

Serum chitotriosidase activity in South African patients with sarcoidosis and tuberculosis

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Background. Chitotriosidase is a chitinase enzyme that is expressed selectively through activated macrophages in humans. Increased activity of chitotriosidase in both bronchoalveolar lavage samples and serum of patients with sarcoidosis has been reported. It has been proposed that chitotriosidase could be used as a potential biomarker for diagnosis, monitoring and prognosis in sarcoidosis patients. However, no studies in a South African (SA) cohort have evaluated this potential role.

Objectives. To analyse serum chitotriosidase activity in treated and untreated sarcoidosis patients, healthy controls and patients with tuberculosis (TB). Sarcoidosis and TB are two diseases of differing aetiology that may be clinically difficult to distinguish between in the SA setting, which is a high-burden area for TB. We hoped to determine whether chitotriosidase activity levels could help differentiate the one disease from the other.

Methods. Serum chitotriosidase activity was measured in an SA cohort of treated and untreated sarcoidosis patients and compared with controls. In addition, activity in sarcoidosis patients was compared with that in TB patients. Overall, chitotriosidase activity was assayed in the serum of 12 biopsy-proven sarcoidosis patients before treatment, 9 sarcoidosis patients after at least a month's treatment, 10 patients with confirmed pulmonary and/or disseminated TB before treatment, and 12 healthy controls. Plasma chitotriosidase activity was assayed as previously described using 4-methylumbelliferyl- β -D-N,N',N''-triacetylchitotriose as a substrate.

Results. Significantly higher serum chitotriosidase activity was observed in sarcoidosis patients, both untreated and treated, compared with controls ($p < 0.05$). Sarcoidosis patients had higher chitotriosidase levels than TB patients, but this difference was not significant. While chitotriosidase activity was lower in patients with TB than in those with sarcoidosis, levels were elevated compared with controls.

Conclusion. Chitotriosidase activity in patients with sarcoidosis was greater than in those with TB, and also greater compared with controls. The increased chitotriosidase activity in sarcoidosis suggests that this enzyme may be involved in the disease pathogenesis. Further investigation is required to validate these findings.

Keywords. Chitotriosidase, sarcoidosis, tuberculosis, biomarker.

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Study synopsis

What the study adds. Serum chitotriosidase activity in South African sarcoidosis and tuberculosis (TB) patients was evaluated. The study adds to the research assessing the significance of serum chitotriosidase in patients with sarcoidosis and TB.

Implications of the findings. Chitotriosidase enzyme activity could potentially serve as a biomarker of possible diagnostic and/or prognostic value in patients with sarcoidosis.

Chitotriosidase is a chitinase enzyme that is expressed selectively through activated macrophages and epithelial cells in humans.^[1] It was initially documented as having markedly elevated activity in patients with Gaucher's disease. Increased activity of chitotriosidase in both bronchoalveolar lavage (BAL) samples and serum of sarcoidosis patients has been reported.^[2-4] It has been proposed that chitotriosidase could be used in patients with sarcoidosis as a potential

biomarker for monitoring as well as a prognostic marker,^[1] and that it may be a therapeutic target.^[5]

The objective of the current study was to analyse serum chitotriosidase activity in a South African (SA) cohort of untreated sarcoidosis patients compared with a group of sarcoidosis patients treated for at least 1 month with corticosteroids. In addition, activity levels were compared between sarcoidosis patients and patients with

tuberculosis (TB) to determine whether levels could differentiate between these two granulomatous disorders of differing aetiology in a high-burden area for TB.

Methods

The results of demographic, clinical, routine laboratory, radiographic and lung function studies were documented in 12 consecutive untreated patients with biopsy-proven sarcoidosis and in 9 patients after at least 1 month of corticosteroid treatment, as well as in 10 patients with newly diagnosed pulmonary and/or disseminated TB and 12 healthy controls. The controls were healthy staff members working in the hospital and laboratory. Sarcoidosis was diagnosed according to the international criteria of the American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders.^[6] TB was diagnosed based on microscopy, culture, molecular biology and phenotypic evidence of *Mycobacterium tuberculosis* (MTB) in sputum by GeneXpert, or on microscopic examination and culture of biopsy specimens from extrapulmonary sites such as the bone marrow and lymph nodes.

For measurement of chitotriosidase levels, blood samples (5 mL) were obtained by venepuncture and collected into ethylenediaminetetra-acetic acid-containing tubes. Plasma and packed cells were separated by centrifugation at 1 500 *g* for 10 minutes and stored at -80° until they were processed. Chitotriosidase was assayed in the stored plasma samples essentially as described by Hollak *et al.*,^[7] using 4-methylumbelliferyl- β -D-N,N',N''-triacetylchitotriose (Sigma-Aldrich, Germany) as an enzyme substrate in McIlvain's phosphate-citrate buffer, pH 5.2, for 1 hour at 37.0° in darkness. The reaction was terminated by adding 2.5 mL of 0.3M glycine/NaOH buffer (pH 10.6). The reaction product, fluorescent 4-methylumbelliferone, was measured using a Perkin-Elmer fluorimeter (Perkin-Elmer, USA) at excitation wavelength 365 nm and 450 nm emission.

Statistical analysis

Chitotriosidase activity was expressed in nmol/h/mL. Data were expressed as medians with interquartile ranges (IQRs). Comparisons between groups were performed using the Mann-Whitney *U*-test and the Kruskal-Wallis test, with significance set at $p < 0.05$. The Spearman test was used to look for correlations between variables. Statistical analysis and graphic representations of data were performed using Prism 4.0 software (GraphPad Software, USA).

Ethical considerations

Written informed consent to participate in the study was obtained from the patients and the control subjects, and ethical clearance from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (ref. no. M121016).

Results

The clinical, diagnostic, laboratory, radiographic and lung function parameters in the cohort of patients with sarcoidosis are documented in Tables 1 - 3, including data for the untreated group (Tables 1 and 2) and the group treated with corticosteroids (Table 3). The

Table 1. Demographic and clinical characteristics of untreated patients with sarcoidosis

Characteristic	n (%) [*]
Patients, N (1 smoker)	12
Ethnicity and sex (5 BM, 4 BF, 1 IM, 2 IF)	
Female	6 (50.0)
Male	6 (50.0)
Biopsy confirmation	12 (100)
Age at disease onset (years), median (IQR); min - max	49 (41 - 53.5); 30 - 60
Symptoms (multiple in some patients)	
Cough	12 (100)
Weight loss	8 (66.7)
Chest pain	5 (41.7)
Night sweats	3 (25.0)
Nil	3 (25.0)
Dyspnoea	2 (16.7)
Skin rash	1 (8.3)
Eye symptoms	1 (8.3)
Arthralgia	1 (8.3)
Loss of appetite	1 (8.3)
Decreased effort tolerance	1 (8.3)
Blocked nose	1 (8.3)
Signs (multiple in some patients)	
Nil	10 (83.3)
Crackles	4 (33.3)
Skin rash	4 (33.3)
Splenomegaly	1 (8.3)
Lymphadenopathy	1 (8.3)
Anterior uveitis	1 (8.3)

BM = black male; BF = black female; IM = Indian male; IF = Indian female;

IQR = interquartile range; min - max = minimum and maximum.

^{*}Except where otherwise indicated.

characteristics of patients with active TB are shown in Table 4, and those of the healthy controls in Table 5.

The 12 patients with sarcoidosis in the untreated group were consecutive biopsy-proven patients (6 males, 9 black and 3 Indian patients), with a median (IQR) age of 49 (41 - 53.5) years (minimum and maximum 30 - 60 years) and a median serum angiotensin-converting enzyme (sACE) level of 105 (68 - 153.5) U/L (minimum and maximum 10 - 342 U/L) (Tables 1 and 2). There were 9 patients with sarcoidosis who had received treatment with corticosteroids for least 1 month and up to 3 months (3 males, 6 black and 3 Indian patients), with a median (IQR) age of 54 (49.5 - 65.5) years (minimum and maximum 43 - 79 years) and a median sACE level of 67 (30.5 - 98.5) U/L (minimum and maximum 28 - 222 U/L) (Table 3). Of 10 patients with newly diagnosed TB, 4 were males, all were black, 6 were HIV positive, and 3 were on antiretroviral therapy; their median

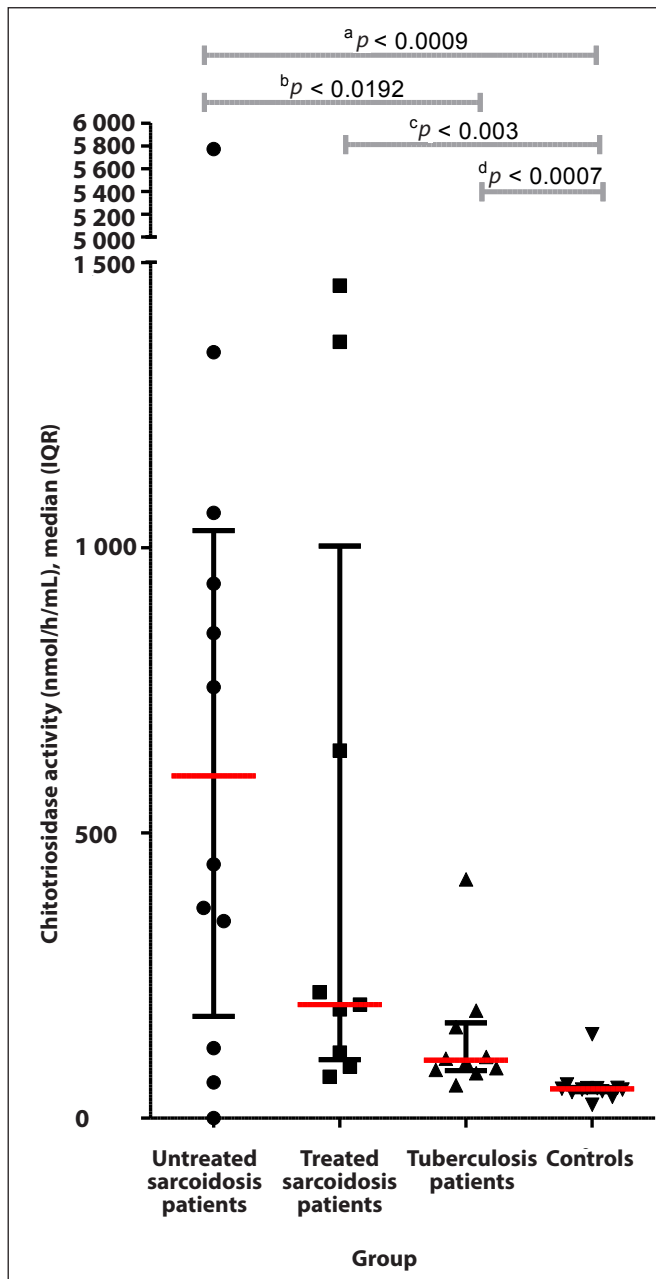


Fig. 1. Serum chitotriosidase activity levels in patients and controls. The red lines represent median levels, with IQRs. (IQR = interquartile range.)

(IQR) age was 36.5 (25 - 45) years (minimum and maximum 18 - 57 years) (Table 4). The demographic data for the 12 healthy controls (10 males), median (IQR) age 50 (45.5 - 51.5) years (minimum and maximum 29 - 55 years), are shown in Table 5.

Table 6 and Fig. 1 show serum chitotriosidase activity in the three patient groups and in the controls. Serum chitotriosidase activity was significantly higher in the sarcoidosis patients than in the controls, both in the untreated ($p < 0.0009$) and the treated ($p < 0.003$) groups. Untreated sarcoidosis patients had significantly higher chitotriosidase activity levels than TB patients ($p < 0.0192$). Although activity was lower in the treated sarcoidosis patients compared with the untreated patients, this difference was not significant. While

Table 2. Details of biopsy sites and laboratory, radiographic and lung function characteristics of untreated patients with sarcoidosis

Variable	n (%) [*]
Patients, N	12
Biopsy sites (sometimes multiple)	
Transbronchial lung	10 (83.3)
Skin	4 (33.3)
Lymph node	3 (25.0)
Supraclavicular	2 (16.7)
Mediastinal	1 (8.3)
Bone marrow trephine	1 (8.3)
Nose mass	1 (8.3)
Open lung	1 (8.3)
sACE (U/L), median (IQR); min - max	105 (68 - 153.5); 10 - 342
Chest radiograph	
Stage I	2 (16.7)
Stage II	6 (50.0)
Stage III	2 (16.7)
Stage IV	2 (16.7)
Lung function tests	
FVC <80%	6 (50.0)
FEV ₁ <80%	4 (33.3)
FEV ₁ /FVC <70%	3 (25.0)
Low DLCO	7 (58.3)

sACE = serum angiotensin-converting enzyme; IQR = interquartile range; min - max = minimum and maximum; FVC = forced vital capacity; FEV₁ = forced expiratory volume in 1 second; DLCO = diffusion capacity for carbon monoxide.

^{*}Except where otherwise indicated.

activity in patients with TB was lower than in sarcoidosis patients, it was significantly higher than in the controls ($p < 0.0007$).

Discussion

In the present study, serum chitotriosidase activity was evaluated for the first time in SA sarcoidosis patients as well as in patients with TB. Chitotriosidase activity was found to be significantly higher in patients with sarcoidosis, both before ($p < 0.0009$) and after treatment ($p < 0.003$), compared with controls. Analysis of serum chitotriosidase activity in our cohort of patients with sarcoidosis verified the increase described in the literature, compared with healthy controls. When comparing serum chitotriosidase levels in TB patients with those in patients with sarcoidosis, two granulomatous diseases of differing aetiology, higher activity was found in the sarcoidosis patients, but this difference was not significant.

Standard serum chitotriosidase activity ranges from 8 to 65 nmol/h/mL.^[8,9] In the present study, activity levels were significantly higher in serum of sarcoidosis patients compared with healthy controls,

Table 3. Demographic, radiographic and lung function characteristics of the treated group of patients with sarcoidosis, after at least 1 month on corticosteroids

Characteristic	n (%) [*]
Patients, N (1 ex-smoker, rest non-smokers)	9
Ethnicity and sex (1 BM, 5 BF, 2 IM, 1 IF)	
Female	6 (66.7)
Male	3 (33.3)
Biopsy confirmation	9 (100)
Age (years), median (IQR); min - max	54 (49.5 - 65.5); 43 - 79
sACE (U/L), median (IQR); min - max	67 (30.5 - 98.5); 28 - 222
Chest radiograph	
Stage I	2 (22.2)
Stage II	1 (11.1)
Stage III	3 (33.3)
Stage IV	3 (33.3)
Lung function tests	
FVC <80%	1 (11.1)
FEV ₁ <80%	4 (44.4)
FEV ₁ /FVC <70%	4 (44.4)
Low DLCO <80%	3 (33.3)

BM = black male; BF = black female; IM = Indian male; IF = Indian female; sACE = serum angiotensin-converting enzyme; IQR = interquartile range; min - max = minimum and maximum; FVC = forced vital capacity; FEV₁ = forced expiratory volume in 1 second; DLCO = diffusion capacity for carbon monoxide.

^{*}Except where otherwise indicated.

Table 4. Characteristics of patients with active tuberculosis

Characteristic	n (%) [*]
Patients, N	10
Ethnicity and sex (all black, 6 HIV positive, 3 on ARVs)	
Female	6 (60.0)
Male	4 (40.0)
Confirmation (8 sputum and 1 bone marrow GeneXpert positive)	9 (100)
Age (years), median (IQR); min - max	36.5 (25 - 45); 18 - 51

ARVs = antiretrovirals; IQR = interquartile range; min - max = minimum and maximum.

^{*}Except where otherwise indicated.

as was shown by Bargagli *et al.*^[10] Significantly raised levels have been reported in patients with sarcoidosis compared with patients with TB, asbestosis, idiopathic pulmonary fibrosis and systemic sclerosis.^[10,11] Bennet *et al.*^[12] showed that chitotriosidase activity correlated with severity of disease, as indicated by the presence of pulmonary fibrosis, multiorgan involvement, and the need for high-dose corticosteroid therapy. Grosso *et al.*^[9] found that serum chitotriosidase activity

Table 5. Characteristics of the healthy controls

Characteristic	n (%) [*]
Controls, N (all non-smokers)	12
Ethnicity and sex (4 BM, 2 BF, 6 WM)	
Female	2 (16.7)
Male	10 (83.3)
Age (years), median (IQR); min - max	50 (45.5 - 51.5), 29 - 55

BM = black male; BF = black female; WM = white male; IQR = interquartile range; min - max = minimum and maximum.

^{*}Except where otherwise indicated.

Table 6. Serum chitotriosidase activity (nmol/h/mL) of patients and controls

Group	n	Median (IQR)	Min - max
Sarcoidosis (untreated)	12	600.3 (178.5 - 1030) ^{*, **}	0 - 5 772
Sarcoidosis (treated)	9	199.0 (102.8 - 1003) ^{***}	72.6 - 1 459
Tuberculosis	10	101.7 (83.5 - 167.0) ^{****}	57.7 - 418.9
Controls	12	51.3 (46.3 - 53.4)	23.8 - 147.7

IQR = interquartile range; min - max = minimum and maximum.

^{*}*p*<0.0009 v. controls, ^{**}*p*<0.0192 v. TB patients, ^{***}*p*<0.003 v. controls, ^{****}*p*<0.0007 v. controls.

may be a useful marker for monitoring sarcoidosis disease activity and prognosis. Harlander *et al.*^[13] reported that chitotriosidase activity correlates with certain sarcoidosis phenotypes such as Löfgren's syndrome, and that serial measurements correlate with clinical symptoms, chest radiographic stage and lung function. While increased chitotriosidase is not specific for sarcoidosis, it has shown promise to be a very sensitive biomarker of active sarcoidosis and has more sensitivity and specificity than other commonly used sarcoidosis biomarkers such as angiotensin-converting enzyme (ACE) and lysozyme.^[14,15]

Approximately 6% of individuals are homozygous for a mutant allele that renders chitotriosidase unstable and enzymatically inactive, resulting in low levels of chitotriosidase in the blood.^[16] It is important to bear this in mind, as it may affect chitotriosidase levels in various diseases.^[17,18] In addition, an age-dependent increase in serum chitotriosidase activity occurs and may affect analysis,^[19] especially with small sample sizes and in the younger HIV cohort with TB in the present study.

Sarcoidosis and TB are both granulomatous disorders, characterised by enhanced alveolar macrophage activation, which in both has an integral role to play in granuloma formation.^[20,21] The observation of substantially higher chitotriosidase activity in patients with sarcoidosis than in patients with TB and controls, as well as evidence of an increase of >10 times compared with controls, indicates that this enzyme may be important in sarcoidosis, and could have a role to play in its pathogenesis.^[22] This test alone is not diagnostic and will be unable to completely differentiate sarcoidosis from TB; however, normal chitotriosidase activity is more likely to suggest TB than sarcoidosis when biopsy reveals granulomatous disease.^[3,22]

Serum ACE levels are not only increased in patients with sarcoidosis. The correlation between chitotriosidase and other serological sarcoidosis markers, for example sACE, found in other studies has indicated that sACE levels are often elevated in various granulomatous pulmonary disorders, including TB, and are two to three times higher than normal in ~50% of patients.^[23-25] The median sACE level in our patients before treatment was 105 U/L (Table 2), and after at least 1 month of corticosteroid treatment it was 67 U/L (Table 3). A correlation between serum chitotriosidase and sACE was not performed in the present study, as the patient numbers were small and sACE levels were not measured in the patients with TB or in the controls.

It is not known what mechanisms lead to increased activity of chitotriosidase in sarcoidosis. This rise is hypothesised to be due to increased activation of macrophages.^[26] Chitotriosidase activity may be increased in the serum of sarcoidosis patients as a result of an unidentified antigen, probably containing chitin, that induces activation of macrophages to produce many mediators, including chitotriosidase.

There is proof that macrophage stimulation with tumour necrosis factor alpha and interferon gamma (IFN- γ) results in an increase in chitotriosidase activity, as well as facilitating the expression of chitotriosidase genes.^[26] In earlier research,^[2] enhanced serum and BAL chitotriosidase activity in stage II - III sarcoidosis patients was noted, especially in chronic disease, where type 2 helper T-cell (Th2) cytokine response predominates, and this is believed to be responsible for fibrosis, with reparative or alternatively activated macrophages.^[27,28] Elias *et al.*^[27] likewise revealed that chitinases and chitinase-like proteins may add to Th2-type inflammation by a mechanism related to interleukin (IL)-13. Th2 cytokines induce activation of the so-called alternative activated macrophages involved in pulmonary fibrotic processes via the production of fibronectin and different mediators (e.g. IL-1 receptors, IL-10, C-C motif chemokine ligand 18, and perhaps chitotriosidase), as well as induction of fibroblast collagen synthesis.^[28]

In MTB infection, the immune response is characterised by macrophage activation, IFN- γ and type 1 helper T-cell (Th1) lymphocyte production.^[29] High Th2 cytokine and low Th1 expression, for example IL-4, was associated with an inadequate response to TB treatment.^[30] An imbalance in Th1/Th2 responses has been reported in both sarcoidosis and TB, concomitant with macrophage activation, although the chitotriosidase activity in the two diseases may rely on entirely different macrophage activation mechanisms or distinctive cytokine responses.

The present study has several limitations, the major one being the small sample size. Moreover, the groups were fairly heterogeneous for ethnicity, age and sex. There was significant clinical phenotypic variation among the sarcoidosis patients. The patients with TB were mainly HIV positive, and we should have included a comparison group of HIV-positive patients without TB. There were few controls, and a significant portion of this group were white. In addition, very high chitotriosidase activity levels, as seen in the present study, are not typical of sarcoidosis; however, there was no evidence of Gaucher's disease or other associated conditions in these patients.

The results should be interpreted with caution, and should be validated by further investigations in a multicentre study with larger patient numbers with specific disease phenotypes. Whether

chitotriosidase could be a sensitive and precise biomarker in sarcoidosis and TB, and whether it could have other roles in these diseases, are interesting possibilities, yet at the same time need to be clarified.

Conclusion

This is the first report of analysis of chitotriosidase activity in the serum of sarcoidosis and TB patients in SA. Chitotriosidase activity was higher in sarcoidosis patients compared with TB patients, and also compared with controls. Although the mechanisms leading to increased chitotriosidase activity in sarcoidosis are unknown, this enzyme may be involved in the disease pathogenesis. Investigations with larger numbers of patients are required to validate these findings. It remains to be established whether chitotriosidase can be a biomarker of diagnosis in sarcoidosis, and whether it has a role in prognosis.

Data availability. The datasets generated and analysed during the present study are available from the corresponding author (RM) on reasonable request. Any restrictions or additional information regarding data access can be discussed with the corresponding author.

Declaration. None.

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Author contributions. RM contributed to the conception, design and execution of the study, data acquisition and analysis, and drafting of the manuscript. IS performed the chitotriosidase enzyme assays for the study. CF contributed to the conception and design of the study, supervised, and substantially revised and critically reviewed the manuscript.

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Conflicts of interest. None.

1. Chang D, Sharma L, Cruz CSD. Chitotriosidase: A marker and modulator of lung disease. *Eur Respir Rev* 2020;29(156):190143. <https://doi.org/10.1183/16000617.0143-2019>
2. Bargagli E, Margollicci M, Perrone A, et al. Chitotriosidase analysis in bronchoalveolar lavage of patients with sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2007;24(1):59-64. <https://doi.org/10.1007/s11083-007-9059-z>
3. Bargagli E, Bennett D, Maggiorelli C, et al. Human chitotriosidase: A sensitive biomarker of sarcoidosis. *J Clin Immunol* 2013;33(1):264-270. <https://doi.org/10.1007/s10875-012-9754-4>
4. Harlander M, Salobir B, Zupančič M, Terčelj M. Bronchoalveolar lavage chitotriosidase activity as a biomarker of sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2015;32(4):313-317.
5. Dymek B, Sklepkiwicz P, Mlacki M, et al. Pharmacological inhibition of chitotriosidase (CHIT1) as a novel therapeutic approach for sarcoidosis. *J Inflamm Res* 2022;15:5621-5634. <https://doi.org/10.2147/JIR.S378357>
6. Crouser ED, Maier LA, Wilson KC, et al. Diagnosis and detection of sarcoidosis: An official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med* 2020;201(8):e26-e51. <https://doi.org/10.1164/rccm.202002-0251ST>
7. Hollak C, van Weely S, van Oers M, Aerts J. Marked elevation of plasma chitotriosidase activity: A novel hallmark of Gaucher disease. *J Clin Invest* 1994;93(3):1288-1292. <https://doi.org/10.1172/JCI117084>
8. Wajner A, Michelin K, Burin MG, et al. Biochemical characterization of chitotriosidase enzyme: Comparison between normal individuals and patients with Gaucher and with Niemann-Pick diseases. *Clin Biochem* 2004;37(10):893-897. <https://doi.org/10.1016/j.clinbiochem.2004.06.008>
9. Grosso S, Margollicci M, Bargagli E, et al. Serum levels of chitotriosidase as a marker of disease activity and clinical stage in sarcoidosis. *Scand J Clin Lab Invest* 2004;64(1):57-62. <https://doi.org/10.1080/00365510410004092>
10. Bargagli E, Margollicci M, Nikiforakis N, et al. Chitotriosidase activity in the serum of patients with sarcoidosis and pulmonary tuberculosis. *Respiration* 2007;74(5):548-552. <https://doi.org/10.1159/000100555>
11. Terčelj M, Salobir B, Simcic S, Wraber B, Zupancic M, Rylander R. Chitotriosidase activity in sarcoidosis and some other pulmonary diseases. *Scand J Clin Lab Invest* 2009;69(5):575-578. <https://doi.org/10.1080/00365510902829362>

12. Bennett D, Cameli P, Lanzarone N, et al. Chitotriosidase: A biomarker of activity and severity in patients with sarcoidosis. *Respir Res* 2020;21(1):6. <https://doi.org/10.1186/s12931-019-1263-z>
13. Harlander M, Salobir B, Zupančič M, Dolenshek M, Vodovnik TB, Terčelj M. Serial chitotriosidase measurements in sarcoidosis – two to five year follow-up study. *Respir Med* 2014;108(5):775-782. <https://doi.org/10.1016/j.rmed.2014.02.002>
14. Popević S, Šumarac Z, Jovanović D, et al. Verifying sarcoidosis activity: Chitotriosidase versus ACE in sarcoidosis – a case-control study. *J Med Biochem* 2016;35(4):390-400. <https://doi.org/10.1515/jomb-2016-0017>
15. Bergantini L, Bianchi F, Cameli P, et al. Prognostic biomarkers of sarcoidosis: A comparative study of serum chitotriosidase, ACE, lysozyme, and KL-6. *Dis Markers* 2019;2019:8565423. <https://doi.org/10.1155/2019/8565423>
16. Boot RG, Renkema GH, Verhoek M, et al. The human chitotriosidase gene: Nature of inherited enzyme deficiency. *J Biol Chem* 1998;273(40):25680-25685. <https://doi.org/10.1074/jbc.273.40.25680>
17. Harlander M, Maver A, Terčelj M, Salobir B, Peterlin B. Common chitotriosidase duplication gene polymorphism and clinical outcome status in sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2015;32(3):194-199.
18. Arndt S, Hobbs A, Sinclair I, Lane AB. Chitotriosidase deficiency: A mutation update in an African population. *JIMD Rep* 2012;10:11-16. https://doi.org/10.1007/8904_2012_193
19. Artieda M, Cenarro A, Gañán A, et al. Serum chitotriosidase activity is increased in subjects with atherosclerosis disease. *Arterioscler Thromb Vasc Biol* 2003;23(9):1645-1652. <https://doi.org/10.1161/01.ATV.0000089329.09061.07>
20. Broos CE, van Nimwegen M, Hoogsteden HC, Hendriks RW, Kool M, van den Blink B. Granuloma formation in pulmonary sarcoidosis. *Front Immunol* 2013;4:437. <https://doi.org/10.3389/fimmu.2013.00437>
21. Patterson KC, Queval CJ, Gutierrez MG. Granulomatous inflammation in tuberculosis and sarcoidosis: Does the lymphatic system contribute to disease? *Bioessays* 2019;41(11):1900086. <https://doi.org/10.1002/bies.201900086>
22. Bargagli E, Maggiorelli C, Rottoli P. Human chitotriosidase: A potential new marker of sarcoidosis severity. *Respiration* 2008;76(2):234-238. <https://doi.org/10.1159/000134009>
23. Grunewald J, Grutters JC, Arkema EV, Saketkoo LA, Moller DR, Müller-Quernheim J. Sarcoidosis. *Nat Rev Dis Primers* 2019;5(1):45. <https://doi.org/10.1038/s41572-019-0096-x>
24. Muthuswamy P, Lopez-Majano V, Ranginwala M, Trainor W. Serum angiotensin-converting enzyme (SACE) activity as an indicator of total body granuloma load and prognosis in sarcoidosis. *Sarcoidosis* 1987;4(2):142-148.
25. Schürmann M. Angiotensin-converting enzyme gene polymorphisms in patients with pulmonary sarcoidosis: Impact on disease severity. *Am J Pharmacogenomics* 2003;3(4):233-243. <https://doi.org/10.2165/00129785-200303040-00002>
26. Malaguarnera L, Musumeci M, di Rosa M, Scuto A, Musumeci S. Interferon-gamma, tumor necrosis factor-alpha, and lipopolysaccharide promote chitotriosidase gene expression in human macrophages. *J Clin Lab Anal* 2005;19(3):128-132. <https://doi.org/10.1002/jcla.20063>
27. Elias JA, Homer RJ, Hamid Q, Lee CG. Chitinases and chitinase-like proteins in TH2 inflammation and asthma. *J Allergy Clin Immunol* 2005;116(3):497-500. <https://doi.org/10.1016/j.jaci.2005.06.028>
28. Prasse A, Pechkovsky DV, Toews GB, et al. A vicious circle of alveolar macrophages and fibroblasts perpetuates pulmonary fibrosis via CCL18. *Am J Respir Crit Care Med* 2006;173(7):781-792. <https://doi.org/10.1164/rccm.200509-1518OC>
29. De Martino M, Lodi L, Galli L, Chiappini E. Immune response to *Mycobacterium tuberculosis*: A narrative review. *Front Pediatr* 2019;7:350. <https://doi.org/10.3389/fped.2019.00350>
30. Domingo-Gonzalez R, Prince O, Cooper A, Khader SA. Cytokines and chemokines in *Mycobacterium tuberculosis* infection. *Microbiol Spectr* 2016;4(5):10.1128/microbiolspec.TB2-0018-2016. <https://doi.org/10.1128/microbiolspec.TB2-0018-2016>

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