

Proteinuria in brucellosis: Is it related to kidney involvement or fever?

Proteinuria in brucellosis

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Abstract

Aim: Brucellosis is a zoonotic disease caused by *Brucella* species. *Brucella* can invade directly the kidney and cause tubule-interstitial injury, abscesses, and granulomatous formation.

In this study, we aim to assess the factors that might have an impact on proteinuria development in brucellosis.

Material and Methods: This is a prospective self-control study. The individuals who were diagnosed with *Brucella* infection between March 2019 and March 2021 were enrolled in the study. Clinical and laboratory features of the participants were noted.

The urine protein creatinine ratio (UPro/UCre) that estimates the 24-hour protein excretion in grams per day was detected before and after the 45-day treatment. Urinary cultures were performed in all patients if the patients had pyuria.

Results: Eighty-seven patients were enrolled in the study. The mean age was 33±18 years. Fifty-two of the patients were male (59.8%). Seven of the patients (8%) had urinary system symptoms (8%). None of the urinary cultures were found to be positive for any microorganism.

UPro/UCre was 407±328 before treatment and 251±155 after treatment ($p=0.003$). When correlation analysis was made, proteinuria before treatment was found to be correlated with *Brucella* titer ($r=0.273$, $p=0.03$) and body temperature ($r=0.387$; $p=0.04$).

Discussion: *Brucella* is a common zoonotic infection that may present with proteinuria in addition to its classic symptoms. The disappearance of proteinuria with antibiotic treatment and the correlation of proteinuria with fever suggest that fever is the leading cause.

Keywords

Brucellosis, Kidney Involvement, Proteinuria

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This study was approved by the Ethics Committee of Van Training and Research Hospital (Date: 2023-08-30, No: 2023/1805)

Introduction

Following the first report of Bruce in 1989, a wide range of kidney involvement due to Brucella infections has been described [1]. Brucella can invade directly into the kidney and cause tubulointerstitial injury, abscesses, and granulomatous changes. Additionally, immune complex disease, vasculitis, IgA nephropathy, and drug adverse reactions involve the other renal outcomes of Brucella [2, 3].

Brucella can be isolated from the patient’s urine; however, renal involvement is not common [4-6]. It has been argued that similar mechanisms of post-infectious diseases may have a key role in the development of renal disease in Brucella, however, the exact pathways of the association are unknown [3, 7]. The most common presentation of renal manifestation in Brucella is proteinuria that does not exceed 2+ on the dipstick and usually resolves when the infection abates.

Data on renal involvement of Brucella depends on the small sample-sized observational studies and case series. In this study, we aim to assess the factors that might have an impact on proteinuria development.

Material and Methods

This is a prospective self-control study. The individuals who were diagnosed with Brucella infection in the infectious diseases and internal medicine outpatient polyclinics between January 2016 and January 2018 were enrolled in the study. Clinical and laboratory features of the participants were noted.

Exclusion criteria: Individuals with reduced ejection fraction heart failures, long-standing diabetes mellitus, and drug-induced nephrotoxicity were excluded.

Measurements: All the patients had biochemical parameters, including renal and liver function tests, CRP, Hb levels, and brucella titers at the beginning of the treatment. If necessary, positive serum samples were examined by serial dilution from 1/40 to 1/10,240. Brucella standard tube agglutination tests were performed. Blood and urine cultures for brucellosis were also obtained. The median value for body temperature (37.5 centigrade degrees) was used as the cutoff point. According to this point, low and high fever groups have been formed.

Proteinuria assessment: Urinary tests of proteinuria were first made by dipstick test and then the spot protein/creatinine ratio was calculated. The urine protein concentration in a spot sample was measured in mg/dL, divided by the urine creatinine concentration, also measured in mg/dL, yielding a number that estimates the 24-hour protein excretion in grams per day. Urinary cultures were performed in all patients if the patients had pyuria.

Differential Diagnosis: Urinary system ultrasonography was performed to exclude causes of renal disease other than Brucella.

Treatment protocols: Patients with acute brucellosis were administered doxycycline and rifampin treatment for 45 days. When rifampin could not be used, ciprofloxacin was given.

Statistical Analysis

Statistical Package for the Social Science (SPSS) for Windows version 20 was used for data analysis. Continuous variables were expressed as mean ± SD, and the categorical variables were expressed as percentages and basic arithmetical means.

A pairwise comparison test was used to compare pre- and post-treatment data. The Kolmogorov–Smirnov test was used for the normality assumption of continuous variables. The T-test was used for normal distribution, and the Mann-Whitney U test was used for abnormal distribution. Dual comparison of discrete variables was performed by the Chi-square test. P<0.05 was considered statistically significant. Pearson’s correlation analysis was utilized for the correlation between proteinuria and body temperature, and Brucella agglutination titers.

Ethical Approval

This study was approved by the Ethics Committee of Van Training and Research Hospital (Date: 2023-08-30, No: 2023/1805). Written informed consent was obtained from all patients before enrollment.

Results

Eighty-seven patients were enrolled in the study. The mean age was 33±18 years. Fifty-two of the patients were male (59.8%). Two of the patients had diabetes mellitus, 4 of the patients had hypertension. The mean systolic blood pressure was 115±12 mmHg, mean diastolic blood pressure was 78±10 mmHg. The mean urea was 29±10, and the mean creatinine was 0.73±0.22.

Table 1. Demographic and clinical findings of patients

Parameter	Patients (n=87)
Age (years)	33±18(15-51)
Gender (male, n, %)	52 (59.8%)
Comorbidities	
Diabetes (n, %)	2 (2.3%)
Hypertension (n, %)	4 (4.6%)
SBP (mmHg)	115±12
DBP (mmHg)	78±10
Hemoglobin (g/dL)	13.6±1.8
Urea (mg/dl)	29±10
Creatinin (mg/dL)	0.73±0.22
AST (mg/dl)	45±15
ALT (mg/dl)	40±29
WBC	7.32±2.77
CRP (mg/L)	30.8±9.9
ESR	42±12
UPro/UCre	407±328
Abbreviations: WBC: White blood cell count, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, Upro: urinary protein, UCre: urinary creatinine	

Table 2. Clinical parameters before and after treatment

Parameter	Before N=87	After N=87	P
Hemoglobin (g/dL)	13.6±1.8	14.1±2.1	0.003
Urea (mg/dl)	29±10	26±7	0.13
creatinine (mg/dL)	0.73±0.22	0.75±0.19	0.53
AST (mg/dl)	45±15	23±9	0.01
ALT (mg/dl)	40±29	22±15	0.01
WBC	7.32±2.77	6.65±1.7	0.54
CRP (mg/L)	30.8±9.9	26.4±2.18	0.00
ESR	42±12	17±8	
UPro/UCre	407±328	251±155	0.003
Abbreviations: Abbreviations: WBC: White blood cell count, ESR: erythrocyte sedimentation rate, CRP:C-reactive protein, Upro: urinary protein, UCre: urinary creatinine			

Table 3. Correlation between proteinuria and biochemical parameters

Variables	r	P value
Brucella titer	0.273	0.03
Body temperature	0.387	0.04

The mean CRP was 30.8±9.9, the mean sedimentation was 42±12. UPro/UCre was 407±328. The mean body temperature was 37.5±0.4 (36.5-38.5) (Table 1). When the patients were grouped according to the presence of fever, proteinuria was significantly higher in patients with body temperature higher than 37.5 (144±220 vs. 300±170; p<0.05). Parameters before and after treatment are shown in Table 2. Hemoglobin was statistically significantly higher after treatment (13.6±1.8 vs. 14.1±2.1; p<0.05). AST was 45±15 before treatment and 23±9 after treatment (p<0.05). ALT, CRP and ESR decreased after treatment (40±29 vs 22±15; p=0.01, 30.8 ±9.9 vs 26.4±2.18; p=0.00, 42±12 vs 17±8; p=0.017). UPro/UCre was 407±328 before treatment and 251±155 after treatment (p=0.003). When correlation analysis was made, proteinuria before treatment was found to be correlated with brucella titer (r=0.273, p=0.03) and body temperature (r=0.387; p=0.04)

Discussion

All of our patients had a history of consuming fresh cheese prepared from unpasteurized or un-boiled milk, and some patients had a history of livestock [8,9]. Most of the patients did not have lower urinary tract symptoms. Almost all of these patients presented with typical brucellosis symptoms such as fever, sweating, headache, and fatigue. Brucellosis has been reported to cause interstitial nephritis, pyelonephritis, and IgA nephropathy [10-12]. It may also cause classified granulomas like those seen in renal tuberculosis [11, 12]. Renal involvement in brucellosis occurs in three ways [4]. The first is transient acute interstitial nephritis or acute pyelonephritis. It usually occurs during acute infection. Clinical manifestations include severe proteinuria, hematuria, pyuria, pain in the back or over the bladder, and dysuria [4]. The second group is a chronic process similar to renal tuberculosis or chronic nonspecific pyelonephritis [5, 8, 13]. The third group is kidney disease associated with brucella endocarditis [2, 9, 10]. Another type of kidney involvement is IgA nephropathy [6, 7]. None of our patients had nephrotic proteinuria, growth in urine culture, or endocarditis. Also, patients with higher blood temperatures have increased proteinuria levels. Proteinuria and nephrotic syndrome associated with bacterial infections are more commonly seen in tuberculosis, syphilis, and leprosy patients [12, 14]. Mild proteinuria has been reported previously in brucellosis [12, 14]. Fever-related proteinuria is frequently seen in non-renal infectious diseases, but [12], the pathogenic mechanism is still unclear; previously, immunological mechanisms by which antigen-antibody complexes induced by infections are transiently deposited on the epithelial side of the glomerular membrane have been proposed [12]. Recently, hematological mechanisms have been suggested [14]. Proteinuria associated

with febrile illness is generally mild [12] and resolves with the resolution of the disease.

Conclusion

In conclusion, Brucella is a common zoonotic infection in our region and may present with proteinuria in addition to its classic symptoms. The disappearance of proteinuria with antibiotic treatment suggests that the leading cause is fever.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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