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Vitamin D Supplementation Does Not Improve the Severity or the Resolution of Ultraviolet B-Induced Acute Erythema

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Key Words
Vitamin D · Photoprotection · Ultraviolet B-induced erythema · Skin cancer · Inflammation

Abstract
Background: Whether vitamin D supplementation alleviates the severity of ultraviolet B (UVB)-induced erythema and/or facilitates its resolution remains undetermined. ***Objective:*** To study the effect of oral vitamin D on UVB-induced erythema and its resolution in fair-skinned subjects. ***Methods:*** UVB-induced erythema was quantified using a Chroma Meter® in 50 volunteers 48 h before and 10 days after the random administration of 200,000 IU vitamin D (n = 40) or placebo (n = 10). Resolution of erythema in both groups was assessed by chromametry 24, 48, and 72 h after vitamin D administration. ***Results:*** No statistical difference between erythema values before and after administration in the vitamin D-supplemented group (p = 0.44) or the placebo group (p = 0.34) was noted. No statistical difference was evident between both groups with respect to resolution of erythema (p = 0.30). ***Conclusion:*** Oral vitamin D supplementation neither improves protection against UVB-induced erythema nor facilitates its resolution.

Introduction

Sunburn is an ultraviolet B (UVB)-induced phenomenon and represents one of the initial cornerstones in the pathogenesis of malignant melanoma and nonmelanoma skin cancer [1, 2]. Hence, photoprotection and sun avoidance are of capital importance in the fight against skin cancer. Patients who have had a melanoma, squamous cell carcinoma, or basal cell carcinoma are at risk of vitamin D deficiency due to the recommendation of sun avoidance, and vitamin D supplementation is common practice in this patient population. However, vitamin D should be given upstream since it could have a preventive role in carcinogenesis. Indeed, previous studies have found that vitamin D supplementation or higher vitamin D serum levels may be associated with a reduced incidence [3] or a better prognosis of skin cancer, respectively [4]. Moreover, solar radiation, via the vitamin D synthesized in the skin, may have a beneficial influence on both the incidence and the outcome of melanoma [5]. However, thorough epidemiologic evidence that adequate vitamin D supplementation or solar exposure protects against nonmelanoma skin cancer [6] and melanoma [3, 5, 7] is lacking.

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Table 1. Study flow chart

Visit	Day						
	1	2	4	14	15	16	17
Induction of UVB erythema	X			X			
Vitamin D serum status	X			X			
Colorimeter (a*-C)		X			X	X	X
200,000 IU vitamin D or placebo			X				

Vitamin D displays a high number of in vitro photoprotective properties. Calcitriol [1α,25-dihydroxyvitamin D_3 or $1,25(OH)_2D_3$] may enhance keratinocyte [8–13], melanocyte [13] and fibroblast [10, 13] survival after UVR exposure by reducing UV-induced promutagenic DNA damage like cyclobutane pyrimidine dimers [8–13], 8-oxo-7,8-dihydro-2-deoxyguanosine [9, 14], 3-nitrotyrosine, and 8-nitroguanosine [9, 15, 16], which are mutagenic and are markers of inflammation and carcinogenesis. Moreover, $1,25(OH)_2D_3$ could also influence the upregulation of p53, allowing improvement of DNA repair [13].

Whether these in vitro results on photoprotection are clinically relevant and whether eventual photoprotective effects are influenced by the vitamin D serum status remain undetermined.

This pilot study evaluated whether oral vitamin D supplementation in fair-skinned healthy individuals affects the severity of UVB-induced erythema and facilitates its resolution.

Materials and Methods

This pilot study was performed in accordance with the Helsinki Protocol (2000) and was approved by the University Hospital Ethics Committee. All study procedures were explained to the volunteers. All participants signed an informed consent form. The sequence of this study is presented in table 1.

Patients

Fifty phototype III [Fitzpatrick's classification type III: fair to matt skin, sometimes burns, always tans (medium tan), a few freckles] young healthy volunteers (males: n = 21, females: n = 29, mean age 22.3 ± 1.9 years, BMI 21.3 ± 1.96) were invited to participate in this study. They comprised a homogenous population in order to reduce the influence of some variables (BMI, age, and no vitamin D supplementation [17]) on vitamin D production. This study was performed in November to minimize natural UVB exposure. The exclusion criteria were as follows: oral vitamin D supplementation, age <18 or >26 years, BMI <18 or >25, a high dietary intake of vitamin D, pregnancy, lactation, skin disease, immunosuppression, photosensitizing drug intake, photosensitizing disease, liver insufficiency, PUVA or UVB therapy, and recent holidays in the sun or sunbed less than 1 month prior to baseline use.

UVB Erythema Induction

A standardized UVB-induced erythema was induced on days 1 and 14 using the Gigatest® UVB-MED Tester UVB-311 (narrowband, 310–315 nm; Medisun®, Brühl, Germany) (table 1). The Medisun Gigatest MED displays 5 test fields, each with a diameter of 15 mm. The 5 dose levels vary from 100 to 13% and are obtained through special high-value coated filters. UVB-induced erythema is a recognized marker for cutaneous inflammation and it is a valuable tool as an indirect marker for increased skin cancer risk [7]. The UVB energy output in the 100% transmission field averages 4 mW/cm^2. The 100% transmission field was used for the colorimetric evaluation as this field was the only field visible with the naked eye in all of the patients on day 3. The Gigatest was applied vertically on each subject's right lower back using an irradiation time of 2.5 min for all subjects, equivalent to 0.6 J/cm^2, for 100% transmission. About 30 min after irradiation, patients were examined at the test site to exclude solar urticaria.

Minimal Erythema Dose Evaluation

A minimal erythema dose (MED) test was performed 24 h after Medisun Gigatest UVB exposure. The number of positive fields visible with the naked eye was evaluated over a total of 5 test fields.

Chroma Meter® Erythema Evaluation

Chroma Meter CR400 (Konica Minolta, Japan) evaluations of the a* parameter according to the L*a*b* mode (CIE 1976, +a/–a: red/green axis, +b/–b: yellow/blue axis, L: lightness) are a well-recognized and validated technique for measuring variations in UVB-induced erythema [18, 19]. Measurements of the a* values of the UVB-induced erythemas were performed in triplicate. The perilesional skin served as a control (C) and its a* value was measured in triplicate. To eliminate interobserver variation, all evaluations were performed by the same investigator under standardized illumination of the study room and positioning of the subject and investigator, as well as at a constant temperature. Chroma Meter measurements were performed on day 2 and on days 15, 16, and 17 (table 1). The difference in erythema intensity in interventional studies is a common measure to evaluate in vivo photoprotection [20].

25(OH)D Analysis

Blood samples were collected on days 1 and 14 (table 1). The samples were tested using a MassChrom® 25-OH-Vitamin D_3/D_2 LC-MS/MS kit with a 3-epi-25-OH-Vitamin D_3 upgrade (LCMS; Gräfelfing, Germany) on the AB SCIEX QTRAP® 5500 system (AB SCIEX; Framingham, Mass., USA). This LC-MS/MS is traceable to the National Institute of Standards and Technology (NIST) reference material SRM 2972 and the ID-LC-MS/MS 25(OH)D reference method procedure. The upgrade procedure allows $25(OH)D_3$ and $25(OH)D_2$ to be separated from their epimeric form 3-epi-25-(OH)-D. The coefficient of variation was <2%. All samples were measured in duplicate.

Oral Vitamin D Supplementation

Two oral doses of 100,000 IU equivalent to 200,000 IU of cholecalciferol (n = 40) and placebo (n = 10), identical in color and consistency, were simultaneously administered in liquid form at

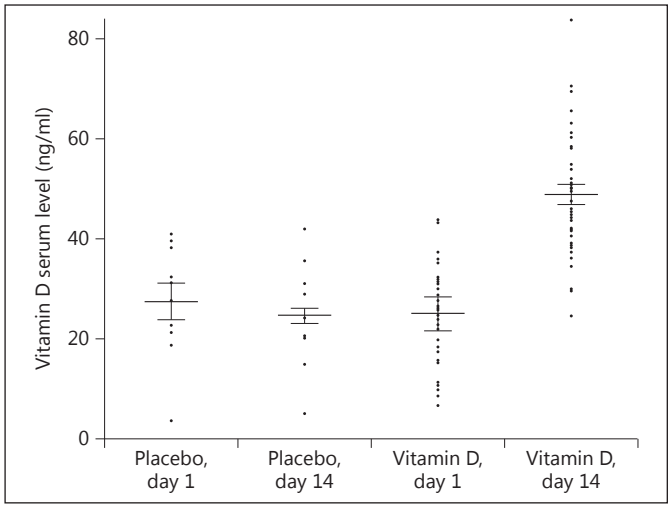

Fig. 1. Vitamin D serum levels of the placebo and vitamin D-supplemented groups on days 1 and 14 (individual values presented as means ± SE).

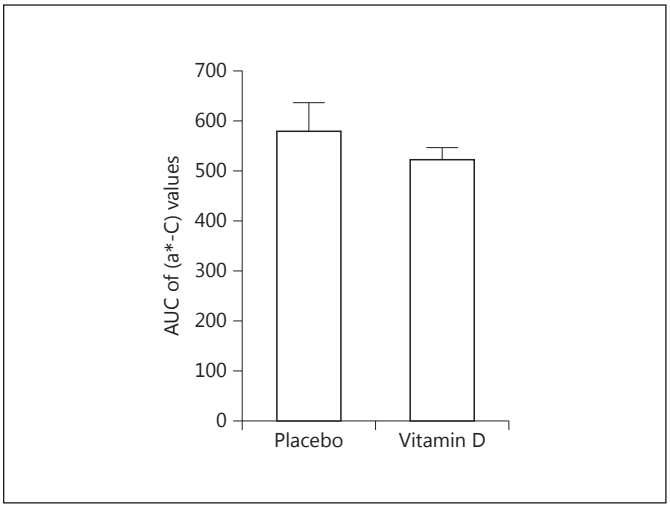

Fig. 2. AUC values of UVB-induced erythema in the placebo and vitamin D-supplemented groups (mean ± SE; not statistically different).

random to the volunteers on day 4 under the supervision of one of the investigators in a blinded manner. The dose of 200,000 IU of vitamin D and collection of blood sample 10 days after administration were chosen according to the results of oral vitamin D supplementation tests showing peak levels between 7 and 15 days [21].

Endpoints

The main outcomes were as follows: (1) mean increase in 25(OH)D after oral vitamin D supplementation (n = 40) versus placebo (n = 10); (2) erythema intensity expressed as (a*-C) on day 15 versus (a*-C) on day 2 in the placebo (n = 10) and vitamin D-supplemented group (n = 40), respectively; (3) alleviation of erythema expressed as the area under the curve (AUC), defined as the total (a*-C) values on days 15, 16, and 17 in the placebo (n = 10) versus the vitamin D-supplemented group (n = 40); (4) photoprotection as assessed by the median number of visible test fields (24 h after Gigatest UVB testing) on day 15 versus day 2, and (5) erythema alleviation expressed as the mean number of visible test fields on days 15, 16, and 17 in the placebo group and the vitamin D-supplemented group.

Statistical Analysis

Data are expressed as means ± SD. A paired Student t test was used to compare increases in 25(OH)D after oral vitamin D supplementation and to compare the changes in (a*-C) on day 15 versus day 2. The Student t test was used to compare (a*-C) and AUC values between the two groups.

$p < 0.05$ was considered statistically significant. Calculations were performed using SAS version 9.3 software (SAS Institute, Cary, N.C., USA) and figures 1–3 were drawn using S-PLUS version 8.1 software.

Results

There was no statistically significant difference in 25(OH)D levels before and after placebo administration in the control group (mean 27.3 ± 11.5 vs. 25.0 ± 10.6 ng/ml, respectively, $p = 0.17$). A statistically significant increase was observed in the vitamin D supplementation group between days 1 and 14 (mean 24.6 ± 9.4 vs. 48.7 ± 12.3 ng/ml, respectively, $p < 0.0001$). The increase in 25(OH)D levels differed significantly between the two groups ($p < 0.0001$; fig. 1).

There was no statistically significant difference in the mean (a*-C) values measured 24 h after UVB-induced erythema before and after vitamin D supplementation (n = 40; 11.4 ± 2.9 on day 2 vs. 11.1 ± 2.8 on day 15, $p = 0.53$), nor was there any statistically difference in the mean (a*-C) values measured 24 h after UVB-induced erythema before and after placebo administration (n = 10; mean 9.7 ± 3.8 on day 2 and 10.9 ± 3.5 on day 15, $p = 0.25$). There was no statistically significant difference between supplemented volunteers and placebo subjects with respect to erythema values 24 h after UVB erythema induction on day 15 ($p = 0.19$).

The mean AUC values were 580 ± 176 in the placebo group and 524 ± 147 in the vitamin D-supplemented group, but these were not statistically significantly different ($p = 0.30$; fig. 2). The temporal evolution of (a*-C) values in the placebo and vitamin D groups is shown in

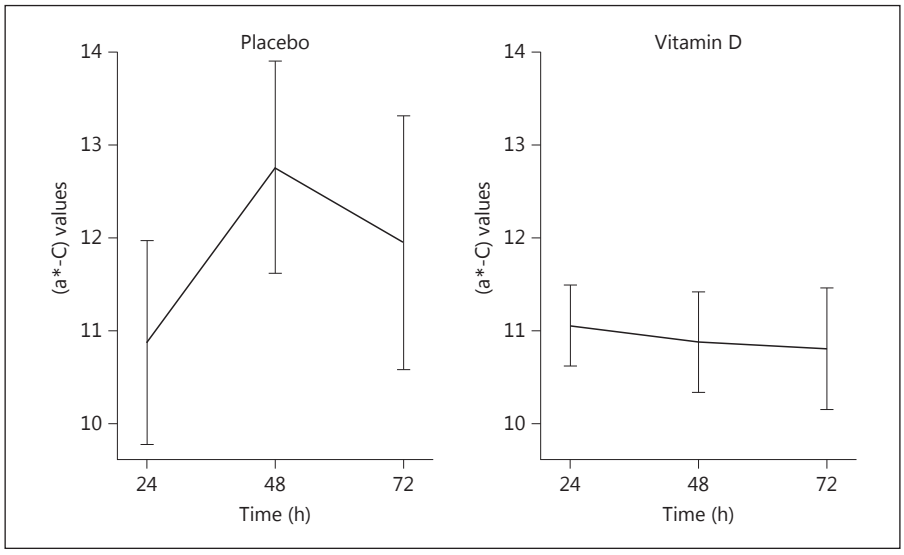

Fig. 3. Temporal evolution of (a*-C) values in the placebo and vitamin D groups.

figure 3 (placebo mean at 24, 48, and 72 h: 10.88, 12.76, and 11.95, respectively; vitamin D mean at 24, 48, and 72 h: 11.06, 10.88, and 10.81, respectively).

The median number of visible test fields at 24 h was 4 (minimum 1, maximum 4, mean 3.6; n = 50), which was equivalent to 0.195 J/cm^2, equivalent to the median MED. The mean number of visible test fields was 3.5 and 3.63 in the placebo and vitamin D-supplemented groups, respectively, on day 2 versus 3.6 in the placebo group on day 15 (n = 10), and 3.83 in the vitamin D-supplemented group (n = 40). These differences were not statistically significant (p = 0.59).

Erythema alleviation was also expressed as the mean number of visible test fields on days 15, 16, and 17. The mean number of visible test fields in the placebo group was 3.6, 3, and 2.8 versus 3.83, 3.5, and 3 in the vitamin D-supplemented group on days 15, 16, and 17, respectively. These differences were not statistically significant.

Discussion

The in vivo effects of vitamin D on the reduction of UVB-induced erythema remain unclear. Several studies have examined the clinical effect of topical calcitriol [22] or calcipotriol [23–26] on the MED in humans, and the results are contradictory. Calcipotriol is a synthetic derivative of calcitriol and it is known to display similar properties in terms of epidermal proliferation, modulation of keratinization, and inflammation [25]. The delay between topical application and UV irradiation varies among studies, potentially influencing the MED. In brief, calcipotriol 0.005% [23–27] applied 15–20 min [25, 27] or immediately before [23, 24, 26] irradiation, with a thick enough layer [23], influenced the MED [23–27], which could reach an increase of 31% [27] or an increase from 22.6 to 54.6 mJ/cm^2 [23]. Two hours after application, the MED returned to baseline [26]. In contrast, when calcitriol or calcipotriol was applied 24 [22], 12 [23], or 2 h before [24] or immediately after [22] irradiation, there was no influence on the UVB-induced erythema [22–24]. Nevertheless, when applied directly after UV exposure, it decreased the density of sunburn cells and the number of thymine dimers [16, 22]. This suggests that the in vitro results do not necessarily correlate with an increase in MED [22].

Vitamin D also displays immunoregulatory properties. The immune effects of calcitriol on in vivo human skin are as yet unspecified [22]. Dietary vitamin D produced a reduction in DNA damage, in cutaneous inflammation, and in immunosuppression after UVB irradiation in a murine model [28]. This could mean that vitamin D counteracts the inhibitory effects of UVB on cutaneous immunity [29] and could be involved in immunomodulation [11]. Interestingly, in humans, UV-induced suppression of a delayed-type hypersensitivity reaction was measured after topical application of calcitriol but it failed to prevent UV-induced immunosuppression [22]. These controversial results can be explained by the differing immune properties of calcitriol in mice and humans and could be dose related, with protective immune effects appearing at higher concentrations (greater ab-

sorption and greater dose relative to body weight in the mouse) [22]. The in vitro immunosuppressive properties of $1,25(OH)_2D_3$ are dependent on genomic pathways and include, among others, inhibition of dendritic cell differentiation and maturation, inhibition of the production of numerous cytokines [30] or T cell proliferation [31] and polarization from a Th1 and Th17 phenotype towards a Th2 phenotype [32]. A recent analysis showed that vitamin D modulates tumor suppression via a mechanism that depends on the amount of vitamin D receptor in the skin [33].

This pilot study revealed that high-dose oral vitamin D supplementation does not have an impact on the severity of a fixed-dose UVB-induced erythema. The mean serum level of cholecalciferol achieved in our study reached 48.7 ± 12.3 ng/ml but may, however, not have been enough to observe any photoprotective effects. Furthermore, there was no improvement or acceleration in the resolution of UVB-induced erythema in the supplemented group and no difference in visual MED in the vitamin D versus placebo groups. These results imply that oral vitamin D supplementation is probably of no use as protective oral therapy against sunburn or as a preventive technique to increase the healing speed of sunburn. It may be that any subtle antierythema effect of vitamin D is only observable at the threshold of erythema and not with supra-MED doses. Indeed, although the groups were all skin type III, they likely had a reasonable range of MED, and so using the highest dose in all participants may have resulted in missing some anti-inflammatory effects at the erythema threshold. Moreover, Chroma Meter measurements were not taken at each participant's MED site, but this was in order to still be able to have a measurable residual erythema on day 17, equaling 72 h after induction. Interestingly, using a fluorescent lamp with an emission spectrum of 280–350 nm and a peak of 310–315 nm, it has been observed that calcitriol [34] and calcipotriol [25] have photoprotective actions against UVB-induced reduction of the viability of cultured keratinocytes [34] or of DNA synthetic activity [25] in certain UVB dose ranges, but this was not observed beyond 50 mJ/cm^2 or 60 mJ/cm^2, respectively. This would imply that calcitriol and calcipotriol are photoprotective only at lower doses of UVB radiation. Thus, the importance of vitamin D for photoprotection should no be overlooked. In the skin, mechanisms of endogenous photoprotection following sun exposure include, among others, increased pigmentation via melanocytes and increased cornification of keratinocytes. It has been previously reported that calcitriol could enhance these processes [35]. Vitamin D can be converted to $1,25(OH)_2D_3$ due to the presence of vitamin D-25 hydroxylase and 25(OH)D-1α-hydroxylase in keratinocytes [7], though the process takes several hours. This suggests that formation of $1,25(OH)_2D_3$ in the skin seems to protect against the next rather than the initial UV irradiation [12], implying that exogenous analogues of calcitriol could represent an added value in sunscreens [35].

In brief, oral vitamin D supplementation in fair-skinned healthy individuals does not improve direct UVB-induced erythema, and secondly single, high-dose, oral supplementation does not reduce the severity of acute UVB-induced inflammation. Hence, oral vitamin D supplementation may not be useful in reducing UVB-induced sunburn but it should not be omitted in the global approach against vitamin D deficiency and skin cancer given its antiproliferative effects, prodifferentiation actions, and inhibitory effects on the migration, invasion, and metastasis of skin cancer [7, 36].

Conclusion

The results of this pilot evaluation suggest that oral, single, high-dose vitamin D supplementation does not improve protection against acute UVB-induced erythema or facilitate its resolution in fair-skinned subjects. The role of oral supplementation of vitamin D in the prevention of skin cancer merits further investigation in order to evaluate the clinical relevance of its beneficial photoprotective in vitro properties.

Disclosure Statement

The authors have no competing interests to declare.

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