Original paper

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Vitamin D supply in patients with rheumatic diseases in Poland – a pilot study

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Abstract

Objectives: In rheumatic diseases, vitamin D supply is recommended as part of the prophylaxis and treatment of osteoporosis, especially in patients undergoing glucocorticoid therapy, but also due to its immunoregulatory and anti-inflammatory properties. We aimed to evaluate serum 25-hydroxy-vitamin D [25(OH)D_3] levels in Polish patients with systemic sclerosis (SSc), systemic lupus erythematosus (SLE) and granulomatosis with polyangiitis (GPA), in relation to various clinical parameters, and to assess the initial range of doses for the purpose of further research.

Material and methods: 112 patients (39 with SLE, 44 with SSc and 29 with GPA), referred to the Department of Rheumatology and Internal Medicine in Poznan, Poland, were enrolled in this retrospective study. Demographic and clinical data were collected, including 25(OH)D_3 serum levels, vitamin D supplementation doses and season of blood sampling.

Results: Mean (SD) serum 25(OH)D_3 concentrations were 31 (19.4) ng/ml for SLE, 28.8 (12.5) ng/ml for SSc and 28 (15.2) ng/ml for GPA, and they did not significantly differ between the groups. Vitamin D levels below the optimal range were found in 43.8% of SLE, 65.9% of SSc and 72.4% of GPA patients. 80% of patients reported vitamin D intake, with a mean daily dose of 1398 IU for SLE, 1345 IU for SSc and 1689 IU for GPA. Vitamin D insufficiency and deficiency were frequent among patients with rheumatic diseases, independently of the diagnosis and season.

Conclusions: Patients with rheumatic diseases seem to require higher doses of vitamin D than recommended for the general population. The present results indicate the necessity to use higher initial doses of vitamin D in this group of patients (2000 to 4000 UI) and to maintain the dose of vitamin D regardless of the change of seasons.

Key words: systemic sclerosis, systemic lupus erythematosus, granulomatosis with polyangiitis, hypovitaminosis D.

Introduction

The classical role of vitamin D in bone metabolism regulation is broadly known [1]. However, after the discovery that vitamin D receptors (VDR) are expressed by several different cells and tissues, not necessarily involved in calcium-phosphate homeostasis [2], scientific attention turned toward the non-classical, extraskeletal properties of vitamin D and its potential pleiotropic effect on human health [3, 4].

In recent decades, low vitamin D levels have been associated with increased incidence of several diseases such as cardiovascular diseases [5], diabetes [6], cancers [7], infectious diseases [8] and autoimmune diseases [9]. However, whether vitamin D deficiency plays a causative role, or is rather a marker of poor health status related to chronic disease, remains unclear, as the majority of the studies concerning these associations are observational in nature, whereas evidence from large-scale clinical trials is lacking [5, 10, 11].

In rheumatic diseases, vitamin D supplementation is recommended primarily in the prevention and management of osteoporosis, especially in patients receiving glucocorticoid therapy [12, 13].

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Nevertheless, due to its immunomodulatory and anti-inflammatory properties, the potential impact of vitamin D on the prevalence and outcomes in rheumatic diseases has been recently investigated [9, 11]. For example, numerous studies have demonstrated vitamin D deficiency in patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) [14–16], as compared to healthy controls. Moreover, vitamin D concentrations have also been negatively correlated with disease activity/severity in both SLE and RA [17–20]. However, further studies are necessary to confirm such a relationship [1].

In the literature, decreased vitamin D levels have also been frequently observed in systemic sclerosis (SSc) [21–23], and several associations have been reported, for instance with disease subtype [21], with specific organ involvement, such as lungs, peripheral vessels or kidneys [24], with digital ulcerations [25] or with extent of skin involvement measured by the Rodnan skin score [23].

Regarding antineutrophil cytoplasmic antibody (ANCA) associated vasculitides (AAV), Perez et al. [26] noted the influence of lower vitamin D serum levels on the increased risk of respiratory infections in patients with GPA. No relationship, though, between $25(OH)D_3$ concentrations and disease activity has been found, but further investigation is needed to determine the prevalence and significance of hypovitaminosis D in AAV.

The aim of this study was to perform an initial evaluation of the vitamin D supply and serum levels among Polish patients with selected rheumatic diseases, i.e. SSc, SLE and GPA, in relation to various clinical features and glucocorticosteroid therapy, and to estimate the initial range of vitamin D doses for the purpose of further research.

Material and methods

A cohort of 112 (39 with SLE, 44 with SSc and 29 with GPA) Caucasian patients, referred to the Department of Rheumatology and Internal Medicine, Poznan University of Medical Sciences, Poland, between October 2017 and July 2019, was enrolled in this retrospective study. We accessed the patient records in September 2019.

All patients fulfilled the adequate disease classification criteria: the revised American College of Rheumatology (ACR) criteria for classification of SLE [27]; the ACR/European League Against Rheumatism (EULAR) 2013 criteria for classification of SSc [28], or the 1990 ACR criteria for the classification of GPA [29], respectively.

Demographic and clinical data were collected, including gender, age, vitamin D and calcium supplementation status, current glucocorticosteroid use, and comorbidities such as osteoporosis, osteoporotic fractures and chronic kidney disease. Serum concentrations of 25-hydroxyvitamin D [$25(OH)D_3$], calcium (normal: 2.15–2.58 mmol/l) and creatinine (normal: 0.67–1.4 mg/dl for men and 0.56–1.2 mg/dl for women) levels were analyzed, as well as the presence of proteinuria (defined as > 0.2 g/24 h or positive urinalysis test).

Patients were grouped according to vitamin D status as follows: deficiency – below 20 ng/ml; insufficiency – between 20 and 30 ng/ml; optimal levels of $25(OH)D_3$ – 30 to 100 ng/ml and potentially toxic concentration – above 100 ng/ml. Seasons of blood sampling were categorized as spring (March–May), summer (June–August), autumn (September–November), and winter (December–February), in order to assess the potential seasonal variation of vitamin D levels.

Statistical analysis was performed using IBM SPSS Statistics 25 software. A p-value < 0.05 was considered to indicate statistical significance. Descriptive statistics were calculated for the collected data. The correlations between analyzed parameters were calculated and their significance examined. Distributions of variables were evaluated for normality using the Shapiro-Wilk test. To compare non-parametric distributions for independent variables, the Mann-Whitney *U*-test and Kruskal-Wallis test were used. If possible, and if the assumptions were met, Student's *t*-test was used to compare the distribution. In addition, the *z*-test for the significance of the difference between two structured indicators was used.

The study has a retrospective character; hence the approval of the Bioethical Commission was not required.

Results

The main clinical characteristics of all 112 participants are presented in Tables I and II. The systemic lupus erythematosus patients were significantly younger than SSc and GPA patients. Women made up the majority of SLE and SSc patients, but less than a half of GPA patients.

Mean serum $25(OH)D_3$ concentrations were below the cutoff for sufficiency in GPA and SSc patients, and slightly above this value in SLE patients, but they did not significantly differ between the groups ($p = 0.54$). Also when comparing the prevalence of vitamin D deficiency/insufficiency/sufficiency between the diseases (Table III), no significant differences were found ($p = 0.36$). Serum concentrations of 25-hydroxyvitamin below the level of 30 ng/ml were found in 43.8% of SLE, 65.9% of SSc and 72.4% of GPA patients.

80% of patients (81.82% of SLE, 71.43% of SSc and 92% of GPA patients) reported vitamin D intake. The mean daily dose of cholecalciferol was 1398 IU for SLE, 1345 IU for SSc and 1689 IU for GPA.

Regarding other laboratory findings, no statistically significant differences were observed in mean serum calcium levels or in the prevalence of impaired renal

Table I. Basic clinical characteristics of patients with systemic lupus erythematosus, systemic sclerosis and granulomatosis with polyangiitis

Parameter	Age [years]	Ca [mmol/l]	25(OH)D_3 [ng/ml]	Cholecalciferol dose [if supplemented] [IU/day]	GC dose [mg/day]
SLE (*n* = 39)					
Min	20	2.03	7.6	400	0
Max	73	2.51	120.8	2000	36
Mean	44.05	2.3286	30.951	1398.18	11.50
SD	14.686	0.11028	19.4073	557.311	7.443
SSc (*n* = 44)					
Min	32	2.18	8.0	500	0
Max	79	2.57	72.6	6000	12
Mean	56.50	2.3815	28.847	1345.19	2.52
SD	12.155	0.10595	12.4845	743.704	3.315
GPA (*n* = 29)					
Min	18	1.85	8.0	400	4
Max	77	2.64	70.7	3000	32
Mean	52.14	2.3718	28.010	1688.70	16.93
SD	14.872	0.15630	15.2263	662.003	8.211

25(OH)D_3 – 25-hydroxyvitamin D, GC – glucocorticosteroid (methylprednisolone), GPA – granulomatosis with polyangiitis, SLE – systemic lupus erythematosus, SSc – systemic sclerosis, Max – maximum, Min – minimum, n – number, SD – standard deviation.

Table II. Prevalence of clinical features of patients with systemic lupus erythematosus, systemic sclerosis and granulomatosis with polyangiitis

Characteristics	SLE	SSc	GPA
Female	36/39 (92.31%)	40/44 (90.91%)	13/29 (44.83%)
Proteinuria > 0.2 g/24 h	11/38 (28.9%)	1/44 (2.3%)	8/29 (27.6%)
Impaired renal function	15/39 (38.5%)	11/44 (25.0%)	11/29 (37.9%)
Osteoporosis	10/38 (26.3%)	7/42 (16.7%)	11/28 (39.3%)
Bone fractures	10/39 (25.6%)	4/42 (9.5%)	8/28 (28.6%)

GPA – granulomatosis with polyangiitis, SLE – systemic lupus erythematosus, SSc – systemic sclerosis.

function (defined as the presence of proteinuria and/or eGFR < 60 ml/min/1.73 m^2), although proteinuria itself was significantly more common in SLE ($p < 0.001$) and in GPA ($p = 0.001$) than in SSc.

As for the prevalence of osteoporosis and bone fractures in each of the three diseases, we found that they were significantly more frequent in GPA than in SSc (osteoporosis: 39.3% vs. 16.7%, $p = 0.0341$; bone fractures: 28.6% vs. 9.5%, $p = 0.0378$). In systemic lupus erythematosus, osteoporosis and bone fractures were also more common than in SSc, but the differences did not reach statistical significance.

Statistical analysis of the correlations between serum 25(OH)D_3 concentrations and selected clinical features was performed for the whole group and for each of the diseases separately. The results are presented in Table IV.

There were no significant correlations between vitamin D levels and age, serum calcium levels, impaired renal function, osteoporosis and history of bone fractures. As for seasonal variations (Table V), observed differences in 25(OH)D_3 levels did not reach statistical significance for any of the investigated diseases.

In systemic lupus erythematosus, 25(OH)D_3 serum concentration was positively correlated with supplemented vitamin D dose. In granulomatosis with polyangiitis, serum 25(OH)D_3 was significantly higher in women than men. In systemic sclerosis, 25(OH)D_3 levels were significantly higher in the group of patients treated with glucocorticosteroids (mean = 33.711) than in the group of patients who did not take steroids (mean = 25.344).

Moreover, in SSc serum 25(OH)D_3 was positively correlated with glucocorticosteroid dose. The comparison of glucocorticosteroid-treated vs. non-treated groups

Table III. Proportions of 25-hydroxyvitamin D [25(OH)D_3] levels among patients with systemic lupus erythematosus, systemic sclerosis and granulomatosis with polyangiitis

25(OH)D_3 level [ng/ml]	SLE		SSc		GPA	
	n	%	*n*	%	*n*	%
Deficiency < 20	12	20.8	10	22.7	8	27.6
Insufficiency 20–30	9	23.0	19	43.2	13	44.8
Normal level 30–100	17	43.6	15	34.1	8	27.6
Potentially toxic > 100	1	2.6	0	0	0	0
Total	39	100.0	44	100.0	29	100.0

25(OH)D_3 – 25-hydroxyvitamin D, GPA – granulomatosis with polyangiitis, SLE – systemic lupus erythematosus, SSc – systemic sclerosis.

Table IV. Correlation coefficients between serum 25(OH)D_3 concentrations and selected clinical and laboratory variables in patients with systemic lupus erythematosus, systemic sclerosis, granulomatosis with polyangiitis

Parameter	SLE		SSc		GPA	
	r	*p*-value	*r*	*p*-value	*r*	*p*-value
Age	0.211	0.197	0.184	0.236	0.231	0.237
Gender	0.311	0.054	0.139	0.374	–0.444	0.016
Serum calcium level	0.222	0.186	0.145	0.372	0.105	0.593
Proteinuria	0.203	0.221	0.0	0.0	–0.236	0.219
Impaired renal function	0.207	0.206	0.265	0.086	–0.329	0.81
Osteoporosis	0.216	0.192	–0.052	0.748	0.269	0.166
Bone fractures	0.154	0.358	–0.058	0.720	0.322	0.094
Cholecalciferol dose	0.415	0.025	0.157	0.340	0.128	0.542
Methylprednisolone dose	0.106	0.539	0.342	0.029	–0.147	0.446

GPA – granulomatosis with polyangiitis, SLE – systemic lupus erythematosus, SSc – systemic sclerosis.

Table V. Seasonal 25(OH)D_3 serum concentrations in patients with systemic lupus erythematosus, granulomatosis with polyangiitis and systemic sclerosis

Disease	Spring	Summer	Autumn	Winter	*p*-value
	25(OH)D_3 mean (SD) concentration [ng/ml]				
SLE	26.94 (13.55)	32.83 (11.11)	38.01 (27.87)	23.57 (16.76)	0.353
GPA	33.65 (16.26)	20.75 (13.36)	26.51 (12.91)	28.24 (20.41)	0.443
SSc	30.61 (12.29)	35.44 (17.73)	25.94 (7.15)	22.21 (9.07)	0.355

25(OH)D_3 – 25-hydroxyvitamin D, GPA – granulomatosis with polyangiitis, SLE – systemic lupus erythematosus, SSc – systemic sclerosis, p-values represent statistical differences in seasonal 25(OH)D_3 concentrations.

was not applicable in SLE and GPA, as only a few patients were not treated with glucocorticosteroids.

Of note, among patients with SLE and SSc (but not GPA), there was also a significant positive correlation between osteoporosis prevalence and supplemented vitamin D dose (r = 0.514, p = 0.005 and r = 0.364, p = 0.019, respectively).

Discussion

The results of our study demonstrate high prevalence of low vitamin D levels among patients suffering from different rheumatic diseases, with 71/112 (63.3%) of them having 25(OH)D_3 concentrations below the optimal level of 30 ng/ml [30]. In particular, 26.8% of the patients showed 25(OH)D_3 deficiency (< 20 ng/ml) and 36.6% had suboptimal levels of 20 to 30 ng/ml.

However, the epidemiologic data reported by Płudowski et al. [31] demonstrated even higher prevalence of low vitamin D concentrations among the Polish population as compared to our group, with 25(OH)D_3 levels below 30 ng/ml in 89.9% of studied volunteers. The possible explanation of such differences is that

the above study was performed during late winter and spring, when the lowest 25(OH)D_3 values are expected in the general population due to lack of vitamin D synthesis in the skin, while in our patients vitamin D levels were measured throughout the year, including summer.

In another study based on the Polish adult population, by Kmieć et al. [32], 25(OH)D_3 sufficiency was recorded only in 1.8% and 14.7% of participants, during autumn and winter, respectively, which also confirms that the prevalence of decreased vitamin D levels is even higher in the general population than in patients suffering from rheumatic disorders, probably due to the lower frequency of its routine supplementation in healthy subjects.

In our study, we found no significant differences among seasonal 25(OH)D_3 concentrations. One likely reason may be that in rheumatic conditions, sunlight exposure is reduced not only by the seasonality, but also by several disease-dependent factors, i.e. reduced mobility, frequent hospitalizations, or avoidance of sunlight exposure in SLE [17, 24]. On the other hand, the great majority of our patients, especially those on glucocorticosteroid therapy, are routinely supplemented with vitamin D throughout the year as part of osteoporosis prophylaxis, and therefore the seasonal variations of vitamin D status may not be so prominent.

We found the vitamin D intake rate relatively high, reaching 80% of the studied population, whereas the mean supplemented doses of cholecalciferol fell within the prophylactic dose range (800–2000 IU/day) recommended for adults in Poland [30].

On the other hand, in our study, a significant correlation between 25(OH)D_3 level and dose of supplemented vitamin D was found only in the SLE group, whereas in GPA and SSc patients standard vitamin D doses did not significantly influence the 25(OH)D_3 status.

Similarly to our results, other studies [33, 34] reported that common vitamin D supplementation does not correct the deficiency in SSc patients. One possible explanation may be the reduced vitamin absorption capacity through the thickened intestine wall in the course of the disease [21].

Higher vitamin D levels in SSc patients treated with glucocorticosteroids (which were administered in this order to relieve the symptoms of myositis and/or interstitial lung disease) might be related to potential anti-inflammatory GS action within intestines and improved intestinal absorption. Various other obtained results of statistical analysis correlating vitamin D doses and vitamin D serum concentrations may be a consequence of either altered intestinal absorption or inconsistent compliance in some patients.

As for granulomatosis with polyangiitis, given the small number of patients recruited to our study, larger-scale investigations are needed to assess the effect of vitamin D treatment on correcting 25(OH)D_3 deficiency.

Interestingly, we found no statistically significant differences in 25(OH)D_3 levels between the SLE, GPA and SSc patients, despite different prevalence of factors known to be associated with vitamin D deficiencies, i.e. osteoporosis, bone fractures and proteinuria [17, 35–38].

Additionally, although the prevalence of 25(OH)D_3 insufficiency/deficiency varied between the diseases (43.8% in SLE, 65.9% in SSc and 72.4% in GPA), the differences did not reach statistical significance ($p = 0.266$).

One possible explanation of the similar frequency of low vitamin D levels among patients with different rheumatic disorders may be that there are other common determinants, such as geographical latitude, nutritional habits, lifestyle or the chronic nature of the disease itself, that play a crucial role in maintaining vitamin D status, irrespectively of the diagnosis.

On the other hand, the lack of statistically significant differences may be due to the too small size of the investigated subgroups, and further studies on larger cohorts are planned to confirm and expand these results showing e.g. the percentage of patients with 25(OH)D_3 levels > 30 ng/ml according to the dosage of vitamin D and selected clinical parameters.

To date, no specific guidelines regarding dosing of vitamin D in Polish patients with rheumatic diseases have been clearly established. However, taking into account the prevalence of vitamin D insufficiency and deficiency in our group, despite its common supplementation, it seems that patients suffering from rheumatic diseases should be recommended to take vitamin D at higher doses than the general population, preferentially adjusted to serum 25(OH)D_3 concentration.

We suggest individualizing the dosage in these patients, starting with 2000 IU of cholecalciferol daily, followed by serum level assessment after 3 months and subsequent appropriate dosage modifications to maintain concentrations within the optimal range.

Conclusions

We have found that the problem of vitamin D insufficiency and deficiency is quite common among patients with rheumatic disorders, despite high frequency of vitamin D supplementation. To date, no recommendations regarding vitamin D supplementary doses have been established for this specific group of patients in Poland.

However, in view of the ongoing studies regarding potential associations between vitamin D concentrations and prevalence and outcomes of rheumatic diseases, it seems reasonable to advise its regular prophylactic administration.

The present results suggest that the cholecalciferol dosage recommended for the general population is not sufficient for patients with rheumatic diseases and that seasonal changes of doses are not advisable in these diseases. The present study supports the use of higher initial daily doses of vitamin D (2000 up to 4000 UI) for patients with rheumatic diseases.

Further research in a large group of patients taking various doses of vitamin D should make it possible to establish the appropriate dosage required in selected rheumatic diseases.

The authors declare no conflict of interest.

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