Increased Vitamin D Serum Levels Correlate with Clinical Improvement of Rheumatic Diseases after Dead Sea Climatotherapy

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ABSTRACT: **Background:** Ultraviolet B (UVB) rays are required by the skin for the production of vitamin D. The intensity of UVB at the Dead Sea area is the lowest in the world. Low vitamin D levels are often associated with musculoskeletal symptoms.

Objectives: To assess the effectiveness of climatotherapy at the Dead Sea on the production of vitamin D in Norwegian patients suffering from various rheumatic diseases and to investigate possible associations between increased vitamin D serum levels, musculoskeletal symptoms and disease severity.

Methods: Sixty Norwegian patients who came to the Dead Sea area for 21 days of medical rehabilitation were divided into three groups according to their diagnosis: chronic pain syndromes, i.e., low back pain or fibromyalgia (Group 1, n=33); rheumatoid arthritis (Group 2, n=16); and osteoarthritis (Group 3, n=11). Serum 25-hydroxyvitamin D (25-OH-D) levels were determined at arrival and prior to departure. The treatment protocol included daily sun exposure (climatotherapy), bathing in the Dead Sea and mineral spring water (balneotherapy), mud applications and fitness classes.

Results: 25-OH-D serum levels increased significantly from 71.3 ± 26.6 nM at arrival to 89.3 ± 23.2 nM prior to departure ($P < 0.001$). Adjusted for the initial levels of pain (assessed by a visual analog scale) and disease severity, a direct correlation was observed between increased 25-OH-D serum levels and pain reduction ($P = 0.012$) and reduction of disease severity ($P = 0.02$).

Conclusions: Climatotherapy at the Dead Sea induces significant changes in vitamin D. Increased 25-OH-D serum levels are associated with reduced musculoskeletal pain and disease severity.

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It has been estimated that brief exposure of the arms and face to sun is equivalent to supplementation of 200 IU of vitamin D_3 per day [1]. The intensity of ultraviolet B radiation at the Dead Sea region (the lowest spot on earth at approximately 420 meters below sea level) is lower than that measured at sea level and above [2]. The two main reasons for this decreased UVB intensity is the attenuation of UVB due to the extra 420 meters the rays have to travel until they reach the ground, and the increased absorption of UVB rays by the relatively high aerosol content of the air above this area created by the high evaporation rate of the very high salt content of Dead Sea water. Despite the lower intensity of UVB at the Dead Sea area, it has been shown that 25-hydroxyvitamin D serum levels in Danish patients with psoriasis increased by 80% after 4 weeks of climatotherapy at the Dead Sea [3] that included long periods of daily sun exposure.

In recent years the discovery of vitamin D receptors in the cells of the immune system and the fact that several of these cells are capable of producing the active metabolite of vitamin D may indicate that vitamin D has immunoregulatory properties. VDR agonists inhibit dendritic cell differentiation and pathogenic pro-inflammatory T cells such as Th1 [4]. Down-regulation of the expression of cytokines, caused by the active metabolite of vitamin D, was demonstrated in human macrophages. Therefore, it has been suggested that treatment with vitamin D might be efficacious in patients with inflammatory and non-inflammatory rheumatic diseases.

Vitamin D deficiency is extremely common in northern latitudes [4]. This is due to the increase in the solar zenith angle, which is smallest at the equator and gradually increases from the equator to the poles, resulting in an increase in the pathlength for the radiation to pass through, thus decreasing its strength.

UVB = ultraviolet B
VDR = vitamin D receptors

Epidemiological evidence indicates a significant association between vitamin D deficiency and an increased incidence of inflammatory autoimmune rheumatic diseases such as rheumatoid arthritis, systemic lupus erythematosus [5], and non-inflammatory diseases such as osteoarthritis [6].

The aims of the present study were twofold: to assess whether climatotherapy at the Dead Sea area increased serum levels of 25-OH-D in Norwegian patients with various rheumatic conditions who underwent 3 weeks of climatotherapy and balneotherapy at the Dead sea area, and to investigate possible associations between serum levels of 25-OH-D, rheumatic pain, and disease activity in various rheumatic conditions.

PATIENTS AND METHODS

Sixty Norwegian patients participated in the study. They came in four organized groups over the course of 2005–2006 for 21 days of medical rehabilitation at the DMZ Medical Center, Lot Spa Hotel, Dead Sea. The patients were divided into three groups according to their musculoskeletal diagnosis, which was obtained from medical documents they brought with them and confirmed by an interview with the medical staff at the DMZ clinic. Group 1 comprised patients with chronic pain syndrome, fibromyalgia or low back pain; Group 2 consisted of patients with osteoarthritis of knees and/or hips; and Group 3, patients with rheumatoid arthritis.

The classical treatment protocol for medical rehabilitation included daily sun exposure and bathing in Dead Sea water, mineral pools, mud applications, fitness classes, and medical consultations with DMZ nurses or doctors. The amount of UVB radiation received through sun exposure was evaluated and expressed in minimal erythemal dose units. MED is defined as the minimal amount of UVB that causes redness of the skin 24 hours after exposure. The calculations were done using the measurements of the daily and hourly UVB intensities recorded in the area. The patients were first ascribed a value of 1 MED in accordance with their photo skin type. Skin type was determined at arrival according to the Fitzpatrick classification: type1 = very light, type 2 = light, type 3 = light intermediate, type 4 = dark intermediate, type 5 = dark, type 6 = very dark. Assuming that the value of 1 MED for patients with skin types 2, 3 and 4 corresponds to 25, 35 and 45 mJ/cm^2, respectively, the amount of UVB radiation absorbed is calculated by the duration of sun exposure and then transformed into MED units.

Patient pain severity was assessed using a visual analogue scale from 0 to10 cm. Physicians' global assessment of disease severity was based on a questionnaire that included items on sleep disturbances, daily activity, impairment of joint mobility, and use of medication such as non-steroidal anti-inflammatory drugs and other pain killers. The maximal score for this questionnaire was 140 points, with higher scores corresponding to higher disease severity. Patients completed the questionnaire and the VAS for pain on the day of arrival on the day before departure.

Serum 25-OH-D levels were determined on the day of arrival and the day before departure using OCTEIA 25-OH-D kits, IDS AC-57F1 (Immunodiagnostic Systems, Boston, UK) based on a specific sheep 25-OH-D antibody [7]. Serum samples were tested in duplicate and the results were expressed in nM (nmol/L). Serum levels above 75 nM were considered optimal, levels between 50 and 75 nM adequate, levels 25–50 nM insufficient, and levels below 25 nM deficient.

STATISTICAL ANALYSIS

Data summaries were performed using SPSS (Version 16.01 or higher, SPSS Inc., Chicago, IL, USA). Data were analyzed using frequency tables, summary statistics, confidence intervals, and *P* values, as appropriate. Continuous variables were compared by *t*-tests or analysis of variance. The 95% confidence interval was calculated using means and standard errors from Student's *t*-test statistics. For continuous variables with non-normal distribution comparisons were evaluated for significance with the Wilcoxon rank-sum test.

Linear regression models were used for the multivariate analysis of associations between changes in vitamin D levels (percent from baseline level), pain VAS, and physicians' report of disease severity. The models included baseline levels of VAS for pain and disease severity scores, age, gender, skin type, and change in vitamin D levels. Stepwise forward regression models with a stay criterion of 0.10 were used. *P* values ≤ 0.05 (two-tailed) were considered significant.

RESULTS

The main clinical and demographic characteristics of the study population are summarized in Table 1. The average age was

25-OH-D = 25-hydroxyvitamin D
MED = minimal erythemal dose
VAS = visual analogue scale

Table 1. Clinical and demographic characteristics of 60 study patients

Variable		Result
Age (yrs, mean ± SD)		62.8 ± 11.6
Gender	Females Males	47 (78.3%) 13 (21.7%)
Skin type	1 2 3 4 5 6	0 15 (25.0%) 44 (73.3%) 1 (1.7%) 0 0
Diagnosis	Chronic pain (Group 1) Rheumatoid arthritis (Group 2) Osteoarthritis (Group 3)	33 (55.0%) 16 (25.7%) 11 (18.3%)

Table 2. 25-OH-D serum level changes (nM) from baseline to departure, by treatment group

	Chronic pain (n=33)	Rheumatoid arthritis (n=16)	Osteoarthritis (n=11)	*P*
Baseline 25-OH-D	75.5 ± 28.1	63.6 ± 27.8	71.8 ± 18.5	0.24
Departure 25-OH-D	88.8 ± 23.8	84.7 ± 22.4	97.3 ± 23.0	0.39
Change in 25-OH-D Median	13.4 ± 24.2 14.0	21.2 ± 21.6 21.5	25.4 ± 28.7 27.0	0.17
% change	25.5 ± 34.7	46.1 ± 45.6	42.0 ± 41.0	0.22

Table 3. Linear regression model for changes in pain (VAS) and physicians' global assessment of disease severity

Variable	Standardized beta	*P*
VAS for pain ($R^2 = 0.36$)		
Baseline	-0.62	< 0.001
Change in 25-OH-D levels	0.20	0.012
Disease severity ($R^2 = 0.50$)		
Baseline	-0.72	0.02
Change in 25-OH-D levels	-0.23	< 0.001

62.8 ± 11.6 years and most of the patients were females (78%). All patients but one had skin type 2 (n=15, 25%) or skin type 3 (n=44, 73.3%). The mean body mass index reached 27.97 kg/m^2. The total accumulative UVB dose for patients with skin types 2 and 3 was 20–21 MED and 37–42 MED, respectively. There were 33 patients in Group 1 (55%), 16 in Group 2 (25.7%) and 11 in Group 3 (18.3%).

At baseline only 22 of 60 patients (36.7%) had optimal 25-OH-D serum levels, 24 patients (40%) had adequate levels, and 14 (23.3%) had insufficient levels. At departure only 3 patients (5%) still had insufficient 25-OH-D serum levels, 13 patients (21.7%) had adequate levels and 44 patients (73.3%) had optimal values. The mean relative change in vitamin D reached 25.2%. Mean serum 25-OH-D levels increased significantly from 71.3 ± 26.6 nM at baseline to 89.3 ± 23.2 at departure ($P < 0.001$).

VAS pain levels improved significantly from 4.88 ± 1.63 to 7.26 ± 1.46 ($P < 0.001$). Physician assessment of disease severity also showed a significant improvement. The total score decreased from 63.5 ± 20.75 to 25.67 ± 15.85 ($P < 0.001$).

No significant association was found between the change in vitamin D and skin type ($P = 0.49$) and the change in vitamin D and disease ($P = 0.12$). Similarly, no significant correlation was found between vitamin D changes and changes in VAS pain severity ($P = 0.54$) or disease severity ($P = 0.16$) among the three study groups. There was a strong correlation between the changes in pain VAS and the physician assessment of disease severity ($r = -0.52$, $P = 0.001$).

Table 2 summarizes changes in 25-OH-D levels from baseline to departure for the three study groups. No significant differences were observed in the changes in vitamin D levels between the three study groups.

There was a significant correlation between changes in 25-OH-D serum levels and changes in pain VAS after standardization to the measurement of VAS for pain at arrival ($P = 0.012$) [Table 3]. Similarly, there was a significant correlation between 25-OH-D serum level change and disease severity change, by physician assessment, adjusted for the initial disease severity ($P = 0.02$).

DISCUSSION

In the current study we show that 3 weeks of climatotherapy at the Dead Sea increased serum levels of vitamin D. This increase is associated with amelioration of musculoskeletal pain and disease severity in patients with inflammatory and non-inflammatory rheumatic diseases.

Deficient 25-OH-D levels are not only detrimental to musculoskeletal health and calcium metabolism, but may also play a role in immunopathology. Active vitamin D (1,25 hydroxyvitamin D) participates in immunodysregulation conditions via down-regulation of Th1 immunity [8]. Epidemiological evidence indicates a significant association between vitamin D deficiency and an increased incidence of autoimmune rheumatic diseases. Studies have shown that vitamin D insufficiency is common in patients with rheumatoid arthritis [9] and that patients with RA have a lower concentration of 25-OH-D than healthy controls [10]. It is not clear whether there is a correlation between serum vitamin D levels and RA activity or whether vitamin D replacement reduces disease activity. Patel et al. [11] reported an inverse association between disease activity and vitamin D metabolites in patients with early polyarthritis. Significantly lower 25-OH-D serum levels were found in RA patients from Estonia (northern Europe) than from Italy (southern Europe). In addition, there was a significant negative correlation between 25-OH-D levels and RA clinical status [12]. In contrast, there was no correlation between serum 25-OH-D levels and disease activity in 121 patients with RA, 22 patients with psoriatic arthritis, and 14 patients with ankylosing spondylitis in a recent study from Israel [12]. Surprisingly, vitamin D deficiency was found in 42.1% of these patients. Only one small open-label intervention study demonstrated a reduction in disease activity following treatment with $1,25(OH)_2D$ in patients with established RA [13]. Since the patients in the present study were from Norway it is not surprising that non-optimal levels of vitamin D (< 75 nM) were found in 63.3%.

Two longitudinal epidemiological studies have shown that low vitamin D levels exacerbate the course of osteoarthritis. One study, using data from the original Framingham study cohort, showed that subjects with lower and middle-tertile vitamin D

RA = rheumatoid arthritis

levels had a threefold increased risk of radiological worsening of preexisting knee osteoarthritis [14]. In the other study [15] the lowest and middle tertiles of vitamin D were associated with a higher incidence of hip osteoarthritis. In contrast, Felson and colleagues [16] reported that vitamin D status is unrelated to the risk of joint space or cartilage loss in knee osteoarthritis.

The association between low vitamin D serum levels and non-specific musculoskeletal pain syndromes, including fibromyalgia, is controversial. In one study, women with fibromyalgia had a significantly higher prevalence of low 25-OH-D serum levels (42.5%) compared to age-matched healthy women (18.9%) [17]. Other studies, including one from Israel [18], did not find lower levels of 25-OH-D in patients with fibromyalgia [19,20].

More than 73% of the patients in the present study attained optimal 25-OH-D serum levels after 3 weeks of daily sun exposure (the average duration of sun exposure was 30 minutes twice daily). Only three patients did not reach adequate vitamin D levels. Their initial values of 25-OH-D were above 25 nM and their body mass index was over 32 kg/m^2. This incomplete response can be explained by insufficient sun exposure (average of 20–21 MED for type 2 skin, and 37–42 MED for type 3 skin).

Public health recommendations for sun exposure of the face, hands and arms (approximately 25% of total body surface area) for 10–20 minutes two to three times a week during the summer months are not always enough to increase 25-OH-D levels to the optimal range [21]. Recently, Diffey [22] used a model to estimate changes in serum 25-OH-D levels as a consequence of sun exposure throughout the year and showed that the current recommendation for 10–20 minutes of daily sun exposure during the summer months in Britain does little to boost overall 25-OH-D levels [23]. However, prolonging the length of sun exposure may compromise skin health and increase the risk of skin malignancies [23] and, therefore, should not be recommended unless strict medical supervision is present, as it is at the Dead Sea [24].

Limitations of this study include the use of a non-validated assessment of disease severity and our inability to assess disease activity using the validated DAS 28 or ACR 20/50 criteria for RA patients or other acceptable criterion for activity of osteoarthritis or fibromyalgia. In addition, the relatively small number of patients in each group did not allow us to perform subgroup analyses.

In conclusion, our study showed that a 3-week stay at the Dead Sea area with minimal daily sun exposure is enough to normalize serum vitamin D storage in patients with rheumatic diseases who, in most cases, have inadequate baseline levels. The concomitant clinical improvement in these patients allows us to propose (again) the hypothesis that increased vitamin D serum levels may reduce musculoskeletal pain. However, despite the recent advances in knowledge related to vitamin D and its beneficial effect in many medical conditions, further studies are needed to determine the effects of vitamin D on disease activity in both inflammatory and non-inflammatory rheumatic diseases.

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