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RESEARCH ARTICLE

Some Serum Biochemical Parameters and Acute Phase Protein Levels in Sheep with Acute Ruminal Lactic Acidosis

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ABSTRACT

This research examined changes in acute phase protein (APP) levels and biochemical parameters in sheep suffer from acute ruminal lactic acidosis (ARLA). Animals in the present study comprised 20 Akkaraman sheep with ARLA and 10 healthy sheep of Akkaraman breed, designated as the control group. All sheep were aged 1–2 years. Ruminal fluid samples were collected from both groups using a suitable tube and examined immediately. Whole blood samples were also taken from the jugular veins of the sheeps. Compared to the control group, sheep with ARLA exhibited significantly increased levels of haptoglobin (Hp) ($p<0.001$), ceruloplasmin (Cp) ($p<0.05$), aspartate aminotransferase (AST) ($p<0.001$), alkaline phosphatase (ALP) ($p<0.001$), blood urea nitrogen (BUN) ($p<0.001$), and creatinine (Crea) ($p<0.001$). In contrast, levels of albumin (Alb) ($p<0.05$), total protein (TP) ($p<0.05$), and iron (Fe) ($p<0.05$) were significantly lower in sheep with ARLA. In conclusion, ARLA induces notable changes in APP concentrations and biochemical parameters in sheep, this could have a significant part in the disease's pathophysiology and diagnosis.

Keywords: Acute ruminal lactic acidosis, Biochemical parameters, Ceruloplasmin, Haptoglobin, Iron, Sheep

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Akut Ruminal Laktik Asidozlu Koyunlarda Bazı Serum Biyokimyasal Parametreleri ve Akut Faz Protein Düzeyleri

ÖZ

Burada sunulan araştırmada akut ruminal laktik asidozlu (ARLA) koyunlarda akut faz protein (APP) düzeyleri ve biyokimyasal parametrelerdeki değişiklikler incelenmiştir. Çalışma popülasyonu ARLA tanısı konulan 20 Akkaraman koyunu ve kontrol grubu olarak aynı ırktan 10 sağlıklı koyundan oluşmuştur. Tüm koyunlar 1-2 yaşındadır. Her iki gruptan da mide sondası kullanılarak ruminal sıvı örnekleri toplanmış ve hemen analiz edilmiştir. Ayrıca tüm hayvanların juguler venlerinden kan örnekleri alınmıştır. Kontrol grubuyla karşılaştırıldığında, ARLA'lı koyunlarda haptoglobin (Hp) ($p<0,001$), seruloplazmin (Cp) ($p<0,05$), aspartat aminotransferaz (AST) ($p<0,001$), alkalen fosfataz (ALP) ($p<0,001$), kan üre azotu (BUN) ($p<0,001$) ve kreatinin (Crea) ($p<0,001$) düzeyleri önemli derecede artmıştır. Buna karşılık, albümin (Alb) ($p<0,05$), toplam protein (TP) ($p<0,05$) ve demir (Fe) ($p<0,05$) düzeyleri ARLA'lı koyunlarda anlamlı derecede düşük olduğu belirlenmiştir. Sonuç olarak, ARLA koyunlarda APP konsantrasyonlarında ve biyokimyasal parametrelerde önemli değişikliklere neden olur ve bu da hastalığın patogenezinde ve tanısında rol oynayabilir.

Anahtar Kelimeler: Akut ruminal laktik asidoz, Biyokimyasal parametreler, Seruloplazmin, Haptoglobin, Demir, Koyun

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INTRODUCTION

Acute ruminal lactic acidosis in domestic ruminants has long been recognized as a management-related disease (Ullah et al. 2013; Abebaw et al. 2024). Commonly referred to as grain overload, grain poisoning, or acute indigestion, this condition occurs in sheep and cattle that consume large quantities of unfamiliar diets high in ruminally fermentable carbohydrates (Ullah et al. 2013; Reis et al. 2018). Such dietary intake promotes the proliferation of Gram-positive bacteria, resulting in a significant alteration in the ruminal microbial population and the accumulation of lactic acid (Danscher 2011). The excessive production of volatile fatty acids (VFAs) and lactic acid reduces the rumen pH to non-physiological levels. This acidification weakens the rumen's buffering capacity, diminishes the efficiency of rumen flora, and impairs fermentation processes. Lactic acid also causes chemical rumenitis, and its absorption into the bloodstream leads to systemic lactic acidosis. Tissue damage, infection, or exposure to pro-inflammatory agents, such as lipopolysaccharide, triggers an acute phase response—a rapid and non-specific defense mechanism (Reis et al. 2018; Abebaw et al. 2024).

The body's early defense mechanisms involve a complex array of systemic reactions to tissue injury, neoplastic growth, immunologic disorders, inflammation, or infection, which are triggered shortly after exposure to an initiating event (Bozukluhan and Gokce 2007). Inflammation induces a nonspecific systemic response known as the acute-phase response (APR). Certain proteins known as acute-phase proteins (APPs) are released into the bloodstream during the APR (Petersen et al. 2004; Gruys et al. 2005; Baydar and Dabak 2014). Negative and positive acute-phase proteins are primarily produced in the liver. Their plasma concentrations can increase various hundredfold in response to inflammatory cytokines, including TNF-α, IL-1, and IL-6 (Petersen et al. 2004). Enhancing antibody synthesis and promoting tissue repair, which prevents more injury and helps recycle cellular waste, are the main functions of APPs. (Gruys et al. 2005).

Haptoglobin (Hp) and ceruloplasmin (Cp) are recognized as key acute-phase proteins (APPs) in sheep. Haptoglobin is a type of globin released by the liver in response to proinflammatory cytokines during inflammatory conditions (Eckersall et al. 2001; Ametaj et al. 2005). One of Hp's primary functions is to reduce iron (Fe) loss, thereby inhibiting bacterial overgrowth through iron limitation (Yang et al. 2003). While many acute-phase proteins are regarded as inflammatory biomarkers in animals, not all are specific to every species. In sheep and cattle, Hp is considered a major and valuable APP for assessing inflammatory responses and for routine health monitoring (Eckersall et al. 2001; Baydar and Dabak 2014; Kaya and Batmaz 2022). For instance, Hp is more specific and sensitive in sheep than C-reactive protein (Kamr et al. 2017).

In the central nervous system (CNS), cereuloplasmin (Cp) serves as an efficient antioxidant, protecting brain cells from oxidative damage. When levels of reactive oxygen species (ROS) and free iron rise due to CNS damage, this function is especially important (Fournier et al. 2009). The serum haptoglobin (Hp) level in healthy sheep shows significant variability, with most studies reporting physiological values below 0.3 mg/mL. However, a serum Hp concentration exceeding 1 mg/mL is widely regarded as an approximate threshold for severe inflammation. Both Hp and Cp have been extensively utilized in studies investigating inflammatory responses in sheep with metabolic and infectious diseases (Aytekin et al. 2015; Kamr et al. 2017; Massoudi et al. 2024). Iron is a constituent of heme and has important physiological roles in many enzymatic reactions. Moreover, significant decreases in serum Fe levels in inflammatory conditions were determined in many studies performed with several animal species (Neumann 2003; Quasim and Bedawi 2023). According to recent studies, decreased serum Fe levels may be useful in determining prognosis, particularly in the acute inflammatory response (Neumann 2003; Baydar and Dabak 2014).

The acute phase response encompasses both local and systemic components, forming a complicated network involving various cell types and organs that produce and respond to a variety of cytokines and other mediators (Baydar and Dabak 2014). The pathophysiologic outcomes of this response include cardiovascular collapse, muscular weakness, renal failure, shock, and death. In animals that remain, complications such as mycotic rumenitis may develop within a few days, hepatic necrobacillosis may occur weeks or months later, and chronic laminitis or ruminal scarring may be observed at slaughter (Allen et al. 2005). Clinically, morbidity rates in affected animals range from 10% to 50%. Case mortality rates in lactic acidosis can reach up to 90% in untreated cases, while treatment reduces mortality to 30%–40% (Radostits et al. 2007).

The present study aimed to investigate and compare serum Hp, Cp, iron, ALP, AST, total protein, albumine, BUN, and creatine levels in sheep with and without ARLA.

MATERIALS and METHODS

Ethical Approval

In the present study, the sheep in the ARLA group were referred by a clinician to the Large Animal Clinics at Balikesir University Veterinary Faculty. The control group comprised sheep housed at the university farm.

Both blood and ruminal contents from the healthy sheep were obtained during routine seasonal clinical examinations.

Animals and Clinical Examination

The study included 20 Akkaraman breed sheep with ARLA (ARLA group) from a single herd, aged 1–2 years, which were receieved to the Veterinary Teaching Hospital, School of Veterinary Medicine at Balikesir University. Additionally, ten healthy same breed sheeps, also aged 1–2 years and housed at the university farm, were included in the control group.

During the clinical examination of the animals (both the ARLA and control groups), pulse and respiratory rates, rumen contraction frequency, rectal temperatures, and dehydration levels were assessed. Furthermore, the mucous membranes and conjunctiva examination of all sheep were performed.

Collection of Rumen Fluid Sample and Examination

Following the clinical examination, rumen fluid samples were collected from both the sheep suffer from ARLA and the healthy sheep using a stomach tube. To minimize saliva contamination, the first portion of fluid obtained was discarded, and the subsequent 200–250 ml of rumen fluid was immediately analyzed (Garry 2002; Kirbas et al. 2014). These samples were evaluated based on pH, color, methylene blue reduction time, odor, and protozoal activity.

After a physical evaluation, the rumen fluid's odor was categorized as either acidic (abnormal) or aromatic (normal). It was classified as either milky grey (abnormal) or oily brownish green (normal). Commercial test strips (ColorpHast, Merck KGaA, Darmstadt, Germany) were used to measure the pH, which was then classified as normal (6–7), moderately low (5–5.9), or very low (4–4.9).

One milliliter of 0.03% methylene blue was combined with twenty milliliters of rumen fluid, and the color shift was compared to an identical fluid tube in order to calculate the methylene blue reduction time. The reduction time was divided into three categories: normal (3–6 minutes), 6–9 minutes, and over 9 minutes. The rumen fluid's protozoal activity was evaluated under a microscope (Olympus BX51, Olympus Optical, Japan) at a magnification of ×40 and classified as either normal, reduced, or nonexistent.

Blood Sample Collection

Blood specimens were obtained from the jugular vein of all sheep. The whole blood samples were centrifuged at 3000 g for ten minutes at room temperature. The serum of the whole blood samples was extracted and stored at -20°C until analysis.

Acute Phase Protein Analyses

Serum Cp and Hp levels were measured spectrophotometrically (Abbott Architect Clinical Chemistry Analyser; model no: C8000, serial number: C802239) by the methods reported by Colombo and Ricterich (1964) and Skinner et al. (1991) respectively.

Serum Biochemistry Analyses

Serum enzyme activities ALP (Alkaline phosphatase FS IFCC mod. 37°C), AST (Kits for BioMajesty® JCA-BM6010/C: ASAT (GOT) FS (IFCC mod.), Alb (Kits for BioMajesty® JCA-BM6010/C: Albumin FS) TP (Kits for BioMajesty® JCA-BM6010/C: Total protein FS), BUN (Kits for BioMajesty® JCA-BM6010/C: Urea FS), Crea (Kits for BioMajesty® JCA-BM6010/C: Creatinine FS) and Fe (Kits for BioMajesty® JCA-BM6010/C: Iron FS Ferene) concentrations were determined with biochemistry analyzer (Mindray-BS400, China) commercial test kits (DDS, Turkey) as colorimetric.

Statistical Analysis

Statistical analysis of the data was performed by the SPSS 20 statistical program package (SPSS Inc, Chicago, IL, USA). Normality analysis was performed with Kolmogorov-Smirnov test. If the data distributes normal, Student's T-test was performed. If the data shows a non-normal distribution Mann- Whitney U test was performed. A significance level of $p<0.05$ was established between the two groups. The data were presented as the mean and the mean of the standard errors. (X±SEM).

RESULTS

Clinical Examination Findings

Table 1 summarizes the clinical symptoms of all sheeps. During the clinical examination, all animals in the ARLA group exhibited engorged and congested scleral vessels, increased heart and respiratory rates, moderate to severe dehydration, and swollen, hyperemic mucous membranes. Additionally, signs of ruminal atony, ruminal stasis, and rising rectal temperatures were present. Furthermore, five sheep died, thirteen developed diarrhea, and some animals showed signs of teeth grinding. In contrast, the clinical examination of the healthy sheeps revealed normal rectal temperatures, heart rates, respiratory rates, and rumen contractions.

Table 1. Clinical signs of sheep with acute ruminal lactic acidosis (ARLA) and control group

Parameter	Control group (n=10)	ARLA group (n=20)
Rectal temparature (T/°C)	Normal in all group	Increased in all group
Heart rate (P/min.)	Normal in all group	Increased in all group
Respiration rate (R/min.)	Normal in all group	Increased in all group
Ruminal stasis	None of them	Available in all group
Ruminal atony	None of them	Available in all group
Ruminal contractions (RC/5 min.)	Normal in all group	Decreased in all group
Mucous membranes	Normal in all group	Dirty hyperemic in all group
Scleral congestion (engorged scleral vessels)	None of them	Available in all group
Diarrhea	None of them	In thirteen animals
Dehydration	None of them	moderate to severe in all group
Death	None of them	In five animals

Ruminal Fluid Analyses Findings

The results of the ruminal fluid analyses for the both groups are given in Table 2.

Table 2. The results of the ruminal fluid analyses of the sheep with acute ruminal lactic acidosis (ARLA) and control group

Parameter	Classification	Control group (n=10)	ARLA group (n=20)
Odor	Aromatic	100	100
	Acidic	0	0
Color	Olive, brownish-green	100	15
	Milky grey	0	85
pH	Normal (6-7)	100	0
	Moderately low (5-5.9)	0	20
	Very low (4-4.9)	0	80
Protozoal activity	Good	100	0
	Reduced	0	15
	None	0	85
Methylene blue reduction time	3-6 minutes (normal)	100	0
	6-9 minutes	0	20
	> 9 minutes	0	80

Biochemical Analyses Findings

Table 3 shows the levels of acute phase proteins, ALP, AST, ALB, TP, BUN, Crea, and Fe in sheep with ARLA and the control group. When sheep with ARLA were compared with the control group, it was determined that Hp ($p<0.001$), Cp ($p<0.05$), AST ($p<0.001$), ALP ($p<0.001$), BUN ($p<0.001$) and creatinine ($p<0.001$) levels increased compared to the control group, while Alb ($p<0.05$), TP ($p<0.05$) and Fe ($p<0.05$) levels decreased compared to the control group.

Table 3. Mean and standart error (X±SEM) of acute phase proteins and biochemical parameters in sheep with acute ruminal lactic acidosis (ARLA) and control group

Parameter	Control group (n=10)	ARLA group (n=20)	*P value*
Haptoglobin (g/L)	0.038±0.014	0.178±0.05	p<0.001
Cp (mg/dl)	9.89±1.74	13.54±4.44	p<0.05
Alb (g/dl)	2.97±0.74	2.35±0.69	p<0.05
AST (U/L)	59.32±4.74	84.25±13.73	p<0.001
ALP (U/L)	62.59±10.26	101.29±20.81	p<0.001
BUN (mmol/L)	4.45±1.81	6.88±1.77	p<0.001
CRSC (µmol/L)	112.90±16.78	154.37±25.90	p<0.001
TP (g/L)	76.14±8.27	61.05±12.86	p<0.05
Fe (µg/dl)	116.92±35.21	74.73±24.81	p<0.05

DISCUSSION

The acute ruminal lactic acidosis is a form of alimentary indigestion caused by the sudden and excessive use of easily fermentable, carbohydrate-rich feeds. It is characterized by a decrease in rumen pH below normal levels and an excessive production of volatile fatty acids in a short period (Chehreh and Fartashvand 2014; Reis et al. 2018; Abebaw et al. 2024). This condition disrupts the microbial fauna and leads to the death of microorganisms, along with other pathological changes such as inflammation and ulceration of the rumen wall (Chehreh and Fartashvand 2014). Pro-inflammatory cytokines released due to inflammation stimulate the synthesis of acute-phase proteins. In this study, elevated concentrations of haptoglobin (Hp) and ceruloplasmin (Cp) were observed in sheep with ARLA, while albumin (Alb) concentrations were found to be decreased. It has been established that haptoglobin (Hp) levels increase in traumatic cases (Hirvonen and Pyörala 1998) and in fasting conditions lasting more than three days (Gruys et al. 2005), as well as in cattle with subacute acidosis (Hp and SAA) and acute ruminal acidosis (Danscher et al. 2011), where acute-phase protein concentrations (SAA, Hp, and fibrinogen) and leukocyte counts are elevated. Additionally, Gonzalez et al. (2010) and Kizil et al. (2018) reported an increase in Hp concentration in goats, suggesting that Hp could serve as a potential indicator of acidosis in this species. However, Berry et al. (2004) found that Hp concentrations did not change in response to inflammation, regardless of diet, in feedlot calves. In the present study, consistent with other research, serum Hp concentrations were found to increase in sheep with ARLA. This increase may be attributed to the immune response triggered by inflammation in the rumen due to a decrease in rumen pH and/or the passage of endotoxins released from the death of microorganisms into the bloodstream.

In studies conducted on sheep (Sheldon et al. 2001) regarding Cp, which consists of a single polypeptide chain, it was reported that Cp concentration increased significantly due to physical stress and trauma during parturition and that this increase may be due to uterine involution and bacterial contamination. Ulutaş et al. (2008) determined that Cp concentration increased insignificantly in goats with mixed helminth infection. It was also reported that Cp levels increased in the first 3 days and reached the highest concentration on the 4th day in calves infected with salmonella (Murata et al. 2004). Aytekin et al. (2015) stated that Cp levels decreased in sheep with bluetongue disease, but this may be due to the storage period of serum samples. In the study, it was found that serum Cp concentration elevated significantly in ARLA group compared to the control group, and the results were compatible with the results of the previous reports.

Serum and plasma albumin concentrations, a negative acute-phase protein, decrease in cases of fasting, liver damage, and malabsorption (Gruys et al. 2005). In this study, the albumin levels were significantly lower in the experimental group compared to the control group. This reduction is likely attributable to the inflammatory response, liver dysfunction, and/or anorexia observed in the patients. It was reported that a decline in serum Fe levels during the acute-phase response (APR) can serve as a valuable diagnostic and

prognostic tool for acute inflammatory diseases in both humans and various animal species (Sunder-Plasmann et al. 1999; Neumann 2003; Baydar and Dabak 2014). Plasma Fe levels have been shown to decline rapidly within 24 hours of inflammation onset (Ratledge and Dover 2000). Reduced intestinal absorption of iron and decreased reticuloendothelial cell release of iron are the causes of this decrease (Nemeth et al. 2004; Andriopoulos et al. 2009). Notably, the organism's overall resistance to bacterial infections rises when plasma Fe levels fall. In 1999, Sund-Plassmann et al. Serum Fe levels in the ARLA group were significantly lower ($p<0.05$) than in the control group in the current investigation. These results are in good agreement with earlier findings.

Prolonged exposure to subacute rumen acidosis persistently activates the liver with pathogenic substances, resulting in hepatic damage, including liver abscesses (Nocek, 1997; Kleen et al., 2003). The damaged liver disrupts both glucose and lipid metabolism. Consequently, it releases harmful molecules into the bloodstream when its filtering ability is overwhelmed (Stone, 2004; Aschenbach et al., 2019). Increased activity of liver enzymes reflects hepatocellular damage, which may be sublethal degeneration or necrosis (Kromer and Hoffman, 1997).

Serum alkaline phosphatase (ALP) activity increases in conditions such as cholestasis, bone destruction, impaired hepatobiliary circulation, and under the influence of endogenous and exogenous glucocorticoids, as well as stress (Kaneko et al. 1997). In our study, the elevated serum ALP activity may be attributed to hepatobiliary circulation disorders, glucocorticoid activity, and/or stress induced by the disease. On the other hand, Alkabi et al., (2019) reported significantly lower ALP levels in sheep with induced ruminal lactic acidosis; however, the reason for this decrease remains unclear. Furthermore, the observed increase in aspartate aminotransferase (AST) activity in this study may have resulted from passive congestion and liver damage (Kaneko et al. 1997; Marchesini et al. 2013; Chehreh and Fartashvand 2014; Alkabi et al. 2019).

Serum total protein (TP) concentration decreases in cases of anorexia, the catabolic effects of glucocorticoids, malnutrition, renal and gastrointestinal losses, liver and kidney diseases, and during the peripartum period (Kaya and Bozkurt 2022). In the present study, the observed reduction in serum TP concentration may be attributed to anorexia, the catabolic effects of glucocorticoids, and/or liver damage.

According to our results, blood urea nitrogen (BUN) concentrations were found to be prominently increased than those in the control group ($p<0.001$). This increase in serum BUN levels is thought to result from the effects of inflammation on the kidneys (Harirforoosh and Jamali 2008). Additionally, conditions such as anorexia, infection, and high fever are known to enhance protein catabolism, leading to elevated serum creatinine concentrations (Gokce and Woldehivet 1999). In this study, the observed increase in serum creatinine concentration may similarly be attributed to increased protein catabolism.

CONCLUSION

ARLA was found to cause significant changes in biochemical parameters, in addition to altering the concentrations of acute-phase proteins in sheep. In conclusion, monitoring changes in serum iron and acute-phase protein levels in sheep with ARLA may provide valuable insights into the pathogenesis and aid in the diagnosis of the disease.

Conflict of interest: The authors have no conflicts of interest to report.

Authors' Contributions: EB and KB contributed to the project idea, design and execution of the study. EB, OM, and AK contributed to the acquisition of data. EB and FK analysed the data. EB, and FK drafted and wrote the manuscript. EB, and FK reviewed the manuscript critically. All authors have read and approved the finalized manuscript.

Ethical approval: This study is not subject to the permission of HADYEK in accordance with the "Regulation on Working Procedures and Principles of Animal Experiments Ethics Committees" 8 (k). The data, information and documents presented in this article were obtained within the framework of academic and ethical rules.

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