Sarcoidosis and calcium homeostasis disturbances—Do we know where we stand?

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Abstract

The majority of cases involving hypercalcemia in the setting of sarcoidosis are explained by the overproduction of calcitriol by activated macrophages. Vitamin D takes part in the regulation of granuloma formation. However, using vitamin D metabolites to assess the activity of the disease is still problematic, and its usefulness is disputable. In some cases, though, a calcium metabolism disorder could be a valuable tool (i.e. as a marker of extrathoracic sarcoidosis). Although sarcoidosis does not cause a decrease in bone mineral density, increased incidence of vertebral deformities is noted. Despite increasing knowledge about calcium homeostasis disorders in patients with sarcoidosis, there is still a need for clear guidelines regarding calcium and vitamin D supplementation in these patients.

Keywords

Sarcoidosis, calcium, vitamin D, hypercalcemia, hypercalciuria, calcitriol, 1,25(OH)₂D₃, 25(OH)D₃

Introduction

Calcium metabolism in the human body is tightly regulated. Although many of the mechanisms of control are still not fully described, the present state of knowledge shows that they are far more complicated than the already known parathyroid hormone—vitamin D feedback loop (Figure 1). The endocrine activity of osteoblasts and osteoclasts, creating a fibroblast growth factor 23-vitamin D axis, seems to be just as important.¹,²

The majority of hypercalcemia cases in sarcoidosis are explained by the overproduction of 1,25(OH)₂D₃ (calcitriol) by activated macrophages. Despite quite convincing evidence supporting this hypothesis, some questions have yet to be completely answered. Moreover, some recent studies suggest that vitamin D supplementation may improve not only calcium homeostasis but also the course of sarcoidosis.³ Naturally, many authors are at odds with this opinion and do not recommend cholecalciferol supplementation in patients with sarcoidosis. Still, it is unknown what factors predispose to calcium homeostasis disorders and how its occurrence changes the outcome. Those, among many other doubts, encouraged us to create a summary and analysis of the knowledge connected with this subject.

In the context of sarcoidosis, vitamin D and its turnover are interesting because of its important role in the regulation of the immune system and the

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process of granulomatous inflammation. It is now known that 1-α-hydroxylase expression is present in many tissues. However, only hydroxylation in kidneys, activated macrophages, and the placenta can influence plasma 1,25(OH)₂D₃ levels.⁴ It has been shown that calcitriol inhibits the production of (interferon gamma) INF-γ, lymphotoxin, interleukin 2 (IL-2), and proliferation of certain T-lymphocyte subpopulations.⁵–⁷ A murine model has also proven that calcitriol inhibits IL-6 and tumor necrosis factor alpha (TNF-α) production by lipopolysaccharide (LPS)-stimulated monocytes and macrophages.⁸ In vitro studies have shown that 1,25(OH)₂D₃ stimulates monocyte proliferation, differentiation, and transformation into epithelioid cells.⁹ On the other hand, it inhibits macrophage differentiation into dendritic cells and inhibits dendritic cell maturation, simultaneously stimulating their apoptosis (Figure 2).¹⁰

Increased expression of TREM-2 (a receptor playing an important role in cell fusion and granuloma formation) on myeloid cells has been found in pulmonary sarcoidosis and, interestingly, compared to subjects with 25(OH)D₃ deficiency (<30 ng/ml), patients with a level between 30 ng/ml and 50 ng/ml had higher total numbers and percentages of TREM2 positive cells in bronchoalveolar lavage fluid.¹¹ Expression of vitamin D receptors has only been found in the alveolar lymphocytes of subjects with sarcoidosis, and not in healthy controls.¹²,¹³ Data about polymorphisms of vitamin D receptor in sarcoidosis are inconsistent. According to Niimi et al., Taq1 polymorphisms seem to be irrelevant. Allele B of Bsm1 alleles is more common in sarcoidosis but does not affect localization nor the course of the disease (101 patients and 105 healthy controls from Japanese population).¹⁴ One smaller study (n = 35) suggests a higher frequency of allele B in sarcoidosis patients and shows allele B to be present more often in patients with Löfgren syndrome.¹⁵ The concentration of vitamin D binding protein is higher in exosomes extracted from bronchoalveolar lavage fluid in patients with sarcoidosis and cerebrospinal fluid from patients with neurosarcoidosis.¹⁶,¹⁷ No relationship has been found between vitamin D binding protein different alleles and the incidence of sarcoidosis.¹⁸

**Epidemiology**

Hypercalcemia occurs in 0.2–4% of the general population. Primary hyperparathyroidism and malignancies are responsible for about 80–90% of all cases.¹⁹ Donovan et al. retrospectively analyzed 101 cases of vitamin D₃-mediated hypercalcemia and concluded that sarcoidosis was an underlying cause of almost 50% of them. Calcitriol serum concentration above 300 pmol/l was suggestive of another etiology of hypercalcemia.²⁰ Moreover, sarcoidosis is the reason behind about 0.5% of cases of hypercalcemia in patients with a history of

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**Figure 1.** Selected aspects of human calcium homeostasis.
malignancies. Depending on the studies and population studied, hypercalcemia affects from 7% up to 18% of patients with sarcoidosis. In a case–control etiologic study of sarcoidosis (ACCESS), a multicenter prospective study with 736 enrolled patients, incidence of sarcoidosis-associated hypercalcemia was 3.7%. However, such a low prevalence could be the result of ethnic composition—44% of the study group consisted of African-Americans. It is suggested that hypercalcemia is less common among these individuals. The biggest up-to-date study found, a single-center retrospective study by Baughman et al. (n = 1606), reports that hypercalcemia appeared in about 6% of sarcoidosis patients. Interestingly, the incidence of hypercalcemia in the Japanese population has been progressively rising between 1974 and 2012. No similar reports regarding the European population have been found.

Evidence about the association between sex and the incidence of hypercalcemia in sarcoidosis has not been confirmed with some studies showing a higher risk among the male population, whereas others show no statistically significant difference between sexes. In the mentioned study, Baughman et al. compared a group of about 100 patients with hypercalcemia to 1500 patients with sarcoidosis without calcium metabolism disturbances and failed to find any differences in sex, age, or ethnicity. The higher incidence of hypercalcemia in summer months, due to greater UV exposure, has also been suggested. A significant risk factor for sarcoidosis-associated hypercalcemia (odds ratio 3.6) found in the ACCESS study (over 470 patients analyzed) is the combination of HLA DRB1*1101 allele and exposure to insecticides.

A more frequent sign of dysregulated calcium homeostasis in sarcoidosis comes in the form of hypercalciuria which may affect between 20% and even 40% of patients. Also, nephrolithiasis is more common in sarcoidosis than in the general population. This complication will occur in 10–14% of patients in the course of the disease. Asymptomatic stones can be found in 2.7% of subjects at the moment of establishing the diagnosis and in approximately 1% of cases, it can be the first symptom of sarcoidosis.

Figure 2. It is well-known that vitamin D plays a complex and still not fully understood role in regulation of immune system. Part of its actions can be directly connected with formation of granuloma. Some of them are presented here.
The pathophysiology of hypercalcemia in sarcoidosis

Increased production of 1,25(OH)_2D_3 is considered to be the main cause of calcium homeostasis disorders in sarcoidosis (Figure 3). Increased calcitriol concentration was observed in a few cases of hypercalcemia in patients with sarcoidosis in the late 1970s. The discovery of hypercalcemia in combination with elevated calcitriol levels in patients with sarcoidosis and accompanying kidney failure was the proof of its extrarenal production. Studies confirmed that homogenate of lymph nodes with sarcoid granuloma produces 1,25(OH)_2D_3. Adams et al. experimentally proved that pulmonary alveolar macrophages from patients with sarcoidosis can hydroxylate 25(OH)D_3 to 1,25(OH)_2D_3 and that the process was augmented in cells derived from patients with hypercalcemia.

Studies in patients with tuberculosis revealed that macrophages activated via toll-like receptor (TLR) 2/1 present increased expression of 1-α-hydroxylase (CYP27B1) and vitamin D receptor. In healthy subjects, pulmonary alveolar macrophages synthesize 1,25(OH)_2D_3 from 25(OH)D_3 after activation by IFN-γ and LPS. Meanwhile, in pulmonary alveolar macrophages harvested from patients with sarcoidosis (including those without hypercalcemia), this process occurs without previous activation. However, exposure to LPS, IFN-γ, IL-2, or leukotriene C4 induces intensification of 1-α-hydroxylation of 25(OH)D_3. In turn, Lawrence et al. observed hypercalcemia in three out of four patients, who presented the highest concentrations of soluble receptors for IL-2. There has also been a case of sarcoidosis exacerbation with the occurrence of hypercalcemia in the course of treatment with IL-2. Interestingly, despite overexpression of CYP27B1 in pulmonary alveolar macrophages of patients with lung cancer (irrespective of histopathological type), no differences in calcium, 25(OH)D_3 or 1,25(OH)_2D_3 levels have been found (in comparison with the control group).

It is known that JAK-STAT, NF-κB, and p38 MAPK pathways play a role in the activation of 1-α-hydroxylase. After inhibiting any of them, CYP27B1 expression decreases. Calcitrol synthesis is tightly regulated in healthy subjects. However, its synthesis in morbid conditions is not so strictly controlled. This has been noted via a couple of different mechanisms. Firstly, 1-α-hydroxylase from macrophages is less susceptible to feedback inhibition by 1,25(OH)_2D_3 (this resistance is enhanced by IFN-γ). Secondly, 1,25(OH)_2D_3 deactivation by 24-hydroxylase is inhibited. Because of this, there may be two effects on
circulating calcitriol: firstly, it may exceed reference values. Secondly, and more frequently, it may stay within normal range but be inadequate to circulating serum calcium level. Arguments for “inadequate normal” 1,25(OH)2D3 concentration as the main cause of sarcoidosis-associated hypercalcemia are presented and commented in Table 1.

A positive correlation between 1,25(OH)2D3 level and calcium concentration has been noted in some observational studies (approximately \( r = 0.55 \)).63–65 However, in one follow-up study with a slightly smaller group \((n = 39)\), this relationship has not been confirmed.66

A few cases of hypercalcemia induced by parathyroid hormone-related protein (PTHrP) have also been described.67–69 The expression of PTHrP was observed in macrophages and giant cells in the majority of patients with granulomatous diseases, sarcoidosis included. Nevertheless, its circulating serum level hardly ever exceeds normal limits.69–72 PTHrP expression is stimulated by factors such as LPS, prostaglandin E (PGE), IL-1, transforming growth factor β (TGF-β), and it most likely acts as an anti-inflammatory agent, which would explain its presence in granuloma cells.70

It is important to remember that sarcoidosis does not exclude other causes of hypercalcemia, beginning with the most common cause: hyperparathyroidism. Such conditions should be excluded during the diagnostic process to enable the introduction of optimal treatment.

### The influence of sarcoidosis and related calcium disturbances on skeletal system

The influence of sarcoidosis on the skeletal system is mediated by two main etiologies, both of which are risk factors for osteoporosis. Firstly, it is mediated by calcium homeostasis disorders, including frequent 25(OH)D deficiency. Secondly, by treatment with corticosteroids.

It has been suggested that sarcoidosis itself causes a reduction of bone mineral density (BMD). Heijackmann et al. found that despite higher concentrations of biochemical markers of bone turnover (procollagen type I amino-terminal pro-peptide—PINP and carboxy-terminal cross-linked telopeptide of type I collagen—ICTP), BMD of the hip was normal and did not change in 4-year follow-up.73,74 Also, Bolland et al., in his 2-year follow-up study of 64 patients with sarcoidosis, failed to find a significant change in BMD in regions such as the lumbar spine, total hip, femoral neck, as well as in total body measurements.75 Two large-group case–control studies did not reveal any increase in a total number of bone fractures caused by sarcoidosis alone.76,77 However, higher occurrence of fractures and deformations within vertebrae has been noted, including in patients with normal BMD.73,74,76,78 The effectiveness of Vitamin D3 and calcium supplementation in improving BMD in patients with sarcoidosis remains unconfirmed.75,79 Surprisingly, Saidenberg-Kermanac’h et al., in a cross-sectional study of 142 patients, showed that vitamin D supplementation paradoxically caused BMD reduction and a higher occurrence of bone fractures.78 There is no doubt that the risk of

| Observation Comment | References |
|--------------------|-----------------------------|
| Hypercaldmia accompanied by normal calcitriol level with a decline in its concentration after glucocorticoid treatment | Unsal et al.58 Berlin et al.,59 Shrayyef et al.,60 Falk et al.61 |
| Lack of calcitriol level decrease despite supplementation of calcium in patients with sarcoidosis | Basile et al.62 |
| Increase of 25(OH)D3 as well as 1,25(OH)2D3 after vitamin D2 supplementation | In healthy subjects, the level of calcitriol should decrease after calcium supplementation Stern et al.63 |

The concentration of 1,25(OH)2D3 in patients with sarcoidosis, even in those with hypercalcemia, usually stays within normal limits. Still, the overproduction of calcitriol is considered to be the leading cause of sarcoidosis-associated hypercalcemia. This leads to the conclusion that there exists a phenomenon of “inadequate normal” 1,25(OH)2D3 concentration in patients with sarcoidosis. The table shows some evidence supporting this theory.
fractures and decreased BMD appear in the course of corticosteroid therapy. Interestingly, population-based studies show that such an effect can be observed only during and up to 3–6 months after the termination of therapy.\textsuperscript{76,77} The meta-analyses of available randomized controlled trials (in all patients, not specifically with sarcoidosis) confirm moderate effectiveness of vitamin D supplementation on preventing steroid-induced BMD decline with no statistically significant effect on the incidence of fractures. Treatment with bisphosphonates is more effective in improving BMD and seems to be effective in reducing the risk of vertebral fractures. The most effective agent, however, seems to be teriparatide.\textsuperscript{80–82} This is an important issue because there is currently a discussion about supplementation with vitamin D and calcium and its potential in bringing about hypercalcaemia and hypercalciuria.\textsuperscript{36,62,83,84} Two retrospective studies of patients visiting the outpatient clinic stand in opposition to each other. In a cohort analysis of almost 400 patients (randomly chosen, divided in two equal groups) Sodhi and Aldrich showed that the group of patients, who at least once had vitamin D prescribed, had an almost two times higher risk of developing hypercalcaemia in a 2-year follow-up.\textsuperscript{85} On the other hand, Kamphuis et al. did not observe a higher incidence of hypercalcaemia in the group using calcium and vitamin D supplementation. In fact, their study showed a protective effect against hypercalcaemia (mean dose 400 UI per day) in the group of 70 patients not treated with corticosteroids (39 with supplementation vs. 31 without supplementation).\textsuperscript{3}

In a randomized trial over 1 year that studied a group of 27 subjects with sarcoidosis taking cholecalciferol supplementation of 50,000 IU/month, there were relevant differences observed in the mean concentration of 25(OH)D\textsubscript{3} ranging from suboptimal average <50 nmol/l to average >75 nmol/l. The authors also observed a small, but statistically significant difference in concentrations of 1,25(OH)\textsubscript{2}D\textsubscript{3}. One patient from the study group developed hypercalcaemia (mean dose 400 UI per day) in the group of 70 patients not treated with corticosteroids (39 with supplementation vs. 31 without supplementation).\textsuperscript{3}

Calcium homeostasis and prognosis

The association between decreased 25(OH)D\textsubscript{3} level and a more severe course of disease has been described.\textsuperscript{12} Kiani et al. compared two groups (n = 40) of patients suffering from sarcoidosis with one group having 25(OH)D\textsubscript{3} concentration <50 nmol/l and the other >50 nmol/l. They found that 25(OH)D\textsubscript{3} deficiency correlated negatively with lung parenchyma involvement (stages II–IV) and tended to predispose to chronic course of disease in a 2-year follow-up.\textsuperscript{87} On the other hand, higher mean concentrations of calcitriol were found in patients with active and untreated sarcoidosis.\textsuperscript{88} Kavathia et al. (in a 59 patient study involving predominantly African-American patients) found a concentration of 1,25(OH)\textsubscript{2}D\textsubscript{3} above 51 pg/ml to be a risk factor for prolonged (>1 year) treatment.\textsuperscript{89}

The correlation between calcitriol concentration and 67 Ga uptake has not been noted,\textsuperscript{90} but 25(OH)D\textsubscript{3} concentration correlated negatively with results of a somatostatin receptor scintigraphy.\textsuperscript{3} In renal sarcoidosis, a correlation between hypercalcemia and complete response to glucocorticoid treatment has been observed (a retrospective study of 46 patients with biopsy-proven renal sarcoidosis).\textsuperscript{28} In the observational study performed on 36 Japanese patients, Hamada et al. observed that ionized calcium level above 1.23 mmol/l was a 100\% specific indicator for extrapulmonary sarcoidosis.\textsuperscript{64}

Management

The management of hypercalcemia depends mostly on the level of calcium. Patients with moderate elevations in serum calcium (12.0–14.0 mg/dl) may develop symptoms when levels rise rapidly. This group of symptomatic patients requires immediate intervention. Intensive treatment is usually necessary when serum calcium concentration exceeds 14 mg/dl. Intravenous rehydration and loop diuretics are the treatment of choice. Bisphosphonates should be given intravenously in case other treatment options are ineffective (Figure 4).\textsuperscript{19} Corticosteroids are the causal first-line treatment in sarcoidosis-associated hypercalcemia. In vitro studies have confirmed that dexamethasone suppresses calcitriol production in sarcoidosis patients’ pulmonary
alveolar macrophages. The treatment schedule of an initial 40 mg dose of prednisone followed by a reduction to 20 mg in 1–2 weeks appears to be effective. Further dose reduction should follow within the upcoming weeks. The decrease of serum calcium level usually takes place a week after the onset of treatment, and calcium excretion in urine decreases after approximately 10 days. A lack of response to treatment within 2 weeks may indicate another cause of hypercalcemia.

Our clinical observations suggest that in cases of progressive kidney failure, when dual etiology (hypercalcemic and sarcoidosis of kidneys) could not be excluded, IV methylprednisolone was effective. Other drugs successfully (but rarely) used in the treatment of calcium homeostasis disorders are (hydroxy)chloroquine and ketoconazole. Both drugs suppress 1-α-hydroxylase and chloroquine additionally stimulates calcitriol deactivation by 24-hydroxylase. Infliximab has also proven to be an effective option in sarcoidosis-associated hypercalcemia in cases of toxicity or resistance to corticosteroids and other immunosuppressive drugs. In a 4-year observational study, a lower incidence of nephrolithiasis was observed in patients with higher dietary calcium intake, which may be related to inhibition of oxalates absorption. While renal calculi in patients with sarcoidosis consist mainly of calcium oxalates, calcium restriction in the diet may produce unexpectedly harmful results.

In the case of hypercalciuria, thiazide diuretics are contraindicated due to their potential to induce hypercalciemia. Some authors suggest a low-calcium diet, but studies seem to question this recommendation. Hypercalciuria persisted in 30% of patients despite calcium restriction in their diet. Further, the use of pharmacotherapy to limit calcium absorption did not improve calcium concentration control. In a 4-year observational study, a lower incidence of nephrolithiasis was observed in patients with higher dietary calcium intake, which may be related to inhibition of oxalates absorption. While renal calculi in patients with sarcoidosis consist mainly of calcium oxalates, calcium restriction in the diet may produce unexpectedly harmful results.

Conclusions
Sarcoidosis-associated hypercalcemia is quite a common problem as it affects about 6% of patients. It is also one of the indications to introduce pharmacotherapy with steroids. Its pathophysiology appears to be quite well explained. Although it seems logical that vitamin D metabolites should be good tools for assessing disease activity, clinically it is not that simple. Increased conversion of 25(OH)D3 to calcitriol suggests that perhaps the ratio of 25(OH)D3 to 1,25(OH)2D3 could be more adequate than absolute values. One study confirms this theory.

Despite our increasing knowledge about calcium homeostasis disorders in patients with sarcoidosis, there is still a need for clear guidelines regarding calcium and Vitamin D supplementation. Papers concerning this problem are inconclusive. It appears that supplementation increases the risk of hypercalcemia but only in a certain group of patients. Nevertheless,
indications for supplementation seem to be limited, as it is probably ineffective in preventing steroid-induced osteoporosis fractures. An improvement in the course of sarcoidosis in patients with corrected vitamin D insufficiency is a tempting perspective, but more evidence is needed.

Management of sarcoidosis-associated hypercalcaemia should start with excluding other causes of elevated calcium levels. Intensive hydration coupled with loop diuretics (if needed, especially in the elderly and patients with heart failure) should be introduced to reduce hypercalcaemia and prevent its acute complication. Corticosteroids should be introduced to remove the cause of calcium metabolism disturbance. Oral treatment with prednisone (doses of 0.5–1 mg/kg a day) is sufficient. In cases of progressive kidney failure, when dual etiology (hypercalcemic and sarcoidosis of kidneys) could not be excluded, IV methylprednisolone would be used.

The complex action of vitamin D on the immune system coupled with the pathophysiology of granulomatous inflammation seen in sarcoidosis could possibly provide new therapeutic targets in the future.

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References
1. Blau JE and Collins MT. The PTH-vitamin D-FGF23 axis. *Rev Endocr Metab Disord* 2015; 16: 165–174.
2. Yokota H, Raposo JF, Chen A, et al. Evaluation of the role of FGF23 in mineral metabolism. *Gene Regul Syst Biol* 2009; 3: 131–142.
3. Kamphuis LS, Bonte-Mineur F, van Laar JA, et al. Calcium and vitamin D in sarcoidosis: is supplementation safe? *J Bone Miner Res* 2014; 29: 2498–2503.
4. Adams JS and Hewison M. Extrarenal expression of the 25-hydroxyvitamin D-1-hydroxylase. *Arch Biochem Biophys* 2012; 523: 95–102.
5. Rottoli P, Muscettola M, Grasso G, et al. Impaired interferon-gamma production by peripheral blood mononuclear cells and effects of calcitiol in pulmonary sarcoidosis. *Sarcoidosis* 1993; 10: 108–114.
6. Muscettola M and Grasso G. Effect of 1,25-dihydroxyvitamin D3 on interferon gamma production in vitro. *Immunol Lett* 1988; 17: 121–124.
7. Müller K and Bendtzen K. Inhibition of human T lymphocyte proliferation and cytokine production by 1,25-dihydroxyvitamin D3. Differential effects on CD45RA+ and CD45R0+ cells. *Autoimmunity* 1992; 14: 37–43.
8. Zhang Y, Leung DYM, Richers BN, et al. Vitamin D inhibits monocyte/macrophage pro-inflammatory cytokine production by targeting mitogen-activated protein kinase phosphatase 1. *J Immunol Baltim Md 1950* 2012; 188: 2127–2135.
9. Ohta M, Okabe T, Ozawa K, et al. In vitro formation of macrophage-epithelioid cells and multinucleated giant cells by 1 alpha,25-dihydroxy vitamin D3 from human circulating monocytes. *Ann N Y Acad Sci* 1986; 465: 211–220.
10. Penna G and Adorini L. 1α,25-Dihydroxyvitamin d3 inhibits differentiation, maturation, activation, and survival of dendritic cells leading to impaired alloreactive T cell activation. *J Immunol* 2000; 164: 2405–2411.
11. Bucova M, Suchankova M, Tibenska E, et al. TREM-2 receptor expression increases with 25(OH)D vitamin serum levels in patients with pulmonary sarcoidosis. *Mediators Inflamm* 2015. Epub ahead of print 2015. DOI: 10.1155/2015/181986.
12. Barna BP, Culver DA, Kanchwala A, et al. Alveolar macrophage cathecinidin deficiency in severe sarcoidosis. *J Innate Immun* 2012; 4: 569–578.
13. Biyoudi-Vouenze R, Cadranel J, Valeyre D, et al. Expression of 1,25(OH)2D3 receptors on alveolar lymphocytes from patients with pulmonary granulomatous diseases. *Am Rev Respir Dis* 1991; 143: 1376–1380.
14. Niimi T, Tomita H, Sato S, et al. Vitamin D receptor gene polymorphism in patients with sarcoidosis. *Am J Respir Crit Care Med* 1999; 160: 1107–1109.
15. Petkovic TR, Pejcić T, Marinkovic M, et al. The role of vitamin D receptor Bsm1 polymorphism in the course of sarcoidosis. *Eur Respir J* 2017; 50: PA980.
16. Taibi L, Boursier C, Clodic G, et al. Search for biomarkers of neurosarcoidosis by proteomic analysis of cerebrospinal fluid. *Ann Biol Clin (Paris)* 2017; 75: 393–402.
17. Martinez-Bravo M-J, Wahlund CJE, Qazi KR, et al. Pulmonary sarcoidosis is associated with exosomal vitamin D-binding protein and inflammatory molecules. *J Allergy Clin Immunol* 2017; 139: 1186–1194.

18. Milman N, Thymann M, Graudal N, et al. Plasma vitamin D-binding protein (GC) factors, immunoglobulin G heavy chain (GM) allotypes and immunoglobulin kappa light chain (KM1) allotype in patients with sarcoidosis and in healthy control subjects. *Sarcoidosis Vasc* 2002; 19: 97–100.

19. Renaghan AD and Rosner MH. Hypercalcemia: etiology and management. *Nephrol Dial Transplant* 2018; 33: 549–551.

20. Donovan PJ, Sundac L, Pretorius CJ, et al. Calcitriol-mediated hypercalcemia: causes and course in 101 patients. *J Clin Endocrinol Metab* 2013; 98: 4023–4029.

21. Soyfoo MS, Brenner K, Paesmans M, et al. Non-malignant causes of hypercalcemia in cancer patients: a frequent and neglected occurrence. *Support Care Cancer* 2013; 21: 1415–1419.

22. Morimoto T, Azuma A, Abe S, et al. Epidemiology of sarcoidosis in Japan. *Eur Respir J* 2008; 31: 372–379.

23. Ungprasert P, Crowson CS, and Matteson EL. Influence of gender on epidemiology and clinical manifestations of sarcoidosis: a population-based retrospective cohort study 1976-2013. *Lung* 2017; 195: 87–91.

24. James DG, Neville E, and Siltzbach LE. A worldwide review of sarcoidosis. *Ann N Y Acad Sci* 1976; 278: 321–334.

25. Studdy PR, Bird R, Neville E, et al. Biochemical findings in sarcoidosis. *J Clin Pathol* 1980; 33: 528–533.

26. Baughman RP, Teirstein AS, Judson MA, et al. Clinical characteristics of patients in a case control study of sarcoidosis. *Am J Respir Crit Care Med* 2001; 164: 1885–1889.

27. Smith C, Feldman C, Reyneke J, et al. Sarcoidosis in Johannesburg – a comparative study of black and white patients. *South Afr Med J* 1991; 80: 423–427.

28. Mahévas M, Lescure FX, Boffia J-J, et al. Renal sarcoidosis: clinical, laboratory, and histologic presentation and outcome in 47 patients. *Medicine (Baltimore)* 2009; 88: 98.

29. Baughman RP, Janovcik J, Ray M, et al. Calcium and vitamin D metabolism in sarcoidosis. *Sarcoidosis Vasc* 2013; 30: 113–120.

30. Sawahata M, Sugiyama Y, Nakamura Y, et al. Age-related and historical changes in the clinical characteristics of sarcoidosis in Japan. *Respir Med* 2015; 109: 272–278.

31. Brito-Zerón P, Sellarés J, Bosch X, et al. Epidemiologic patterns of disease expression in sarcoidosis: age, gender and ethnicity-related differences. *Clin Exp Rheumatol* 2016; 34: 380–388.

32. Abernathy RS. Childhood sarcoidosis in Arkansas. *South Med J* 1985; 78: 435–439.

33. Hoffmann AL, Milman N, and Byg KE. Childhood sarcoidosis in Denmark 1979–1994: incidence, clinical features and laboratory results at presentation in 48 children. *Acta Paediatr Oslo Nor* 1992 2004; 93: 30–36.

34. Robinson PJ and Olinsky A. Sarcoidosis in children. *Aust Paediatr J* 1986; 22: 291–293.

35. Smith MJ and Hey GB. Recurring ‘red eyes’ due to seasonal hypercalcaemia. *Postgrad Med J* 1976; 52: 86–89.

36. Papapoulos SE, Clemens TL, Fraher LJ, et al. 1,25-dihydroxycholecalciferol in the pathogenesis of the hypercalcaemia of sarcoidosis. *Lancet Lond Engl* 1979; 1: 627–630.

37. Cronin CC, Dinneen SF, O’Mahony MS, et al. Precipitation of hypercalcaemia in sarcoidosis by foreign sun holidays: report of four cases. *Postgrad Med J* 1990; 66: 307–309.

38. Wiemeyer A, Schwarzew E, Mathias K, et al. Acute kidney failure in a recurrence of sarcoidosis at the height of summer. *Dtsch Med Wochenschr* 1946 1996; 121: 165–168.

39. Rossman MD, Thompson B, Frederick M, et al. HLA and environmental interactions in sarcoidosis. *Sarcoidosis Vasc* 2008; 25: 125–132.

40. Lancina Martín JA, Garcia Freire C, Bustó Castañón L, et al. Sarcoidosis and urolithiasis. *Arch Esp Urol* 1995; 48: 234–239.

41. Iannuzzi MC, Rybicki BA, and Teirstein AS. Sarcoidosis. *N Engl J Med* 2007; 357: 2153–2165.

42. Berliner AR, Haas M, and Choi MJ. Sarcoidosis: the nephrologist’s perspective. *Am J Kidney Dis* 2006; 48: 856–870.

43. Bell NH, Stern PH, Pantzer E, et al. Evidence that increased circulating 1 alpha, 25-dihydroxyvitamin D is the probable cause for abnormal calcium metabolism in sarcoidosis. *J Clin Invest* 1979; 64: 218–225.

44. Barbour GL, Coburn JW, Slatopolsky E, et al. Hypercalcaemia in an anephric patient with sarcoidosis: evidence for extrarenal generation of 1,25-dihydroxyvitamin D. *N Engl J Med* 1981; 305: 440–443.

45. Maesaka JK, Batuman V, Pablo NC, et al. Elevated 1,25-dihydroxyvitamin D levels: occurrence with sarcoidosis with end-stage renal disease. *Arch Intern Med* 1982; 142: 1206–1207.
46. Mason RS, Frankel T, Chan YL, et al. Vitamin D conversion by sarcoïd lymph node homogenate. Ann Intern Med 1984; 100: 59–61.

47. Adams JS, Sharma OP, Gacad MA, et al. Metabolism of 25-hydroxyvitamin D3 by cultured pulmonary alveolar macrophages in sarcoidosis. J Clin Invest 1983; 72: 1856–1860.

48. Adams JS, Singer FR, Gacad MA, et al. Isolation and structural identification of 1,25-dihydroxyvitamin D3 produced by cultured alveolar macrophages in sarcoidosis. J Clin Endocrinol Metab 1985; 60: 960–966.

49. Adams JS, Chen H, Chun R, et al. Substrate and enzyme trafficking as a means of regulating 1,25-dihydroxyvitamin D synthesis and action: the human innate immune response. J Bone Miner Res 2007; 22(Suppl 2): V20–V24.

50. Reichel H, Koeffler HP, Barbers R, et al. Regulation of 1,25-dihydroxyvitamin D3 production by cultured alveolar macrophages from normal human donors and from patients with pulmonary sarcoidosis. J Clin Endocrinol Metab 1987; 65: 1201–1209.

51. Adams JS, Modlin RL, Diz MM, et al. Potentiation of the macrophage 25-hydroxyvitamin D-1-hydroxylation reaction by human tuberculous pleural effusion fluid. J Clin Endocrinol Metab 1989; 69: 457–460.

52. Dusso AS, Kamimura S, and Gallieni M, et al. gamma-Interferon-induced resistance to 1,25-(OH)2D3 in human monocytes and macrophages: a mechanism for the hypercalcemia of various granulomatoses. J Clin Endocrinol Metab 1997; 82: 2222–2232.

53. Adams JS, Gacad MA, Diz MM, et al. A role for endogenous arachidonate metabolites in the regulated expression of the 25-hydroxyvitamin D1-hydroxylation reaction in cultured alveolar macrophages from patients with sarcoidosis. J Clin Endocrinol Metab 1990; 70: 595–600.

54. Lawrence EC, Berger MB, Brousseau KP, et al. Elevated serum levels of soluble interleukin-2 receptors in active pulmonary sarcoidosis: relative specificity and association with hypercalcemia. Sarcoidosis 1987; 4: 87–93.

55. Logan T and Bensadoun E. Increased disease activity in a patient with sarcoidosis after high dose interleukin 2 treatment for metastatic renal cancer. Thorax 2005; 60: 610–611.

56. Yokomura K, Suda T, Sasaki S, et al. Increased expression of the 25-hydroxyvitamin D(3)-1alpha-hydroxylase gene in alveolar macrophages of patients with lung cancer. J Clin Endocrinol Metab 2003; 88: 5704–5709.

57. Stoffels K, Overbergh L, Giulietti A, et al. Immune regulation of 25-hydroxyvitamin-D3-1alpha-hydroxylase in human monocytes. J Bone Miner Res 2006; 21: 37–47.

58. Unsal A, Basturk T, Koc Y, et al. Renal sarcoidosis with normal serum vitamin D and refractory hypercalcemia. Int Urol Nephrol 2013; 45: 1779–1783.

59. Berlin JL, Palamaner Subash Shantha G, Yeager H, et al. Serum vitamin D levels may not reflect tissue-level vitamin D in sarcoidosis. BMJ Case Rep 2014. Epub ahead of print 24 March 2014. DOI: 10.1136/bcr-2014-203759.

60. Shrayyef MZ, DePapp Z, Cave WT, et al. Hypercalcemia in two patients with sarcoidosis and Mycobacterium avium intracellulare not mediated by elevated vitamin D metabolites. Am J Med Sci 2011; 342: 336–340.

61. Falk S, Kratzsch J, Paschke R, et al. Hypercalcemia as a result of sarcoidosis with normal serum concentrations of vitamin D. Med Sci Monit Int Med J Exp Clin Res 2007; 13: CS133–CS136.

62. Basile JN, Liel Y, Shary J, et al. Increased calcium intake does not suppress circulating 1,25-dihydroxyvitamin D in normocalcemic patients with sarcoidosis. J Clin Invest 1993; 91: 1396–1398.

63. Stern PH, De Olazabal J, and Bell NH. Evidence for abnormal regulation of circulating 1 alpha,25-dihydroxyvitamin D in patients with sarcoidosis and normal calcium metabolism. J Clin Invest 1980; 66: 852–855.

64. Hamada K, Nagai S, Tsutsumi T, et al. Ionized calcium and 1,25-dihydroxyvitamin D concentration in serum of patients with sarcoidosis. Eur Respir J 1998; 11: 1015–1020.

65. Adams JS, Gacad MA, Anders A, et al. Biochemical indicators of disordered vitamin D and calcium homeostasis in sarcoidosis. Sarcoidosis 1986; 3: 1–6.

66. Alberts C and van den Berg H. Calcium metabolism in sarcoidosis. A follow-up study with respect to parathyroid hormone and vitamin D metabolites. Eur J Respir Dis 1986; 68: 186–194.

67. Krikorian A, Shah S, and Wasman J. Parathyroid hormone-related protein: an unusual mechanism for hypercalcemia in sarcoidosis. Am J Pathol 1998; 152: 17–21.
Fierer J, Burton DW, Haghighi P, et al. Hypercalcemia in disseminated coccidioidomycosis: expression of parathyroid hormone-related peptide is characteristic of granulomatous inflammation. Clin Infect Dis 2012; 55: e61–e66.

Pandian MR, Morgan CH, Carlton E, et al. Modified immunoradiometric assay of parathyroid hormone-related protein: clinical application in the differential diagnosis of hypercalcemia. Clin Chem 1992; 38: 282–288.

Bucht E, Eklund A, Toss G, et al. Parathyroid hormone-related peptide, measured by a midmolecule radioimmunoassay, in various hypercalcemic and normocalcaemic conditions. Acta Endocrinol (Copenh) 1992; 127: 294–300.

Heijckmann AC, Huijberts MSP, De Vries J, et al. Bone turnover and hip bone mineral density in patients with sarcoidosis. Sarcoidosis Vasc 2007; 24: 51–58.

Heijckmann AC, Drent M, Dumitrescu B, et al. Progressive vertebral deformities despite unchanged bone mineral density in patients with sarcoidosis: a 4-year follow-up study. Osteoporos Int 2008; 19: 839–847.

Bolland MJ, Wilsher ML, Grey A, et al. Bone density is normal and does not change over 2 years in sarcoidosis. Osteoporos Int 2015; 26: 611–616.

Bours S, de Vries F, van den Bergh JPW, et al. Risk of vertebral and non-vertebral fractures in patients with sarcoidosis: a population-based cohort. Osteoporos Int 2016; 27: 1603–1610.

Oshagbemi OA, Driessen JHM, Pieffers A, et al. Use of systemic glucocorticoids and the risk of major osteoporotic fractures in patients with sarcoidosis. Osteoporos Int 2017; 28: 2859–2866.

Saidenberg-Kermanac’h N, Semerano L, Nunes H, et al. Bone fragility in sarcoidosis and relationships with calcium metabolism disorders: a cross sectional study on 142 patients. Arthritis Res Ther 2014; 16: R78.

Bolland MJ, Wilsher ML, Grey A, et al. Randomised controlled trial of vitamin D supplementation in sarcoidosis. BMJ Open 2013; 3: e003562.

Amin S, LaValley MP, Simms RW, et al. The role of vitamin D in corticosteroid-induced osteoporosis: a meta-analytic approach. Arthritis Rheum 1999; 42: 1740–1751.

Allen CS, Yeung JH, Vandermeer B, et al. Bisphosphonates for steroid-induced osteoporosis. Cochrane Database Syst Rev 2016; 10: CD001347.

Amiche MA, Albaum JM, Tadrous M, et al. Efficacy of osteoporosis pharmacotherapies in preventing fracture among oral glucocorticoid users: a network meta-analysis. Osteoporos Int J 2016; 27: 1989–1998.

Boon ES, Cozijn D, and Brombacher PJ. Enhanced production of calcitriol, and hypercalcemia in a patient with sarcoidosis provoked by daily intake of calcitriol. Eur J Clin Chem Clin Biochem 1993; 31: 679–681.

Satathi V, Karethaimaia H, and Goel A. High-dose vitamin D supplementation precipitating hypercalcemic crisis in granulomatous disorders. Indian J Endocrinol Metab 2017; 21: 815–819.

Sodhi A and Aldrich T. Vitamin D supplementation: not so simple in sarcoidosis. Am J Med Sci 2016; 352: 252–257.

Capolongo G, Xu LHR, Accardo M, et al. Vitamin-D status and mineral metabolism in two ethnic populations with sarcoidosis. J Investig Med 2016; 64: 1025–1034.

Kiani A, Abedini A, Adcock IM, et al. Association between vitamin D deficiencies in sarcoidosis with disease activity, course of disease and stages of lung involvements. J Med Biochem 2018; 37: 103–109.

Bansal AS, Bruce J, Hogan PG, et al. An assessment of peripheral immunity in patients with sarcoidosis using measurements of serum vitamin D3, cytokines and soluble CD23. Clin Exp Immunol 1997; 110: 92–97.

Kavathia D, Buckley JD, Rao D, et al. Elevated 1,25-dihydroxyvitamin D levels are associated with protracted treatment in sarcoidosis. Respir Med 2010; 104: 564–570.

Infante JR, Pacheco C, Torres-Avisbal M, et al. Pulmonary activity in sarcoidosis: 67 Ga uptake quantification and plasma determination of 1,25-dihydroxyvitamin D. Rev Esp Med Nucl 2002; 21: 275–280.

Sharma OP. Hypercalcemia in granulomatous disorders: a clinical review. Curr Opin Pulm Med 2000; 6: 442–447.

Burke RR, Rybicki BA, and Rao DS. Calcium and vitamin D in sarcoidosis: how to assess and manage. Semin Respir Crit Care Med 2010; 31: 474–484.

Adams JS, Sharma OP, Diz MM, et al. Ketoconazole decreases the serum 1,25-dihydroxyvitamin D and calcium concentration in sarcoidosis-associated hypercalcemia. J Clin Endocrinol Metab 1990; 70: 1090–1095.

Bia MJ and Insogna K. Treatment of sarcoidosis-associated hypercalcemia with ketoconazole. Am J Kidney 1991; 18: 702–705.

Barré PE, Gascon-Barré M, Meakins JL, et al. Hydroxychloroquine treatment of hypercalcemia in a patient with sarcoidosis undergoing hemodialysis. Am J Med 1987; 82: 1259–1262.
96. O’Leary TJ, Jones G, Yip A, et al. The effects of chloroquine on serum 1,25-dihydroxyvitamin D and calcium metabolism in sarcoidosis. *N Engl J Med* 1986; 315: 727–730.

97. Thumfart J, Müller D, Rudolph B, et al. Isolated sarcoid granulomatous interstitial nephritis responding to infliximab therapy. *Am J Kidney Dis* 2005; 45: 411–414.

98. Huffstutter JG and Huffstutter JE. Hypercalcemia from sarcoidosis successfully treated with infliximab. *Sarcoidosis Vasc* 2012; 29: 51–52.

99. Dwarakanathan A and Ryan WG. Hypercalcemia of sarcoidosis treated with cellulose sodium phosphate. *Bone Miner* 1987; 2: 333–336.

100. Waron M, Weissgarten J, Gil I, et al. Sarcoid nephrocalcinotic renal failure reversed by sodium cellulose phosphate. *Am J Nephrol* 1986; 6: 220–223.

101. Littlewood T, Hunter A, Beck P, et al. Treatment of hypercalcaemia in sarcoidosis with flurbiprofen. *Br Med J Clin Res Ed* 1983; 287: 1762–1763.

102. Meyrier A, Valeyre D, Bouillon R, et al. Different mechanisms of hypercalciuria in sarcoidosis. Correlations with disease extension and activity. *Ann N Y Acad Sci* 1986; 465: 575–586.

103. Fuss M, Pepersack T, Gillet C, et al. Calcium and vitamin D metabolism in granulomatous diseases. *Clin Rheumatol* 1992; 11: 28–36.

104. Rizzato G and Colombo P. Nephrolithiasis as a presenting feature of chronic sarcoidosis: a prospective study. *Sarcoidosis Vasc* 1996; 13: 167–172.

105. Lemann J. Composition of the diet and calcium kidney stones. *N Engl J Med* 1993; 328: 880–882.

106. Thomas WC. Urinary calculi in hypercalcemic states. *Endocrinol Metab Clin North Am* 1990; 19: 839–849.

107. Rohmer J, Hadjadj J, Bouzerara A, et al. Serum 1,25(OH)2 vitamin D and 25(OH) vitamin D ratio for the diagnosis of sarcoidosis-related uveitis. *Ocul Immunol Inflamm* 2018; 5: 1–7.