

# Renal Disorders in Pulmonary Sarcoidosis Patients

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**Introduction.** The frequency of kidney disorders varies in pulmonary sarcoidosis patients. Since the prevalence of kidney disorders among Iranian sarcoidosis patients is uncertain, this study aimed to evaluate kidney disorders and associated manifestations in Iranian pulmonary sarcoidosis patients.

**Materials and Methods.** One hundred patients with confirmed granuloma as pulmonary sarcoidosis were studied for renal disorders. Size of urinary tract and the presence of renal stones were checked via clinical examination and urinary organ ultrasonography. Patients' 24-hour urine sample was examined for pH, calcium, protein (over 250 mg) and creatinine (over 1.4 mg).

**Results.** Thirty-three percent of the patients expressed renal disorders simultaneously. Uric acid in pulmonary sarcoidosis patients could be correlated with the probability of developing renal stone. In addition, 1,25-dihydroxyvitamin D levels above 30 ng/mL and uric acid levels above 7 mg/dL in urine were directly correlated with renal disorders in sarcoidosis patients.

**Conclusions.** Urinalysis is an easy and reliable method for assessing renal disorders in sarcoidosis patients. The current study proposes inclusion of urinalysis in routine checkups of sarcoidosis individuals.

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## INTRODUCTION

Sarcoidosis is a multiorgan disease with indefinite etiology. Sarcoidosis patients can represent noncaseating granuloma in multiple organs and frequently in the lungs.<sup>1</sup> Granuloma is the clusters of immunity particles that result in tissue inflammation and ulceration in the sarcoidosis patient.<sup>2</sup> The immune response of the body to a microbial or chemical agent as beryllium, zirconium, aluminium, tuberculosis mycobacteria, nontuberculosis mycobacterium, fungi, and spirochetes, would be the most feasible causes of onset of sarcoidosis symptoms.<sup>3-8</sup>

Former studies have demonstrated that pulmonary disorder and kidney failure manifestation could be associated in sarcoidosis patients.<sup>9</sup> The frequency of kidney dysfunctions has been reported about 3% to 48% in patients with pulmonary sarcoidosis.

It is stated that the late and improper diagnosis of kidney disorders in sarcoidosis patients results in the high frequency of kidney disorders in such cases.<sup>10,11</sup> The widespread renal lesions manifestations are diverse from tubulointerstitial granulomatosis unto nongranulomatous nephritis.<sup>10,12,13</sup> The most important mechanism of kidney failure in sarcoidosis patients is an elevation in 1,25-dihydroxyvitamin D production, which results in increased calcium absorption of intestine, increased bone intake and, as a consequence, hypercalciuria with or without hypercalcemia. Approximately, 2% to 20% of sarcoidosis patients experience hypercalcemia, while, 24% to 40% of sarcoidosis cases possess hypercalcemia.<sup>3</sup> Ultimately, this disturbance in calcium metabolism leads to nephrocalcinosis, nephrolithiasis, and kidney malfunctions.<sup>14</sup> Even sarcoidosis patients

that show normal calcium concentrations possess abnormal 1,25-dihydroxyvitamin D levels that puts them at risk of kidney failure.<sup>15</sup>

The absorbency of dietary calcium in 50% of sarcoidosis cases is exceeded. Various clinical manifestations are varied from acute kidney impairments to chronic kidney disorders (Figure 1). However, acute symptoms appear to be more prevalent.<sup>10</sup> Previous studies indicated that measuring serum creatinine levels in sarcoidosis patients with normal of kidney functioning showed kidney disorders in many of them.<sup>11</sup> The study of kidney biopsy is the definitive diagnostic method and corticosteroids are the first-line treatment in kidney failure.<sup>12</sup> The kidney function shows a good response in most patients after 30 days of treatment. Only a small number of patients would be remaining dependent on dialysis.<sup>16</sup> The prevalence of renal sarcoidosis patients in Iran is not distinct.<sup>7,16</sup> Moreover, timely diagnosis and treatment of renal sarcoidosis patients, greatly reduces the kidney damages. Hence, the current study was conducted

on Iranian patients with pulmonary sarcoidosis to determine the prevalence of renal disorders and the associated clinical manifestations.

**MATERIALS AND METHODS**

The sample size of the current descriptive study was calculated to be 100 individuals. One hundred patients with definitive diagnosis of pulmonary sarcoidosis were studied between January 2017 and March 2018. The inclusion criteria were 18 years old and over, sarcoidosis proven by biopsy, and had no coexisting chronic respiratory disease. The exclusion criteria were smoking, diagnosis of tuberculosis, and correlated diseases with abnormal vitamin D concentrations.

Ethics approval and health indemnification issues were in accordance with declaration of Helsinki. Privacy of patient information principle was carried out. After explicating the study procedure to the patients, they signed the consent forms. Clinical symptoms and baseline demographic characteristics, including age, sex, and nationality

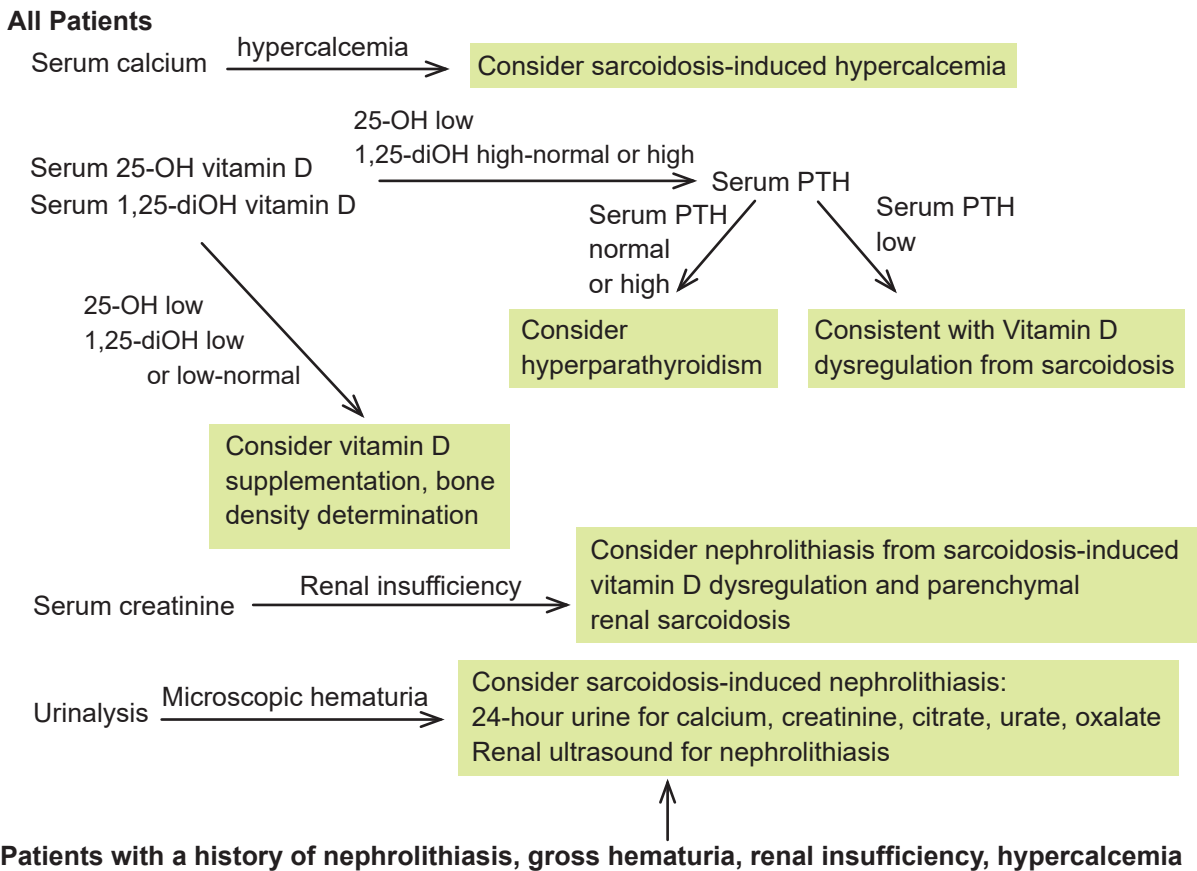


Figure 1. Sarcoidosis and its association with kidney involvement.<sup>16</sup>

were recorded for further analysis. Other collected data from patients included weight, history of diabetes mellitus, hypertension, polycystic kidney, kidney calculi, current medications, family history for renal stone, history of renal stone surgery, and laboratory findings such as fasting blood glucose, hemoglobin, hematocrit, erythrocyte sedimentation rate, serum creatinine, blood urea nitrogen, calcium, phosphorus, uric acid, thyroid stimulating hormone, intact parathyroid hormone (PTH), C-reactive protein, vitamin D, and protein-creatinine ratio and calcium in 24-hour urine. Patients also underwent ultrasonography, chest radiography, and echocardiography. Patient's extrapulmonary outbreaks were also recorded.

The data of patients were collected in a period of 2 to 4 months and finally classified and analyzed. Echocardiography was applied for diagnosis of pulmonary hypertension. Further examinations of complications in the right side of the heart were carried out on patients suspected to have pulmonary hypertension. Electrocardiography was used to investigate cardiac conflicts, especially cardiac pathway disorders, as well as erythema due to granulomatosis and cardiac ischemia. Pulmonary involvement such as hilar adenopathy, as well as involvement of lung parenchyma was investigated by chest radiography. High-resolution computed tomography was used for checking the parenchymal pulmonary fibrosis. Renal disorders in terms of size of urinary tract and presence of stones, checking pH, proteinuria, hematuria, and presence of crystals in the urine were studied by kidney ultrasonography examination. Ultimately, a creatinine level higher than 1.4 mg/dL and a calcium level over 250 mg/24 h urine were considered abnormal.

Most of patients received glucocorticoids for 6 to 12 months. Generally, treatment was started by high-dose medication and was followed by reducing to a minimum effective level of medication. In the event of recurrence of the disease after the discontinuation of glucocorticoid therapy, the patient was re-treated with glucocorticoid. In patients with intolerance to glucocorticoids, methotrexate was prescribed to reduce the inflammation and inhibit the immune system. Patients with development in sever symptoms despite of glucocorticoid treatment, received further medications including azathioprine, leflunomide,

and cyclophosphamide. Patients were followed up 6 months after the recovery, for evaluating recurrence of renal symptoms.

The SPSS software (Statistical Package for the Social Sciences, version 21.0, SPSS Inc, Chicago, IL, USA) software was used for statistical analyses. Continuous variables were expressed as mean  $\pm$  standard deviation or median (minimum to maximum). Categorical variables were expressed as frequencies and percentages. Different parameter correlations were determined by the Spearman rank correlation coefficient. Continuous variables between-group comparisons were evaluated using the nonparametric Mann Whitney U test. Otherwise, the chi-square test was used to evaluate categorical variables between-group comparisons. Differences in the mean were calculated by the Student *t* test and the Kruskal-Wallis test, considering a *P* value less than .05.

## RESULTS

One hundred patients were included; 52% of patients were females and 48% were males. The patients' age range was between 17 and 68 years (mean age,  $12.47 \pm 5.9$  years). Sarcoidosis occurred in most of the patients in January or February. Seventy-six of the 100 patients with biopsy-proven pulmonary sarcoidosis showed lymphadenopathy and 24% had parenchymal abnormalities. Thirty-three percent of the patients also presented kidney disorders simultaneously. In 88.7% of the patients with laboratory studies, blood calcium level was in the range of 9 mg/dL to 10 mg/dL, and only 1% of the patients had a calcium level greater than 14 mg/dL (hypercalcemia). Ninety percent of the patients presented a thyroid hormone level between 0.3  $\mu$ U/L and 4.5  $\mu$ U/L. In 65.7% of the patients, PTH levels were recorded in the range of 10  $\mu$ g/mL to 35  $\mu$ g/mL. Moreover, 34.9% of the patients showed a PTH level of 35  $\mu$ g/mL to 70  $\mu$ g/mL.

The erythrocyte sedimentation rate level was above 50 mm/h in 10% of the patients. It was observed between 12 mm/h and 36 mm/h in 50.7% of the patients and less than 12 mm/h in 35.4% of them. Blood phosphorus was obtained around 5.5 mg/dL in 96.7% of the patients. Blood phosphorus was above 5 mg/dL in 3.6% of the patients. In 58.9% of the patients, blood urea nitrogen was higher than 20 mg/dL, while 31.8% of patients had a level less than 24 mg/dL.

Creatinine level was less than 1.4 mg/dL in 92% of the patients and it was greater than 1.4 mg/dL in 8%. In 7.6% of the patients, uric acid level was greater than 9 mg/dL. However, 7.7% of patients showed a uric acid level less than 6 mg/dL. Fifteen percent of the patients had a positive acute phase C-reactive proteins. The 24-hour urine calcium level was below 250 mg/dL in 80% of the patients; it was observed above 250 mg/dL in 20% of the patients.

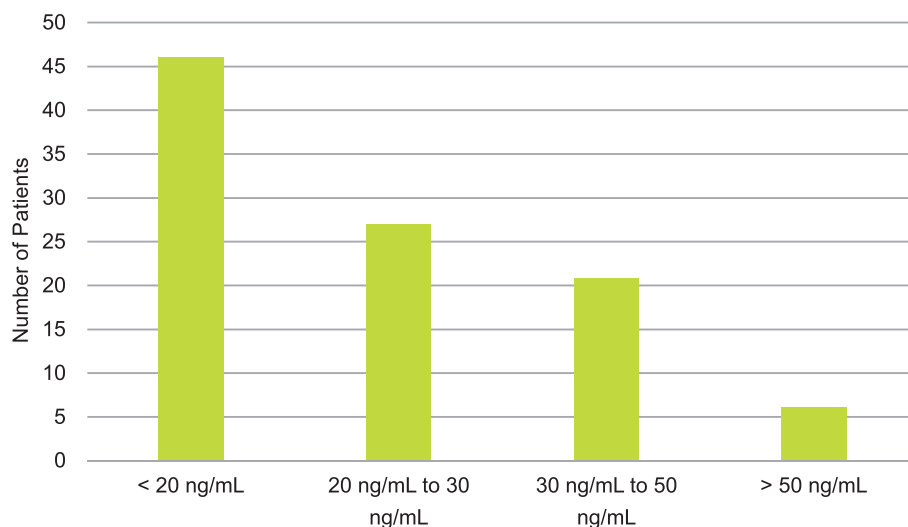
The quantity of 24-hour urine proteins in 5% of individuals was greater than 300 mg/mL, showing individuals with proteinuria. Ultrasonography demonstrated that 81.6% of the patients experienced regular renal system. Overall, 15.5% of the sufferers had kidney stones contributing to 2.9% of individuals experienced preexisting renal stones. The time period of sarcoidosis involvements was considerably associated with kidney stones ( $P < .001$ ). The urine amount of vitamin D was below 20 ng/mL in 46.0% of the patients (Figure 2). A urine 1,25-dihydroxyvitamin D over 30 ng/mL revealed considerable relationship with the frequency of kidney stones ( $P < .001$ ).

Of the patients, 68.8% showed a urinary calcium value higher than 250 mg/dL. A urinary calcium greater than 250 mg/dL (hypercalciuria) showed a significant correlation with the incidence of kidney stones ( $P = .04$ ), and 7.6% of patients experienced a greater than 9 mg/dL of uric acid proportion. However, 7.7% of patients showed a uric acid below 6 mg/dL. Also, there was a meaningful distinction between frequency of renal disorder in the patients

with more than 7 mg/dL uric acid and patients with lowering 7 mg/dL uric acid ( $P = .01$ ).

In 43% of the patients, heart rate fraction was 55%, as well as in only 3% of patients, discharge fraction was 65%. Both the variables of left ventricular hypertrophy and pH were normal. However, ejection fraction varied among the patients. In 23.7% of the patients, the proportion of hematocrit was 45% to 42% as well as in 48.9% of patients, the proportion of hematocrit was below 42%. A hematocrit over 45% was experienced by 27.9% of the individuals. In 13% of the patients, hemoglobin was 12.5 g/dL, and in 59% of cases hemoglobin was obtained between 12.5 g/dL and 14.5 g/dL. In 79% of the patients, fasting blood glucose was less than 100 mg/dL, and only 7% of the patients had a high blood sugar level of 125 mg/dL and higher.

Urinalysis was normal in 82.7% of the patients, and in 12% of patients and 3.5% of them had protein and crystalline in urine, respectively. Proteinuria over 300 mg confirmed a considerable connection with ejection fraction and history of disease in the patient. The correlation among proteinuria and ejection fraction was  $-0.88$  ( $P = .045$ ). The correlation between proteinuria and time period of disorder was 95% ( $P = .02$ ). Eleven percent of the sufferers exhibited greater than 4.1 mg/dL of creatinine. Also, there was clearly significant distinction between frequency of kidney disorders and creatinine quantities over 4.1 mg/dL as well as in the patients with very low creatinine levels ( $P < .001$ ). Excessive creatinine and vitamin D,



**Figure 2.** Frequency of different amounts of blood vitamin D3 in vitro in patients under study.

hypertension, and lung disease failed to exhibit any considerable relationship. Also, the correlation among higher creatinine with vitamin D was not significant ( $P = .59$ ). Relationship among higher creatinine with hypertension and pulmonary disorder was approximately 24.2% ( $P = .60$ ) and  $-0.56$  ( $P = .19$ ), correspondingly. Also, the correlation between excessive creatinine and hypercalciuria was not significant ( $P = .90$ ). Proteinuria exhibited a nonsignificant favourable relationship with age, creatinine levels, and duration of the disease. Proteinuria also proved a nonsignificant negative correlation with kidney involvement and sexuality of the patients.

## DISCUSSION

The accurate diagnosis of renal sarcoidosis directly relates to the dysfunction of urinary tract and mortality in sarcoidosis individuals. The golden purpose of detecting the renal sarcoidosis involves the accurate assessment of clinical disorders in kidney and urinary tract.<sup>17</sup> Previous studies demonstrated that individuals with impaired kidney and elevated levels of blood urea nitrogen and creatinine indicated a high prevalence of renal sarcoidosis.<sup>18-20</sup> In the current study, the calcium values in 88.66% of pulmonary sarcoidosis individuals were within 9 mg/dL to 10 mg/dL. The level of calcium in pulmonary sarcoidosis individuals in a former study was reported 14 mg/dL that was a little higher than current results.<sup>21</sup> Despite former studies, there is no precise strategy for assessing calcium metabolism in pulmonary sarcoidosis patients.<sup>22</sup>

Generally, enhancement of the activity of  $1\alpha$ -hydroxylase that converts 25-hydroxyvitamin D to 1,25-hydroxyvitamin D (active form of vitamin D) results in the disorder of vitamin D in sarcoidosis. This increases the absorption of calcium in intestine and excretion of calcium in kidneys which causes hypercalcemia, hypercalciuria, hyperuricemia, nephrolithiasis, nephrocalcinosis, and severe damage to the kidney.<sup>9</sup> On this issue, due to the enhanced concentration of vitamin D, the concentration of PTH decreases.<sup>22</sup> In a prior study, PTH was reported around 5.9 pg/mL.<sup>21</sup> It is supposed that higher PTH levels in the present study is due to differences in the studied population. In the current study, a 1,25-dihydroxyvitamin D level lower than 20 ng/mL was shown in 46.0%

of the patients, which justifies the higher level of PTH in contrast to previous studies.<sup>21</sup>

The current study indicates the relationship between uric acid and the possibility of developing kidney stones across pulmonary sarcoidosis individuals. In addition, a significant correlation was displayed between hypercalciuria and the incidence of renal stones ( $P = 0.04$ ). In sarcoidosis patients without a history of nephrolithiasis, solitary hypercalciuria is not an indicator for treatment since hypercalciuria is a common phenomenon in sarcoidosis and the side effects of hypercalciuria treatment may develop nephrolithiasis.<sup>1,3,23</sup> The present study showed that 1,25-dihydroxyvitamin D levels above 30 ng/mL beside uric acid levels above 7 mg/dL in urine sample directly demonstrate renal disorders in sarcoidosis patients. Contrary to previous reports, in the present study renal disorders were frequently observed in men.<sup>19</sup>

Corticosteroids were the first choice of treatment in the current study. The rate of glomerular filtration rate, which figures in minimizing renal stones, is increased by corticosteroids. On the other hand, it has been reported that IgA activity is correlated with renal inaccuracies. Therefore, administration of glucocorticoids is likely to have a positive effect on the improvement of renal sarcoidosis by inhibiting IgA activity. Generally, based on creatinine level, hypercalcemia presence and protease activity, the prevalence of renal sarcoidosis in the present study was about 33%.

Some limitations with this research might be of interest for outcomes presentation. Initially, final results are not able to totally characterize frequency of kidney disorders in sarcoidosis affected individuals in Iran since the research did not include the entire society of the country. Secondly, healthcare criteria in patients; average duration of disease, major damaged joints, and principal signs and symptoms; could hardly be regarded as a result of the restricted data extracted from involved individuals.

## CONCLUSIONS

We propose that urine investigation to be included as a simple and reliable method for evaluating renal involvement in routine checkups of sarcoidosis patients. However, further studies would be necessary to elucidate the exact extent of renal sarcoidosis patients in Iran.

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## CONFLICT OF INTEREST

None declared.

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