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Evaluation of Total and Lipid-Bound Sialic Acids, Trace and Macro Elements, and Some Biochemical Parameters in Dogs with Babesiosis

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ABSTRACT The present study was designed to investigate the changes at the levels of total sialic acid (TSA), lipid-bound sialic acid (LSA), trace and macroelements, and some biochemical parameters in dogs naturally infected with babesiosis. While babesiosis group consisted of seven dogs which were diagnosed with babesiosis clinically and parasitologically (ELISA), control group consisted of seven healthy dogs. Serum TSA and LSA levels in blood samples were measured spectrophotometrically by Sydow and Katapodis methods, respectively. Some biochemical parameters and macroelement measurements were performed using a modular autoanalyzer device. Trace mineral measurements were performed by ICP-MS technique. Compared to the healthy group, dogs with babesiosis had considerably higher TSA and LSA levels. Serum AST, ALP, LDH and CK enzyme activities and CRP, glucose, globulin, total bilirubin, urea, uric acid, creatinine and BUN levels of the babesiosis group significantly increased, while total protein level significantly decreased. The changes in ALT enzyme activity and triglyceride, cholesterol, HDL, LDL, HDL-CDL and ferritin levels were not statistically significant. Zinc, copper, magnesium, sodium, and potassium levels of the babesiosis group decreased significantly, while iron and chlorine levels increased significantly ($p<0.05$). Changes in calcium and phosphorus levels were not statistically significant. In conclusion, babesiosis caused significant changes in the levels of sialic acid (SA), biochemical parameters and elements in dogs.

Keywords: *Babesiosis, Biomarker, Dogs, Minerals, Sialic acids.*

ÖZ

Babesiosisli Köpeklerde Total ve Lipide Bağlı Sialik Asitler, İz ve Makro Elementler ile Bazı Biyokimyasal Parametrelerin Değerlendirilmesi

Bu çalışma doğal olarak babesiosis ile enfekte köpeklerde, total sialik asit (TSA), lipide-bağlı sialik asit (LSA), iz ve makro elementler ile bazı biyokimyasal parametrelerin seviyelerinde meydana gelen değişiklikleri araştırmak için planlandı. Klinik ve parazitolojik olarak (ELISA) babesiosis tanısı konulan 7adet köpek hasta grubunu, 7 adet sağlıklı köpekte kontrol grubuoluşturdu. Kan örneklerinde serum TSA ve LSA düzeyleri sırasıyla Sydow ve Katapodis metotları ile spektrofotometrik olarak ölçüldü. Bazı biyokimyasal parametre ve makro element ölçümleri modüler oto analizör cihazında gerçekleştirildi. İz mineral ölçümleri ICP–MS tekniği ile çalışıldı. Sağlıklı grup ile karşılaştırıldığında babesiosisli köpeklerde serum TSA ve LSA seviyelerinin önemli derecede yüksek olduğu belirlendi ($p<0.05$). Babesiosisli grupta serum AST, ALP, LDH ve CK enzim aktiviteleri ile CRP, glukoz, globulin, total bilirubin, üre, ürik asit, kreatinin ve BUN seviyelerinde önemli derecede yükselme, total protein seviyesinde ise önemli düzeyde azalma olduğu saptandı ($p<0.05$). ALT enzim aktivitesi ile trigliserit, kolesterol, HDL, LDL, TIBC ve ferritin seviyelerindeki değişikliklerin istatistiki olarak anlamlı olmadığı belirlendi ($p>0.05$). Babesiosisli grupta çinko, bakır, magnezyum, sodyum ve potasyum seviyelerinin önemli derecede azaldığı, demir ve klor seviyelerinin ise önemli derecede arttığı tespit edildi ($p<0.05$). Kalsiyum ve fosfor seviyelerindeki değişikliklerin istatistiki olarak anlamlı olmadığı belirlendi ($p>0.05$). Sonuç olarak, babesiosisin köpeklerde serum sialik asit, biyokimyasal parametreler ve elementlerin seviyelerinde önemli değişikliklere yol açtığı görüldü.

Anahtar Kelimeler: *Babeziyoz, Biyobelirteçler, Köpek, Mineraller, Sialikasidler.*

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INTRODUCTION

Canine babesiosis is a blood parasitic disease caused by various *Babesia* species (*B. vogeli, B. gibsoni, B. canis, B. vulpes and B. rossi*). The clinical symptoms of the disease include high fever, hemolytic anemia, icterus, and hemoglobinuria. The severity of these clinical symptoms varies depending on the factors related to the animal (resistance, age, breed, etc.) and the number of agents ingested (Uilenberg 2006; Crnogaj et al. 2017; Selcin and Oguz 2022). The pathogenesis of babesiosis is associated with hemolytic anemia. Babesia species increase the number of free radicals in erythrocytes and thus, cause oxidative stress. As a result of lipid peroxidation occurring in the erythrocyte membrane due to oxidative stress, erythrocytes are hemolyzed, and thus, hemolytic anemia occurs (Solano-Gallego and Baneth 2011; Crnogaj et al. 2017).

Sialic acid (SA), which is synthesized from fructose-6-phosphate in the organism, is one of the most important components of glycoconjugates (glycoprotein, glycolipid, and proteoglycan). A significant portion of SA, which is a component of membrane composition, is bound to proteins and is called as protein-bound sialic acid (PSA) while the remaining part is bound to lipid and is called as lipoprotein sialic acid (LSA).

The sum of PSA and LSA constitutes total sialic acid (TSA) (Lacin 2001). SA is also found in the last chain of several acute-phase proteins and thus, is used as an important marker of inflammatory diseases (Esmaeilnejad et al. 2020). Serum SA levels change in parallel with the damage to cells or tissues.

Important information regarding the disease's diagnosis and prognosis is provided by these alterations (Sydow et al. 1988; Taskın and Deger 2021). Along with the destruction of erythrocytes, the serum levels of SAs in the membrane structure increase (Ertekin et al. 2000). Recently, the SA level has been evaluated in the studies conducted on animals infected with hemoprotozoan parasites and it has been found that there is a close correlation between the SA level and the parasitemia rate (Esmaeilnejad et al. 2020).

Minerals are the substances necessary for the occurrence and maintenance of vitality events by participating in different structural and functional activities of the organism. Imbalances caused by abundance or deficiency of minerals cause some pathological conditions (Mert et al. 2008). Changes in the levels of mineral substances developing due to infectious diseases are also caused by decreased nutrient uptake, increased losses and impaired utilization due to the disease. Vitamin and mineral deficiencies make animals susceptible to parasitic diseases (Dede et al. 2008).

Biochemical parameters are used for diagnosis and prognosis of the disease and monitoring of treatment efficacy. With the help of biochemical parameters, it is possible to have an idea about both the physiological status of organs and tissues and the pathological conditions that occur (Turgut 2000). In hemoprotozoan diseases, significant changes occur in blood biochemical parameters as well as clinical findings in the host (Deger et al. 2005).

This study was designed to investigate the changes in the levels of TSA, LSA, trace and macroelements, and some biochemical parameters in dogs naturally infected with babesiosis.

MATERIAL AND METHODS

This study, ethics committee approval was obtained from Van Yuzuncu Yil University Animal Testing Ethics Committee on 31.01.2023 with the number 2023/03-02.

The current study was conducted on 91 stray dogs of different ages and sexes that were brought to the Animal Care and Rehabilitation Center of the Van Metropolitan Municipality from city center and surrounding districts of Van for neutering. The animals were starved the day before neutering and were given water only for the last 12 hours.

Blood samples were collected from the vena cephalica antebrachii of the dogs with at least two clinical symptoms such as high fever, icterus, weakness, increased respiration and pulse rate in 10 ml gel vacuum biochemistry tubes according to the method. The blood was centrifuged at 3000 rpm for 10 minutes and the serums were separated. The serumsobtained were screened for Babesia canis IgG antibodies using BABESIA-ELISA DOG (Afosa, Germany). Seven dogs that tested positive were included in the Babesia group. Seven dogs that were found to be healthy by clinical examination and negative by ELISA were included in the healthy group.

Biochemical Analysis

TSA analysis of the serumswas performed according to the method developed by Sydow et al. (1988). This method is based on the formation of a pink-colored complex with the Erlich reagent by SA released via hydrolysis with acid. The absorbance of the pink color forming at 525 nm is proportional to the amount of TSA. LSA analysis was performed according to the method developed by Katapodis et al. (1982). This method is based on the formation of blue-colored complexes with resorcinol reagent by sialic acids released in an acidic medium after extraction of the lipid phase. The absorbance of the blue color forming at 580 nm is proportional to the amount of LSA. The amounts of TSA and LSA were calculated by using a standard graph prepared with N-acetylneuraminic acid (NANA).

Creatine kinase (CK),alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), gamma glutamate transferase (GGT), glucose, globulin, total bilirubin, total protein, triglyceride, cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), total iron binding capacity (TIBC), ferritin, urea, uric acid, creatinine, blood sodium, potassium, magnesium, calcium, phosphorus, chlorine and blood urea nitrogen (BUN), measurements in the serums were performed by a modular auto analyzer (Cobas Integra 800, Roche) using a commercially available kit.

Zinc, copper, and iron measurements in the serums were performed by using Inductively Coupled Plasma-Mass Spectrometry (ICP-MS, Thermo Scientific).

Statistical Analysis

SPSS (22) software was used to assess the data. Shapiro-Wilk test was used to assess whether the data were normally distributed for each parameter. Independent Samples T-test was used to determine the statistical difference between the groups. The results obtained were given as X±SD. The significance level was assessed as $p<0.05$. Sample selection was not made from the population. Seven sick dogs were included in the study. Seven healthy dogs were taken as the control group. Therefore, power analysis was not performed.

RESULTS

In the analysis of 91 serum samples collected from the stray dogs via the ELISA method, 7 (7.69%) were found to be positive for *Babesia canis* IgG antibodies. Serum TSA and LSA levels significantly increased in dogs naturally infected with babesiosis compared to the healthy group ($p<0.05$, Table 1).

Table 1: Serum total sialicacid (TSA) and lipid bound sialicacid (LSA) levels in healthy and babesiosis groups.

Parameters	Healthy group (n=7) (X ± SD)	Babesiosis group (n=7) (X±SD)	p
TSA (mg/dl)	21.79±4.09	30.08±8.27*	0.035
LSA (mg/dl)	8.44±1.28	10.17±1.06*	0.018

*p<0.05, indicates the importance between parameters on the sameline.

AST, ALP, LDH, CK and GGT enzyme activities, CRP, glucose, globulin, total bilirubin, urea, uric acid, creatinine and BUN levels significantly increased in dogs naturally infected with babesiosis compared to the healthy group ($p<0.05$).

However, the total protein level significantly decreased ($p<0.05$). The changes in ALT enzyme activity and triglyceride, cholesterol, HDL, LDL, TIBC, and ferritin levels were not statistically significant ($p>0.05$, Table 2).

Zinc, copper, magnesium, sodium, and potassium levels significantly decreased in dogs naturally infected with babesiosis compared to the healthy group, while iron and chlorine levels significantly increased ($p<0.05$).

There were no statistically significant changes in the levels of calcium or phosphorus ($p>0.05$, Table 3).

Table 2: Biochemical parameter levels of healthy and babesiosis groups.

Parameters	Healthy group (n=7) (X ± SD)	Babesiosis group (n=7) (X±SD)	p
AST (U/L)	25.71±11.05	48.28±21.76*	0.031
ALT (U/L)	29.00±9.62	32.85±8.91	0.452
ALP (U/L)	30.00±9.16	52.42±23.16*	0.045
LDH (U/L)	50.57±26.26	127.14±52.22*	0.005
CK (U/L)	9.77±5.50	32.36±12.38*	0.005
GGT (U/L)	2.18±1.25	4.34±1.32*	0.009
CRP (µg/ml)	14.14±2.79	61.57±3.20*	0.001
Glucose (mg/dl)	50.14±54.78	112.28±21.48*	0.016
Globulin (g/dl)	1.81±0.37	4.32±1.07*	0.049
Total protein (g/dl)	7.15±0.86	5.96±0.78*	0.021
Total bilirubin (mg/dl)	0.96±0.17	4.11±1.35*	0.047
Triglyceride (mg/dl)	34.85±17.33	39.14±20.59	0.924
Cholesterol (mg/dl)	219.71±88.87	170.14±52.46	0.287
HDL (mg/dl)	117.85±32.06	111.42±35.34	0.827
LDL (mg/dl)	51.00±21.80	54.00±34.80	0.270
TIBC (µg/dl)	258.40±2.17	260.28±1.71	0.051
Ferritin (µg/l)	99.70±15.71	111.91±1.40	0.785
Urea (mg/dl)	44.37±16.28	64.51±3.07*	0.045
Uricacid (mg/dl)	2.13±1.35	5.59±1.99*	0,003
Creatinine (mg/dl)	0.914±0.19	1.75±0.67*	0,001
BUN (mg/dl)	24.04±2.81	60.44±2.38*	0,005

*p<0.05, indicates the importance between parameters on the same line. Aspartate aminotransferase **(AST)**, alanine aminotransferase **(ALT)**, alkaline phosphatase **(ALP)**, lactate dehydrogenase **(LDH)**, creatine kinase **(CK)**, gamma glutamyltransferase **(GGT)**, C-reactive protein **(CRP)**, high-density lipoprotein **(HDL)**, low density lipoprotein **(LDL)**, total iron binding capacity **(TIBC)**, blood urea nitrogen **(BUN).**

Table 3: Trace and macro element levels of healthy and babesiosis groups.

Parameters	Healthy group (n=7) (X ± SD)	Babesiosis group (n=7) (X±SD)	p
Zinc (µg/g)	5.70±1.15	1.42±0.84*	0.001
Copper (µmol/L)	5.60±1.60	3.85±0.90*	0.028
Iron (µmol/L)	101.98±21.26	162.04±50.88*	0.020
Magnesium (mg/dL)	3.18±0.37	2.76±0.27*	0.032
Calcium (mg/dL)	8.18±1.37	9.33±0.59	0.063
Phosphorus (mmol/L)	1.14±0.10	1.06±0.03	0.240
Sodium (mmol/L)	148.71±3.54	135.57±1.51*	0.031
Potassium (mmol/L)	5.48±0.71	3.86±0.44*	0.044
Chlorine (mmol/L)	111.57±3.86	124.42±3.40*	0.003

*p<0.05, indicates the importance between parameters on the same line.

DISCUSSION AND CONCLUSION

Babesiosis is a protozoan blood disease caused by species of the genus Babesia. (Furlanello et al. 2005). In babesiosis, severe systemic disorders occur with the breakdown of erythrocytes. The disease causes single or multiple dysfunctions in organs such as kidneys, liver, and muscles. Many of the clinical symptoms seen in babesiosis are caused by both hemolytic anemia which occurs after hemolysis of erythrocytes and the inflammatory response (Erkılıc et al. 2019). At least two of the clinical signs, including high temperature, icterus, weakness, and faster breathing and heartbeat, were present in the dogs employed in the current investigation

SA is found on the outer surface of cell membranes in forms bound to glycoproteins and glycolipids. SA performs as a membrane receptor, participates in the control of cellular activation, and is crucial in host-pathogen interactions. SA is widely distributed in many tissues and body fluids. Therefore, SA is an important biomarker used in the evaluation of inflammatory diseases (Esmaeilnejad et al. 2020). SA levels increase significantly in metabolic, bacterial, parasitic, and viral diseases (Aytekin 2020). Previous studies reported that SA levels were significantly higher in cattle (Ertekin et al. 2000; Esmaeilnejad et al. 2020), sheep (Deger et al. 2007), and horses (Shahbazi and Hassanpour 2017) infected with different *Babesia* species compared to the control group. In a study conducted on dogs infected with *Babesia canis canis*, serum TSA levels were found to be high (Kırmızıgul et al. 2015). In the present study, serum TSA and LBSA concentrations were found to be significantly higher in the dogs with babesiosis compared to the healthy dogs. The release of SA from glycolipids or glycoproteins in the cell membrane of parasitized erythrocytes may be responsible for this increase.

Biochemical parameters are widely used to assess the clinical status of patients. Babesiosis biochemical profile changes are correlated with the degree of hypoxia and the severity of the disease (Gokce et al. 2013). In the present study, ALT, AST, ALP and GGT enzyme activities were higher in the dogs with babesiosis compared to the healthy dogs. These increases in enzyme activities are thought to be caused by the liver damage. In the studies conducted with dogs with babesiosis, ALT, AST (Furlanello et al. 2005; Yadav et al. 2011; Gonde et al. 2017; Erkılıc 2019), ALP (Furlanello et al. 2005; Crnogaj et al. 2010; Gonde et al. 2017) and GPT (Sudhakara Reddy et al. 2016) enzyme activities were found to be significantly higher than the values of the healthy dogs. However, in some studies, ALT and GGT (Crnogaj et al. 2010) and ALP, ALT, and AST (Niwetpathomwat et al. 2006) enzyme activities were found to be the same in babesiosis infections in dogs.

Skeletal muscle degeneration occurs in babesiosis (Yeruham et al. 2003). While Furlanello et al. (2005) reported that CK enzyme activity was high in the dogs infected with *Babesia*, Gokce et al. (2013) reported that CK and LDH enzyme activities were high in the dogs infected with *Babesia*. In accordance with these studies, in the current study, an increase in CK and LDH enzyme activities was found in the dogs with babesiosis. These increases might have been increased by the fact that dogs perform vigorous exercise or babesiosis causes muscle damage in dogs. Rhabdomyolysis has thus been identified as a side effect of B. canis rossi infection (Jacobson and Lobetti 1996).

In the present study, glucose levels were found to be high in dogs with babesiosis (Crnogaj et al. 2010; Yadav et al. 2011). This increase in glucose levels may be caused by increased oxidative stress and glucose mobilization. In contrast to this result, studies conducted in the dogs infected with babesiosis reported that glucose levels decreased (Keller et al. 2004; Sudhakara Reddy et al. 2016) and remained unchanged (Gonde et al. 2017).

In the present study, total protein levels significantly decreased and globulin levels significantly increased in dogs with babesiosis when compared to the healthy dogs. The decrease in the total protein level might have been caused by liver and kidney dysfunction. It is thought that it may have been formed depending on a decrease in protein synthesis due to malnutrition caused by infection. In addition, an increase in the globulin fraction in response to antigenic stimulation may be responsible for the increase in globulin level. In the studies conducted with dogs with babesiosis, it was found that total protein levels decreased (Furlanello et al. 2005; Crnogaj et al. 2010; Yadav et al. 2011; Sudhakara Reddy et al. 2016) and globulin levels did not change (Sudhakara Reddy et al. 2016; Gonde et al. 2017).

In the studies conducted in dogs infected with *Babesia canis*, it was reported that total bilirubin levels did not change (Furlanello et al. 2005; Crnogaj et al. 2010).

In contrast to the literature, total bilirubin levels significantly increased in dogs with babesiosis in the current study (Yadav et al. 2011). Extensive hemolysis of erythrocytes and liver dysfunction may be responsible for the increase in bilirubin levels.

Hemolysis of erythrocytes is a common cause of renal failure, and this causes azotemia and increased creatinine, urea and BUN in the blood plasma, which is supported bysignificantly higherlevels of urea, uric acid, creatinine, and BUN in the dogs with babesiosis when compared to healthy dogsin the current study (Sudhakara Reddy et al. 2016; Gonde et al. 2017; Erkılıc 2019). This increase might have been caused by the damage occurring in the kidneys. However, Niwetpathomwat et al. (2006) and Crnogaj et al. (2010) found that urea and creatinine levels did not change in the dogs with babesiosis.

Lipid metabolism is crucial in babesiosis due to the reason that most of the blood parasites cannot synthesize their own lipids and transfer them from host plasma (Mrljak et al. 2014). Different data are obtained on the lipid profile in *Babesia* infections in dogs. Milanović et al. (2019) found that cholesterol and HDL levels decreased significantly, while there was no significant change in triglyceride level. Eichenberger et al. (2016) detected that there was a significant decrease in triglyceride levels, while cholesterol levels did not change. Rossi et al. (2014) reported that HDL levels were significantly lower. In another study, it was found that cholesterol and triglyceride levels increased significantly in *Babesia canis* infection, HDL levels decreased, and the change in LDL levels was not significant (Mrljak et al. 2014). In the present study, changes in serum lipid profile in infected dogs were not statistically significant.

Levels of acute phase proteins (APPs) increase in the conditions such as inflammation, tissue damage, oxidative stress, malignant neoplasms, and bacterial, viral, and parasitic diseases. Thus, they are considered as important biomarkers. C-reactive protein (CRP) and ferritin levels, which are positive acute phase proteins, increase after the acute phase response (Karnezi et al. 2016). β-globulin CRP initiates the removal of pathogenic microbes or necrotic cells from the host. In the present study, increased serum CRP levelwas found to be significant in the dogs with babesiosis (Ulutas et al. 2005; Matijatko et al. 2007). This increase indicates the presence of inflammation and infection. In contrast to this result, Koster et al. (2009) reported that there was no difference between surviving and deceased dogs with babesiosisin terms of the CRP level. To the best of our knowledge, there is no study evaluating the ferritin level in babesiosis. Martinez Subiela et al. (2014) reported that ferritin level was significantly higher in the dogs with leishmaniasis when compared to healthy dogs. In contrast, Karnezi et al. (2016) found that ferritin levels did not change in the dogs with ehrlichiosis. In a study conducted in humans with babesiosis, serum ferritin levels were found to be high and it was stated that ferritin can be used as a diagnostic marker in babesiosis (Cunha et al. 2015). According to the results of the current investigation, there was no statistically significant difference in the ferritin levels between the dogs with babesiosis and the healthy dogs.

Total iron binding capacity (TIBC) is a negative acute phase protein and an indirect indicator of transferrin content. It has been reported that there is a decrease in TIBC essentially in diseases with inflammatory features (Khaki et al. 2018). In this study, it was determined that there was no statistical difference in TIBC between infected and healthy dogs (Itoh and Itoh 1992). However, Furlanello et al. (2005) found that TIBC decreased in dogs with babesiosis.

It has been emphasized that there is an indirect loss of essential body nutrients due to accelerated metabolism or consumption during the clinical course of infectious diseases (Chaudhuri et al. 2008). In previous studies, serum copper and zinc levels were found to be significantly lower in dogs with babesiosis compared to the control group (Chaudhuri et al. 2008; Teodorowski et al. 2021).

In the present study, a statistically significant decrease in serum zinc and copper levels and a statistically significant increase in iron levels were found in the dogs with babesiosis compared to the healthy dogs. Micronutrients such as copper and zinc are essential components of the antioxidant defense, which plays an important role in preventing free radical-induced damage. Copper and zinc play a role in the synthesis of various isoenzymes of SOD, the antioxidant enzyme; therefore, the decreased levels of zinc and copper in infected dogs may be caused by their increased utilization. The increase in iron levels may be caused by intravascular hemolysis of erythrocytes associated with infection. In contrast to the results of the current study, a study reported that iron levels significantly decreased in dogs with babesiosis (Chaudhuri et al. 2008).

In this study, a statistically significant decrease in phosphorus, magnesium, potassium, and sodium levels and a statistically significant increase in chlorine levels were found in the infected dogs compared to the healthy dogs. The change in calcium was not significant. Decreased serum mineral levels might have been caused by malnutrition, decreased absorption, and renal and intestinal dysfunction. Supporting the results of our study, it was found that potassium and sodium levels decreased, and chlorine levels increased with *Babesia canis* infection (Leisewitz et al. 2001; Zygner et al. 2012). In contrast to these studies, Eichenberger et al. (2016) found that potassium was higher than the reference value, while sodium, phosphate, calcium, and chlorine levels were within normal limits in dogs infected with *Babesia canis*.

The results indicated that babesiosis caused significant changes in the levels of serum sialic acid, biochemical parameters, and elements in dogs.

CONFLICTS OF INTEREST

The authors report no conflicts of interest.

AUTHOR CONTRIBUTIONS

Idea / Concept: UO, YD, BO
Supervision / Consultancy: UO, YD, BO
Data Collection and / or Processing: UO, BO
Analysis and / or Interpretation: UO, YD, BO
Writing the Article: YD
Critical Review: YD, BO

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