Prospective Investigation of 25(OH)D_3 Serum Concentration Following UVB Narrow Band Phototherapy in Patients with Psoriasis and Atopic Dermatitis

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Abstract. *Vitamin D deficiency represents a major health issue. It is a worldwide endemic and is associated with a broad variety of severe diseases. The skin is a key tissue for the human body's vitamin D endocrine system. It represents a target tissue for biologically active vitamin D metabolites. Approximately 90% of the human body's requirements of vitamin D have to be synthesised in the skin by the action of UVB-radiation. However, individual factors that influence a person's cutaneous synthesis of vitamin D are still not well understood. In our present prospective study we investigated the effect of UVB narrow band (UVBnb, 311 nm) and PUVA phototherapy on 25(OH)D_3 serum concentration, in patients with psoriasis, atopic dermatitis and a few cases with other dermatoses (n=41). We found that two weeks of UVBnb treatment resulted in an increase of 25(OH)D_3 serum concentration from 11.4 to 20.5 ng/ml ($p<0.001$), while in contrast PUVA-treatment did not significantly alter vitamin D status. These findings question the hypothesis of a relevant vitamin D metabolizing effect of UVA. Psoriasis patients showed a trend for a stronger increase in 25(OH)D_3 serum levels following UVBnb compared to patients with atopic dermatitis. Patients with relatively low baseline serum 25(OH)D_3 concentrations had a stronger increase in 25(OH)D_3 concentrations compared to patients with relatively high 25(OH)D serum concentrations. In general patients with skin types (Fitzpatrick) I and II (median=14.3 ng/ml) had a higher baseline of 25(OH)D_3 serum concentration compared to patients with skin types III (median=11.2 ng/ml) or IV-V (median=12.3 ng/ml), although these differences were not statistically significant ($p=0.106$). Baseline 25(OH)D_3 serum concentrations were correlated with presence of genetic variants (SNPs of VDR, CYP2R1, VDBP/GC) that influence vitamin D status, and with other individual factors such as body mass index, age and gender. We also investigated the effect of phototherapy on blood pressure and a variety of laboratory parameters such as CRP, HbA1c, LDL, HDL, triglycerides and cholesterol. In conclusion, our pilot study shows that UVBnb phototherapy efficiently increases 25(OH)D_3 serum concentration and reports interesting preliminary findings that have to be re-evaluated in larger follow-up studies.*

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Vitamin D deficiency represents a major health issue (1). It is a worldwide endemic and associated with a broad variety of severe diseases (1). The skin is a key tissue for the human body's vitamin D endocrine system (1-3). It represents a target tissue for biologically-active vitamin D metabolites (1-3). Approximately 90% of the human body's requirements of vitamin D have to be synthesized in the skin by the action of UVB-radiation (1-3). However, the factors that influence the cutaneous synthesis of vitamin D are still not well understood (4-14). In this prospective pilot study we investigated the effect of UVB narrow-band (UVBnb, 311 nm) and PUVA phototherapy, two well established phototherapy regimens (14-19), on 25(OH)D_3 serum concentration in patients with psoriasis, atopic dermatitis and a few cases with other dermatoses (n=41).

Materials and Methods

Study population. The study population consisted of 41 patients with different types of skin diseases (psoriasis, n=19; atopic dermatitis, n=5; other diagnoses including cutaneous T-cell lymphoma, lichen ruber, eczema, n=17), that were treated with phototherapy (nbUVB/311 nm, 5x/week; or cream/bath PUVA) following standard procedures (14-18, at the Department of Dermatology of the Saarland University Hospital.

Venous blood samples were obtained for biochemical analyses, immediately processed and separated. The serum samples were aliquoted and stored at –40˚C. All blood samples were colected between October and April to minimize seasonal variations. 25-Hydroxyvitamin D serum levels [25(OH)D] and other laboratory parameters of interest (CRP, HbA1c, LDL, HDL, triglycerides and cholesterol) were analyzed at the Department of Clinical Chemistry and Laboratory Medicine (Saarland University Hospital Homburg) using the LIAISON 25-OH Vitamin D-Assay (DiaSorin, Dietzenbach, Germany) and other well-accepted assays, respectively. Using a self-administered questionnaire, study subjects were asked to provide additional information related to skin type, BMI, use of solarium and sunscreens, and lifestyle. This study was approved by the ethics committee of the "Ärztekammer des Saarlands" and was conducted in accordance with the "Declaration of Helsinki." Written informed consent was obtained from all participants.

Analysis of genetic variants (SNPs) of vitamin D receptor (VDR), vitamin D binding protein (VDBP, GC), and CYP2R1. Using pre-designed genotyping assays, the following genetic variants (SNPs) were analyzed, as published previously (20): rs731236 (*VDR*), rs7975232 (*VDR*), rs2107301 (*VDR*), rs11574143 (*VDR*), rs757343 (*VDR*), rs2060793 (*CYP2R1*), rs4588 (*VDBP*), rs2282679 (*VDBP*), and rs7041 (*VDBP*). The SNP rs1155563 (VDBP) was analyzed using a Custom Taqman SNP Genotyping Assay. For control purposes, a minimum of 10 percent of all samples were analyzed twice. No deviations were detected. All ready-to-use TaqMan SNP Genotyping assays (40x concentrated) and TaqMan Genotyping Mastermix (2x concentrated) were purchased from Applied Biosystems (Foster City, CA, USA) and applied according to the manufacturer's instructions. PCR amplification was carried out in 384 well plates (Frame Star 384, purple frame, Thermo Fisher, Waltham, MA, USA) in an Eppendorf 384-well Mastercycler (Eppendorf, Hamburg, Germany). Reactions were performed in a total volume of 5 μl including 1 μl genomic DNA (10 ng/μl). Genotyping was done using a Taqman 7200 HT (Applied Biosystems).

Statistical analyses. We calculated the following values of 25(OH)D serum concentration: mean, median, minimum, maximum and standard deviation (SD). Statistical analyses were performed using standard procedures including analysis of variance (ANOVA), Student's *t*-test, or Mann-Whitney-*U*-Test (SPSS 20, IBM Co., Armonk, USA). Where applicable, non-parametric tests were chosen because of an uneven distribution of 25(OH)D serum concentration in the analyzed cohort.

Results

Comparison of baseline 25(OH)D_3 serum concentration in individuals with different skin types. Individuals with skin types (Fitzpatrick) I and II (median=14.3 ng/ml) had a higher baseline 25(OH)D_3 serum concentration compared to patients with skin types III (median=11.2 ng/ml) or IV-V (median=12.3 ng/ml), although these differences were statistically (ANOVA) not significant (p=0.424) (Table I).

Association of baseline 25(OH)D_3 serum concentration with age, gender, type of skin disease, BMI and lifestyle. Using ANOVA, no statistically significant association of baseline 25(OH)D_3 serum concentration with age, gender, type of skin disease, BMI, or several lifestyle-related factors (solarium use, sunscreen use, fish meals) was found (Table I). Sub-group analysis revealed a statistically significant (p=0.049) higher baseline 25(OH)D_3 serum concentration in individuals that used sunscreens regularly (median=16.8 ng/ml) compared to never using sunscreens (median=6.2 ng/ml) (Table I).

Table I. *Relevance of various factors for baseline 25(OH)D3 serum concentration*.

Variable	n	Baseline 25(OH)D_3 serum concentration		*p*-Value
		Mean (SD) [ng/ml]	Median [ng/ml]	
Gender				0.699
Male	16	11.56 (10.14)	8.90	
Female	25	12.72 (8.705)	10.50	
Skin disease				0.163
Atopic dermatitis	5	14.34 (8.86)	13.3	
Psoriasis	19	11.49 (11.09)	8.6	
Other skin diseases	17	12.53 (7.13)	11.4	
Skin-type (Fitzpatrick)				0.424
I-II	7	14.46 (8.1)	14.3	
III	12	10.10 (8.36)	11.15	
IV-VI	11	14.72 (10.4)	10.3	
Fish meals				0.163
≥ 1x/week	2	6.20 (0.283)	6.20	
<1x/week	27	13.74 (9.07)	11.50	
Solarium use				0.150
Regular	2	24.45 (6.15)	24.45	
Rarely	7	13.45 (10.40)	8.80	
Never	21	11.46 (8.34)	10.90	
Sunscreen use				0.052
Regular	9	17.77 (12.48)	16.80	(0.049 for
Rarely	15	12.41 (6.29)	11.40	regular
Never	6	6.38 (4.91)	6.20	*vs*. never)
Age	50	48.52 (16.24)	48	0.823
BMI	50	27.0 (6.21)	25.15	0.109

Association of baseline 25(OH)D_3 serum concentration with genetic variants (SNPs) of VDR, CYP2R1, VDBP/GC. When baseline 25(OH)D_3 serum concentrations were correlated with the presence of several genetic variants (SNPs) of VDR, VDBP/GC, and CYP2R1, that are candidates to influence vitamin D status, statistically significant associations were found for rs4588 (VDBP, p=0.028), rs1155563 (VDBP, p=0.040) and rs2282679 (VDBP, p=0.049) (Table II).

UVBnb phototherapy increases 25(OH)D_3 serum concentration. Two weeks of UVBnb treatment resulted in an increase of 25(OH)D_3 serum concentration from 11.4 to 20.5 ng/ml (p<0.001), while in contrast PUVA-treatment did not significantly alter vitamin D status (Table III). These findings

Table II. *Relevance of various genetic variants (SNPs) for baseline 25(OH)D_3 serum concentration.*

				Baseline 25(OH)D_3 serum concentration			
Gene- SNP	DNA-Genotype	Assay-Genotype	n [%]	Mean	SD	Median	*p*-Value
VDBP	C/A	G/T	20 [52.6]	11.27	8.7	9.9	0.028
rs4588	C/C	G/G	17 [44.7]	14.81	9.9	12.3	
	A/A	T/T	1 [2.6]	1.0	0	1	
VDBP	T/G	A/C	21 [55.3]	11.6	8.0	10.9	0.855
rs7041	T/T	A/A	5 [13.2]	13.9	13.7	11.0	
	G/G	C/C	12 [31.6]	13.8	10.2	11.0	
VDBP	C/T	G/A	17 [44.7]	9.43	7.4	6.4	0.040
rs1155563	T/T	A/A	21 [55.3]	15.1	10.1	11.5	
	C/C	G/G	0	-	-	-	-
VDBP	C/A	G/T	20 [52.6]	12.4	9.2	10.6	0.049
rs2282679	C/C	G/G	1 [2.6]	1.0	-	1.0	
	A/A	T/T	17 [44.7]	13.4	9.5	11.5	
VDR	A/C	A/C	15 [39.5]	11.8	10.2	8.8	0.667
rs7975232	A/A	A/A	16 [42.1]	13.6	9.2	12.4	
	C/C	C/C	7 [18.4]	11.9	9.0	11.4	
VDR	T/C	A/G	13 [33.3]	12.8	10.3	9.5	0.814
rs731236	T/T	A/A	14 [36.8]	11.0	7.4	10.85	
	C/C	G/G	11 [28.9]	14.3	10.9	12.3	
VDR	G/A	C/T	7 [18.4]	10.8	6.6	10.3	0.870
rs757343	G/G	C/C	29 [76.3]	13.1	10.2	10.5	
	A/A	T/T	2 [5.2]	12.0	0.6	11.95	
VDR	T/C	A/G	13 [34.2]	13.6	9.4	11.4	0.658
rs2107301	T/T	A/A	4 [10.5]	8.8	5.3	10.9	
	C/C	G/G	21 [55.3]	12.7	10.1	10.5	
VDR	G/A	C/T	8 [21.1]	12.3	4.7	12.0	0.431
rs11574143	G/G	C/C	30 [78.9]	12.7	10.3	10.25	
	A/A	T/T	0	-	-	-	-
CYP2R1	A/G	A/G	24 [63.2]	13.5	10.8	11.45	0.915
rs2060793	A/A	A/A	3 [7.9]	9.3	3.8	10.5	
	G/G	G/G	11 [28.9]	11.5	6.8	10.3	

question the hypothesis of a relevant vitamin D metabolizing effect of UVA. Psoriasis patients showed a trend for a stronger increase in 25(OH)D_3 serum levels following UVBnb compared to patients with atopic dermatitis. Patients with relatively low baseline serum 25(OH)D_3 concentrations had a stronger increase in 25(OH)D_3 concentrations compared to patients with relatively high 25(OH)D serum concentrations. UVBnb and PUVA-treatment improved the dermatological conditions.

Effect of phototherapy on blood pressure and on selected laboratory parameters (CRP, HbA1c, LDL, HDL, triglycerides and cholesterol). When we investigated the effect of phototherapy on blood pressure and a variety of laboratory parameters such as c-reactive protein (CRP), hemoglobin A1c (HbA1c), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides and cholesterol, only for LDL/HDL index a statistically significant effect was found (Table IV).

Discussion

In conclusion, this pilot study demonstrates as a major finding that UVBnb phototherapy efficiently induces cutaneous vitamin D synthesis. In contrast, PUVA treatment

Table III. *Effect of phototherapy on 25(OH)D_3 serum concentration.*

	nbUVB 25(OH)D_3 conc.[ng/ml]	n	PUVA 25(OH)D_3 conc. [ng/ml]	n	*p*-Value PUVA *vs.* nbUVB
Baseline	11.4 (5.3-17.2)	24	10 (6.7-13.3)	17	0.832
1 Week	13.5 (6.8-17.4)	31	9.5 (6.5-13.8)	15	0.206
2 Weeks	20.15 (16.1-28.9)	22	10.1 (7.1-14.9)	11	<0.001

	25(OH)D_3 serum concentration [ng/ml]			*p*-Value		
UV-Therapy	Baseline (0)	1 Week	2 Weeks	0 *vs.* 1 week	0 *vs.* 2 weeks	1 week *vs.* 2 weeks
nbUVB	11.4 (5.3-17.2)	13.5 (6.8-17.4)	20.15 (16.1-28.9)	0.116	<0.001	0.002
PUVA	10 (6.7-13.3)	9.5 (6.5-13.8)	10.1 (7.1-14.9)	0.184	0.887	0.205

Median (with 25-75 percentile) and *p*-value (Mann-Whitney-*U*-test) are shown at different time points.

Table IV. *Effect of nbUVB and PUVA phototherapy on selected clinical and laboratory parameters. Median (with 25.-75. Percentile) and p-value are shown at different time points.*

A Baseline	nbUVB	n	PUVA	n	*p*-Value
Cumulative dose [J/cm^2]	0	35	0	20	
RR sys [mmHg]	130 (118-144)	35	145 (120-154)	19	
RR dias [mmHg]	73 (65-84)	35	81 (73-95)	19	
CRP [ng/l]	2.4 (1.1-4.7)	33	3.1 (1.2-7.0)	21	0.770
HbA1c mM	36 (31-43)	25	36 (31-44)	20	0.963
HbA1c %	5.4 (5.0-6.1)	25	5.4 (5.0-6.2)	20	
HDL-Cholesterol [mg/dl]	57 (40-68)	27	59 (38-68)	21	0.560
LDL- Cholesterol [mg/dl]	114 (93-150)	25	128 (89-146)	16	0.925
Triglycerides [mg/dl]	136 (102-193)	34	137 (78-233)	21	0.795
Cholesterol total [mg/dl]	207 (172-230)	34	190 (165-233)	21	0.716
LDL/ HDL Index	2.13 (1.33-3.50)	25	2.67 (1.51-3.67)	16	0.541
1 Week UV-Therapy					
Cumulative dose [J/cm^2]	0.90 (0.60-1.35)	35	2.75 (1.50-3.50)	20	
RR sys [mmHg]	125 (115-135)	35	130 (122-143)	17	
RR dias [mmHg]	77 (67-83)	35	78 (69-85)	17	
CRP [ng/l]	1.6 (0.7-3.6)	25	1.5 (0.1-3.7)	10	0.659
HbA1c mM	32 (29-35)	17	38 (29-44)	8	0.114
HbA1c %	5.3 (4.6-5.6)	17	5.4 (4.6-6.2)	8	
HDL-Cholesterol [mg/dl]	56 (40-69)	23	51 (40-61)	11	0.726
LDL- Cholesterol [mg/dl]	110 (92-151)	23	126 (99-162)	11	0.554
Triglycerides [mg/dl]	173 (125-223)	26	162 (82-211)	11	0.654
Cholesterol total [mg/dl]	204 (190-220)	26	208 (173-252)	11	0.921
LDL/ HDL Index	1.88 (1.34-4.20)	23	2.71 (1.55-4.31)	11	0.904
2 Weeks UV-Therapy					
Cumulative dose [J/cm^2]	1.9 (1.4-2.9)	22	6.0 (4.25-7.75)	13	
RR sys	130 (117-140)	20	128 (119-136)	13	
RR dias	81 (72-90)	20	80 (71-85)	13	
CRP	3.0 (1.4-6.8)	13	2.0 (0.6-4.9)	7	0.662
HbA1c mM	38 (32-41)	11	35 (31-48)	6	0.880
HbA1c %	5.4 (4.8-5.9)	11	5.4 (5.1-6.5)	6	
HDL-Cholesterol [mg/dl]	49 (41-79)	15	43 (28-60)	7	0.231
LDL- Cholesterol [mg/dl]	126 (113-142)	15	145 (91-160)	7	0.526
Triglycerides	146 (85-175)	15	207 (127-464)	7	0.098
Cholesterol total	217 (184-234)	15	224 (206-248)	7	0.397
LDL/ HDL Index	2.20 (1.56-3.58)	15	3.5 (2.47-3.95)	7	0.169

Table IV. *continued*

Table IV. *continued*

nbUVB	Baseline (0)	1 Week (1)	2 Weeks (2)	*p*-Values 0-1	0-2	1-2
Cumulative dose [J/cm^2]	0	0.90 (0.60-1.35)	1.9 (1.4-2.9)			
RR sys [mmHg]	130 (118-144)	125 (115-135)	130 (117-140)	0.253	0.341	0.830
RR dias [mmHg]	73 (65-84)	77 (67-83)	81 (72-90)	0.647	0.301	0.485
CRP [ng/l]	2.4 (1.1-4.7)	1.6 (0.7-3.6)	3.0 (1.4-6.8)	0.928	0.459	0.758
HbA1c [mM]	36 (31-43)	32 (29-35)	38 (32-41)	0.104	0.772	0.421
HbA1c [%]	5.4 (5.0-6.1)	5.3 (4.6-5.6)	5.4 (4.8-5.9)			
HDL-Cholesterol [mg/dl]	57 (40-68)	56 (40-69)	49 (41-79)	0.332	0.259	0.457
LDL- Cholesterol [mg/dl]	114 (93-150)	110 (92-151)	126 (113-142)	0.112	0.850	0.023
Triglycerides [mg/dl]	136 (102-193)	173 (125-223)	146 (85-175)	0.094	0.795	0.358
Cholesterol, total [mg/dl]	207 (172-230)	204 (190-220)	217 (184-234)	0.647	0.993	0.143
LDL/ HDL Index	2.13 (1.33-3.50)	1.88 (1.34-4.20)	2.20 (1.56-3.58)		0.030	0.421
PUVA						
Cumulative dose [J/cm^2]	0	2.75 (1.50-3.50)	6.0 (4.25-7.75)			
RR sys [mmHg]	145 (120-154)	130 (122-143)	128 (119-136)	0.272	0.021	0.139
RR dias [mmHg]	81 (73-95)	78 (69-85)	80 (71-85)	0.272	0.142	0.726
CRP [ng/l]	3.1 (1.2-7.0)	1.5 (0.1-3.7)	2.0 (0.6-4.9)	0.170	0.615	0.353
HbA1c [mM]	36 (31-44)	38 (29-44)	35 (31-48)	0.752	0.654	
HbA1c [%]	5.4 (5.0-6.2)	5.4 (4.6-6.2)	5.4 (5.1-6.5)			
HDL-Cholesterol [mg/dl]	59 (38-68)	51 (40-61)	43 (28-60)	0.220	0.233	0.500
LDL- Cholesterol [mg/dl]	128 (89-146)	126 (99-162)	145 (91-160)	0.543	0.104	0.622
Triglycerides [mg/dl]	137 (78-233)	162 (82-211)	207 (127-464)	0.789	0.224	0.818
Cholesterol, total [mg/dl]	190 (165-233)	208 (173-252)	224 (206-248)	0.969	0.068	0.739
LDL/ HDL Index	2.67 (1.51-3.67)	2.71 (1.55-4.31)	3.5 (2.47-3.95)		0.196	0.562

did not significantly alter vitamin D status, questioning the hypothesis of a relevant vitamin D metabolizing effect of UVA. Two weeks of UVBnb treatment resulted in a statistically significant and strong increase of 25(OH)D_3 serum concentration from 11.4 to 20.5 ng/ml ($p<0.001$). Although the number of participants in our cohort was relatively low, we next tried to identify individual factors that may influence baseline vitamin D status and/or 25(OH)D_3 serum concentration following UV phototherapy and that could be analyzed in larger, specifically designed follow-up studies. Interestingly, psoriasis patients showed a trend for a stronger increase in 25(OH)D_3 serum levels following UVBnb compared to patients with atopic dermatitis. In agreement with previous reports (5), individuals with relatively low baseline serum 25(OH)D_3 concentrations had a stronger increase in 25(OH)D_3 concentrations compared to patients with relatively high 25(OH)D serum concentrations.

At present, the relevance of skin type/skin pigmentation for a person's vitamin D status is controversially discussed in the literature (4, 5, 8, 10, 11). Interestingly, individuals with skin types (Fitzpatrick) I and II (median 14.3 ng/ml) had in our pilot study a higher baseline 25(OH)D_3 serum concentration compared to patients with skin types III (median=11.2 ng/ml) or IV-V (median=12.3 ng/ml), although these differences were not statistically (ANOVA) significant ($p=0.424$). In conclusion, these findings support the concept that skin types I, II have a higher efficacy in synthesizing vitamin D following UVB exposure compared to darker skin. Using ANOVA, no statistically significant association of baseline 25(OH)D_3 serum concentration with age, gender, type of skin disease, BMI, or several lifestyle-related factors (solarium use, sunscreen use, fish meals) was found. Sub-group analysis revealed a statistically significant ($p=0.049$) higher baseline 25(OH)D_3 serum concentration in individuals that used sunscreens regularly (median=16.8 ng/ml) compared to never using sunscreens (median=6.2 ng/ml). It can be speculated that sunscreen use represents an indicator of outdoor activities and high UV exposure, that cause the relatively high baseline 25(OH)D_3 serum concentration. Moreover, considering the low number of participants, our findings are well in line with previous studies that report an association of age, BMI and solarium use with vitamin D status (12, 13).

When baseline 25(OH)D_3 serum concentrations were correlated with the presence of several genetic variants (SNPs of VDR, CYP2R1, VDBP/GC) that influence vitamin D status, statistically significant associations were found for rs4588 (VDBP, $p=0.028$), rs1155563 (VDBP, $p=0.040$) and rs2282679 (VDBP, $p=0.049$). These findings highlight the importance of genetic variants of VDBP/GC for a person`s individual vitamin D status (21).

When we investigated the effect of phototherapy on blood pressure and a variety of laboratory parameters such as CRP, HbA1c, LDL, HDL, triglycerides and cholesterol, only for the LDL/HDL index a statistically significant effect was found. However, considering the low number of participants and the short study period, our findings are well in line with previous studies that report an association of UV exposure and/or vitamin D status with diabetes, lipid profile, and CRP (22-25). In conclusion, our pilot study shows that UVBnb phototherapy efficiently increases $25(OH)D_3$ serum concentration and reports interesting preliminary findings that have to be re-evaluated. Due to the relatively low number of participants and the short study period, the significance of our findings needs to be confirmed in larger follow-up studies, that should also consider skin type and related genetic variants (26).

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