



Research Article

Examination of NRF2, Heme Oxygenase, and neopterin levels in brucellosis

Nihayet Bayraktar¹, Busra Ozturk¹, Mehmet Celik², Mehmet Resat Ceylan², Mehmet Bayraktar³

¹Department of Medical Biochemistry, Harran University Faculty of Medicine, Sanliurfa, Türkiye

²Department of Infection Diseases, Harran University Faculty of Medicine, Sanliurfa, Türkiye

³Department of Medical Microbiology, Harran University Faculty of Medicine, Sanliurfa, Türkiye

Abstract

Objectives: *Brucella* species are highly infectious organisms that can gain access to the human body through various routes, including the gastrointestinal and respiratory tracts, conjunctiva, and eroded skin. In some cases, they may also enter the bloodstream directly, as in transfusion-related cases or via transplacental transmission. The aim of this study was to evaluate the potential role of serum anti-inflammatory and antioxidant factors such as nuclear factor erythropoietin-2 (NRF2), heme oxygenase (HO-1), and neopterin in brucellosis and to investigate their relationship with serologic anti-*Brucella* antibody findings.

Methods: A total of 90 patients with brucellosis and 30 healthy control individuals were included in the study. The patient group was divided into three subgroups according to antibody titers: 30 patients with a 1/160 titer, 30 patients with a 1/320 titer, and 30 patients with a 1/640 titer. Blood samples were collected and transferred into biochemistry tubes containing gel. The tubes were then centrifuged at 4000 rpm for 10 minutes to separate the serum. The separated serum samples were stored at -80°C. Serum levels of NRF2, HO-1, and neopterin were measured using the ELISA method.

Results: No significant differences in biomarker levels were observed between gender or age groups. However, biomarker levels varied significantly according to antibody titer. Healthy controls exhibited the lowest levels of NRF2, HO-1, and neopterin, whereas the 1/640 titer group exhibited the highest levels. NRF2, HO-1, and neopterin levels increased progressively with rising anti-*Brucella* antibody titers ($p < 0.01$).

Conclusion: NRF2, HO-1, and neopterin levels were positively correlated with antibody titers, suggesting that these biomarkers may play a role in the immune response to brucellosis. Further studies with larger patient groups are needed to better understand and confirm these findings.

Keywords: Brucellosis, heme oxygenase, neopterin, NRF2

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Brucellosis is a globally widespread infectious disease in both animals and humans and is considered a debilitating zoonotic disease. It can occur in men and women of all ages, most commonly in the 15–35 age group. The disease also has synonyms such as "Mediterranean fever" or "Malta fever" [1, 2]. Routes of infection include the gastrointestinal tract, respiratory tract, conjunctiva, and abraded skin [3]. When risk groups are examined, priority is given to those who earn their living from livestock farming, slaughterhouse workers, veterinarians, and veterinary research labo-

ratory workers [4, 5]. Nrf2 is a cellular sensor of oxidative and electrophilic stress. Nrf2 is a nuclear factor that controls the expression and coordinated induction of a group of genes encoding detoxifying enzymes, drug transporters, anti-apoptotic proteins, and proteasomes. Modulation of NRF2 protein and enzymes occurs in response to oxidative stress and infection. In the presence of inflammation or oxidative stress, NRF2 undergoes phosphorylation and nuclear translocation, which leads to the transcription of proteins and antioxidant enzymes [6].

Address for correspondence: Mehmet Bayraktar, MD. Department of Medical Microbiology, Harran University Faculty of Medicine, Sanliurfa, Türkiye

Phone: +90 507 634 35 99 **E-mail:** mrtmehmet@yahoo.com **ORCID:** 0000-0003-2306-6531

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When Nrf2 is activated in the nucleus, it stimulates and initiates the production of antioxidant enzymes such as catalase, glutathione, and superoxide dismutase. Antioxidant enzymes neutralize up to one million free radicals per second [7]. Nrf2 is activated to correct the body's oxidative stress state, ensure cell survival, and maintain the redox homeostasis of cells by regulating the induced expression of phase II detoxifying enzymes and antioxidant enzymes [8]. The Nrf2 protein is expressed in different tissues of the body (such as the liver, kidney, spleen, and heart). Phosphorylated Nrf2 forms a heterodimer with the Maf protein and is then associated with antioxidant response elements that activate HO-1 expression [9]. HO-1 catabolizes free heme into Fe^{2+} , carbon monoxide (CO), and biliverdin. Heme catabolism by HO-1 produces biliverdin, which can be converted to bilirubin by biliverdin reductase. Heme catabolism by HO-1 also produces CO, a gas transmitter that regulates cellular signaling [10]. The stress-sensitive HO-1 isoenzyme provides protection against programmed cell death. This cytoprotective effect inhibits the pathogenesis of various immune-mediated inflammatory diseases. HO-1 expression is often induced in response to oxidative stress [11]. Heme oxygenase is the rate-limiting enzyme in heme metabolism, and its function is essential to limit oxidative tissue damage in both acute and chronic hemolytic injuries [12]. It has implications in many diseases, particularly cancer, Alzheimer's disease, and infections [13].

Neopterin and its unoxidized form, 7,8-dihydroneopterin, are relatively sensitive inflammatory markers because they are produced at sites of inflammation. It is an antioxidant synthesized by monocytes/macrophages that is produced upon interferon-gamma stimulation. 7,8-dihydroneopterin rapidly scavenges superoxide and hypochlorite, products of the inflammatory response, to form highly fluorescent neopterin [14]. These factors maintain the dual balance of 7,8-dihydroneopterin and neopterin to measure inflammation and oxidative stress [15]. Neopterin is a frequently used clinical marker to indicate immune activation during inflammation in various

conditions and stresses [16]. We conducted this study to find out biochemical abnormalities of certain parameters (HO-1, NRF2, and neopterin) in patients with brucellosis and their correlation with *Brucella* Wright agglutination results.

Materials and Methods

This study consisted of brucellosis patients who applied to the Harran University Faculty of Medicine Infectious Diseases Polyclinic. This study was approved by the Harran University Faculty of Medicine Clinical Research Ethics Committee on 18.10.2021, in the 1st session, with decision number HRU/21.18.16. Our study was designed in accordance with the criteria specified in the Declaration of Helsinki. Accordingly, written informed consent was obtained from each subject. The patients were composed of a total of 120 individuals from four groups: 1/160 titer group, 1/320 titer group, 1/640 titer group, and healthy control group without brucellosis.

Preparation of samples: This study consisted of brucellosis patients who did not receive any antimicrobial therapy and presented to the Infectious Diseases Outpatient Clinic of Harran University Faculty of Medicine. A total of 90 patient groups were formed; 1/160 titer groups, 1/320 titer groups, and 1/640 titer groups were composed; 20 were female and 10 were male in each group. The mean age of the 1/160 titer group was (45.20 ± 18.24) years; the mean age of the 1/320 titer group was (40.17 ± 14.95) years; and the mean age of the 1/640 titer group was (42.80 ± 17.16) years; and the mean age of each group was similar. In this study, a healthy control group was recruited from Harran University staff. Thirty healthy individuals, 18 females and 12 males, with a mean age of 40.70 ± 13.91 years were included in the study. The study included 30 volunteers aged 40.70 ± 13.91 years without any disease history or pathology. They were collected from the staff of Harran University, and those with a BMI below 28 were selected (Fig. 1).

Blood samples were collected as patient and control samples. The collected blood was transferred to gel-containing

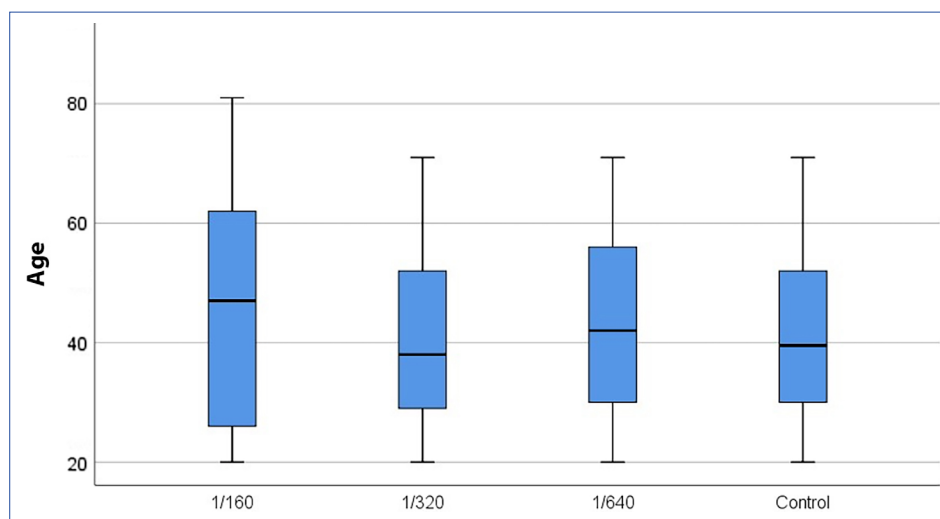


Figure 1. Age levels of the study groups (years; means \pm standard deviation).

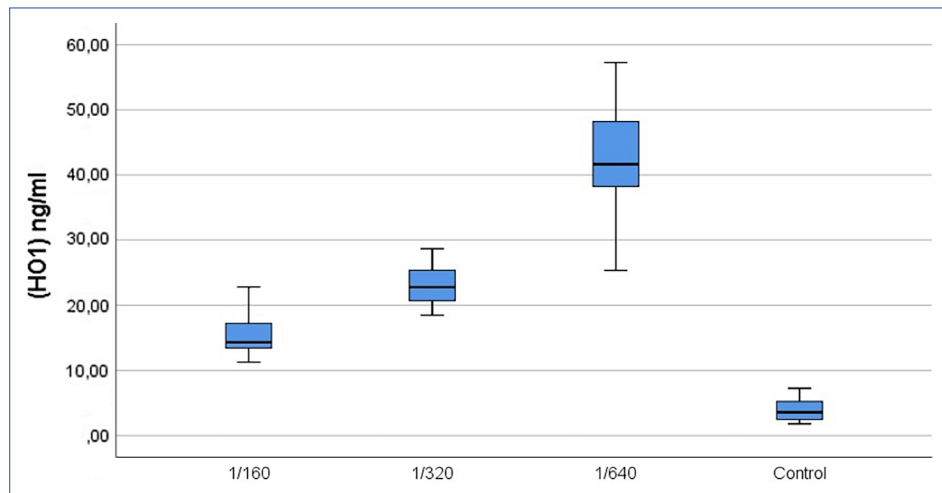


Figure 2. Heme Oxygenase-1 Levels in the study groups (means +/- standart deviation).

(biochemistry) tubes. Then, the blood was centrifuged at 4000 rpm for 15 minutes to separate the serum. The sera were stored in a deep freezer at -80°C for use. The separated sera were studied with the kit branded NRF2 ELISA Kit, Bioassay Technology Laboratory (BT Lab) (Catalog No: E3244Hu), Sensitivity: 0.11 ng/mL, CV (%) = SD/mean \times 100; Intra-assay: CV<8%; Inter-assay: CV<10%; Human Heme Oxygenase-1 ELISA Kit (HO-1), Bioassay Technology Laboratory (BT Lab) (Catalog No: E0932Hu), Sensitivity: 0.05 ng/mL; CV (%) = SD/mean \times 100; Intra-assay: CV<8%; Inter-assay: CV<10%; and Human Neopterin ELISA Kit, Bioassay Technology Laboratory (BT Lab) (Catalog No: E3155Hu), Sensitivity: 0.061 mmol/L; CV (%) = SD/mean \times 100; Intra-assay: CV<8%; Inter-assay: CV<10% (Fig. 2).

Statistical analysis

Statistical analyses were performed using the SPSS version 23.0 program. The conformity of variables to normal distribution was examined using histogram graphics and the Kolmogorov–Smirnov/Shapiro–Wilk test. Mean, standard deviation, and median values were used when presenting descriptive analyses. The Kruskal–Wallis test was used to evaluate variables that did not show a normal distribution (nonparametric) among more than two groups. The Bonferroni multiple comparison test was used to investigate the source of significant differences among the studied groups. Frequency and per-

centage values were used when presenting categorical variables, and the analysis of categorical variables was performed using the chi-square (exact) test. The Spearman correlation test was used to evaluate the relationships between quantitative variables. Cases in which the p-value was below 0.05 were considered statistically significant.

Results

The study included a total of 120 patients, with a mean age of 42.22 ± 16.08 years. Of the participants, 65% were female. The mean measurements were 21.10 ± 14.70 ng/mL for HMOX1, 64.32 ± 31.13 ng/mL for NRF2, and 10.73 ± 6.43 nmol/L for neopterin. The individuals were classified into four groups (1/160, 1/320, 1/640, and healthy control), each comprising 25% of the total participants (Table 1).

A total of 120 participants were included in the study. Participants were divided into four groups (1/160, 1/320, 1/640, and Healthy Control). Mean measurements for HMOX1, NRF2, and neopterin were shown for the participants (Table 1).

NRF2 levels were significantly lower in the control group compared to the other groups. Furthermore, levels in the 1/320 group were statistically significantly lower than those in the 1/160 and 1/640 groups, and neopterin levels in the 1/160 group showed a statistically significant difference compared to the 1/320 and 1/640 groups ($p < 0.05$; Table 1; Fig. 3).

Table 1. Comparison of clinical measurement values among study groups									
	1/160		1/320		1/640		Control		p
	Mean±SD	Median	Mean±SD	Median	Mean±SD	Median	Mean±SD	Median	
Age	45.20±18.24	47.00	40.17±14.95	38.00	42.80±17.16	42.00	40.70±13.91	39.50	0.706
HO-1 (ng/mL)	15.27±2.52	14.31 ^a	23.14±2.81	22.77 ^b	42.01±8.65	41.65 ^c	3.96±1.55	3.55 ^d	<0.001
NRF2 (ng/mL)	72.74±35.99	90.74 ^a	73.85±5.66	71.86 ^b	87.48±11.27	90.79 ^a	23.20±7.22	23.23 ^c	<0.001
Neopterin (nmol/L)	9.03±1.65	8.76 ^a	14.66±2.00	14.88 ^b	17.60±2.94	17.95 ^b	1.61±0.70	1.66 ^c	<0.001

^{a,b,c,d}: Kruskal Wallis Test, Chi-Square Test, Bonferroni Method. The study did not identify a significant correlation between group and gender. Furthermore, there were no significant age differences among the groups. (Fig.1). SD: Standard deviation.

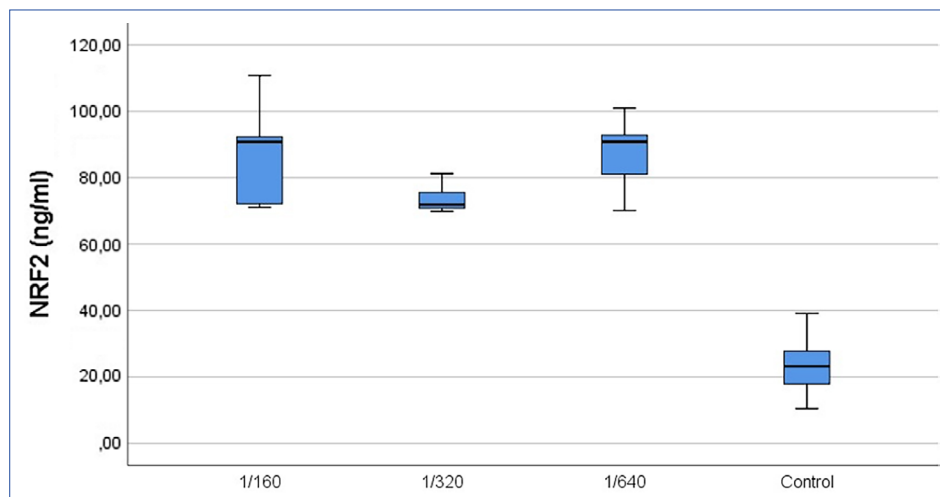


Figure 3. NRF2 levels in the study groups (means +/- standart deviation).

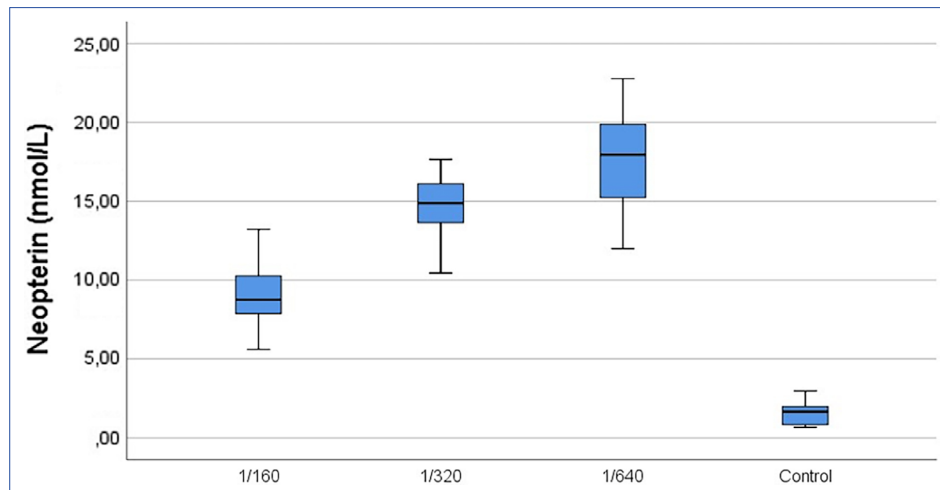


Figure 4. Neopterin Levels in the study groups (means +/- standart deviation).

Neopterin measurement levels were ranked from lowest to highest as follows: Control, 1/160, 1/320, and 1/640 (Fig 4; Table 2). Relationships between variables were examined within each group. As a result of the study, a moderate, negative, and significant correlation was found between HO-1 (ng/mL) and NRF2 (ng/mL) in the 1/160 titer group ($r=-0.407$; $p<0.05$). In addition, a low, positive, and significant correlation was found between HO-1 (ng/mL) and neopterin (nmol/L) measurements in the control group ($r=0.368$; $p<0.05$) (Table 2).

Discussion

The most important feature of *Brucella* is its ability to survive and multiply in both phagocytic and non-phagocytic cells [17]. While the findings of this study provide important information, some diagnostic limitations exist. The inability to confirm the diagnosis of brucellosis with PCR or culture, and the inadequacy of serological tests alone, reduced diagnostic certainty and limited the interpretability of the results. Activation of antioxidant response elements is primarily achieved through the modulation of proteins and enzymes that com-

bat inflammation and oxidative stress. NRF2 is typically degraded via the ubiquitin–proteasome pathway [18]. When the body is exposed to inflammation or oxidative stress, NRF2 is phosphorylated and transported to the nucleus, contributing to the body's antioxidant mechanisms and leading to the transcription of proteins and antioxidant enzymes. These compounds can be regulated to provide protection against oxidative stress [19].

The autonomic nervous system helps restore homeostasis through inflammation and oxidative stress, triggering synapses as a secondary effect. Ngo et al. [20] suggested that NRF2 is a well-known regulator of oxidative stress and that lovastatin (UEI) provides protection against acute viral myocarditis through NRF2 activation; NRF2 can be activated by immune and inflammatory processes. Although there is a lack of correlation between *Brucella* antibody titers and the clinical picture of brucellosis [21], to our knowledge, there is no clinical study in the literature that directly measures the relationship between NRF2/HO-1 and neopterin levels with serological titers (e.g., 1/160 and above) in brucellosis [21]. Significant

Table 2. Correlation of clinical measurements within the groups

(HMOX1) ng/mL	NRF2 (ng/mL)		Neopterin (nmol/L)
(HO-1) ng/mL	1.000	-0.407*	0.092
	.	0.026	0.640
NRF2 (ng/mL)	-0.311	1.000	-0.031
	0.108	.	0.875
Neopterin (nmol/L)	0.092	-0.031	1.000
	0.640	0.875	.
(HO-1) ng/mL	1.000	0.092	-0.027
	.	0.628	0.888
NRF2 (ng/mL)	0.092	1.000	0.192
	0.628	.	0.310
Neopterin (nmol/L)	-0.027	0.192	1.000
	0.888	0.310	.
(HO-1) ng/mL	1.000	-0.058	-0.126
	.	0.765	0.514
NRF2 (ng/mL)	-0.058	1.000	0.160
	0.765	.	0.408
Neopterin (nmol/L)	-0.126	0.160	1.000
	0.514	0.408	.
(HO-1) ng/mL	1.000	0.028	0.368*
	.	0.884	0.046
NRF2 (ng/mL)	0.028	1.000	0.003
	0.884	.	0.986
Neopterin (nmol/L)	0.368*	0.003	1.000
	0.046	0.986	.

changes were observed in NRF2, NO, and neopterin levels in brucellosis patients at different antibody titers (1/160, 1/320, and 1/640) ($p < 0.05$; Table 1; Fig. 3). NRF2/HO-1, on the other hand, is involved in the cellular oxidative stress response and the anti-inflammatory response of tissues. There is a clear relationship between increased NRF2 levels and an increased immune response [22]. Our study showed a positive correlation between increased immune response and increased NRF2 levels (Table 1). Activation of the NRF2 signaling pathway can prevent oxidation by reducing the production of free radicals and decreasing oxidative damage in the myocardium [23]. According to some research findings, NRF2 has been shown to reduce cell damage and oxidative stress and to exhibit an anti-inflammatory function that suppresses tumor formation [24].

Neopterin is a biochemical marker associated with cell-mediated immunity. Serum neopterin levels indicate the activation phase of the cellular immune system, which is important in the pathogenesis and progression of various diseases, and elevated neopterin levels have been detected before the onset of clinical symptoms [25]. Skogmar et al. [26] conducted a study on serum neopterin concentrations before, during, and after antituberculosis treatment in patients with tuberculosis. Michalak et al. [27] showed that urinary neopterin levels were significantly higher in patients with active tuberculosis compared to latently infected individuals. Chauvin et al. [28]

demonstrated that high neopterin levels were a strong independent predictor of cardiovascular events. Thomas et al. [29] measured neopterin levels in a small cohort of 20 influenza patients and found that 80% of the patients had levels above the upper limit of normal at symptom onset (within 48 hours). Furthermore, a rapid decrease in neopterin levels was observed during recovery between days 5 and 14, with levels returning to normal after day 14. In our study, neopterin levels showed a statistically significant difference between brucellosis patients (1/160, 1/320, and 1/640) and healthy controls ($p < 0.05$; Table 1; Fig. 4). These results suggest that neopterin, a biomarker of immune activation, has an anti-inflammatory effect and can provide insight into disease severity and the healing process as an indicator of immune response [30]. The studies mentioned above show that neopterin reduces oxidative stress in various diseases. Neopterin levels can therefore be used to assess disease activity and response to treatment.

HO-1 is considered a primary protein and cytoprotective mechanism involved in diseases caused by oxidative and inflammatory damage. It acts as a catalyst for reactions involving heme, pro-oxidants, and free radicals with an iron atom at the center and has been shown to have antitumor effects [31]. Due to its antioxidant and genome-protective activities, HO-1 may have protective effects against carcinogens and reduce the likelihood of tumor formation [32]. One study investigated the beneficial effects of reducing microglial HO-1 in aged mice exposed to an inflammatory challenge and identified reduced iron accumulation in the brain as a key mechanism. This finding suggests that HO-1 induction is beneficial due to its antioxidant and anti-inflammatory properties [33]. Another study evaluated the role of HMOX1 in *Brucella* infection and demonstrated that it induces HO-1 expression in macrophages. When HO-1 is deactivated or its activity is inhibited, the intracellular growth of *Brucella* is significantly reduced [34, 35]. In our study, statistically significant differences were observed in HO-1 levels in the serum of brucellosis patients at titers of 1/160, 1/320, and 1/640 compared with healthy controls ($p < 0.05$; Table 1). Based on the relationship between titers and antigen-antibody levels, higher heme oxygenase levels were found in the 1/640 titer group compared to the other groups. These results were thought to be related to oxidative and inflammatory factors. Ojeda et al. [11] showed that HO-1 activation is reduced in brucellosis patients and that enzyme levels are related to disease severity.

Limitations

The limitation of our study is that the diagnosis of brucellosis was made according to clinical and serological findings, and confirmatory culture positivity and PCR tests were not performed. However, further studies may be conducted in the future that could contribute to the diagnosis and treatment of the disease. Another limitation is the small number of patients. Increasing the number of patients and control groups to improve the reliability of the study could eliminate this limitation and yield more reliable data.

Conclusion

Antibody titers are one of the measures of the systemic humoral immune response to brucellosis. NRF2/HO-1 and neopterin levels increase with increasing antibody titers. These biomarkers are related to cellular oxidative stress and the anti-inflammatory responses of tissues. They indicate an immune response system that reduces oxidative stress and exhibits anti-inflammatory effects against brucellosis and may serve as potential biomarkers for clinical brucellosis outcomes instead of antibody titers.

Disclosures

Ethics Committee Approval: The study was approved by the Harran University Faculty of Medicine Clinical Ethics Committee (no: HRU/21.18.16, date: 18/10/2021).

Informed Consent: Informed consent was obtained from all participants.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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