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Diagnostic Value Of Blood-Soluble Urokinase Plasminogen Activator Receptor Levels In Brucellosis

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ABSTRACT

Objective: Plasma suPAR levels indicate immune activation. This research aimed to determine whether there was a difference in serum suPAR levels between patients with brucellosis and the control group and to evaluate the diagnostic value of serum suPAR levels.
Methods: A total of 46 patients with brucellosis diagnosed clinically, serologically, and bacteriologically at our institution were included in the study: 21 acute, 15 subacute, and 10 chronic. Twenty-eight of the patients were male, and 18 were female. The control group included 35 healthy individuals (26 female and 9 male) with no prior history of brucellosis.
Results: Serum suPAR levels were significantly higher in the brucellosis group than in the control group. This difference was statistically significant ($p < 0.001$). When CRP and suPAR levels were compared, suPAR levels were significantly higher in patients with CRP values above the threshold value. This difference was statistically significant ($p = 0.04$). When serum suPAR levels were compared in patients with acute, subacute, and chronic brucellosis, no statistically significant difference was found, unlike between the patient and control groups ($p = 0.697$). Pre-treatment SUPAR levels were higher in patients under treatment and in those who completed treatment, and the difference was statistically significant ($p = 0.033$).
Conclusion: This research demonstrated that suPAR levels can be a diagnostic marker for brucellosis, but these values cannot be used to distinguish between acute, subacute, and chronic forms of the disease. Studies with larger patient populations are necessary to confirm the biological significance of the results.

Keywords: Brucellosis, Soluble Urokinase-Type Plasminogen Activator Receptor (suPAR), C-reactive Protein (CRP).

INTRODUCTION

Brucellosis is caused by a Gram-negative intracellular bacterium that can lead to clinical conditions such as endocarditis, arthritis, osteomyelitis, and meningitis in humans. It is one of the most common zoonoses worldwide. Brucellosis carries a high morbidity for both humans and animals. It is a significant public health problem in many developing countries. Due to the risk of chronicity and high morbidity, the development of effective vaccines and new diagnostic markers is necessary (1). The cellular immune system plays a crucial role in infections involving intracellular pathogens, such as brucellosis. T-cell subsets, cytokines, and cytokine-activated macrophages and lymphocytes play crucial roles in protective immunity against such intracellular pathogens (2).

In acute brucellosis, elevated inflammatory markers are observed. The most commonly used biochemical marker in clinical practice is C-reactive protein (CRP). Recently, the soluble urokinase-type plasminogen activator receptor (suPAR) has emerged as an interesting biomarker. Soluble urokinase-type plasminogen activator receptor is the soluble form of the urokinase-type plasminogen activator receptor and is primarily released from neutrophils, activated T lymphocytes, and macrophages. The urokinase-type plasminogen activator (uPA) system consists of a protease, the urokinase-type plasminogen activator receptor (uPAR), and inhibitors released by various cells (3).

Plasma suPAR levels indicate immune activation. Increased levels have been shown in tuberculosis, Human Immunodeficiency Virus (HIV), malaria, pneumococcal pneumonia, sepsis, Crimean-Congo Hemorrhagic Fever, and viral infections of the central nervous system. Therefore, it is an indicator that can be used to monitor the diagnosis and treatment of various infections (4). Within the scope of this research, we aimed to determine whether there was a difference in serum suPAR levels between patients with brucellosis and the control group and to evaluate the diagnostic value of serum suPAR levels.

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METHOD

A total of 46 patients with brucellosis diagnosed clinically, serologically, and bacteriologically at our institution were included in the study: 21 acute, 15 subacute, and 10 chronic. Twenty-eight of the patients were male, and 18 were female. The control group included 35 healthy individuals (26 female and 9 male) with no prior history of brucellosis. Serum samples from 46 patients with brucellosis and 35 healthy individuals were used in the study.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Our institution has granted ethics committee approval with protocol number 2012613, and informed consent has been obtained from all participants.

Diagnostic criteria for brucellosis were defined as the growth of Brucella species in blood cultures (BACTEC 9000, Becton-Dickinson, USA), accompanied by clinical findings, or a titer of 1/160 or higher using SAT or Coombs' SAT in a single serum sample. The suPARnostic ELISA kit (Virogates, Denmark) was used in this study. The suPARnostic ELISA test is a double monoclonal antibody sandwich ELISA method in which the sample and peroxidase-conjugated anti-suPAR are mixed and incubated together. Recombinant suPAR standards were calibrated against healthy human blood donor samples. Results were analyzed in ng/ml of suPAR detected by the kit.

Brucellosis was diagnosed based on clinical symptoms and signs consistent with the disease, as well as positive blood culture results and/or elevated Brucella antibody levels in serological tests. suPAR levels were measured using a sandwich enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's protocol. Valid results can be obtained by multiplying the values determined in serum samples by 1.25. In the assay, suPAR standards, curve control samples, and patient samples were mixed with peroxidase-conjugated anti-suPAR in a white microwell mixing plate. This solution was then transferred from the white microwell plate to optically clean anti-suPAR-coated microwells. During a 1-hour incubation period, a sandwich structure containing solid-phase antibody, suPAR, and peroxidase-conjugated antibodies was allowed to form. After a wash step to remove unbound material, the chromogenic substrate was added to the wells. The intensity of the blue color formed was expected to be parallel to the amount of suPAR in the sample. After a 20-minute incubation in the dark, sulfuric acid was added to stop the reaction. The absorbance at 450 nm was measured in a microtiter plate reader after the wells turned yellow. A calibration curve was prepared using suPAR standards. The concentration of suPAR in the patient sample was determined. Because serum samples were used in our study, the results were obtained by multiplying the determined values by the specified coefficient.

Statistical Analysis

Patient data collected within the scope of the study were analyzed using the IBM Statistical Package for the Social Sciences (SPSS) for Windows, version 26.0 (IBM Corp., Armonk, NY). Frequency and percentage for categorical data, and mean and standard deviation for continuous data, were provided as descriptive statistics. For comparisons between groups, the “Independent Sample T-test” was used for two groups, and the “Pearson Chi-Square Test” was used to compare categorical variables. For non-normally distributed data, the Mann-Whitney U test was used for two-group comparisons and the Kruskal Wallis test was used for more than two-group comparisons. The results were considered statistically significant when the p-value was less than 0.05.

RESULTS

A total of 46 patients were included in the study (18 females and 28 males). The median age of the patients was 43±15.71 (range 20 – 86) years. The control group included 35 individuals, 26 females and 9 males. The median age in the healthy control group was 36±8.41 (range 28 – 63) years. The age was higher in the brucellosis patient group than in the healthy controls. This difference was not statistically significant (p = 0.186) (Table 1).

Table 1. Comparison of age and gender of patient and control groups.

	N	%	N	%
	Patient Group		**Control Group**	
Female	18	39,1	26	74,3
Male	28	60,9	9	25,7
Total	46	100,00	35	100,00
Age (Mean±Standard Deviation)	43±15.71		36±8.41	

Twenty-one of our patients were diagnosed with acute brucellosis, 15 with subacute brucellosis, and 10 with chronic brucellosis. Symptoms lasting less than eight weeks were considered acute, those lasting between eight weeks and one year were considered subacute, and those lasting longer than one year were considered chronic (Table 2).

A possible source of infection was identified in 34.7% of the cases (n = 16). Raw milk products, especially fresh cheese, were consumed in 9 cases (19.56%). Six (13%) cases had a history of direct contact with animals. One case (2.17%) was a veterinarian. The source could not be identified in 65.21% (n = 30) of the cases. The most common complaint in our patients was fever (69.56%), followed by back pain (36.95%) and arthralgia (36.95%). The most common physical examination findings in our cases were fever (34.78%), followed by osteoarticular involvement (30.43%) and hepatomegaly (6.52%).

Table 2. Symptoms of brucellosis cases.

Symptoms	N	%
Fever	32	69,56
Lower back pain	20	36,95
Arthralgia	17	36,95
Weakness	15	32,60
Sweating	14	30,43
Headache	8	17,39
Myalgia	8	17,39
Loss of appetite	3	6,52
Vomiting	2	4,35
Nausea	2	4,35

When serum suPAR levels were evaluated in the patient and control groups, suPAR levels were significantly higher in the brucellosis group than in the control group. This difference was statistically significant ($p < 0.001$). When CRP and suPAR levels were compared, suPAR levels were significantly higher in patients with CRP values above the threshold value. This difference was statistically significant ($p = 0.04$). When serum suPAR levels were compared in patients with acute, subacute, and chronic brucellosis, no statistically significant difference was found, unlike between the patient and control groups ($p = 0.697$) (Table 3).

Pre-treatment SUPAR levels were higher in patients under treatment and in those who completed treatment, and the difference was statistically significant ($p = 0.033$). When suPAR levels were compared between patients with brucellosis and systemic involvement and those without, no significant difference was found ($p = 0.908$) (Table 3).

Brucella spp. was detected in cultures from 10 of 12 patients' blood samples and 2 of their cerebrospinal fluid samples. When suPAR levels were compared between patients with positive cultures and those without, no statistically significant difference was observed ($p = 0.0702$) (Table 3).

Brucella spp. was detected in cultures from 10 of 12 patients' blood samples and 2 of their cerebrospinal fluid samples. When suPAR levels were compared between patients with positive cultures and those without, no statistically significant difference was found ($p = 0.0702$) (Table 3).

Table 3. suPAR levels in patient and control groups

suPAR (ng/mL)	Patient Group	Control Group	P - Value	
Mean Values (min – max)	**7,5 (3,3-48,1)**	**3,1 (1,1- 9,9)**	**P** <0.001	
CRP and suPAR levels in patients with brucellosis				
Mean Values (min – max)	**6,5 (3,3-18)**	**8,8 (4,9- 48,1)**	**P = 0.04**	
suPAR levels in patients with acute, subacute and chronic brucellosis				
	Acute Cases	**Subacute Cases**	**Chronic Cases**	**P - Value**
Mean Values (min – max)	**6,8 (3,3- 48,1)**	**7,7 (3,5- 18)**	**8,8 (3,8- 19,6)**	**0.697**
suPAR levels before treatment, during treatment, and after treatment.				
	Cases before treatment	**Cases under treatment**	**Cases whose treatment has been completed**	**P - Value**
Mean Values (min – max)	**8,9 (4,3- 48,1)**	**6,2 (3,3- 18)**	**5,6 (3,8- 9,4)**	**0,033**
suPAR levels in patients with system involvement and patients without system involvement				
	System Involvement	**No System Involvement**	**P – value**	
Mean Values (min – max)	**7,6 (3,5- 14,6)**	**7,4 (3,3- 48,1)**	**P = 0.908**	
suPAR levels in patients with positive culture and in patients with no positive culture				
	Culture Growth	**No Culture Growth**	**P – value**	
Mean Values (min – max)	**9,5 (6,1- 48,1)**	**7,2 (3,3- 19,6)**	**P = 0.072**	

DISCUSSION

Brucellosis is one of the most common zoonotic diseases caused by the brucellosis bacteria, and cases often involve direct or indirect contact with animals. While the disease has been eradicated in developed countries through animal vaccination and pasteurization of milk and dairy products, it remains a significant health problem in underdeveloped and developing countries, including Turkey. Animal vaccination and milk pasteurization are the two most important ways to combat brucellosis (6).

In Turkey, brucellosis is an infectious disease with a high morbidity rate and low mortality. While the disease is more common in males in countries with a low incidence of brucellosis due to occupational risk, it is known that there is no gender difference in the prevalence in countries where it is endemic. In our study, males were more commonly affected (60.9%). The disease is seen in almost all age groups, but it affects young adults more frequently. The incidence is lower in children and the elderly. Studies have found the mean age to range from 27 to 43 (6). The mean age of the cases in our study was 43 years. Especially in endemic countries like ours, brucellosis affects the productive age group, leading to significant morbidity and economic losses.

In endemic countries, the primary mode of transmission is consumption of unpasteurized milk and dairy products, while inhalation is more prevalent in developed countries. Studies conducted in Turkey have reported a history of raw milk and dairy product consumption ranging from 21% to 80% (7). Additionally, 19.56% of our cases (n = 9) had consumed raw dairy products, especially fresh cheese. 15% (n = 7) of the cases had a history of direct contact with animals, including one who was a veterinarian with occupational exposure. The source could not be identified in 65.21% (n = 30) of the cases.

In our cases, the time between symptom onset and presentation to our outpatient clinic ranged from 1 week to 13 months. When evaluated by clinical form, 21 (25.9%) were acute, 15 (18.5%) were subacute, and 10 (12.3%) were chronic. Other studies have observed a shift in the rates of acute and subacute onset. Increasing awareness of the disease across all clinical branches also reduces the risk of progression to subacute forms. In our study, no statistically significant difference in serum suPAR levels

was observed among patients with acute, subacute, and chronic brucellosis. However, larger studies are needed to determine whether there is a correlation between the clinical forms of brucellosis and suPAR levels. Brucellosis is a systemic infectious disease that can affect many organs and tissues. Brucella infections do not have specific symptoms distinguishing them from other infections. They can present with very different clinical symptoms and signs and can be confused with many other diseases. In the reviewed articles, fever was found in 59-100% of patients, sweating in 41-91%, fatigue in 58-98%, muscle pain in 14-60%, joint pain in 40-84%, headache in 20-64%, weight loss in 10-53%, anorexia in 31-73%, rash in 3-15%, splenomegaly in 11-50%, hepatomegaly in 9-55%, peripheral arthritis in 5-30%, and lymphadenopathy in 3-28% (8 – 12). In our cases, the most common symptom was fever (69.56%). Low back pain (43.47%) and arthralgia (36.95%) were the second and third most common symptoms, respectively.

The most common complication of brucellosis is osteoarticular disease, and its prevalence has been reported at varying rates across studies. Suspicion and screening with sensitive radiological methods increases the likelihood of detecting this complication. In studies conducted in Turkey, osteoarticular complications have ranked first, with rates ranging from 14% to 68% (13, 14). In our study, osteoarticular involvement was also the most common complication.

Brucellosis is most easily diagnosed by a positive SAT test titer of 1/160 in the presence of clinical signs and symptoms. However, a definitive diagnosis of this disease can be made by culturing the agent. With semi- and fully automated blood culture systems introduced in recent years, these bacteria can be grown more quickly and at higher rates. Studies conducted in Turkey have reported bacterial growth rates of 6-73% (15, 16). In studies with low rates, it was noted that blood cultures were not performed for all patients and that patients had previously received antibiotic treatment. In our study, using Bactec 9000 (Becton, Dickinson, USA) automated blood culture systems, Brucella spp. was grown in blood cultures from 10 of 12 patients and in CSF cultures from 2. However, because blood cultures are not obtained from all patients presenting to our outpatient clinic, it is unknown whether bacteremia is present in patients with brucellosis. In our study, Brucella spp. No statistically significant difference in suPAR levels was found between patients with growth in culture and those without.

Antigen-specific T cell activation, CD4+ and CD8+ T cells, and humoral immune responses contribute to host immunity against Brucella infections. However, the primary protective immune response is cellular immunity. Two main types of reactions are involved in cellular immunity. T-cell-derived cytokines kill microorganisms, while CD8 cytolytic T lymphocytes lyse infected cells (17).

Cytokines, particularly IF-ɣ, neopterin, and IL-12, have been reported to be elevated in relapsed cases of brucellosis infection (18). Increased suPAR levels in various clinical conditions may be due to increased uPAR expression and degradation or an increase in the number of uPAR-expressing cells such as monocytes and macrophages. The most likely source of in vivo suPAR appears to be the degradation of uPAR by uPA or other proteases in monocytes and endothelial cells. suPAR has been reported as an indicator, particularly studied in adults, where serum levels are increased in various infectious and malignant diseases, and its effectiveness in determining treatment efficacy and disease prognosis. It is suggested that elevated plasma suPAR levels during infection reflect uPAR upregulation in neutrophils, monocytes, and vascular cells. It is an indicator of increased neutrophil and monocyte activity. With its return to normal levels after appropriate treatment, suPAR can be used as an indicator of treatment efficacy and prognosis.

Plasma suPAR levels have been investigated in infectious diseases such as tuberculosis, HIV infection, sepsis, and Crimean-Congo Hemorrhagic Fever, as well as in non-infectious diseases such as malignancies and dermatological diseases. Increased suPAR levels have been reported in systemic inflammatory response syndrome, bacteremia, and sepsis, and high levels are associated with a poor prognosis in critically ill patients. In this patient group, suPAR has predictive value similar to that of disease severity scores. The diagnostic significance of suPAR relative to other markers, such as CRP and procalcitonin (PCT), has not been fully defined. In a study conducted in a mixed population of septic

and non-septic critically ill patients, serum suPAR levels during intensive care admission were found to be higher than in healthy volunteers. In healthy volunteers, the mean serum suPAR level was 2.44 ng/mL, whereas in critically ill patients, it was 9.80 ng/mL. SuPAR levels were higher in septic patients than in nonseptic patients, with the highest levels observed in patients with decompensated liver disease. Mortality was higher in patients with elevated serum suPAR levels at admission to the intensive care unit. SuPAR has been shown to be an independent predictor of ICU and long-term mortality in critically ill patients (19).

Recently, numerous studies have investigated the diagnostic utility of suPAR in sepsis patients and its relationship with other markers. In a study examining the diagnostic value of suPAR, PCT, and CRP in 132 patients with systemic inflammatory response syndrome, suPAR levels were significantly higher in patients with positive blood cultures than in those without. As with PCT, suPAR levels distinguished bacteremic from non-bacteremic patients (20). In our study, no statistically significant difference in suPAR levels was observed between patients with Brucella spp. infection. growth in culture and in patients without culture growth.

In infectious diseases, classical markers such as fever, white blood cell count, and CRP are unreliable in predicting disease severity and mortality risk. PCT has advantages over these classical markers, but it is not ideal. Compared to commonly used markers, suPAR has even better prognostic value than PCT. PCT values were not examined in our cases. However, our study found a statistically significant correlation between CRP and suPAR levels in patients with brucellosis. However, because suPAR can be elevated in both infectious and non-infectious diseases, it was concluded that it is not a brucellosis-specific marker.

SuPAR has prognostic properties in cardiovascular diseases. Human carotid plaque and plasma suPAR levels are higher in patients with cardiac symptoms. Additionally, increased plaque suPAR levels have been found to correlate with the tendency of atherosclerotic plaque to rupture (21). In ST-segment elevation myocardial infarction, suPAR has been shown to be a stable plasma marker for all-cause mortality and recurrent myocardial infarction (22).

In a study of patients with inhalation burns requiring mechanical ventilation, suPAR levels in bronchoalveolar lavage fluid were measured for the first time. While pulmonary suPAR levels were higher in patients with inhalation burns than in mechanically ventilated patients without inhalation burns, no significant difference was found between serum suPAR levels. Pulmonary suPAR levels correlated with inflammation and coagulation, but not with fibrinolysis. Serum suPAR levels were predictive of mechanical ventilation duration and intensive care unit length of stay. Pulmonary suPAR levels were considered diagnostic for patients with inhalation burns, while serum suPAR levels were considered prognostic (23). The prognostic value of suPAR was not investigated in our study.

In our study, based on the hypothesis that suPAR serum levels may change in brucellosis when cellular immunity is active, we compared suPAR levels in brucellosis patients with those of a healthy control group. Serum suPAR levels were significantly higher in patients with brucellosis than in the control group. This prospective study, conducted to determine the utility of suPAR as a biomarker for the diagnosis of brucellosis, is the second in this group. In a study by Karsen et al. (24), pre- and post-treatment plasma suPAR levels in patients with acute brucellosis were found to be statistically significantly higher than in the control group, similar to our study.

In a study by Eugen-Olsen et al. (25), serum suPAR levels were higher in patients with active tuberculosis (TB) than in TB-negative patients. Following treatment, suPAR levels decreased to levels observed in TB-negative patients. SuPAR levels are increased in TB patients and have been shown to be associated with mortality. A study from Turkey reported that plasma suPAR levels in patients with Crimean-Congo Hemorrhagic Fever, a tick-borne zoonotic viral infection, are a valuable biological indicator for diagnosis and predicting mortality (26). In our study, pre- and post-treatment plasma suPAR levels in brucellosis patients were significantly higher than those in the control group.

Previous studies have shown that suPAR levels, a component of the uPA system, are elevated in malignant, inflammatory, and infectious diseases and are a good indicator for assessing disease course and prognosis, as well as treatment efficacy. We believe that suPAR levels can serve as an important marker for diagnosing and monitoring brucellosis cases. However, suPAR levels are insufficient to distinguish between acute, subacute, and chronic forms of brucellosis. However, controlled clinical studies are needed on a larger number of cases and in patients with acute, subacute, and chronic brucellosis. As a result, thousands of people contract the disease each year, causing physical disability and loss of labor in humans, as well as morbidity, mortality, and economic loss in both humans and animals. Studies in our country have reported that infections account for 34-64% of the etiologies of fever of unknown origin, collagenous diseases for 4-23%, neoplasms for 11-26%, and other causes for 2-16% (27). In some series in our country, brucellosis is the second most common infectious disease after tuberculosis. Infectious diseases are common in our country, and before initiating any treatment, diseases with nonspecific signs and symptoms, such as brucellosis, should always be considered in the differential diagnosis of fever of unknown origin.

CONCLUSION

In conclusion, our study demonstrated that suPAR levels can serve as a diagnostic marker for brucellosis, but these values cannot be used to distinguish between acute, subacute, and chronic forms of the disease. Studies with larger patient populations are necessary to confirm the biological significance of the results. Furthermore, there is a need to assess changes in these mediators in response to treatment.

DESCRIPTIONS

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AI Statement: The authors used AI and AI-assisted Technologies (Grammarly and MS Word Editor) in the writing process. These technologies improved the readability and language of the work but did not replace key authoring tasks such as producing scientific or medical insights, drawing scientific conclusions, or providing clinical recommendations. The authors are ultimately responsible and accountable for the contents of the whole work.

Consent for Publication: The original article is not under consideration by another publication, and its substance, tables, or figures have not been published previously and will only be published elsewhere.

Data Availability: The data supporting this study's findings are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Ethical Declaration: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Our institution has granted ethics committee approval. As this was retrospective research, no informed consent was obtained from participants.

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