Vitamin D, Parathyroid Hormone, and Acroosteolysis in Systemic Sclerosis

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ABSTRACT. ***Objective.*** Sclerodactyly with acroosteolysis (AO) and calcinosis are prominent features of systemic sclerosis (SSc), but the pathogenesis of these findings is poorly understood. Vitamin D and parathyroid hormone (PTH) have a crucial role in bone metabolism and resorption and may affect AO and calcinosis. We assessed vitamin D and PTH in patients with SSc.

Methods. Medical records of 134 consecutive patients with SSc (American College of Rheumatology criteria) followed at the rheumatology department during the years 2003–2006 were reviewed for clinical assessment, laboratory evaluation [including 25(OH) vitamin D, calcium, phosphorus, alkaline phosphatase, PTH, creatinine, and albumin]; imaging data confirming AO and/or calcinosis. Patients followed routinely at least once a year were included (81 patients). Of these, 60 patients' medical records were found to have complete, relevant clinical, laboratory, and radiographic imaging.

Results. Thirteen patients had diffuse disease and 47 limited disease — 51 women and 9 men, 44 Jews and 16 Arabs; mean age 55 ± 14 years; disease duration 8 ± 6 years. AO with or without calcinosis was observed in 42 patients (70%). Vitamin D deficiency was found in 46% of patients (16 out of 44 Jewish patients, 10 out of 16 Arab patients). PTH was elevated in 21.7% of patients. Significant correlations were observed between acroosteolysis and PTH ($p = 0.015$), calcinosis ($p = 0.009$), and disease duration ($p = 0.008$), and between PTH and vitamin D levels ($p = 0.01$). All patients had normal serum concentrations of calcium, phosphorus, magnesium, and albumin, and liver and kidney functions.

Conclusion. In this group of Mediterranean patients with SSc, the incidence of vitamin D deficiency and secondary hyperparathyroidism was surprisingly high. This finding correlated with the occurrence of AO and calcinosis. Low levels of vitamin D may reflect silent malabsorption and might be a risk factor for secondary hyperparathyroidism and bone resorption. Traditional dress habits and low exposure to sun may contribute to vitamin D deficiency in an Arab population but do not explain all the findings. The pathogenesis of these findings needs to be corroborated in other SSc populations. (First Release Oct 1 2008; J Rheumatol 2008;35:2201–5; doi:10.3899/jrheum.071171)

Key Indexing Terms:
ACROOSTEOLYSIS SYSTEMIC SCLEROSIS CALCINOSIS
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Systemic sclerosis (SSc) is a connective tissue disease characterized by vascular, immune, and fibrotic changes in the skin and in internal organs. Acroosteolysis (AO) and calcinosis are characteristic findings in SSc; they can be observed by eye or be diagnosed by hand radiographs[1,2]. Their prevalence has been estimated as 22%–80% and 10%–50%, respectively[3-5]. AO is characterized by terminal digital tuft resorption that leads to "sharpening" of the phalanx and in severe cases to destruction of the distal phalange, resulting in tapering of the fingers[1,2]. Most of the amorphous calcifications (calcinosis) in SSc are located in hands, although other sites have also been reported[1,2]. The pathogenesis of AO and calcinosis is poorly understood. They were both associated with vascular digital and systemic complications, suggesting a role for vascular injury in pathogenesis[5]. We treated a patient with SSc with calcinosis and rapidly progressive AO (Figure 1) who eventually was found to have a parathyroid adenoma. This led to the hypothesis that secondary hyperparathyroidism might be involved in the pathogenesis of AO and calcinosis in SSc.

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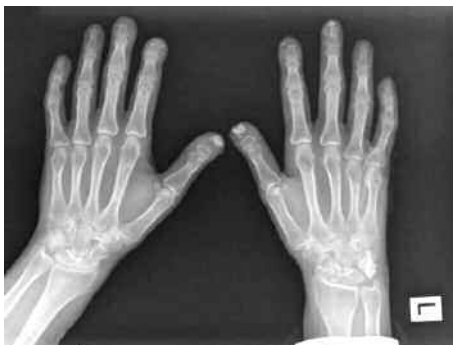

Figure 1. Hand radiograph of the patient with SSc and hyperparathyroidism.

Many disorders may lead to secondary hyperparathyroidism, among them, vitamin D deficiency.

Our aim was to assess vitamin D and parathyroid hormone (PTH) in patients with SSc and look for a possible correlation between PTH and vitamin D levels and AO and calcinosis.

MATERIALS AND METHODS

This was a retrospective review of medical records of 134 consecutive patients with SSc (according to American College of Rheumatology criteria) seen at the Rheumatology Department of Rambam Health Care Campus, Haifa, during the years 2003–2006, with approval from the local ethics committee. Patients followed routinely at least once a year were included (81 patients). Clinical, laboratory, and imaging data were recorded, including demographic data, SSc subtype, disease duration (date of first non-Raynaud's symptom), duration of Raynaud's phenomenon, recurrent diarrhea, recent weight loss, physical examination, modified Rodnan skin score (MRSS), and imaging data (radiographs of hands or sites of underlying calcinosis). Laboratory tests included complete blood count, erythrocyte sedimentation rate, liver and kidney function tests, serum levels of calcium, phosphorus, magnesium, alkaline phosphatase, 25(OH) vitamin D, prothrombin time, international normalized ratio, and PTH. Immunoassay Elecsys PTH Test System was used for quantitative determination of intact PTH in plasma or serum, and DiaSorin 25(OH) D ^{125}I radioimmunoassay kit was used for quantitative determination of 25(OH) vitamin D in plasma or serum. Normal levels of PTH and 25(OH) vitamin D were defined as 15–65 ng/l, 12–55 ng/ml, respectively. Starting in mid-2003, SSc patients followed at our department were usually tested for PTH and 25(OH) vitamin D and underwent yearly hand radiograph. AO was defined as evidence of terminal digital tuft resorption on hand radiographs. Radiographs were evaluated by 2 rheumatologists, and in cases where there was not consensus, by a musculoskeletal radiologist.

Statistical analysis was undertaken using descriptive statistics, Student's t test, and Mann-Whitney rank test to compare variables of the groups, chi-square test to look for a relationship between AO and PTH or vitamin D; Spearman's correlation was used for possible associations between AO, calcinosis, PTH, vitamin D, disease duration, and age. Multiple linear regression was used, with AO as the dependent variable and PTH, vitamin D, calcinosis, disease duration, age, weight loss, and diarrhea as the independent variables for predictive modeling.

RESULTS

Study population. Out of 81 SSc patients followed routinely, 60 patients' medical records were found to have complete, relevant clinical, laboratory, and imaging data and were included into the study. Most patients were women (n = 51, 85%), with a mean (range) age of 55 (20–83) years and disease duration of 8 (1–25) years. Forty-seven patients (78.3%) had limited cutaneous disease (mean MRSS 3.2 ± 1.7) and 13 (21.7%) had diffuse disease (mean MRSS 9.8 ± 4.3)[6]. Demographic, clinical, and laboratory data are summarized in Table 1.

AO and calcinosis. AO with or without calcinosis was observed in 42 patients out of 60 (70%): 16 (26.7%) had AO alone, 26 (43.3%) had AO and calcinosis, 2 (3.3%) had calcinosis alone, and 16 (26.7%) had no radiologic abnormalities (Table 2). All 13 patients with diffuse SSc had AO.

PTH and vitamin D. The most remarkable finding was the high percentage (46%) of patients with hypovitaminosis [25(OH) vitamin D < 12 ng/ml], especially among the Arab patients (10/16 Arab patients and 16/44 Jewish patients, respectively). Ethnicity (Arab origin) was significantly correlated to hypovitaminosis ($p = 0.009$). Four of the patients had severe hypovitaminosis [25(OH) vitamin D < 5 ng/ml]. PTH was elevated in 13 patients (21.7%), all of whom had low serum vitamin D (9.4 ± 1.8 ng/ml). PTH was normal in 15/26 patients with low vitamin D. All patients had normal concentrations of calcium, phosphorus, albumin, magnesium, and liver and kidney function tests. Six patients received coumadin therapy for different indications. Prothrombin time and international normalized ratio were normal in all other patients. Forty percent of patients with AO (17/42) and 56% of patients with no radiological abnormalities (9/16) received calcium and vitamin D supplements. No significant correlation was found between calcium supplementation and vitamin D levels or AO.

Correlation between PTH, vitamin D, AO, and calcinosis. Low concentrations of vitamin D (7.3 ± 2.2 ng/ml) were found in half the patients with AO with or without calcinosis, compared to only 28% in those without AO (8.2 ± 1.8 ng/ml). High PTH (80.4 ± 22.8 ng/l) was found in 13/42 patients with AO. However, all patients without AO had normal PTH (41.3 ± 13.5 ng/l). A statistically significant relationship was found between AO and PTH (chi-square with 1 degree of freedom = 5.936, $p = 0.015$), but not between AO and vitamin D (chi-square with 1 degree of freedom = 0.578, $p = 0.447$; Figure 2).

AO was also found to be associated with calcinosis ($p = 0.009$) and disease duration ($p = 0.008$). Statistically significant relationships were found between PTH and vitamin D ($p = 0.01$, $r = –0.312$), and between calcinosis, age ($p = 0.024$), and disease duration ($p = 0.005$), but not between PTH or vitamin D and disease duration or severity.

Thirteen patients with small-bowel involvement of SSc (defined as recurrent diarrhea and/or pseudoobstruction and imaging findings of pseudoobstruction or pneumatosis cystoides intestinalis on abdominal CT or small-bowel series) had intermittent diarrhea, with significant weight loss in 6 of them, but no significant association was found between diar-

Table 1. Demographic, clinical, and laboratory measures.

Characteristic	Total	AO	Without AO
Female/male, n	51/9	35/7	16/2
Ethnicity, Jews/Arabs, n	44/16	30/12	16/2
Disease form, limited/diffuse, n	47/13	29/13	18/0
Age, mean ± SD yrs	55 ± 14	54.3 ± 14.2	56 ± 17.6
Disease duration, mean ± SD yrs	8 ± 6	9 ± 6.3	5.8 ± 5.7
PTH, mean ± SD ng/l	45.9 ± 22.7	49 ± 26.1	39.6 ± 10.5
25(OH) vitamin D, mean ± SD ng/ml	13.8 ± 7.2	13.3 ± 7.6	14.8 ± 6.8

AO: acroosteolysis, PTH: parathyroid hormone.

Table 2. Radiologic abnormalities.

Observation	No. of Patients
Acroosteolysis alone	16
Acroosteolysis + calcinosis	26
Calcinosis alone	2
No acroosteolysis, no calcinosis	16

rhea or weight loss and AO or calcinosis. Mean vitamin D in patients with diarrhea and/or weight loss was 13 ± 8.1 ng/ml and 9.2 ± 3.6 ng/ml, respectively. Patients without diarrhea and/or stable weight had mean vitamin D of 14.6 ± 7.2 and 14.4 ± 6.9 ng/ml, respectively.

DISCUSSION

Twenty-one percent of our patients (all with AO) had elevated PTH. Taking into consideration the normal calcium and phosphorus concentration in these patients, we may assume that hyperparathyroidism was secondary to low vitamin D levels. The high prevalence of vitamin D hypovitaminosis among patients (46%) is puzzling, considering the high sun exposure in our Mediterranean country.

Most patients in our study had limited disease, obviating

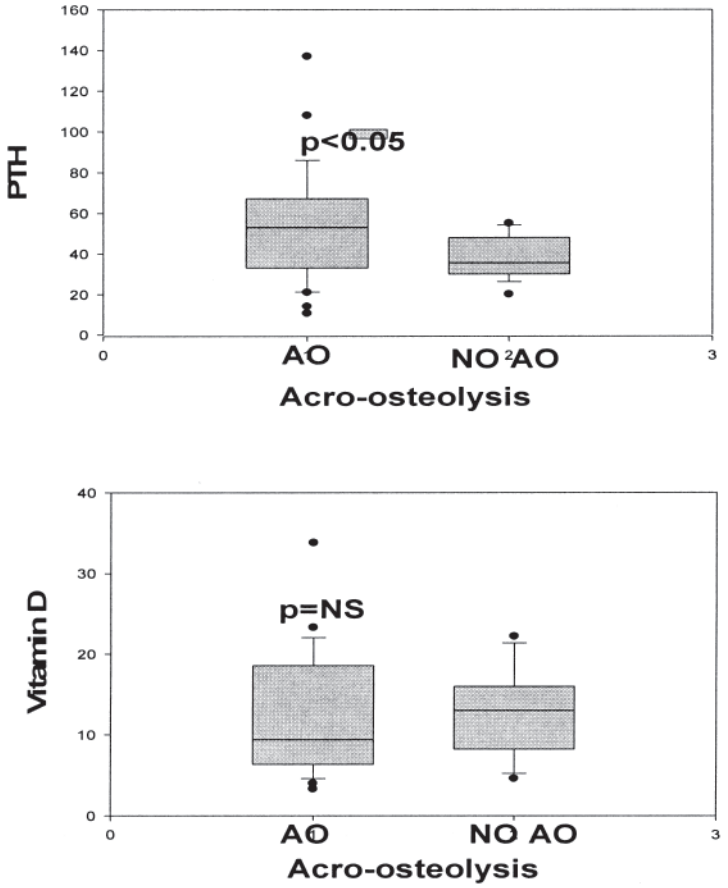

Figure 2. Correlation between levels of PTH, Vitamin D 25OH, and the presence of acroosteolysis (AO)

any connection between the amount of skin involvement and inadequate endogenous vitamin D production by the skin after exposure to ultraviolet B light.

Three factors might contribute to low concentrations of vitamin D in our patients, as follows.

(1) Low sun exposure and traditional dress habits: The clothing that religious Arab women or Orthodoxic Jewish women wear expose very little skin to sunshine. Several studies showed a correlation between traditional dressing habits and low vitamin D[7-9] and even showed a relationship between these dressing habits and development of rickets and osteomalacia[10].

(2) Malabsorption: The small bowel is frequently involved in patients with SSc (50%–70%), and abnormal motility patterns, mostly asymptomatic, have been found in 80%–88% of patients[11-13]. Although we found no significant correlation of diarrhea or weight loss with low vitamin D among our patients, we did not test all patients for malabsorption, and silent malabsorption might contribute to vitamin D deficiency.

(3) Inflammatory disease: There is mounting evidence that vitamin D plays a role in modulation of the immune system. Vitamin D maintains equilibrium between T helper 1 (Th1) and Th2 cells. Calcitriol (1,25 dihydroxyvitamin D) can inhibit the synthesis of mRNA of macrophage-derived cytokines such as interleukin 1 (IL-1), IL-6, IL-12 and tumor necrosis factor-α (TNF-α), suppress the IL-2 secretion of Th1 cells, and decrease the antigen-presenting activity of macrophages to lymphocytes[14-18]. Epidemiologic data indicate low vitamin D concentrations in autoimmune diseases such as rheumatoid arthritis, inflammatory bowel disease, and multiple sclerosis[19-22]. In a small study in 20 patients with scleroderma, concentrations of 25(OH) vitamin D, 24-25-$(OH)_2$ vitamin D, and vitamin D-binding protein were within the normal ranges, although significantly lower concentrations of 1,25 $(OH)_2$ vitamin D were found in patients with calcinosis[23]. In a larger study (45 SSc patients), the same authors described high levels of PTH that correlated with calcinosis[24].

High PTH concentrations, among other factors, might play a role in development of AO in SSc. Low levels of vitamin D are one of the main causes of secondary hyperparathyroidism. There are no satisfactory explanations why only half our patients with low vitamin D developed secondary hyperparathyroidism. The duration of exposure to low vitamin D levels might contribute to this; we had insufficient data to confirm this, and in our clinic once vitamin D hypovitaminosis is found, the patient receives vitamin D supplements.

Vitamin D and PTH play a crucial role in bone metabolism. Serum levels of 25(OH) vitamin D are the best indicator to assess vitamin D deficiency[14]. Low 25(OH) vitamin D levels are associated with low calcium absorption rates, hyperparathyroidism, and increased bone turnover[14]. PTH upregulates the expression of receptor activator of nuclear factor-κB ligand (RANKL) and macrophage-colony stimulating factor (M-CSF) on stromal cells and osteoblasts, and downregulates expression of osteoprotegerin. RANKL and M-CSF induce commitment of stromal cells to the osteoclast phenotype. The osteoclasts provide an optimal acidic extracellular microenvironment for organic matrix degradation by cathepsin K[25].

The prevalence of AO with or without calcinosis in our patients was quite high (70%), similar to some previous reports, but not to all[3-5]. At our tertiary referral center, our cohort might include more patients with moderate to severe disease, and this might partially explain the high prevalence of AO.

The causative mechanisms leading to AO in patients with SSc remain to be elucidated, although vascular injury has been implicated as a major factor[5]. We suggest that secondary hyperparathyroidism to low vitamin D might contribute to development of AO in some patients.

We are aware of the limitations of the retrospective design of our study and the selective characteristics of patients seen in a tertiary referral center. However, as the largest national center dedicated to scleroderma patients, consulting patients from all over the country, we suggest that our findings of an association between PTH and AO might be representative for these patients, and merits further investigation in large-scale prospective studies. Revealing the pathophysiologic mechanism might lead to novel therapeutic options for the prevention and treatment of a condition for which no current therapy is available.

Our study revealed a relatively high prevalence of acroosteolysis and secondary hyperparathyroidism among patients with SSc. A positive and statistically significant correlation was found between AO and PTH levels. These observations raise the question whether these findings are distinctive for our population only, and whether vitamin D supplementation might lower the risk of AO in SSc. This remains to be corroborated in other SSc populations and in larger prospective studies.

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