Vitamin D Supplementation in Sarcoidosis: A Double-Edged Sword

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Abstract
Sarcoidosis is complicated by disordered vitamin D and calcium metabolism, which has important implications on disease activity and bone health. Although the majority of the patients with sarcoidosis are typically deficient in 25-hydroxyvitamin D, repletion of vitamin D is controversial in light of the hypercalcemia risk. Presently, there are no clear guidelines regarding vitamin D supplementation as a part of osteoporosis prevention in patients with vitamin D deficiency and sarcoidosis. We report a patient with sarcoidosis who presented with severe hypercalcemia following vitamin D supplementation and review the debated role of vitamin D supplementation in vitamin D-deficient sarcoid patients.

Keywords
► Sarcoidosis
► vitamin D deficiency
► hypercalcemia

Introduction
There is an extremely high prevalence of vitamin D deficiency in India, necessitating widespread vitamin D supplementation.¹ Weekly oral cholecalciferol (60,000 units) for 6 to 8 weeks is the most commonly used regimen in India.²

Sarcoidosis is a multisystem disease of unknown cause, characterized by the presence of activated T-cells, mononuclear phagocytes, and noncaseating granulomas.³ The prevalence of hypercalcemia in patients with sarcoidosis is reported to be approximately 5 to 11%. Activated macrophages in sarcoid granulomas are capable of upregulating extrarenal 1α-hydroxylase which can result in hypercalcemia. Expression of parathyroid hormone-related protein (PTH-rP) in sarcoïd macrophages, exerting an autocrine action of 1α-hydroxylase, has also been reported. Also, increased levels of IFN-γ in sarcoidosis is known to stimulate the production of 1,25 dihydroxyvitamin D by alveolar macrophages.⁴ While hypercalcemia complicating sarcoidosis is well-known, severe hypercalcemia of more than 14 mg/dL has been rarely reported.⁵

Although a majority of the patients with sarcoidosis are typically deficient in 25-hydroxyvitamin D, repletion of vitamin D is controversial in light of the hypercalcemia risk. Presently, there are no clear guidelines regarding vitamin D supplementation as a part of osteoporosis prevention in patients with vitamin D deficiency and sarcoidosis.
report a patient with sarcoidosis who presented with severe hypercalcemia following vitamin D supplementation and discuss the review of literature regarding role of vitamin D supplementation in vitamin D-deficient sarcoid patients.

**Case Report**

A 50-year-old lady presented with a history of generalized weakness, vague abdominal pain, and significant weight loss of about 15 kgs in the preceding 9 months. She also gave a history of on and off fever, night sweats, and dry cough. She was initially hospitalized under the care of a general surgeon with the suspicion of symptomatic cholelithiasis. Documentation of hypercalcemia on a routine evaluation prompted a referral to endocrinology.

General physical examination was non-contributory, and peripheral lymphadenopathy could not be appreciated. Per abdomen examination revealed hepatosplenomegaly. On further probing regarding vitamin D supplementation, the patient gave a history of having received 60,000 IU vitamin D3 once a week for 4 weeks for vitamin D deficiency 3 weeks before presentation to our hospital. Laboratory investigations at this time showed a high erythrocyte sedimentation rate (ESR) (90 mm/hr) with a calcium level of 17.1 mg/dL. She was treated with intravenous fluid hydration, loop diuretics, and renal corrected dose of zoledronic acid. She was discharged with a corrected Serum ACE (U/L) level of 2.47 mg/dL, vitamin D3 level of 6.29 ng/mL, phosphorus 7 mg/dL, and alkaline phosphatase of 187 IU/L. Her creatinine level was 1.66 mg/dL. The estimated glomerular filtration rate (GFR) (calculated through the Cockcroft–Gault equation) was 40 mL/min. Serum parathyroid hormone (PTH) was at 3.60 pg/ml with corresponding corrected calcium of 17.1 mg/dL. She was started on oral prednisone at 0.5 mg/kg, which led to a gradual fall and normalization in calcium levels and improvement in renal functions over 2 months.

**Discussion**

Sarcoidosis is complicated by disordered vitamin D and calcium metabolism, which has important implications with regard to disease activity and bone health. It is essential that we optimize the levels of vitamin D in patients with sarcoidosis due to the following reasons: First, vitamin D is an essential immunomodulator that may have a positive effect in patients with sarcoidosis. Kamphuis et al noted that disease activity of sarcoidosis measured by somatostatin receptor scintigraphy (SRS) correlated negatively with serum levels of 25-(OH)D. Thus, a low serum level of 25-(OH)D could be a possible risk factor for disease activity in sarcoidosis. Second, untreated patients with sarcoidosis have low bone mineral density (BMD) compared to age-matched controls. Third and most importantly, bone health in patients with sarcoidosis is further affected by the long-term use of corticosteroids in treating the active disease.

On the other hand, several studies have shown that administering vitamin D to patients with sarcoidosis increases the risk of hypercalcemia. Overton et al reported hypercalcemia in 11/120 (9.2%) patients after high-dose vitamin D (50,000 IU per week for 8 weeks) supplementation. Of these, 81.8% had baseline hypercalcemia and 36.4% received pharmacological doses of vitamin D supplementation. Unfortunately, baseline calcium and vitamin D levels before supplementation were not available. We speculate that baseline calcium levels might have been high, leading to severe hypercalcemia with supplementation.

**Table 1** Biochemical parameters at presentation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (mg/dl)</td>
<td>11.3</td>
</tr>
<tr>
<td>WBC count (cells/mm³)</td>
<td>8000</td>
</tr>
<tr>
<td>Platelet count (cells/mm³)</td>
<td>468000</td>
</tr>
<tr>
<td>ESR (mm 1st hr)</td>
<td>90</td>
</tr>
<tr>
<td>Total protein (g/dl)</td>
<td>8.1</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>2.47</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>14.1</td>
</tr>
<tr>
<td>Phosphorous (mg/dl)</td>
<td>7</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU/L)</td>
<td>187</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.66</td>
</tr>
<tr>
<td>Vitamin D (ng/mL)</td>
<td>29.27</td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>3.60 (normal range: 15-68.3)</td>
</tr>
<tr>
<td>1,25 dihydroxyvitamin D (pg/ml)</td>
<td>&gt; 200 (normal range: 19.9-79.3)</td>
</tr>
<tr>
<td>Serum ACE (U/L)</td>
<td>140 (normal range: 12-68)</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme; ESR, erythrocyte sedimentation rate; PTH, parathyroid hormone; WBC, white blood cell.
The optimal dose and treatment targets for vitamin D deficiency in sarcoidosis patients are not known. There is a need for randomized clinical trials to determine the safety of vitamin D dosing, as suggested by guidelines for the general population, in the sarcoidosis group. However, from the available data, most patients with sarcoidosis appear to tolerate smaller doses of vitamin D (200 to 400 IU daily) without manifesting hypercalcemia. As for the vitamin D targets in sarcoidosis, Saidenberg-Kernamac’h et al observed that serum 25-hydroxyvitamin D between 10 and 20 ng/mL was significantly associated with higher BMD in patients with sarcoidosis. Conversely, values greater than 20 ng/mL were associated with increased risk of fracture, probably related to increased bone resorption by increased formation of 1,25 dihydroxy vitamin D. The authors suggested that in sarcoidosis patients, known to be more sensitive to formation of 1,25 dihydroxy vitamin D, the optimal range of 25 hydroxyvitamin D levels might be lower than that desirable for the general population.

**Conclusion**

This case highlights the importance of practicing caution when prescribing vitamin D, particularly in patients with a background of granulomatous diseases. Cautious replacement of vitamin D in smaller doses, aiming for a lower target of vitamin D approaching 20 ng/dl, may be a reasonable approach to the treatment of vitamin D deficiency in normocalcemic patients with sarcoidosis. A further prospective interventional investigation involving larger cohorts of patients is warranted to determine an optimal treatment regimen.

**Note**

Informed consent was obtained from all individual participants included in the study. All procedures performed in the study involving human participants were in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Conflict of Interest**

None declared.

**References**