

ORIGINAL RESEARCH

Serum 25-hydroxyvitamin D increases with NB-UVB and UVA/UVB phototherapy in patients with psoriasis and atopic dermatitis in Western Australia

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ABSTRACT

Background/Objective: The benefit of NB-UVB phototherapy on serum 25-hydroxyvitamin D [25(OH)D] levels in patients with inflammatory skin conditions has been reported in the northern hemisphere. Vitamin D status is known to differ between geographical latitudes. The objective of this study was to investigate the influence of NB-UVB and UVA/UVB phototherapy on the 25(OH)D serum levels in patients with psoriasis and atopic dermatitis in Western Australia.

Methods: A total of 35 patients with psoriasis or atopic dermatitis requiring phototherapy thrice weekly for a minimum of 4 weeks were enrolled. Of these, 20 patients completed the study. Serum vitamin D levels were measured at baseline and at approximately 6 weeks into phototherapy. Data were adjusted for season, patients' age, sex, skin condition and Fitzpatrick skin phototype.

Results: There was a statistically significant increase in serum 25(OH)D from pre- to post-NB-UVB and UVA/UVB phototherapy ($P < 0.0001$), with a mean raw increase of 34.6 (25) nmol/L; or 45.1 (7.5) nmol/L when adjusted for covariates. This was also true for patients receiving NB-UVB phototherapy with a baseline vitamin D of <80 nmol/L ($P < 0.05$) and >80 nmol/L ($P < 0.004$).

Conclusions: NB-UVB and UVA/UVB phototherapy significantly increased 25(OH)D serum level in patients with psoriasis and atopic dermatitis in Western Australia. Our study cohort had a higher baseline vitamin D level and a lower percentage increase of serum 25(OH)D post-phototherapy than the increases reported in the literature from cohorts in the northern hemisphere.

Key words: 25-hydroxyvitamin D, broadband, Fitzpatrick skin phototype, narrowband, NB-UVB, phototherapy, UVA/UVB, vitamin D, western Australia.

INTRODUCTION

Adequate vitamin D levels are important in maintaining overall calcium homeostasis and the importance of the role played by vitamin D in the immune system is becoming clear.¹ Vitamin D insufficiency has been reported to be common in patients with psoriasis.^{2–4} Ultraviolet phototherapy has been a long-term, safe and effective treatment for a number of inflammatory skin diseases, including atopic dermatitis and psoriasis. NB-UVB 311 nm has become the mainstay of phototherapy treatment, replacing the previously widely used broadband UVB (280–315 nm).

Several studies have demonstrated the effectiveness of NB-UVB in clearing psoriasis, while also significantly increasing serum 25-hydroxyvitamin D (25[OH]D).^{4–12} Feldmeyer and colleagues reported an increase in serum 25(OH)D concentration as a result of phototherapy with NB-UVB and UVA/NB-UVB, while UVA1 alone resulted in a lower serum 25(OH)D concentration post-phototherapy.⁵

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Conflict of interest: none

Abbreviations:

25(OH)D	25-hydroxyvitamin D
FSP	Fitzpatrick skin phototype

Vitamin D photosynthesis can vary depending on geographical latitude, as well as the season, the level of air pollution, cloud cover, skin pigmentation, aging and general health conditions.^{13,14}

We investigated the serum levels of 25(OH)D before and after a course of phototherapy in a Western Australian cohort, and compared these results with current data from northern latitudes.

METHODS

The study included 35 patients with psoriasis or atopic dermatitis who had received phototherapy for treatment of their presenting dermatoses. The patients attended two private dermatology clinics in Fremantle, Western Australia, between August 2012 and November 2013.

Design

A prospective observational study was conducted, with the aim of measuring 25(OH)D levels in patients with psoriasis or atopic dermatitis pre- and post-phototherapy with NB-UVB (311 nm) or UVA/UVB (370 nm/290–320 nm). The study was approved by the Human Research Ethics Committee and was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR.org.au identifier: ACTRN12611001150954). All participants signed a written consent form to be included in the study.

Phototherapy

All patients received either NB-UVB or UVA/UVB therapy thrice weekly for a minimum of 4 weeks. This correlated with the minimum requirement for a patient to achieve some therapeutic response from phototherapy for their atopic dermatitis or psoriasis. The aim was to measure the initial serum 25(OH)D level prior to the commencement of phototherapy, and at approximately 6 weeks after its commencement.

Phototherapy was performed with Ultra-Violet Cabinets (Australian Ultra Violet Services, Victoria, Australia) equipped with NB-UVB (311 nm) TL-01 tubes; or UVA (370 nm) TL-10 tubes and broadband UVB (290–320 nm) TL-12 tubes. The initial dose was dependent on the patient's skin phototype. The phototherapy treatment course was titrated to the response to treatment.

Depending on its tolerability to the patient, and provided there were no side-effects the NB-UVB dosage was increased by 0.05 J/cm² each session to reach a maximum dose of 1.20 J/cm².

The UVA/UVB treatment protocol consisted of parallel therapy with UVA and broadband UVB. UVA was given at a starting dose of 0.5 J/cm² and broadband UVB at a starting time of 30 s. Depending on patient tolerance, UVA and UVB were increased by 0.5 J/cm² to a maximum dose of 6 J/cm²; and by 30 s at subsequent visits to a maximum time of 5 min, respectively.

Primary outcome

The measurement of vitamin D levels in patients pre- and post- NB-UVB or UVA/UVB phototherapy through a blood test measuring 25(OH)D serum levels.

Patients

In total, 35 patients were eligible for the study, meeting the inclusion criteria of being male and female patients aged over 18 years with a dermatological skin condition (psoriasis or atopic dermatitis) for which NB-UVB or UVA/UVB phototherapy was indicated. The choice of phototherapy type was determined by the severity of the skin disease.

Patients on vitamin D or vitamin D and calcium supplements were excluded from the study.

Statistical methods

Summary statistics are presented as means (SD). A Student's paired *t*-test was used to compare mean serum 25(OH)D levels pre- and post-phototherapy. The effect of therapy on Vitamin D levels was further explored via regression modelling. As successive measures on the same patient were expected to be correlated, generalised estimating equations¹⁵ were applied using an autoregressive correlation structure to account for the intra-individual dependence of measurements. Adjustments for age, sex, diagnosis and season were made in the model. All tests were two-sided and statistical significance was set at 5%. The statistical analysis was performed in the R statistical computing environment.¹⁶

RESULTS

Of the 35 patients surveyed in the study, 14 dropped out as a result of not following through with the measurement of their second serum 25(OH)D level post-phototherapy and one patient was removed from the study due to the commencement of systemic therapy.

Of the remaining 20 patients, three were treated with UVA/UVB and 17 with NB-UVB. Among the latter, one had hand and foot phototherapy for the entire course of treatment, while one other had 15 of 24 NB-UVB treatments as hand and foot phototherapy. These two patients were excluded, leaving a group of 18 whole-body phototherapy patients for analysis. Figure 1 summarises the patient cohort according to the inclusion and phototherapy modality.

Among the 18 patients analysed, 15 had psoriasis (14 treated with NB-UVB) and three had atopic dermatitis (one treated with NB-UVB). There were 12 female patients, and six male patients. The patients' mean (SD) age was 48 (SD 14), with a range of 28–81 years. Patients had a mean of 19 (4.4) phototherapy treatments each, with an average of 53 (18) days between beginning and end of treatment. There were three patients with Fitzpatrick skin phototype (FSP) I, 15 with FSP II, and two with FSP III. No patients had FSP IV–VI.

Figure 1 Flowchart of patients' participation in current study. AD, atopic dermatitis; H&F, hand and foot; Pso, psoriasis.

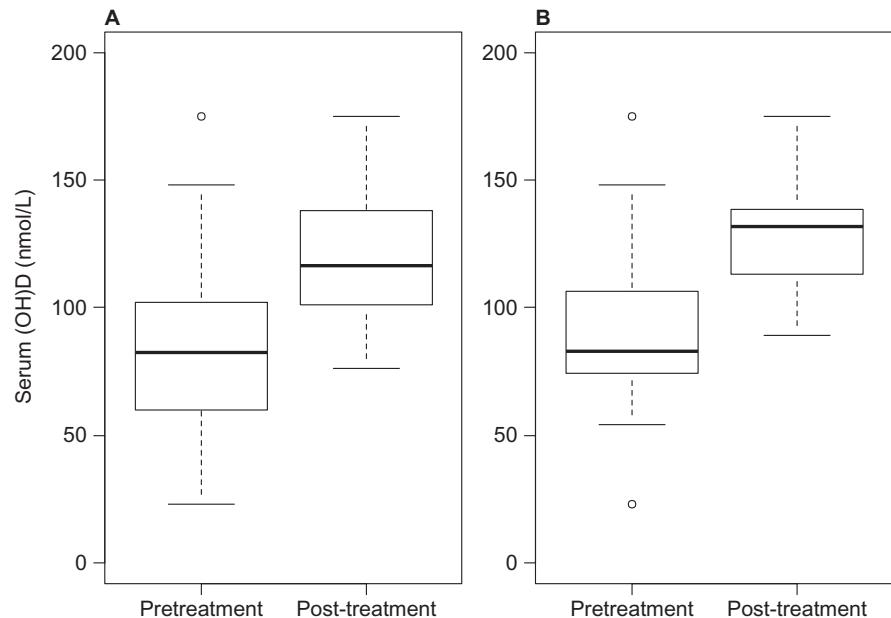
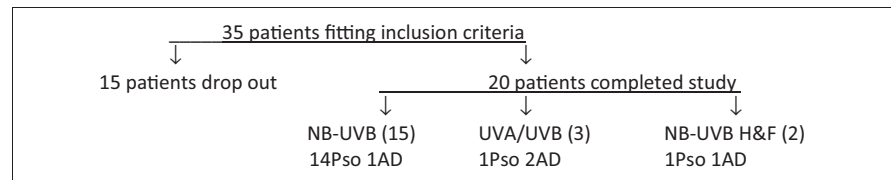


Figure 2 Boxplots of serum 25-hydroxyvitamin D (5[OH]D) pre- and post-phototherapy. A, NB-UVB; UVA/UVB ($n = 18$); B, NB-UVB only ($n = 15$).

Vitamin D level at commencement of study

Among the 18 patients who received whole-body phototherapy, 12 had sufficient vitamin D levels at the commencement of the study, four patients had vitamin D levels in the range of 50–74 nmol/L, one patient had an insufficient vitamin D level (26–49 nmol/L) and one patient was deficient in vitamin D (<25 nmol/L).

Effect of treatment on vitamin D

The distributions of vitamin D pre- and post-treatment in all participants ($n = 18$) and in the NB-UVB only subset ($n = 15$) are illustrated in Figure 2. In all participants the range of measured serum 25(OH)D concentration pre-phototherapy was 23–175 nmol/L. The difference in serum vitamin D between the beginning and end of the treatment varied from –9 to 92 nmol/L. The pattern of individual changes in serum vitamin D is illustrated in Figure 3.

With respect to the 18 patients treated with either NB-UVB or UVA/UVB therapy, there was strong statistical evidence of an increase in vitamin D between beginning and end of treatment ($P < 0.001$). The mean raw increase was 34.6 (25) nmol/L. In the 15 patients treated with NB-UVB alone, the treatment effect remained significant, with a 35.5 (27.2) nmol/L increase in serum vitamin D level post-phototherapy ($P < 0.001$). This effect was slightly larger (though not significantly so) in patients with a baseline

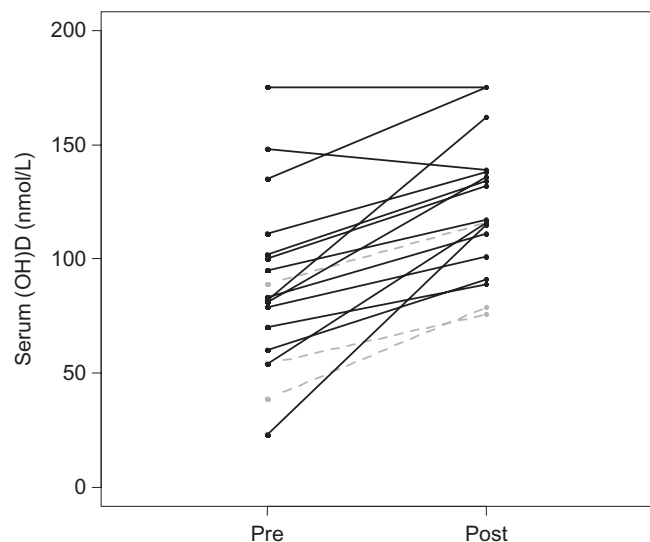


Figure 3 Vitamin D level pre- and post-phototherapy (not adjusted for season). — NB-UVB patients. --- UVA/UVB patients.

vitamin D level below 80 nmol/L than those with a baseline level of 80 nmol/L or more (mean vitamin D increases of 45.2 and 30.7 nmol/L respectively. (Table 1).

The two patients excluded from the above data analysis due to being treated only or in part with hand and foot phototherapy had a small increase in serum vitamin levels

Table 1 Summary statistics for the analysis group; mean (SD) for continuous variables and counts (%) for categorical variables. *P* values are from a Student's paired *t*-test comparing vitamin D pre- (t_1) and post-treatment (t_2)

All participants ($N = 18$)				
Age (years, mean)		48 (14)		
Treatment: NB-UVB only (n , %)		15 (83%)		
Number of treatments		19 (4.4)		
Male (n , %)		6 (33%)		
Diagnosis: psoriasis (n , %)		15 (83%)		
25(OH)D (nmol/L)	n	t_1	t_2	<i>P</i> value
All	18	87.8 (38.0)	122 (29.6)	<0.001
NB-UVB only	15	95.2 (38.5)	129 (27.1)	<0.001
NB-UVB				
Baseline <80	5	57.2 (21.4)	102 (12.8)	0.032
Baseline $\geq$ 80	10	111 (31.7)	142 (22.1)	0.004

25(OH)D, 25-hydroxyvitamin D.

Table 2 Results from multiple regression model of vitamin D level pre- and post-treatment, with adjustment for covariates (18 participants)

Predictor	Estimate	<i>P</i> value
NB-UVB and UVA/UVB phototherapy	45.1	<0.001
Age	-1.8	<0.001
Season	-14.5	0.013
Sex (male)	-15.8	0.062
Diagnosis	-15.8	0.456

from pre- to post-phototherapy of 6 nmol/L and 9 nmol/L. This increase in serum vitamin D level was below the mean raw increase of 34.6 (25) nmol/L seen in the whole-body phototherapy cohort.

Influence of covariates on serum vitamin D level

From the regression analysis, after adjusting for season of sampling, age, sex and diagnosis of participant, there was an estimated 45.1 (7.5) nmol/L increase in vitamin D due to the phototherapy treatment ($P < 0.001$, see Table 2). Age was found to be negatively associated with vitamin D level ($\beta = -1.8$, $P < 0.001$). In this cohort, there was only weak statistical evidence of a lower vitamin D in male participants ($\beta = -15.8$, $P = 0.062$) and no statistical evidence that vitamin D differed by diagnosis ($\beta = -15.8$, $P = 0.456$).

Seasonal adjustment

Having accounted for the effect of phototherapy, there was evidence of an estimated 14.5 nmol/L drop in vitamin D with each change of season (autumn > winter > spring) ($P = 0.013$, Table 2). There was, however, no statistical evidence that the treatment effect differed between seasons ($P = 0.719$, not shown).

Influence of Fitzpatrick skin phototype on serum vitamin D level

Distributions of serum 25(OH)D pre-phototherapy, post-phototherapy, and overall, compared with patients' FSP I–III, are presented in Figure 4. The overall mean serum vitamin D was lower in FSP III patients, with a level of 85.8 (43.7) nmol/L, compared with a 101.3 (47.8) nmol/L for FSP I patients, and 106.9 (34.3) nmol/L for FSP II patients. This difference is most notable pretreatment. As far as post-treatment levels are concerned, the three FSP cohorts have very similar means of serum vitamin D, although the mean for FSP I and FSP III patients are slightly lower than for FSP II patients.

There was no statistical evidence from the ANOVA results that the FSP is by itself a significant predictor of change in vitamin D level, at either pre- or post-phototherapy (both $P > 0.05$).

When we adjust for all covariates there is some statistical evidence that serum vitamin D is significantly different in FSP I and FSP III ($P = 0.085$, $P = 0.013$).

Estimates of treatment effect are similar for analysis including and not including FSP, demonstrating an estimated increase in vitamin D due to phototherapy treatment of 44.7 (7.1) nmol/L ($P < 0.001$), compared with 45.1 (7.5) nmol/L ($P < 0.001$), respectively.

DISCUSSION

There are limited data relating to vitamin D levels pre- and post-phototherapy in psoriasis and atopic dermatitis patients in an Australian cohort. In our present study serum vitamin D was found to be elevated following NB-UVB phototherapy treatment in psoriasis and atopic dermatitis patients residing in Western Australia. Our study confirms the results of previous studies showing that NB-UVB significantly increases serum 25(OH)D in patients with inflammatory skin conditions residing in Switzerland, Kuwait, Finland, Spain, Poland, Ireland, Sweden and Norway. (Table 3)

We were able to compare the percentage increase of serum 25(OH)D at baseline and at the end of NB-UVB phototherapy in our Western Australian cohort with previous data from countries from northern latitudes. An interesting observation in our study was that the baseline or pre-phototherapy serum vitamin D level in our patient cohort was higher than that found in previous data in the literature from the northern latitudes. This could possibly be related to the southern latitude of Western Australia or the sun exposure and clothing habits of our patient cohort, which could not be entirely controlled for.

Furthermore, our overall percentage increase in serum vitamin D level from pre- and post-phototherapy of 38% over 12–27 phototherapy treatments, was relatively lower than in countries in northern latitudes, which demonstrated a mean increase in serum vitamin D of 91% after 9–36 treatments of NB-UVB phototherapy. (Table 3)

Cicarma and colleagues¹² reported that in patients with a baseline serum vitamin D > 80 nmol/L, the increase in serum 25(OH)D post-NB-UVB phototherapy was not

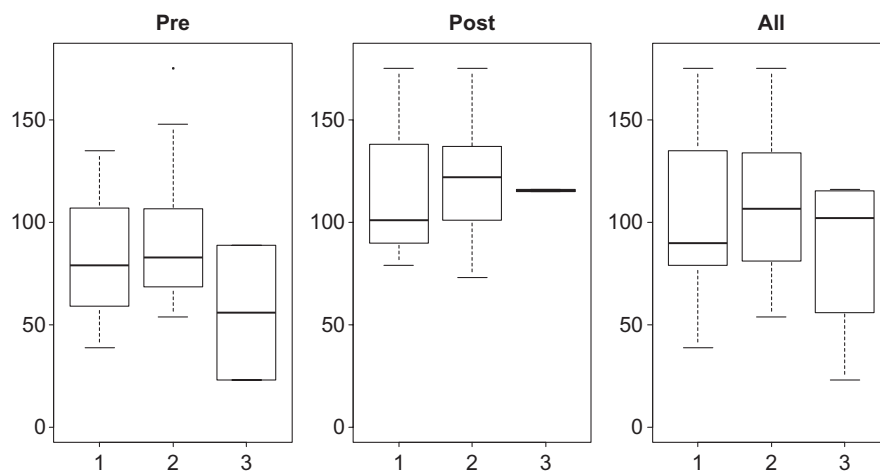


Figure 4 Box plots of serum 25-hydroxyvitamin pre-phototherapy, post-phototherapy and overall. Fitzpatrick skin phototype 1–3 (horizontal axis).

significant. Our study presents data that show otherwise. For patients with a baseline serum vitamin D level of >80 nmol/L, our study demonstrated that NB-UVB phototherapy resulted in a significant increase in serum vitamin D level ($P < 0.01$).

Our data also support previous observations in the literature that the lower the starting serum 25(OH)D concentration, the higher the response in vitamin D level is to NB-UVB treatment.^{12,17} It has been suggested in the literature that during ultraviolet-B exposure to the skin, but not during oral vitamin D supplementation, a negative feedback mechanism controls vitamin D synthesis to prevent overdosing and vitamin D toxicity.¹⁸ In the current study, one patient had a high pre-phototherapy serum vitamin D level of 148 nmol/L and then had a lower serum vitamin D level of 139 nmol/L post-NB-UVB phototherapy. In a contrasting observation of our collated data, another patient had a relatively high pre-phototherapy serum vitamin D level of 135 nmol/L and with phototherapy their serum vitamin D level continued to increase to >175 nmol/L. This trend was also noted in a second patient whose pre-phototherapy serum vitamin D level was >175 nmol/L and remained at this elevated level post-phototherapy. Environmental factors may explain these trends, relating to outdoor activities, sunscreen use or clothing habits.

Of the 12 patients with sufficient vitamin D levels (>75 nmol/L) at the commencement of the study, 11 patients had an increase in serum vitamin D level post-treatment, despite having had adequate levels at baseline. As mentioned above, one patient showed a reduction in serum vitamin D level post-treatment from 148 nmol/L to 139 nmol/L. This patient had a history of phototherapy in the months prior to our treatment, but not in the preceding 6 weeks. All patients with vitamin D levels below the sufficient range showed an increase in their serum vitamin D with phototherapy.

In two recent studies, NB-UVB phototherapy has been found to be superior to an oral supplementation of cholecalciferol 20 ug and 40 ug daily in increasing serum 25(OH)D concentration.^{19,20} Our study excluded patients who were on vitamin D or calcium supplementation to

exclude confounding results and the risk of toxicity. A recent study demonstrated that in patients given 20 ug daily oral cholecalciferol supplementation their serum vitamin D concentrations remained far below 250 nmol/L, which is considered safe with regard to toxicity.²¹ Though further studies are required this suggests that it may not be necessary to advise against the voluntary intake of oral vitamin D supplementation in patients with psoriasis who require NB-UVB phototherapy for treatment.⁷

A limitation of the study was the small sample size of patients in both the NB-UVB phototherapy group and the UVA/UVB phototherapy group. This prevented comparison with and commentary on previous studies such as that by Osmancevic and colleagues, who found serum vitamin D in psoriasis patient increased less with NB-UVB than with broadband UVB phototherapy.¹¹ Furthermore, our observations of the effect of FSP on the serum vitamin D level with phototherapy is limited by the small sample size with no patients fitting FSP IV–VI.

Other limitations of this current study include the wide age range of the study participants and the choice of phototherapy being determined by the skin disease severity, hence not allowing for randomisation. It was also not possible to control for sun exposure and the clothing habits of the studied group, which may have had some influence on the results.

Conclusion

NB-UVB and UVA/UVB phototherapy significantly increased serum vitamin D levels in patients with psoriasis and atopic dermatitis in Western Australia. This was also true for patients treated with NB-UVB phototherapy with a baseline vitamin D of <80 nmol/L and >80 nmol/L. Our study cohort had a higher baseline vitamin D level and a lower percentage increase of serum 25(OH)D post-phototherapy than the increases reported in the literature from cohorts in the northern hemisphere. Our study supports the benefit of phototherapy on serum vitamin D levels and may be an additional education point when counselling patients on

Table 3 NB-UVB given in different studies to patients with inflammatory skin conditions requiring phototherapy and its effect on serum 25-hydroxyvitamin D (25[OH]D) concentration

Study	Country of Study	Latitude	Inflammatory skin condition	Patients <i>N</i>	NB-UVB treatments <i>n</i>	Pre-phototherapy 25(OH)D nmol/L		Post-phototherapy 25(OH)D nmol/L		<i>P</i> value	Increase %
						Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD		
Present study, 2014	Australia	52.06° S	Psoriasis (14) AD (1)	15	19 ^s	93.2 ± 38.3	128.7 ± 27.1	<0.001	38		
Feldmeyer <i>et al.</i> , 2014 ⁵	Switzerland	46.83° N	Psoriasis (25) Vitiligo (5)	38	36 [†]	55.2 ± 25.7	98.5 ± 30.5	<0.001	79		
Al-Mutairi and Shaaban, 2014 ⁶	Kuwait	29.37° N	Mycosis fungoides (2) Mallorca acne (1) Psoriasis	93	24	51.5 ± 14.4	56.8 ± 5.2	<0.001	80		
Ala-Houhala <i>et al.</i> , 2014 ¹⁷	Finland	64.00° N	Psoriasis	9	18	74.1 ± 22.9	117 ± 28.9	0.0039	58		
Romani <i>et al.</i> 2012 ⁴	Spain	40.43° N	Psoriasis	50	27 ^s	56.0 ± 25.5	77 ± 33.5	<0.001	113		
Lesiak <i>et al.</i> 2011 ⁸	Poland	52.22° N	Psoriasis	17 Winter 13 Summer	20 20	60.5 ± 21.2 92.9 ± 23.2	106.6 ± 37.2 115.8 ± 25.7	<0.001 <0.001	76 25		
Ryan <i>et al.</i> , 2010 ⁹	Ireland	53.00° N	Psoriasis	29	18 ^s	57.5	147.5	<0.001	157		
Vähävihu K <i>et al.</i> , 2010 ¹⁰	Finland	64.00° N	Psoriasis AD	18 18	15 15	56.8 ± 12.5 52.2 ± 12.2	96.7 ± 13.4 100.4 ± 24.7	<0.001 <0.001	163 212		
Osmanovic <i>et al.</i> , 2009 ¹¹	Sweden	59.35° N	Psoriasis	42	26 ^s	87 ± 29.7	138 ± 43.9	<0.001	59		
Cicarma <i>et al.</i> , 2009 ¹²	Norway	61.00° N	Psoriasis (12) AD (5)	11 (baseline 25(OH)D < 80 nmol/L)	9–15	66 ± 9	108.7 ± 27.7 [‡]	<0.001	62		
			Vitiligo (1) Itch (1) ^{††}	7 (baseline 25(OH)D > 80 nmol/L)	9–15	111.5 ± 22.4	120.6 ± 20.7	0.36	8		

[†]Patients supplemented with oral cholecalciferol, 20 ug daily. [‡]7 of 12 psoriasis patients received topical calcipotriol. [§]mean. [¶]max. ^{††}1 patient excluded from study, skin condition not specified. AD, atopic dermatitis.

phototherapy. Future studies with a larger sample size would allow further analysis of the effects of phototherapy on vitamin D levels.

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