

ORIGINAL ARTICLE

Serum 25-hydroxyvitamin D levels in patients with atopic eczema and the influence of narrowband ultraviolet B phototherapy

Rebecca F. Rose, Christina Williams, Thomas Oliphant, Fiona Browne, David Turner & Victoria Goulden

Dermatology Department,
Chapel Allerton Hospital, Leeds,
UK.

Key words:

atopic eczema; narrowband
ultraviolet B phototherapy;
vitamin D

Correspondence:

Dr Rebecca F. Rose, BM, BCh,
Dermatology Department, Chapel
Allerton Hospital, Harrogate
Road, Leeds LS7 4SA, UK.
Tel: +44 113 3924354
Fax: +44 113 3923565
e-mail:
rebecca.rose@leedsth.nhs.uk

Accepted for publication:

31 January 2014

Conflicts of interest:

None declared.

SUMMARY

Background

Narrowband ultraviolet B phototherapy (nbUVB) is an established treatment modality for patients with severe atopic dermatitis (AD) and is known to increase serum vitamin D levels (SVD). The relationship between SVD and AD remains unclear.

Objectives

To assess SVD and disease severity in patients with AD before and after nbUVB and establish whether a change in SVD correlates to response to nbUVB.

Methods

A single-centre, open observational study recruited 21 male and 17 female patients with AD between November and April. Eczema severity was measured using the SCORAD tool, and serum 25-hydroxyvitamin D3 levels were determined before and after nbUVB, which was administered thrice weekly.

Results

Nine patients had severe AD, 23 moderate and six mild, as indicated by SCORAD measurements. Seventeen patients completed the study. Median SVD increased from 45 nmol/l pre-treatment to 169 nmol/l post-treatment (95% CI 2.9–5.0 times baseline) ($P < 0.0001$). Mean SCORAD reduction following nbUVB was significant at 21.9 units (95% CI, 14.9–28.9) ($P < 0.0001$). No evidence of a relationship between change in SCORAD and change in SVD was found.

Limitations

A significant number of patients failed to complete the study.

Conclusions

Patients with AD are at risk of vitamin D deficiency. Correlation between this and disease severity has been postulated, but this study does not provide confirmatory evidence.

Photodermatol Photoimmunol Photomed 2014; 30: 287–293

It has long been recognized that Vitamin D is essential in maintaining normal calcium metabolism and bone density and that it is involved in the control of cell growth. A growing body of literature also suggests that vitamin D affects both innate and adaptive immune mechanisms through the stimulation of Toll-like receptors (TLRs), particularly TLR2 and TLR4, increasing the production of pro-inflammatory cytokines and potentially influencing T helper type 2 responses (1–3). These findings may help to explain the role of vitamin D in allergic diseases, including skin disease. However, the role of vitamin D in the pathogenesis and management of atopic dermatitis (AD) remains controversial, with studies linking both high and low vitamin D levels to an increased risk of developing the disease (4, 5). Peroni *et al.* (6) report an inverse association between vitamin D levels and severity of AD in children, and Javanbakht *et al.* (7) show a significant improvement in eczema severity scores with oral vitamin D in combination with vitamin E, though not in vitamin D alone. In contrast, Sidbury *et al.* (8) found no statistically significant change in the severity of AD in a study evaluating the effect of vitamin D supplementation in children.

Narrowband ultraviolet B phototherapy (nbUVB) is an effective treatment modality for AD and has been shown to increase serum vitamin D levels (9), but it is unclear if this is a relevant factor in treatment response. The aim of this study was to assess serum vitamin D levels (SVD) and disease severity in patients with AD before and after treatment with nbUVB and establish whether change in SVD corresponded to response to nbUVB.

METHODS

Study design and ethics

This was a single-centre, open observational study conducted in the Department of Dermatology, Leeds Teaching Hospitals NHS Trust. Ethical approval was given by Leeds (West) Research Ethics Committee, and all subjects gave informed consent to participate. All aspects of the study were conducted according to the principles of the Declaration of Helsinki.

Participants

Thirty-eight adults with a clinical diagnosis of AD requiring treatment with nbUVB were consecutively enrolled in the study. Twenty-one males and 17 females participated, mean age 40 years (range 19–77). The patients were recruited over a 2-year period, but only between the months of November and April to limit seasonal influence

on SVD. Exclusion criteria included diseases known to alter serum vitamin D metabolism, such as chronic renal failure (estimated glomerular filtration rate < 30 ml/min/1.73 m²), primary biliary cirrhosis and malabsorption syndromes, as well as porphyria and photosensitive disorders. Other exclusion criteria included vitamin D supplementation, phototherapy or having gone on a holiday to a sunny place in the 2 months prior to the study; systemic therapy for AD within 4 weeks of recruitment; and planning to have a holiday in a sunny place during treatment with nbUVB.

Baseline assessments for eczema severity

The severity of AD in patients was determined using the validated Scoring Atopic Dermatitis (SCORAD) clinical assessment tool (10) both before and after treatment with nbUVB (see Fig. 1). The SCORAD values were used to define AD as severe (> 50), moderate (25–50) or mild (< 25) (11).

Vitamin D analysis and definitions

Serum 25-hydroxyvitamin D levels were measured both before and on discontinuation of treatment with nbUVB. The method used to measure vitamin D was tandem mass spectrometry. Using this method, levels of 25-hydroxyvitamin D₂ and D₃ were measured, and then results were totalled. At our institute, concentrations below 20.0 nmol/l are interpreted as Vitamin D deficiency; 20.0–60.0 nmol/l suggests Vitamin D depletion and may be inadequate to maintain optimal skeletal health, while greater than 60 nmol/l suggests Vitamin D sufficiency, and greater than 500 nmol/l suggests Vitamin D toxicity (12). The coefficient of variations calculated for quality control specimens to indicate the reliability of vitamin D level measurement in our institute during the study period are listed in Table 1. Our laboratory also participates in the Vitamin D External Quality Assessment Scheme (DEQAS) and obtained certificates of proficiency from 2009 to 2012 by meeting the performance target set by the advisory panel.

Total IgE concentrations were measured for all patients prior to treatment (normal range 0–120 kU/l).

Phototherapy

Narrowband UVB phototherapy was carried out in a Waldmann 7001 cubicle equipped with 40 TLO1 nbUVB fluorescent tubes (311 nm ± 2 nm). The initial irradiation dose was 70% of the minimal erythema dose, which was

SCORAD
EUROPEAN TASK FORCE
ON ATOPIC DERMATITIS

INSTITUTION _____

PHYSICIAN _____

Last Name _____ First Name _____

Date of Birth: ____/____/____ DD/MM/YY

Date of Visit: ____/____/____

Topical Steroid used:
Potency (brand name) _____
Amount / Month _____ (6)
Number of flares / Month _____

Figures in parenthesis for children under two years

A: EXTENT Please indicate the area involved _____

B: INTENSITY _____

CRITERIA	INTENSITY
Erythema	
Edema/Papulation	
Oozing/crust	
Excoriation	
Lichenification	
Dryness *	

MEANS OF CALCULATION
INTENSITY ITEMS (average representative area)
0 = absence
1 = mild
2 = moderate
3 = severe
* Dryness is evaluated on uninvolved areas

C: SUBJECTIVE SYMPTOMS
PRURITUS+SLEEP LOSS _____

SCORAD $A/5 + 7B/2 + C$ _____

Visual analog scale (average for the last 3 days or nights)
PRURITUS (0 to 10) _____ 0 _____ 10
SLEEP LOSS (0 to 10) _____ 0 _____ 10

TREATMENT: _____

REMARKS: _____

European Task Force on Atopic Dermatitis/SCORAD

Fig. 1. Scoring Atopic Dermatitis (SCORAD) clinical assessment tool.

determined by phototesting. Treatment was given three times per week with incremental increases of 20% at each visit, adjusted according to the erythema response. The whole body was exposed during treatment except for male genital protection, and a face shield was provided if the face was uninvolved. If there was facial involvement, then a face shield was used as soon as the eczema responded to treatment.

Statistical analysis

Power calculations indicated that 50 patients were required to power the study. This was based on our target

of 80% power to find a 50% increase in vitamin D levels following nbUVB. It was felt that power would be increased further by the fact that there would be correlation between readings within individuals. Using a database of patients previously referred for nbUVB in this centre, it was predicted that adequate numbers would be recruited over two winters, and hence ethical approval was sought for that time period. Unfortunately, recruitment was less than expected, primarily due to patients not wishing to have blood tests taken. Serum vitamin D levels and SCORAD data pre- and post-treatment with nbUVB were compared. Baseline SVD was compared with baseline severity of eczema. As the serum vitamin D levels were

Table 1. Vitamin D levels measured in quality control specimens in our institute during the study period

	First winter of enrolment	Second winter of enrolment
D2	13.2 (8.3)	16.9 (5.4)
	21.1 (7.5)	27.4 (6.5)
	34.3 (7.7)	44.8 (7.9)
	54.6 (5.6)	68.5 (7.1)
	71.4 (7.6)	87.8 (10.1)
D3	17.9 (6.9)	18.7 (6.1)
	24.2 (8.0)	33.7 (5.8)
	34.3 (7.4)	52.9 (5.6)
	62.4 (5.7)	74.9 (4.6)
	79.0 (6.1)	94.9 (8.4)

Data are given as mean vitamin D levels (nmol/L) followed by coefficient of variation in parentheses (%).

skewed, the vitamin D levels were logged prior to analysis. Analysis of variance was performed on these logged SVD data to determine if the vitamin D levels were lower in patients with moderate and severe eczema. Further analysis was then performed to see if there was a relationship between the change in SCORAD and the change in SVD. Paired *t*-tests and Wilcoxon signed-rank tests were used to analyse the data. All analyses were carried out in Statsdirect Version 2.7.8. For all statistical analyses, $P < 0.05$ was considered significant.

RESULTS

Of the 38 patients recruited to the study, 19 were male and 19 female, with a mean age of 41 years (range 19–78 years). Using the SCORAD index, nine patients were classified as having severe disease, 23 as having moderate disease and six as having mild disease. A total of 17 patients completed the study; the remainder either stopped attending for nbUVB or failed to attend for formal assessment at end of treatment. Mean total IgE level was 803 kU/l (range 9 to > 5000).

Pre- and post-treatment SVD levels were recorded in 15 patients after a mean of 31 exposures (range 11–40) and a mean cumulative dose of 390.07 J/cm² (range 4.23–834.45) (see Table 2). Median SVD was 45 nmol/l pre-treatment and 169 nmol/l post-treatment, with an average increase of 3.8 times the baseline level (95% CI, 2.9–5.0 times baseline), demonstrating a highly statistically significant increase ($P < 0.0001$). Baseline and final SCORAD data were available for 17 patients. Mean SCORAD reduction following nbUVB was significant at 21.9 units (95% CI,

Table 2. Results from the patients completing the study

Patient number	SCORAD before treatment	Serum vitamin D level before treatment (nmol/l)	Serum vitamin D level after treatment (nmol/l)	SCORAD after treatment	Total IgE (kU/l)	Starting nbUVB dose (J/cm ²)	Number of exposures when measurements were repeated	Cumulative nbUVB dose (J/cm ²) when measurements were repeated
1	40.7	21.1	114.8	9.6	758	0.072	38	383.39
2	23.9	64.4	166.3	18.3	355	0.215	26	245.11
3	44.5	40.1	180.4	11.9	13.9	0.179	30	374.06
4	47.5	60	150.1	5.3	281	0.149	28	393.02
5	37.1	22.7	96.8	41.7	4616	0.104	37	503.65
6	39.9	41.1	N/A	12.1	> 5000	0.215	27	270.94
7	26	17.7	241.2	14.4	> 5000	0.149	38	631.20
8	45.6	15.4	67.5	13.2	98.6	0.215	40	834.45
9	51.4	21.1	84.8	20.9	822	0.149	25	152.52
10	24.3	63.6	143.1	14.4	54.1	0.215	11	4.23
11	30	40.1	N/A	11.4	124	0.215	29	352.55
12	31	110.2	169	4.5	9	0.149	35	391.94
13	46.6	47.4	187	44.1	> 5000	0.215	28	308.84
14	72.6	44.7	169	32.1	3806	0.149	30	346.16
15	56.4	32.4	188	30.8	1445	0.215	40	711.50
16	23.1	49.4	189	12.2	11.8	N/A	34	N/A
17	35.3	56.7	177	7.2	844	0.149	25	337.54

N/A, not available.

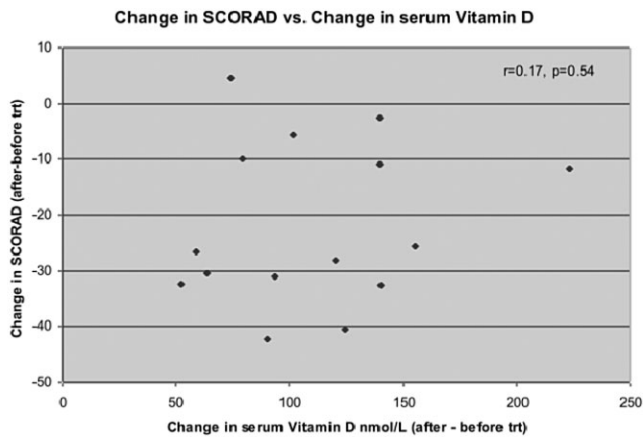


Fig. 2. Plot showing the relationship between the change in SCORAD and change in vitamin D levels; correlation coefficient = 0.17.

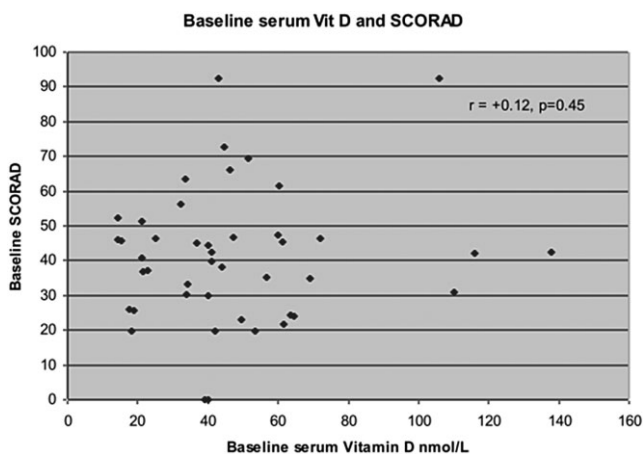


Fig. 3. Plot showing the relationship between baseline SVD and baseline SCORAD.

14.9–28.9) ($P < 0.0001$). However, no evidence of a relationship between change in SCORAD and change in SVD was found (Fig. 2). While the mean SVD was lowest for patients with severe eczema (according to their SCORAD data) and highest for patients with mild eczema, the median values did not follow this pattern. In addition, analysis of variance of SVD showed there was no evidence of a relationship between these values and SCORAD grouping ($P = 0.77$). The coefficient of correlation between baseline SVD and baseline SCORAD values (Fig. 3) lacked significance at 0.12 ($P = 0.45$), suggesting there is no relationship between SVD and severity of AD.

DISCUSSION

AD is the most common inflammatory skin disease in childhood (13) and persists into adulthood in approxi-

mately 30% of patients (14). The disease poses a significant economic burden to the individual (15) and to health services (16). AD may be more common in countries with less natural sunlight (17), and vitamin D deficiency is associated with higher latitude (18); hence, a potential relationship between these parameters is here considered. Only 11 of the 38 patients recruited to this study (29%) had a normal SVD at baseline, which may be a skewed result given that recruitment took place in winter months, when SVD will be lower. Previous studies also confirm that vitamin D deficiency or depletion is common in patients with AD and much higher than in healthy subjects (9, 19). It is, however, unclear whether vitamin D directly contributes to the pathogenesis of AD or occurs as a consequence of the disease and reduced skin exposure. There is an increasing body of literature linking vitamin D levels to a wide range of diseases, including solid organ tumours, autoimmune disease and cardiovascular disease, with significant implications for patients with low SVD (20, 21).

Vitamin D level is challenging to measure, with numerous assays available and a lack of standardization of results. The DEQAS scheme in which our laboratory participates is useful in validating assays and individual laboratory performance. In view of the challenges that measurement and interpretation of vitamin D levels poses, other markers of vitamin D status have been considered. Parathyroid hormone (PTH) is one such marker due to its role in converting the different metabolites of vitamin D and the fact that it is usually inversely proportional to vitamin D levels in many patient groups. However, for a number of reasons, it is not thought to be a reliable substitute for vitamin D measurement, including the fact that levels can vary widely at a given vitamin D concentration; in addition, levels depend on age and renal function. For this reason, PTH was not measured in this study (22).

Vitamin D is synthesized in the skin when keratinocytes are induced by ultraviolet B to convert 7-dehydrocholesterol to vitamin D (23). This study demonstrates evidence of a statistically significant increase in SVD and fall in SCORAD following the treatment with nbUVB. This is in keeping with previous studies showing that nbUVB can increase SVD in AD and psoriasis patients (9) and in healthy people (24) and that nbUVB reduces SCORAD in patients with AD (9). The mechanisms by which nbUVB improves AD include induction of the immunosuppressive cytokine interleukin-10 by keratinocytes and, possibly, lymphocyte apoptosis. Currently there is no evidence that nbUVB improves AD as a direct result of the influence on SVD (25).

Contrary to the findings of a study in children with AD where the authors observed a statistically significant

negative correlation between baseline SVD and baseline SCORAD, suggesting an inverse relationship between SVD and severity of disease (6), our study does not provide evidence of a relationship between baseline SVD and baseline SCORAD values. Although Peroni *et al.* recruited a number of patients similar to the number recruited for this study, there was a more even distribution of patients with mild ($n = 15$), moderate ($n = 13$) and severe ($n = 23$) disease according to SCORAD assessment. In our study, the majority of participants were classified as having moderate or severe atopic eczema, which probably reflects the practice of treating patients with more severe disease with phototherapy. This, together with small patient numbers, may have influenced the lack of relationship between SVD and disease severity in this study. However, a further recent study by Samochocki *et al.* similarly failed to demonstrate an association between SVD in adult patients with AD and disease severity as indicated by SCORAD (26).

Javanbakht *et al.* (7) report a four-arm parallel-group study comparing vitamin D and E individually and in combination against placebo in patients with AD. Results were available for 45 patients, including adults and children. There was no statistical improvement in SCORAD in the vitamin D group compared with placebo, but there was one for vitamin D combined with vitamin E over a 60-day period. The numbers in each of the arms of this study were small. Sidbury *et al.* (8) treated five children with worsening yet predominantly mild AD during winter with vitamin D supplementation for 1 month but did not analyse SVD. Although the results suggested that the treated arm may have benefited from vitamin D, they were not statistically significant. A recent Cochrane review concluded that there is currently no evidence to support the treatment of AD with vitamin D on the basis of these two studies (27). More recently published investigations continue to report conflicting findings. Samochocki *et al.* demonstrated a fall in SCORAD when patients with AD, selected because of frequent skin infection, received vitamin D supplementation (26). In contrast, a study by

Hata *et al.* failed to show an improvement in eczema severity when patients with AD received oral vitamin D for 3 weeks (28).

The main limitation of our study is that a significant number of patients failed to attend for the final assessment visit or had incomplete data. The reasons for this included patients discontinuing phototherapy prior to completion of the full treatment course, patients failing to attend for the repeat vitamin D measurement and, in a small number of cases, blood samples not reaching the laboratory. A further factor is the small number of patients recruited. This was exacerbated by recruiting only during winter months, thus limiting the number of patients eligible considerably, despite running the study over two winters. Future studies may need to be multicentre in order to recruit more patients to ensure larger numbers complete the study and allow regression analysis. Other limitations include the aforementioned selection bias, which resulted in the inclusion of more patients with moderate to severe disease and may potentially have skewed the results. We elected not to include a control group of patients in this study, as the majority of eczema patients requiring phototherapy have significant disease, such that it would not be ethical to randomize them to a non-treatment or topical therapy-only arm. In addition, the other studies published to date on this topic included many variables that could potentially have confounded their results, including Fitzpatrick skin type (28), body mass index (28), season of recruitment and dose of vitamin D administered. It is important that future research in this field attempt to standardize these parameters in order to provide a definitive answer to this question.

ACKNOWLEDGEMENTS

This study was funded by the charitable organization Leeds Foundation for Dermatological Research. We gratefully acknowledge the contribution of Dr Helen Fields for her assistance in the vitamin D analysis.

REFERENCES

1. Benson AA, Toh JA, Jariwala SP. The role of vitamin D in the immunopathogenesis of allergic skin diseases. *Allergy* 2012; **67**: 296–301.
2. Gombart AF, Borregaard N, Koeffler HP. Human cathelicidin antimicrobial peptide (CAMP) gene is a direct target of the vitamin D receptor and is strongly up-regulated in myeloid cells by 1,25-dihydroxyvitamin D₃. *FASEB J* 2005; **19**: 1067–1077.
3. Wintergerst ES, Maggini S, Hornig DH. Contribution of selected vitamins and trace elements to immune function. *Ann Nutr Metab* 2007; **51**: 301–323.
4. Bäck O, Blomquist HK, Hernell O *et al.* Does vitamin D intake during infancy promote the development of atopic allergy? *Acta Derm Venereol* 2009; **89**: 28–32.
5. Oren E, Banerji A, Camargo CA Jr. Vitamin D and atopic disorders in an obese population screened for vitamin D deficiency. *J Allergy Clin Immunol* 2008; **121**: 533–534.
6. Peroni DG, Piacentini GL, Cametti E, Chinellato I, Boner AL. Correlation

- between serum 25-hydroxyvitamin D levels and severity of atopic dermatitis in children. *Br J Dermatol* 2011; **164**: 1078–1082.
7. Javanbakht MH, Keshavarz SA, Djalali M *et al.* Randomized controlled trial using vitamins E and D supplementation in atopic dermatitis. *J Dermatol Treat* 2011; **22**: 144–150.
 8. Sidbury R, Sullivan AF, Thadhani RI, Camargo CA Jr. Randomized controlled trial of vitamin D supplementation for winter-related atopic dermatitis in Boston: a pilot study. *Br J Dermatol* 2008; **159**: 245–247.
 9. Vähävihi K, Ala-Houhala M, Peric M *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* 2010; **163**: 321–328.
 10. European Task Force on Atopic Dermatitis. Severity scoring of atopic dermatitis. *Dermatology* 1993; **186**: 23–31.
 11. Oranje AP, Glazenburg EJ, Wolkerstorfer A, de Waard-van der Spek FB. Practical issues on interpretation of scoring atopic dermatitis: the SCORAD index, objective SCORAD and the Three-Item Severity score. *Br J Dermatol* 2007; **157**: 645–648.
 12. Morris HA. Vitamin D: a hormone for all seasons – how much is enough? Understanding the new pressures. *Clin Biochem Rev* 2004; **25**: 21–32.
 13. Hoare C, Li WPA, Williams H. Systematic review of treatments for atopic eczema. *Health Technol Assess* 2000; **4**: 1–191.
 14. Williams HC. Epidemiology of atopic dermatitis. *Clin Exp Dermatol* 2000; **25**: 522–529.
 15. Kemp AS. Cost of illness of atopic dermatitis in children: a societal perspective. *Pharmacoeconomics* 2003; **21**: 105–113.
 16. Herd RM, Tidman MJ, Prescott RJ, Hunter JA. The cost of atopic eczema. *Br J Dermatol* 1996; **135**: 20–23.
 17. Weiland SK, Hüsing A, Strachan DP, Rzehak P, Pearce N; ISAAC Phase One Study Group. Climate and the prevalence of symptoms of asthma, allergic rhinitis, and atopic eczema in children. *Occup Environ Med* 2004; **61**: 609–615.
 18. Lucas RM, Ponsonby AL, Dear K *et al.* Vitamin D status: multifactorial contribution of environment, genes and other factors in healthy Australian adults across a latitude gradient. *J Steroid Biochem Mol Biol* 2013; **136**: 300–308.
 19. Vähävihi K, Ylianttila L, Salmelin R *et al.* Heliotherapy improves vitamin D balance and atopic dermatitis. *Br J Dermatol* 2008; **158**: 1323–1328.
 20. Holick MF, Chen TC. Vitamin D deficiency: a worldwide health problem with health consequences. *Am J Clin Nutr* 2008; **87**: S1080–S1086.
 21. Tuohimaa P, Pukkala E, Scelo G *et al.* Does solar exposure, as indicated by the non-melanoma skin cancers, protect from solid organ cancers: vitamin D as a possible explanation. *Eur J Cancer* 2007; **43**: 1701–1712.
 22. Prentice A. Vitamin D deficiency: a global perspective. *Nutr Rev* 2008; **66** (10 Suppl. 2): S153–S164.
 23. Holick MF. The cutaneous photosynthesis of previtamin D₃: a unique photoendocrine system. *J Invest Dermatol* 1981; **77**: 51–58.
 24. Vähävihi K, Ylianttila L, Kautiainen H *et al.* Narrowband ultraviolet B course improves vitamin D balance in women in winter. *Br J Dermatol* 2010; **162**: 848–853.
 25. Weichenthal M, Schwarz T. Phototherapy: how does UV work? *Photodermatol Photoimmunol Photomed* 2005; **21**: 260–266.
 26. Samochocki Z, Bogaczewicz J, Jeziorkowska R *et al.* Vitamin D effects in atopic dermatitis. *J Am Acad Dermatol* 2013; **69**: 238–244.
 27. Bath-Hextall FJ, Jenkinson C, Humphreys R, Williams HC. Dietary supplements for established atopic eczema. *Cochrane Database Syst Rev* 2012; (2): CD005205.
 28. Hata TR, Audish D, Kotol P *et al.* A randomized controlled double-blind investigation of the effects of vitamin D dietary supplementation in subjects with atopic dermatitis. *J Eur Acad Dermatol Venereol* 2013 [Epub ahead of print].