Vitamin D Supplementation: Not So Simple in Sarcoidosis

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ABSTRACT

Introduction: Americans are increasingly receiving vitamin D supplementation, often based on low-measured 25-hydroxy-vitamin D (25-OH-vit D). In sarcoidosis, there is often increased metabolism of 25-OH-vit D to 1,25-dihydroxy-vitamin D (1,25-OH-vit D), so 25-OH-vit D may remain low, despite high levels of 1,25-OH-vit D. In such cases, vitamin D supplementation may lead to hypercalcemia.

Methods: We randomly selected 196 patients with sarcoidosis who received at least 1 prescription of vitamin D between 2005 and 2011 and 196 control patients. Primary outcome was the incidence of hypercalcemia during the 2 years following the vitamin D prescription. A secondary outcome was the proportion of patients who had received vitamin D prescriptions and who had adequate blood work performed before the prescription.

Results: The 25-OH-vit D and 1,25-OH-vit D levels were measured in only 70% and 23%, respectively, of those receiving supplementation. Hypercalcemia was noted more frequently in the group that received vitamin D (42.3%) as compared with the nonsupplemented group (18.3%), $P < 0.0001$. Patients who received a vitamin D prescription developed moderate and severe hypercalcemia more frequently (12.8%) as compared to the group that did not receive vitamin D (3.6%), $P = 0.001$. In multivariate analysis, having a prescription for vitamin D increased the risk of developing hypercalcemia to approximately 2-fold. The risk of developing hypercalcemia (odds ratio = 4.1) was increased with renal failure.

Conclusions: Our study demonstrates that a substantial proportion of patients with sarcoidosis who receive vitamin D are not getting appropriate pretesting. This increases their risk for developing hypercalcemia.

Key Indexing Terms: Vitamin D; Sarcoidosis; Hypercalcemia. **[Am J Med Sci 2016;352(3):252–257.]**

INTRODUCTION

Vitamin D insufficiency, diagnosed as 25-hydroxy-vitamin D (25-OH-vit D) < 30 ng/ml, is increasingly being recognized in the US population. Its prevalence increased from 56% in 1989-1994 to 77% in 2001-2004.[1] One consequence has been increased reported use of vitamin D supplements by women over 60 years of age, up from 30% in 1998 to 56% in 1994.[2] Following a similar trend, in the Nurses' Health Study, usage of vitamin D supplements increased from 4.2% in 1986 to 32.2% in 2006.[3]

Sarcoidosis is a relatively common granulomatous inflammatory condition of unknown cause, potentially affecting any organ, most commonly lymph nodes, skin, eyes, joints, and lungs. Abnormal calcium metabolism is a common but not universal feature of sarcoidosis. Reports suggest that hypercalcemia occurs in 2-27% of patients with this disease,[4-8] with perhaps the most reliable estimate at 11%.[9] The largest case-control study of sarcoidosis, "A Case Control Etiologic Study Of Sarcoidosis" study, had 736 patients with sarcodosis of whom 3.7% developed hypercalcemia over a 2-year period.[10] More recently, a cohort of 1,606 patients with sarcoidosis from the University of Cincinnati had a 6% incidence of hypercalcemia, and 23% of patients reported a present or previous history of hypercalcemia.[11] Hypercalciuria occurs more frequently, with reports up to 67%.[12] The etiology for elevated calcium levels is, in most cases, excessive levels of 1,25-dihydroxy-vitamin D (1,25-OH-vit D), produced by conversion of 25-OH-vit D to 1,25-OH-vit D, by the sarcoid granulomas.[13]

Sarcoidosis is considered a contraindication for high-dose vitamin D supplementation,[13] but, because 25-OH-vit D levels are often low, despite high levels of the active metabolite 1,25-OH-vit D, and because supplementary vitamin D is generally considered harmless and unselectively recommended by many doctors and nutritionists, it is possible that patients with sarcoidosis are receiving inappropriate vitamin D supplementation. Baughman et al[11] reported that out of 261 patients with sarcoidosis, 83.5% had low levels of 25-OH-vit D and more than 70% of the patients who had a low 25-OH-vit D level had an elevated 1,25-OH-vit D level. Similarly, in a study of bone health in 142 patients with sarcoidosis, approximately 75% of patients had 25-OH-vit D levels less than 20 ng/mL, and the mean 25-OH-vit D level was 14.5 ng/mL.[14] Both these studies suggest that if vitamin D supplementation is based solely on the 25-OH-vit D level in patients with sarcoidosis, a fairly large percentage of sarcoid patients would receive vitamin D supplementation. A possible consequence could be increased incidence of renal and salivary stones and of clinically significant hypercalcemia.

This study aimed to delineate vitamin D prescription practices among patients with sarcoidosis seen at outpatient clinics in and around Bronx, New York, and delineate clinical consequences that may arise because of such practices. We also wanted to explore demographic and various clinical factors that may increase the risk of hypercalcemic adverse effects in this group of patients.

MATERIALS AND METHODS

Study Design

The study collected data from a retrospective cohort of patients diagnosed with sarcoidosis who had at least 1 clinical outpatient visit for their sarcoidosis at the outpatient clinics affiliated with Montefiore Medical Center, Bronx, New York, between January 1, 2005 and December 31, 2011. Patients had to be 18 years of age or older, have had at least 1 clinical visit for sarcoidosis during the study period and have had at least 1 serum calcium level drawn during the study period. Patients were required to have been diagnosed with sarcoidosis for at least a year before the clinic visit. Patients with no serum calcium levels during the defined period were excluded. Patients known to have alternative reasons for hypercalcemia (multiple myeloma, metastatic cancer with bony metastases and hyperparathyroidism) were also excluded. Clinical events in the 2 years after initial prescription (in the vitamin D supplemented group) or 2 years after the first contact during study period (in the nonsupplemented group) were recorded.

The study was approved by the Albert Einstein College of Medicine Institutional Review Board (under Protocol No. 12-01-010E).

Methodology

The retrospective cohort was generated using Clinical Looking Glass, Montefiore Medical Center's clinical data aggregation software. Patients meeting the inclusion criteria were divided into 2 groups based on whether they received a prescription for vitamin D during the study period or not. Among 1,882 patients who met the inclusion criteria, 405 patients did receive and 1,407 did not receive vitamin D prescriptions during the study period. Charts were then selected at random (with the aid of a random number table) within the 2 groups for detailed review to verify the accuracy of the inclusion and exclusion criteria, to verify prescribed vitamin D doses and to determine clinical outcome. A total of 520 charts were reviewed in detail. Further, 128 patients were excluded as they either did not meet inclusion criteria as defined earlier on detailed review or met exclusion criteria. The final analysis included 196 patients with sarcoidosis who had received at least 1 vitamin D prescription during the study period (henceforth called Group D) and 196 patients with sarcoidosis who did not receive any vitamin D prescriptions during the study period (henceforth called Group S).

Vitamin D deficiency was defined as a 25-OH-vit D level of less than 20 ng/mL and vitamin D insufficiency was defined as a 25-OH-vit D level between 20 ng/mL and 30 ng/mL. The 1,25-OH-vit D levels were considered normal if they were between 10 pg/mL and 75 pg/mL. We extracted details from the vitamin D prescriptions to determine approximate daily dose and length of treatment. The patients were divided into 3 groups based on the daily vitamin D dose (low dose $<$1,000 units per day; moderate dose 1,000-4,000 units per day; high dose $>$4,000 units per day). Details about steroid therapy in the 3 months preceding a hypercalcemia event were also noted. Patients were classified as taking no steroids, low-dose steroids ($\leq$ 15 mg equivalent prednisone per day) or high-dose steroids ($>$15 mg prednisone per day for more than 2 weeks). Renal failure was defined as serum creatinine $>$1.1 mg/dL in females and $>$1.2 mg/dL in males.

Primary Outcome

The primary outcome was the prevalence of any detected hypercalcemia (symptomatic or asymptomatic) that may or may not have required hospitalization during the first 2 years after initial contact (Group S) or 2 years after the first prescription (Group D). Hypercalcemia was defined as calcium levels greater than 10.2 mg/dL. Mild hypercalcemia was defined as calcium levels between 10.2 mg/dL and 11.9 mg/dL. Calcium levels greater than or equal to 12 were defined as moderate-to-severe hypercalcemia.

Secondary Outcomes

A secondary outcome was the proportion of patients who had received vitamin D prescriptions and who had adequate blood work performed before the prescription.

DATA ANALYSIS

We assumed a rate of hypercalcemia of 11%, based on the published literature.[9] To detect a 10% difference in hypercalcemic complication rates between the 2 groups, we estimated a total sample size of 505, based on a power of 80% and alpha of 0.05.

The data were analyzed using IBM SPSS Statistics for Windows, Version 21 (IBM Corp., Armonk, NY, U.S.). For univariate analysis of categorical data, we used chi-square test. For univariate analysis of continuous data, Student's *t*-test was used. For multivariate analyses, multivariate logistic regression analysis was used.

RESULTS

Demographic features of both groups are listed in Table 1. Both groups were approximately 50% female, predominantly African American, and had similar mean age. Approximately 25% of patients in each group were on steroids in the 3 months preceding their highest calcium level. The proportion of patients with renal failure was similar in both groups, as was the median