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Evaluation of Serum Soluble Urokinase Plasminogen Activator Receptor, Lipopolysaccharide Binding Protein, Ceruloplasmin and Haptoglobin Levels in Dogs with Symptoms of Diarrhea Infected with *Toxocara canis*

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The objective of this study was to evaluatie serum soluble urokinase plasminogen activator receptor (suPAR), lipopolysaccharide binding protein (LBP), ceruloplasmin and haptoglobin levels in dogs with symptoms of diarrhea infected with *Toxocara canis (T. canis)*. The infected animal animal group consisted of 30 dogs of different genders and breeds, aged 1-6 months, brought to the Department of Internal Medicine of the Kafkas University Faculty of Veterinary Medicine with complaints of anorexia, diarrhea and vomiting, and were diagnosed with *T. canis* by fecal examination. The control group consisted of 20 dogs at 1-6 month age, that were found to be healthy after clinical and laboratory examination. Blood samples were taken once from infected and healthy dogs for the analysis of hematology and serum biochemistry. The infected animal group had a lower erythrocyte count, hemoglobin concentration, and hematocrit value than the control group ($P<0.05$). Furthermore, serum suPAR ($P<0.001$), LBP ($P<0.001$), ceruloplasmin ($P<0.001$), and haptoglobin ($P=0.003$) concentrations in the infected animal group were significantly higher than in the control group. In conclusion, serum suPAR, LBP, ceruloplazmin and haptoglobin levels changed in *T. canis*-infected puppies with diarrhea. Additionally, not many studies have been found on suPAR and LBP in veterinary medicine. We think that this study will be a source of information for new studies on this subject.

Key Words: *Acute phase protein, dog, lipopolysaccharide binding protein, soluble urokinase plasminogen activator receptor, Toxocara canis*

Toxocara canis ile Enfekte İshal Semptomlu Köpeklerde Serumda Çözünür Ürokinaz Plazminojen Aktivatör Reseptörü, Lipopolisakkarit Bağlayıcı Protein, Seruloplazmin ve Haptoglobin Düzeylerinin Değerlendirilmesi

Bu çalışmanın amacı, *Toxocara canis (T. canis*) ile enfekte ishal semptomları olan köpeklerde serumda çözünebilir ürokinaz plazminojen aktivatör reseptörü (suPAR), lipopolisakkarit bağlayıcı protein (LBP), seruloplazmin ve haptoglobin düzeylerinin değerlendirilmesidir. Bu çalışmanın hasta hayvan materyalini Kafkas Üniversitesi Veteriner Fakültesi İç Hastalıkları Anabilim Dalına iştahsızlık, ishal ve kusma şikayetiyle getirilen 1-6 aylık yaşlarda, farklı cinsiyet ve ırklarda dışkı muayenesi ile *T. canis* teşhisi konmuş 30 köpek oluşturmuştur. Kontrol grubunu ise aynı yaş grubunda klinik ve laboratuar muayenesi sonucu sağlıklı olduğu görülen 20 köpek oluşturmuştur. Hasta ve sağlıklı köpeklerden bir kez kan örneği V. cephalica antebrachi'den alınarak hematolojik ve biyokimyasal analizler yapılmıştır. Hasta grubun eritrosit sayısı, hemoglobin konsantrasyonu ve hematokrit değeri kontrol grubuna göre daha düşük buluunmuştur ($P<0.05$). Ayrıca hasta grupta serum suPAR ($P<0.001$), LBP ($P<0.001$), seruloplazmin ($P<0.001$) ve haptoglobin ($P=0.003$) konsantrasyonları kontrol grubuna göre önemli ölçüde yüksek bulunmuştur. Sonuç olarak, ishal semptomu olan *T. canis* ile enfekte yavru köpeklerde serum suPAR, LBP, seruloplazmin ve haptoglobin düzeyleri değişiklik göstermiştir. Ayrıca veteriner hekimlikte suPAR ve LBP ile ilgili çok fazla çalışmaya rastlanılmamıştır. Yapılan bu çalışmanın bu konuyla ilgili yeni yapılacak çalışmalara bir kaynak olacağını düşünüyoruz.

Anahtar Kelimeler: *Akut faz protein, köpek, lipopolisakkarit bağlayıcı protein, çözünebilir ürokinaz plazminojen aktivatör reseptör, Toxocara canis*

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Introduction

Toxocara leonina (*T. leonina)* and *Toxocara canis (T. canis)* are gastrointestinal nematodes that cause diarrhoea in dogs, and the disease caused by them is known as ascaridiosis (1, 2).

Ascaridiosis is one of the most important zoonotic diseases worldwide (3). The disease is most common in dogs younger than 6 months old (4). The disease is transmitted by the fecal-oral and placental routes (5). Ascaridiosis causes, vomiting, growth retardation, immunosuppression, tympani, constipation, and mechanical obstruction in the digestive tract in puppies (6). The mechanism of the development of anemia is due to the absorption capacity violation of the mucous membrane invaded with toxocara. Long-term B12 deficiency is a serious disease. It appears within the development of megaloblastic anemia and/or neurological disorders (3). *Toxocara canis* causes paralysis of motor neurons. The probable cause of mental stagnation and hind leg paralysis is paralysis of motor neurons (4).

Fecal examination plays an important role in the diagnosis of the disease (7). There are biomarkers that have recently been used in disease diagnosis and provide information about disease severity (6). In recent years, studies on biomarkers have been emphasized in order to evaluate the severity of disease in digestive system diseases caused by various reasons in dogs (8-10). Soluble urokinase plasminogen activator receptor (suPAR) is a biomarker released by monocytes, neutrophils, macrophages, and T cells that is involved in a variety of immunological reactions, including migration, adhesion, differentiation, and proliferation (11). It plays an important role in the assembly of inflammatory cells by showing chemotaxic properties (12). As a result, serum suPAR levels are important in determining both the severity of inflammation and the infected animals prognosis (13). The polypeptide-structured liposaccharide binding protein (LBP) is an acute phase reactivator produced by the liver and muscles (14). The molecular weight of this protein is 58 kDa. Its primary function is to bind endotoxins and form the LBP-endotoxin complex, which then stimulates Toll-like receptors and initiates the inflammatory response via cytokine release (15). An acute phase response occurs with the occurrence of damage in living tissues. The primary goal is to eliminate both tissue damage and pathogens that cause damage (16). The liver produces acute-phase proteins during the inflammatory response, and their levels change before clinical signs of the disease appear. Ceruloplasmin and haptoglobin are among the important acute-phase proteins (17).

The assessment of biomarkers, acute phase proteins, parasitological examination clinical and haematological findings provides critical information for confirming the diagnosis and determining the severity of the disease. The aim of this study was to determine the changes in serum suPAR, LBP, ceruloplasmin, haptoglobin levels in dogs infected with *Toxocara canis*.

Materials and Methods

Research and Publication Ethics: This study was initiated after approval was obtained from the Local Ethics Committee for Animal Experiments of Kafkas University (KAU-HADYEK/2023-002).

Animals: Animal material of this study consisted of 30 dogs of different breeds and genders at the age of 1-6 months that were diagnosed with *T. canis* based on stool examination and brought to the Department of Internal Medicine of the Faculty of Veterinary Medicine of Kafkas University with complaints of anorexia, diarrhea, and vomiting. Twenty dogs with healthy clinical and laboratory findings formed the control group. Clinical and vital signs were examined to determine the control group. However, microscopic fecal examination was performed. Those with normal clinical and vital signs and no ascarid eggs in their stool were included in the control group. Age of the control group was less than 6 months. The sick dogs were brought to our clinic within 24 hours after they started to show clinical symptoms without any other treatment or medication. Clinical examinations of the animals in the infected animal and control groups were performed and rectal body temperature, pulse rate per minute, and respiratory rate were determined.

Collection of Blood Samples: Blood samples were collected from sick dogs before treatment and from healthy dogs once with the help of holder and compatible sterile needle tip (Vacuette®, Greiner Bio-One GmbH, Austria) into vacuum gel serum tubes (BD Vacutainer®, BD, UK) and vacuum EDTA blood tubes (BD Vacutainer®, BD, UK) *V. cephalica* taken from antebrachi. To obtain serum, the blood samples were centrifuged at 3000 rpm for 10 minutes (Hettich Rotina 380R®, Hettich, Germany). The serum samples were kept at -20ºC until used for analysis

Biochemical and Hematological Analyses: Total leukocyte count (WBC), erythrocyte count (RBC), haematocrit percentage (Hct), haemoglobin concentration (Hb), lymphocyte count (Lym), monocyte count (Mon), granulocyte count (Gra) were determined from whole blood samples using a complete blood counting device (VG-MS4e®, Melet Schloesing, France), were measured.

The serum samples were analyzed for alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), alkaline phosphatase (ALP) enzyme activities while glucose, urea and total bilirubin (TBIL) levels using a fully automatic biochemistry device (Mindray BS120®, Mindray Medical Technology, Istanbul, Türkiye).

Commercial canine specific ELISA kits were used to determine serum suPAR (Dog suPAR ELISA Kit®, Cat No: ELK9083, ELK Biotechnology, China) and LBP (Dog LBP ELISA Kit®, Cat No: ELK9084, ELK Biotechnology, China) concentrations. ELISA tests were carried out according to the manufacturer's instructions, and optical density was determined using an ELISA reader (Epoch®, Biotech, USA) at 450 nm. Regression analysis was used to read the suPAR and LBP values. Haptoglobin and ceruloplasmin levels were determined using the colorimetric method (18, 19). Başbug et al. (20), reported that the specificity of this ELISA Kits was 93.3% in their study on dogs.

Fecal Examination: The fecal samples from 1-6 months old dogs with diarrhea were collected at the Kafkas University, Veterinary Faculty Animal Hospital and were transferred in sterile fecal sample containers with animal information recorded and kept at 4ºC until examination. Firstly, the adult forms of the helminths (*T. canis*) were screened in the macroscopically examined samples and then all the fecal samples were examined under a light microscope by fulleborn flotation technique using saturated saline solution (specific gravity: 1.45) for the identification of egg forms. Species identifications were made using the relevant literature based on the morphological characteristics of the detected helminth eggs (21, 22). Fecal samples taken from dogs with diarrhea were used with triple rapid test kits (Canine Parvovirus, Giardia, Coronavirus Antigen-Ag Test, Asan Easy Test, China) and those with negative test results were included in the study.

Statistical Analysis: Statistical analysis of the data was performed using SPSS® (SPSS 26.0, Chicago, IL, USA) software. The statistical differences between the groups with normal distributions according to the Shapiro-Wilk test were compared by the independent sample t-test. The obtained results were given as the mean ± standard error of the mean (SEM). P<0.05 was considered statistically significant in the evaluation of the results (23).

Results

Clinical examination of the dogs revealed vomiting, growth retardation, abdominal distension, anaemia, anorexia, mental stagnation, and temporary hind leg paralysis. Clinical examinations were performed on the infected animals, and vital signs including body temperature, respiratory rate/minute, and pulse rate/minute were statistically assessed (Table 1). According to the findings, the rectal body temperature in the infected animal group was significantly higher than in the control group (P<0.001), whereas respiratory rate/minute and pulse rate/minute did not differ (P>0.05).

Clinical and hematological findings of sick and healthy dogs are given in Table 1. A comparison was made between the infected animal group and the control group. Among the haematological parameters; RBC ($x10^6$/µL), Hct (%), and Hb (g/dL) (P<0.001), Mon ($x10^3$/µL) count (P<0.05) showed statistically significant differences when compared to the control group. Since the animals in the infected animal group had anemia, RBC, Hb and Hct levels decreased significantly. In addition, WBC ($x10^3$/µL), LYM ($x10^3$/µL), Gra ($x10^3$/µL) counts among haematological parameters were not statistically different (P>0.05) in the infected animal group compared to the control group.

Biochemical findings of sick and healthy dogs are given in Table 2. In serum biochemistry, statistically significant results were found according to ALT (P<0.05), AST (P<0.05), GGT (P<0.05), ALP (P<0.001) and TBIL (P<0.05) levels in the infected animal and control groups. Urea, TBIL and Glucose levels showed no statistical difference between the patient and control groups (Table 2). Serum suPAR (P<0.001), LBP (P<0.001), ceruloplasmin (P<0.001) and haptoglobin (P<0.05) concentrations were significantly higher in the infected animal group compared to the control group (Figure 1A, 1B, 1C, 1D).

Table 1. Mean and standard error values of hematological and vital signs in patient and control dog

Parameters	Patient (n=30) Mean±SEM	Control (n=20) Mean±SEM	Reference (2)	P
WBC ($x10^3$/µL)	5.76±0.97	6.62±0.44	5.5-16.9	0.433
RBC ($x10^6$/µL)	4.95±0.31	9.49±0.14	5.5-8.5	<0.001
HCT (%)	31.27±1.24	63.85±1.12	37-55	<0.001
Hb (g/dL)	10.59±0.47	15.29±0.30	12-18	<0.001
Lym (m/mm^3)	1.29±0.26	1.79±0.30	1-4.9	0.235
Mon (m/mm^3)	0.66±0.13	0.30±0.02	0.1-1.4	0.016
GRA (m/mm^3)	4.76±0.92	4.52±0.21	3-13.6	0.799
T (^oC)	37.09±0.33	38.75±0.08	38.5	<0.001
P (Heart beat/min)	145.70±9.23	127.35±3.88	70-125	0.075
R (Respiratory rate/min)	46.53±4.13	45.40±2.29	15-45	0.812

WBC: Total leukocyte count, **RBC:** Erythrocyte count, **HCT:** Hematocrit, **Hb:** Hemoglobin concentration, **Lym:** Lymphocyte count, **Mon:** Monocyte count, **GRA:** Granulocyte count, **T:** Rectal temperature, **P:** Heart beats/min, **R:** Breaths/min. P<0.05 indicates statistical significance. **SEM**: Standard error of mean.

Table 2. Mean and standard error values of biochemical findings in patient and control dogs

Parameters	Patient (n=30) Mean±SEM	Control (n=20) Mean±SEM	Reference (2)	P
ALT (U/L)	34.65±7.72	63.87±4.84	10-88	0.007
AST (U/L)	46.05±7.72	29.87±1.73	10-88	0.049
GGT (U/L)	2.57±0.14	3.70±0.35	1-10	0.007
ALP (U/L)	217.23±8.35	147.78±7.62	20-150	<0.001
Urea (mg/dL)	78.08±2.09	79.52±2.90	28.68-53.5	0.681
TBİL (mg/dL)	0.17±0.05	0.02±0.009	0.1-0.06	0.071
Glucose (mg/dL)	79.60±3.31	72.70±1.37	60-110	0.062

ALT: Alanine aminotransferase, **AST:** Aspartate aminotransferase, **GGT:** Gamma glutamyl transferase **ALP:** Alkaline phosphatase, **TBIL:** Total bilirubin. P < 0.05 indicates statistical significance. **SEM:** Standard error of mean.

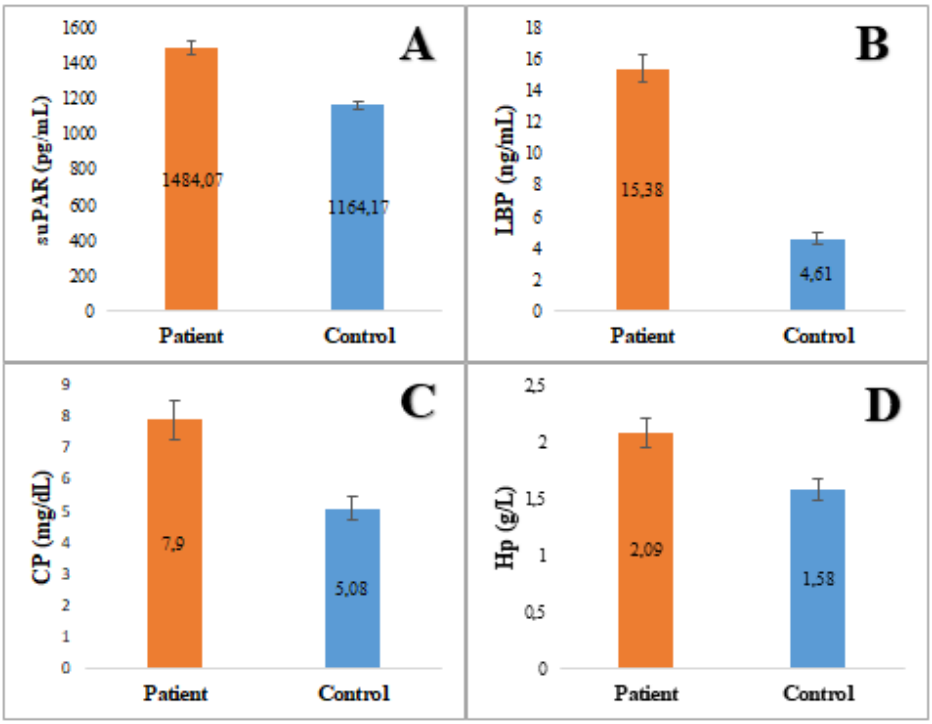

Figure 1. Comparison of suPAR, LBP, ceruloplasmin (CP) and haptoglobin (Hp) concentrations in the patient and healthy group. **A.** Comparison of suPAR concentrations in the patient and healthy group (P<0.001). **B.** Comparison of LBP concentrations in the patient and healthy group (P<0.001). **C.** Comparison of ceruloplasmin concentrations in the patient and healthy group (P<0.001). **D.**Comparison of haptoglobin concentrations in the patient and healthy group (P=0.003).

Discussion

During the migration of larva into the intestines in puppies with *T. canis*, abdominal distension, cachexia, growth retardation are observed (24).

All of the sick dogs in our study had a tense abdominal wall, retarded growth and a depressed state. The agent causes internal bleeding as a result of intestinal perforation, which causes anaemia in puppies infected with *T. canis*. Hb, Hct, and RBC, which are used to evaluate anemia in sick dogs, were found to be statistically low in the current study compared to the control, most likely since the causative agent caused internal bleeding by causing intestinal perforation (26). In this manuscript, necropsy was performed on two of the dogs in infected animal group that died. As a result of necropsy, it was observed that there was bleeding due to perforation in the intestines, consistent with the literature.

In infected dogs elevations in liver enzymes might be observed during the migration of the larva the difference here was found to be significant. During the migration of the larvae, mechanical damage occurs in the liver. There is an increase in liver enzyme activity due to this damage (26). Despite the statistical difference, GGT, ALP, ALT, and AST enzyme activities remained within normal reference values in the current study (Table 2). It is stated in the literature that liver enzyme activity will not increase unless 75% damage occurs in the liver (27). We think that the reason why ALT and GGT levels, which are important indicators of liver damage, are low in the infected animal group may be due to the fact that liver damage is less than 75%.

The level of suPAR increases in body fluids in infectious and tumoral diseases and in cases where immune response develops. Serum suPAR levels, as a result, provide information about the degree of immune response (28). Serum suPAR is released by monocytes, neutrophils, macrophages, and T cells and is involved in a variety of immunological functions, including migration, adhesion, differentiation, and proliferation. Its amount in leukocytes increases in inflammatory conditions (11). In our study, the infected animal group had a statistically higher number of monocytes and serum suPAR levels than the control group, which could be the cause of increased as a result of inflammation. The correlation table has been omitted from the manuscript to avoid ambiguity. suPAR is released from monocytes. Depending on the inflammation, there is an increase in the number and activation of monocytes. Depending on the activation in monocytes, the serum suPAR level increases. We think that an immune response is formed against parasitic invasion and thus contributes to the increase in suPAR.

Gucsav and Akyuz (29) found that increased suPAR levels in dogs with parvoviral enteritis were associated with the development of systemic inflammatory response syndrome. The reason for the increase in suPAR level in the infected animal group, similar to our study, could be the development of severe

inflammation as a result of *T. canis* damage in the intestines. An increase in serum suPAR indicates activation of the immune system and inflammatory response. It provides information on both the severity of inflammation (which increases in inflammatory and infectious diseases) and the disease prognosis (13, 30, 31). Infected animals with high suPAR levels have a poor prognosis (28, 32, 33).

Lipopolysaccharide binding protein is an acute phase protein produced by the liver for the organism's immune response to endotoxins (14, 15). It has a very important role in the differentiation of systemic inflammatory response syndromes (SIRS) of infectious and noninfectious origin (15, 34). The possibility of SIRS development in dogs in our study may have increased the LBP levels in the infected animal group compared to the control group. Furthermore, haptoglobin and ceruloplasmin levels were found to be statistically higher in the infected animal group compared to the control group, indicating that the inflammation was severe. Given that LBP induction is slow and elimination is rapid, it should be used in conjunction with other biomarkers to determine the severity of an inflammation (15). Odabaşı and Bülbül (35) report that an increase in LBP levels occurs 6-8 hours after infection. The fact that the sick dogs were brought in within a short period of time (within 24 hours of the disease onset) was found to be consistent with the fact that LBP increased significantly more than other acute-phase proteins. LBP quickly reflects the severity of the inflammation.

Acute phase proteins derived from the liver are produced in response to acute phase stimuli such as inflammation, tissue damage, and infection (36, 37). Haptoglobin is another acute-phase protein concentration of which rises during acute infection, inflammation, and trauma and provides information about disease severity (29, 38).

In a study on puppies with parvoviral enteritis, haptoglobin concentration increased due to perforation and inflammation in the intestine caused by gastroenteritis (29). The statistically higher haptoglobin concentration in the infected animal group compared to the control group in our study is most likely the result of intestinal destruction and severe inflammation. *T. canis* larval liver migration may also stimulate haptoglobin synthesis. Ceruloplasmin protects cells against oxidative damage and has cytoprotective activity (39). Ceruloplasmin can also be used to detect infection and inflammation (40). In many studies, ceruloplasmin concentration increased due to infection (37, 39, 41). Increased ceruloplasmin concentrations in the infected animal group compared to the control group in our study could be the result of inflammation, similar to haptoglobin.

In conclusion, serum suPAR, LBP, ceruloplazmin and haptoglobin levels changed in *T. canis*-infected puppies with diarrhea. The parameters examined showed a significant increase. Furthermore, given the fact that there are few studies on suPAR and LBP in veterinary medicine, this study will be a source of new research in this field.

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