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Accepted author version posted online: 22 Feb 2018.
Published online: 22 Feb 2018.

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Serum 25-hydroxyvitamin D levels in patients with skin diseases including psoriasis, infections, and atopic dermatitis

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ABSTRACT

The pathogenetic role of vitamin D as well as its clinical correlation in inflammatory skin diseases is still uncertain. This study aimed to compare serum levels of 25(OH) vitamin D (calcidiol) in outpatients suffering from different skin diseases using the same laboratory method in one study. In routine serum samples of 1,532 patients from the previous 12 months we identified retrospectively 180 (mean age 49.4 years, 80 female, 100 male) and 205 (mean age 36.3 years, 116 female, 89 male) patients with psoriasis (PSO) and atopic dermatitis (AD), respectively. Clinical disease activity and quality of life was evaluated using Physicians Global Assessment Scores (PGA), Dermatology Life Quality Index (DLQI), and a Visual Analog Scale for pruritus in AD, respectively. The median 25(OH)D serum level of all patients (22.97 ng/mL, range 2.61–96.0, n = 1,461) was significantly lower in comparison to healthy controls (41.6 ng/mL, range 16.9–77.57, $p < 0.0001$, n = 71). In PSO and AD we measured 21.05 ng/mL (44% < 20 ng/mL) and 22.7 ng/mL (39% < 20 ng/mL), respectively (p = 0.152). Among all subgroups, patients with severe acute or chronic infectious skin diseases had the lowest median 25(OH)D serum levels (17.11 ng/mL, n = 94, 66% <20 ng/mL, $p < 0,001$ vs. AD, $p = 0,007$ vs. PSO). For PSO and AD there was no significant correlation between 25(OH)D levels and PGA scores and DLQI values, respectively, or the extent of pruritus in AD. 25(OH)D serum levels in inflammatory skin diseases might correlate more with the type of disease and the degree of inflammation than with clinical activity itself.

Introduction

Numerous recent publications have demonstrated that the biologically active form of vitamin D [1,25-dihydroxyvitamin D3;1,25(OH)2D3] can influence immune function as well as differentiation and growth of many cell types in addition to its well described central role in calcium/phosphate homeostasis.[1] There is increasing evidence that vitamin D modulates responses of the innate and adaptive immune system resulting in inhibition of inflammation and enhancement of defense mechanisms.[2] Epidemiological studies have revealed an association between vitamin D status and numerous chronic diseases including cardiovascular diseases, diabetes mellitus, metabolic syndrome, certain malign tumours (e.g. breast, colon, prostate), diseases of the brain (multiple sclerosis, schizophrenia, depression),

infections (upper respiratory tract, tuberculosis), autoimmunity and allergy.[1] However, its pathogenetic role as well as its clinical correlation in different skin diseases is still uncertain.[3,4]

Recently it was reported that low serum levels of 25-hydroxyvitamin D [25(OH)D] were inversely correlated with the clinical activity of inflammatory skin diseases, such as atopic dermatitis, suggesting that a person's vitamin D status may have some modulatory function on inflammatory skin diseases.[3] It is also known that 1,25(OH)2D3 and its active analogues are effective for the treatment of the autoimmune disease psoriasis. However, due to large variations in study design and clinical parameters to date the contradictory results do not yet allow a clear recommendation

of vitamin D supplementation for patients with chronic skin diseases.

Given the positive effects of UVB treatment in many chronic diseases which are not restricted to the skin and the positive effects for most inflammatory skin diseases following direct sun exposure during the summer at least a partial role for vitamin D for improvement of the degree of inflammation is widely accepted.[5]

There is also evidence that a vitamin D deficit has an impact on mortality regardless of the risk of bone fracture.[6,7] Since patients with severe psoriasis may die prematurely due to a significant increased risk for cardiovascular disease,[8,9] a further evaluation of the role of vitamin D status might be of relevance for both prevention and treatment. Coimbra et al. had reported that giving very high doses of vitamin D3 to patients with psoriasis, who were on a low calcium diet, was effective in treating this autoimmune disorder.[10]

Against the background of the growing evidence on the complex role of vitamin D for extraskeletal regulatory functions with putative impact for dermatology, controlled studies focusing on the significance of vitamin D status and how they relate to skin diseases associated with inflammation or autoimmune activity. Here we report a retrospective analysis of routine serum samples comparing 25(OH)D levels of 1,532 patients with different skin diseases and allergic conditions at their first appointment without prior vitamin D supplementation.

Patients and methods

This study aimed to compare serum levels of 25(OH)D [calcidiol] in outpatients suffering from different skin diseases and allergies. Where applicable clinical activity and quality of life parameters were measured and compared. All patients had given their informed consent to allow routine blood testing to analyse the cause of their disease. We analysed all samples from all patients who had a clinical indication for vitamin D measurement as a routine diagnostic procedure. We retrospectively examined the routine diagnostic data for a twelve months period (July 2015-June 2016). This included patients of either sex (age 3–87 y) on their first visit to the clinic for diagnosis of their skin disease. Patients who had used vitamin D supplementation within the previous 12 months were excluded from analysis. Samples were also excluded if biotin-containing drugs had been taken within the previous

12 months, due to a known biochemical interaction with the 25(OH)D antibody assays.

The following subgroups were differentiated:

- Subgroup **a** (n = 1,461, age range 3–87 years, mean age 43.5 years, 56.8 % female, 43.2% male) contained serum samples from patients with clear diagnoses of skin diseases or allergies (e.g. allergic rhinitis, allergic skin reactions due to drugs or insects stings). Among this group a further classification into specific diagnosis was performed.
- Subgroup **b** (n = 71, age range 8–83 years, mean age 49.2 years, 75.1 % female, 23.9% male) consisted of serum samples from patients without any inflammatory, infectious or allergic disease. These patients had neither any chronic illnesses nor drug intake. Since our centre offers a routine check-up for all age groups in terms of preventive medicine this subgroup can be defined as "healthy controls". As this was a retrospective study, the control group was not matched socio-economically to the patient group. We have no structured documentation on lifestyle or outdoor habits of both groups.

Clinical evaluation for atopic dermatitis and psoriasis was performed using Physicians Global Assessment Scores (PGA score for atopic dermatitis: 0 = clear, no inflammatory signs of atopic dermatitis, 5 = erythroderma,[11] PGA score for psoriasis, ranging from 0 = clear, no signs for psoriasis, post inflammatory hyperpigmentation may be present to 4 = severe disease, bright to deep dark coloration, severe thickening with hard edges, severe scaling[12]). Quality of life was evaluated using the Dermatology Life Quality Index[13] (DLQI). In atopic dermatitis intensity of pruritus was assessed by patients via a visual analogue scale (VAS 0 = no pruritus, 10 = extreme pruritus). PGA, DLQI, and VAS for pruritus have been implemented as routine parameter for all patients almost 10 years ago.

Blood samples for analysis were collected for routine laboratory tests and were immediately processed. Serum for 25(OH)D analysis was allowed to coagulate for 20 min, centrifuged (2,000 g for 10 min), and frozen at $-80°C$ until further assessment.

We used the 25-hydroxycholecalciferol test (Cat. No. HYE-5334, DRG Instruments GmbH, Marburg, Germany).[14]

In brief, this is a competitive solid phase enzyme-linked immunosorbent assay (ELISA) on the HYBRID

XL analyser (DRG Instruments GmbH, Marburg, Germany). The assay is based on competition of the endogenous form of 25(OH)D with the 25(OH) D-biotin conjugate for binding to the well-coated vitamin D binding protein. This assay detected 25(OH)D3 with a specificity of 99%. Sensitivity was evaluated according to guideline of Clinical & Laboratory Standards Institute, Wayne, PA, USA: the limit of blank is 2.3 ng/mL, the limit of detection is 4.6 ng/mL, the limit of quantification is 7.3 ng/mL. The range of assay is between 4.6 ng/mL and 130 ng/mL.

Statistical analyses were performed using multiple linear regression analysis according to Spearman (excel 2013, stata 13). Differences between groups were analysed using the Kruskal-Wallis nonparametric ANOVA with Dunn's post-hoc test.

Results

We performed a retrospective analysis of routine serum samples of 1,532 patients (age range 3–87 years, mean age 43.8 years, 58% female, 42% male) at their first appointment in our centre. The overall median 25(OH)D level of all samples was 23.52 ng/mL (range 2.63– 96.0).

The median 25(OH)D value of **subgroup a** (n = 1,461) was 22.97 ng/mL (range 2.61 –96.0). The median 25(OH)D value of **subgroup b** (n = 71) was 41.6 ng/mL (range 16.9–77.57) $p < 0.0001$ vs. subgroup a).

Figure 1a shows a median of 25(OH)D levels below 30 ng/mL for all age ranges of patients vs. healthy controls (Fig. 1b). Although it might have been expected that vitamin D deficiency was more common among the older population no trend was seen in the patients between 60 and 90 years (n = 317). In babies, infants and adolescents with significant skin diseases and/or allergies median values were below 30 ng/mL.

In Table 1 the distribution of the different diagnostic clusters of **subgroup a** with the corresponding mean values of 25(OH)D level is listed. Inflammatory skin diseases (such as atopic dermatitis, psoriasis, non-atopic eczemas, hand eczema), vitiligo as an autoimmune disease, diffuse alopecia, infections, acne and rosacea dominate the size of the subpopulations due to the specialization of our centre. Among chronic inflammatory skin diseases patients suffering from
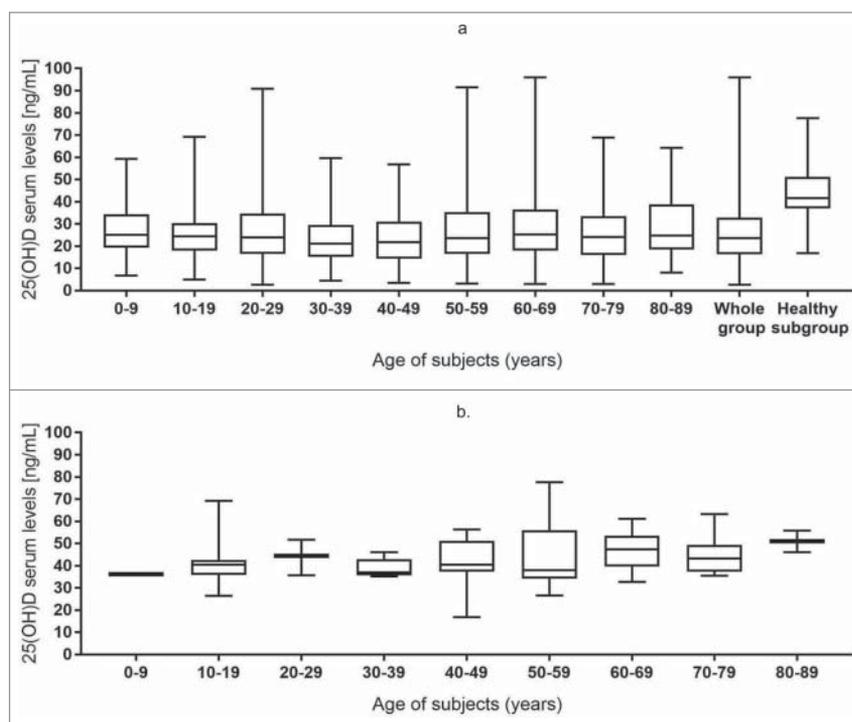
**Figure 1.** Scatter Plot of Serum 25(OH)D Levels Relative to Patient Age of Study Population (Fig. 1a) and Healthy Subgroup (Fig. 1b). Data are shown as box and whisker plots, whereby the box extends from the 25th percentile to the 75th percentile, with a horizontal line at the median (50th percentile) and the whiskers extend down to the smallest value and up to the largest.

Table 1. Distribution of diagnoses sorted by the size of the subpopulation in descending order.

Diseases	n	M	F	Mean 25(OH)D level [ng/mL]	Standard Deviation	25(OH)D level % ≤ 20 ng/mL	Mean age (y)
Atopic dermatitis	205	89	116	24.2	11.5	39.0%	36.3
Psoriasis vulgaris	180	100	80	22.6	10.7	43.9%	49.4
Non-atopic eczema	133	67	66	25.0	12.7	38.3%	47.2
Vitiligo	113	57	56	24.5	10.9	41.2%	38.2
Male pattern baldness	111	22	89	32.1	16.9	20.7%	46.6
Severe acute and/or chronic infectious diseases of the skin[1]	94	48	46	19.2	9.5	66.0%	44.3
Acne vulgaris	86	31	55	27.4	14.5	27.9%	21.2
Others[2]	80	33	47	27.1	9.9	26.3%	48.2
Rosacea subtype II (papulopustular rosacea)	70	24	46	25.6	12.3	30.0%	53.7
Allergic rhinitis	69	33	36	27.0	12.6	36.2%	35.7
Hand eczema	68	24	44	25.3	12.7	38.2%	44.9
Chronic urticarial	42	19	23	25.4	13.0	33.3%	44.8
Malign tumour of the skin	28	17	11	21.4	12.1	55.2%	70.2
Acne tarda	23	3	20	26.8	14.7	39.1%	40.1
Pruritus	23	14	9	23.5	12.2	52.2%	65.7
Perioral dermatitis	22	0	22	26.6	17.5	45.5%	46.5
Food allergy	19	6	13	20.8	9.8	52.6%	38.2
Rosacea subtype I (erythematotelangiectatic rosacea)	18	6	12	32.5	13.9	5.6%	49.3
Severe allergic reaction	16	8	8	18.4	8.9	62.5%	50.9
Alopecia areata	15	6	9	21.3	12.1	46.7%	38.8
Acne conglobata	11	5	6	21.0	5.3	36.4%	20.1
Prurigo	11	7	4	21.6	9.3	54.5%	57.5
Lichen planus	10	5	5	31.2	24.1	40.0%	63.1
Allergic Asthma	6	3	3	17.4	12.2	50.0%	45.2
Burn out syndrome	5	5	0	19.0	9.4	40.0%	43.2
Rosacea conglobata	2	0	2	14.0	1.7	100.0%	36.5
Subgroup a (total)	1,461	632	829	24.9	12.7	38.9%	43.5
Healthy subgroup b	71	17	54	44.1	10.7	1.4%	49.2

[1]severe acute skin infections mean for example zoster. acute abscess. severe impetigo and chronic recurrent skin infections mean for example chronic abscesses. severe chronic folliculitis. severe recalcitrant pityriasis versicolor. etc.
[2]subgroup of inflammatory skin diseases (e.g. granuloma anulare. lupus erythematosis) with smaller numbers of patients.

psoriasis tended to have lower serum 25(OH)D levels in comparison with atopic dermatitis patients but this did not achieve statistical significance ($p = 0.08$, Fig. 2).

All subgroups from the most frequent single diagnoses of the study had significantly different serum 25 (OH)D levels when compared to the healthy controls ($p < 0.001$ Table 2; for statistical reasons the mixed
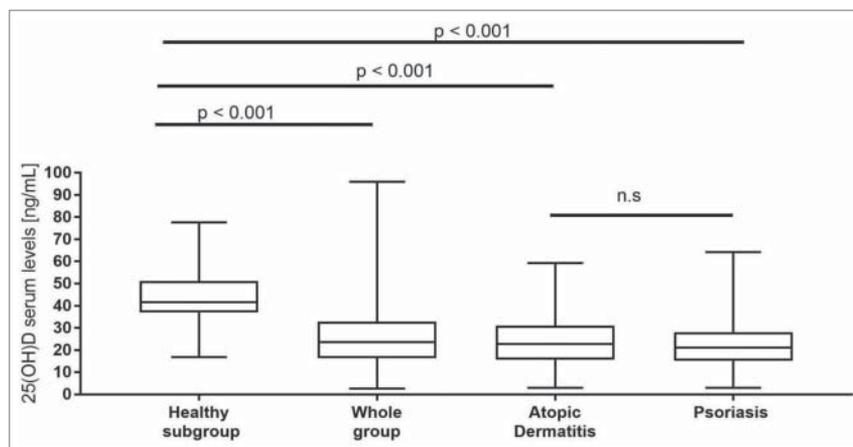
Figure 2. Median Serum 25(OH)D Levels (ng/mL ± SD) in Atopic Dermatitis and Psoriasis in Comparison with the Whole Study Population and Healthy Controls at their First Appointment in our Centre. Data are shown as box and whisker plots, whereby the box extends from the 25th percentile to the 75th percentile, with a horizontal line at the median (50th percentile) and the whiskers extend down to the smallest value and up to the largest. *Note*: As the data are not normally distributed, we performed the non-parametric Kruskal-Wallis test in combination with Dunn's post-hoc test to compare the respective diagnostic groups.

Table 2. Comparative significance calculation of the most frequent diagnoses also in comparison to the healthy subgroup regarding the mean values of 25(OH)D in the serum. Differences between groups were analyzed using the Kruskal-Wallis nonparametric ANOVA with Dunn's post-hoc test. Diagnoses are listed according to the size of the corresponding subgroup.

DUNN'S POST-HOC TEST	AD	Psoriasis vulgaris	Non-atopic eczema	Vitiligo	Male pattern baldness	Infectious diseases	Acne vulgaris	Rosacea subtype II	Allergic rhinitis	Hand eczema	Chronic urticaria	Healthy subgroup
AD		0.080	0.301	0.432	<0.001	<0.001	0.059	0.225	0.081	0.371	0.419	<0.001
Psoriasis vulgaris	0.080		0.039	0.086	<0.001	0.007	0.004	0.039	0.009	0.091	0.149	<0.001
Non-atopic eczema	0.301	0.039		0.383	<0.001	<0.001	0.152	0.376	0.179	0.468	0.448	<0.001
Vitiligo	0.432	0.086	0.383		<0.001	<0.001	0.104	0.289	0.127	0.433	0.467	<0.001
Male pattern baldness	<0.001	<0.001	<0.001	<0.001		<0.001	0.021	0.005	0.025	0.002	0.006	<0.001
Infectious diseases	<0.001	0.007	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001	<0.001	0.004	<0.001
Acne vulgaris	0.059	0.004	0.152	0.104	0.021	<0.001		0.276	0.485	0.171	0.189	<0.001
Rosacea subtype II	0.225	0.039	0.376	0.289	0.005	<0.001	0.276		0.299	0.365	0.360	<0.001
Allergic rhinitis	0.081	0.009	0.179	0.127	0.025	<0.001	0.485	0.299		0.193	0.208	<0.001
Hand eczema	0.371	0.091	0.468	0.433	0.002	<0.001	0.171	0.365	0.193		0.477	<0.001
Chronic urticaria	0.419	0.149	0.448	0.467	0.006	0.004	0.189	0.360	0.208	0.477		<0.001
Healthy subgroup	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	

subgroup of "other" diseases was excluded in this table). Patients with infectious diseases (severe acute {e.g. zoster, acute abscess, severe impetigo} or chronic recurrent skin infections {e.g. chronic abscesses, severe chronic folliculitis, severe recalcitrant pityriasis versicolor}) also had significantly different 25(OH)D levels compared to all other groups. The percentage of patients with 25(OH)D levels below 20 ng/mL was very high (66%, Table 1) in the group with skin infections. There were no other significant differences between the groups for patients with atopic dermatitis, vitiligo, hand eczema or chronic urticaria. Patients with psoriasis vulgaris had significantly different 25 (OH)D levels from those with non-atopic eczema, acne vulgaris, rosacea subtype II and allergic rhinitis. Although patients suffering from severe allergic reactions (following insect bite or severe drug reactions) had a high percentage of samples (62.5%) with 25 (OH)D levels <20 ng/mL, the smaller sample size may account for the lack of significant differences to other groups. Patients with male pattern baldness (n = 111), however, had significantly higher 25(OH) D levels (32.1 ± 16.9 ng/mL) than all other patient groups with more than 40 patients per group (Tables 1 and 2).

Measuring quality of life in dermatological conditions has become an important tool in the evaluation of therapeutic strategies for more than the last two decades, whereby the questionnaire of the DLQI can be considered as well established in all chronic inflammatory skin diseases.[13]

Quality of life impairment was significantly higher in patients suffering from atopic dermatitis than in psoriatic patients (mean DLQI 10.3 ± 0.7 vs. 8.3 ± 0.6, $p = 0.0032$). We found no correlation between quality of life, as measured by the DLQI, and 25(OH)D levels for patients with atopic dermatitis and psoriasis (Table 3), respectively. Similarly, no correlation was observed when data from the other patient groups were analysed (r = 0.022, $p = 0.752$, n = 196, data not shown).

The Physician's Global Assessment Score (PGA) for psoriasis (grade 0 to 4) and for atopic dermatitis (grade 0–5) were used in the present study for the evaluation of the severity of inflammatory skin diseases. Both tools are routinely employed in patient

Table 3. Correlations of diagnosis-specific severance indicators with 25(OH) vitamin D serum level.

	Correlation with Vitamin D serum levels[1]	p-value	n
DLQI Value			
DLQI Atopic dermatitis	0.107	0.27	106
DLQI Psoriasis vulgaris	0.077	0.43	109
VAS Pruritus			
VAS Atopic dermatitis	−0.065	0.42	155
PGA			
PGA Psoriasis vulgaris	0.035	0.70	118
PGA Atopic dermatitis	−0.089	0.27	155

[1] *Note:* Correlations are calculated as Spearman's Rho.

assessment in our centre. For both diseases no significant (inverse) correlations were observed (Table 3).

Manifestation of pruritus in atopic dermatitis can be assessed individually marking a visual analogue scale. Patients in our centre are asked to fill the VAS at the beginning of the consultation. We did not find a significant correlation between the individual serum 25(OH)D values and the extent of pruritus ($p = 0.42$, Table 3).

Discussion

The importance of vitamin D as the "sunshine hormone" for skeletal health is well documented.[1,15] For more than a decade vitamin D has been recognized for reducing risk for non-communicable diseases including cardiovascular diseases, diabetes mellitus, multiple sclerosis, depression, dementia, cancer, autoimmune diseases, allergies, asthma as well as chronic infections, including skin infections.[15-17] Whether the discussed pleiotropic non-skeletal functions of vitamin D are an association or represent a cause-effect-relationship remains unclear. Recent evidence, using Mendelian randomization studies focusing on genetic variants of vitamin D metabolism in order to reduce confounders, has confirmed an increased risk at least for multiple sclerosis in patients with vitamin D deficiency.[18]

The vitamin D receptor (VDR) is expressed in a variety of tissues and immune cells including activated T and B lymphocytes, neutrophils, macrophages and dendritic cells and regulates more than 2000 different genes.[1,19,20] Through VDR the hormone strengthens defense mechanisms against various pathogens and inhibits inflammatory activity of the innate and acquired immune system.[2,19]

By increasing the expression of antimicrobial peptides (e.g., cathelicidin and β-defensins) and positive effects on skin barrier function, vitamin D stabilizes the immunologic integrity of skin functions.[21] Numerous further vitamin D mediated effects on immune and inflammatory responses (e.g. inhibition of Toll-like receptor production of monocytes, enhancement of anti-inflammatory release of IL-10 by mast cells, reduction of the activity of dendritic cells by lipopolysaccharides, inhibition of the release of proinflammatory cytokines from Th1 cells, inhibition of B cell function with reduced release of IgE)[20,22] suggest at least partial involvement of vitamin D in acute or chronic inflammatory or allergic conditions of the skin.

To our knowledge our observations provide the first comparison of serum 25(OH)D levels in a broad spectrum of different skin diseases and allergic conditions using the same laboratory method in one study.

Typical examples of frequent chronic inflammatory diseases in our Centre are psoriasis and atopic dermatitis. Vitamin D is involved in many pathogenetic substeps of inflammatory processes of both diseases.[3] With the knowledge of putative anti-inflammatory/immune-protective effects of vitamin D we expected to measure low or at least lowered levels in chronic inflammation of the skin when compared to healthy persons. The vast majority of the samples tested here over a period of one year had low to very low serum 25(OH)D levels. This reflects our clinical experience during the last five years since the determination of the serum 25(OH)D levels was taken into our routine diagnostic protocol.

The problem of all studies dealing with vitamin D status and its relationship with acute and chronic illnesses are inconsistent standards and recommendations from academic societies and experts about definitions of "insufficiency", "deficiency", "optimal range" and/or on the amount of vitamin D substitution (Table 4). Serum measurements of 25(OH)D were employed to investigate vitamin D status; this is the standard test. However, it must be appreciated that there are alternate pathways for vitamin D activation. Using a variety of analytical methods employing mass spectrometry, a number of other vitamin D

Table 4. Variation of definitions of vitamin D status.

Vitamin D Council Definition[67]	Endocrine Society Definition[26,68]	Institute of Medicine Definition[69]	"Central Europe"[70]
Deficient: 0–40 ng/mL	Deficiency ≤ 20 ng/mL	Risk/deficiency ≤12 ng/mL	Deficient: ≤ 20 ng/mL
Sufficient: 40–80 ng/mL	Insufficiency = 20–29 ng/mL	Risk/insufficiency = 12–20 ng/mL	Suboptimal: 20–30 ng/mL
High normal: 80–100 ng/mL	Preferred range = 40–60 ng/mL	Sufficient = 20 ng/mL	Optimal: 30–50 ng/mL

metabolites have been reported in human serum.[23] These methods are not available in the routine clinical setting. However, for many years we have clinically been following the recommendation of 25(OH)D ranging between 40 and 60 ng/mL being considered to be "optimal" (preferred range) for healthy people.[1,24-26] For inflammatory skin diseases we also have almost no knowledge about the variations of vitamin D metabolism and recognition, such as VDR polymorphisms, vitamin D binding protein polymorphisms, extrarenal 1 alpha hydroxylase activity, micro RNAs etc.[27]

Psoriasis and infections

Topical vitamin D analogues have been used in the treatment of psoriasis for a long time. These analogs have been shown to have not only potent inhibitory effects on hyperproliferative keratinocytes but they also are effective in inducing the terminal differentiation.[28] The anti-inflammatory effect of 1,25(OH)2D3 and its analogs is based on the reduction of (pro) inflammatory cytokines from Th1 and Th17 cells, which are increased in the psoriasis plaques.[3] However, clinically, it has been known for years that a pronounced inflammatory psoriasis cannot be treated adequately with this group of drugs, which might be explained by certain VDR polymorphisms and alterations in psoriatic cells to respond to 1,25(OH)2D3.[29]

Among all the chronic inflammatory skin diseases examined here, the 25(OH)D serum level was lowest with a median of 21.05 ng/mL in patients with plaque psoriasis (psoriasis vulgaris), only in patients with severe acute or chronic recurrent skin infections on the skin did we find significantly lower levels. The median serum value in psoriasis was highly significantly lower in comparison to healthy patients who came to our Centre for a micronutrient check without inflammatory skin diseases, any systemic diseases or drug intake (p <0.0001). 45.1% of patients with psoriasis had a serum 25(OH)D level below 20 ng/mL. Gisondi et al. demonstrated a prevalence of 25(OH)D levels below 20 ng/mL in 145 psoriatic patients of 57.8%.[30] One likely explanation is that psoriatic patients are less likely to expose skin surfaces that have psoriatic lesions to the sun when in a public setting.

In contrast to Kamangar et al., we could not demonstrate a significant (inverse) clinical correlation with respect to clinical activity (PGA, DLQI).[31] This may be due to the heterogeneous incidence of inflammatory comorbidities with possible interactions with vitamin D (e.g., psoriasis arthritis, arteriosclerosis, diabetes mellitus, obesity, non-alcoholic steatohepatitis, inflammatory bowel diseases, depression) in psoriasis patients.[32]

Orgaz-Molina and coworkers also demonstrated significantly lower serum 25(OH)D levels in psoriatic patients than in control subjects even after adjusting for confounding factors in a multivariate analysis (odds ratio 2.89, 95% confidence interval 1.02–7.64, p < 0.03 for vitamin D insufficiency).[33] In their study low 25(OH)D levels were also negatively associated with CRP and BMI which were not examined in this study.[33]

Supportive for an important role of vitamin D in psoriasis might be the recent information, that patients with psoriasis have a significantly elevated risk for fractures (OR for vertebral fractures 2.23).[34] The increasing incidence and prevalence rates of psoriasis with increasing degree of geographic latitude might also indicate a certain role for vitamin D in the pathogenesis of psoriasis.[35]

The suspected autoimmune pathogenesis of psoriasis has recently been proven.[36] Since vitamin D has been suggested to play a central role in regulation of autoimmunity, the significance of 25(OH)D serum levels, the extrarenal production of 1,25(OH)2D resulting in its transcriptional regulation of immune cells, including Th1, Th17, Th2, regulatory T, and natural killer T cells as well as VDR polymorphisms in these diseases has also to be taken into account for psoriatic patients.[37]

Since the 1930s successful oral substitution of vitamin D in psoriasis patients has been demonstrated in different studies.[3] The question arises, however, whether an oral supplementation of vitamin D achieving an "optimal" 25(OH)D serum level of 40–60 ng/mL[38] might be beneficial in psoriasis especially with today's knowledge of increased cardiovascular risk[8,32] and numerous inflammatory comorbidities in psoriasis patients[32] for which – independent of psoriasis – a modulating role of vitamin D has also been discussed in publications of recent years.[16] Therefore re-evaluation of therapeutically supportive vitamin D supplementation is urgently needed.

Perez and co-workers observed an improvement of 88% after oral 1,25(OH)2D3 treatment in 85 patients with psoriasis, with approximately 27% of patients

healing completely, 36% having a moderate and 25% showing a slight improvement without causing hypercalcemia.[39] High oral doses of vitamin D3 (35,000 IU once daily) for six months in association with a low-calcium diet led to a significant improvement of Psoriasis Area and Severity Index (PASI) score in nine patients with psoriasis without significant side effects.[10] Also earlier work has demonstrated drastic improvement following oral administration of vitamin D in severe cases.[40,41] Successful treatment of psoriasis with narrow band UVB at 311 nm in a recent study was attributed to an increased cutaneous synthesis of vitamin D.[42]

However, there is currently no new available data on oral vitamin D supplementation in psoriasis. Prospective randomized controlled clinical trials should be performed with respect to these comorbidities of psoriatic patients to evaluate potential additive or synergistic effects as a viable treatment option.[31,43]

A further interesting aspect concerns unwanted side effects of systemic treatment in psoriasis. Particularly with the use of immunomodulatory and immunosuppressive substances, such as TNFα blockers, there is a higher prevalence for infections, in particular to trigger tuberculosis.[44] Nasopharyngitis is also frequently described in newer classes of substances, such as IL-17A blockers.[45]

In a recent review, Zittermann and co-workers elaborated the preventive aspects of vitamin D supplementation in tuberculosis and acute respiratory effects in a meta-analysis which showed that prophylactic oral vitamin D substitution is even more successful in the investigated disease groups than an additive therapeutic use.[46] With respect to the low 25(OH)D values we measured in our study, we recommend a randomized controlled prospective study with substitution of vitamin D vs. placebo in patients receiving TNFα blockers or other biologic agents in order to reduce the rate of infections as side effects of the treatment.

Our own data showed a severe vitamin D deficiency in severe acute or chronic recurrent skin infections. The median 25(OH)D level of this subgroup (n = 94) was lowest in comparison with the ten most frequent other subgroups (17.11 ng/mL).

These findings might confirm clinically the important immunological control function of vitamin D for the skin. In addition to pluripotent effects on dendritic cells and T cells of acquired immune functions, an increase of innate epithelial defense mechanisms of the epithelial surfaces against microorganisms by increasing antimicrobial peptides and enhancement of the skin barrier appears to play a central role for the anti-infective effects of vitamin D.[47] This was not a focus of this work, but it provides very important implications for the treatment of patients suffering from such diseases (see also next passage).

Atopic dermatitis

The pathogenesis of atopic dermatitis is complex and well described in detail[48]: besides damage and dysfunction of the epidermal barrier and dysbalance between Th1 and Th2 cells, lack of antimicrobial peptides on the skin surface leads to a significantly increased risk of bacterial and viral skin infections.[49]

The role of vitamin D in atopic dermatitis has been recently reviewed.[3,20] Despite the inconsistent data, the majority of published case reports as well as smaller controlled studies demonstrate that vitamin D might be important in this disease (Table 5).

An inverse correlation between the quantity of serum vitamin D and the production of both IgE and specific IgE has been documented by Sharief and coworkers.[50]

Knowing that obesity can cause vitamin D deficiency,[51] Oren et al. demonstrated a fivefold increase of probability for atopic dermatitis compared with controls with 25(OH)D higher than 30 ng/mL in obese atopic individuals with documented vitamin D deficiency [25(OH)D serum levels below 10 ng/mL].[52] Hata and coworkers confirmed this observation.[53]

Our data found a low vitamin D serum level in patients with atopic dermatitis (median 22.7 ng/mL), the value was highly significantly lower than in the group of patients without skin diseases or allergies. 37.4% of patients with atopic dermatitis had a vitamin D serum level below 20 ng/mL at their first appointment, thus a clinically relevant deficiency with respect to the majority of international definitions (Table 4). However, a statistical significant difference from patients with forms of non-atopic eczema was not observed (median 24.12 ng/mL)

Both the clinical activity and patient's evaluation of intensity of pruritus showed an inverse correlation with the level of the individual vitamin D serum values. Lack of significance might be explained by insufficient discrimination using the PGA score instead of using the SCORAD index.

A differentiated inverse correlation between 25(OH)D serum levels and the severity of atopic dermatitis have meanwhile been found in various international studies (Table 5). However, as in psoriasis and other systemic inflammatory diseases clear proof of a cause-effect relationship is yet lacking.

Several publications have found a correlation between the degree of skin infections in atopic dermatitis and a low vitamin D level,[54-56] which can be generally confirmed by our observation finding the lowest mean 25(OH)D serum level in patients with skin infections.

Further studies have shown an increased risk of occurrence of food allergies at low vitamin D levels.[57-59] Patients in our investigation with "isolated" food allergy exhibited a very low median vitamin D serum level of 19.5 ng/mL. However, due to the small size of the subgroup (n = 19) no significant differences to the other subpopulations were found.

The fact that few studies with a positive or no significant association between the activity of atopic dermatitis and the corresponding 25(OH)D serum levels were published (Table 5), argues for the need to harmonize the methods of measurement and definitions of "deficiency" and "optimal range" for vitamin D internationally and to conduct prospective controlled studies. This also applies the complexity of vitamin D

supplementation in intervention studies in terms of the amount, loading dose at low baseline 25(OH)D level, duration, dose interval, instructions for intake with lipids, resorption, interaction with drugs, adjustment for body weight/BMI, VDR polymorphisms, sun exposure, pigmentation status, nutritional habits, etc.[60] Due to the heterogeneity of the case series, case reports and the variety of different designs of published studies, no concrete recommendation can be made at the present.

Even assuming an "optimal" range for 25(OH)D in the serum is defined between 40–60 ng/mL, it is also not clear yet whether a long-term (!) level of 40 ng/mL or 60 ng/mL physiologically or pathophysiologically or supraphysiological/"pharmacological" levels > 60 ng/mL[61] make a difference for the patient with inflammatory skin diseases.

According to our extensive experience with this disease and in the absence of approved systemic therapeutics without severe unwanted long term effects, a daily oral substitution with vitamin D supplements (always in combination with vitamin K2 to prevent hypercalcemia) is reasonable to yield steroid-sparing effect at an "optimal range" for 25(OH)D at least 40 ng/mL. We have observed much higher clinical efficacy when serum levels range between 50–60 ng/mL permanently (unpublished results).

Summarizing on one hand the known effects of vitamin D on protective immune functions of the skin, production of antimicrobial peptides, positive influence on stratum corneum barrier function and the known high incidence of viral and bacterial skin infections, the reduced concentrations of cathelicidin as well as the diminished barrier functions in atopic dermatitis on the other hand, our results could implicate that it appears to be logical to work out a strategy using vitamin D at least as part of a therapeutic concept.

In addition, our results from patients with allergic rhinitis and allergic asthma should be also mentioned, since both diseases are often associated with atopic dermatitis. The median 25(OH)D serum levels for patients who came to us for seasonal or perennial rhinitis (n = 69) or isolated allergic asthma (n = 6) was 25.1 ng/mL and 16.33 ng/mL respectively. The small number of asthmatic patients did not allow statistical calculations. In rhinitis, the value was significantly lower than in healthy checkup patients (p <0.0001), but did not significantly differ from atopic dermatitis.

Table 5. Relationship between 25(OH)D serum levels or oral vitamin D supplementation and clinical activity of atopic dermatitis [changed and updated according to Quirk SK et al.[20]].

Negative (inverse) correlation	Positive (direct) correlation	No significant correlation
Akan et al., 2013[71]	Heimbeck et al., 2013[82]	Berents et al., 2016[84]
Amestejani et al., 2012[72]	Wawro et al., 2014[83]	Chawes et al., 2014[85]
Baek et al., 2014[57]		Chiu et al., 2013[86]
Baiz et al., 2013[73]		Hata et al., 2014[53]
Camargo et al., 2014[74]		Robl et al., 2016[87]
Cheng et al., 2014[75]		Samochocki et al., 2013[54 a]
Gilaberte et al., 2015[76]		Thuesen et al., 2015[88]
Grant et al., 2016[77]		
Han et al., 2015[78]		
Javanbakht et al., 2011[79]		
Lee et al., 2013[76]		
Oren et al., 2008[52]		
Osborne et al., 2012[59]		
Peroni et al., 2011[55]		
Samochocki et al., 2013[54 a]		
Sidbury et al., 2008[80]		
Udompataikul et al., 2015[56]		
Wang et al., 2014[81]		

[a]Authors could not find a significant difference between serum vitamin D levels of 95 AD patients and 58 healthy controls. Vitamin D supplementation, however, improved clinical scores of patients.

Yang and coworkers have recently demonstrated a high prevalence between a vitamin D deficiency and symptoms of allergic rhinitis in a large group of 3,720 primary school children in Korea.[62] A recent meta-analysis in this context revealed a large heterogeneity of the available studies and concluded that an inverse correlation between vitamin D in the serum and the activity of the rhinitis was only clearly detectable in children, but not in adults.[63] For prevention of allergic rhinitis by administering vitamin D supplements in pregnancy or early childhood evidence is currently still lacking.[63]

A Cochrane meta-analysis in asthma from 2016 has shown a probable benefit of the use of vitamin D for both the reduction of asthma attacks and the use of medical interventions.[64] To date, the published studies have not shown clearly whether the positive effects are only restricted to patients with a low initial serum level of vitamin D. Especially children and patients with severe asthma attacks are underrepresented in the studies to date. Additional clinical trials are required. However, the pathogenetic role of vitamin D for airway remodeling in chronic asthma is already well documented.[65]

Despite increasing and convincing evidence for a significant role of vitamin D for central regulation of metabolism and the immune system, the preventive or therapeutic approach of vitamin D supplementation should always have a holistic view. Against this background fascinating new findings from gut microbiome research demonstrated variation in vitamin D receptor influencing also the large functional network of gut microbiota.[66]

In summary, to our knowledge our work provides the first comparison of serum levels of 25(OH)D in a broad spectrum of different skin diseases and allergic conditions that's used the same methodology to measure serum 25(OH)D levels. We found significantly reduced 25(OH)D serum levels in most of the investigated inflammatory skin diseases in comparison to healthy persons. Although clear definitions of vitamin D insufficiency and deficiency are still lacking, according to the present study we see the highest need to consider vitamin D supplementation for primary or secondary prevention for infectious skin diseases and psoriasis. In inflammatory skin diseases 25(OH)D serum level might correlate more with the type of disease and the degree of inflammation than with clinical activity of the skin disease or allergic reaction itself.

We suggest to further define endotypes of atopic dermatitis and psoriasis with distinct subtypes of inflammatory comorbidities (such as allergic asthma, allergic rhinitis, food allergies with allergic reactions on the gastrointestinal tract and arthritis, cardiovascular diseases, depression, IBD, respectively). These subtypes might benefit differentially from vitamin D supplementation. Further studies are necessary to elucidate these questions.

Supporting information

Disclosure of potential conflicts of interest

Funding

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