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Recent advances in the pathogenesis, diagnosis, and management of sarcoidosis: A comprehensive narrative review

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Abstract

Sarcoidosis is a heterogeneous multisystem disorder of unknown etiology, characterized by the formation of epithelial non-caseating granuloma. While pulmonary and intrathoracic lymph node involvement represent the primary clinical manifestations, the disease frequently affects extrathoracic organs, including the skin, eyes, brain, heart, and musculoskeletal system; cardiac and neurological involvement are critical determinants of overall prognosis. Recent advances in pathogenesis highlight a complex interplay between genetic predisposition, autoimmunity, and environmental triggers such as silica dust, mycobacteria, and *Cutibacterium acnes*. Clinically, pathognomonic presentations such as Löfgren's syndrome and Heerfordt syndrome aid in rapid diagnosis, while modern imaging techniques such as ^{18}F-FDG PET/CT and cardiac MRI have significantly improved the classic Scadding chest radiography staging by detailing extrathoracic disease activity. In addition, the rapid integration of artificial intelligent and machine learning technologies enhances diagnostic accuracy through automated image analysis, biomarker identification, and personalized disease course prediction. Current treatment strategies are focusing on risk-stratified management, shifting from traditional corticosteroids and immunosuppressants to targeted biological agents for organ-threatening diseases. A multidisciplinary strategy is essential for therapy and follow-up. Treatment does not need to be given to every patient. The decision regarding treatment should be made after a thorough multidisciplinary evaluation based on clinical, radiological, and additional findings. The main medication is corticosteroids; however, methotrexate, azathioprine, and in some instances, TNF-α blockers, along with various other biological agents, may be used.

Keywords: Sarcoidosis; Hilar lymphadenopathy; Artificial intelligence; Biomarkers; Precision medicine

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1. Introduction

Sarcoidosis is a multisystem disease characterized by the formation of non-caseating epithelioid granulomas. It primarily affects the lungs but can also involve other organ

systems, including the skin, musculoskeletal system, eyes, brain, and heart. The precise etiology of the disease remains unknown; however, its prevalence varies globally, and it can be lethal if not diagnosed and treated promptly and effectively.[1,2]

The integration of artificial intelligence (AI) technologies has led to significant shifts in perspectives regarding the diagnosis, treatment, and monitoring of certain diseases in daily practice. For example, the use of AI technologies in the diagnosis and management of cardiac sarcoidosis is becoming increasingly common.[3-9]

The aim of this review was to summarize the developments in sarcoidosis pathogenesis, diagnosis, and treatment considering the advancements in medical technologies and AI technology over the past five years.

2. Methods

This study was designed as a comprehensive, structured narrative review aiming to synthesize recent advances in immunopathogenesis, multimodal imaging, AI integration, and targeted therapies of sarcoidosis. The literature search was conducted through the PubMed/MEDLINE database, a leading global database for biomedical and clinical life sciences, covering articles published between January 1, 2021, and June 1, 2026.

The search strategy included original research, clinical trials, randomized controlled trials, guideline consensus statements, and systematic reviews published in English. The predefined keyword queries and the ratios of retrieved articles to selected articles (within parentheses) are as follows: "Pathogenesis of Sarcoidosis" (25/2), "Diagnosis of Sarcoidosis" (336/46), "AI and Sarcoidosis" (119/15), "Therapy of sarcoidosis" (2309/47), and "Diet in sarcoidosis" (28/9).

3. Results

After reviewing abstracts and titles, overlapping studies and duplicate entries were excluded across search categories, resulting in the inclusion of 77 unique articles for which full English texts were available. Additionally, seven more articles from previous years were used, bringing the total number of articles to 84.

3.1. Sarcoidosis: Definition and brief historical information

Sarcoidosis is a systemic and multisystemic inflammatory disease characterized by non-caseous granulomas, the etiology of which is not fully understood.[10] Although the exact cause of the disease is unknown, several epidemiological data provide insight into its probable occurrence. These statistics provide valuable information in addition to the genetic components that have been previously studied. The first documented cases of sarcoidosis were discovered in the second half of the 18th century. The beginning of this period coincides with the start of the Industrial Revolution worldwide. During this period, numerous factories were built, leading to increased direct or indirect contact between humans and both above-ground and underground natural resources, as well as increased exposure to various chemical and biological pollutants.[10-15]

Although the disease most often affects the lungs and mediastinal/hilar lymph nodes, it can affect almost any organ or tissue in the body, including the skin, eyes, liver, spleen, heart, and central nervous system. The clinical course of the disease is heterogeneous; some cases present with an acute or subacute course that resolves spontaneously, while another group of patients experiences a chronic and progressive process that can lead to organ failure and resistant fibrosis.[14,16,17]

3.2. Epidemiology and risk factors

Sarcoidosis can occur in all races and age groups worldwide, but exhibits significant geographical, racial, and gender differences in incidence and clinical manifestations (incidence is highest in Northern European countries and African Americans).[1,2,18] It is more common in women than men, and while the disease generally peaks between the ages of 30 and 50, it can also show a bimodal distribution in older age groups.[19]

Environmental and occupational exposures have an important place in etiopathogenesis. Beryllium, silica, inorganic powders, metals, and some microbial agents (*e.g.*, *Cutibacterium acnes* [which was formerly known as *Propionibacterium acnes*], Mycobacterium species) have been shown to trigger the granulomatous response in susceptible individuals.[20-22]

In recent years, the importance of occupational and environmental exposure in the etiology of sarcoidosis has been emphasized. Chemical or organic-microbial compounds found in the workplace play a significant role in the etiology of sarcoidosis.[1,21] Occupational groups with increasing prevalence include foresters, firefighters, construction workers, rock wool and glass wool workers, miners, sales sector employees, office personnel, and healthcare workers[1] Occupational and environmental exposure has been shown to be particularly significant, with a 2.8-fold increase in the incidence of sarcoidosis in the years following the September 11, 2001, attacks on the World Trade Center, among those working in firefighting and debris removal.[23] Various other causes

have also been implicated, including exposure to silica dust, mycobacteria, *C. acnes* and autoimmunity.[21,24,25] The incidence of sarcoidosis is eight times higher among tuberculosis cases, and *Mycobacterium tuberculosis* DNA has also been detected in sarcoid nodules. However, treatment models involving anti-tuberculosis agents have proven ineffective.[13,14] Higher *Propionibacterium* catalase expression was detected in sarcoid culture isolates compared to isolates from non-sarcoid lymph nodes, and this was primarily detected in sinus macrophages. Bacterial catalase plays a vital role in the intracellular survival and persistence of bacteria within host cells during latent infection. It contributes to granuloma formation and increased Th1 immune responses in individuals with sarcoidosis. This relationship has been more frequently documented in the Japanese population. *C. acne* has been isolated from sterile mediastinal lymph node tissues.[25] This information shows that the role of *C. acnes* in the pathophysiology of sarcoidosis cannot be ignored.

Smoking is considered a preventive measure against sarcoidosis. Indeed, 75% of sarcoidosis cases are non-smokers. Bronchoalveolar lavage fluids of smokers show higher $CD8^+$ T cells (and consequently a lower CD4/CD8 ratio) and higher alveolar macrophages.[26] While serum angiotensin-converting enzyme (ACE) activity is reported to be higher in smokers, sarcoidosis activity remains similar between smokers and non-smokers.[27,28] Recent research suggests that genetic traits influence smoking behavior and sarcoidosis development, with certain genetic factors increasing susceptibility to the disease.[29] These data should not be interpreted as a recommendation for sarcoidosis or healthy individuals to start smoking, and it is strongly advised that smoking should be avoided.

Numerous other factors, such as living in rural areas, not using tap water, drinking unprocessed milk, and exposure to crystalline silica dust, have been associated with the development of sarcoidosis.[1,21] There is a proposed association between obesity and sarcoidosis.[1] Silicone breast implants have been reported to increase the incidence of sarcoidosis.[21,24] However, much of this data is based on unverified observations and needs to be supported by future studies.

3.3. Immunopathogenesis of sarcoidosis

The pathogenesis of sarcoidosis is based on a complex immunological response in a genetically predisposed host, triggered by a yet not fully identified environmental or persistent antigen (microbial or inorganic), resulting in disruption of cellular signaling pathways and metabolic processes.[24,30,31] This response has a wide variety of cellular components. It is a chronic process involving both innate and adaptive immune systems, through antigen-presenting innate immune system cells and T cell response and polarization, resulting in macrophage activation and polarization.[32]

The disease is fundamentally caused by a localized cellular immune response dominated by $CD4^+$ T lymphocytes. Antigen-presenting cells (dendritic cells and alveolar macrophages) present the antigen to $CD4^+$ T cells via HLA class II molecules.[24,29] This interaction leads to a pronounced Th1 and Th17 polarization.[26,33] Interferon-gamma (IFN-γ) and interleukin (IL)-2, released from Th1 cells, stimulate the transformation of macrophages into epithelioid cells and multinucleated giant cells. Th17 cells and their cytokine IL-17 play a critical role in neutrophil recruitment and the maintenance of granulomatous inflammation.[33-35]

The development and progression of sarcoid granulomas involve both innate and acquired immunological mechanisms. Th1 activity is elevated in sarcoidosis. Various cytokines, including tumor necrosis factor alpha (TNF-α), IL-1β, IL-6, IL-12, IL-23, and transforming growth factor beta (TGF-β), released in response to endogenous or exogenous antigenic stimuli undetectable by macrophages and dendritic cells, activate T cells and promote Th1 polarization, demonstrating the effectiveness of the acquired immune system. Th17 cells, the main pathogenic $CD4^+$ T helper cell subset, play a role in granuloma formation. Th17.1 cells are higher in the mediastinal lymph nodes of sarcoidosis patients compared to healthy controls, and increased Th17.1 levels in bronchoalveolar lavage fluid are associated with the progression of chronic disease.[33,36]

The outer periphery of the granuloma consists of Th1 and Th17.1 T cells, while the presence of B lymphocytes is limited; the inner region is occupied by epithelioid macrophages. Typically, there is no necrosis in granulomas. Non-necrotizing epithelioid granulomas are a pathological feature of sarcoidosis, characterized by an innate immune response involving active macrophages that differentiate into epithelioid and large cells, as well as dendritic cells. Hematoxylin-eosin staining is commonly used for the examination of sarcoid material, and CD68-positive histiocytes are detected.[11,24]

The Janus kinase (JAK)-STAT signaling pathway is activated in the peripheral blood, lung tissue, and lymph nodes of sarcoidosis patients by IFN-γ, particularly for STAT1, and by IL-17 for STAT3. The results of therapies targeting these pathways are similarly promising.[36-38]

Macrophages have recently attracted attention. Stimulation of pro-inflammatory M1 macrophages leads to their subsequent transformation into M2

macrophages, which initiate the fibrotic process.[39] Activated macrophages differentiate into epithelial macrophages and multinucleated giant cells, facilitating granuloma formation and persistence. Increased mTORC1 (mammalian rapamycin target complex 1) activity has been observed in macrophages, and this increased mTORC1 activity appears to be an effective pathway in maintaining granulomas.[30,40,41] mTORC activation plays a crucial role in monitoring cellular metabolic activities. Suppression of mTORC can trigger autophagy. Activation of mTORC1 modulates innate immune cell inflammatory responses in monocytes, macrophages, and dendritic cells. It has been reported that activation of mTORC1 by deletion of Tsc2 (Tsc2: upstream inhibitor of mTOR complex 1) in macrophages is sufficient for the initiation and maintenance of granulomas; Molecularly, mTORC1 inhibits apoptosis by inducing cell cycle kinase CDK4 expression and metabolic reprogramming, and induces macrophage proliferation, and is also associated with disease progression in human sarcoidosis.[42]

Experimental studies in mice have shown that genetic deletion of the mTORC upstream inhibitor Tsc2 (tuberous sclerosis complex) leads to spontaneous formation of lung sarcoid-like granulomas. The same study showed that genetic deletion of Tsc2 in CD11c-expressing myeloid cells leads to constitutive activation of mTORC1, resulting in inflammatory infiltrates in the hearts of mice, predominantly composed of Mac-2$^+$ macrophages and associated with increased interstitial and perivascular fibrosis. This model suggests that therapeutic administration of the mTORC1 inhibitor everolimus can prevent cardiac sarcoidosis-like pathological features.[42] In a series of four patients with cardiac sarcoidosis, mTOR blockers were reported to be beneficial and significantly reduced cardiac PET activity. Observations suggest that the mTORC pathway could be an important therapeutic target for sarcoidosis in the future.[43] Serum amyloid A (SAA) contributes to the maintenance of chronic granulomatous inflammation; autoantigens, such as vimentin, with its potential role in autoimmunity, are also of interest and require further investigation.[24,44] In summary, if a genetic predisposition exists, various environmental events can trigger the onset of the disease. Both innate and acquired immune systems cooperate in the development of the disease.

Other pathogenic mechanisms involved in the immune pathogenesis of sarcoidosis are summarized below:

Upregulation of the pentose phosphate pathway (PPP), which is crucial for maintaining NADPH supply during acute oxidative stress in macrophages, and variations in other metabolic processes are associated with changes in cytokine production and phagocytosis activity. Stimulation of PPP in macrophages provides the metabolic energy and redox balance necessary for granuloma formation and viability.[45]

Excessive secretion of ACE and local activation of the renin-angiotensin-aldosterone system (RAAS) in granulomatous tissues creates a tissue response that increases the severity of inflammation. This aldosterone-dependent mechanism, which supports early granuloma formation, may be a future therapeutic target.[46,47]

Increasing evidence highlights the crucial role of monocytes in the immunopathogenesis of sarcoidosis. The concept of trained immunity, particularly in relation to the presumed role of immune metabolism and epigenetics, opens new perspectives for understanding sarcoidosis pathology. Maladaptation of innate immune cellular memory (maladaptive trained immunity) is among the current concepts explaining why the inflammatory response becomes chronic even when the antigen is removed.[31]

In recent years, an increasing number of studies have shown that sarcoidosis may result from the interaction between microbial signals, immune regulation, and tissue microenvironments in at least a subgroup of patients. Numerous studies demonstrate that gut and lung microbiota modulate the immune response. Dysbiosis can affect the disease phenotype by triggering systemic immune activation.[48-51] In addition, *C. acnes* and inorganic micronized particles detected in tissues are thought to be among the main factors of ongoing chronic immune activation.[21,25] These also indicate that regulatory measures or treatments targeting the interstitial microbiota will be considered in the treatment of sarcoidosis.

The immunopathogenic mechanisms of sarcoidosis are summarized in Figure 1.

3.4. Clinical manifestations and phenotypes

Sarcoidosis primarily presents with intrathoracic symptoms, but it can also cause numerous extrathoracic symptoms and mimic many other diseases. In this respect, it has been called a "great mimicker." The symptoms of the disease vary depending on the localization of the affected organ, the extent of inflammation, and the activity of the process.[11,16] The most typical intrathoracic finding of sarcoidosis is hilar mediastinal lymphadenopathies, detected in up to 90% of patients.[13,36] Currently, incidental diagnosis on chest X-ray is possible in only 8.4% of patients, whereas in older series this rate was between 20% and 60%.[13,52] Respiratory symptoms are recorded in almost half of the patients at presentation: cough in up to 50% of cases, shortness of breath in 18%–51%, and chest

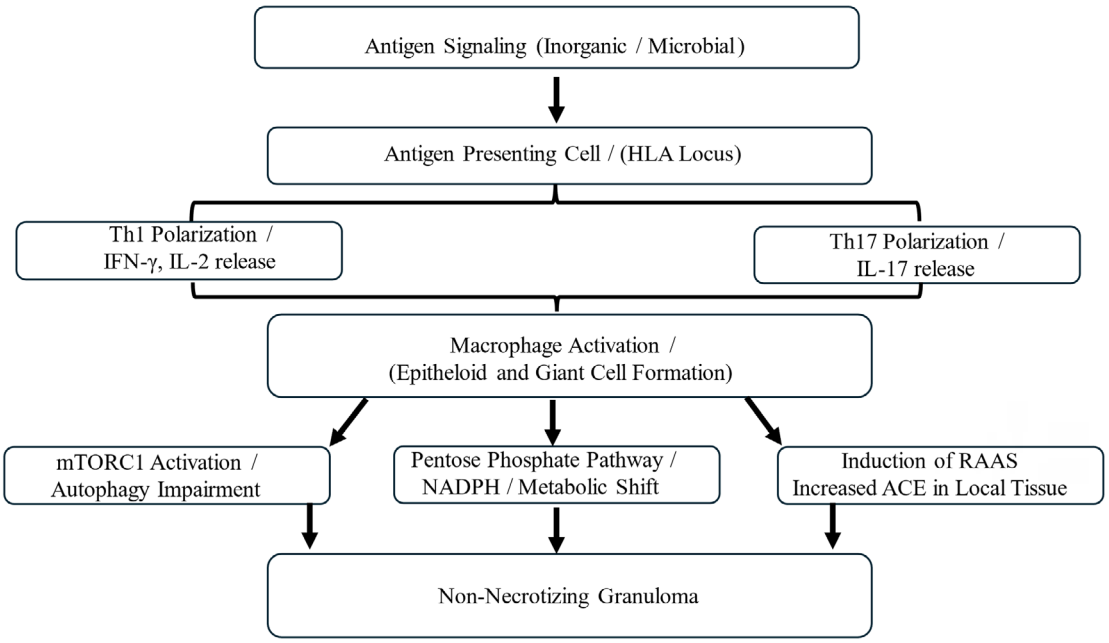


Figure 1. Immunopathogenesis of sarcoidosis
Abbreviations: ACE: Angiotensin-converting enzyme; HLA: Human leukocyte antigen; IFN-γ: Interferon gamma; IL: Interleukin; mTORC1: Mechanistic target of rapamycin complex 1; NADPH: Nicotinamide adenine dinucleotide phosphate (reduced form); RAAS: Renin-angiotensin-aldosterone system.

pain in 9%–23%.[13,36] Chronic dyspnea is most common in patients with delayed diagnosis, as seen in 10% of patients diagnosed at radiographic stage 4.[13,53] Lung auscultation findings are often normal on initial examination; however, crackling sounds may be detected if fibrosis has progressed.[13,54] Unlike other pulmonary fibrosis diseases such as idiopathic pulmonary fibrosis, scleroderma, and rheumatoid arthritis, sarcoidosis is usually located in the middle-upper lobes rather than the lower lobes.[11,13]

Extrapulmonary symptoms include skin lesions, cardiac involvement, uveitis, lacrimal gland, as well as joint, neurological, and other organ involvement.[13,36]

3.4.1. Skin lesions

Common cutaneous manifestations include raised papules, raised erythematous plaques, and painful subcutaneous nodules. Erythema nodosum (raised painful red nodular lesions on the pretibial region) may be seen in sarcoidosis and associated with a good prognosis. It is especially accompanied by Löfgren's syndrome. The presence of this lesion should be a warning for sarcoidosis when it is accompanied by bilateral hilar lymphadenopathy. Lupus pernio and erythema nodosum can be diagnosed by an experienced clinician without biopsy based on clinical features.[11,13]

Lupus pernio is a severe manifestation of cutaneous involvement, marked by violaceous lesions primarily affecting the face, particularly the nose, cheeks, and ears. Untreated conditions may result in lasting cosmetic issues. Lupus pernio is more frequent in individuals of African descent than in Caucasians and often associated with bone cysts, upper respiratory tract involvement, and pulmonary fibrosis. It indicates a serious illness that requires treatment.[13,36]

3.4.2. Cardiac sarcoidosis

Sarcoidosis may initially present with cardiac or neurological symptoms and may occur in isolation without accompanying radiological thoracic abnormalities, making diagnosis difficult.[55,56] Cardiac sarcoidosis is a type of arrhythmic cardiomyopathy.[55] Isolated cardiac sarcoidosis, seen in up to 25% of cases, is typically associated with systemic disease and presents diagnostic challenges.[55,56] Clinical symptoms occur in approximately 5% of cases; however, cardiac involvement can be detected in 20% of cases through comprehensive imaging and in 47% of cases during autopsy.[13,55] In recent years, there has been an increase in observations due to increased awareness and advances in diagnostic methods. Primary cardiac manifestations include conduction abnormalities,

ventricular arrhythmias, and heart failure that can lead to sudden death. ECG abnormalities associated with cardiac involvement typically include isolated bundle branch block and fascicular blocks; the right bundle branch block is more common. Other findings may include QRS complex disruption, pathological Q waves, ST-T wave alterations, and varying degrees of conduction block.[55]

The diagnosis of cardiac sarcoidosis is confirmed by the distinctive clinical, laboratory, and imaging findings associated with sarcoidosis. In their absence, the diagnosis of cardiac sarcoidosis should be made through close collaboration between the clinician, radiologist, nuclear medicine specialist, and, if necessary, pathologist.[55,56] Endomyocardial biopsy often presents challenges related to technical difficulties and irregular tissue involvement. Current recommendations do not support its routine use due to insufficient sensitivity.[13,55] Pericardial involvement is also quite rare in sarcoidosis and may lead to pericarditis and, very rarely, constrictive pericarditis. Fainting with no other cause, unexplained shortness of breath, marked palpitations, high-grade atrioventricular block, unexplained ventricular arrhythmia, or the presence of coronary artery disease, especially in individuals under 60 years of age, or echocardiographic findings such as decreased left ventricular ejection fraction, regional wall aneurysm, or basal septal thinning without another cause, should alert the physician to the possibility of cardiac sarcoidosis.[55]

3.4.3. Ocular sarcoidosis

Uveitis is the most common manifestation of ocular sarcoidosis, which can present as anterior, intermediate, posterior, unilateral, or bilateral. Anterior uveitis is defined by clinical manifestations including ocular redness and discomfort. Examination may reveal keratic precipitates termed mutton-fat, formed by desquamated cells due to inflammation in the anterior chamber.[11,13] Further findings may encompass angle and iris nodules, elevated intraocular pressure unrelated to steroid use, and/or newly developed posterior synechiae. Intermediate uveitis is characterized by visual disturbances and the perception of "floaters," along with vitreous opacities, snowdrifts, and macular edema observed during examination. Exclusion of multiple sclerosis is necessary.[16] Posterior uveitis is characterized by visual disturbances. Examination may reveal macular edema, nodular and/or segmental periphlebitis (wax drops), and peripheral chorioretinal lesions. All components of the eye can be impacted, potentially resulting in symptoms including orbital lesions, conjunctival deposits, scleritis, and optic nerve involvement. Eye complaints necessitate evaluation by a qualified ophthalmologist to differentiate them from conditions such as Behcet's disease, which may affect the eye, central nervous system, and skin. It may also be necessary to differentiate diseases such as tuberculosis, which can result in granulomatous uveitis. A conjunctival biopsy may be conducted when considered necessary.[16,57]

3.4.4. Lacrimal gland involvement

Sarcoidosis of the lacrimal gland is common, impacting around two-thirds of individuals affected. It often leads to dryness. Clinically, dry eyes can range from a minor inconvenience to a condition that may result in significant corneal damage. Inflammation of the lacrimal drainage system, including the puncta, canaliculi, nasolacrimal sac, duct, and nasal meatus, can also result in tearing. Granulomatous inflammation may affect the eyelids, conjunctiva, sclera, or cornea and may cause cosmetic problems, pain due to mass effects, or alterations in vision. Involvement of cranial nerves can lead to visual disturbances due to optic neuropathy or dysfunction of extraocular muscles.[11,13,58] This condition can affect the lacrimal and thyroid glands, leading to thyroid nodules and thyroid dysfunction. It can also affect the pituitary/hypothalamic axis, causing hypogonadism and syndrome of inappropriate antidiuretic hormone[36]

3.4.5. Sarcoid arthropathy and peri-arthropathy

Joint conditions, both inflammatory and non-inflammatory, frequently occur in patients with sarcoidosis, impacting intra-articular and extra-articular tissues. Acute inflammatory arthritis, primarily oligoarticular and impacting the lower extremities, may manifest in up to 10% of all patients. Löfgren syndrome is a distinct phenotype of sarcoidosis, characterized by bilateral ankle arthritis or periarthritis. This condition is generally self-limiting and benign, although it is often associated with pain. Chronic granulomatous infiltrative arthritis is notably uncommon and may sometimes demonstrate resistance to pharmacological interventions. Granulomatous inflammation can affect various articular and peri-articular structures, resulting in a range of clinical manifestations, including bursitis, enthesopathies, sacroiliitis, and, in some cases, significant tissue damage, such as joint erosions and tendon ruptures. Dactylitis and nodular tenosynovitis, while uncommon, are regarded as highly specific musculoskeletal manifestations of sarcoidosis.[13,35,59] It is essential to consider sarcoidosis in young to middle-aged individuals exhibiting bilateral ankle arthritis in rheumatology clinics.[59]

Bone involvement is also observed in sarcoidosis. Approximately 15% of patients experience hand involvement. Lytic lesions, characterized as bone cysts, are observed in the phalangeal bone heads of the hands and feet. Sclerotic lesions are observable in the spine and

pelvis. These may be mistaken for metastases. Comparable lesions are observed in the pelvic region. The spine and pelvic bones are frequently identified as the primary sites of involvement in certain series. It is reported that bone involvement frequently presented asymptomatically, being incidentally detected in half of the patients. They noted that finger pain resulting from dactylitis was the primary complaint in symptomatic cases. Reports indicate that thoracic and extrathoracic lymph nodes, pulmonary and cutaneous involvement, as well as hypercalcemia rates, were higher in cases of bony sarcoidosis compared to sarcoidosis patients without bony involvement.[11,16,59]

3.4.6. Neurological involvement

Neurosarcoidosis is a rare condition compared to pulmonary sarcoidosis that can cause cranial nerve palsies, aseptic meningitis, peripheral neuropathy, and myopathy, most commonly involving the facial nerves. It is reported to occur at a frequency of 3% to 9% in various references. It is more common in women and non-Caucasians. Brain parenchyma and cranial neuropathy represent the most prevalent areas of involvement. Cranial neuropathy constitutes 50% of all neurological manifestations and typically presents at the onset of systemic disease. Facial neuropathy constitutes 70% of cranial neuropathy cases and may present bilaterally and synchronously; however, sequential neuropathies are also observed. Reports indicate the occurrence of mononeuropathies impacting all cranial nerves. Isolated hearing loss can occur and may respond significantly to corticosteroid therapy; however, hearing is typically not maintained over time. Cranial polyneuropathy, also known as parasellar or orbital apex disease, can affect multiple cranial nerves, leading to a clinical syndrome characterized by dysphonia and dysphagia due to involvement of the inferior nerves. Seventy-five percent of brain diseases in neurosarcoidosis result from leptomeningitis, which may present as mild and focal or as widespread, invasive, and destructive lesions. Spinal cord sarcoidosis is an uncommon yet potentially severe condition that may manifest paraplegia, paralysis, incontinence, and cauda equina syndrome. Another form of neurosarcoidosis is Heerfordt syndrome (uveoparotid fever). Heerfordt syndrome is characterized by uveitis, bilateral parotid enlargement, fever, and facial paralysis, and, along with Löfgren's syndrome, represents the pathognomonic symptoms of sarcoidosis.[13,58]

3.5. Recent developments in sarcoidosis diagnosis and imaging

The diagnosis of sarcoidosis is based on the presence of compatible clinical and radiological findings, histopathological demonstration of non-necrotizing granulomatous inflammation in at least one tissue, and exclusion of alternative diseases that produce a similar clinical picture.[10,11,13,16] Minimally invasive endoscopic procedures, including transesophageal endosonography (EUS) and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), supplemented by endobronchial biopsy, have improved diagnostic yields.[60-62]

3.5.1. Advances in tomography, PET-CT and radiomics

In recent years, imaging technologies have gone beyond simply making a diagnosis and have reached the stage of differentiating active inflammation from permanent fibrosis and predicting the response to treatment. Imaging also plays a critical role in differentiating malignancy.[63-65]

High-resolution tomography (HRCT) and smart section analysis: HRCT is a fundamental tool in detecting perilymphatic modular involvement, peribronchovascular thickening, and micronodular distributions.[54,63] In recent developments, structural data models obtained from computed tomography sections; it quantitatively differentiates sarcoidosis-related fibrosis from conditions such as tuberculosis or idiopathic pulmonary fibrosis.[63,64]

^{18}F-FDG PET/CT and active granuloma mapping: FDG-PET/CT is the gold standard, especially in assessing the extent of organ involvement and selecting the most active nodule/tissue for invasive biopsy.[63,64] In cardiac sarcoidosis, it plays a critical role in monitoring treatment response by measuring myocardial inflammation and metabolic activity with quantitative SUV (standardized uptake value) values.[4,5,55]

Radiomic models, which extract pixel-level tissue texture from CT and PET images that the human eye cannot perceive, can distinguish sarcoidosis nodules from lung cancer and tuberculous lymphadenitis with high accuracy. AI-based quantitative analyses in cardiac PET/CT imaging measure disease activity with complete objectivity by eliminating inter-observer differences.[4,5,65]

Figure 2 summarizes the diagnostic procedures for sarcoidosis.

3.5.2. Biomarkers, clinical use and practical implications

In sarcoidosis, an ideal biomarker is expected not only to diagnose the condition but also to predict disease activity, organ involvement burden, treatment response, and potential relapses.[66,67] Since a single biomarker does not meet all these requirements in current practice,

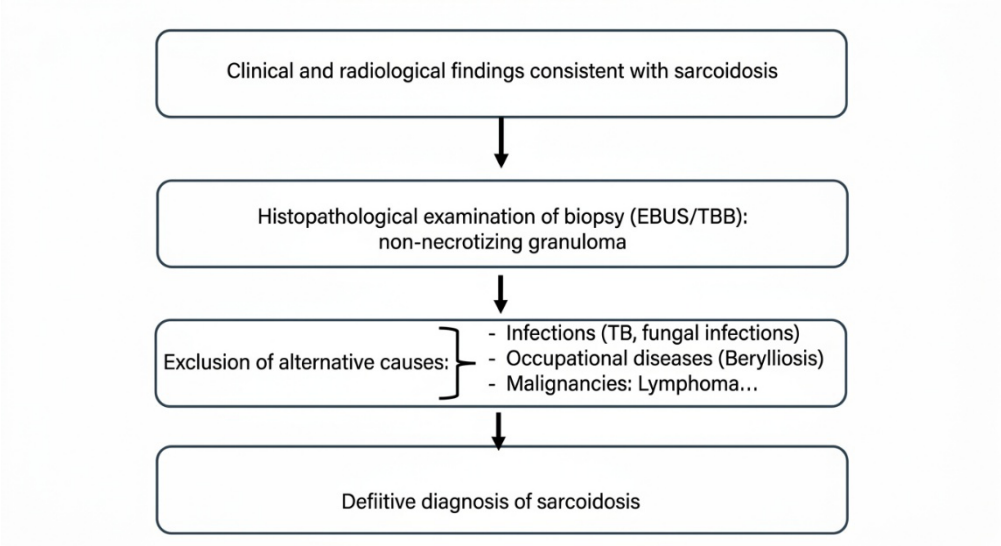


Figure 2. Diagnosis of sarcoidosis

multiple analysis approaches that evaluate serological, cellular, and molecular parameters together are gaining prominence.[44,67,68]

Serum angiotensin-converting enzyme (ACE): ACE synthesized by epithelioid cells and multinuclear giant cells; reflects the total systemic granuloma burden.[46,47] Its sensitivity (57%–68%) and specificity (70%–80%) are limited for diagnosis of sarcoidosis.[28,69] It tends to be elevated in chronic active cases rather than acute disease. A normal ACE level does not rule out a diagnosis of sarcoidosis.[27,70] Various medication and genetic ACE polymorphisms or mutations interact with serum ACE levels in normal persons and sarcoid patients. Insertion/deletion (I/D) polymorphisms or rare mutations in the *ACE* gene can show significantly elevated serum ACE levels even without granulomatous disease.[27,47] In patients using ACE inhibitors, ACE levels are artificially suppressed.[69,70] Therefore, in patients taking ACE inhibitors or suspected of having genetically determined ACE elevation, sIL-2R or chitotriosidase should be preferred over ACE for follow-up. Serum ACE level is not a diagnostic parameter on its own. It should only be used as supplementary data to support the diagnosis in patients with compatible clinical/histopathological findings.[27,69] In a patient with a high ACE level, a decrease in levels after treatment may indicate a response to treatment; a sudden increase in a stable patient may indicate an asymptomatic/subclinical relapse.[28,70]

Soluble interleukin 2 receptor (sIL-2R): sIL-2-R is an extracellular receptor subunit shed from the surface of activated $CD4^+$ T lymphocytes. It is a direct indicator of an active T-cell-mediated cellular immune response.[24,33] Meta-analyses show that the sensitivity and specificity of sIL-2R in the diagnosis of sarcoidosis are significantly higher compared to serum ACE.[34] In cases suspected of extrapulmonary organ involvement (*e.g.*, neurosarcoidosis or cardiac sarcoidosis) and with normal ACE levels, sIL-2R is a sensitive screening parameter.[34,55] In patients who have started corticosteroid or biological therapy (anti-TNF), the rapid decrease in sIL-2R levels is the most reliable early serological sign that tissue-level inflammation has been suppressed.[37]

Serum chitotriosidase activity: Chitotriosidase is a chitinase enzyme secreted by activated tissue macrophages. It reflects the macrophage/epithelial cell activity in the granuloma center.[66] Concering its diagnostic value, it correlates directly with disease activity and total granuloma mass. There is a strong correlation between the extent of lung parenchymal involvement and serum levels. Monitoring sIL-2R or chitotriosidase during the tapering period of steroid dose reduction in patients with chronic pulmonary sarcoidosis is guiding in predicting relapses that may occur before radiological and functional deterioration begins.[66,71]

Bronchoalveolar lavage (BAL) cell analysis and $CD4^+/CD8^+$ ratio: Elevated $CD4^+/CD8^+$ ratio in BAL fluid reflects lymphocytic alveolitis and immune phenotype in the lung micrometabolic environment.[26,71] An increase in lymphocyte ratio in BAL fluid (usually >15%–20%) and a $CD4^+/CD8^+$ ratio above 3.5 has high specificity (85%–90%) for sarcoidosis.[26] In cases where tissue biopsy is difficult

or contraindicated; consistent HRCT findings and a BAL $CD4^+/CD8^+$ ratio > 3.5 significantly increase the probability of diagnosis, provided that alternative diagnoses such as tuberculosis and idiopathic pulmonary fibrosis are excluded.[26,63] Detection of a low $CD4^+/CD8^+$ ratio due to an increase in $CD8^+$ in BAL does not completely rule out sarcoidosis; however, hypersensitivity pneumonia or drug-induced pulmonary reactions should be ruled out first.[26]

Serum amyloid A (SAA) and tissue fibrosis markers: SAA is an acute phase reactant released from the liver and accumulating at the granuloma localization. Although not specific to sarcoidosis, persistently high SAA levels have been associated with chronic inflammation and a progressive fibrotic lung phenotype.[44] Unlike many other chronic inflammatory diseases, amyloidosis is rare in patients with sarcoidosis. But patients showing high SAA and persistently high CRP levels indicate a high-risk group for progressive fibrosis. Early addition of steroid-sparing disease-modifying antirheumatic drugs (DMARDs) (methotrexate, *etc.*) should be considered in these patients.[13,44,72]

Figure 3 summarizes the clinical use and daily practical implications of biomarkers.

3.5.3. Future molecular biomarkers: omics and precision medicine

Recent studies have shown that specific microRNA and tRNA-derived small RNA (tsRNA) panels, stably present in circulation and tissues, have the potential to elucidate the cellular and translational immunopathogenesis of sarcoidosis and offer minimally invasive liquid biopsy diagnostic tools that could serve as an alternative to invasive tissue biopsies in the future. These epigenetic biomarker profiles can map pathways regulating macrophage activation and T cell responses, classify patients according to their molecular endotypes, and predict early on whether the disease will follow an acute and spontaneously regressive course or a chronic, resistant, and fibrotic phenotype. Furthermore, within the framework of personalized medicine (precision medicine), they can function as pharmacogenomic markers predicting patients' treatment response to corticosteroids, DMARDs, anti-TNF or JAK inhibitors, and by targeting pathological RNA sequences that trigger granulomatous inflammation (anti-miRNA/antagomirs, *etc.*), they can become innovative direct therapeutic targets in resistant cases.[40,73]

Numerous studies have shown that sarcoidosis is not merely a classical immunological response, but a disease

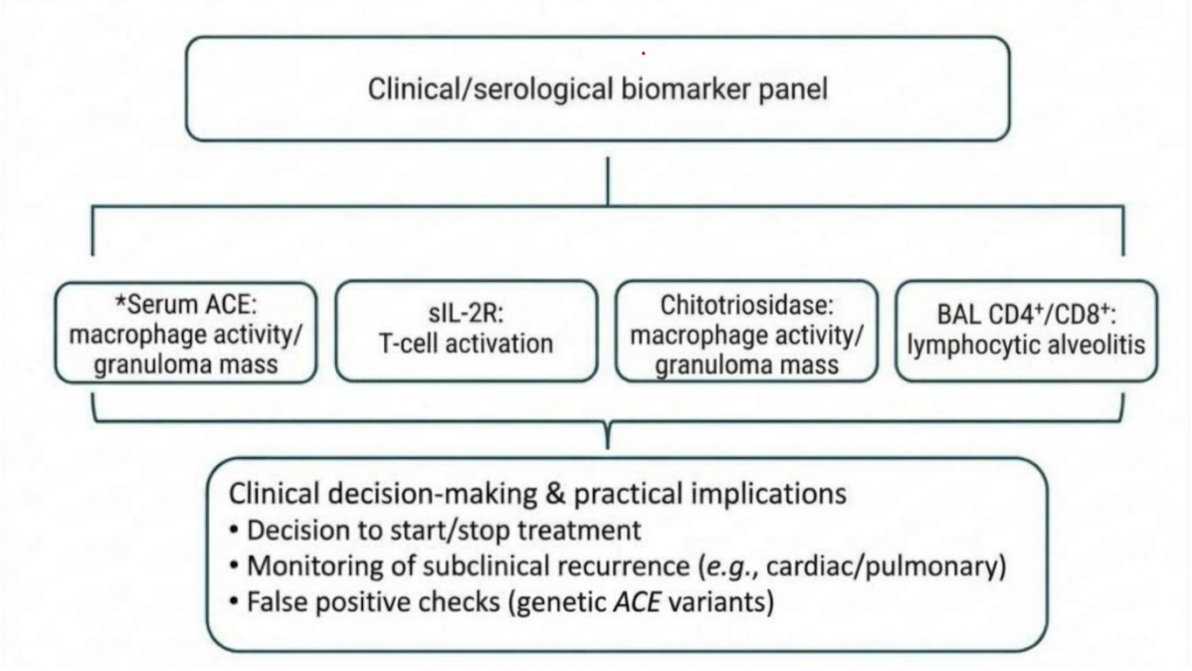


Figure 3. Commonly used biomarkers in diagnosis and monitoring of sarcoidosis. *: 20%–50% of serum ACE levels are determined by genetic variation (I/D polymorphism in intron 16 of the *ACE* gene). A healthy individual with the DD genotype may naturally have high basal ACE levels, while a sarcoidosis patient with widespread granulomatous disease (genotype II) may have ACE levels within "normal" limits. This masks the granulomatous burden. Abbreviations: ACE: Angiotensin-converting enzyme; BAL: Bronchoalveolar lavage; sIL-2R: Soluble interleukin 2 receptor.

progressing through significant metabolic reprogramming (immunometabolism) and lipid metabolism dysfunction at the cellular level. MALDI-MSI and advanced metabolomic analyses play a critical role in elucidating the pathogenesis by revealing specific lipid signatures (sphingolipids, phospholipids, *etc.*) and changes in metabolic signaling pathways at the cellular level within the granulomatous microenvironment. This data allows for more precise classification of sarcoidosis patients according to their metabolic phenotypes and molecular endotypes, while also paving the way for new treatment strategies focused on personalized medicine (precision medicine) targeting impaired cellular energy and lipid metabolism.[74-76]

On the other hand, certain studies predict a shift in sarcoidosis treatment from the traditional monotherapy approach to a personalized medicine (precision medicine) model targeting patient-specific biological and molecular mechanisms. Multiple omics panels combining genomic, transcriptomic, and proteomic data to overcome the limitations of traditional biomarkers allow for the classification of patients according to their molecular endotypes at the time of diagnosis. Integration of these omics-based approaches into routine clinical practice will serve as a predictive guide, not only predicting the course and risk of disease progression but also identifying specific pathway activations such as type 1 interferon and JAK-STAT early on, thereby determining which medication (corticosteroids, anti-TNF, or JAK inhibitors like tofacitinib) should be initiated for the patient and predicting treatment response.[38,67,68]

Table 1 presents a summary of clinical settings and practical considerations where biomarkers can be used.

3.6. Sarcoidosis treatment and precision approaches in pharmacotherapy based on genetic/molecular markers

The current principle in the treatment of sarcoidosis is not to routinely administer drug therapy to every patient, but to follow a personalized strategy based on organ function threat, risk of progression, and molecular profiles.[77-79] In other words, some patients do not need drug therapy or at least aggressive treatment. For example, patients with only incidental bilateral hilar lymphadenopathy, normal lung function tests (spirometry, DLCO), and those who are asymptomatic should be monitored without treatment.[13,14,36] In typical Löfgren's cases presenting with erythema nodosum and bilateral hilar lymphadenopathy without organ threat, the disease usually regresses spontaneously (spontaneous remission 80%–90%). Only short-term NSAIDs (nonsteroidal anti-inflammatory drugs) should be given, and systemic steroids should be avoided.[11,13] HLA-DRB1*03 (HLA-DR3) carriers are frequently associated with a benign, acute, and spontaneously resolving disease course; aggressive immunosuppression should be avoided in these patients.[29,78,79]

In pulmonary sarcoidosis with systemic involvement and loss of function, corticosteroids are traditionally the first-line treatment. However, to limit steroid toxicity, conventional synthetic DMARDs such as methotrexate or azathioprine are included in the treatment regimen as steroid-sparing agents.[13] In line with the World Association of Sarcoidosis and other Granolumatous Disorders (WASOG) consensus report, reducing to lower maintenance doses and adding second-line agents (DMARDs) earlier to the protocol has become the standard approach to prevent cumulative side effects associated with long-term and high-dose corticosteroid use.[71-82]

Cardiac sarcoidosis is a life-threatening clinical condition characterized by myocardial granulomatous infiltration, electrical conduction disorders, fatal ventricular arrhythmias, and a risk of heart failure, thus requiring an urgent and multidisciplinary approach. Current recommendations for cardiac sarcoidosis management are based on rapid suppression of active

Table 1. Clinician's guide to the use of biomarkers

Clinical scenario	Proposed biomarker	Practical clinical approach
Initial diagnostic support and suspicion	BAL $CD4^+/CD8^+$ ratio + sIL-2R	$CD4^+/CD8^+ > 3.5$ indicates a strong diagnosis. Systemic activity is confirmed with sIL-2R.
Patient monitoring in ACE inhibitor treatment	Serum chitotriosidase / sIL-2R	ACE levels are unreliable; monitoring is done with chitotriosidase or sIL-2R.
Treatment response and relapse monitoring	Serial sIL-2R and serum ACE	If parameters begin to rise while the medication is being reduced, subclinical relapse should be considered.
Predicting chronic fibrosis risk	SAA + sIL-2R	Elevated levels indicate a chronic/fibrotic course; early immunosuppression is planned.

Abbreviations: ACE: Angiotensin-converting enzyme; BAL: Bronchoalveolar lavage; SAA: Serum amyloid A; sIL-2R: Soluble interleukin 2 receptor.

myocardial inflammation, prevention of sudden cardiac death, and arrhythmia control.[56,79] High-dose systemic corticosteroids are initiated as the first step to rapidly reduce inflammation, while conventional DMARDs, such as methotrexate or mycophenolate mofetil, are incorporated early into the protocol to limit steroid side effects and maintain remission. In cases resistant to standard immunosuppressive therapy or showing refractory myocardial activity, targeted synthetic molecules such as anti-TNF biological therapies (particularly infliximab) and JAK inhibitors are potent and effective treatment options for both regression of granulomatous lesions and preservation of cardiac function. In addition to pharmacological treatments, implantable cardioverter defibrillator (ICD) implantation and the integration of guideline-compliant antiarrhythmic/heart failure therapies in high-risk patients with high-grade atrioventricular block or ventricular arrhythmia play a crucial role in reducing mortality due to coronary artery disease.[14,17,37,55]

In non-anterior sarcoidosis uveitis, combining corticosteroids with conventional DMARDs as first-line treatment provides more effective control in preventing relapses and reducing the risk of vision loss compared to steroid use alone.[57]

The demonstration that hyperactive mTORC1 signaling and impaired autophagy in macrophages maintain granuloma continuity reveals that mTOR inhibitors, such as sirolimus and everolimus, are a novel therapeutic option in resistant or fibrotic phenotypes.[30]

In the pathogenesis of sarcoidosis, granuloma formation and persistent inflammatory response are driven by a marked immunometabolic reprogramming (Warburg-like effect) in which glucose uptake in macrophages and T cells is increased, the mTORC1 pathway is overactivated, and energy production shifts from oxidative phosphorylation to aerobic glycolysis.[30]

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors, a group of drugs popular in the treatment of diabetes mellitus and heart and kidney diseases, have recently studied in the management of inflammatory diseases including sarcoidosis.[80] SGLT-2 inhibitors modulate glucose flux, the AMPK/mTOR axis, and mitochondrial dynamics at the cellular level, suppressing NLRP3 inflammasome activation, pro-inflammatory cytokine release, and tissue-level oxidative stress, while simultaneously regulating the RAAS.[46]

The fact that the combination of SGLT-2 inhibitors with ARBs significantly reduces 5-year all-cause mortality in sarcoidosis patients without increasing the risk of major adverse events such as sepsis and respiratory failure can be considered a clinical manifestation of this metabolic targeting.[80] SGLT-2 inhibition offers a powerful drug repurposing and adjuvant treatment strategy that provides a survival advantage by limiting the hypermetabolic granuloma micropath and chronic inflammation in sarcoidosis along the metabolic axis. The potential of SGLT-2 inhibitors to reduce sarcoidosis-related mortality by modulating cellular metabolic reprogramming and cardiopulmonary inflammation in granulomatous tissues is considered a promising strategy that can be added to future treatment algorithms.[81] However, more comprehensive studies are needed before algorithms can be included as treatment recommendations.

In the pathogenesis of sarcoidosis, the gut-lung axis is central to the complex interaction between host immunity and microbiota; dysbiosis, which disrupts mucosal barrier integrity, chronically stimulates toll-like receptors (TLRs) and pattern recognition receptors (PRRs) in the lungs, allowing microbial ligands to infiltrate the systemic circulation, and can exacerbate granulomatous responses in genetically predisposed hosts to *C. acnes*, Mycobacterium, or fungal antigens. Decreased levels of short-chain fatty acids (SCFAs; such as butyrate and propionate) weaken Treg-mediated immune tolerance, triggering pathological Th1/Th17 polarization and granuloma development; antibiotics such as macrolides and tetracyclines exhibit direct anti-inflammatory and anti-MMP effects, but also carry the risk of deepening dysbiosis by suppressing microbial diversity. Considering this two-way mechanism: Dietary modifications, microbiota restoration with postbiotic (*i.e.*, SCFA) supplementation or targeted probiotics, and multiple omics approaches based on 16S rRNA/metagenomic profiling offer a critical translational target in sarcoidosis for both predicting the disease phenotype and developing innovative adjuvant treatment strategies that limit hyperinflammation.[49-51,82]

Several markers can be used to make treatment decisions by monitoring inflammation serologically. For example, sIL-2R levels have high sensitivity in monitoring T cell-mediated granulomatous activity and treatment-induced tissue-level inflammation suppression. sIL-2R monitoring is particularly helpful in detecting asymptomatic exacerbations and guiding decisions to start or discontinue treatment.[34] Organ-specific treatment principles for sarcoidosis are summarized in Table 2.

3.7. Dietary and nutritional recommendations for sarcoidosis patients according to stage and clinical condition

Sarcoidosis manifests across various radiological and clinical stages characterized by fluctuating disease

Table 2. Organ-specific treatment strategies

Organ/Type of involvement	First-line treatment	Second and third-line treatments
Pulmonary sarcoidosis	Corticosteroids/Methotrexate	Methotrexate/azaioprin/leflunomid/MMF/infliximab, nintedanib
Cardiac sarcoidosis	High-dose corticosteroids	Anti-TNF therapy (infliximab), ICD implantation, arrhythmia management
Neurosarcoidosis	High-dose pulse steroid	Methotrexate, mycophenolate, infliximab
Ocular uveitis	Topical/Systemic steroids	Adalimumab, immunomodulators
Pulmonary hypertension due to sarcoidosis	Oxygen, targeted vasoactive agents	Vasodilator therapy (WASOG consensus principles)

Abbreviations: ICD: Intracardiac defibrillator; MMF: Mycophenolate mofetil; TNF: Tumor necrosis factor; WASOG: World Association of Sarcoidosis and other Granulomatous Disorders.

activity and immunological profiles. Gut microbiota dysbiosis—triggered by factors such as low-fiber diets, high consumption of processed foods, or antibiotic use—compromises intestinal barrier integrity ("leaky gut"), depletes protective short-chain fatty acids (like butyrate), and shifts the balance from anti-inflammatory Treg cells toward pro-inflammatory Th17 responses; this process can exacerbate systemic, chronic granulomatous inflammation. Therefore, assessing the patient's baseline colonic dysbiosis status is crucial before initiating general dietary recommendations. Restoring gut homeostasis through a fiber-rich, anti-inflammatory Mediterranean-style diet—while avoiding Western-style processed foods high in fructose and additives—alongside strategies to boost butyrate-producing commensals or target the microbiome, helps re-establish immune tolerance and balance Treg/Th17 populations, offering promising therapeutic potential for suppressing disease activity in sarcoidosis.[48-51] Although there are limited studies specifically on sarcoidosis, a nutritional approach as outlined below may be recommended within the context of general health and existing clinicopathological evidence.

In sarcoidosis, the excessive increase in 1-alpha-hydroxylase enzyme activity in granulomatous macrophages excessively increases vitamin D synthesis, thereby enhancing calcium absorption. Therefore, nutritional management should be individualized according to the stage of the disease, calcium balance, and medications used.[50,83] In the acute phase with low/moderate systemic inflammatory load, such as stage I and Löfgren's syndrome, a Mediterranean-type anti-inflammatory diet including fresh vegetables and fruits with high antioxidant capacity should be adopted, and fiber-rich foods and fermented products should be consumed to support the gut-lung axis.[48-51] In contrast, in patients with elevated serum or 24-h urine calcium levels or widespread active granulomas in active granulomatous phases II–IV, daily calcium sources such as milk and dairy products should be restricted, uncontrolled vitamin D supplementation should be strictly avoided, and prolonged exposure to direct sunlight should be limited. To prevent the risk of edema, hypertension, and hyperglycemia in patients receiving corticosteroid therapy, a salt-free and low-glycemic index diet should be followed; in cases with a risk of steroid osteoporosis but normal serum/urinary calcium levels, calcium and vitamin D supplementation should only be given under strict biochemical monitoring and periodic check-ups.[72,83] In patients with sarcoidosis, 1,25-dihydroxyvitamin D levels should be measured instead of the routinely measured 25-hydroxyvitamin D level. For support of microbiota and the gut–lung axis, fiber-rich foods and fermented products should be consumed.[49-51]

3.8. AI-supported diagnostic and clinical applications in sarcoidosis

AI and deep learning algorithms are promising technologies for the future in the diagnosis, phenotyping, and clinical management of sarcoidosis, a heterogeneous, multi-systemic, and complex disease. These technologies now play a crucial role, particularly in improving diagnostic sensitivity, reducing inter-observer variability, and detecting early stages of organ involvement.

Deep learning and radiomic models in CT images can rapidly differentiate sarcoidosis-related parenchymal or lymphatic lesions from lung cancer screenings and other parenchymal lung diseases. This significantly reduces false positives and the risk of unnecessary invasive biopsies by accelerating diagnostic differentiation in large-scale screenings.[8] Variability in the manual interpretation of myocardial inflammation due to physician experience

is overcome with AI-based quantification.[4,5,67] End-to-end automated measurement under CT guidance and objective quantification of ^{18}F-FDG uptake both provide diagnostic standardization and allow objective monitoring of treatment response with millimeter activity scores.[4,5]

AI models (AI-ECG) that process standard 12-lead ECG data can detect latent cardiac involvement in the initial stages by capturing micro-voltage, repolarization, and conduction anomalies that the human eye cannot perceive. This inexpensive and non-invasive screening method, combined with clinical scoring algorithms, allows for early filtering of high-risk patients without the need for invasive procedures.[6,7] However, many studies in literature are still based on pilot or single-center cohort studies. Multicenter validations are needed for AI models to enter widespread clinical use. In addition, the wide phenotypic variability of sarcoidosis, electrical overlaps with other non-ischemic cardiomyopathies, dependence on pre-cardiac PET myocardial glucose suppression diet, and the "black box" nature of deep learning (the decision-making mechanism cannot be fully explained) are key obstacles to overcome in clinical confidence and integration.[3]

3.9. Multi-omics analyses, precision medicine, and future prospects

Sarcoidosis management is evolving from the traditional "one-size-fits-all" approach to a precision medicine model targeting patient-specific biological mechanisms This transformation is based on the integration of AI with molecular data; this allows for the processing of genomic, transcriptomic, proteomic, and metabolomic data with AI and bioinformatics tools, enabling the classification of patients not only according to their clinical findings but also according to their underlying molecular endotypic mechanisms.[67,68,75] The precision biomarker panels developed in this way predict disease progression, relapse risk, and especially patient groups that will respond to steroid or targeted immunosuppressive therapies, enabling early selection of the most appropriate agent and monitoring of biological efficacy.[64,67,68,75] Simultaneously, more homogeneous, sensitive, and reliable endpoints are standardized in clinical trials under the leadership of WASOG and international consortia.[71,84] Full integration of AI with multiple omics data, advanced imaging (^{18}F-FDG PET/CT) and electrophysiological signals will minimize diagnostic delays in sarcoidosis and enable the implementation of accurate, safe and personalized treatment strategies before irreversible organ damage develops.

4. Conclusion

Although there are still some dark spots in the pathogenesis of sarcoidosis, in recent years our understanding of the disease has shifted from viewing it solely as a localized granulomatous reaction to recognizing it as a complex, systemic disorder driven by genetic predisposition, immune dysregulation, and profound immunometabolic reprogramming (such as mTORC1 activation). The diagnostic and monitoring environment is transforming significantly thanks to advanced multimodal imaging, objective PET/CT quantification, and AI-assisted ECG and radiographic models that identify subclinical organ involvement, particularly cardiovascular and central nervous system involvement, at earlier stages. Parallel to these developments, treatment paradigms are moving from long-term, high-dose corticosteroid monotherapies to precision medicine strategies with early steroid-saving conventional DMARDs, targeted biological drugs, JAK inhibitors, and emerging metabolic modulators such as SGLT-2 inhibitors, along with stage-specific nutrition and nutrition-focused interventions.

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Ethics approval and consent to participate

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