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ORIGINAL ARTICLE

Vitamin D levels after UVB radiation: effects by UVA additions in a randomized controlled trial

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SUMMARY

Background
Ultraviolet B (UVB) radiation increases the serum level of 25-hydroxyvitamin D [25(OH)D]. However, the impact of UVA on vitamin D synthesis by UVB is poorly understood clinically.

Objective
To examine how different combinations of UVA and UVB radiation affect S-25(OH)D for the same vitamin D–weighted exposure.

Materials and Methods
Healthy participants were recruited and subsequently divided into four comparable groups regarding initial 25(OH)D value. The different radiations given were whole-body UVB ($n = 23$), UVAB ($n = 23$) and UVA (n = 10). The controls (n = 19) had no intervention. The exposure times were chosen to give the same calculated vitamin D effective dose (suberythemal exposures ≤1 standard erythema dose). Blood samples were collected before the first irradiation (t0), immediately after the last (fifth) irradiation (t1) and then after another 2 days after the last (fifth) irradiation (t2).

Results
UVB and UVAB radiation significantly increased 25(OH)D levels. In the UVA group the increase was less with the same vitamin D–weighted radiation dose.

Conclusions
Short sessions of UVB or UVAB radiation with the same vitamin D–weighted exposure increased 25(OH)D levels. The UVA dose does not influence 25(OH)D levels under short exposure times. However, there was a significantly lower increase of 25(OH)D levels during longer UVA irradiation (≥9 min).

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Vitamin D is a fat-soluble vitamin and steroid hormone with the function of maintaining an accurate calcium and phosphorus homeostasis in plasma in the human body (1–3). Humans obtain vitamin D from diet (exogenously) and from exposure to ultraviolet B (UVB) radiation in sunlight (endogenously) (4, 5).

Several studies indicate that ultraviolet radiation (UVR) possibly photo-degrades more of the previtamin D3 than it might create in the skin for high UV levels with wavelengths in the spectral region above UVB (6–8). This has relevance to a widespread use of UVA sunbeds (9, 10). To our knowledge, the influence of UVA on plasma 25(OH)D concentrations has never been clinically examined in any comprehensive manner and therefore needs further investigation. Thus, the purpose of this study was to examine how different wavelengths of UV radiation change plasma levels of 25(OH)D in situations when the same vitamin D-effective UV radiation was given as calculated from measured spectra of phototherapy treatment cabins ('UVB', 'UVA', 'UVAB') and the CIE (commission Internationale de l'Eclairage) vitamin D action spectrum (11).

MATERIAL AND METHODS

Design

A randomized controlled trial was carried out from December 2011 to March 2012, i.e. during the Swedish winter with temperatures around and below freezing point. This is a period when UV exposure from the sun is negligible in Stockholm, Sweden (59°N). The solar UV index, which is the World Health Organization (WHO)/World Meteorological Organization's internationally accepted measure of erythemal solar UV intensity at noon, is '≤1' and well within the WHO exposure category 'low' (12, 13). Ethical approval was obtained from the Regional Ethical Review Board in Stockholm.

Participants

Potential participants were recruited from the Stockholm area by advertisement in a newspaper for healthy male and females aged 20–65 years. Of 400 responders, 269 were excluded for the following reasons: intake of supplements containing vitamin D during the past 8 weeks, sun holiday or use of sunbeds during the study, treatment with UV radiation during the past 3 months, local treatment with creams containing calcipotriol, severe kidney or liver disease, thyroid disease, diabetes mellitus, body mass index (BMI) > 27.9, pregnancy or age < 18 or > 65 years. The 131 remaining individuals were screened for 25(OH)D and total cholesterol in December 2011 and in the beginning of January 2012.

Of the 131 screened participants, 20 were excluded before the start of the study because of the exclusion criteria mentioned above. The final sample of 111 participants was split into different groups based on their 25(OH)D value. The ranges were < 20 nmol/l, 20–29 nmol/l, 30–39 nmol/l, 50–59 nmol/l, 60–69 nmol/l and > 70 nmol/l. The participants were coded. Each code revealed the participants' 25(OH)D value and skin type. The 111 participants were then distributed evenly with consideration to baseline 25(OH) vitamin D into four exposure groups: UVB (27 participants), UVAB (28 participants), UVA (28 participants) and controls (28 participants). Fourteen participants were dropouts because of lack of time, and the other 22 were too late to enrol because spring was near. In all, 75 participants completed the full 2 weeks of the study.

Weight and height were measured, and BMI was calculated. All participants self-assessed their skin type according to the Fitzpatrick skin phototype system.

Procedure

UV exposures and collection of blood samples followed a predetermined schedule. The participants were irradiated five times during 2 weeks. Blood samples from the controls were taken the first and the last day of the 2 weeks.

The different radiations given included whole-body radiation exposure in phototherapy cabins with UVB (280–320 nm) (Lamps: Waldmann UV6, 100W; Waldmann Medizintechnik, Villingen-Schwenningen, Germany), whole-body radiation with UVA (320–400 nm) (Lamps: Waldmann PUVA, 100 W, Waldmann Medizintechnik), or combined as UVAB (280–400 nm). Both the UVA and UVAB boxes were equipped with 26 vertically arranged UV fluorescent tubes. In the UVAB box 6 of the tubes were UVB and 20 were UVA. The UVAB box was used to administer the UVB exposures with only the 6 UVB lamps lit, or the UVAB exposures with all 26 lamps lit. The UVA exposures were administered in the UVA box. The UV irradiance was measured by the Swedish Radiation Safety Authority using a portable factory-calibrated diode array spectroradiometer (SolaHazard, Solatell, 4D Controls Ltd, Redruth, Cornwall, UK) to measure the spectral distribution in the UV boxes (Fig. 1) (14). The irradiation time for the different UV irradiations had been calculated to give exposures according to the CIE action spectrum for the production of previtamin D_3 in human skin (Table 1) (11). All given UV doses were

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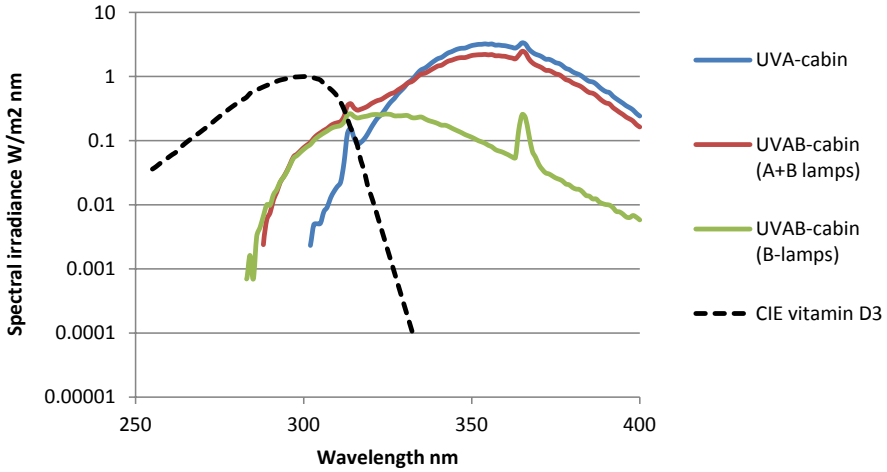

Fig. 1. Spectral irradiance of the different exposure types and relative spectral efficiency of the CIE action spectrum for previtamin D3.

Table 1. Exposure table for irradiation

Radiation	Erythema effective irradiance (W/m^2)	Minutes/SED (1 SED = 100 J/m^2)	Vitamin D effective irradiance (W_{Deff}/m^2)	Time for comparable vitamin D exposure of 85J_{Deff}/m^2
UVAB	0.90	1.9	1.41	60 s
UVB	0.86	1.9	1.40	61 s
UVA	> 0.13*	< 12.8*	≈ 0.16*	9 min

*See measurements discussed under 'Procedure'.
SED, standard erythema dose.

suberythemal (≤ 1 standard erythema dose). The vitamin D effective exposure was chosen to correspond to a 1-min exposure in the UVAB box with all lamps lit. The exposure (85 J_{Deff}/m^2) can be estimated to correspond to 5 min of midday summer solar exposure in southern Sweden, or 2 min in the Canary Islands (15).

UVB radiation was present in all three irradiations. The UVB percentages of the total irradiance were 4.7% in the UVAB box with both UVA and UVB tubes, 30% with only UVB lamps and 0.7% measured in the UVA box according to the portable spectroradiometer (SolaHazard). This spectroradiometer is accurate when measuring high levels of UVB or UVA, but underestimates low irradiance levels of UVB in the presence of high levels of UVA by a factor of 2, according to comparisons with a double grating laboratory spectroradiometer (Optronic mod 742, Optronics Laboratories, Orlando, FL, USA) with high stray light rejection and a National Institute of Standards and Technology–traceable calibration for UVA-lamps measured by SolaHazard to have '0.7% UVB'. A broadband UV radiometer (Solarmeter mod. 6.4, Solartech Inc., Harrison Township, MI, USA), sensitive to and calibrated by the manufacturer for vitamin D–weighted radiation, was used to confirm the exposure time in the UVA box (Table 1).

Blood samples were collected at baseline before irradiation (t0), after the last (fifth) irradiation (t1) and 2 days after the last (fifth) irradiation (t2). Blood samples were analyzed for serum 25(OH)D, plasma-PTH, plasma-calcium, serum-calcium++, plasma-phosphatase and plasma-cholesterol.

The serum samples for 25(OH)D analysis were frozen and stored at −80°C until the end of the experiment and then analyzed in one batch. The analysis was performed using the LIASON 25-hydroxyvitamin D Assay (DiaSorin, Inc., Stillwater, MN, USA) and the chemiluminescent immunoassay technique. The coefficients of variation for inter-assay analyses with this method are 18.4% at 25(OH)D level of 39.5 nmol/l and 11.7% at 121.25 nmol/l. To minimize uncertainties due to inter-batch differences all 25(OH)D samples were assayed in one batch.

Statistical analyses

The primary end point in the study was the changes in serum 25(OH)D after UV exposure of different UV wavelengths. Descriptive statistics for 25(OH)D were presented as means (±SD). Differences in 25(OH)D were analyzed using a mixed linear model with one between-group factor

(irradiation: UVA, UVAB, UVB and control) and one within-group factor (time: t0, t1 and t2), as well as the interaction between irradiation and time. An unpaired *t*-test was used to compare changes in vitamin D levels between the groups. The correlation between 25(OH)D and skin photo type was examined using Spearman's rank correlation. An unpaired *t*-test was applied when skin types were grouped into two groups (I–III vs. V–VI) and correlated to 25(OH)D. The correlation between BMI and cholesterol was assessed by Pearson's correlation coefficient (r), as well as for analysis of the increase of 25(OH)D in relation to baseline values. The association between any increase of 25(OH)D and different skin types was evaluated by Spearman's rank-order correlation. *P* values < 0.05 were considered statistically significant. Statistica 10.0 (StatSoft®, Inc. Tulsa, OK, USA) and SAS® System 9.1 (SAS Institute Inc., Cary, NC, USA) were used for statistical treatment of data.

RESULTS

Baseline characteristics

Seventy-five participants completed the 2-week study period. The participants in the four groups did not differ significantly in age, sex and BMI.

Unintentionally, the skin types were unevenly distributed. Relevant baseline characteristics (t0) of the participants are shown in Table 2.

Of the 75 participants, 63 (83%) had 25(OH)D < 50 nmol/l, and of these, 15% had 25(OH)D < 25 nmol/l at t0. The mean baseline value of plasma 25(OH)D concentration was 38.8 nmol/l. There was no statistically significant difference in 25(OH)D between the groups at the start of the study ($P = 0.73$).

Blood samples and 25(OH)D changes

The interaction between irradiation and 25(OH)D was statistically significant ($P < 0.001$), indicating that the effect over time differed between the groups. The three exposure groups increased their values of 25(OH)D significantly from baseline to t2, whereas no significant changes could be demonstrated for the controls. There was no difference in 25(OH)D level just after and 2 days after the treatment (Table 3). We saw a significantly lower increase of vitamin D after the longer UVA irradiation. The estimated mean change for UVAB was 13.6 nmol/l [95% confidence interval (CI) 11.1–16.1, $P < 0.001$], for UVB 11.1 nmol/l (95% CI 8.6–13.7, $P < 0.001$) and for UVA 4.4 nmol/l (95% CI 0.64–8.1, $P = 0.02$). The mean change for the controls was –1.42 nmol/l (95% CI –4.1–1.2, $P = 0.29$). There were significant differences between the groups, except between UVAB and UVB for vitamin D changes. A subset consisting of the skin types II and III is congruent with the overall result (Table 4).

No significant correlations were found between different skin types and baseline 25(OH)D ($r_s = –0.15$, $P = 0.19$).

Table 2. Baseline characteristics (t0) of the study groups

	UVB group (*n* = 23)	UVAB group (*n* = 23)	UVA group (*n* = 10)	Control group (*n* = 19)
Number of women	16 (70%)	17 (74%)	7 (70%)	16 (84%)
Age (years)	45 (23–62)	44 (24–65)	41 (20–65)	46 (20–65)
Skin type I; II; III; IV; V; VI	4; 7; 9; 3; 0; 0	0; 5; 13; 4; 1; 0	0; 3; 4; 0; 2; 1	1; 10; 7; 0; 0; 1
BMI (kg m^2)	24.3 (18.6–27.2)	23.5 (19.4–27.3)	22.6 (20.7–25.2)	23.1 (20.1–27.3)

Values are means (range) or numbers.

Table 3. Estimated means and SEM for 25-Hydroxyvitamin D (25(OH)D, nmol/L) in serum at t0, t1 and t2

Group	Baseline (t0)	After the last UV session (t1)	2 days after the last UV-session (t2)
UVB	38.1 (2.78)	49.2 (2.78)	49.7 (2.81)
UVAB	37.4 (2.78)	49.7 (2.79)	51.0 (2.80)
UVA	41.2 (4.21)	45.6 (4.21)	45.9 (4.24)
Controls	39.6 (2.93)		38.1 (2.96)

Values presented as means (SEM, standard error of the mean).

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Table 4. Estimated means change for the subset of skin types II and III ($n = 58$) before (t0) and after exposures (t2)

	25-Hydroxyvitamin D (25(OH)D) in serum	
Irradiation	nmol/L	CI 95%
UVB	12.0	8.8–15.2
UVAB	13.6	10.6–16.6
UVA	4.2	–0.7–9.0
Controls	–1.6	–4.6–1.4

However, grouping the skin types into I–III and IV–VI resulted in a significant association ($P = 0.008$) between skin type and baseline 25(OH)D. The mean value in group I–III was 40.6 (SD 12.8) nmol/L and 29.5 (SD 12.9) nmol/L in group IV–VI. No significant association was found between baseline 25(OH)D and BMI ($r = -0.13$, $P = 0.28$) or between baseline 25(OH)D and cholesterol ($r = 0.19$, $P = 0.10$). Concerning the exposure of participants, a negative correlation was seen between baseline 25(OH)D values and the change from t0 to t2 ($r = -0.34$, $P = 0.018$). Because this result could be caused by the regression to the mean phenomenon, the mean value at baseline and t2 was correlated against the difference. Thereafter, the correlation between baseline 25(OH)D values and the change from t0 to t2 was no longer significant ($r = -0.10$, $P = 0.49$). No association was observed between Δ25(OH)D and skin type ($r = -0.14$, $P = 0.34$). Even after dividing the skin types into I–III and IV–VI, there was still no significant association ($r = -0.20$, $P = 0.17$).

There was no statistical differences in plasma-PTH, plasma-calcium, serum-calcium++ or plasma-phosphatase at baseline or during the study in the different groups.

DISCUSSION

Our study showed that healthy participants were able to produce significant amounts of vitamin D from a few low doses of UVB or UVAB exposure. The production was found to occur regardless of skin type, BMI and cholesterol value. The increase of vitamin D in the UVA group was significantly lower than in the UVB and UVAB group. However, the total number of subjects in the UVA group was only 10. UVA in our study had no effect after brief exposure times. Although possibly some photodegradation of previtamin D may occur as a result of longer exposure times to UVA irradiation.

The 7-dehydrocholesterol is converted to previtamin D_3 as the skin is exposed to UV radiation and further converted to vitamin D_3 in a heat-dependent process. Vitamin D_3 will be metabolized in the kidneys to 25(OH)D and finally to the active $1,25(OH)_2$ in the liver. Additional UVR exposure can convert previtamin D_3 to inactive lumisterol, toxisterols and tachysterol. MacLaughlin *et al.* have shown that both previtamin D_3 and $tachysterol_3$ absorb radiation to at least 325 nm and 335 nm. They exposed $tachysterol_3$ and previtamin D_3 dissolved in an organic solvent to radiation between 315 and 340 nm and observed an accumulation of $lumisterol_3$ (5). Their findings are of interest in relation to our results.

Solar exposure is a major contributor to previtamin D_3 formation in human skin, short exposures to midday summer sun are sufficient and prolonged exposure does not result in more of the vitamin. The conversion of 7-DHC to previtamin D_3 has its peak in the UVB region and terminates near the UVB-UVA boundary (5), although the CIE action spectrum is extended further by mathematical extrapolation to 330 nm and not based on experimental data (11). MacLaughlin *et al.* observed a nearly threefold conversion of 7-DHC to previtamin D_3 for narrow-band UVB (295 ± 5 nm) as compared with simulated solar radiation in surgically obtained type III human skin, although doses given are unclear (5). A study by Webb *et al.* on action spectra for both photoproduction and photodegradation of previtamin D_3 in human skin indicated a slight shift toward longer wavelengths for photodegradation that may be of significance for strong UVA (7). Thieden *et al.* (8) investigated how sunbeds with UVA lamps and 0.5% or 1.4% UVB affected 25(OH)D in plasma. The participants were irradiated for 3 weeks and received eight sunbed sessions. The first four sessions were 6 min each, followed by four 12-min sessions. In the 0.5% UVB group the average increase from day 0 to day 9 was 25%, whereas in the 1.4% UVB group it was 58%. The observed increase in vitamin D levels was dependent on the dose but reached a plateau already after four sunbed sessions (8). Based on their findings, we expected a smaller increase in the UVAB group. However, our study differed in several aspects. The main discrepancy between the studies was the UV exposure times. In our study everyone received the same vitamin D–weighted UV radiation dose and none of the participants developed erythema. Thieden *et al.*, on the other hand, reported erythema in a few participants.

In our study the exposure times for UVB and UVAB irradiation were short (61 and 60 s for UVB and UVAB, respectively). When UVB irradiation is short and intense, we have shown that the UVA dose does not matter and hence does not influence vitamin D level. Thus, if there were a photodegradation process instigated by UVA, 1 min is probably not long enough to initiate the degradation of

25(OH)D. Our results from the UVAB and UVB groups provide unambiguous support that short UVB exposures increase 25(OH)D, regardless of UVA content. With longer exposures (≥ 9 min), there might be an influence from UVA, as indicated in Tables 3 and 4.

We found that Δ25(OH)D was positively correlated to a low baseline value of 25(OH)D. Consequently, the increase of 25(OH)D was largest in the participants with the lowest baseline values, an observation reported previously (6, 16, 17). However, such a significant relationship could depend on the regression to the mean phenomenon. To avoid this possibility we correlated the mean value from t0 and t2 to the difference and found no correlation. There was no significant difference in 25(OH)D at t1 (after the fifth and last irradiation) and t2 (2 days after the last irradiation). We took two tests because we do not completely know when vitamin D is maximal after UV exposure. A difference might not be expected as the decrease after irradiation might take longer time (17). In addition, no relation was observed between 25(OH)D and BMI. Our finding is in accordance with some studies (6, 18) but in contrast to others (19). However, our relatively narrow BMI range could be one possible reason for the lack of association. In contrast to Bogh *et al.* (16), we did not find a relation between 25(OH)D and cholesterol. The skin photo types were (unintentionally) unevenly distributed, with more skin type V and VI in the UVA group than in the UVB (no skin type V or VI) and UVAB (one skin type V) group. Because fewer participants were included in the UVA group, the percentage of dark-skinned participants was 30% in this group compared with only 4% in the UVAB group (and 0% in the UVB group). We found no relation between skin type and baseline 25(OH)D after analyzing skin types I–VI separately. Although when skin types were grouped into two groups (I–III and IV–VI), a distinction was obvious, with significantly higher values in group I–III. This difference may not be caused by skin colour, but by behaviour and genetics in that several genes control vitamin D synthesis (20). There is also a theory that a relation could exist in summer, where sun exposure causes the melanin to penetrate into the epidermis, which could be a reason why people with dark skin may have a higher risk of vitamin D deficiency (16). However, we found no evidence of a correlation between Δ25(OH)D and skin type, indicating that skin type does not matter while producing 25(OH)D during very short UV exposure. These findings are similar to those of Bogh *et al.* (16). McKenzie *et al.* also found a high variability in 25(OH)D from person to person in response to UV irradiation (21). Variability also might have influenced our results.

In our study we used the CIE vitamin D action spectrum to calculate UV exposure times of the boxes (11). The CIE vitamin D action spectrum of the skin's synthesis of vitamin D is based on studies performed on surgically removed skin (1, 22) using mercury quartz lamps mainly with narrow-band emissions in the UVB, and from data end points within the UVB region, it is extrapolated beyond 315 nm up to 330 nm (11). Others have suggested that the action spectrum may be incorrect (21, 23, 24). Of course, a UVB end point might also help explain the result of our UVA group as an alternative to possible slow photodegradation effects of prolonged irradiations.

The participants might not represent the typical Swedish population regarding vitamin D status. However, because we included both genders with a wide age range, we hoped to minimize any selection bias. A major strength of our study is that it was performed in the winter when sun exposure is minimal and therefore could not affect the results.

CONCLUSION

Short suberythemal sessions of UVB and UVAB radiation with the same vitamin D–weighted exposure increase plasma 25(OH)D to the same degree. The UVA dose, in the UVAB radiation, does not have an effect on 25(OH)D levels during short exposure times. For longer exposures (≥9 min); however, UVA may decrease the level of Δ25(OH)D.

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