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Investigation of serum ischemic-modified albumin, galectin-3, paraoxonase-1, and myeloperoxidase activity levels in patients with acute brucellosis

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ABSTRACT

Objectives: Infection remains current as an important discussion topic in the etiological factors of atherosclerosis. Ischemic-modified albumin (IMA), galectin-3 (gal-3), paraoxonase-1 (PON-1), and myeloperoxidase (MPO) are biomolecules that play an important role in the pathogenesis of atherosclerosis. Our aim is to investigate serum IMA, gal-3, PON-1, and MPO activity in acute brucellosis infection.

Materials and Methods: Forty patients with acute brucellosis and 40 healthy individuals were included in the study. Serum IMA, gal-3, PON-1, and MPO activity were analyzed by the ELISA method.

Results: In acute brucellosis infection, serum gal-3, IMA, and MPO activities were found to be significantly increased compared to the control group, and PON-1 activity was found to be significantly decreased compared to the control group ($p < 0.001$). There was a positive correlation between serum IMA, and MPO activity ($r = 0.707$ $p = 0.000$) and a negative correlation ($r = -0.943$, $p = 0.000$) between PON-1 activity. There was a positive correlation between serum gal-3 and MPO activity ($r = 0.683$, $p = 0.000$) and IMA level ($r = 0.927$, $p = 0.000$) and a negative correlation between PON-1 activity ($r = -0.951$, $p = 0.000$).

Conclusion, it was found that serum gal-3, IMA levels and MPO activity increased, while PON-1 activity decreased. These results showed that the oxidant-anti-oxidant balance is impaired in acute brucellosis infection. In addition, these results indicate that brucella infection may be increase the risk of atherosclerosis. Further studies are needed to support our findings.

KEYWORDS
IMA; galectin-3; PON-1; MPO; atherosclerosis; acute brucellosis

Introduction

Brucella infection is a zoonotic disease and continues to be a serious public health problem in many developing countries [1]. Brucella types are facultative intracellular bacteria. They can live and reproduce in macrophages. Therefore, they can produce chronic infections [2]. Bacteria pass into phagocytic cells such as polymorphonuclear neutrophils (PMNs) and macrophages and are killed by reactive oxygen and nitrogen species [3,4]. Reactive oxygen products (ROS) play an important role in the removal of phagocytosed bacteria. ROS produced as a result of metabolism causes protein oxidation. Therefore, lipid peroxidation and DNA damage occur [5]. Therefore, brucella infection activates macrophages and increases the production of cytokines, chemokines, free radicals, and nitric oxide [6].

In tissue ischemia, free radicals, and various diseases, the molecular structure of albumin changes and the binding ability of free metal ions such as cobalt, copper, and nickel to the N-terminal sequence of the amino group of albumin decreases. As a result, ischemia-modified albumin (IMA), the isoform of albumin, occurs [7,8]. IMA has been proposed as an early biomarker for diseases associated with ischemia and oxidative stress, including myocardial infarction, cerebrovascular diseases, diabetes mellitus, and renal failure [9–11]. Galectin-3 (Gal-3) is a member of B-galactosyl-binding proteins expressed in many tissues, such as epithelial cells, immune cells, endothelial cells, and sensory neurons. Gal-3 plays an important role in many biological functions such as fibrosis, cell growth, inflammation, transformation, differentiation, and host defense [12]. Paraoxonase-1 (PON-1) is an antioxidant enzyme associated with high-density lipoprotein (HDL) with paraoxonase, arylesterase, and dyazoxonase activities [13]. Myeloperoxidase (MPO), released during inflammation, is an oxidative enzyme found in phagocytes. MPO can cause protein and lipid modification, resulting in increased oxidation levels of these molecules. Therefore, it causes an increase in the level of oxidized LDL and atherosclerosis [14]. It has been found that antioxidants, which are the remnants of oxidative stress, are depleted in Brucella infection. Therefore, it has been stated that oxidative stress may result in brucella etiological factors [15]. There is a limited amount of research in the literature regarding the biomarkers in acute brucellosis infection. Therefore, our aim is to investigate the mechanism of these potential biomarkers in the pathophysiology of atherosclerosis in acute brucella infection.

Methods

Our study was carried out in Mardin Training and Research Hospital Clinical Microbiology and Infectious Diseases clinic with the approval of the ethics committee (Ethic approval

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no: 04.05.2021 and numbered 4-15) received by Mardin Artuklu University Scientific Research and Publication Ethics. Our study was evaluated by two experts. Forty patients diagnosed with acute brucella were included in our study. The diagnosis of acute brucella infection was made by the isolation of compatible bacteria from blood sample with titers ≥1:160 and/or serum agglutination test, together with clinical symptoms and signs, as determined by ELISA for the presence of specific IgM antibodies against brucella [2]. The control group was selected from healthy individuals. In addition, attention was paid to the fact that the control group had similar characteristics to the patient group in terms of age, gender and BMI. Autoimmune diseases, thyroid dysfunction, diabetes mellitus, metabolic diseases, cardiovascular diseases, pregnancy, kidney diseases, chronic diseases, alcohol, smoking, pulmonary diseases, hypertension, acute and chronic inflammation and drug use were determined as the exclusion criteria of our study.

Analysis of serum IMA, GAL-3, PON-1, and MPO activity levels

All participants in the study were informed before the study. Venous blood was taken from the patients diagnosed with acute brucella and the control group and taken into the biochemistry tube. It was then centrifuged at 3000 rpm for 10 min. The serum samples obtained were kept in a deep freezer at −80°C until the study day. Serum IMA, gal-3, PON-1, and MPO activity levels were measured with commercial enzyme-linked immunosorbent assay (ELISA) kits (BTLAB, Kit LTD, China). The absorbance was read at 450 nm by a BIOTEK (ELx800TM, USA) microplate reader.

Statistical analysis

Compliance of the data with normal distribution was checked with Kolmogorov – Smirnov and Shapiro- Wilk tests. The Student-T test was used for the normal distribution parameters, and the Mann Whitney-U test was used for the comparison of the paired groups for the parameters that were not normally distributed. In the comparison with the Kruskal–Wallis Test, two-fold comparisons were made with the Mann–Whitney -U test by making Bonferroni corrections to understand which group caused the statistical difference.

Results

Forty acute brucella patients and 40 healthy controls were included in our study. The mean age of those with acute brucellosis (19 females and 21 males) was 33,00 ± 7,78 years, while the mean age of the control group (20 females and 20 males) was 33,20 ± 7,90 years. There were no significant differences between the groups in age, gender, and body mass index ($p > 0.05$) (Table 1).

Table 1. The demographic values of the brucellosis group and control group.

		Control group	Patient group	
Gender	Female	20 (50,0%)	19 (47,5%)	
	Male	20 (50,0%)	21 (52,5%)	*p*
BMI (kg/m^2)		22,32 ± 1,54	22,21 ± 1,38	0,342
Age (Year)		33,20 ± 7,90	33,00 ± 7,78	0,962

Note: Data are expressed as mean ± SD (standart deviation), BMI: Body mass index.

Table 2. Serum IMA, Gal-3, PON-1, and MPO levels in the brucellosis group and control group.

Parameters	Control group	Patient group	95% confidence interval of the difference Lower -Upper	*p*
IMA (ng/ml)	149,16 ± 93,10	217,52 ± 150,40*	12,67–124,04	0,017
Gal-3 (pg/ml)	408,28 ± 159,74	711,56 ± 621,50*	101,28–505,27	0,005
PON-1 (ng/ml)	220,30 ± 146,37	141,25 ± 64,59 *	28,68–129,40	0,003
MPO (ng/ml)	22,62 ± 12,85	30,86 ± 15,02*	2,01–14,46	0,010

Notes: Data are expressed as mean ± SD (standart deviation), $p < 0.01$* the degree of significance of comparison between the patient and control group.
Abbrevations: IMA: Ischemic modified albumin:, gal-3: galectin-3, PON-1: paraoxonase-1, and MPO: myeloperoxidase.

The mean serum IMA levels in patients with acute brucellosis and healthy individuals were 217,52 ± 150,40 ng/ml, and 149,16 ± 93,10 ng/ml respectively. The mean serum gal-3 levels in patients with acute brucellosis and healthy individuals were 711,56 ± 621,50 ng/ml, and 408,28 ± 159,74 ng/ml respectively. The mean serum PON-1 levels in patients with acute brucellosis and healthy individuals were 141,25 ± 64,59 ng/ml, and 220,30 ± 146,37 ng/ml respectively. The mean serum MPO levels in patients with acute brucellosis and healthy individuals were 30,86 ± 15,02 ng/ml, and 22,62 ± 12,85 ng/ml respectively. The serum gal-3, MPO ($p < 0.01$), and IMA levels were found to be higher in patients with acute brucellosis compared to the control group. PON-1 levels were found to be lower in patients with acute brucellosis compared to the control group. This difference was found to be statistically significant compared (Table 2, Figure 1).

A negative ($r = -0.943$, $p = 0.000$) correlation was found between positive PON-1 activity between serum IMA and MPO activity ($r = 0.707$ $p = 0.000$). There was a positive correlation between serum gal-3 and MPO activity ($r = 0.683$ $p = 0.000$) and IMA level ($r = 0.927$ $p = 0.000$) and a negative correlation between PON-1 activity ($r = -0.951$ $p = 0.000$) Table 3.

A cut-off gal-3 of 348,41 predicted the difference between the acute brucellosis group and the control group, with 32,5% sensitivity and 97,5% specificity. (ROC area under the curve [AUC] of 0,56). A cut-off IMA of 348,41 predicted the difference between the acute brucellosis group and the control group, with 25% sensitivity and 97,5% specificity (ROC AUC of 0,61 95%). A cut-off PON-1 of 278,7 predicted the difference between the acute brucellosis group and the control group, with 27,5% sensitivity and 97,5% specificity (ROC AUC of 0,64). A cut-off MPO of 35,50 predicted the difference between the acute brucellosis group and the control group, with 47% sensitivity and 85% specificity (ROC AUC of 0,65 95%). Figure 2

Discussion

It has been reported that cardiac complications are rarely observed in brucella infection [16]. However, many case reports have been reported that brucella infection causes endocarditis [17]. There are statements in the literature that brucella infection may cause vascular complications and pose a risk for atherosclerosis. However, the mechanism of infection in the pathophysiology of atherosclerosis is not fully known. There are different opinions about whether

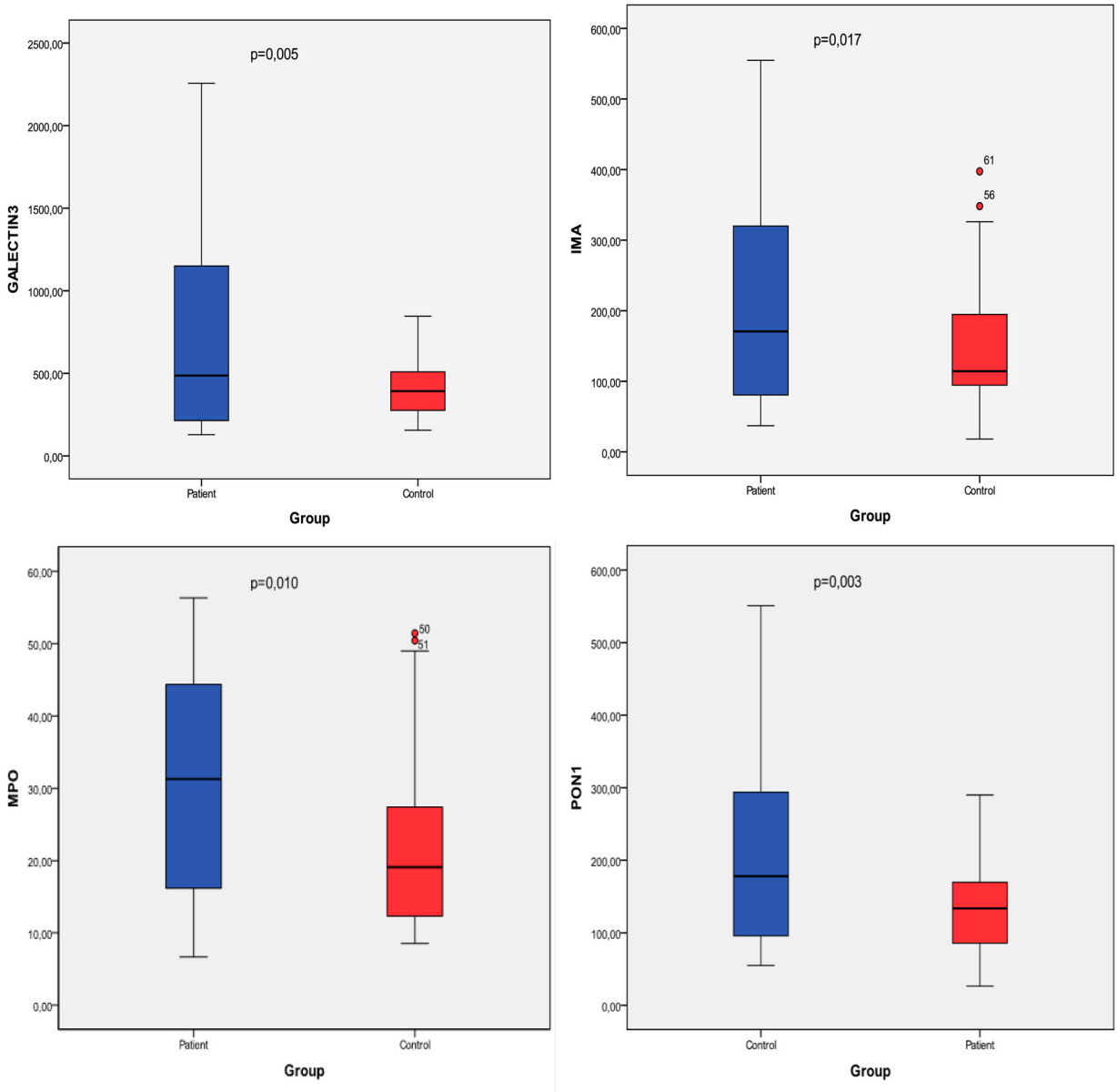

Figure 1. Serum Gal-3, IMA, MPO, and PON1 levels in the brucellosis group and control group.

infection causes vascular complications. For this reason, it has been suggested that the indirect effect of cytokines or toxins may cause an immune reaction to brucella antigen on the vascular walls, as well as direct endothelial damage and damage to the vascular endothelium [18,19]. Gürsoy et al. [20] stated that it can disrupt endothelial functions in patients with brucella infection without causing chronic symptoms. It has been reported that some microorganisms such as *Chlamydia pneumoniae* and *Human cytomegalovirus* can cause endothelial dysfunction by affecting the artery walls [21]. Cetin et al. [22] in their study on pediatric patients with brucella infection reported that there was more heart involvement than expected and that this could be more like subclinical heart involvement. We hypothesized the study

Table 3. The relationship between measuring parameters in patient group with Spearman correlation.

Parameters		BMI	Age	Gal-3	IMA	MPO	PON-1
BMI	r	1					
	p						
Age	r	0,012	1				
	p	0,941					
Gal-3	r	0,111	0,181	1			
	p	0,493	0,263				
IMA	r	0,155	0,235	**0,927****	1		
	p	0,339	0,144	**0,000**			
MPO	r	**0,322***	0,119	**0,683****	**0,707****	1	
	p	0,043	0,464	**0,000**	**0,000**		
PON-1	r	0,096	0,209	**−0,951****	**−0,943****	**−0,731****	1
	p	0,557	0,195	**0,000**	**0,000**	**0,000**	

Note: $p < 0.01$* *, $p < 0.05$*.
Abbrevations: BMI: Body mass index, IMA: Ischemic modified albümin:, gal-3: galectin-3, PON-1: paraoxonase-1, and MPO: myeloperoxidase.

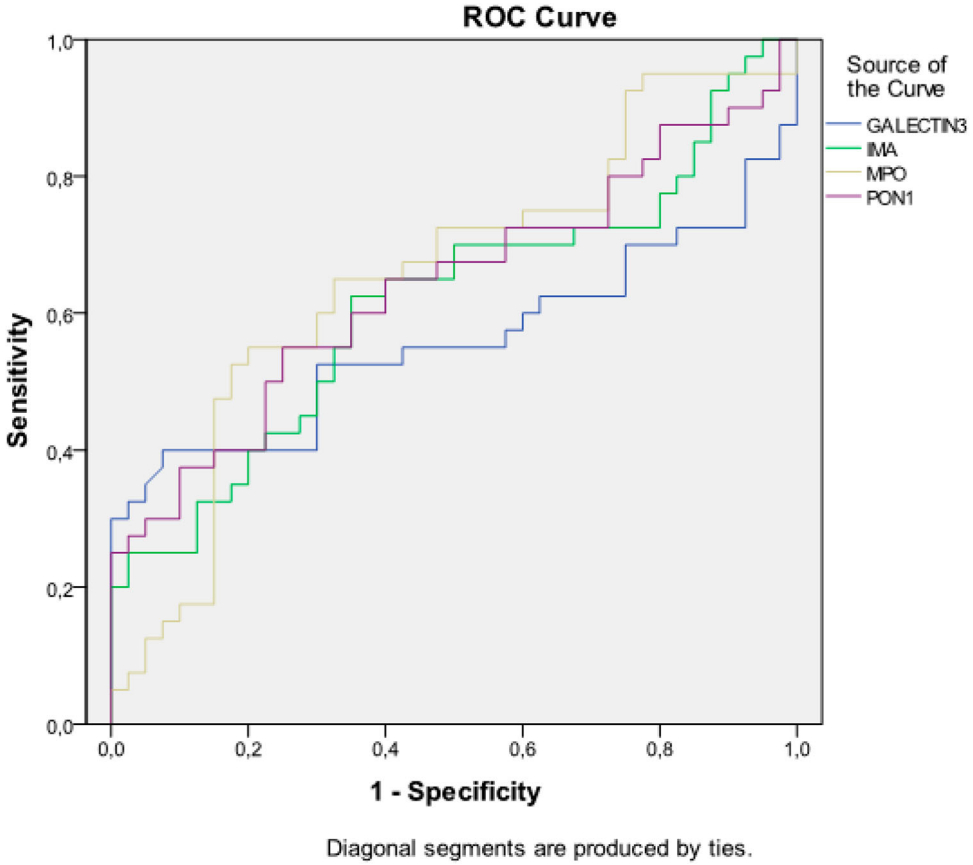

Figure 2. The ROC curve analysis of IMA, Gal-3, PON-1, and MPO for prediction between the frequently control group between in patients with brucellosis. Abbrevations: IMA: Ischemic modified albumin, gal-3: galectin-3, PON-1: paraoxonase-1, and MPO: myeloperoxidase.

to evaluate the role of IMA, gal-3, PON-1, and MPO biomarkers, which are used in the evaluation of the etiopathogenesis of atherosclerosis in patients with acute brucellosis infection, in the pathophysiology of the disease.

In our study, we found that serum IMA, gal-3, and MPO levels increased significantly compared to the control group, and PON-1 activity decreased significantly. A positive correlation was found between serum IMA and MPO activity, and a negative correlation was found between PON-1 activity. There was a positive correlation between serum gal-3 and MPO activity and IMA level and a negative correlation between PON-1 activity.

There have been many studies evaluating the relationship between IMA levels and different diseases. IMA is the product formed by the oxidation of albumin and it has been shown that there is a positive correlation between oxidative stress and IMA. IMA formation is mainly related to the oxidative stress response caused by ischemia-reperfusion injury cardiac and extra-cardiac events [23,24]. IMA, which is accepted as a biomarker in the pathophysiology of myocardial ischemia, has been reported to have early diagnostic value for myocardial ischemia [25]. In vivo studies, serum IMA level has been evaluated in the pathogenesis of different diseases such as multiple sclerosis, pre-eclampsia, acute appendicitis, and non-cardiogenic ischemic pneumonia [26–29]. Only one study was found investigating the role of IMA level in the etiopathogenesis of brucella infection. Aslan et al. found high serum IMA levels in patients with relapse brucellosis. It has been shown that IMA levels can be an indicator of oxidative stress [30]. In our study, we found that serum IMA levels increased significantly in patients with acute brucella infection. The high level of IMA in our study indicates that it may increase neutrophil infiltration in brucella infection, and therefore, anti-oxidant levels may decrease and ROS production may increase. In addition, the strong positive correlation between serum IMA and an inflammatory marker gal-3 and MPO activity shows that inflammation can induce the production of oxidative stress. While induction of oxidative stress and cytokine release indicates that it may be a risk factor for endothelial damage, it also suggests that it may be a risk factor for atherosclerosis.

Gal-3 is a molecule that plays an active role in the acute inflammatory response process, including neutrophil activation and adhesion molecule [31]. Gal-3 is an inflammatory biomolecule capable of inducing the release of pro-inflammatory cytokines IL-6 and TNF-alpha by inducing macrophages [32]. Therefore, gal-3 has been evaluated as an inflammatory cytokine that plays an active role in the acute response process involving the chemoattraction of macrophages/monocytes [33]. Studies have shown that gal-3 causes oxidative stress by increasing hyperoxide secretion [34]. Many studies have reported that gal-3 contributes to macrophage differentiation, the formation of foam cells, and endothelial dysfunction [35]. Increased serum gal-3 levels have been reported in diseases associated with chronic kidney and heart failure [36,37]. The gal-3 expression has been shown in the pathophysiology of cardiovascular diseases such as atherosclerosis, acute ischemic stroke, acute coronary syndrome and heart failure, arterial hypertension, cardiomyopathies, or atrial fibrillation [32]. In our study, we found that serum gal-3 levels increased significantly in patients with acute brucella infection. Tana et al. [38] in their experimental study on brucella abortus mice, it was reported that gal-3 expression was increased and that pro-inflammatory

molecules may be activated by increasing this expression. The results of our study are compatible with the literature. However, this molecule has not been analyzed in humans with brucella infection. Our study is the first clinical study in this respect. The high level of gal-3, an inflammatory marker in acute brucella infection, suggests that the inflammatory cascade may be activated. In light of this information, the fact that the gal-3 molecule is elevated in the pathophysiology of brucellosis suggests that it may be a risk factor for the formation of atherosclerosis, with the mechanism that it may cause endothelial dysfunction by affecting vascular homeostasis. However, large-scale studies are needed to evaluate brucellosis infection as an etiological risk factor in the pathophysiology of atherosclerosis.

PON-1 is an enzyme associated with HDL and is an antioxidant enzyme that protects the LDL molecule from oxidative modification [39]. Therefore, it has been reported that PON-1 plays an important role in atherosclerosis by protecting lipoproteins from oxidative modification [40]. It has been shown that a decrease in PON-1 activity may cause inflammation, which is considered a risk factor in the pathophysiology of many different diseases, and also oxidative stress [41]. Studies on PON-1 have been conducted in different diseases. It has been observed that PON-1 levels decrease in patients with ischemic heart disease, type-2 diabetes mellitus, ischemic heart disease with periodontitis, and patients with atrial fibration [42–44]. It has been reported that PON-1 activity decreases in patients with *Helicobacter pylori* and *Hepatitis C* [45,46]. Different results were obtained from studies evaluating the relationship between PON-1 and brucella infection. Demirpençe et al. PON-1 activity did not change in brucella infection [47]. Esen et al. showed that serum PON-1 activity was decreased in patients with acute brucella patients [48]. Apostolou et al. [49] showed that PON-1 activity is decreased in patients with acute brucella infection. They also reported that brucella infection was associated with atherogenic changes. Mackness et al., reported that low PON-1 activity may be an independent risk factor for cardiovascular diseases [50]. Melek et al. reported that lipid peroxidation and nitric oxide production increased in organs such as the liver and spleen in the first days of infection in their study on brucella infection, inflammation, and oxidative stress in the long term [51]. In our study, we observed that PON-1 activity decreased in patients with acute brucella infection. The literature results also support our findings. In light of the findings of our study, decreased PON-1 activity suggests that it may be related to lipid peroxidation. In addition, the negative correlation between PON-1 activity and serum IMA and gal-3 levels indicates that ROS production is increased in acute brucella infection. Decreased PON-1 activity in acute brucellosis infection indicates that it may be an etiological risk factor for vascular complications that play a role in the atherosclerosis process.

MPO, an important enzyme of neutrophils, is the key enzyme for the formation of HOCl from HO in the presence of chloride ions. HOCl is a powerful oxidant known to have several cytotoxic effects on bacterial cells [52]. It has been reported that high circulating MPO level is associated with strong endothelial dysfunction [53]. It has been reported that the risk of cardiovascular disease decreases in individuals with low MPO levels. Studies reporting increased levels of MPO in circulation have shown an increased incidence of coronary artery disease [54,55]. A limited number of studies have been found in the literature evaluating the relationship between acute brucella infection and serum MPO activity. Karahocagil et al. [56] reported that MPO activity increased significantly in patients diagnosed with acute brucella. In our study, we observed that serum MPO activity increased significantly in patients with acute brucella. The high MPO activity in brucella infection indicates that the oxidant–antioxidant balance is disrupted in favor of oxidative stress, and this mechanism may impair endothelial dysfunction. In addition, the sensitivity of IMA, gal-3, PON-1, and MPO biomarkers analyzed in our study was found to be very low due to the low area under the ROC curve, but the likelihood ratios of these tests were observed to be good.

The present study has several limitations. One of the main limitations is that general inflammatory parameters were not included in the study. Another important limitation is that duration of disease was not followed up in the study.

In conclusion, in our study, it was found that serum IMA, gal-3 levels, and MPO activity increased and PON-1 activity decreased. These results strongly showed that the oxidant-antioxidant balance in the pathophysiology of brucella is disrupted and oxidative stress. In addition, the high level of potential biomarkers in the pathogenesis of atherosclerosis in acute brucella infection makes our study valuable as it indicates that even acute brucella infection may increase the risk of atherosclerosis. Large-scale studies are needed to evaluate the importance and physiopathology of these biomarkers in the pathogenesis of the disease.

Data availability statement

The data presented in this study are available upon request from the corresponding author.Is Previously Presented? This study was previously presented as oral presentation. (TBS INTERNATIONAL BIOCHEMISTRY CONGRESS 2022 33rd NATIONAL BIOCHEMISTRY CONGRESS, 26-30 OCTOBER 2022, İZMİR, TURKEY)

Disclosure statement

No potential conflict of interest was reported by the author(s).

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