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REVIEW PAPER

The role of vitamin D and its supplementation in sarcoidosis – current status

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ABSTRACT

Introduction and aim. Sarcoidosis is a chronic autoimmune-related inflammatory disease characterized by non-caseating granuloma formation. The macrophages accumulating in granulomas express increased 1alpha hydroxylase activity. Increased extrarenal 1,25-dihydroxyvitamin D synthesis can lead to hypercalcemia and its complications. However, 25-hydroxyvitamin D deficiency and insufficiency are virtually universal among sarcoidosis patients. The aim of this study was to explain the complex role of vitamin D and to its metabolites and discuss the possible benefits and risks associated with the administration of exogenous vitamin D to patients with sarcoidosis.

Material and methods. PubMed and Scopus databases were searched for reviews about The role of vitamin D and its supplementation in sarcoidosis. The authors have analyzed a total of 107 full-text articles published between January 2000 and November 2024, with additional articles identified by bibliography analysis.

Analysis of literature. The potential benefits of vitamin D supplementation in sarcoidosis are promising in terms of reducing the inflammatory response, counteracting disease progression, reducing bone fracture risk, and minimizing the pharmacotherapy needed for disease control. However, the risk of hypercalcemia should not be neglected.

Conclusion. Despite the increased risk of hypercalcemia, vitamin D supplementation in patients with sarcoidosis should be considered. Each patient's benefits-to-risks ratio of vitamin D supplementation should be assessed individually and the intervention should be closely monitored both before and during implementation.

Keywords. bone mineral density, disease course, hypercalcemia, sarcoidosis, supplementation, vitamin D

Introduction

Sarcoidosis is a chronic autoimmune-related inflammatory disease characterized by non-caseating granuloma formation. The lungs and lymphatic system are the sites most frequently affected. Other organs such as the skin, heart, eyes, liver, and spleen may also be involved.[1]

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The symptoms of sarcoidosis are nonspecific and include persistent cough, dyspnea, fatigue, weight loss, fever, night sweats, and erythema nodosum. More characteristic clinical manifestations may be observed depending on the affected area.[2,3] The definitive etiology of sarcoidosis remains unknown; however, various hypotheses have been proposed, including disruption of innate immunity or the role of mycobacteria.[4]

Currently, the development and phenotype of sarcoidosis in individual patients are widely dependent on the interplay between genetic, environmental and non-environmental factors.[2]

The prevalence of sarcoidosis varies between one and 160 per 100,000 depending on the geographical region and ethnicity.[5] The incidence among Blacks is three times higher than among Whites. Sarcoidosis usually occurs between 20 and 60 years of age.[6] Additionally, women are more commonly affected than men.[5] Other populations at increased risk of developing sarcoidosis are individuals of black ancestry or relatives with sarcoidosis.[7]

The challenges of sarcoidosis treatment include the variety of manifestations and the heterogeneity of the disease's course.[8] A wide range of medicines, including glucocorticosteroids (GCS), methotrexate, azathioprine and monoclonal antibodies, such as infliximab or adalimumab, are used.[9] Despite evolving pharmacotherapy options, GCS remain the mainstay of therapy in sarcoidosis patients.[10] https://pubmed.ncbi.nlm.nih.gov/35838355/ The optimization of treatment efficacy and disease activity, as well as counteracting the side effects of chosen pharmacologic interventions remain a challenge.

Calcitriol is one of the key hormones in calcium and phosphorus metabolism. Its interaction with PTH, calcitonin, and fibroblast growth factor 23 allows one to maintain adequate levels of calcium and phosphorus in the body, protecting from risks associated with both their abundance and scarcity.[11] Additionally, the impact on the immune system is complex.

Due to the most common side effect of GCS, osteoporosis, paired with a complicated role of vitamin D and its metabolites in sarcoidosis, together with the anti-inflammatory properties of calcitriol, the role of vitamin D supplementation in sarcoidosis is particularly intriguing.

However, a consensus on vitamin D supplementation in patients with sarcoidosis has not yet been reached. Due to risks about the concerns of hypercalcemia risks and the potential benefits of vitamin D supplementation in sarcoidosis patients, understanding the role of vitamin D in the pathogenesis of the disease and its metabolites' mutual impact and influence of its metabolites on the course of the disease is crucial. Previous research has addressed these connections; however, due to the rapid evolution of data on vitamin D's role and impact on sarcoidosis, we believe a timely re-evaluation is necessary. Although previous reviews discuss several aspects addressed in our review, by including recent studies, our article provides an up-to-date analysis of the current knowledge. Furthermore, in our article we include aspects of sarcoidosis and vitamin D supplementation in this population not recently juxtaposed in a single article, including disease pathophysiology, genetic predispositions, bone health, disease course, hypercalcemia, and its potential consequences in patients with sarcoidosis, offering to bridge gaps left by previous reviews. We propose a clinical approach based on the currently available data, underline knowledge gaps, and suggest areas for future research.

Aim

In this review, our aim is to explain the complexities of vitamin D's role in sarcoidosis pathogenesis, the complex relationship between its metabolites, and discuss possible benefits and risks associated with exogenous vitamin D administration in sarcoidosis patients. We propose a clinical approach to vitamin D supplementation among sarcoidosis patients.

Material and methods

The authors reviewed the literature by searching PubMed and Scopus databases. The search entries included various combinations of the following phrases: sarcoidosis, vitamin D, cholecalciferol, supplementation, bone mineral density, coarse, protracted treatment. The selected articles were published between January 2000 and November 2024 by titles and abstracts, excluding conference presentation abstracts, posters, and studies not consistent with and exceeding our review's purpose. Additional articles were extracted from the bibliographies of the screened articles. In the final analysis the authors included a total of 107 full-text articles: reviews, meta-analyses, randomized-controlled trials, cross-sectional studies, research articles, retrospective cohort studies, register-based studies, cohort studies, case-control studies, and a few case reports. The studies were focused on the pathophysiology of sarcoidosis, altered vitamin D metabolism, risk of hypercalcemia, bone health, disease course, and current knowledge on vitamin D supplementation in patients with sarcoidosis.

Analysis of literature

Sarcoidosis – pathophysiology

Several factors have been consistently associated with the development of sarcoidosis. At the genetic level, the Annexin A11 (ANXA11) gene – involved in the regulation of apoptosis – and its variations have been reported to impact the susceptibility to sarcoidosis.[12,13] The T allele of the rs1049550 ANXA11 gene was found to be

protective against the development of sarcoidosis, reducing the susceptibility to sarcoidosis by 30-40% depending on the studied population.[13,14] Conversely, the A allele of rs2789679 was more frequent among sarcoidosis patients compared to controls (p=0.00004, odds ratio (OR) 1.42, 95%, confidence interval (CI) 1.17 to 1.73), similarly to the T allele of rs2819941 (p=0.0006, OR 1.41, 95%; CI 1.16 to 1.71).[13]

Although a direct link is still being discussed, mycobacterial infections are considered a factor in the development of sarcoidosis. The connecting agent is cathelicidin, an antimicrobial peptide directed against mycobacteria.[15]

In their review, Gupta et al. indicate that the prevalence of sarcoidosis is greater in populations with a higher tuberculosis (TB) incidence, especially when a decline in the prevalence of TB occurs. This is consistent with molecular and immunological studies that suggest mycobacterial antigens (*Mycobacteria tuberculosis* in particular) as inciting agents of sarcoidosis.[16]

Sarcoidosis is a mainly granulomatous disease. The formation of non-caseating granulomas in sarcoidosis is related to overstimulation of the inflammatory system, often in the absence of a clear infectious agent. The exaggerated immune response is related to CD4+ T lymphocyte activation, their accumulation at the affected site, macrophage aggregation and subsequent formation of non-caseating granulomas. The overproduction of pro-inflammatory cytokines such as tumor necrosis factor (TNF-α), interleukin (IL) 6, interferon gamma (IFN-γ) contribute to tissue inflammation. B lymphocytes also accumulate in granulomatous tissue, with their altered maturation and function further contribute to the disease progression.[15,17] Their role in the pathogenesis is related to accompanying hypergammaglobulinemia, antigen presentation, and formation of immune complexes.[18,19]

Vitamin D – physiological metabolism

Physiologically, 7-dehydrocholesterol in the skin absorbs UVB radiation and undergoes isomerization to become vitamin D (cholecalciferol). However, vitamin D is considered inactive until hydroxylation. It is first hydroxylated in the liver to form a partially active 25-hydroxyvitamin D (25OHD). The full metabolic potential is reached after the second hydroxylation, most of which occurs in the kidneys when 1,25-dihydroxyvitamin D (calcitriol, 1,25-(OH)2D) is formed. Although dietary sources of cholecalciferol, such as fish, egg yolks, and some dairy products, continue to play a role, sunlight exposure remains the main source of cholecalciferol.[20] The kidneys play a crucial role in the formation of calcitriol by catalyzing the formation of last step in the active hormones and they are also primarily responsible for the catabolism of calcitriol. The renal CYP24A1 is key in the breakdown of calcitriol, helping maintain its adequate levels.[21] This negative feedback loop, which consists of decreased calcitriol synthesis with increased catabolism, is tightly regulated by calcium and phosphorus levels, parathormone (PTH) and is also product dependent: Increased calcitriol levels inhibit PTH release and decrease renal expression of 1alpha hydroxylase, decreasing the risk of hypercalcemia.[22] The 1,25(OH)2D synthesized at granulomatous sites also stimulates macrophage expression of 24-hydroxylase. It facilitates the conversion of calcitriol to less active metabolite and also thought to limit 25OHD availability to enzymes, thus increasing the 25OHD:1,25(OH)2D ratio.[23]

The role of vitamin D in immunity

Calcitriol modulates both the innate and adaptive immune responses.[24] It stimulates the expression of antimicrobial proteins, especially cathelicidin. This may help combat mycobacteria, which are considered inciting agents of the development of sarcoidosis.[25] Cathelicidin promotes autophagy in human monocytes and macrophages killing mycobacteria directly. It induces an inflammatory response by activating scavenger receptors, activating pro-inflammatory intracellular pathways, and enhancing cytokines and chemokines, including IL-6 and IL-10, monocyte chemoattractant protein (MCP) 1 and 3 in human peripheral blood mononuclear cells.[26,27] In severe sarcoidosis, cathelicidin levels are reduced compared to healthy individuals. Cathelicidin deficiency can impede the resolution of lung inflammation in patients with severe sarcoidosis, as the regulation of immune cells and pro-inflammatory cytokines is then impaired.[28]

In addition to cathelicidin stimulation, calcitriol promotes autophagy and thus destruction of intracellular pathogens. It reduces intracellular replication of phagocyte-free bacteria. Moreover, local synthesis of calcitriol, mediated by macrophages, promotes anti-inflammatory reactions by modulating T lymphocyte response. It suppresses the effector Th1 and Th17 lymphocytes while promoting the regulatory lymphocyte response of T, leading to a reduction in the inflammatory reaction. Studies show that calcitriol modulates cytokine expression in a concentration-dependent manner, generally promoting anti-inflammatory cytokine production and reducing anti-inflammatory cytokine stimulations, particularly IL-1, IL-2, IL-12, and IFN-γ. Research shows that calcitriol may also reduce prostaglandin production and TNF-α expression and secretion, further modulating the immune response.[24,29]

Calcitriol also affects B-lymphocyte-dependent immune processes. It reduces B lymphocyte memory and autoantibody production, crucial in the pathogenesis of sarcoidosis.[30-32] Despite conflicting evidence, it is suggested that the hormone affects B lymphocyte dif-

ferentiation, aggregation, activation threshold, and immunoglobin production.[33–38]

Altered vitamin D metabolism in sarcoidosis

The aggregation of macrophages is particularly important in cholecalciferol metabolism among sarcoidosis patients. Activated macrophages exhibit 1alpha hydroxylase expression. Their accumulation in sarcoid granulomas leads to increased enzyme levels, resulting in an increased 25OHD to 1,25(OH) 2D. Although renal calcitriol production is tightly regulated by the negative feedback loop, there is no product-controlled inhibition in immune cells. The production of 1alpha hydroxylase by immune cells is mainly controlled by proinflammatory cytokines produced in granulomas. Calcitriol production is promoted by production at site IL-1 and IL-2, TNF-α with IFN-γ shown to directly increase 1 alpha hydroxylase expression in macrophages, further increasing calcitriol production in sarcoid granulomas.[22,39]

Hypercalcemia risk in sarcoidosis

The increased extrarenal 1,25(OH)2D synthesis that occurs in sarcoid granulomas may lead to hypercalcemia and its complications. Hypercalcemia occurs in around 11% of patients with sarcoidosis - it may be symptomatic or asymptomatic; unmasked by exogenous vitamin D administration, or, with its complications, present as the first clinical characteristic of sarcoidosis.[40–52] Hypercalcemia, especially when chronic, can lead to various complications such as digestive tract dysfunction, coma, life-threatening arrhythmias, or kidney damage.[53] The increased levels of serum calcium may affect the electrical conductivity resulting in abnormal heart rhythms. Electrocardiographic manifestations include PR and QRS interval prolongation, T wave flattening, or the presence of a Q-wave.[54,55] The abnormal calcium metabolism is also linked to hypercalciuria. It occurs in approximately 50% of patients with sarcoidosis and may lead to nephrolithiasis, noted in 10% to 14% of sarcoidosis patients.[56–59] In up to 3.6%, kidney stones can be the first clinical presentation of sarcoidosis.[60] In addition to nephrolithiasis, nephrocalcinosis leading to kidney injury may occur. This complication is seen in up to 50% of patients with renal involvement.[61] Calcium level monitoring and evaluation of vitamin D metabolites assessment in correlation with clinical image are of key importance in patients with sarcoidosis.[48,49,62]

Sarcoidosis and vitamin D status

According to Burke et al. 25OHD deficiency and insufficiency are virtually universal among sarcoidosis patients, with 97% of sarcoidosis patients in the studied group with a 25OHD concentration below 28 ng/mL. Despite the 25OHD deficiency, 71% of these patients had 1,25(OH)2D levels equal to or greater than the median clinical value in the reference population (33.5 pg/mL).[22] The paradox presented by the authors sheds light on the importance of studies on the safety of vitamin D supplementation among patients with sarcoidosis, with a focus on possible risks of vitamin D toxicity. However, while the review, published in 2010, highlights challenges in adequate management of vitamin D metabolites levels, it does not include recent findings on complicated calcium homeostasis in sarcoidosis patients. Furthermore, while the authors advise caution, they do not include clinical trials on vitamin D supplementation – its safety and efficacy – among patients with sarcoidosis. The review lacks a patient-centered focus and focuses on biochemical findings without addressing outcomes such as the management of concentration-dependent symptoms of vitamin D metabolites.

Sarcoidosis and bone health

Studies show that the risk of bone deformities and bone fractures among sarcoidosis patients is significantly greater compared to studies on their incidence among healthy populations. In their cross-sectional study, Heijckmann et al. reported a prevalence of vertebral deformities among patients with sarcoidosis despite unchanged bone mineral density (BMD), 32% ($p < 0.05$) in the follow-up study, and 26% of patients developing either new or progressive deformities. Despite the unchanged BMD, the described deformities bore marks of osteoporotic fractures. Furthermore, the described pre-follow-up deformities occurred in a population with a mean age of 43 years, with half of the affected populations receiving GCS therapy.[63,64] These results suggest that patients with sarcoidosis may be at increased risk of vertebral deformities regardless of their BMD. This underlies the importance of early assessment and the introduction of appropriate interventions in this group of patients, as well as the need to establish more appropriate indicators of fracture risk among sarcoidosis patients. However, the lack of a control group, the small sample size (66 patients), and the short follow-up (4 years) limit the study's generalizability. Furthermore, potentially confounding factors have not been extensively assessed.

A similar study by Saidenberg-Kermanac'h et al. on 142 patients with histologically confirmed sarcoidosis delivered similar results, with 23.5% of patients with a history of fractures despite the mean age of 51 years and normal mean BMD. The risk factors associated with the increased risk of fracture included GCS treatment, low dietary calcium, as well as serum 25OHD levels that did not meet the 10–20 ng/mL interval.[65] This suggests that standard supplementation guidelines for the general population may not be adequate for patients with sarcoidosis and randomized-controlled trials in this population are necessary. Again, the lack of a control group,

not enough extensive analysis of potentially confounding factors, cross-sectional study design, and lack of implementation of advanced imaging techniques limit the ability to draw general conclusions from this study.

Boures et al. conducted a retrospective cohort study in a large population of 5 722 sarcoidosis patients matched with 28 704 controls, concluding that patients with sarcoidosis are at increased risk of clinical vertebral fractures (adjusted relative risk (RR) 1.77; 95%; CI 1.06–2.96) but not any fractures (adjusted RR 0.87; 95% CI 0.77–0.99); and the use of GCS use among sarcoidosis patients causes an increased risk of any fractures (adjusted RR 1.50; 95% CI 1.20–1.89).[66] While recent GCS use is taken into consideration, no details on the total dose or duration of therapy have been included. Furthermore, lack of BMD measurements or attribution of potential confounding factors prevents fully informed conclusions on the causes of fractures. Further prospective research on the relationship between fracture prevalence and vitamin D metabolites' levels is necessary for establishing vitamin D's role in bone health in sarcoidosis patients.

In a 2018 meta-analysis by Yong et al., no increased risk of fracture or loss of bone mineral in sarcoidosis has not been identified.[67] The authors did not include the previously described studies in the analysis and mostly focused mainly in patients treated with the available studies on premenopausal and not with GCS. Other studies have also found no correlation between sarcoidosis and decreased BMD regardless of baseline vitamin D status and oral GCS use, and one study suggesting possible decreases in BMD in female patients. 1,25(OH)2D has been suggested to the increased bone turnover as a cause of increased fracture risk among sarcoidosis patients.[63,65,68] A single center cross-sectional study on 262 patients, matched with healthy controls, found that in sarcoidosis patients, the increased fragility fracture risk correlates with the severity of lung disease severity and potential disease activity.[69] The BMD T scores of the sarcoidosis patients were significantly lower than those of healthy controls in the lumbar spine and total hip ($p<0.01$ and $p<0.05$, respectively). Furthermore, fragility fractures were more prevalent among patients with sarcoidosis, reaching 30.6% compared to 12.3% in the control group. The link between bone health and lung function of sarcoidosis patients showed decreases in forced vital capacity, lungs diffusion capacity of the lungs for carbon monoxide, and forced expiratory volume in the first second among sarcoidosis patients with low BMD and multiple vertebral fractures.[69] Again, the study lacks details on GCS dosage, proper assessment of confounders. Together with the cross-sectional design of the study, the limitations suggest that more longitudinal research is needed. A summary of the studies analyzed, with their main focus and key findings, is presented in Table 1.

Table 1. Sarcoidosis and bone health summary

Study	Focus	Key findings
Bolland et al. [63]	Bone turnover and hip BMD	Bone turnover normal
Heijckmann et al. [64]	Vertebral deformities and BMD change over 4 years	Progressive vertebral deformities occurred despite stable BMD
Saidenberg-Kermanac'h et al. [65]	Bone fragility and calcium metabolism disorders	Increased fracture risk correlated with calcium metabolism disorders
Bours et al. [66]	Risk of vertebral and non-vertebral fractures	Increased fracture risk in sarcoidosis patients compared to controls
Yong et al. [67]	Bone mineral loss and fracture	Lower BMD and increased risk of fracture in sarcoidosis patients compared to the general population
Bolland et al. [68]	Changes in BMD over 2 years	Hip BMD normal and stable over 2 years
Cameli et al. [69]	Evaluation of BMD and fracture risk	Lower BMD and higher fracture risk identified in specific sarcoidosis populations

Vitamin D status and course of sarcoidosis

Studies show that despite an increase in serum 1,25(OH)2D sarcoidosis patients often suffer from 25OHD deficiency.[22,70] Furthermore, an association between decreased serum 25OHD to the 1,25 (OH) 2D ratio and disease activity, severity, chronicity, and protracted treatment has been noted.[65,71–74] Higher serum 25OHD is also associated with lower disease activity implicating that described dysregulation may affect prognosis.[65,75]

Kiani et al. and Mihailovic-Vucinic et al. describe a statistically significant correlation between vitamin D deficiency and sarcoidosis chronicity.[74,76] According to a cross-sectional study on 80 sarcoidosis patients by Kiani et al., the 0–1 respiratory involvement in sarcoidosis is not correlated with vitamin D deficiency (Mann-Whitney test; $p=0.243$). However, a possible progression of pulmonary sarcoidosis to stage 2-4 lung involvement by 25OHD deficiency has been described (Pearson Chi-Square=4.266; degrees of freedom (df)=1; $p=0.039$). 25OHD deficiency has also been suggested to play a role in the development of acute and active sarcoidosis. However, the study by Kiani et al. involves only serum 25OHD measurements but not 1,25(OH)2D3 levels. Evaluation of the levels of both metabolites would provide more comprehensive understanding of the impact of vitamin D on disease course. Additionally, the lack of a control group, the evaluation of disease activity based on 24-hour urinary calcium levels – which is not a definitive marker of sarcoidosis – are important limitations of the study.[76]

Mihailovic-Vucinic et al. have also noted an inverse correlation between serum 25OHD levels and disease activity markers. They found a statistically significant correlation between disease chronicity and low serum 25 (OH) D levels (Chi-Squar e=6.044; df=2; $p=0.014$).

Furthermore, the majority of patients with high calcium levels in the 24h urine sample had absolute 25(OH)D deficiencies, despite a statistically significant correlation between calcium urine levels (24 hour urine) and serum vitamin D in the studied group (ChiSquare=6.759; df=2; p=0.034).[74] Their study underscores the complex role of vitamin D in sarcoidosis pathogenesis, immune function and dysfunction, as well as disease activity, measured by serum angiotensin-converting enzyme levels. Despite promising results, the cross-sectional study design, limited sample size and sample diversity, lack of control group, and conclusions drawn based on 25OHD3 levels not juxtaposed to the level (not measured) limit the generalizability and its potential role in guidelines development.[74]

Similar results were obtained in a retrospective study by Kamphius et al., where the authors concluded that vitamin D scarcity may affect sarcoidosis activity. Although a negative correlation ($p < 0.001$) between 25OHD levels and disease activity – measured by somatostatin receptor scintigraphy - no additional markers of either disease activity or inflammation were implemented, limiting the comprehensibility of this aspect of the study. Furthermore, serum calcium levels were not significantly correlated with 25OHD or 1,25(OH)2D levels ($p = 0.52$ and $p = 0.07$, respectively).[75] However, this study did not investigate only vitamin D supplementation but calcium and vitamin D supplementation, and the study lacked a standardized supplementation protocol. The retrospective study design and limited follow-up data are additional study limitations.[75]

Kavathia et al. have conducted a complementary study linking increased 1,25(OH)2D levels with prolonged systemic treatment in patients with sarcoidosis. The authors demonstrated that serum 1,25(OH)2D levels are positively correlated with the severity and prolonged treatment of sarcoidosis. Patients in the highest quartile of 1,25(OH)2D levels had significantly increased odds (OR: 1.82; with 95% CI: 1.11–2.99) of chronic phenotype. In particular, 71% of patients with $1,25(OH)_2D$ levels greater than 51 pg / ml had chronic treatment status (SCAC Class 6 requiring repeated regimens of systemic immunosuppressive therapy or >1 year of therapy). However, no significant differences were observed in serum 1,25(OH)2D3 levels by chest radiograph stage or Sarcoidosis Severity Score were noted. Despite clear cutoff levels and specific and targeted focus of the study, its cross-sectional design, small sample size (59 patients), limited diversity of the studied population, and lack of evaluation of 25OHD levels limit the study and suggest that more research is necessary to fully assess the role of vitamin D in the treatment of patients with chronic disease.[73] A summary of the analyzed studies, with their main focus and key findings, is presented in Table 2.

Table 2. Vitamin D status and sarcoidosis course summary

Study	Focus	Key findings
Burke et al. [22]	Calcium and vitamin D in sarcoidosis	The high 1,25(OH)2D associated with hypercalcemia and granuloma activity suggested cautious monitoring of vitamin D metabolites
Heijckmann et al. [64]	BMD, calcium, and vitamin D in sarcoidosis	The dysregulation of calcium and vitamin D metabolism affects bone health and potentially disease activity
Saidenberg-Kermanac'h et al. [65]	Bone fragility and calcium-vitamin D metabolism	Elevated 1,25(OH)2D levels observed in a subset of patients despite low to normal 25OHD levels, patients with high 1,25(OH)2D levels exhibited markers of increased disease activity
Filipovic et al. [71]	Vitamin D deficiency and sarcoidosis activity	Low 25OHD is associated with increased disease activity and worse outcomes
Scullion et al. [72]	Role of vitamin D in pulmonary inflammation	Vitamin D deficiency linked to increased inflammation highlighted potential role of Vitamin D in modulating activity of lung sarcoidosis

Vitamin D supplementation and risk of hypercalcemia in sarcoidosis patients

In their study discussed previously, Kamphius et al. determined that sarcoidosis patients without calcium and vitamin D supplementation were at increased risk of developing hypercalcemia than those supplemented; however, this finding was described as not statistically significant. Simultaneous GCS use and vitamin D supplementation correlated with a lower risk of hypercalcemia than sole vitamin D supplementation ($p<0.001$). Although the calcium concentration being higher than healthy controls, calcium levels were not correlated with vitamin D status.[75] Gwadera et al. found no significant correlation between calcium or vitamin D levels and disease activity, despite some inflammatory markers are correlating with increased calcium level. The design of the cross-sectional study, the small sample size of 58 patients, lack of a 1,25(OH)2D assessment significantly limit the generalizability of the study.[77] These results may indicate that vitamin D supplementation with concurrent GCS therapy may not only decrease the risk of hypercalcemia, but both interventions can act jointly to limit inflammation and disease progression, further reducing the risk of hypercalcemia. However, more detailed large-scale longitudinal studies are necessary to elucidate the relationship between calcium, vitamin D, and sarcoidosis.

In their randomized controlled trial, Bolland et al. introduced vitamin D supplementation in a group of patients with sarcoidosis with normal calcium levels and serum 25OHD levels below 20 ng/L. Compared to the control group, vitamin D did not exhibit significant dif-

ferences in serum calcium levels, but showed increases in their 25OHD serum levels. The intervention included supplementation of 50 000 IU of cholecalciferol per week for 4 weeks and 50 000 IU per month in the following 11 months. The authors noted one case of asymptomatic hypercalcemia and one case of asymptomatic hypercalciuria. Despite an appropriate study design, it only included 27 patients with sarcoidosis, limiting its statistical power.[78]

Again, a positive correlation between vitamin D supplementation and serum 25OHD levels but not with serum calcium levels has not been confirmed in the cross-sectional study previously discussed in 142 sarcoidosis patients by Saidenberg-Kermanac et al.[65]

In their study, Capolongo et al. concluded that hypercalciuria and nephrolithiasis associated with sarcoidosis are not related to endogenous calcitriol synthesis. They have also noted a surprising decline in serum 1,25(OH)2D levels after vitamin D replacement. Despite a relatively small sample size, the study included a total of 86 Caucasian and African American sarcoidosis patients, providing a comparative perspective. The results provide valuable information on the role of vitamin D in sarcoidosis, however a relatively short-follow up time, the observational design of the study and the lack of adequate analysis of the correlation with disease activity limit the study's potential as the basis for safe and effective supplementation strategies.[79] Table 3 presents a summary of the studies analyzed, with their main focus and key findings.

Table 3. Vitamin D supplementation and hypercalcemia risk in sarcoidosis patients summary

Study	Focus	Key findings
Saidenberg-Kermanac'h et al. [65]	Calcium metabolism disorders in sarcoidosis	Vitamin D dysregulation associated with hypercalcemia in a significant subset of patients
Kamphuis et al. [75]	Safety of vitamin D and calcium supplementation	Supplementation often led to hypercalcemia and increased 1,25(OH2)D levels detected in susceptible individuals
Gwadera et al. [77]	Vitamin D, calcium and phosphate status	Hypercalcemia associated with high 1,25(OH)2D levels, even in mild supplementation cases, an individual approach to supplementation needed
Bolland et al. [78]	Vitamin D supplementation randomized controlled trial	Hypercalcemia developed in 11% of supplemented patients
Capolongo et al. [79]	Vitamin D and mineral metabolism in sarcoidosis	Hypercalcemia is more frequent in individuals with elevated baseline 1,25(OH)2D

Vitamin D supplementation – current guidelines

Despite increasing knowledge on the pathogenesis of sarcoidosis and the mechanism by which the immune system, vitamin D and calcium metabolisms are dysregulated, there are still no clear guidelines on vitamin D supplementation in sarcoidosis. The available literature underlines the importance of an individual approach to each patient, with an emphasis on appropriate pre-testing. Laboratory tests should precede the decision on vitamin D supplementation in a particular patient. Patients with sarcoidosis who receive vitamin D supplementation should undergo regular assessments not only 25OHD serum levels but also of 1,25(OH)2D serum levels. Serum calcium, urine calcium concentration, and renal function should also be monitored. In each case, supplementation should be adjusted to change sources of cholecalciferol, calcitriol, and calcium, such as diet and sun exposure, individually. Such an approach is advised to minimize the risk of hypercalcemia and its complications.[80]

There is no consensus on the appropriate nor completely safe dose of vitamin D that can be universally recommended to patients. However, starting with low doses (eg 400 800 IU per day), with close monitoring of laboratory and clinical parameters, seems reasonable. High-dose vitamin D supplementation is not recommended as it may cause a hypercalcemic crisis in patients with sarcoidosis.[22,62,68,75,78]

The increased sensitivity to vitamin D and its metabolites among patients with sarcoidosis supports some authors' suggestion that the desirable ranges of 25OHD and 1,25(OH)2D may be lower than those proposed in the general population[65], however, more research on advised reference range is necessary. In their recent review, Gianella et al. extensively discuss the role of vitamin D in sarcoidosis. The authors underscore that despite the potential beneficial effects of vitamin D supplementation on innate immunity in sarcoidosis patients, the possible risks of the intervention have limited the number of prospective clinical trials that address the intervention's efficacy and safety of the intervention.[81]

Conclusion

The number of potential benefits of vitamin D supplementation in sarcoidosis is highly promising in terms of reducing the inflammatory response, counteracting disease progression, reducing bone fracture risk, and minimizing pharmacotherapy needed for disease control. Despite the increased risk of hypercalcemia in patients with sarcoidosis, vitamin D is not indisputably responsible. The potential risks of hypercalcemia associated with vitamin D supplementation in this group should not outweigh the potential benefits of supplementation, as well as the risk of vitamin D hypovitaminosis. Due to the lack of universal guidelines, each patient's benefits to risks ratio of vitamin D supplementation should be assessed individually and the intervention should be closely monitored both before and during implementation.

Declarations

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Author contributions
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The authors declare no competing interests.

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Not applicable.

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