

INVESTIGATIVE REPORT

Narrowband Ultraviolet B Exposures Maintain Vitamin D Levels During Winter: A Randomized Controlled TrialToni KARPPINEN^{1,2}, Meri ALA-HOUHALA^{1,2}, Lasse YLIANTTILA³, Hannu KAUTIAINEN⁴, Heli VILJAKAINEN⁵, Timo REUNALA¹ and Erna SNELLMAN^{1,2}¹Medical School, University of Tampere, ²Department of Dermatology, Tampere University Hospital, Tampere, ³Radiation and Nuclear Safety Authority, Helsinki, ⁴Unit of Primary Health Care, Helsinki University Central Hospital and Department of General Practice, University of Helsinki, and Unit of Primary Health Care, Kuopio University Hospital, Helsinki and Kuopio, and ⁵Children's Hospital, Helsinki University Central Hospital and University of Helsinki, Helsinki, Finland

Exposure to solar ultraviolet B radiation during the summer months is the main source of vitamin D (VD) for people living in northern latitudes. The aim of this study was to determine whether artificial narrowband ultraviolet B (NB-UVB) whole-body exposures could maintain VD levels in winter. The intervention group received 2 standard erythema doses (SEDs) of NB-UVB exposures every second week from October 2013 to April 2014. In October 2013 serum 25-hydroxyvitamin D concentrations were 78.3 nmol/l in the intervention group ($n=16$) and 76.8 nmol/l in the control group ($n=18$). By April 2014 the concentrations had increased by 11.7 nmol/l ($p=0.029$) in the intervention group and decreased by 11.1 nmol/l ($p=0.022$) in the control group. The baseline VD concentration showed a negative correlation ($p=0.012$) with body mass index (BMI). In conclusion, a suberythema NB-UVB dose of 2 SED every second week maintains and even increases serum VD concentrations during the winter. A high BMI seems to predispose subjects to low levels of VD. *Key words: 25-hydroxyvitamin D; ultraviolet B; narrow-band ultraviolet B; body mass index.*

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Toni Karppinen, Department of Dermatology, Tampere University Hospital, PO Box 2000, FIN-33521 Tampere, Finland. E-mail: karppinen.toni.t@student.uta.fi

Vitamin D (VD) insufficiency is a worldwide issue (1). VD is synthesized from 7-dehydrocholesterol in response to ultraviolet B (UVB) radiation and its key role is in adjusting the serum calcium level to enable metabolic functions, signal transduction and neuromuscular activity (2). VD insufficiency has been linked to chronic skeletal (3) and extra-skeletal diseases, such as obesity and type 2 diabetes mellitus (4, 5). The best indicator of VD status is its circulating form, 25-hydroxyvitamin D [25(OH)D] (2). Levels above 50 nmol/l are thought to be sufficient for calcium and bone homeostasis, but the optimal level for extra-skeletal effects is unclear (6). The Institute of Medicine (Washington DC, USA) recommends a dietary intake of VD supplements of 15

µg daily for people aged 1–70 years and 20 µg daily for those older than 70 years (7). In addition to VD supplements, artificial ultraviolet B (UVB) light treatments increase VD concentrations (8). Narrowband ultraviolet B (NB-UVB) exposures given 3 times a week increase serum 25(OH)D concentrations even more than does 20 µg or 40 µg oral cholecalciferol daily (9, 10). Bogh et al. (11) showed that 1 standard erythema dose (SED) of broadband ultraviolet B (BB-UVB) every second week can be used to maintain serum 25(OH)D concentrations during the winter (11). On the other hand, as NB-UVB is better tolerated (12), widely used (13), and provides a higher vitamin D action spectrum-weighted irradiance dose (14), we examined its ability to maintain summer levels of vitamin D throughout the winter period.

MATERIALS AND METHODS

Subjects

Thirty-seven healthy volunteers were randomized to an intervention group ($n=18$) or a control group ($n=19$). Inclusion criteria were: age 18 years or older; and avoidance of solarium visits, phototherapy, sunny holidays and vitamin D supplementation during a 1-month washout period prior to the trial and during it. Exclusion criteria were: pregnancy, skin disease, previous skin cancer, intake of photosensitizing drugs; and Fitzpatrick's skin reactive type 1 (15). Recruitment began on 1 September 2013 and the trial was carried out at the Department of Dermatology of Tampere University Hospital from 7 October 2013 to 5 May 2014. The principal investigator assessed the skin types of the volunteers. VD intake at the onset was estimated by means of a 3-day food frequency questionnaire. Altogether 34 subjects completed the trial (Table I). Two intervention subjects were disqualified for failing to follow the irradiation schedule and one control subject was disqualified for taking VD supplements. All 3 were excluded from the analyses. The protocol was approved by the ethics committee of Tampere University Hospital, and all the volunteers gave their informed consent in advance.

Randomization and sample size calculation

Volunteers were randomized to the intervention and control groups in blocks of 2 using a web-based validated program (Research Randomizer (<http://www.randomizer.org>)). The primary investigator randomized and enrolled all the participants. The trial was designed to show an inter-group difference in 25(OH)D of at least 12 nmol/l, with an α -value of 0.05 and a β -value of 0.90. An assumed standard deviation (SD) of 9 nmol/l for the

Table I. Demographics, vitamin D intake and plasma parathyroid hormone concentrations at baseline in the narrow-band ultraviolet B (NB-UVB)-treated and control groups

	NB-UVB n=16	Control n=18	p-value
Males/females, n	3/13	1/17	0.32
Age, years, mean (range)	35 (21–61)	36 (20–61)	0.76
BMI, kg/m ² , mean ± SD	23.0 ± 1.9	25.2 ± 3.4	0.029
Fitzpatrick's skin type II/III/IV, n	8/7/1	8/10/0	0.61
Vitamin D intake, µg/day, mean ± SD	7.0 ± 3.7	6.7 ± 2.2	0.78
Parathyroid hormone, pmol/l, mean ± SD	3.8 ± 1.1	4.2 ± 1.2	0.32

BMI: body mass index; SD: standard deviation.

25(OH)D analyses at 50 nmol/l was used. Thus, it was considered necessary that 12 volunteers per group should complete the trial.

Narrowband ultraviolet B treatment

The intervention group received a total of 13 NB-UVB whole-body exposures, given every other week for 24 weeks with a Waldmann UV 7002 cabin equipped with 42 TL01 tubes (Schulze & Böhm, Brühl, Germany). The first NB-UVB non-weighted total UV dose was 170 mJ/cm² (1 SED), which was subsequently increased to 340 mJ/cm² (2 SED). One SED is equivalent to an erythemal effective radiant exposure of 10 mJ/cm² CIE (16). The cabin was calibrated by the Nuclear Safety Authority of Finland using an Ocean Optics S2000 spectroradiometer. After correction for stray light and other systematic errors, the estimated measurement uncertainty (2σ) of the Ocean Optics S2000 is 14% (17) and the measurements are traceable to the National Institute of Standards and Technology, USA. Previously measured lamp spectra were used for the NB-UVB (TL01) and BB-UVB (Waldmann UV6) dose calculations (18).

Serum 25-hydroxyvitamin D and parathyroid hormone measurements

Blood samples for 25(OH)D analyses were drawn at the onset, and at weeks 6, 14, 20, 26 and 30. During the intervention period the samples of the intervention group were taken just before the scheduled exposure to UVB. The samples were centrifuged and plasma was stored at -20°C and analysed for 25(OH)D by enzyme immunoassay (Roche Diagnostics, Mannheim, Germany). Plasma parathyroid hormone (PTH) samples were taken at the onset of the trial and at 14 weeks. Blood was collected into ethylenediaminetetraacetic acid (EDTA) tubes, centrifuged and analysed by immunochemiluminometric assay.

Statistical analysis

Confidence intervals (95% CI) were obtained by bias-corrected bootstrapping (5,000 replications). Statistical comparisons were made using the analysis of *t*-test co-variance (ANCOVA). In

the case of violation of the assumptions (e.g. non-normality) a bootstrap-type test was used. Longitudinal measures for continuous outcomes were analysed using a bootstrap-type generalized estimating equations (GEE) model, the GEE having been developed as an extension of the general linear model for analysing longitudinal and other correlated data. GEE models take into account the correlation between repeated measurements in the same subject, they do not require complete data, and a fit can be achieved even when observations for some individuals are lacking at certain time-points. No adjustment was made for multiple testing. When comparing the increases in VD concentrations, the model was adjusted for the baseline value, body mass index (BMI) and Fitzpatrick's skin type. Pearson's χ^2 -test was used when comparing nominal data. The STATA 13.1, StataCorp LP (College Station, TX, USA) statistical package was used for the analyses.

RESULTS

Vitamin D intake and NB-UVB exposures

The mean ± SD daily VD intake at onset was 7.0 ± 3.7 µg in the intervention group and 6.7 ± 2.2 µg in the control group (*p* = 0.78) (Table I). The intervention group received 13 NB-UVB exposures over 24 weeks, implying a cumulative NB-UVB dose of 25 SED, which corresponds to a physical dose of 4.25 J/cm². No adverse effects were detected.

Serum 25-hydroxyvitamin D concentrations

The mean baseline serum VD concentration in October was 78.3 nmol/l in the intervention group and 76.8 nmol/l in the control group (Table II, Fig. 1) showing a moderate negative correlation with BMI (*r* = -0.43, *p* = 0.012). The mean ± SD concentrations in the intervention group peaked at 104.5 ± 40.2 nmol/l in February, i.e. in week 20 (Fig. 1), and had a mean increase of 11.7 nmol/l (*p* = 0.029) by the end of the intervention period, in April (week 26), at which point the mean for the control group had decreased by 11.1 nmol/l (*p* = 0.022, Fig. 1, Table II). The difference between the groups was statistically highly significant (*p* < 0.001) when adjusted for the baseline value, BMI and Fitzpatrick's skin type. During the 1-month follow-up period the mean concentration of VD in the intervention group decreased by 10.6 nmol/l (*p* < 0.001) and that in the control group by 2.7 nmol/l (*p* = 0.18; Fig. 1, Table II).

Table II. Serum 25-hydroxyvitamin D concentrations in the narrow-band ultraviolet B (NB-UVB)-treated and control groups at baseline and at the end of the intervention period (week 26)

	Serum 25-hydroxyvitamin D (nmol/l)		
	NB-UVB group n=16	Control group n=18	p-value
Baseline (October 2013), mean ± SD	78.3 ± 36.1	76.8 ± 26.6	0.90 ^a
Week 26 (April 2014), mean ± SD	88.7 ± 29.2	65.8 ± 23.9	0.019 ^a
Change from baseline to week 26, mean (95% CI)	11.7 (1.9–20.0) ^b	-11.1 (-19.4 to -2.7) ^c	0.0017 ^a
Change from week 26 to 30, mean (95% CI)	-10.6 (-15.1 to -5.9) ^d	-2.7 (-6.1–0.8) ^e	0.015 ^a

^aNot adjusted; ^b*p* = 0.029; ^c*p* = 0.022; ^d*p* < 0.001; ^e*p* = 0.18.

SD: standard deviation; 95% CI: 95% confidence interval.

Parathyroid hormone concentrations

The mean ± SD initial PTH levels were 3.8 ± 1.1 pmol/l in the intervention group and 4.2 ± 1.2 pmol/l in the control group (*p* = 0.32), while those at week 14 were 3.7 ± 1.4 pmol/l and 4.7 ± 1.8 pmol/l, respectively (*p* = 0.11) (Table I).

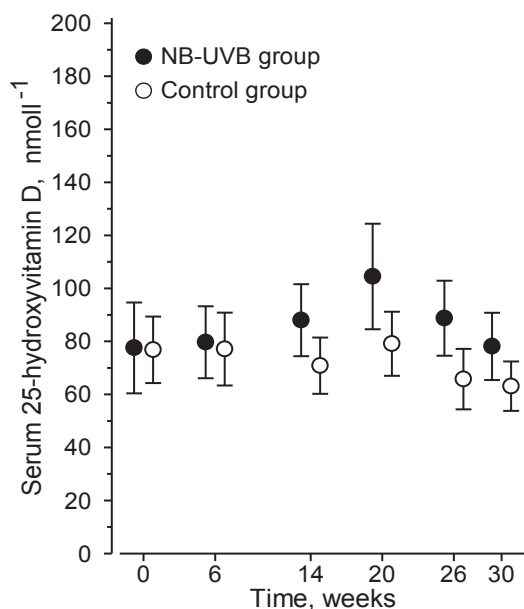


Fig. 1. 25-Hydroxyvitamin D concentrations in the narrow-band ultraviolet B (NB-UVB)-treated and control groups during the intervention (weeks 0–26) and follow-up periods (weeks 26–30).

DISCUSSION

The results of this study show that an artificial NB-UVB exposure of 2 SED every second week maintained VD concentrations throughout the winter, whereas levels in the control group decreased. No adverse effects were observed. The NB-UVB dose was small, given that an average Dane receives 1.5 SED of solar UV radiation daily in July (19). Bogh et al. (11) have shown that a BB-UVB exposure of 1 SED every second week will maintain summer levels of VD. They gave 9 BB-UVB exposures over 16 weeks and observed a non-significant decrease of 4.7 nmol/l from the baseline concentration of VD of 72.0 nmol/l. In the present trial we gave 13 NB-UVB exposures over 24 weeks and achieved a significant increase of 11.7 nmol/l over a baseline concentration of VD of 78.3 nmol/l. The dose (2 SED vs. 1 SED) and the length of exposure (24 vs. 16 weeks) seem to be the major reasons for the better VD response in our volunteers, although the fact that the vitamin D action spectrum-weighted irradiance dose (14) for an exposure of 1 SED is higher with NB-UVB (23 mJ/cm² CIE) than with BB-UVB (16 mJ/cm² CIE) may also have had an effect. It should be noted that the highest concentration of VD was observed at week 20 (Fig. 1), before the last 3 NB-UVB exposures were given. The subsequent decrease in concentration may have been due to negative feedback in the 25(OH)D system (20).

The administration of UVB irradiation over a long period of time raises a question regarding the potential risks related to UV-induced immunosuppression. The human action spectrum for immunosuppression peaks at UVA and UVB wavelengths, as measured by UV-

induced suppression of elicitation of delayed or contact type hypersensitivity (CHS) to nickel (21, 22). The most sensitive UVA wavelength is 370 nm, where the minimum immunosuppressive physical dose is 409.4 mJ/cm² (21). In the present trial a 1 SED dose was equal to an integrated non-weighted dose of 11 mJ/cm² between 360 and 390 nm for both NB-UVB and BB-UVB lamps, which is below the immunosuppressive dose. In the UVB range immunosuppression peaks at 300 nm and no immunosuppression has been recorded at 322 nm (22). With a 1 SED dose of NB-UVB or BB-UVB the minimum immunosuppressive dose is not exceeded, but it could be exceeded with a 2 SED dose of either NB-UVB or BB-UVB. However, suppression of the recall type (efferent) immunity, such as the patch-testing existing nickel allergy, is just one possible end-point of the immune response. Other potentially more relevant end-points are the suppression of the induction of either local (CHS) or systemic delayed type hypersensitivity (the afferent immunity) (23, 24). Even though no association between NB-UVB treatment and skin cancer has been observed (25), there are no safe limits for phototherapy. What is "safe" for one individual is not safe for another (26, 27). Both UVB and UVA cause signature mutations in DNA, and UVA wavelengths promote photoaging. As regards the mutagenic potential of NB-UVB and BB-UVB, they appear to be equal (28).

We found a moderate negative correlation between BMI and baseline VD status in our volunteers. A meta-analysis has confirmed the occurrence of low VD concentrations among obese subjects, suggesting that the reason for this may be volumetric dilution of 25(OH)D in the fat tissue (29). A high BMI therefore seems to predispose subjects to VD insufficiency, which in turn increases the risk of contracting VD-related diseases (3–5). The dietary VD intake was 7.0 µg in the intervention group and 6.7 µg in the control group. These intakes were approximately the same as in our previous study with healthy subjects (8), but remained lower than in the recent national survey carried out in Finland (30). Only a few of the present volunteers were receiving the estimated average requirement of 10 µg dietary VD daily, and none had reached the recommended dietary allowance of 15 µg (7). It seems that an additional 10 µg VD supplement is needed to ensure adequate VD status in the adult population (7, 31).

We have shown previously that regular NB-UVB exposures increase serum VD concentrations more than 20 µg of oral cholecalciferol daily (9). In addition, NB-UVB exposures increased the mean VD concentration by as much as 58% in patients with psoriasis who were receiving a 20 µg oral cholecalciferol supplement daily (32). Lagunova et al. (33) compared the effect of VD supplementation (50 µg oral cholecalciferol daily) and 10 UVB exposures to a total dose of 23.8 SED on VD concentration in a 1-month study. Both interventions increased serum 25(OH)D concentrations similarly, by

20–25 nmol/l. The total UVB dose was comparable to the 25 SEDs given in our study, but the intervention period was only 5 weeks compared with our 24 weeks. In the following commentary, UV dose-response studies with more careful and possibly safer exposure protocol were warranted (34). The strengths of our study are the randomized and controlled design, the long time-frame covering all winter, and the similarity of the groups. A limitation of our study is the need to standardize further the analytical methods for 25(OH)D, as suggested by Volmer et al. (35).

Our goal was to examine the capacity of low-dose NB-UVB exposures to maintain VD concentrations during the winter. The results confirmed that the 2 SED dose given every second week from October to April was enough to maintain the baseline concentrations of VD and even to increase them, suggesting that a NB-UVB dose of 1 SED might be appropriate for this purpose. A parallel comparison of continuous NB-UVB exposures and the recommended oral VD supplementation of 10 µg daily during the winter should be carried out (7, 31).

In conclusion, a suberythemal dose of NB-UVB of 2 SED given to healthy subjects every second week over the winter months can maintain and even increase post-summer VD concentrations.

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