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Proteinuria in sarcoidosis: Prevalence and risk factors in a consecutive outpatient cohort

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Abstract. *Introduction:* While sarcoidosis has been recognized as a potential cause of proteinuria, no study has systematically evaluated the prevalence and risk factors for proteinuria in sarcoid patients. *Methods:* Consecutive sarcoid patients followed in a university clinic were identified prospectively. All patients with spot urine protein-to-creatinine ratio (UPCR) between 11-2012 and 07-2015 were included in the analysis. Proteinuria was defined as a spot UPCR equal to or exceeding 0.3 mg/mg. The primary goal of the study was to determine the prevalence of proteinuria in this sarcoidosis cohort. *Results:* Our study cohort consisted of 190 sarcoidosis patients (65% female, 82% white, mean age of 53 years (range 24-88)). Proteinuria was present in 14/190 (7%) of this cohort. Only5/190 patients (2.5%) had proteinuria who did not have a risk factor for proteinuria. Estimating the 24-hour urine protein excretion by extrapolating from the spot UPCR, proteinuria was moderate in amount (mean 1.60, range 0.32-5.06 mg/mg). Proteinuric patients received a lower mean daily dose of corticosteroids compared to those without proteinuria (0 mg vs 4.7 mg of prednisone); however, this difference did not reach statistical significance (p = 0.20). *Conclusion:* Our study found proteinuria in 7% of the 190 sarcoid patients. More than half of the patients with proteinuria had a known risk factor for proteinuria other than sarcoidosis. Proteinuria is uncommon in sarcoidosis, and, when it occurs, it should not be assumed that sarcoidosis is the cause without investigating alternative causes of proteinuria. *(Sarcoidosis Vasc Diffuse Lung Dis 2017; 34: 142-148)*

Key words: proteinuria, sarcoidosis, prevalence

Introduction

Sarcoidosis is a multisystem granulomatous inflammatory disease of unknown etiology. The reported prevalence of sarcoidosis renal involvement has been estimated between 3-23% (1). This wide range of incidence estimates suggests that the true incidence of renal involvement in sarcoidosis is unknown. The clinical presentation of renal sarcoidosis can range from an asymptomatic state to acute kidney injury requiring renal replacement therapy. Renal sarcoidosis manifestations vary from kidney disease related to calcium metabolism dysregulation such as nephrocalcinosis, and nephrolithiasis, to granulomatous or non-granulomatous tubule-interstitial nephritis (1,2). Renal failure from sarcoidosis is rare, with reported incidence ranges from 0.7% to 4.3% in previous clinical series of sarcoidosis patients (2).

Proteinuria is an important prognostic factor in stratifying the risk of cardiovascular disease and

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chronic kidney disease progression (3-8). In addition to its prognostic significance, successful treatment of proteinuria may reduce the burden of end-stage renal disease, cardiovascular disease, and improve survival (9-11). Only a handful of studies have examined prevalence of proteinuria in renal sarcoidosis. Although these studies have suggested that proteinuria might be common in renal sarcoidosis (12-14), they involved highly selected cohorts. To the best of our knowledge, no study has systematically examined the prevalence and risk factors for proteinuria in sarcoidosis using patient data collected consecutively. We conducted a prospective study of consecutive sarcoidosis patients to determine the prevalence and the risk factors for proteinuria.

Methods

Potential study subjects were identified from a prospective sarcoidosis database that we had previously established at our institution. In these patients sarcoidosis was diagnosed by standardized criteria (15,16). Consecutive patients who had a spot urine protein and creatinine data available in our database at their initial clinic visit between January 2012 and July 2015 were included in the analysis. The following data were obtained concerning each subject from review of the medical records: a) Demographics: Age, gender, race, height, weight, body surface area; b) Comorbidities associated with proteinuria: Diabetes, hypertension, lupus nephritis, Human Immunodeficiency Virus (HIV) infection, hepatitis B and C infection, pregnancy, chronic kidney disease, glomerulonephritis and congestive heart failure; c) Use of medication which can interfere with protein excretion; d) the use of anti-sarcoidosis treatment and anti-sarcoidosis medication; e) serum electrolytes, f) spot urine protein and creatinine.

In this study, proteinuria was defined as spot urine protein-to-creatinine ratio (UPCR) equal to or exceeding 0.3 mg/mg. According to the Kidney Disease Outcomes Quality Initiative guidelines of the US National Kidney Foundation, this method of determining proteinuria is preferred, rather than timed urine collections (24 hr urine protein collection) (17). The spot UPCR in mg/mg is roughly equal to the 24 h protein excretion in g/day/1.73 m^2 body surface area (18).

We used descriptive statistics for continuous and categorical variables (frequency distributions, percentages, means and standard deviations). Logistic regression model was used for risk prediction of proteinuria. The differences between proteinuria and non- proteinuria groups were obtained by using z- test.

The primary goal of the study was to determine the prevalence of proteinuria in our sarcoidosis cohort. The secondary goal was to identify risk factors associated with proteinuria in our sarcoidosis cohort.

Institutional review board approval was obtained for this study. All study procedures were carried out in accordance with the Declaration of Helsinki regarding research involving human subjects.

Results

One hundred and ninety patients were included in this study. The demographic and clinical characteristics are shown in Table 1. There was no difference in age, sex, or race between the proteinuria and non-proteinuria group. Nearly one third (62/190) of the patients had alternative causes of proteinuria.

Proteinuria was present in 14/190 (7%) of total cohort (Figure 1). There was no significant difference in the demographic data between sarcoidosis patients with proteinuria and without proteinuria (Table 2). However, patients with proteinuria had a statistically significant lower mean eGFR as compared to those without proteinuria (56.7 vs 78.7 mL/min/1.73 m^2, $P<0.01$). The prevalence of hypertension, diabetes and chronic kidney disease was higher in sarcoidosis patients with proteinuria as compared to those without proteinuria. Estimating the 24-hour urine protein excretion by extrapolating from the UPCR, proteinuria was moderate in amount (mean 1.60, range 0.30-5.06 mg/mg). At the time of spot urine collection, only 45/190 (24%) of the cohort were receiving prednisone at a mean dose of 5 mg/day. Compared to those without proteinuria, patients with proteinuria were receiving a lower mean daily dose of corticosteroids (3.9 mg vs 5.1 mg of prednisone); however, this difference did not reach statistical significance ($p = 0.70$).

Sixty-eight percent (130/190) of our cohort had no alternative risk factors for proteinuria (diabetes, hepatitis B or C infection, HIV, pregnancy, systemic

Table 1. Clinical characteristics of study cohort

Variables	Cohort with presence of alternative causes of proteinuria (N=190)	Cohort with absence of alternative causes of proteinuria* (N=130)
Age in years (range)	52.8 (24-88)	51.9 (25-81)
Time since diagnosis of sarcoidosis (Median), years	6.17 (0.04-57.45)	6.77 (0.04-57.45)
Sex, N, (%)		
Male	68, (35%)	49, (38%)
Female	123, (65%)	81, (62%)
Race, N, (%)		
White	155, (82%)	32, (65%)
Black	31, (16%)	11, (22%)
Other	4, (2%)	6, (13%)
Sarcoidosis, N, (%)		
Pulmonary	177, (92.7%)	119, (91.6%)
Extra-pulmonary	115, (60.2%)	83, (63.5%)
Comorbidities, N, (%)		
Hypertension	72, (38%)	40, (31%)
Chronic kidney disease†	20, (10%)	7, (5%)
Diabetes	31, (16%)	
Hepatitis B	2, (1%)	
Hepatitis C	1, (0.5%)	
HIV	1, (0.5%)	
SLE	2, (1%)	
Congestive heart failure	5, (2.5%)	
Pregnancy	0, (0%)	
Glomerulonephritis	0, (0%)	

*: Diabetes, systemic lupus erythematosus, HIV, Hepatitis B, Hepatitis C, glomerulonephritis, congestive heart failure, pregnancy, non-steroidal anti-inflammatory drug use.
†: Evidence of kidney damage (pathological, urine abnormality, imaging or blood test) or GFR < 60 mL/min/1.73mm^2 for ≤ 3 months, with or without kidney damage
HIV: Human Immune Virus Infection; SLE: Systemic lupus erythematosus

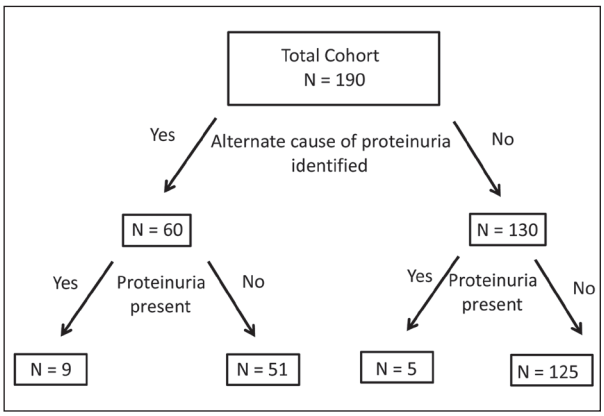

Fig. 1. Flowchart of cohort with and without proteinuria

lupus erythematosus, congestive heart failure, and glomerulonephritis) and 5/190 patients (2.5%) had proteinuria without any obvious risk factor other than sarcoidosis (Table 3). Proteinuria in these 5 patients was mild to moderate in amount (Mean 0.54, range 0.33-0.81 mg/mg). In these 130 patients without a risk factor for proteinuria, patients with proteinuria had a significantly lower mean eGFR than non-proteinuria (52.2 vs 80.9 mL/min/1.73 m^2, P<0.01). A higher prevalence of hypertension and chronic kidney disease was noted among patients with proteinuria as compared to non-proteinuria. Fifty percent 7/14 patients with proteinuria had CKD, out of which 2 had biopsy proven renal sarcoidosis and other 2 had nephrolithiasis, that was thought to be secondary to vitamin D dysregulation from sarcoidosis. Patients with proteinuria were more commonly on dihydropyridine and less commonly on ACE inhibitors.

We examined the effect of anti-sarcoidosis treatment on proteinuria. Using 2×2 contingency table with Fischer exact test, there was no significant difference in the use of prednisone between sarcoidosis patients with or without proteinuria (P=0.58) (Data not shown here).

Table 2. Comparison of cohort with proteinuria (>0.3g/dl) and non-proteinuria

Risk factors	Proteinuria (N=14)	Non-proteinuria (N=176)	P Value
Age	56.2 (26-80)	51.6 (25-81)	0.32
Mean dose of prednisone (mg)	3.9	5.1	0.70
Sex, N (%)			1.0
Male	2 (33%)	62 (35.2%)	
Female	4 (67%)	114 (64.8%)	
Race, N (%)			
White	4 (67%)	144 (82.2%)	
Black	2 (33%)	27 (15.4%)	1.0
Other	0	4 (2.4%)	
Chronic kidney disease*	8 (57.1%)	12 (6.8%)	<0.01
Hypertension	10 (71.4%)	61 (34.6%)	0.028
Risk factors			
Diabetes	4 (28.5%)	26 (14.7%)	
Hepatitis B	1 (7.1%)	1 (0.6%)	
Hepatitis C	0 (0%)	1 (0.6%)	
Human Immune Virus	1 (7.1%)	0 (0%)	
SLE	1 (7.1%)	1 (0.6%)	
Congestive heart failure	1 (7.1%)	4 (2.2%)	
Pregnancy	0 (0%)	0 (0%)	
Glomerulonephritis	0 (0%)	0 (0%)	
Cohort with atleast one risk factor	8 (57.1%)	52 (29.5%)	0.06
Medications affecting proteinuria			
NSAID	3 (21.4%)	26 (14.2%)	
ACE/ARB	4 (28.5%)	41 (23.2%)	
CCB- Dihydropyridine	8 (57.1%)	14 (8%)	
CCB-Non Dihydropyridine	1 (7.1%)	4 (2.2%)	
Cohort taking atleast one medication	9 (64.3%)	49 (27.8%)	0.01
Anti-sarcoidosis treatment			
Prednisone	4 (28.5%)	41 (23.2%)	
Methotrexate	0 (0%)	8 (4.5%)	
Lefluonamide	1 (7.1%)	1 (0.6%)	
Hydroxychloroquine	0 (0%)	7 (4%)	
Chloroquine	0 (0%)	0 (0%)	
Infliximab	0 (0%)	7 (4%)	
Adalimumab	0 (0%)	0 (0%)	
Azathioprine	1 (7.1%)	3 (1.7%)	
Mycophenolate	0 (0%)	0 (0%)	
Cohort taking atleast one anti-sarcoidosis medication	4 (28.4%)	63 (35.7)	0.78

*: Evidence of kidney damage (pathological, urine abnormality, imaging or blood test) or GFR < 60 NSAID: Non-steroidal anti-inflammatory drug; ACE/ARB= Angiotensin-converting enzyme/Angiotensin II receptor blocker; CCB: Calcium channel blocker, SLE: Systemic Lupus Erythematosus

Discussion

This study demonstrates that proteinuria is uncommon in sarcoidosis. More than half of sarcoidosis patients in our cohort with proteinuria had potential alternative causes of proteinuria. Only 5/190 (2.5%) demonstrated proteinuria without being at risk for an alternative cause of proteinuria other than sarcoidosis. Importantly, the proteinuria in this subgroup was mild. Therefore, proteinuria in sarcoidosis patients should not be assumed to be the result of sarcoidosis itself and alternative causes of proteinuria must be carefully considered. Identifying the cause of proteinuria is clinically important, as proteinuria is a strong, independent predictor of increased risk all-cause mortality and cardiovascular mortality in patients (3,4,6,7). Even though the degree of proteinuria was mild in our cohort, those with pro-

Table 3. Comparison of cohort with proteinuria (>0.3 g/dl) and non-proteinuria without alternative causes of proteinuria*

Demographic/Clinical Characteristic	Proteinuria (N=5)	Non –proteinuria (N=125)	P value
Age	62.8 (49-80)	51.6 (25-81)	0.20
Mean dose of prednisone (mg)	0	4.7	0.30
eGFR (mL/min/1.73 m^2)	52.2 (45.7-80)	80.9 (25.7-151.4)	<0.01
Sex, N (%)			
Male	1 (20%)	47 (38%)	1.00
Female	4 (80%)	77 (62%)	
Race, N (%)			
White	3 (60%)	102 (83%)	
Black	2 (40%)	17 (13%)	0.99
Other	0 (0%)	4 (3%)	
Chronic kidney disease†	3 (60%)	4 (3.2%)	<0.01
Hypertension	3 (60%)	35 (28.2%)	0.30
Medications affecting proteinuria			
ACE/ARB	0 (0%)	24 (19%)	
Calcium Channel Blocker	3 (60%)	7 (6%)	
Dihydropyridine	0 (0%)	3 (2%)	
Non dihydropyridine	3 (60%)	29 (23%)	
Cohort taking atleast one medication			0.16
Anti-sarcoidosis medications			
Prednisone	0 (0%)	27 (22%)	
Methotrexate	0 (0%)	5 (4%)	
Lefluonamide	0 (0%)	1 (1%)	
Hydroxychloroquine	0 (0%)	5 (4%)	
Chloroquine	0 (0%)	0 (0%)	
Infliximab	0 (0%)	5 (4%)	
Adalimumab	0 (0%)	0 (0%)	
Azathioprine	0 (0%)	3 (2%)	
Mycophenolate	0 (0%)	0 (0%)	
Cohort taking atleast one anti-sarcoidosis medication	0 (0%)	35 (28%)	0.38

*: Diabetes, Systemic lupus erythematosus, HIV, Hepatitis B, Hepatitis C, Glomerulonephritis, Congestive heart failure, Pregnancy, non-steroidal anti-inflammatory use.
eGFR: Estimated glomerular filtration rate; ACE/ARB= Angiotensin-converting enzyme/Angiotensin II receptor blocker
†: Evidence of kidney damage (pathological, urine abnormality, imaging or blood test) or GFR < 60 mL/min/1.73mm^2 for ≤ 3 months, with or without kidney damage

Table 4. Summary of published studies describing proteinuria in sarcoidosis

Author (Ref)	N	Population	Prevalence of proteinuria	Degree of proteinuria
Mahevas (13)	47	renal sarcoidosis	31/47 (66%)	Mild (median, 0.7 g/24 h; range, 0-2.7 g/24 h)
Berliner (12)	94	renal sarcoidosis	18/94(19%)	Mild, Majority <1g
Pasquet (14)	11	GIN in sarcoidosis	9/11 (82%)	Mild, (Mean 0.84g/24 h; range 0-2g/24 h)
Chopra	190	Consecutive sarcoid cases	5/191 (2.6%)	Mild, (Mean 0.54, range 0.33-0.81 mg/mg)

teinuria had a statistically significantly lower eGFR, suggesting that this subgroup is at risk for potential future renal complications.

Previous estimates of proteinuria in sarcoidosis patients have involved case reports, small case series, or highly selected cohorts. The prevalence of proteinuria was found in 66% of French sarcoidosis patients with histologically proven renal sarcoidosis (13). Berliner and colleagues (12) summarized 94 cases of sarcoid granulomatous interstitial nephritis documented in the literature, and found that 19% (18/94) had proteinuria with the vast majority of patients having

proteinuria of 1 g/d or less. In these reports, however, the method used to determine proteinuria was not specified or consistent. These reports did not examine consecutive cases; therefore, these results do not reflect the frequency or severity of proteinuria in an unselected cohort of sarcoidosis patients. In addition, these reports did not address the alternative causes of proteinuria. Finally, patients in those reports had an advanced degree of chronic kidney disease. Unlike the above-cited reports (12,13), we examined consecutive sarcoidosis patients, investigated the alternative causes of proteinuria and used a standard test for the evaluation of proteinuria. We similarly found that the degree of proteinuria was mild. Of the patients in our cohort with proteinuria, 4/14 (29%) had either renal sarcoidosis or nephrolithiasis related to vitamin D dysregulation from sarcoidosis. This suggests that the frequency of proteinuria in sarcoidosis may be much higher than that found in our consecutive patient cohort and approach the frequency in the aforementioned reports of renal sarcoidosis cohorts.

The prevalence of chronic kidney disease and hypertension was higher in sarcoidosis patients with proteinuria as compared to the non-proteinuria cohort. It is conceivable that hypertension might have resulted in mild degree of proteinuria in this group of patients. Compared to sarcoidosis patients without proteinuria, proteinuria patients were prescribed dihydropyridine calcium channel blockers (that may increase proteinuria) more frequently and used ACE inhibitors less commonly; the differences in the use of these anti-hypertensives may have accounted for a portion of the proteinuria cases (19,20).

Our study had several limitations. First, our sample size was relatively small, and very few patients had proteinuria after excluding those with alternative causes of proteinuria, that may have limited our ability to identify risk factors and the effect of anti-sarcoidosis treatment on proteinuria. Second, our cohort was heterogeneous in terms of the point in their clinical course when the spot urine was collected. Some patients had a diagnosis of sarcoidosis recently established, whereas others had carried the diagnosis for many years. Many patients in our cohort did not have a spot urine collected while having evidence of active disease while they were not receiving anti-sarcoidosis therapy. Future studies should address these limitations to accurately assess the presence of proteinuria in sarcoidosis.

In summary, our study revealed that proteinuria is uncommon in sarcoid patients. More than half of the sarcoidosis patients with proteinuria had a known risk factor for proteinuria other than sarcoidosis. Therefore, it should not be assumed that sarcoidosis is the cause without further investigations into the source of proteinuria. When proteinuria is present in sarcoidosis, it is usually mild. Despite the fact that proteinuria is not common in sarcoidosis, the consequences of proteinuria suggest that it should be screened for in all sarcoidosis patients.

Conflicts of Interest:
MAJ: consultant for Janssen, Celgene, Questcor, Mistubishi-Tanabe, Novartis. AA: No conflict of interest relevant to the project.

Contribution of authors individually:
MAJ is the guarantor of the paper, and takes responsibility for the integrity of the work as a whole, from inception to published article. All authors were involved in the study design. PB, HC, RZ performed the data collection and data entry. All authors contributed to the writing of the manuscript.

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