and CYP27B1 levels are significantly lower ($p<0.001$), but the cathelidicin levels do not differ ($p=0.34$) in the patients with psoriasis compared with the healthy subjects. NB-UVB exposure did not change CYP27A1 mRNA, CYP27B1 mRNA or cathelidicin mRNA levels in the patients with psoriasis (A: $p=0.17$; B: $p=0.070$; C: $p=0.88$) but the decrease is significant (A: $p<0.001$; B: $p=0.002$; C: $p<0.001$) in the healthy subjects.

the response to UVB treatment (27). Moreover, there is evidence that during UVB exposure to the skin, but not during oral supplementation, a negative feedback mechanism controls vitamin D synthesis to prevent overdosing and vitamin D toxicity (28). It is noteworthy in this context, that 1 of the present patients had an exceptionally high level of serum 25(OH)D, i.e.130 nmol/l at baseline and she was the only one to respond to NB-UVB exposure with decreased serum 25(OH)D.

In addition, although the patients and healthy subjects continued with oral cholecalciferol supplementation, serum 25(OH)D concentrations started to decrease one month after NB-UVB exposure. This is in agreement with our previous NB-UVB studies (15, 23) and demonstrates that even rather high continuous oral vitamin D supplementation is not sufficient to maintain serum 25(OH)D levels achieved by a short course of NB-UVB exposure. It has been reported that NB-UVB exposure given twice a month maintains the levels of 25(OH) D achieved in the summer (29). Therefore, a similar schedule could be applicable to the NB-UVB-treated patients with psoriasis during the winter in order to maintain sufficient vitamin D.

A previous study in UVB-treated organ cultures showed that CYP27A1 and CYP27B1 in the keratinocytes are capable of hydroxylating precursors into the active form of vitamin D, i.e. $1,25(OH)_2D$ (13). Thus, both enzymes could be regarded as surrogate markers for vitamin D metabolism. In the present study the expression levels of CYP27A1 and CYP27B1 at baseline were low in the psoriatic lesions compared with healthy skin and did not change during NB-UVB treatment. At first, the low baseline level of CYP27B1 in psoriasis lesions seems difficult to explain. However, the patients with psoriasis were supplemented with oral cholecalciferol, and it could be that the metabolism of vitamin D in the psoriasis lesions is far more active than in the normal skin of healthy subjects. Due to this, the low CYP27A1 and CYP27B1 activities in the psoriasis lesions at baseline and after NB-UVB exposure, and also in the normal skin after NB-UVB exposure, could be due to a very sensitive natural feedback controlling mechanism in cutaneous vitamin D synthesis (6, 7).

Antimicrobial peptides seem to have a role in the pathogenesis of skin inflammation in psoriasis (21, 30). In agreement with our previous study (15), we found in psoriasis lesions at baseline significantly increased mRNA expression of HBD2. We could also show that repeated NB-UVB exposure reduced HBD2 expression in healing psoriasis lesions. In contrast to HBD2, we found no increased mRNA expression of cathelicidin in the psoriasis lesions, either at baseline or after NB-UVB exposure. This is surprising with regard to the findings of our previous study (15). The continuous

Table III. *Vitamin D metabolizing enzyme and antimicrobial peptide mRNA expression levels in the psoriasis lesions of 12 patients and normal skin of 13 healthy subjects at baseline and at 9th narrow-band UVB (NB-UVB) exposure*

	Psoriasis			Healthy subjects		
	Baseline Mean ± SD	At 9th NB-UVB Mean ± SD	*p*-value	Baseline Mean ± SD	At 9th NB-UVB Mean ± SD	*p*-value
CYP27A1	0.16 ± 0.85	0.23 ± 0.13	0.17	1.05 ± 0.34	0.43 ± 0.14	<0.001
CYP27B1	0.69 ± 0.14	0.60 ± 0.18	0.070	1.04 ± 0.35	0.63 ± 0.18	0.0017
Cathelicidin	1.81 ± 1.51	1.70 ± 1.58	0.88	1.32 ± 0.99	0.12 ± 0.08	<0.001
Human β-defensin-2	41,739 ± 65,700	1,497 ± 1,037	0.002	159.65 ± 302.49	471.84 ± 328.71	0.041

Table IV. *Narrow-band UVB (NB-UVB) treatments given in different studies to patients with psoriasis in winter significantly increase serum 25-hydroxyvitamin D (25(OH)D) concentration*

	Patients *n*	NB-UVB treatments *n*	25(OH)D at baseline nmol/l Mean ± SD	25(OH)D at the end nmol/l Mean ± SD	Increase %
Present study, Finland[a]	12	9	74.1 ± 22.9	87.3 ± 16.0	17
	9	18		117.3 ± 28.9	58
Romani et al., 2012 (10), Spain	50	27[b]	36.0 ± 26.3	77.0 ± 33.5	113
Lesiak et al., 2011 (17), Poland	17	10	60.5	101.8	68
	17	20		106.8	73
Ryan et al., 2010 (16), Ireland	29	18[b]	57.5	147.5	155
Vähävihu et al., 2010 (15), Finland	18	15	36.8 ± 12.5	96.7 ± 13.4	163
Osmancevic et al., 2009 (14), Sweden	18	26[b]	71 ± 17	118 ± 39	66

[a]Patients supplemented with oral cholecalciferol, 20 μg daily.
[b]Mean.

oral supplementation with vitamin D before the study, with possible accumulation of vitamin D precursors and $1,25(OH)_2D$ in the psoriasis lesions and activation of negative feedback mechanisms, could again be a reason for this finding. Overall, the present cathelidicin and vitamin D-metabolizing enzyme gene expression results suggest that the normal skin of healthy subjects reacts more actively to NB-UVB exposure than the inflamed skin of psoriasis lesions. It is, however, noteworthy that in spite of these gene expression differences the patients with psoriasis and healthy subjects showed similar NB-UVB responses in the serum 25(OH)D concentration.

Knowledge of the risk of vitamin D insufficiency is well-accepted. In Finland, for example, there are recommendations for children and pregnant women to use up to 10 μg and for elderly people up to 20 μg daily of oral vitamin D supplementation (31). Moreover, vitamin D products are actively marketed and voluntary supplementation especially during winter months is now also common among dermatological patients. Many patients with psoriasis will receive NB-UVB treatment, which is effective and, in the short-term, is considered safe with regard to risk of skin malignancy (32, 33). The present NB-UVB study documented that even though the patients with psoriasis received oral cholecalciferol 20 μg daily their serum 25(OH)D concentrations remained far from 250 nmol/l. Levels below this are considered safe with regard to toxicity (34) and, therefore, we conclude that there is no need to stop voluntary oral vitamin D supplementation whenever patients with psoriasis need to start NB-UVB treatment. In addition, in the present study patients with psoriasis supplemented with oral cholecalciferol showed a similar significant decrease in PASI score, as did the patients with no oral vitamin D supplementation in our previous study (15). This suggests that the response to NB-UVB treatment in psoriasis is not dependent on whether the patient is supplemented with oral vitamin D.

In conclusion, this study showed that, although the patients with psoriasis received continuous oral cholecalciferol supplementation, NB-UVB exposure increased serum 25(OH)D concentration by 58%. In healing psoriasis lesions NB-UVB treatment did not alter the expression of vitamin D-metabolizing enzyme and cathelidicin mRNA, but decreased the expression of HBD2 mRNA.

ACKNOWLEDGEMENTS

This study was supported by National Graduate School of Clinical Investigation (M.A-H), and by Competitive Research Funding of the Tampere University Hospital (Grants 9K104 and 9M089). The authors would like to thank nurses Pirjo Honko and Tuija Valjakka for providing the NB-UVB exposure in the study.

The authors declare no conflicts of interest.

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