Evidence for Abnormal Regulation of Circulating
1α,25-Dihydroxyvitamin D in Patients
with Sarcoidosis and Normal Calcium Metabolism

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A B S T R A C T The effects of vitamin D, 2.5 mg (100,000 U)/d for 4 d, on serum calcium, serum 25-
hydroxyvitamin D (25-OHD), and serum 1α,25-dihydroxyvitamin D [1α,25(OH)2D] were compared in 17
normal subjects and 6 patients with sarcoidosis who had normocalcemia and no history of hypercalcemia.
The diagnosis was confirmed histologically in each of
them. Vitamin D increased mean serum 25-OHD from
30±4 to 99±15 ng/ml (P < 0.001) and did not change
mean serum 1α,25(OH)2D (32±3 vs. 29±3 pg/ml) or
mean serum calcium (9.5±0.1 vs. 9.6±0.1 mg/dl) in the
normal subjects. In contrast, vitamin D increased mean
serum 25-OHD from 19±3 to 65±19 ng/ml (P < 0.05),
increased mean serum 1α,25(OH)2D threefold from
40±7 to 120±24 pg/ml, and increased mean serum
calcium from 9.4±0.2 to 9.8±0.2 mg/dl (P < 0.01).
There was a significant positive correlation between
the serum 1α,25(OH)2D and serum calcium in these
individuals (r = 0.663, P < 0.01) but not in the normal
subjects. The results (a) provide further evidence for
abnormal regulation of circulating 1α,25(OH)2D in
sarcoidosis and (b) indicate that the abnormality
may exist in patients with normal calcium metabolism.
Thus, the defect in vitamin D metabolism in sarcoid
apparently is more common than was previously
recognized.

I N T R O D U C T I O N
Available evidence indicates that the abnormal cal-
cium metabolism in sarcoidosis results from increases

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in circulating 1α,25-dihydroxyvitamin D [1α,25-
(OH)2D].1 Mean plasma 1α,25(OH)2D is increased and
serum immunoreactive parathyroid hormone is sup-
pressed in patients with sarcoidosis and hyper-
calcemia who do not have primary hyperparathy-
roidism (1, 2). Further vitamin D, 0.25 mg (10,000 U)/d
for 12 d, increases serum 1α,25(OH)2D abnormally in
patients with normocalcemia and a history of hyper-
calcemia but does not alter serum 1α,25(OH)2D ab-
normally in subjects or patients with sarcoid who have
normal calcium metabolism (1). Thus, the increased
sensitivity to vitamin D in sarcoid results from in-
creases in serum 1α,25(OH)2D. Finally, hypercalcemia
and the increases in circulating 1α,25(OH)2D are cor-
rected after treatment with glucocorticoids (1, 2).

In our previous investigation this dose of vitamin D
produced a modest but significant increase in mean
serum 1α,25(OH)2D (which remained well within
the normal range) in the patients with sarcoidosis and
normal calcium metabolism (1). To determine whether
an abnormal response of serum 1α,25(OH)2D might
be elicited with a larger dose of vitamin D, the effects
of 2.5 mg (100,000 U)/d for 4 d of the vitamin
were compared in normal subjects and patients
with sarcoidosis who had a normal serum calcium
and had never had hypercalcemia.

M E T H O D S
17 adult normal subjects, 9 men and 8 women ranging in
age from 21 to 56 yr, and 6 patients with sarcoidosis, 4 men
and 2 women ranging in age from 23 to 58 yr, were studied.
They were hospitalized at the Clinical Research Center of
the Indiana University Medical School or of the Medical
University of South Carolina. Each of them was given a con-

1 Abbreviations used in this paper: 1α,25(OH)2D, 1α,25-
dihydroxyvitamin D; 25-OHD, 25-hydroxyvitamin D.
constant daily diet estimated to contain 400 mg/d of calcium and 900 mg of phosphorus and a constant fluid intake. Vitamin D₃, 2.5 mg (100,000 U/d) for 4 d, was given as a single morning dose. Fasting blood samples were obtained on the 1st d before vitamin D and again on the 5th d, 24 h after the last dose of the vitamin, for determination of calcium (3, 4), phosphorus (5), creatinine (6, 7), 25-hydroxyvitamin D (25-OHD), and 1α,25(OH)₂D. In the patients, 24-h urines were collected and analyzed for calcium (4).

Serum 25-OHD was measured in triplicate by the competitive protein-binding method with vitamin D-deficient rat serum (8) as described (1). The normal range for the method in this laboratory is from 10 to 80 ng/ml (1).

Serum 1α,25(OH)₂D was measured by bioassay as described (1, 9). The mean value in normal subjects is 32±2 pg/ml and the range is from 15 to 55 pg/ml (n = 33). The 95% confidence values (mean±2 SD) are 13–52 pg/ml. The interassay variation is 9.1% (n = 17).

Student’s t test was used to determine the significance of differences between paired or unpaired samples (10). Correlation coefficient was carried out with a Hewlett-Packard calculator (model 9815A, Hewlett-Packard Co., Palo Alto, Calif).

**RESULTS**

The diagnosis of sarcoidosis was confirmed histologically in each of the patients (Table I). None of them had hypercalcemia and none had received steroids for at least 1 yr before the study. Serum calcium was normal in each of them and urinary calcium was above 200 mg/d in one of them.

The effects of vitamin D, 2.5 mg/d for 4 d, were examined in 17 normal subjects and in 6 patients with sarcoid (Table II). In the normal subjects vitamin D increased mean serum 25-OHD significantly, but did not alter mean serum calcium, phosphorus, creatinine, or 1α,25(OH)₂D.

In contrast, vitamin D increased mean serum calcium, phosphorus, 25-OHD, and 1α,25(OH)₂D and did not change mean serum creatinine in the patients. The increases in serum 1α,25(OH)₂D ranged from 57% in patient F to 797% in patient D and averaged 195%. Whereas before vitamin D mean serum 1α,25(OH)₂D was not significantly different between the normal subjects and patients, after vitamin D it was significantly higher in the patients than in the normal subjects (P < 0.001). Furthermore, there was a significant positive correlation between the serum 1α,25(OH)₂D and serum calcium in the patients (Fig. 1) but not in the normal subjects. Urinary calcium averaged 116, 139, 239, 72, and 214 mg/d.

### TABLE I

**Clinical Findings in Patients with Sarcoidosis**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Serum Ca</th>
<th>Urinary Ca</th>
<th>Biopsy</th>
<th>Hypercalcemia*</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>58</td>
<td>F</td>
<td>9.0</td>
<td>112</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>B</td>
<td>27</td>
<td>M</td>
<td>9.4</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>C</td>
<td>33</td>
<td>F</td>
<td>9.2</td>
<td>174</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>D</td>
<td>26</td>
<td>M</td>
<td>9.5</td>
<td>255</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>E</td>
<td>31</td>
<td>M</td>
<td>9.6</td>
<td>86</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>F</td>
<td>23</td>
<td>M</td>
<td>9.6</td>
<td>156</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

* By history.

### TABLE II

**Effects of Vitamin D₃ on Serum Calcium, Phosphorus, Creatinine, 25-OHD, and 1α, 25(OH)₂D**

<table>
<thead>
<tr>
<th></th>
<th>Calcium</th>
<th>Phosphorus</th>
<th>Serum creatinine</th>
<th>25-OHD*</th>
<th>1α,25(OH)₂D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects (17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>9.5±0.1</td>
<td>4.1±0.1</td>
<td>0.9±0.1</td>
<td>30±4</td>
<td>32±3</td>
</tr>
<tr>
<td>Vitamin D₁</td>
<td>9.6±0.1</td>
<td>4.1±0.1</td>
<td>1.0±0.1</td>
<td>99±15</td>
<td>29±3</td>
</tr>
<tr>
<td>P value</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>NS</td>
</tr>
<tr>
<td>Patients (6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>9.4±0.2</td>
<td>3.9±0.3</td>
<td>1.0±0.1</td>
<td>19±3</td>
<td>40±7</td>
</tr>
<tr>
<td>Vitamin D₁</td>
<td>9.8±0.2</td>
<td>4.2±0.3</td>
<td>1.0±0.1</td>
<td>65±19</td>
<td>120±24§</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>NS</td>
</tr>
</tbody>
</table>

Results are given as mean±SE.

* Serum 25-OHD was measured in 12 normals before vitamin D and in 9 normals after vitamin D.

† Vitamin D₃, 2.5 mg/d for 4 d, was given by mouth.

§ The difference between control and treated values is not significant (t =2.05) because of the marked increase in serum 1α,25(OH)₂D from 34 to 305 pg/ml in patient D. If these values are omitted, mean serum 1α,25(OH)₂D increased from 42±8 to 83±13 pg/ml (t = 6.06, P < 0.01) in the other patients.
in five patients (A, C, D, E, and F, respectively) during the 4-d period of vitamin D administration and therefore changed very little (Table I).

**DISCUSSION**

Our studies show a clear impairment in the regulation of circulating 1α,25(OH)₂D in a group of patients with sarcoid and apparent normal calcium metabolism. The results provide additional evidence that increases in serum 1α,25(OH)₂D are responsible for the abnormal calcium metabolism in this disease (1, 2) and suggest that the defect in vitamin D metabolism is more common than was previously recognized.

The mechanism for the abnormal vitamin D metabolism in sarcoidosis has not been elucidated. Hypercalcemia was recently reported in a patient with sarcoid who had developed renal failure and had undergone bilateral nephrectomy in preparation for kidney transplantation (11). The hypercalcemia responded to steroids and was associated with suppression of serum immunoreactive parathyroid hormone and increases in serum 1α,25(OH)₂D. Serum calcium and serum 1α,25(OH)₂D values correlated with each other. The findings in this patient support the possibility that in sarcoid the production of 1α,25(OH)₂D may occur in tissues other than that of the kidney.

Our observations in normal subjects suggest that the renal production of 1α,25(OH)₂D is tightly regulated. The findings are consistent with those obtained in patients with vitamin D intoxication, who show increases in serum 25-OHD and not 1α,25(OH)₂D (12). In the rat, vitamin D intoxication with hypercalcemia is characterized by increases in serum 25-OHD and decreases in serum 1α,25(OH)₂D (13). In contrast, vitamin D intoxication in the cow is characterized by increases in all of the metabolites of vitamin D including the vitamin itself, 25-OHD, 24,25-dihydroxyvitamin D, as well as 1α,25(OH)₂D (14).

Urinary calcium did not change appreciably during the 4 d of treatment with vitamin D in our patients despite the increases in serum 1α,25(OH)₂D and modest but significant increases in serum calcium, which remained within the normal range. We demonstrated previously in two patients with sarcoid and a history of hypercalcemia that vitamin D, 250 μg/d for 12 d, increased both serum 1α,25(OH)₂D and urinary calcium. Serum calcium remained within the normal range. The increases in serum 1α,25(OH)₂D were noted by the 5th d of administration of vitamin D and preceded the increases in urinary calcium. Urinary calcium did not change during the initial 4 d of vitamin D. Thus, the period of observation in the present study was too short an interval for an increase in urinary calcium to occur.

**ACKNOWLEDGMENTS**

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**REFERENCES**


