

## CALCIUM AND VITAMIN D METABOLISM IN SARCOIDOSIS

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**ABSTRACT.** *Background:* Sarcoidosis associated hypercalcemia (SAHC) may be secondary to excessive levels of 1,25-(OH)<sub>2</sub> vitamin D<sub>3</sub> produced by autonomous 1- $\alpha$ -hydroxylase activity within the granulomas. The frequency, treatment, and consequences of hypercalcemia remain unclear. *Study Design and Methods:* Two patient cohorts were studied. In Cohort 1, the prevalence of hypercalcemia in 1606 sarcoidosis patients seen during a six year period was analyzed along with treatment and outcome. Cohort 2 consisted of 261 sarcoidosis patients with measured 25-(OH) vitamin D<sub>3</sub> and 1,25-(OH) vitamin D<sub>3</sub> levels. In forty patients, serial levels of 25-(OH) vitamin D<sub>3</sub> and 1,25-(OH) vitamin D<sub>3</sub> were measured at least three months apart without change in therapy. *Results:* SAHC was identified in 97 of 1606 (6%) of patients studied and additional nine (0.6%) patients had primary hyperparathyroidism. Post treatment follow up was available in 86 SAHC patients. Hypercalcemia improved in >90% of patients, including eight patients treated solely with vitamin D supplement withdrawal. Renal insufficiency, documented in 41 (42%) of SAHC patients, improved with hypercalcemia treatment. In 80% of Cohort 2 patients low 25-(OH) vitamin D<sub>3</sub> levels were measured with only one patient having a low 1,25(OH)<sub>2</sub> vitamin D<sub>3</sub> level. Elevated 1,25(OH)<sub>2</sub> vitamin D<sub>3</sub> levels, which were measured in 11% of patients, were higher for those with a history of hypercalcemia. *Conclusion:* Sarcoidosis associated hypercalcemia, which is often accompanied by renal insufficiency, responds to treatment of sarcoidosis and withdrawal of vitamin D supplementation. Measurement of serum vitamin 1,25(OH)<sub>2</sub> vitamin D<sub>3</sub> appears to best evaluate vitamin D status in sarcoidosis patients. (*Sarcoidosis Vasc Diffuse Lung Dis* 2013; 30: 113-120)

**KEY WORDS:** hypercalcemia, vitamin D, calcium, renal failure, hyperparathyroidism

### INTRODUCTION

Sarcoidosis is a multi-organ disease associated with granulomatous infiltration of unknown cause (1). Hypercalcemia is encountered in sarcoidosis patients with an estimated incidence between 2-27% (2-4). Increased serum calcium can lead to renal insufficiency and may resolve with treatment (5, 6).

Hypercalcemia can also lead to nephrolithiasis, a common manifestation of sarcoidosis (7).

The mechanisms of hypercalcemia in sarcoidosis appear to be multifactorial. One factor appears to be upregulated and autonomous 1- $\alpha$ -hydroxylase activity within the granulomas of sarcoidosis leading to increased conversion of 25-(OH) vitamin D<sub>3</sub> to 1,25-(OH)<sub>2</sub> vitamin D<sub>3</sub> (8-10). However, patients with normal levels of both forms of vitamin D may still develop hypercalcemia (11). In some cases, parathyroid adenomas are causative for the hypercalcemia measured in sarcoidosis patients (12, 13).

Patients receiving chronic glucocorticoids are routinely recommended supplementation with vitamin D for prevention of osteoporosis (14). In sarcoi-

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dosis, the decision of who and when to supplement with vitamin D3 remains unclear (17, 18).

Reduced 25-(OH) vitamin D3 has been reported with normal and even increased 1,25-(OH)<sub>2</sub> vitamin D3 (19). Currently it is unknown which vitamin D level (25 vs. 1,25) represents true deficiency in sarcoidosis (18). In the current study, we examined three clinical questions: 1) the incidence and consequence of hypercalcemia in patients with sarcoidosis; 2) the relationship between vitamin D 25 and 1,25 to hypercalcemia in sarcoidosis patients; 3) and the reproducibility of vitamin D 25 and 1,25 measurements in patients with sarcoidosis.

## METHODS

Adult patients were recruited from the Interstitial Lung Disease/Sarcoidosis Clinic at the University of Cincinnati. Patients were diagnosed with sarcoidosis based on criteria of the American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and Other Granulomatous Disease (1). The studies were approved by the University of Cincinnati Institutional Review Board.

### *Incidence and consequences of hypercalcemia*

Cohort 1 was derived from a large single-centered database that was collected from the University of Cincinnati of those seen in a dedicated Interstitial Lung Disease/Sarcoidosis Clinic between 2002 and 2008. The test results were entered into a database (ACCESS, Microsoft). All visits were reviewed and information recorded including age, sex, race, chest x-ray stage (20), organ involvement (21), systemic therapy, use of supplemental calcium and/or vitamin D, as well as serum calcium, creatinine and parathyroid hormone (PTH) level. An immunochemiluminometric assay was used to measure 25-(OH) vitamin D3 and column chromatography followed by radioimmunoassay was used to determine 1,25-(OH)<sub>2</sub> vitamin D3 level. A patient was considered hypercalcemic if serum calcium was greater than 10.2 mg/dL. For hypercalcemic patients, the visit with the highest calcium reported and the subsequent visits were further analyzed with serum creatinine, PTH level, and all systemic therapy noted. Using laboratory normal values, renal insufficiency

was defined as a creatinine greater than 1.1 mg/dL in females and 1.2 mg/dL in males.

Hypercalcemic patients were divided into two groups based on serum PTH levels. Patients with hyperparathyroidism were assessed independently from those with hypercalcemia and normal PTH. Patients with a normal PTH and hypercalcemia were considered as having sarcoidosis associated hypercalcemia (SAHC). The clinical outcome of those patients was assessed after discontinuing vitamin D supplementation where applicable and instituting or changing systemic therapy. In those patients with SAHC and renal insufficiency failure, subsequent renal function was noted after change in systemic therapy.

### *The relationship between 25-(OH) vitamin D3 and 1,25-(OH)<sub>2</sub> vitamin D3 to hypercalcemia in sarcoidosis*

Cohort 2 was derived from a database which was created of sarcoidosis patients seen in the Interstitial Lung Disease/Sarcoidosis Clinic in 2011 who had vitamin D levels measured. In these patients, baseline demographics, serum levels for calcium, 25-(OH) vitamin D, 1,25-(OH)<sub>2</sub> vitamin D, serum PTH level and creatinine were measured. Due to possible other reasons for elevated calcium, those with hyperparathyroidism and renal failure were excluded from further analysis. Normal values for 25-(OH) vitamin D3 and 1,25-(OH)<sub>2</sub> vitamin D3 are 32.0 to 100.0 ng/ml and 10.0 to 75.0 pg/ml respectively.

### *The reproducibility of 25-(OH) vitamin D3 and 1,25-(OH)<sub>2</sub> vitamin D3*

Patients on stable vitamin D supplementation and systemic medication for sarcoidosis had paired vitamin D levels measured at least three months apart. The reproducibility was analyzed for serum 25-(OH) vitamin D3 and 1,25-(OH)<sub>2</sub> vitamin D3. Additionally, the proportion of patients was calculated for whom the vitamin D classification changed from low, normal, or elevated values.

### *Statistics*

Comparison between groups and within groups was performed using Student T test with the corre-

lation coefficient calculated. Chi square analysis was used to compare the frequency of race and gender between groups. A linear correlation was used to calculate the coefficient r value. A p value of less than 0.05 was considered significant.

**RESULTS**

*Incidence and consequences of hypercalcemia*

*Cohort 1:* Over the six years of study, a total of 1606 sarcoidosis patients were seen during 13,576 clinic visits. A serum calcium measurement was recorded in 10,977 visits. Hypercalcemia was measured in 106 (6.6%) patients. Hyperparathyroidism was identified in 9 (0.6%) patients. Seven patients underwent parathyroidectomy, one patient refused surgery, and one patient was followed without surgery. The remaining 97 (6.0%) patients were classified as SAHC. Table 1 compares the demographic features of the hypercalcemic patients to 1500 contemporary sarcoidosis patients seen at the University of Cincinnati Interstitial Lung Disease/Sarcoidosis Clinic without hypercalcemia. There was no significant difference between the hypercalcemic and normocalcemic patients in terms of race, gender, or age.

Of those with SAHC, 20 (20%) were receiving systemic sarcoidosis therapies at baseline. Of these, 16 (16%) were on monotherapy and 4 (4%) were on dual therapy. Nine patients were receiving hydroxychloroquine, seven prednisone, four methotrexate, and four azathioprine. Vitamin D supplementation was reported by 21 of the 97 hypercalcemic patients. Clinical outcomes of hypercalcemia were determined in 86 patients with 11 patients lost to follow-up. In 81

of these 86 patients (94%) hypercalcemia improved with normalization occurring in 78 (91%). In eight patients (9%), calcium and vitamin D supplementation withdrawal sufficiently treated the hypercalcemia. Therapy for SAHC is summarized in Table 2.

Forty-one (42%) patients with SAHC developed renal insufficiency as defined by a serum creatinine greater than 1.1 mg/dL in females and 1.2 mg/dL in males. Thirty seven patients had at least one repeat creatinine measured after six months of hypercalcemia therapy. Figure 1 demonstrates the initial (1.78±0.752 mg/dL) and follow-up (1.16±0.293 mg/dL) serum creatinine levels.

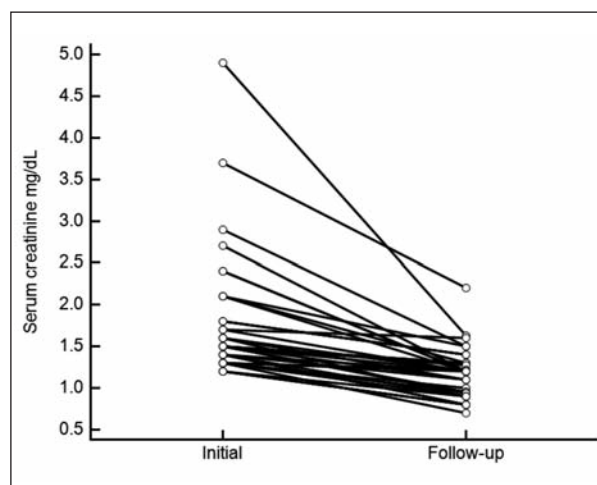
**Table 2.** Outcome of Therapy for Sarcoidosis Associated Hypercalcemia (SAHC) in Cohort 1

Intervention	Number of patients	Sole intervention	Normalization*
Prednisone	47	15	41 (87%)†
Hydroxychloroquine	34	15	28 (82%)
Methotrexate	15	4	14 (93%)
Azathioprine	5	2	5 (100%)
Leflunomide	3	2	3 (100%)
Cyclophosphamide	1	1	1 (100%)
Infliximab	1	1	1(100%)
Vitamin D discontinuation	21	8	19 (90%)

\*Normalization of measured serum calcium after therapy  
 †Number with normal serum calcium (percent of those treated).  
 Patients may have received more than one therapy.

**Table 1.** Characteristics of hypercalcemic versus non hypercalcemic sarcoidosis patients in Cohort 1

	Hypercalcemia due to sarcoidosis	Hypercalcemia due to hyperparathyroidism	Sarcoidosis patients without hypercalcemia
Number	97	9	1500
Female	69 (71%)	8 (88%)	1067 (71%)
Caucasian	63 (64%)	5 (62%)	845 (56%)
Age			
Median (range) years	55 (33-81)	63 (39-76)	51 (19-87)



**Fig. 1.** The serum creatinine levels at initial evaluation for hypercalcemia and the lowest serum creatinine after at least six months of therapy in Cohort 1.

Although a significant decrease was measured ( $p < 0.0001$ ), only 20 of 37 (54%) patients experienced final serum creatinine normalization.

*The relationship between 25-(OH) vitamin D3 and 1,25-(OH)2 vitamin D3 to hypercalcemia in sarcoidosis*

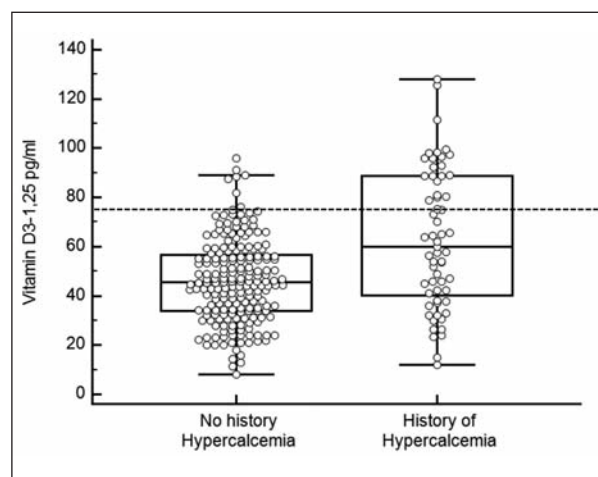
**Cohort 2:** The second database consisted of 270 sarcoidosis patients seen in the Interstitial Lung Disease/Sarcoidosis clinic during the first six months of 2011 with measured vitamin D. Nine patients were excluded from additional analysis, as five of these patients experienced moderate to severe renal failure (serum creatinine  $> 3.0$  mg/dL) and four additional patients developed hyperparathyroidism. Of the remaining 261 patients with sarcoidosis, 18 (6.9%) were hypercalcemic at baseline and 61 (23.4%) had a history of SAHC currently or in the past. Table 3, which summarizes the features of these patients, reveals no difference between the groups in terms of gender, race, or age.

Although no patient had an elevated 25-(OH) vitamin D3 level, 218 patients (83.5%) had reduced levels. On the other hand, 1,25-(OH)2 vitamin D3 was elevated in 29 (11%) and reduced in only 1 (0.4%) patient. There was a significant correlation between the 25-(OH) and 1,25-(OH) vitamin D3 ( $r = 0.2689$ ,  $p < 0.0001$ ).

Four of the 18 patients with initial hypercalcemia had elevated 1,25-(OH) vitamin D3 levels. There was no difference between the hypercalcemic and normocalcemic patients in values for either serum 25-(OH) vitamin D3 (current hypercalcemia =  $22.6 \pm 14.11$  ng/ml (Mean  $\pm$  standard deviation); current normal calcium =  $22.3 \pm 11.37$  ng/ml) or 1,25-(OH)2 vitamin D3 (current hypercalcemia =  $54.3 \pm 24.24$  pg/ml; current normal calcium =  $49.8 \pm 20.98$  pg/ml).

There were 61 patients with a history of hypercalcemia. Of these, 22 (36.1%) had an elevated serum 1,25-(OH)2 vitamin D3 level. As depicted in Figure 2, the serum 1,25-(OH)2 vitamin D3 level was significantly higher for those with a history of hypercalcemia ( $63.0 \pm 27.92$  pg/ml) compared to those without a history of hypercalcemia ( $46.2 \pm 16.89$  pg/ml,  $p < 0.001$ ). However, there was no difference in the 25-(OH) vitamin D3 levels for those with or without a history of hypercalcemia. Of the 61 patients with a history of hypercalcemia, 58 (95%) had low 25-(OH) vitamin D3 levels, including 23 patients with levels below 20 ng/ml (Figure 3).

Twenty nine patients had an elevated 1,25-(OH)2 vitamin D3 level with only one patient (3%) untreated at the time of measurement. Of those with normal 1,25-(OH)2 vitamin D3 levels, 30/229 (13%) of patients were not on current therapy (Chi square = 1.447,  $p > 0.05$ ).



**Fig. 2.** 1,25-(OH)2 vitamin D3 levels for patients with or without history of hypercalcemia in Cohort 2. There was a significant difference between the groups ( $p < 0.001$ ). Dotted line indicates the upper limit of normal value for 1,25-(OH)2 vitamin D3

**Table 3.** Demographic features of patients with measured 25-(OH) vitamin D3 and 1,25-(OH)2 vitamin D3 levels in Cohort 2

	All	Current hypercalcemia		History of hypercalcemia	
		No	Yes	No	Yes
Number	261	243	18	200	61§
Female	207 (79%)*	192 (79%)	15 (83%)	160 (80%)	47 (75%)
Caucasians	131 (50%)	124 (51%)	7 (39%)	97 (48%)	34 (55%)
Age, years	53 $\pm$ 10.1 †	53 $\pm$ 10.2	52 $\pm$ 9.8	53 $\pm$ 10.2	53 $\pm$ 10.7

\* Number (percent of total in the group)

† Mean  $\pm$  standard deviation

§ Includes ten patients with hypercalcemia at time of study

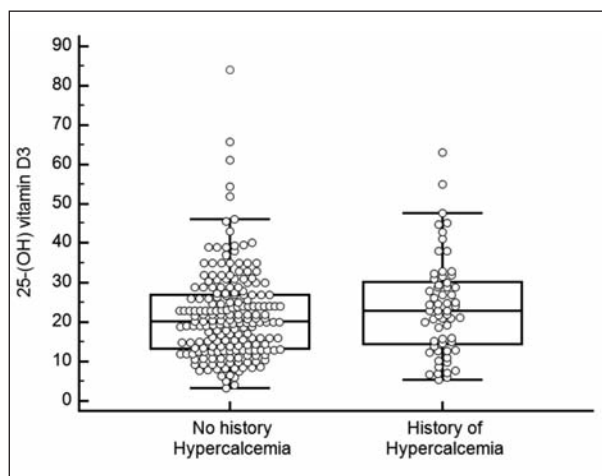


Fig. 3. 25-(OH) vitamin D3 levels for patients with or without a history of hypercalcemia in Cohort 2. There was no significant difference between the groups.

*The reproducibility of 25-(OH) vitamin D3 and 1,25-(OH)2 vitamin D3*

Serial vitamin D levels were measured at least three months after initial assessment in forty patients in Cohort 2 who did not change systemic therapy or vitamin D supplementation. None of the patients with renal failure or hyperparathyroidism had known repeat vitamin D studies. There was a significant correlation between the initial and follow-up serum 1,25-(OH)<sub>2</sub> vitamin D3 levels (Figure 4A,

$r=0.7984$ ,  $p<0.0001$ ) and serum 25-(OH) vitamin D3 levels (Figure 4B,  $r=0.6576$ ,  $p<0.0001$ ). There were six cases of 1,25-(OH)<sub>2</sub> discordance with three patients experiencing initial high levels with subsequent normalization and three cases with the reverse. Likewise, for 25-(OH) vitamin D3, there were seven cases of discordance between the initial and follow-up measurements with three cases changing from low to normal levels and four cases changing from normal to low levels.

## DISCUSSION

In a retrospective analysis of all sarcoidosis patients seen in our clinic from 2002 to 2008, SAHC was documented in six percent of our patients, with 23% of patients reporting a present or prior history of hypercalcemia. Previous studies have reported an incidence of hypercalcemia between 2-27% (2, 4, 22-24). The United States multicenter A Case Controlled Etiologic Study of Sarcoidosis (ACCESS) evaluated patients within six months of sarcoidosis diagnosis. That study found hypercalcemia to be more common in men and Caucasians (2). In the current study, we were unable to demonstrate an effect of race, gender, or age on the prevalence of hypercalcemia.

During the six years of the study period, six percent of our 1606 sarcoidosis patients developed one or more episodes of hypercalcemia. Of the 106 hy-

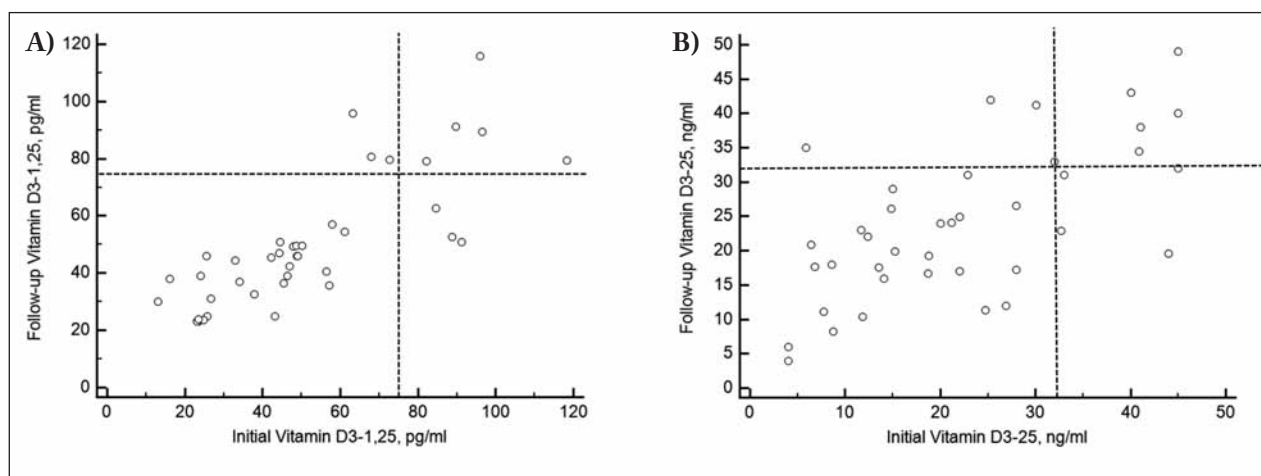


Fig. 4. Forty patients in Cohort 2 with paired measurements determinations at least three months apart with no change in medication or vitamin D3 supplements. (A) shows the correlation between initial and follow-up 1,25-(OH)<sub>2</sub> vitamin D3 ( $r=0.7984$ ,  $p<0.0001$ ). Dotted line indicates the upper limit of normal value for 1,25-(OH)<sub>2</sub> vitamin D3. (B) shows the correlation between initial and follow-up 25-(OH) vitamin D3 ( $r=0.6576$ ,  $p<0.0001$ ). The dotted line indicates the lower limit of normal value for 25-(OH) vitamin D3



percalcemic patients, nine had hyperparathyroidism. Several investigators have reported hyperparathyroidism as a cause of hypercalcemia in sarcoidosis (25, 26). It is unclear if sarcoidosis patients are at higher risk for hyperparathyroidism. Interestingly, we found an overall incidence of hyperparathyroidism of 0.6%, which was lower than general population based studies of primary hyperparathyroidism (27, 28). However, those studies concluded that primary hyperparathyroidism is more common in woman with advanced age (28, 29). Although our sarcoidosis population is predominantly female, the average age was younger than the general population studies (28, 29).

Several agents including corticosteroids and anti-malarial agents such as chloroquine and hydroxychloroquine (8, 18, 30, 31), have been reported as effective in treating hypercalcemia in sarcoidosis. In addition, evidence based recommendations suggest useful alternatives to corticosteroids (1, 32). SAHC may respond to specific agents such as ketoconazole which can affect vitamin D3 metabolism (33). Bisphosphonates such as pamidronate can be beneficial in treating hypercalcemia, but the benefit is short-lived and usually requires administration with other agents (34, 35).

In the current study, sufficient follow-up was available to determine the efficacy of therapy in 86 patients with SAHC. As summarized in Table 2, serum calcium improved in all patients, with normalization achieved in 94%. Although prednisone was the most commonly prescribed agent, in less than one third of those cases was it the sole agent. Hydroxychloroquine was prescribed in more than one third of our patients; however, it was successful as a single agent in less than half of those patients. Methotrexate was the most commonly used cytotoxic agent which may reflect its popularity as a steroid sparing drug in sarcoidosis (36). Other cytotoxic agents and infliximab, an anti-tumor necrosis factor monoclonal antibody useful for refractory sarcoidosis (32), were prescribed in some cases (32).

The pathogenesis of renal dysfunction in sarcoidosis can be multifactorial, including interstitial nephritis with or without granulomas (37) and hypercalcemia (5, 38). In a series of 47 sarcoidosis patients with biopsy confirmed interstitial nephritis, Mahevas et al. found hypercalcemia in one third of cases (37). In the current study, renal insufficiency was documented in over forty percent of our SAHC

patients using serum creatinine measures. We chose not to correct for age in this study, since patients were followed over a prolonged period. The lack of correction for age may lead to an over estimate of renal dysfunction for this group. However, the serial studies support that an elevated serum calcium was probably a reflection of renal dysfunction due to hypercalcemia. In 37 patients, renal function was assessed after at least six months of hypercalcemia treatment. In all cases, serum calcium normalized. Figure 1 reveals that serum creatinine improved in almost all cases; however, serum creatinine normalization occurred in less than half of patients. This suggests that hypercalcemia was not the sole culprit for renal dysfunction.

In 21 of the 86 cases of SAHC, patients received supplemental vitamin D and calcium. This rate of supplementation probably reflects the recommendations of vitamin D supplementation during chronic steroid usage. All patients were advised to stop supplemental vitamin D and calcium; and for eight patients, this was the only intervention required. Reports of sarcoidosis and other granulomatous diseases confirm that vitamin D supplementation can lead to hypercalcemia (39, 40) perhaps secondary to autonomous 1-alpha-hydroxylase production (41).

To evaluate the effect of 1-alpha-hydroxylase activity, we investigated 25-(OH) and 1,25-(OH)<sub>2</sub> vitamin D3 levels in a separate group of 261 sarcoidosis patients without hyperparathyroidism or moderate to severe renal failure (45). We found that 25-(OH) vitamin D3 levels were low in 84% of the sarcoidosis patients. However, only one patient (0.4%) had a low 1,25-(OH)<sub>2</sub> vitamin D3 level. Although significant correlation existed between the two vitamin D levels, the 25-(OH) vitamin D3 level poorly predicted the 1,25-(OH)<sub>2</sub> vitamin D3 level (Figure 2). More than 70% of patients with elevated 1,25-(OH)<sub>2</sub> vitamin D3 had low levels of 25-(OH) vitamin D3.

Autonomous 1-alpha-hydroxylase seems to be the most likely mechanism for our findings. Increased 1-alpha-hydroxylase activity has been reported in granulomas of patients with active sarcoidosis (10), and we found that increased 1,25-(OH)<sub>2</sub> vitamin D3 levels were associated with hypercalcemia. This supports the concept that autonomous 1-alpha-hydroxylase was a common reason for increased 1,25-(OH)<sub>2</sub> vitamin D3.

Kavathia et al. found elevated levels of 1,25-(OH)<sub>2</sub> vitamin D<sub>3</sub> in a large cohort of chronic disease sarcoidosis patients requiring prolonged therapy (19). In the current study, only one patient with an elevated 1,25-(OH)<sub>2</sub> vitamin D<sub>3</sub> level was untreated for sarcoidosis at the time of evaluation, versus thirty untreated patients with normal 1,25-(OH)<sub>2</sub> vitamin D<sub>3</sub> levels. Although the proportion of untreated patients in the two groups was statistically insignificant, over 85% of the patients with measured vitamin D<sub>3</sub> levels were receiving concurrent sarcoidosis therapy.

Appropriate usage of vitamin D and calcium supplementation in sarcoidosis remains controversial. Some investigators have suggested that patients with low 25-(OH) vitamin D<sub>3</sub> receive supplementation (31, 42). This recommendation is based in part on improved resolution of tuberculosis seen with vitamin D supplementation (15, 16). However, this increased rate of resolution may enhance the granulomatous response and lead to subsequent disease worsening. Others have suggested that both 25-(OH) vitamin D<sub>3</sub> and 1,25-(OH)<sub>2</sub> vitamin D<sub>3</sub> along with serial serum calcium be measured (17, 18). We found the measurement of 1,25-(OH)<sub>2</sub> vitamin D<sub>3</sub> as reproducible as measurement of 25-(OH) vitamin D<sub>3</sub>. For 15% of patients, repeat measurement of 1,25-(OH)<sub>2</sub> vitamin D<sub>3</sub> led to reclassification of patients from normal to high levels or vice versa. However 17.5% of patients undergoing repeat measurement of 25-(OH) vitamin D<sub>3</sub> had reclassification from low to normal levels or vice versa.

A limitation of our study was that serum calcium was not measured in all patients. Also, therapy may have altered the serum calcium measurement and therefore the prevalence of hypercalcemia may have been underestimated in certain groups, such as men and Caucasians. We demonstrated that treatment of sarcoidosis could be effective in treating the hypercalcemia. However, many patients were hypercalcemic while on some form of therapy for their sarcoidosis. In those cases, we felt the patient's sarcoidosis was undertreated. Because we did not have all patients on maximal therapy for their sarcoidosis at all times, we were unable to correct for therapy as a possible confounder for determining prevalence of SAHC. Most patients had multiple determinations of serum calcium. Therefore we may have overestimated the overall prevalence of hypercalcemia.

However, most patients with SAHC had more than one elevated serum calcium level. Most patients with SAHC required changes in therapy or calcium supplements for their repeat calcium to normalize.

In conclusion, we identified hypercalcemia in over 5 percent of sarcoidosis patients with renal dysfunction noted in forty percent of these cases. In some circumstances, vitamin D supplementation alone appeared to be the culprit. Although sarcoidosis treatment controlled hypercalcemia and improved renal function, in the majority of patients mild renal dysfunction persisted. Increased 1,25-(OH)<sub>2</sub> vitamin D<sub>3</sub> was measured in many hypercalcemic patients, thus the measurement of this vitamin may be useful for determining which patient should receive vitamin supplementation. On the other hand 25-OH vitamin D levels were unreliable in determining the safety of vitamin D administration in sarcoidosis. Since serum 1,25-diOH vit D levels did not necessarily decline to normal with therapy, it may not be a good endpoint to ensure resolution of the calcium dysregulation problem of sarcoidosis.

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