Review

Calcium metabolism in sarcoidosis and its clinical implications

M. Conron, C. Young and H. L. C. Beynon

Department of Medicine, The Royal Free Hospital, London, UK

Abstract

Objective. To examine the clinical implications of disturbed calcium metabolism in sarcoidosis and how the pathophysiology affects management strategies.

Methods. The literature concerning calcium metabolism in sarcoidosis was reviewed.

Results. Dysregulated calcium metabolism is a well-recognized complication of sarcoidosis, resulting in hypercalcaemia (prevalence 5–10%), hypercalcuria (40–62%) and reduced bone density (40–55%). Extrarenal synthesis of calcitriol [1,25(OH)2D3] is central to the pathogenesis of abnormal calcium homeostasis, but alterations in parathyroid hormone (PTH) activity and the expression of PTH-related peptide have also been demonstrated. The immunosuppressive properties of calcitriol suggest that the raised levels seen in sarcoidosis could represent an adaptive response to the undefined antigen that causes sarcoidosis.

Conclusions. The mechanisms of abnormal calcium metabolism in sarcoidosis need to be understood when treating hypercalcaemia, hypercalcuria and corticosteroid-induced osteoporosis. Studies are required to determine if the currently available therapies for osteoporosis are safe and effective in sarcoidosis.

It has long been recognized that disturbances of calcium metabolism can be a feature of sarcoidosis. Hypercalcaemia in association with sarcoidosis was first described by Harrel et al. in 1939 [1] and since then an increased risk of hypercalcuria and reduced bone density has also been demonstrated [2]. This review will focus on the pathogenesis of abnormal calcium metabolism and the impact it has in sarcoidosis. We will also outline management strategies for the most common clinical problems associated with disturbances in calcium homeostasis.

Clinical manifestations

Hypercalcuria is the most common defect of calcium metabolism in sarcoidosis, with a prevalence of 40–62% in published series [3, 4]. Clinically significant hypercalcaemia is less frequent and is generally asymptomatic, occurring in approximately 5% of patients [5]. Long-standing hypercalcaemia and hypercalcuria can cause nephrocalcinosis, which accounts for over half the patients with sarcoidosis who have renal impairment [6] and is the major cause of chronic renal failure. Other renal complications of sarcoidosis due to abnormal calcium metabolism include nephrolithiasis in approximately 10% of patients [7], and more rarely tubular disorders such as nephrogenic diabetes insipidus [8]. Symptomatic hypercalcaemia presenting with dehydration, polyuria and an altered conscious state is a rare but recognized complication of sarcoidosis.

Patients with sarcoidosis frequently require treatment with prolonged courses of oral corticosteroids. In addition to the well-documented increased risk of osteoporosis and fracture posed by corticosteroids [9–11], there is some evidence that patients with sarcoidosis may have a greater incidence of reduced bone density than the general population prior to commencing treatment. In a study of corticosteroid-naïve subjects with sarcoidosis, Rizzato et al. [2] found that 61% of the subjects had a vertebral bone mineral density that was more than one standard deviation below normal, i.e. a Z score of less than −1.

Pathogenesis of abnormal calcium metabolism

Calcium homeostasis is a complex inter-relationship between gastrointestinal absorption, bone turnover, renal excretion and protein binding. Tight regulation of this system is primarily controlled by levels of vitamin D, parathyroid hormone (PTH) and calcitonin, but is also influenced by thyroid and sex hormones. In sarcoidosis there is dysregulation of these hormonal and cellular pathways, leading to the clinical problems discussed above.
**Vitamin D**

The majority of vitamin D in the body is in the form of cholecalciferol (D$_3$), the remainder being ergocalciferol (D$_2$). Only small amounts of cholecalciferol are obtained from foods rich in vitamin D (e.g., fish oils and dairy products), while ergocalciferol is obtained entirely from the diet [12]. Vitamin D$_2$ is technically a hormone, as its total requirements can be obtained from adequate exposure to sunlight. The synthesis of vitamin D$_3$ is initiated in the skin with the conversion of previtamin D$_3$ to previtamin D$_3$, a reaction catalysed by ultraviolet light B [13]. Previtamin D$_3$ then isomerizes spontaneously to cholecalciferol, which undergoes 25-hydroxylation in the liver followed by 1-$\alpha$ hydroxylation in the kidney to form calcitriol [1,25(OH)$_2$D$_3$], the metabolically active form of vitamin D$_3$ [14]. The 25-hydroxylation step in the liver is not tightly regulated, unlike the 1-$\alpha$ hydroxylation, which is controlled by PTH and calcitriol. PTH is stimulated by circulating vitamin D metabolites and low levels of ionized calcium to form a bioregulatory loop. It is not clear if hypocalcaemia also has a direct action on 1-$\alpha$ hydroxylation in addition to its effect on PTH secretion. Once formed, calcitriol regulates calcium homeostasis by increasing the gastrointestinal absorption of calcium and phosphate [15], in addition to stimulating osteoclast-mediated bone resorption and new bone formation by osteoblasts [16].

**Vitamin D in sarcoidosis.** A link between elevated vitamin D levels and sarcoidosis was proposed over 50 yr ago, when increases in serum calcium were noted after ingestion of cod liver oil, which contains vitamin D [1]. Subsequent observations that hypercalcaemia can be caused by increased exposure to sunlight [5] and treated by reducing vitamin D intake [17] lent further support to this theory. The association was confirmed when Bell et al. [18] demonstrated that raised calcitriol levels in hypercalcaemic patients with sarcoidosis returned to normal with resolution of hypercalcaemia. An extrarenal source of vitamin D was suspected when an anephric patient with sarcoidosis was found to have high levels of calcitriol [19]. Under normal conditions the synthesis of calcitriol occurs entirely in the kidney, although animal models have demonstrated that other tissues are capable of synthesizing the hormone [20]. In 1983 the extrarenal source of calcitriol in sarcoidosis was shown to be the alveolar macrophage, which contained the 1-$\alpha$ hydroxylase enzyme and produced calcitriol when cultured *in vitro* [21, 22]. Additional work has shown that tissue macrophages at other sites also produce calcitriol [23].

Absent feedback mechanisms cause the dysregulation of calcitriol production by macrophages in sarcoidosis. In renal tubular cells high levels of calcitriol cause down-regulation of 1-$\alpha$ hydroxylase [24] and up-regulation of 25(OH)D$_2$24-hydroxylase, which converts 25(OH)D$_3$ into 24,25(OH)$_2$D$_3$, the metabolically inactive form of vitamin D$_3$. In alveolar macrophages there is no down-regulation of 1-$\alpha$-hydroxylase in response to high levels of calcitriol, and the up-regulation of 25(OH)D$_2$24-hydroxylase requires much higher levels of 25(OH)D$_3$ [25].

**Role of calcitriol in sarcoidosis.** Calcitriol has immunoregulatory properties and the raised levels in sarcoidosis may represent a favourable adaptive response [26]. High-affinity receptors for calcitriol are present on dendritic cells, lymphocytes and macrophages [27], which are key immune effector cells in sarcoidosis [28–30]. Calcitriol has been shown to down-regulate the activation [31] and proliferation of lymphocytes, probably through the inhibition of interleukin-2 (IL-2) [32] and interferon-$\gamma$ (IFN-$\gamma$) [33]. Activation and proliferation of T-cells, spontaneously expressing the T helper 1 type cytokines IL-2 and IFN-$\gamma$, has been demonstrated repeatedly in sarcoidosis [34, 35]. Additional studies using gene knockout mice have demonstrated that IL-2 and especially IFN-$\gamma$ are necessary for a granulomatous response [36–39]. It is therefore conceivable that the calcitriol-mediated inhibition of IFN-$\gamma$ and IL-2 is an attempt by the body to down-regulate T-cell activity at sites of inflammation.

**Parathyroid hormone**

PTH release is primarily stimulated by low levels of ionized calcium and circulating vitamin D metabolites, but is also affected by $\beta$ and histamine-2 receptor agonists as well as by magnesium. Apart from its previously mentioned role in up-regulating the 1-$\alpha$ hydroxylation of 25(OH)$_2$D$_3$, PTH has other important sites of action, synergizing with calcitriol to stimulate

![Fig. 1. Protocol for the management of hypercalcaemia in sarcoidosis.](image-url)
osteoclasts, promoting the tubular absorption of calcium and inhibiting phosphate reabsorption in the kidney.

**Parathyroid hormone in sarcoidosis.** PTH release is inhibited by hypercalcaemia and high levels of calcitriol, which explains why the PTH level is suppressed in sarcoidosis [40]. There exist in the literature over 50 case reports of patients with hyperparathyroidism in association with sarcoidosis [41, 42], prompting some to suggest an association [43, 44]. Given the relative frequency of the two conditions [45], it is more likely, however, that they occur independently.

**Parathyroid hormone-related peptide**

In 1987 a novel protein was identified in a number of patients with hypercalcemia of malignancy [46]. This protein had properties similar to PTH and was termed parathyroid hormone-related peptide (PTHrP). Precursor PTHrP is transcribed from a gene located on the short arm of chromosome 12, which then undergoes tissue-specific post-translational modification to produce three distinct peptide hormones, all of which share homology with PTH at its amino-terminal end and act on PTH receptors. In addition to its role in hypercalcemia of malignancy, PTHrP is involved in the differentiation of human cells and in calcium metabolism in sarcoidosis. The recent observation of high PTHrP levels in two patients with hypercalcaemia and sarcoidosis prompted Zeimer et al. [47] to look for evidence of PTHrP gene expression in sarcoid granulomas. Immunohistochemical analysis identified PTHrP protein in 85% of the 20 specimens of sarcoid tissue and the messenger RNA in 58%.

PTHrP has similar properties to PTH, stimulating 1,25-hydroxylation of 25(OH)D$_3$ and affecting bone turnover. Unlike PTH, PTHrP gene expression is not regulated by calcium and vitamin D metabolites, but rather by TNFα and IL-6 [48], two cytokines that are up-regulated in sarcoidosis [30, 48]. It is possible that TNFα and IL-6 produced by macrophages have autocrine actions, up-regulating PTHrP expression and therefore increasing calcitriol synthesis.

**Management of abnormal calcium homeostasis**

The following investigations are necessary to assess calcium homeostasis in patients presenting with sarcoidosis (Fig. 1). Serum calcium and albumin should be measured so that an estimate of the ionized calcium level can be calculated, as well as 24-h urine collection for calcium excretion. If renal impairment, hypercalcaemia or significant hypercalciuria (>400 mg/24 h) is detected, 24-h creatinine clearance and abdominal ultrasound investigations should be performed to exclude urolithiasis or nephrocalcinosis. Hypercalcaemia detected in a patient presenting with acute sarcoidosis requires no further assessment, and studies suggest that monitoring the response to corticosteroid therapy is acceptable practice [49]. The hypercalcaemia of primary hyperparathyroidism is not responsive to corticosteroids [42, 44] and should be excluded only if hypercalcaemia fails to resolve on corticosteroid treatment. Hypercalcaemic patients without histological confirmation of sarcoidosis require careful investigation, as lymphoma can present with lymphadenopathy and raised serum calcium. A 24-h measurement of calcium excretion should be performed in all patients, as the absence of hypercalcaemia does not exclude the presence of significant hypercalciuria [49].

**Hypercalcaemia**

There are no firm guidelines governing which patients require treatment for hypercalcaemia. It is generally accepted that a corrected serum calcium concentration of >3.50 mmol/l or evidence of renal complications in the presence of a lesser degree of hypercalcaemia is an indication for therapy [50]. Patients with uncomplicated hypercalcaemia of <3.0 mmol/l probably do not require immediate treatment, but should be observed carefully because calcium levels fluctuate [5].

Severe hypercalcaemia is uncommon in sarcoidosis [51]. Rarely, patients may present with renal failure, an altered mental state or a corrected serum calcium concentration of >3.50 mmol/l, requiring emergency treatment. The early management of severe hypercalcaemia involves rehydration to correct volume depletion, a loop diuretic to promote renal calcium secretion, and corticosteroids. To date corticosteroids have been the first-line therapy in hypercalcaemic sarcoidosis because of their effectiveness in rapidly restoring normocalcaemia and the lack of a recognized alternative therapy. Corticosteroids are of value in all forms of hypercalcaemia as they reduce gastrointestinal calcium absorption and inhibit osteoclast function [52, 53], but are particularly effective in sarcoidosis because of their effects on vitamin D metabolism. Although corticosteroids have no effect on 1,25-hydroxylase in the renal tubular cell, they are potent inhibitors of this enzyme in the macrophage [25, 54]. Corticosteroids also bind to cytokine promoter regions in the macrophage nucleus, down-regulating IL-2 and IFNγ expression [55] and resulting in reduced PTHrP production by macrophages.

Most patients present with the management problem of asymptomatic low-grade hypercalcaemia, the treatment of which aims to prevent long-term renal and bone complications. It is accepted practice that all patients be advised to minimize their exposure to sunlight, avoid fish oils rich in vitamin D and maintain a fluid intake of >2 l per day [51, 56]. Although many centres advise avoiding dairy products and calcium-containing antacids [51], it is not our practice to recommend a low-calcium diet as there is little evidence that it affects calcium balance and it may increase the risk of nephrolithiasis. A moderate dose of prednisolone (15–25 mg/day) is an effective treatment for hypercalcaemia and, if there is an alternative indication for corticosteroids, is the logical first-line therapy. Because corticosteroids may exacerbate hypercalciuria [57], it is our practice to repeat the 24-h measurement of urinary calcium excretion soon after commencing therapy.
Patients who do not have an indication for corticosteroids other than hypercalcaemia, or in whom corticosteroids are relatively contraindicated, may be started on ketoconazole. Ketoconazole is an imidazole antifungal agent that inhibits the cytochrome P450-linked enzyme systems involved in steroid synthesis [53, 58]. Recognition that 25(OH)D₃-1α-hydroxylase is a P450-dependent enzyme system led to the use of ketoconazole in primary hyperparathyroidism as a means of reducing calcitriol synthesis [59, 60]. Although the literature supporting the use of ketoconazole in combination with corticosteroids for hypercalcaemic sarcoidosis is limited to isolated case reports [53, 56], it has been our experience that the addition of ketoconazole results in the dose of corticosteroids being significantly reduced in all patients and ceased in some. Hydroxychloroquine also causes inhibition of 25(OH)D₃-1α-hydroxylase [61] and can be considered for patients who are intolerant of ketoconazole or who develop abnormal liver function tests. Methotrexate and azathioprine are frequently used as adjuvant therapy for patients with sarcoidosis. Although they do not have any direct effect on calcium metabolism, they may help control hypercalcaemia by reducing the granuloma burden.

Hypercalcuria

The pathogenesis of hypercalcuria in sarcoidosis is not fully understood. The maximum absorption rate for calcium is not increased and it is felt that hypercalcuria is due mainly to the capacity of the tubular reabsorptive mechanisms for calcium being exceeded [62]. Renal tubular cells do not express receptors for calcitriol and elevated levels of calcitriol contribute to hypercalcuria only indirectly, through increased gastrointestinal absorption and bone resorption.

In general, the management of hypercalcuria involves minimizing the risk of nephrolithiasis, through maintenance of a high urinary volume and by minimizing exposure to sunlight. As mentioned previously, recent studies have questioned the utility of a low-calcium diet in hypercalcuria. Up to 85% of renal stones in the general population contain calcium [63], an observation that reasonably reflects stone composition in patients with sarcoidosis [51]. The hypothesis that dietary intake of calcium influences stone formation is based on the observation that approximately one third of patients with nephrolithiasis have primary hypercalcuria [64], and limiting dietary calcium intake will reduce stone formation by decreasing urinary calcium excretion [65]. Despite this relationship, two large-scale epidemiological studies have failed to demonstrate that higher mean calcium intakes correlate with a higher rate of nephrolithiasis [66, 67]. In fact, one study published by Curhan et al. [68] found an inverse relationship that reached statistical significance. While a protective effect of dietary calcium may seem counterintuitive, the association may have a physiological explanation. It has been noted that gastrointestinal absorption of oxalate increases with intraluminal binding of calcium to fat in malabsorptive syndromes [69] and with dietary restriction of calcium [70]. Increased oxalate absorption results in higher levels of oxaluria. Oxalate saturation increases rapidly with small increases in urinary oxalate [71], so any factor that increases oxaluria may contribute to the formation of calcium oxalate stones.

Corticosteroids generally reduce hypercalcuria, and they do this through the inhibition of calcitriol synthesis. If there is isolated hypercalcuria associated with nephrolithiasis and no other indication for corticosteroids, a therapeutic trial of a thiazide diuretic is indicated. Thiazide diuretics act on the distal convoluted tubule to inhibit calcium excretion, and have been shown in two large randomized trials to reduce the risk of recurrent nephrolithiasis in idiopathic hypercalcuria by approximately 50% [72, 73]. Although thiazide diuretics have the potential to affect the lipid profile adversely and there are no large trials detailing their effectiveness in sarcoidosis, we feel their use is justified in patients with hypercalcuria when there is a history of nephrolithiasis.

Osteoporosis

The primary and secondary prevention of glucocorticoid-induced osteoporosis in sarcoidosis is often complicated by coexistent disturbances in calcium metabolism. Given the increased frequency of hypercalcaemia, hypercalcuria and possibly reduced bone density, should the management of osteoporosis in sarcoidosis differ significantly from that outlined in recently published recommendations for the management of glucocorticoid-induced osteoporosis? In the absence of evidence specifically addressing the issue of osteoporosis treatment in sarcoidosis, we largely follow the recommendations outlined by Eastell et al. [74] for the management of glucocorticoid-induced osteoporosis, with some minor modifications to accommodate the young age of many patients and the disturbances in calcium metabolism unique to sarcoidosis. In this section we do not intend to provide a comprehensive review of glucocorticoid-induced osteoporosis management, but rather plan to highlight how current guidelines can be adapted for sarcoidosis patients.

Initial assessment. In addition to the routine investigations to exclude a secondary cause of osteoporosis, such as hypogonadism, osteomalacia, myeloma and thyrotoxicosis, we perform a 24-h urinary calcium collection. Although earlier guidelines recommended this investigation [75], it was seldom performed and has been omitted from current guidelines. It is our practice to treat significant hypercalcuria prior to commencing osteoporosis therapies that may exacerbate this problem.

Bone mineral density. When corticosteroids are indicated for sarcoidosis, patients generally receive >15 mg/day for >6 months, which places them at high risk of developing osteoporosis. We therefore feel that, whenever possible, dual-energy X-ray-based absorptiometry of the lumbar spine and femoral neck should be performed. The presence of lifestyle factors predisposing to osteoporosis makes the assessment of bone density more necessary.
Therapeutic interventions. Although primary prevention studies suggest that cholecalciferol is not entirely effective in preventing glucocorticoid-induced bone loss [76], it is well tolerated by patients and is used routinely in our sarcoidosis clinic once hypercalcaemia has been excluded. There is evidence that cholecalciferol can cause hypercalcaemia in patients with sarcoidosis [40, 41], although clinical experience suggests that it can be given safely in this population. As a precaution, however, we routinely measure serum calcium and urinary calcium excretion 1 month after commencing therapy. Unfortunately, because of the young age of most sarcoidosis patients, the benefits of hormone replacement for hypogonadism can seldom be exploited. Currently available data indicate that bisphosphonates are the most effective agents for the primary and secondary prevention of glucocorticoid-induced osteoporosis [77, 78]. While the evidence for using cyclical etidronate in the primary prevention of glucocorticoid-induced osteoporosis is impressive, its safety has yet to be proven in large-scale trials involving young, fertile patients. It is therefore our current practice to limit the use of bisphosphonates to patients who had a reduced bone mass before they began to take corticosteroids, postmenopausal women and those who have shown significant loss of bone mass while receiving suitable hormone replacement (if required) and cholecalciferol. Given that the data on the use of bisphosphonates in sarcoidosis involve alendronate and that this medication may be less likely than etidronate to exacerbate hypercalcaemia, we favour the use of alendronate when a bisphosphonate is indicated. In a primary prevention trial involving men and premenopausal women, Gonnelli et al. [79] found that alendronate 5 mg/day over a period of 1 yr resulted in an improvement of 0.8% in distal radius bone mineral density compared with a 4.5% loss at the same site in 1995;54:801.

Conclusion

Patients with sarcoidosis can present with urolithiasis, osteoporosis and hypercalcaemia related to dysregulated production of calcitriol. Unfortunately, the importance of abnormal calcium homeostasis is often under-appreciated in the pathogenesis of these problems. Increased understanding of factors affecting calcium metabolism in sarcoidosis has led to the use of ketoconazole and hydroxychloroquine in hypercalcaemia and thiazide diuretics in hypercalcaemia. The institution of safe and effective bone protection therapy is necessary in sarcoidosis patients, who are often young and require a prolonged course of corticosteroid. Our primary and secondary prevention measures for osteoporosis are based on current management guidelines for glucocorticoid-induced osteoporosis. Although many agents used for the prevention of osteoporosis have the potential to cause problems in sarcoidosis patients with abnormal calcium metabolism, clinical experience has found these agents to be relatively safe. Further investigation of metabolic bone disease in sarcoidosis is required to confirm the accuracy of existing data that suggest that steroid-naïve patients have an increased risk of osteopenia and to find out whether there are important differences in the mechanisms of bone loss in this population.

References

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