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Original Article

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A Retrospective, Single-Center Study Analyzing Kidney Functions in Sarcoidosis

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ABSTRACT

Objective: Sarcoidosis is a complex chronic disease of unknown etiology that is characterized by non-caseating granulomas. Lung and lymph node involvement is most common; however, various kidney function disorders may occur in these patients. This study aimed to investigate kidney and rarely assessed features in patients with sarcoidosis.
Methods: This study evaluated pulmonary sarcoidosis patients aged 18 years and over, who presented to the nephrology outpatient clinic of SBU Tepecik Training and Research Hospital. In addition to the general sarcoidosis parameters, serum 25(OH)D level, tubular functions, and aortic arch calcification were also investigated.
Results: Our study included 105 patients, of whom 74 (70.5%) were females and 31 (29.5%) were males. The mean age was 46.78 ± 12.54 years. The history of nephrolithiasis was present in 21 (20%) and aortic calcification was determined in 18 (17.1%) patients. The 25(OH)D level was below 20 ng/mL in 75 (71.4%) patients, and 21 (20%) patients were hypercalcemic. Smoking history was determined in 24 (22.9%) patients, and 25(OH)D levels (cut-off 20 ng/mL) were higher in smokers than non-smokers. Additionally, a rare finding of asymptomatic renal tubular acidosis was detected in 4 (3.8%) patients. The 24-hour urine calcium excretion was >250 mg/day in 27 (25.7%) patients, and 40 (38.1%) patients were hypercalcemic and/or hypercalciuric.
Conclusion: Our study revealed a low 25(OH)D level. The incidence of aortic arch calcification as a possible marker of atherosclerosis was also higher than expected and the frequency was higher in patients with higher 25(OH)D levels. As a rarely examined entity in patients with sarcoidosis, renal tubular acidosis type I was detected in 4 patients. Beyond classical kidney findings other features should be analyzed in sarcoidosis.
Keywords: Sarcoidosis, vitamin D, acidosis, renal tubular, vascular calcification

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INTRODUCTION

Sarcoidosis (Besnier–Boeck–Schaumann disease) is a non-caseating granulomatous, chronic inflammatory disease that can affect multiple systems in the body and is not always easy to diagnose. Either it can be incidentally recognized with nonspecific findings or it may present with serious clinical situations. Clinical, radiological, and histological parameters are used in diagnosis. Lung and lymph node involvement is most common; however, different kidney function disorders may occur in patients with sarcoidosis. Traditionally, the best-known kidney disorders include hypercalciuria and/or hypercalcemia. Additionally, kidney involvement may occur as nephrocalcinosis/nephrolithiasis, abnormal kidney tubular function, interstitial nephritis (granulomatous/non-granulomatous), acute kidney injury, kidney failure, glomerulonephritis, nephrogenic diabetes insipidus, renovascular hypertension (HT), and obstructive kidney disease. Particularly, nephrocalcinosis/nephrolithiasis is important in that it can lead to kidney failure. However, ambiguous points are determined in the pathophysiology of kidney and metabolic disorders in

sarcoidosis, and more detailed research has emerged on these issues in recent years. Therefore, this study aimed to examine the rarely investigated features of our patients with sarcoidosis, as well as the well-known parameters and the relationship between them. Aortic calcification is recognized as an indicator of atherosclerosis/vascular disorders and has been shown to predict mortality in some specific populations. Considering that aortic calcification is also associated with calcium metabolism, it is also investigated in patients with sarcoidosis.

METHODS

This study retrospectively evaluated 105 patients with pulmonary sarcoidosis aged 18 and over, who were followed up between June 2016 and November 2018 at the SBU Tepecik Training and Research Hospital nephrology outpatient clinic. Patients were diagnosed with histopathological, clinical, and radiological methods according to the American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders statement on sarcoidosis.[1] Patients under calcium and vitamin D treatments, patients with thiazide use, patients with known primary hyperparathyroidism, malignancy, and recent blood transfusion history, as well as those with known autoimmune disease and chronic obstructive pulmonary disease were excluded from the study. Demographic and epidemiological (age, gender, and disease duration) findings, basic biochemical tests, 24-hour urinary calcium, potassium, uric acid, phosphorus, protein, and albumin excretion, hemogram, complete urinalysis, antinuclear antibody (ANA), and anti-neutrophil cytoplasm autoantibody levels were examined. Serum calcium level of ≥10.3 mg/dL was accepted as hypercalcemia. The level of 25(OH)D, the main form of vitamin D in circulation, was determined to effectively evaluate vitamin D adequacy.[2,3] According to serum 25(OH)D level, vitamin D deficiency was defined as <20 ng/mL 25(OH)D and vitamin D insufficiency was defined as 21-29 ng/mL 25(OH)D.[3] Venous blood gases were examined in all patients. Urinary anion gap (UAG) and serum anion gap (SAG) parameters were calculated in patients with metabolic acidosis (HCO_3 of <22 mEq/L and serum pH of <7.35), which evaluate sodium, potassium, and chloride in spot urine, and sodium, chloride, and bicarbonate levels in serum: UAG = $([Na^+]+[K^+]-[Cl^-])$ and SAG = $([Na^+]-[Cl^-]+[HCO_3^-])$, respectively. The SAG value was considered normal in 7-14. Renal tubular acidosis (RTA) was defined as metabolic acidosis with normal SAG and positive UAG values. Patients diagnosed with RTA were classified as type I distal RTA if urine pH is >5.5 and serum potassium is low/normal, type II if urine pH is <5.5 and serum potassium is low/normal, and type IV if serum potassium is >5.5 mEq/L.[4] Findings such as chronic diseases, current or past treatments, chest x-rays, tobacco use, history or presence of kidney stones, and disease stages were recorded. Chest x-rays and thoracic computed tomography (CT) images were used at the center, where they were radiologically followed. Scadding criteria were used in staging pulmonary sarcoidosis.[5] Urinary ultrasonography was performed in all patients. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (SBU Tepecik Training and Research Hospital (Date: February 15, 2022, decision no: 2022 /02-09) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

MAIN POINTS

- Kidney manifestations of sarcoidosis may occur in different presentations.
- 25(OH)D levels of >15 ng/mL were associated with more frequent nephrolithiasis in patients.
- Beyond classical kidney findings of sarcoidosis other rarely assessed features such as aortic calcification or renal tubular acidosis should be evaluated.

Statistical Analysis

The statistical analyses were conducted using the Statistical Package for Social Sciences for Windows version 18 (SPSS Inc., Chicago, Ill, USA) pocket program. The Kolmogorov–Smirnov test was used to assess the normal distribution of variables. Quantitative data were expressed as mean ± standard deviation, and qualitative data as numbers and percentages (n, %). The *t*-test and Mann–Whitney *U*-test were used to compare parametric and nonparametric independent groups, respectively. The chi-square test was used to compare categorical groups. A *P*-value of <.05 was considered statistically significant.

RESULTS

This study included 105 patients, of whom 74 (70.5%) were females and 31 (29.5%) were males. The mean age was 46.78 ± 12.54 years, and the mean disease duration was 40.02 ± 28.04 months. Of all patients, 31.4% were in the second-third decade, 51.5% were in the fourth-fifth decade, and 17.2% were in the sixth-seventh-eighth decades. Diabetes mellitus (DM) was determined in 18 (17.1%) patients, HT in 24 (22.9%) patients, and chronic kidney disease without kidney replacement therapy in 4 (3.8%) patients. Some biochemical values are shown in Table 1. Some cases (n = 28) were examined due to the uncertainty of Angiotensin-converting enzyme (ACE) level specificity, which revealed a mean value of 56.59 ± 53.41. Patient evaluation according to their stages revealed that 55.2% were at stage 1, 39% at stage 2, 4.8% at stage 3, and 1% at stage 4. Smoking history was present in 24 (22.9%) patients. Gastrointestinal system involvement was determined in 2 (1.9%), history of uveitis in 6 (5.7%), and erythema nodosum in 6 (5.7%) patients. History of nephrolithiasis was present in 21 (20%) and aortic calcification (thorax CT) in 18 (17.1%) patients. (Figure 1) Obstructive kidney disease was not detected in any patients. The ANA positivity was determined in 18 patients. In 75 patients (71.4%), 25(OH)D level was >20 ng/mL, and 21 (20%) patients were hypercalcemic. The 24-hour urinary protein was >150 mg/day in 14 (13.3%) and >300 mg/day in 4 (3.8%) patients. The parathyroid hormone

Table 1. Laboratory Results

Variables		Variables	
Creatinine (mg/dL)	0.88 ± 0.23	pH	7.41 ± 0.04
Sodium (mmol/L)	140.05 ± 2.58	HCO_3 (mEq/L)	24.17 ± 2.24
Potassium (mEq/L)	4.39 ± 0.38	PTH (pg/nL)	53.09 ± 45.22
Calcium (mg/dL)	9.90 ± 0.47	Uric acid (mg/dL)	5.53 ± 1.55
Phosphorus (mg/dL)	3.50 ± 0.58	C3 (mg/dL)	123.69 ± 24.69
Protein (g/dL)	7.65 ± 0.55	C4 (mg/dL)	24.02 ± 6.21
Albumin (g/dL)	4.34 ± 0.30	Urinary density	1018.66 ± 7.26
Globulin (g/dL)	3.32 ± 0.52	25(OH)D (ng/mL)	16.87 ± 14.05
Leukocyte/ mm^3	7.110.00 ± 1.997.19	24-hour urinary sodium (mmol/day)	128.44 ± 98.38
Neutrophil/mm^3	4.500.48 ± 1.584.21	24-hour urinary potassium (mmol/day)	71.31 ± 64.10
Hemoglobin (g/dL)	13.22 ± 1.39	24-hour urinary calcium (mg/day)	224.15 ± 351.51
Hematocrit (%)	40.07 ± 3.81	24-hour urinary uric acid (mg/day)	791.72 ± 980.56
Platelet/mm^3	281.971.43 ± 68.861.55	24-hour urinary protein (mg/day)	118.37 ± 190.09
MPV (fL)	8.66 ± 0.93	24-hour urinary phosphorus (mg/day)	854.70 ± 1.126.16
RDW (%)	14.71 ± 2.16	24-hour urinary albumin (mg/day)	12.02 ± 28.51

MPV, mean platelet volume; RDW, red cell distribution width.

(PTH) level was higher in females and smoking frequency was higher in males (Table 2). The 25(OH)D level (cut-off 20 ng/mL) was higher in smokers than in non-smokers. (P = .042) (Figure 2). Urine pH was ≤5.5 in 46 patients (43.8%) and ≥6.5 in 24 patients (23%). The urine tests examination revealed that 28 patients had ≥+1 leukocyturia (26.6%) and 23 had ≥+1 erythrocyturia (21.9%). In 27 patients (25.7%), the 24-hour urine excretion was >250 mg/day, and the number of patients with hypercalcemia and/or hypercalciuria (cut off ≥250 mg/day) was 40 (38.1%). Our study revealed that 3 patients were hypophosphatemic (<2.5 mg/dL) and 2 patients were hyperphosphatemic (>4.5 mg/dL).

DISCUSSION

Sarcoidosis is a complex chronic disease of unknown etiology that is characterized by non-caseating granulomas in tissues and can be seen in any race and age. Genetic tendency (HLA-DRB1*14, HLA-DRB1*15, HLA-DRB1*1101, and HLA-DPB1*0101), exaggerated immune response associated with alveolar macrophages and T lymphocyte activation, and the release of chemokines, such as interleukin (IL)-18, tumor necrosis factor (TNF) α, interferon-gamma, and IL-15, has been emphasized to play a role in pathogenesis. Especially organisms, such as Mycobacteria and *Propionibacterium acnes*, have been accused as etiological agents, as well as exposure to certain metals (beryllium, aluminum, and zirconium) and insecticides.[6] It is more common in women in Scandinavia and in African Americans; however, in an epidemiological study conducted in our country, the estimated annual incidence was 4/100 000.[7] The most common time interval of the disease is 3-5 decades. Similar to previous publications, most of our patients were females, and 82.9% were in the second-fifth decades. Female/Male was 2.38, which is higher than the rates found in other epidemiological studies but was compatible with another study in northern Iran, a nearby geographic region.[8] The gender evaluation revealed that female patients were older than males; however, the disease duration in males was longer, even if not statistically significant. The 24-hour urinary excretion of calcium, albumin, protein, uric acid, and phosphorus was statistically higher in males than females, as well as of sodium and potassium, but without significance. Renal tubular functions in males were more prominent than in females, and their differences between genders may be important in nephrological follow-up and should be taken into consideration.

Different studies have indicated a negative relationship between tobacco use and the risk of developing sarcoidosis.[9,10] Our

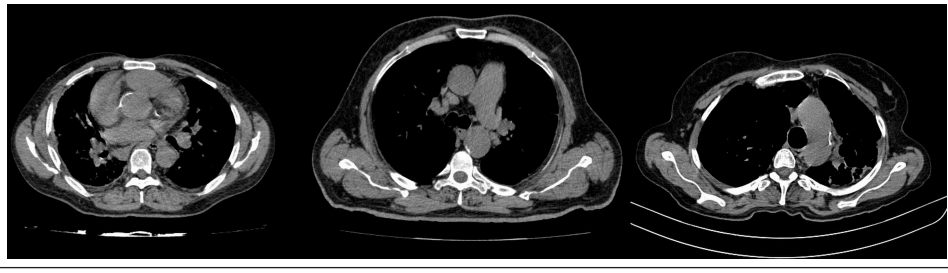

Figure 1. Some examples of computed tomography of chest demonstrating aortic calcification.

Table 2. Comparison of Some Parameters Between Genders

	Female (n = 74)	Male (n = 31)	*P*
Age (years)	49.39 ± 11.41	40.55 ± 13.11	**.002**
Duration of disease (months)	35.91 ± 22.95	49.84 ± 36.09	.117
Parathyroid hormone (pg/mL)	60.08 ± 50.44	36.39 ± 22.09	**.003**
Urinary protein excretion rate (mg/day)	93.88 ± 57.50	176.82 ± 334.98	**.0019**
Urinary albumin excretion rate (mg/day)	10.49 ± 27.03	15.68 ± 31.94	**.047**
Urinary calcium (mg/day)	206.43 ± 395.79	266.46 ± 211.01	**.002**
Urinary uric acid (mg/day)	689.87 ± 882.61	1.034.84 ± 1.162.32	**.002**
Urinary phosphorus (mg/day)	743.30 ± 1.122.17	1.120.62 ± 1.108.46	**.002**
Urinary sodium (mmol/day)	123.51 ± 106.15	140.23 ± 77.03	.103
Urinary potassium (mmol/day)	71.01 ± 65.60	72.03 ± 61.38	.548
Cigarette smoking (n, %)			
Yes	10 (41.7%)	14 (58.3%)	**<.001**
No	64 (69.0%)	17 (21.0%)	

Bold indicates statistical significance.

study revealed that 22.9% of patients with a history of smoking (current/ex-smoker) were more common in males, similar to the conducted epidemiological studies in Türkiye (26.6% current and ex-smokers). The study by Cardoso et al[11] has a similar rate (24.4%). As a different and interesting finding, 25(OH)D level (cut-off 20 ng/mL) was higher in our patients with smoking history, whereas lower in non-smokers.

The ANA positivity was determined in 17.1% of patients in our study. Another study from Türkiye by Kobak et al[12] reported a rate of 28.5%, which was significantly higher than the control group that consisted of healthy individuals. Sarcoidosis, which is accepted as an autoimmune disease, may accompany other systemic autoimmune diseases or immunological/molecular similarities in etiology according to some hypotheses.[13] Additionally, concurrent connective tissue diseases (Sjogren and scleroderma) have been reported in sarcoidosis. The number of patients with positive ANA may be attributed to these entities. The kidney biopsy in the study by Kamata et al[14] was positive in 3 of 16 cases (ANA in 1 case, anti-glomerular basement membrane (anti-GBM) antibody in 1 case, and anti-SS-A/SS-B in 1 case); however, none were diagnosed with any autoimmune diseases. Similarly, our study also revealed a positive cytoplasmic antineutrophil cytoplasmic autoantibodies (cANCA) in 1 patient, and perinuclear antineutrophil cytoplasmic autoantibodies (pANCA) was negative in all patients.

Kidney involvement, which is assumed to be less frequent than in other systems, may occur as hypercalcemia/hypercalciuria, nephrocalcinosis/nephrolithiasis, abnormal renal tubular function, interstitial nephritis, glomerulonephritis, nephrogenic diabetes insipidus, renovascular HT, and obstructive kidney disease. Particularly, nephrocalcinosis/nephrolithiasis is important since it can lead to kidney failure.

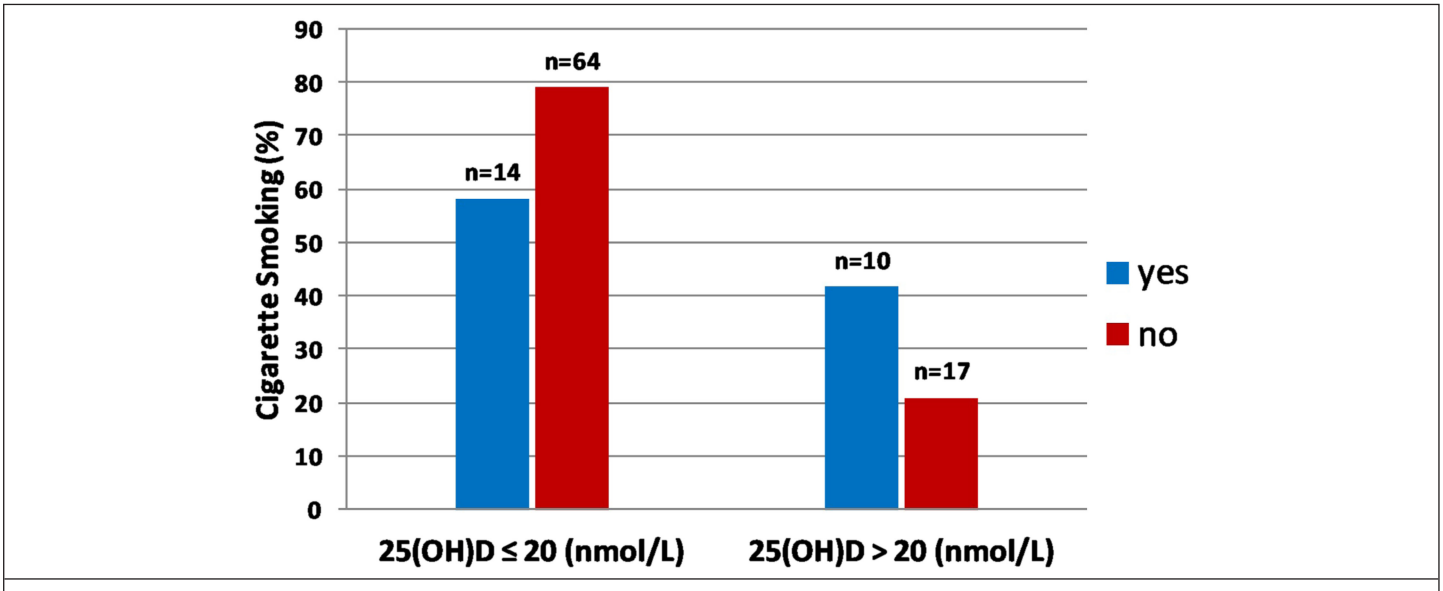

Figure 2. Association between smoking and 25(OH)D.

Kidney involvement and hypercalcemia are associated with higher chronicity and poor prognosis, and abnormal calcium metabolism is more frequently associated with relapse.[15,16] Therefore, close nephrological monitoring becomes important in patients with kidney involvement and/or calcium homeostasis abnormalities. Gray zones are still present in calcium metabolism in patients with sarcoidosis; however, hypercalcemia is hypothetically assumed to mainly occur through the following pathways: (A) systemic transformation from 25(OH)D to $1,25(OH)_2D$ and increase in serum $1,25(OH)_2D$ level through 1-α hydroxylase produced in activated monocytes or macrophages, (B) increasing the expression of PTH-related peptide (PTHrP) with the release of TNF-α and IL-6 from activated mononuclear cells in sarcoid granulomas (hypercalcemia + normal 25(OH)D + ↓iPTH with negative feedback effect of hypercalcemia), (C) calcium-sensing receptor (CaSR) mutations or polymorphisms, and (D) conversion from 25(OH)D to $1,25(OH)_2D$ at tissue level with 1-α hydroxylase production in local monocytes or macrophages in sarcoid granulomas (hypercalcemia + iPTH N/↓ and PTHrP+25(OH)D normal/low-increased). The last hypothesis suggested that it remains at the tissue level due to local activation and that measurable levels cannot be detected in the systemic circulation.[17-21] The first hypothesis is considered to be the most commonly accepted approach; however, Mahévas et al[22] revealed a significant correlation between kidney biopsy granuloma scores and serum calcium levels. Our study did not find a significant difference between PTH and 25(OH)D levels between patients with hypercalcemia and without hypercalcemia.

The 25(OH)D is the major circulating vitamin D_3 metabolite and is widely used as a marker in evaluating vitamin D adequacy.[3] Our study revealed a low 25(OH)D level (16.87 ± 14.05 ng/mL). Studies reveal different results, such as 25(OH)D may be reduced or normal (not increased) in patients with or without hypercalcemic sarcoidosis, whereas $1,25(OH)_2D$ levels may be normal or increased (decrease not common).[23-25] The study of Papanikolaou et al[26] revealed low level 25(OH)D (deficiency + insufficiency) in 64% of patients. The comparison of 64 patients with sarcoidosis with 53 patients with non-sarcoidosis pulmonary diseases as the control group revealed no significant difference between serum 25(OH)D levels (26 ± 14 ng/mL vs. 23 ± 9 ng/mL). However, the statistical significance in the deficiency group (<20 ng/mL) and in the normal group resulted in the insufficiency (<30 ng/mL) group in favor of the control group. Additionally, higher levels of $1,25(OH)_2D$ and serum calcium were detected in the insufficient group compared to the control group. Varying results in different studies incompatible with normal regulation mechanisms cause uncertainty in the etiological approach. Not all patients with hypercalcemia can be grouped under the normal/low 25(OH)D and high $1,25(OH)_2D$ headings in sarcoidosis.

Hypercalciuria is more common in patients with sarcoidosis than hypercalcemia (40%-62% vs. 10%-17%).[27] Our study revealed a lower 24-hour urinary calcium excretion (209.92 ± 381.44 vs. 259.73 ± 264.56) in patients with low 25(OH)D levels (<20 ng/mL), although it was not statistically significant. Non-smoking, nonexistent history of nephrolithiasis, and non-HT were significantly higher in those with 24-hour urine calcium excretion of ≤250 mg/day (n = 78) (P = .01, P = .01, and P = .042, respectively).

Nephrolithiasis is another type of kidney involvement and maybe the first form of presentation in 4% of patients.[28-30] It is important due to obstructive urologic problems and since it carries long-term risk for chronic kidney disease. The literature reported a higher frequency of nephrolithiasis (10%-15%) in patients with sarcoidosis than in the general population (11% males and 7% females).[29-31] Our study revealed this rate at 20%. The relationship between 25(OH)D level and nephrolithiasis in patients without sarcoidosis is controversial.[32,33] A study, which included 16 286 adults, revealed no significant difference in 25(OH)D levels between the groups with and without stone history.[34] A meta-analysis that evaluated 32 observational studies revealed that 25(OH)D levels were similar in patients with calcium stone and control group, but $1,25(OH)_2D$ levels were significantly higher in patients with nephrolithiasis. The subgroup analyses revealed higher $1,25(OH)_2D$ and 25(OH)D levels in patients with hypercalciuric nephrolithiasis than those with normocalciuric nephrolithiasis and the control group. This result predicted that high levels of 25(OH)D accompanied by hypercalciuria may cause an increased frequency of nephrolithiasis.[35] In the National Health and Nutrition Examination Survey (NHANES) III cross-sectional study, the association of high serum 25(OH)D levels with prevalent nephrolithiasis (or history) could not be demonstrated.[34] The retrospective study by Eisner et al[36] included 169 patients with nephrolithiasis, which revealed no association with serum 25(OH)D and 24-hour urinary calcium excretion. Interestingly, our study revealed that patients with 25(OH)D levels of >15 ng/mL have more frequent nephrolithiasis than those with a lower rate (P = .016). The examination of patients with a history of nephrolithiasis revealed a higher level of 25(OH)D (21.10 ± 11.87 vs. 15.81 ± 14.42, P = .009). The level of 25(OH)D was more significant in predicting nephrolithiasis than hypercalcemia/hypercalciuria (P = 0.016 vs. P = 0.081). Although not statistically significant, 24-hour urine calcium excretion was higher in patients with a history of nephrolithiasis (274.38 ± 254.83 mg/day vs. 211.59 ± 371.98 mg/day). A study that compared patients with sarcoidosis in 2 different ethnic populations revealed a higher 24-hour urinary calcium excretion in the nephrolithiasis group than that in the non-nephrolithiasis group. However, hypercalciuria status was not associated with 25(OH)D and $1.25(OH)_2D$ levels. The authors concluded that this vitamin D-independent hypercalciuria may be due to impaired renal tubular calcium reabsorption or tubulointerstitial involvement.[37]

Mortality is higher in sarcoidosis than in the general population, and deaths from cardiac origin are more frequently

reported. Yong et al[38] revealed that arterial stiffness is increased in sarcoidosis, with a high risk of subclinical atherosclerosis. Vascular calcification due to its association with high-risk parameters for both cardiovascular mortality, such as coronary artery calcification and arterial stiffness and left ventricular hypertrophy, is an important finding. Aortic arch calcification (AAC) is an entity associated with mortality in some patient groups and can be detected by simple radiological imaging techniques.[39] The literature reported that apart from case reports, aortic calcification is not much evaluated in patients with sarcoidosis. Our study revealed a 17.1% incidence of AAC. None of our patients had a history of coronary artery disease or heart failure. Additionally, our study revealed that the frequency of AAC was higher in patients with 25(OH) D levels of >15 ng/mL compared to the lower ones ($P = 0.008$). Similarly, the high frequency of nephrolithiasis in patients above this level was interesting since it is a possible indicator of abnormal calcium deposition (Figure 3). The dominant cells in the lesions are activated macrophages (similar to those in sarcoidosis) and secrete proinflammatory cytokines (TNF α, IL6) in patients with calcific aortic valve.[40] Some similarities in the pathophysiological mechanisms of sarcoidosis and atherosclerosis have been suggested. Chitinase 1 released from activated macrophages was detected in both atherosclerosis and pulmonary sarcoidosis. Additionally, lipid metabolism disorders and oxidative stress played a role in the inflammation in sarcoidosis.[41] Many studies reported that aortic calcification increases with increasing age. Our study revealed that the mean age was 46.78 ± 12.54 years; however, patients with AAC were both older and had higher urine albumin excretion rates (day) (60.83 ± 7.54 vs. 48.87 ± 11.37, $P < .001$, median value min–max 6.36 [2.80-135.20] vs. 5.00 [0.17-193.80], $P = 0.015$, respectively). All these data reveal that early atherosclerosis /subclinical atherosclerosis should be investigated, and risk assessment should be done in patients with sarcoidosis. Our study revealed less common DM and HT in patients without AAC ($P = 0.045$, $P = 0.017$, respectively).

Hypercalcemia/hypercalciuria is the most common kidney complication of sarcoidosis; however, renal tubular functions should also be evaluated in these patients. Hypercalcemia can lead to impaired acidification balance. Renal tubular acidosis occurs as a result of a deficiency in the bicarbonate retention of the kidneys or organic acid excretions. Therefore, non-anion gap (hyperchloremic) metabolic acidosis and urinary acidification impairment occur. This acid–base disturbance can be seen during normal or slightly decreased glomerular filtration rate values. Our study revealed asymptomatic RTA type I in 4 patients. This clinical condition had not been studied in detail in previous studies. Some characteristics of these cases are indicated in Table 3. None of our patients had a history of DM, HT, smoking, and nephrolithiasis. All were evaluated as type 1 RTA (dRTA). Although not as much as the type seen in infancy and childhood, complications such as recurrent kidney stone, nephrocalcinosis, hypokalemia, and bone disease may occur in dRTA during adulthood.

CONCLUSION

Kidney functions should be evaluated at the first diagnosis and during follow-up in sarcoidosis. Calcium metabolism in sarcoidosis seems to be different and more complex than usual. Widespread vitamin D deficiency/insufficiency especially in populations that are studied in recent years may have created these discordances among studies and should not be overlooked. Adding the overall vitamin D inadequacy in the studied population as a correcting factor would be rational in

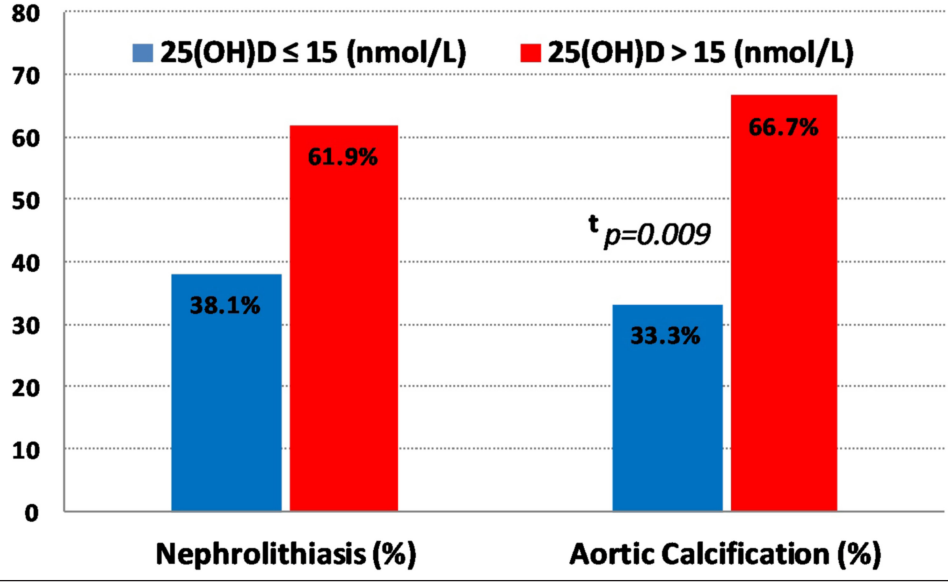

Figure 3. Association between 25(OH)D and aortic calcification/nephrolithiasis.

Table 3. Some Characteristics of Patients with Renal Tubular Acidosis

	Case 1	Case 2	Case 3	Case 4
Age (years)	45	33	34	34
Gender	F	F	M	M
Duration of disease (months)	44	39	42	56
Stage	I	II	I	I
Creatinine (mg/dL)	0.7	1	1	0.8
Serum calcium (mg/dL)	9.3	10	10	10.4
24-hour urinary calcium (mg/day)	217	137.6	53.5	216.3
25(OH)D (ng/mL)	7.7	5.1	12	9

the approach to hypercalcemia in sarcoidosis. No guideline recommendation is available due to the common variations in the studies of patients with sarcoidosis, as well as the different results. High $1,25(OH)_2D$ levels seem to explain hypercalcemia in this group of patients; however, subgroups appeared where it cannot be clearly explained. Renal tubular acidosis, another kidney complication, can easily be overlooked in this patient group unless a detailed evaluation is made.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of SBU Tepecik Training and Research Hospital, (Date: February 15, 2022, decision no: 2022 /02-09).

Informed Consent: Written informed consent was obtained from patients.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.A., F.D.Ü.; Design – A.A., F.D.Ü.; Supervision – S.E., M.T.; Resources – F.D.Ü., E.Y.; Materials – F.D.Ü., A.A., E.Y.; Data Collection and/or Processing –A.A., F.D.Ü., F.R.Ö.; Analysis and/or Interpretation – H.A.; Literature Search – A.A.; Writing Manuscript – A.A., H.A.; Critical Review – S.E., M.T.; Other – E.Y.

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