Significantly Decreased Serum 25-Hydroxyvitamin D Levels in a Large German Systemic Sclerosis Cohort

To the Editor:

Rios Fernandez, *et al*[1] have reported significantly decreased serum 25-hydroxyvitamin D (25OHD) levels in patients with systemic sclerosis (SSc) from the south of Spain. Since 25OHD levels have been studied predominantly in sun-rich countries such as Italy, Spain, and Israel[1,2,3,4,5,6,7], we evaluated the serum levels of 25OHD in a large cohort of patients with SSc from Germany.

Patients with SSc were prospectively recruited over a 2-year period (n = 137). Patients were taking no 25OHD substitution. The study was conducted in accord with the Declaration of Helsinki and followed a protocol approved by our institutional review board; informed consent was obtained from all subjects.

Where appropriate, the diagnosis was based on clinical, histological, and serological findings. Two subtypes of SSc, diffuse cutaneous SSc and limited cutaneous SSc, were distinguished, as described[8]. A standardized full examination was performed in all patients[9]. Serum 25OHD levels were assessed using the direct competitive chemiluminescence Liaison® immunoassay. The lowest reportable value is 4 ng/ml, based on an interassay precision that approximates 20% CV (functional sensitivity). Data analysis of serum 25OHD levels was performed using the MedCalc Software statistical package (MedCalc, Mariakerke, Belgium). Distribution of data was assessed by the D'Agostino-Pearson test. Normally distributed data were expressed as mean and SD, non-normally distributed data as medians and range. Data were analyzed using the chi-square test, Kendall's tau coefficient of rank correlation, and multiple regression procedure. P values < 0.05 were considered significant.

Clinical data of patients with SSc is given in Table 1. Data on serum 25OHD levels proved to be non-normally distributed, showing a significant coefficient of skewness, 1.13 ($p < 0.0001$; Figure 1). Median detectable serum 25OHD levels (n = 133, excluding 4 cases) were 13.1 ng/ml (range 4.1–47.8 ng/ml). Forty-nine (137/35.8%) patients (including 4 with serum 25OHD levels < 4 ng/ml) had 25OHD deficiency (i.e., 25OHD < 10 ng/ml), 74 (133/54%) had 25OHD insufficiency (25OHD ≥ 10 < 30 ng/ml), and only 14 (137/10.2%) patients had serum 25OHD levels within the normal range (30–100 ng/ml). There was no significant relationship between serum 25OHD levels and clinical variables including SSc subtypes, lung fibrosis, renal involvement, gastroesophageal reflux disease, digital ulcers, modified Rodnan skin score, antinuclear autoantibodies, age, sex, body mass index, and therapy.

Experimental studies on 25OHD have revealed a novel role in the immunopathogenesis of autoimmune diseases. Disorders such as systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis have all been associated to some extent with 25OHD deficiency[10]. Arnson, *et al*[3] found that patients from Israel with SSc had significantly lower serum 25OHD concentrations compared to healthy controls; moreover, fibrosis of the cutaneous tissue appeared to be inversely related to the 25OHD concentration.

In patients from Italy with SSc, Caramaschi, *et al*[6] recently found a mean 25OHD concentration of 15.8 ± SD 9.1 ng/ml. Indeed, 25OHD insufficiency and deficiency were found in 43 (66.3%) and 19 (29.2%) cases, respectively. Patients with 25OHD deficiency showed longer disease duration, lower diffusing lung capacity for carbon monoxide, higher estimated pulmonary artery pressure, and higher values of C-reactive protein in comparison with patients with 25OHD insufficiency. No patient showed evidence of overt malabsorption[6].

Vacca, *et al*[5] investigated 25OHD concentrations in 2 independent SSc populations from northern France (n = 90) and south Italy (n = 66). Insufficiency and deficiency rates were very high and were comparable between the 2 populations. These rates were not influenced by 25OHD supplementation, which was not statistically different in the 2 groups. In the combined populations, a significant negative correlation was found between low 25OHD levels and European Disease Activity Score, and low levels of 25OHD were associated with the systolic pulmonary artery pressure[5]. By contrast, Belloli, *et al*[2] did not find significantly decreased 25OHD levels in Italian patients with SSc compared to a control group of patients with osteoarthritis.

We have shown that 25OHD deficiency is substantial in a country with moderate sun exposure. However, the 25OHD levels and frequencies of 25OHD deficiency observed in our trial were comparable to the 25OHD data from patients with SSc studied in sun-rich countries[1,2,3,4,5,6,7]. Hence, 25OHD deficiency in patients with SSc is probably not dependent on the geographic location[5]. Similar to the research of Rios Fernández, *et al*[1] and Calzolari, *et al*[7], we found no significant relationships between decreased serum 25OHD levels and clinical features of patients with SSc.

Nevertheless, based on our findings and much evidence in the literature, it is worthwhile to examine 25OHD deficiency in SSc; and further research is needed to determine the pathogenetic significance of 25OHD deficiency in SSc and to demonstrate the benefits of correcting 25OHD status in these patients[1,5].

Table 1. Clinical data and serum 25-hydroxyvitamin D (25OHD) levels of patients with systemic sclerosis (SSc; n = 137) [limited type (n = 76, 55.5%); diffuse type (n = 61, 44.5%)].

Characteristic	
25OHD*, median (range), ng/ml	13.1 (4.1–47.8)
< 10 ng/ml	49 (137/35.8%)
≥ 10 < 30 ng/ml	74 (137/54%)
≥ 30 ng/ml	14 (137/10.2%)
Male/female	18/119 (13.1%/86.9%)
Age, yrs, mean ± SD	56 ± 13.6
Antibodies (%)	
No antibodies	22 (16.1)
ANA without specific antibodies	30 (21.9)
Anticentromere	58 (42.3)
SCL-70	27 (19.7)
Digital ulcers (%)	
No ulcers	103 (75.2)
Active ulcers	17 (12.4)
History of ulcers	17 (12.4)
Kidney disease (%)	
Yes	4 (2.9)
No	133 (97.1)
GERD (%)	
Yes	73 (53.3)
No	64 (46.7)
Lung fibrosis (%)	
Yes	73 (53.3)
No	64 (46.7)
Modified Rodnan skin score, mean ± SD	10.1 ± 7.3
Body mass index, median (range)	24 (13–43)
Treatment (%)	
No therapy	55 (40.1)
MTX or azathioprine	14 (10.2)
Corticosteroids	17 (12.4)
Corticosteroids plus MTX or azathioprine	14 (10.2)
Other therapy or combination	37 (27.1)

* Excluding 4 cases with 25OHD levels < 4 ng/ml. GERD: gastroesophageal reflux disease; MTX: methotrexate; ANA: antinuclear antibody.

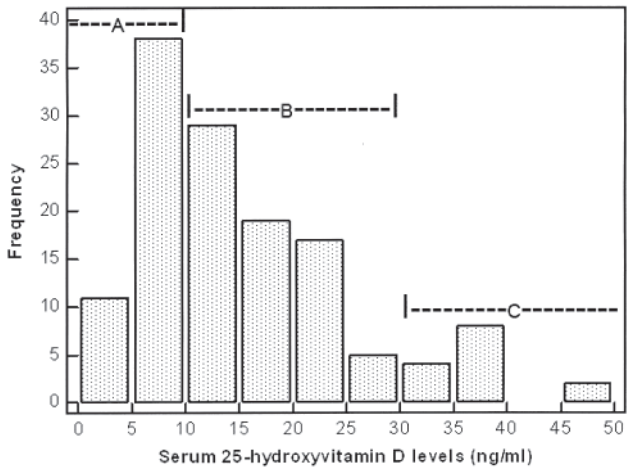

Figure 1. Serum 25-hydroxyvitamin D (25OHD) levels in 137 patients with systemic sclerosis (A: 25OHD deficiency, B: 25OHD insufficiency, C: normal range of 25OHD). There is non-normal distribution of data (coefficient of skewness 1.13; $p < 0.0001$).

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