

## Vitamin D Metabolites in Generalized Scleroderma

### *Evidence of a Normal Cutaneous and Intestinal Supply with Vitamin D*

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Vitamin D metabolites in serum were analysed in 20 patients with generalized scleroderma. The concentration of 1,25-dihydroxyvitamin D was normal, however, significantly lower concentrations ( $p < 0.05$ ) were found in 7 patients with cutaneous calcinosis in comparison with 13 patients with no calcinosis. Concentrations of 25-hydroxyvitamin D, 24,25-dihydroxyvitamin D, and vitamin D-binding protein (Gc globulin) were all within the normal range. The 24,25-dihydroxy-vitamin D level correlated with the duration of disease ( $r = 0.4453$ ,  $p < 0.05$ ), and 25-hydroxyvitamin D tended to correlate ( $r = 0.3016$ , NS).

The study strongly indicates that cutaneous synthesis, intestinal absorption and hepatic hydroxylation of vitamin D are not deficient in scleroderma. A relative but specific decrease in the renal hydroxylation to 1,25-dihydroxyvitamin D, i.e. the active hormone, as the disease progresses and calcinosis occurs, is suspected. *Key words: Systemic; Calcinosis.* (Received January 3, 1985.)

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Cutaneous calcinosis occurs in about 40% of patients with generalized scleroderma (1). Recent endocrinological studies showed that patients with generalized scleroderma and calcinosis have increased concentration of parathyroid hormone in their blood and evidence of a mild secondary hyperparathyroidism (2). Another study showed a lower concentration of the active vitamin D hormone, i.e. 1,25-dihydroxyvitamin D, in patients with calcinosis in comparison with patients with no calcinosis (3). The hyperparathyroid state may be secondary to deficient intestinal absorption of calcium due to a decreasing formation of 1,25-dihydroxyvitamin D in scleroderma during progress of the disease.

Vitamin D synthesized in the skin or absorbed from the intestines is hydroxylated in the liver to 25-hydroxyvitamin D, and further hydroxylated to 1,25-dihydroxyvitamin D (active hormone) or 24,25-dihydroxyvitamin D (inactive metabolite) in the kidneys (4, 5, 6). Translocation of vitamin D from the skin into the blood stream is determined by a specific carrier protein, i.e. the vitamin D-binding protein (4, 7).

The purpose of this study was to assess if decreasing 1,25-dihydroxyvitamin D in generalized scleroderma possibly related to calcinosis is due to deficient hydroxylation in the liver and the kidneys, intestinal vitamin D malabsorption, or deficient vitamin D synthesis in diseased skin.

## MATERIAL AND METHOD

Twenty patients (14 females, 6 males) with generalized scleroderma were studied. No patient taking vitamin D prophylaxis was included. The mean age was 52.8 years (range 31-67). The mean duration of scleroderma was 8.3 years (range 1-22). Patients were treated with inhibitors of collagen synthesis as described by Asboe-Hansen (8). Eighteen received penicillamine in combination with glutamine, one chlorpromazine, and one glutamine only. Seven patients had cutaneous calcinosis verified by radiography. The study was performed in the winter period from December to March.

Blood samples were taken in the morning. Serum Calcium 'total', Calcium 'ion', and phosphate were determined by standard methods. Serum 1,25-dihydroxyvitamin D, 24,25-dihydroxyvitamin D, 25-hydroxyvitamin D, and vitamin D-binding protein (Gc protein) were analysed by Medicinsk

Laboratorium, Copenhagen, by radioimmunoassay and immune-chemical techniques of the laboratory.

Statistical methods employed were the Wilcoxon rank sum test and the Spearman correlation coefficient.  $p < 0.05$  was considered significant.

## RESULTS

Results of analyses of Calcium and vitamin D in the serum are shown in Table I. The only significant difference between patients with calcinosis and patients with no calcinosis was a decreased concentration of 1,25-dihydroxyvitamin D ( $p < 0.05$ ) in the former. However, patients with calcinosis tended to have greater concentrations of both 25-hydroxyvitamin D and 24,25-dihydroxyvitamin D as compared to patients with no calcinosis.

Analysis of the relation between duration of scleroderma and vitamin D metabolites as well as the carrier protein showed a positive correlation between 24,25-dihydroxyvitamin D and duration ( $r = 0.4453$ ,  $p < 0.05$ ) and a tendency to a correlation to 25-hydroxyvitamin D ( $r = 0.3016$ , NS) while other relations were definitely insignificant (1,25-dihydroxyvitamin D,  $r = 0.1419$ , NS; vitamin D-binding protein,  $r = 0.2289$ , NS).

## DISCUSSION

This study confirmed previous findings of different blood levels of 1,25-dihydroxyvitamin D in scleroderma with calcinosis and scleroderma with no calcinosis, i.e. a decreasing level in calcinosis (3). Concentrations of 25-dihydroxyvitamin D were both within normal ranges.

Patients with rachitis, osteomalacia, cirrhosis of the liver and intestinal conditions with malabsorption have a decreased level of 25-dihydroxyvitamin D in the blood (5). Thus, despite cutaneous as well as frequent internal involvement of patients with generalized scleroderma this study strongly indicated that the cutaneous synthesis and intestinal absorption of vitamin D, and the hydroxylation in the liver were all normal.

Decreasing 1,25-dihydroxyvitamin D concentrations in scleroderma patients with calcinosis might be due to a relative and selective defect in the renal hydroxylation, as the

Table I. Calcium, phosphate, and vitamin D metabolites in serum of patients with generalized scleroderma related to cutaneous calcinosis

|                              | Calcium<br>'total'<br>(mmol/l) | Calcium<br>'ion'<br>(mmol/l) | Phos-<br>phate<br>(mmol/l) | 25-(OH)<br>vit. D<br>(nmol/l) | 24,25-(OH) <sub>2</sub><br>vit. D<br>(nmol/l) | 1,25-(OH) <sub>2</sub><br>vit. D<br>(pmol/l) | Vit. D-<br>binding<br>protein<br>( $\mu$ mol/l) |
|------------------------------|--------------------------------|------------------------------|----------------------------|-------------------------------|---|--|---|
| Calcinosis ( $n = 7$ )       |                                |                              |                            |                               |   |  |   |
| Mean                         | 2.34                           | 1.22                         | 1.18                       | 44.3                          | 3.24  | 71.1   | 5.51  |
| SD                           | 0.06                           | 0.07                         | 0.14                       | 26.0                          | 2.62  | 30.9   | 1.04  |
| No calcinosis ( $n = 13$ )   |                                |                              |                            |                               |   |  |   |
| Mean                         | 2.45                           | 1.26                         | 0.99                       | 32.9                          | 1.85  | 103.0  | 5.67  |
| SD                           | 0.14                           | 0.05                         | 0.17                       | 22.9                          | 2.00  | 39.8   | 1.05  |
| Entire material ( $n = 20$ ) |                                |                              |                            |                               |   |  |   |
| Mean                         | 2.41                           | 1.25                         | 1.06                       | 37.6                          | 2.37  | 92.9   | 5.61  |
| SD                           | 0.13                           | 0.06                         | 0.18                       | 24.2                          | 2.28  | 38.4   | 1.02  |
| Normal range                 | 2.2-2.6                        | 1.15-1.35                    | 0.80-1.48                  | 18.5-82.0                     | 0.37-3.90                                     | 24-(50)-158 <sup>a</sup>                     | 3.6-6.6   |

<sup>a</sup> Distribution in healthy individuals unsymmetric with concentrations of 50-158 pmol/l only occasionally.

significantly increasing level of 24,25-dihydroxyvitamin D during the course of scleroderma might indicate.

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