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J N Basile, ... , J Shary, N H Bell

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Research Article

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Increased Calcium Intake Does Not Suppress Circulating 1,25-Dihydroxyvitamin D in Normocalcemic Patients with Sarcoidosis

Jan N. Basile, Yair Liel, Judith Shary, and Norman H. Bell

Department of Medicine, Medical University of South Carolina, Charleston, South Carolina 29425, and the Ralph H. Johnson Department of Veterans Affairs Medical Center, Charleston, South Carolina 29401-5799

Abstract

Ca absorption is regulated by $1,25(\text{OH})_2\text{D}$, and serum values vary inversely with Ca intake. In sarcoidosis, $1,25(\text{OH})_2\text{D}$ is produced by alveolar macrophages in response to γ -interferon, and patients may develop hypercalcemia after prolonged exposure to sunlight and increased dermal production of vitamin D_3 . To determine if increased Ca intake suppresses serum $1,25(\text{OH})_2\text{D}$ in normocalcemic patients and to identify those at risk, 17 normal subjects and 11 patients were studied on a metabolic ward for two and one-half days while receiving first 400 and then 1,000 mg/d of Ca. On the low Ca intake, serum angiotensin-converting enzyme (ACE), an index of disease activity, was higher in only three of the patients than in the controls, mean serum $1,25(\text{OH})_2\text{D}$ was higher in the patients, and mean serum total Ca, serum Ca^{++} , and urinary Ca were not different in the two groups. On the higher Ca intake, mean urinary Ca increased in both groups, but mean serum $1,25(\text{OH})_2\text{D}$ was suppressed only in the normal subjects. Thus, $1,25(\text{OH})_2\text{D}$ production is abnormally regulated, indicating that (a) normocalcemic patients with sarcoidosis are at risk for developing abnormal Ca metabolism, and (b) a better index of disease activity is provided by the oral Ca suppression test than by serum ACE. (*J. Clin. Invest.* 1993. 91:1396–1398.) Key words: sarcoidosis • calcium • 1,25-dihydroxyvitamin D • 25-hydroxyvitamin D • angiotensin-converting enzyme

Introduction

Circulating $1,25(\text{OH})_2\text{D}$ is the major determinant of intestinal absorption of calcium (1, 2). Values are increased when calcium intake is low and are reduced when calcium intake is high (1, 2). $1,25(\text{OH})_2\text{D}$ binds to its receptors in intestinal mucosa to enhance the transport of calcium (3). Renal production of the metabolite is closely regulated by PTH (4, 5), calcium (6), and phosphate (7, 8) so that, even in vitamin D intoxication, hypercalcemia and abnormal calcium metabolism are caused by elevation of serum 25-hydroxyvitamin D [$25(\text{OH})\text{D}$]¹ and

not $1,25(\text{OH})_2\text{D}$ (9). Abnormal calcium metabolism in sarcoidosis results from increased circulating $1,25(\text{OH})_2\text{D}$ that is produced by alveolar macrophages and probably by other cells in the granuloma (10–12).

We demonstrated previously that administration of small doses of vitamin D, 10,000 U/d for 12 d, to normocalcemic patients with sarcoidosis and no history of abnormal calcium metabolism increased serum $1,25(\text{OH})_2\text{D}$ and urinary calcium in each of them (13) and that administration of larger doses of vitamin D, 100,000 U/d for 4 d, to normocalcemic patients without a history of abnormal calcium metabolism increased serum $1,25(\text{OH})_2\text{D}$ and serum calcium in each of them (14). In contrast, mean serum calcium and mean serum $1,25(\text{OH})_2\text{D}$ did not change in the normal subjects. These studies indicate that production of $1,25(\text{OH})_2\text{D}$ in sarcoidosis is not normally regulated, even in patients with a normal serum calcium.

In view of these findings, an investigation was performed in normal subjects and normocalcemic patients with sarcoidosis to identify those at risk for developing abnormal vitamin D and calcium metabolism. The utility of serum ACE to indicate activity of the disease also was investigated (15, 16).

Methods

17 normal subjects, 10 men and 7 women, and 11 patients with sarcoidosis, 5 men and 6 women, were admitted to the General Clinical Research Center of the Medical University of South Carolina for 2.5 d. They ranged in age from 20 to 48 yr. The diagnosis of sarcoidosis was confirmed histologically in each of the patients. All of them were given a daily diet containing 400 mg of calcium and 900 mg of phosphate. Fasting blood samples were obtained for measurement of serum calcium (17), Ca^{++} , inorganic phosphate (18), ACE, $25(\text{OH})\text{D}$ (19, 20) and $1,25(\text{OH})_2\text{D}$ (20) and two consecutive 24-h urine samples were obtained for measurement of calcium (17) and inorganic phosphate (18). Urinary creatinine (21) was determined to ensure that urine collections were complete. Both the normal subjects and patients were readmitted for a second study after they had been given elemental calcium (calcium carbonate), 200 mg by mouth 3 times a day for 1 week (22). The added calcium was continued during the second study. Statistical analyses were carried out with Student's paired and unpaired *t* tests.

Results

There were eight black and three white patients (Table I). The diagnosis in each of them was established by biopsy. None of them had had hypercalcemia, serum calcium and serum Ca^{++} were normal in all of them, and urinary calcium was increased in two of them. Serum ACE was elevated in three patients, but serum $1,25(\text{OH})_2\text{D}$ was elevated in only one patient. As judged by clinical findings—the presence of skin lesions, uveitis, dyspnea, easy fatigue, abnormal liver function tests, ele-

Address correspondence and reprint requests to Dr. Norman H. Bell, Ralph H. Johnson Department of Veterans Affairs Medical Center, 109 Bee Street, Charleston, SC 29401-5799.

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1. Abbreviations used in this paper: ACE, angiotensin-converting enzyme; $25(\text{OH})\text{D}$, 25-hydroxyvitamin D.

Table I. Clinical Findings in Patients with Sarcoidosis

Patient	Age	Sex	Race	Serum calcium	Serum 1,25(OH) ₂ D	Serum ACE	Urinary calcium	Biopsy	Hypercalcemia*
	yr			mg/dl	pg/ml	U	mg/d		
A	29	M	B	9.4	31	33	115	+	—
B	35	M	B	9.4	39	29	169	+	—
C†	38	F	B	9.0	38	68	201	+	—
D	39	M	B	9.4	28	22	122	+	—
E	31	F	B	9.4	64	68	78	+	—
F	26	F	W	8.7	44	30	188	+	—
G	22	M	B	9.0	42	28	20	+	—
H	39	F	W	8.7	44	29	313	+	—
I†	48	F	B	9.5	39	35	244	+	—
J	48	M	W	9.3	22	19	225	+	—
K	35	M	B	9.4	41	54	79	+	—

* By history.

† Subsequently developed hypercalcemia.

Urine values are the mean of two consecutive 24-h collections.

vated serum ACE or abnormal chest x-ray—all of the patients except one had active disease. One patient eventually died of pulmonary insufficiency caused by sarcoidosis.

In control studies, mean serum ACE was significantly higher, mean serum 25(OH)D was significantly lower in the patients than in the normal subjects, and mean serum calcium, serum Ca⁺⁺ and phosphate and urinary calcium were not different in the two groups (Table II). Mean urinary phosphate was significantly higher in the normal subjects than in the patients.

Increasing the calcium intake from 400 to 1,000 mg/d significantly increased mean urinary calcium by 44%, lowered mean urinary phosphate in the normal subjects, and significantly increased mean urinary calcium by 50% in the patients (Table II). Mean serum calcium, serum Ca⁺⁺, and serum 25(OH)D did not change in either the normal subjects or patients. Mean serum phosphate increased modestly in the normal subjects in response to the calcium, but did not change in

the patients. The increased calcium intake significantly lowered mean serum 1,25(OH)₂D in the normal subjects but not in the patients (Table II, Figure 1).

Discussion

As noted already, we found that administration of modest doses of vitamin D to normocalcemic patients either with or without a history of hypercalcemia produced increases in serum 1,25(OH)₂D and abnormal calcium metabolism in each of them (13, 14). The present findings showing failure of increased calcium intake to diminish serum 1,25(OH)₂D in another group of normocalcemic patients with sarcoidosis who had no history of hypercalcemia provide evidence for abnormal vitamin D metabolism by a different means. In similar studies it was found that increases in calcium intake from 400 to 1,000 mg/d did not alter serum 1,25(OH)₂D in two patients with sarcoidosis in whom serum values were abnormally ele-

Table II. Effects of Increased Calcium Intake on Vitamin D and Calcium Metabolism in Normal Subjects and Patients with Sarcoidosis

Treatment	Serum Ca	Serum Ca ⁺⁺	Serum P	Serum 25(OH)D	Serum ACE	Serum 1,25(OH) ₂ D	Urinary Ca	Urinary P
	mg/dl	mg/dl	mg/dl	ng/ml	U	pg/ml	mg/d	mg/d
Normal subjects (17)								
Control	9.0±0.1	5.04±0.01	4.1±0.1	15±2	23±2	33±1	134±14	753±42
Calcium	9.0±0.1	5.04±0.01	4.3±0.1	14±2		20±1	193±20	584±33
P value	NS	NS	<0.01	NS		<0.001	<0.001	<0.01
Patients (11)								
Control	9.2±0.1	5.03±0.05	3.9±0.2	8±2*	38±5†	39±3*	159±26	584±41*
Calcium	9.2±0.1	5.05±0.05	3.9±0.2	11±2		38±3†	238±29	521±29
P value	NS	NS	NS	NS		NS	<0.001	NS

Results are given as mean±SE.

* P < 0.05 vs. values in normal subjects.

† P < 0.01 vs. values in normal subjects.

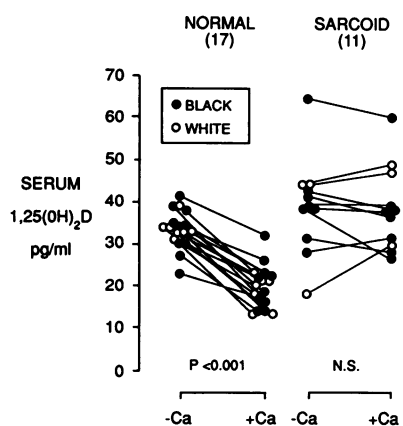


Figure 1. Effects of increases in calcium intake on serum 1,25-dihydroxyvitamin D in normal subjects and patients with sarcoidosis. Calcium intake was 400 mg/d (-Ca) and then 1,000 mg/d (+Ca).

vated (22). Two of our patients eventually developed hypercalcemia, and hydroxychloroquine corrected the abnormal vitamin D and calcium metabolism in one of them (23). In view of the demonstration of abnormal regulation of vitamin D metabolism in our patients, it would appear that all normocalcemic patients with sarcoidosis are at risk for developing hypercalcemia and its consequences, renal stones, renal lithiasis, chronic renal failure, and even death (13, 24).

Serum ACE activity was abnormally elevated in only three of the patients. In contrast, the calcium suppression test was abnormal in all the patients. Thus, this test provides a better index of disease activity than serum ACE activity.

The reduction in urinary phosphate and the modest but significant increase in serum phosphate in the normal subjects as a consequence of increased calcium intake are attributed to inhibition of secretion of PTH and possibly to binding of calcium to phosphate in the intestine and prevention of its absorption.

In summary, our studies show that increases in calcium intake from 400 to 1,000 mg/d lowered serum 1,25(OH)₂D in 17 normal subjects but not in 11 normocalcemic patients with sarcoidosis who had no history of abnormal calcium metabolism. The results indicate that regulation of circulating 1,25(OH)₂D in these patients is abnormal and that they are at risk for developing hypercalcemia and hypercalciuria. In patients such as these, it is important that they be followed closely on a low calcium diet and that they be instructed to avoid vitamin D supplements and exposure to sunlight, especially in the summer.

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