RESEARCH ARTICLE

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Investigation of Lipid Mobilization and Oxidative Stress Parameters in The Serum Before and After Surgery of Cows with Left Displacement Abomasum

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Abstract

Left Abomasum Displacement (LDA) is one of the most important metabolic diseases caused by negative energy balance during the early lactation period for high milk efficient cows. This study aimed to investigate the lipid mobilization and oxidative stress parameters in cows with LDA before and after the operation. In this research, cows with LDA (n=16) were divided into three groups that are before operation (pre-op LDA), immediately after the operation (post-op LDA), and on the 10th day after the operation (post-op 10 LDA). Control groups were formed from early lactation cows (n=8) and dry period (n=8). In serum samples collected from the study groups, total cholesterol, HDL and LDL cholesterol, triacylglycerol, free fatty acid (FFA), β-hydroxybutyric acid (BHBA), malondialdehyde (MDA) levels, and AST, GGT activities were determined spectrophotometrically, total antioxidant level (TAS), total oxidant level (TOS) and paraoxonase 1/arylesterase (PON1/ARES)] enzyme activity was measured according to the procedure of the colorimetric kit. Serum TOS and MDA levels increased in cattle with pre-op LDA compared to control groups, and MDA levels decreased to normal levels in both groups after the operation. TAS levels and PON1/ARES activities decreased in cattle with pre-op LDA compared to control groups and increased gradually in post-op groups. Serum total cholesterol, HDL, and LDL cholesterol levels decreased in cattle with pre-op LDA compared to the control groups and did not return to normal levels in the groups with post-op LDA. While BHBA levels and AST activities increased in cattle with pre-op LDA compared to control groups, they reached normal values in cattle with LDA on the post-op 10th day. It has been concluded that in evaluating the diagnosis, treatment, and prognosis of the disease in dairy cows with LDA, oxidative stress parameters such as TAS, TOS, and PON1/ARES may be used together with lipid parameters.

Keywords: Dairy cow, displacement abomasum, lipid mobilization, oxidative stress.

INTRODUCTION

Abomasum Displacement (AD) is one of the economically important and multifactorial digestive system diseases frequently encountered in high milk-yielding cows. It mostly occurs within 2-4 weeks (transitional period) after birth. Etiological factors are mainly disturbances in energy metabolism that partially begin in the dry period. Apart from that, stress is closely related to nutritional and metabolic disorders. Decreased abomasal contractility, atonia, dilatation, decreased ruminal volume, hypocalcemia, endotoxemia, alkalemia, hypergastrinemia, and hyperinsulinemia may be predisposing factors for displacement. Meanwhile, genetic predisposition should not be ignored. 80-90% of abomasum displacements are left abomasum displacements (LDA). In LDA, the abomasum slides left and ventrally towards the rumen. In addition, the omasum, reticulum, and liver are also displaced (Maden et al. 2012; Sezer et al. 2012; Aly et al. 2016). Many cattle with LDA are affected by fatty liver and inflammatory disorders or concomitant diseases such as mastitis, metritis, placental abruption, and bacterial infections (pneumonia, etc.). Thus, sudden decreases in milk yield are seen as a result of loss of appetite and nutritional stress. The disease has great economic importance in dairy cattle due to treatment costs and loss of production. 95% of left-displaced cattle return to normal after surgical correction. Surgical intervention is a widely accepted and cost-effective treatment to reduce the financial loss caused by AD. Correction of abomasal motility causes gas evacuation and returns the abomasum to its normal anatomical position (Markiewicz et al. 2009; Guzelbektes et al. 2010; Aly et al. 2016)

Reactive oxygen species (ROS) occur in living organisms under physiological and pathological conditions. They are neutralized by enzymatic and non-enzymatic antioxidants. If the balance between ROS formation and the antioxidative system is disturbed, oxidative stress occurs. Oxidative stress is thought to be the main risk factor in the reduction of mechanisms and the development of diseases. Farm animals, especially young animals in the first week of their lives and animals in the transition period are in the high-risk group for oxidative stress. It has been reported in recent years that oxidative stress is also effective in the pathogenesis of AD (Fürll et al. 2003; Celi P, 2011; Durgut et al. 2016).

Negative energy balance (NEB), which causes fat mobilization from adipose tissue, is seen in transitional animals with increased LDA risk. Accordingly, high concentrations of free fatty acids (FFAs) are produced in the blood. The increased FFA enters the mitochondria of

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hepatocytes and is then oxidized to produce energy. Subsequently, increased oxidation of FFAs generates a large amount of ROS and causes an increase in lipoperoxide formation. As a result, changes occur in the prooxidative/antioxidative state. These changes hurt immune and inflammatory functions. This inflammatory response may alter gastrointestinal motility and further trigger abomasal hypomotility (Turk et al. 2008; Ghazy et al. 2016). In addition, it has been determined that loss of appetite and consequently increased beta-hydroxybutyric acid (BHBA) levels in cattle with LDA have oxidative stress effects on smooth muscle cells (Tian et al. 2014). As a result, it has been suggested that BHBA may cause some stomach diseases, including bovine LDA (Tian et al. 2014). In short, lipid metabolism and oxidative stress in cattle during the lactation period and especially during the transition period seem to be a part of metabolic adaptation against low energy balance (Turk et al. 2013). Therefore, studies on clinical and laboratory findings of cattle with LDA have an important role in controlling the disease and preventing its complications. Although there are many studies on the effect of AD on some biochemical changes that reflect the nutritional status of cattle in the postpartum period, limited studies are evaluating the oxidant-antioxidant status in cattle with LDA (Hasanpour et al. 2011; Maden et al. 2012; Mamak et al. 2013; Aly et al. 2016; Durgut et al. 2016).

The present study, it was aimed to investigate the lipid mobilization and some oxidative stress parameters before and after the operation in cattle with LDA. Thus, it is expected that the data obtained will contribute to the information about the diagnosis, treatment, and prognosis of the disease.

MATERIALS AND METHODS

Selection of Animals and Collection of Serum Samples

The patient group of this project consists of Holstein cattle (2.5-3 years old) diagnosed with LDA in early lactation (1-3 weeks of lactation) and referred to the operation who applied to the Surgery Clinic of Veterinary Faculty in Burdur Mehmet Akif Ersoy University (Turkey) between 2017 and 2018 years. The study protocol was approved by the Burdur Mehmet Akif Ersoy University Animal Experiments Local Ethics Committee (Burdur/ TURKEY, Approval number, 304; Approval date, 02 August 2017). Auscultation and ausculto-percussion were used in the clinical diagnosis of abomasum displacement. These procedures were performed at the level of the 11th, 12th, and 13th ribs, in the intercostal space, and the left fasting trough. Routine examinations were performed by listening to "metallic ringing" on auscultation and "ping" sounds on ausculto-percussion. In animals diagnosed with LDA, the abomasum was fixed to the anatomical sites by applying the left paralumbal abomasopexy technique with a toggle pin (Wilson DG, 2008). After the operation, i.m. antibiotic (Redipen injectable suspension 100 ml/Sanovel) treatment was administered for five days.

Sick animals were followed at three different times before the operation (pre-op LDA), immediately after the operation (post-op LDA), and on the 10th day after the operation (post-op 10 LDA). In addition, the control group created for comparison was formed from clinically healthy Holstein cattle in early lactation (n=8) and dry period (6-9 months pregnant, n=8) cattle from Burdur region, TURKIYE farms.

Blood samples were drawn in vacuum tubes with gel from the jugular vein of sick animals grouped pre-operatively (pre-op LDA), immediately post-operatively (post-op LDA), and 10 days post-operatively (post-op10 LDA). Similarly, the blood of the control group cattle (early lactation and dry period) was also collected in gel vacuum tubes. Collected blood was centrifuged following coagulation at 500xg for 15 minutes and the serums were separated. Serum samples were stored at -20ºC to measure lipid parameters and oxidative stress markers.

Measurement of Serum Oxidative Stress Parameters

Malondialdehyde (MDA) Level Assay. MDA, which was revealed as a marker of lipid peroxidation (LPO) as a result of degradation of membrane lipids due to oxidative damage, was performed according to modification of the methods of Satoh (1978) and Yagi (1984). The method is based on the spectrophotometric measurement of the pink-colored MDA-TBA2 complex formed as a result of the reaction of malondialdehyde (MDA), one of the aldehyde products of LPO, and thiobarbituric acid (TBA) at 532nm.

Paraoxonase 1/Arylesterase (PON1/ARES) Activity Assay. PON1 enzyme activity was determined using the Rel Assay Diagnostics (Gaziantep/Turkey) Arylesterase (ARES) activity measurement kit. One unit of ARES activity is 1 μmol phenol/min and expressed as kU/L serum (Ayar et al. 2017; Haagen and Brock, 1992).

Serum Total Oxidant Status (TOS) and Total Antioxidant Status (TAS) Assay. Colorimetric Rel Assay Diagnostics (Gaziantep/Turkey) kit was used for serum TOS and TAS measurement. Measurements were made according to the kit principle (Erel O, 2004; Erel O, 2005).

Measurement of Serum Lipid Parameters

Serum T-Chol was determined colorimetrically according to the method of Zak et al. (1957), and serum HDL-Chol was done according to the method of Warnick et al. (1985). Serum LDL-Chol was calculated from a formula according to Friedewald et al. (1972). Serum-free fatty acid (FFA) (Biovision, USA) and β-hydroxybutyric acid (BHBA) (Cayman, USA) measurements were performed according to the colorimetric kit procedures. Triacylglycerol (TG) and gamma-glutamyl transferase (GGT) measurements were performed in the Gesan Chem 200 (Italy) autoanalyzer with the kit reagents. Serum aspartate transaminase (AST) enzyme activity was performed according to Reitman and Frankel's method (1957).

Statistical Analysis

The data of the research were analyzed with SPSS 24.0 package program. Continuous variables were expressed as mean ± standard deviation, median (minimum and maximum values), and categorical variables were expressed as numbers and percentages. Shapiro-Wilk test was used to examine the fit for normal distribution. One-Way Analysis of Variance in comparison of independent group differences when parametric test assumptions are met; When parametric test assumptions were not met, Kruskal Wallis Analysis of Variance was used to compare independent group differences. Tukey and Bonferroni corrected the Mann-Whitney U test used for pairwise comparisons when there was a significant difference between the three groups. Analysis of Variance in Repeated Measures when parametric test assumptions are provided independent group comparisons; Friedman Test was used when parametric test assumptions were not met. Bonferroni method and Wilcoxon paired-sample test with Bonferroni correction was used for pairwise comparisons

when there were significant differences between the three measurements. In addition, Pearson Correlation analysis was applied to examine the relationships between numerical variables. The statistically significant difference of $p<0.05$ was accepted.

RESULTS

MDA and TOS as lipid peroxidation markers and PON1/ARES and TAS parameters as antioxidant parameters were evaluated in cattle with LDA and control group (Table 1). An increase in serum TOS levels was observed in groups with LDA compared to control groups, but this increase was statistically significant (p=0.008) only in the post-op 10 LDA group. No significant change was observed between groups with LDA (p=0.364) (Figure 1). MDA levels were found to be significantly increased in cattle with pre-op LDA compared to control groups (p=0.002) (Figure 2). The serum TAS values were significantly lower (p=0.0001) in the pre-op LDA group compared to the control groups. Although there was a gradual increase in TAS levels in the post-operative LDA groups no statistically significant difference was found compared to the control groups (Figure 3). PON1/ARES activities were significantly lower in the pre-op LDA group than in the control group (p=0.0001) and post-operative groups (p=0.0001). Also, post-op LDA and post-op 10 LDA groups had significantly higher PON1/ARES activity than the control groups (p=0.0001) (Figure 4).

Table 1. Changes in oxidative stress parameters between control groups (Dry and Lactation) and groups of dairy cattle with LDA.

		Dry Period (Control 1)	Lactation Period (Control 2)	Pre-op LDA (Patient 1)	Post-op LDA (Patient 2)	Post-op10 LDA (Patient 3)	p1	p2	p3	p4
TOS (µmol/l)	A.O ± S.S Med (min-max)	3.29 ± 2.53 2.29 (0.29-7.94)	4.4 ± 3.33 4.8 (0.29-8.82)	8.47±8.33 5.74 (1.47 - 28.53)	8.47 ± 8.33 5.74 (1.47 - 28.53)	6.51 ± 4.37 5.61 (0.59 - 15.88)	0.173 (kk=3.507)	0.131 (F=2.184) -	0.008* (F=5.817) α; β	0.364 (F2=1.045) -
TAS (mmol/l)	A.O ± S.S Med (min-max)	0.8 ± 0.41 0.58 (0.43 - 1.56)	0.84 ± 0.3 0.82 (0.36 - 1.31)	**0.25 ± 0.14** 0.23 (0.08 - 0.63)	**0.25 ± 0.14** 0.23 (0.08 - 0.63)	0.64 ± 0.2 0.72 (0.23 - 0.84)	0.0001* (kk=20.235) α; β	0.367 (kk=2.006) -	0.569 (kk=1.127) -	0.0001* (F2=62.09) φ; ψ; γ
PON1/ ARES (kU/l)	A.O ± S.S Med (min-max)	943.24 ± 116.49 942.26 (779.07 - 1092.28)	996.87 ± 175.32 983.71 (776.44 - 1219.93)	**740.99 ± 105.66** 719.19 (629.05 - 985.68)	**740.99 ± 105.66** 719.19 (629.05 - 985.68)	1784.17 ± 307.36 1877.93 (1234.41 - 2156.92)	0.0001* (kk=15.897) α; β	0.0001* (kk=23.348) α; β	0.0001* (F=544.349) α; β	0.0001* (F2=404.6) φ; ψ; γ
MDA (µmol/l)	A.O ± S.S Med (min-max)	1.92 ± 0.58 2.13 (1.14 - 2.6)	2.35 ± 2.13 1.72 (0.73 - 7.38)	**4.79 ± 3.14** 3.38 (1.77 - 13.42)	**4.79 ± 3.14** 3.38 (1.77 - 13.42)	1.66 ± 0.36 1.66 (1.04 - 2.08)	0.002* (kk=12.712) α; β	0.47 (kk=1.511) -	0.085 (kk=4.93) -	0.0001* (kk2=20.85) φ; γ

*p<0.05 statistically significant difference; p1: control 1- control 2 - patient 1; p2: control 1- control 2 - patient 2; p3: control 1 - control 2 - patient 3; p4: only difference between patient groups; α: control 1 - patient groups; β: control 2 - patient groups; δ: control 1 - control 2; φ: patient 1 - patient 2; ψ: patient 1 - patient 3 ; γ: patient 2 - patient 3; kk: Kruskal Wallis Analysis of Variance; F: One-Way Analysis of Variance; kk2: Friedman Test; F2: Analysis of variance in repeated measurements

Table 2. Changes in biochemical lipid parameters in control groups (Dry and Lactation) and groups of dairy cattle with LDA

		Dry Period (Control 1)	Lactation Period (Control 2)	Pre-op LDA (Patient 1)	Post-op LDA (Patient 2)	Post-op10 LDA (Patient 3)	p1	p2	p3	p4
TG (mmol/l)	A.O ± S.S Med (min-max)	0.24 ± 0.08 0.22 (0.17 - 0.43)	0.22 ± 0.19 0.16 (0.05 - 0.64)	0.26 ± 0.06 0.28 (0.13 - 0.36)	**0.15 ± 0.05** 0.16 (0.07 - 0.23)	**0.15 ± 0.06** 0.13 (0.09 - 0.31)	0.142 (kk=3.899) -	0.055 (kk=5.795) -	0.021* (kk=7.771) α	0.0001* (F2=17.538) φ; ψ
T-Chol (mmol/l)	A.O ± S.S Med (min-max)	3.77 ± 0.39 3.78 (3.03 - 4.26)	5.3 ± 0.85 5.24 (4.24 - 6.43)	**2.31 ± 0.88** 2.13 (1.18 - 4.57)	1.66 ± 0.35 1.6 (1.22 - 2.3)	2.15 ± 0.51 2.08 (1.62 - 3.6)	0.0001* (F=39.815) δ; α; β	0.0001* (kk=26.027) α; β	0.0001* (kk=25.46) α; β	0.001* (F2=8.373) φ; γ
HDL-Chol (mmol/l)	A.O ± S.S Med (min-max)	1.96 ± 0.61 1.99 (1.27 - 2.67)	3.17 ± 0.54 3.17 (2.19 - 3.86)	**1.81 ± 0.6** 1.73 (1.04 - 3.27)	1.13 ± 0.37 1.12 (0.63 - 1.85)	1.75 ± 0.37 1.74 (0.99 - 2.45)	0.001* (kk=13.604) β; δ	0.0001* (kk=21.412) β	0.0001* (kk=15.582) β; δ	0.0001* (F2=13.157) φ; γ
LDL-Chol (mmol/l)	A.O ± S.S Med (min-max)	1.71 ± 0.48 1.71 (1 - 2.3)	2.03 ± 0.94 2.11 (0.51 - 3.27)	**0.5 ± 0.5** 0.34 (0.01 - 1.7)	0.45 ± 0.41 0.35 (0.02 - 1.61)	0.33 ± 0.29 0.25 (0.02 - 1.04)	0.0001* (kk=18.00) α; β	0.0001* (kk=19.884) α; β	0.0001* (kk=21.61) α; β	0.74 (kk2=0.603) -
AST (U/l)	A.O ± S.S Med (min-max)	8.98 ± 0.67 8.66 (8.4 - 10.33)	7.61 ± 0.88 7.84 (6.47 - 8.92)	**21.84 ± 13.01** 15.84 (9.6 - 45.6)	18.96 ± 13.23 14.16 (7.68 - 45.6)	10.95 ± 4.53 10.56 (6.72 - 24)	0.0001* (kk=24.713) α; β	0.0001* (kk=16.478) β	0.041* (kk=6.366) β	0.001* (kk2=13.238) φ; ψ
GGT (U/l)	A.O ± S.S Med (min-max)	16.53 ± 5.97 14.74 (10.4 - 25.43)	22.78 ± 3.61 23.76 (15.26 - 26.59)	34.5 ± 20.52 24.74 (13.99 - 80.46)	35.87 ± 21.67 23.76 (12.83 - 77.92)	31.37 ± 14.36 22.95 (15.95 - 57.34)	0.036* (kk=6.673) α	0.046* (kk=6.141) α	0.036* (kk=6.675) α	0.074 (F2=2.842) -
FFA (µmol/l)	A.O ± S.S Med (min-max)	209 ± 98.24 209 (75 - 330)	196.88 ± 59.73 215 (75 - 262)	207.38 ± 79.54 215 (35 - 316)	209.06 ± 101.22 229 (21 - 424)	241.38 ± 96.82 256 (75 - 384)	0.882 (kk=0.252) -	0.949 (F=0.052) -	0.472 (F=0.772) -	0.108 (F2=2.401) -
BHBA (mmol/l)	A.O ± S.S Med (min-max)	0.52 ± 0.21 0.57 (0.18 - 0.87)	0.84 ± 0.89 0.57 (0.38 - 3.04)	**2.1 ± 1.76** 1.54 (0.18 - 5.37)	1.74 ± 1.55 1.35 (0.24 - 4.98)	**0.93 ± 0.66** 0.85 (0.28 - 2.43)	0.033* (kk=6.801) α	0.235 (kk=2.895) -	0.489 (kk=1.43) -	0.01* (kk2=9.125) ψ

*p<0.05 statistically significant difference; p1: control 1 - control 2 - patient 1; p2: control 1 - control 2 - patient 2; p3: control 1 - control 2 - patient 3; p4: the only difference between patient groups; α: control 1 - patient groups; β: control 2 - patient groups; δ: control 1 - control 2; φ: patient 1 - patient 2; ψ: patient 1- patient 3; γ: patient 2 - patient 3; kk: Kruskal Wallis Analysis of Variance; F: One-Way Analysis of Variance; kk2: Friedman Test; F2: Analysis of variance in repeated measurements

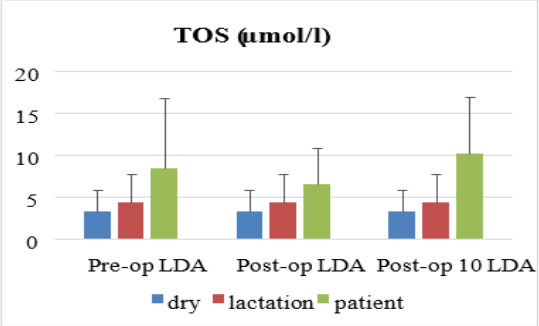

Figure 1. Changes in serum TOS levels between groups with LDA and control groups

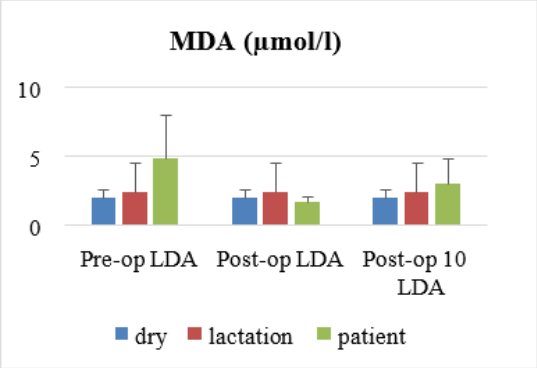

Figure 2. Changes in serum MDA levels between groups with LDA and control groups

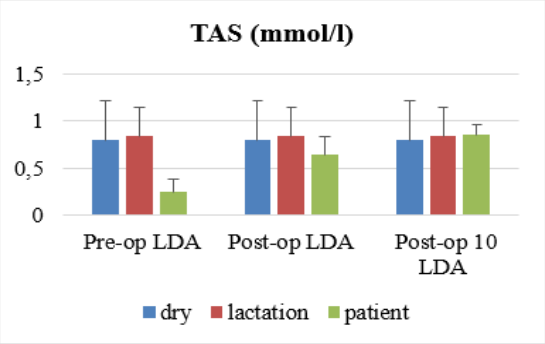

Figure 3. Changes in serum TAS levels between groups with LDA and control groups

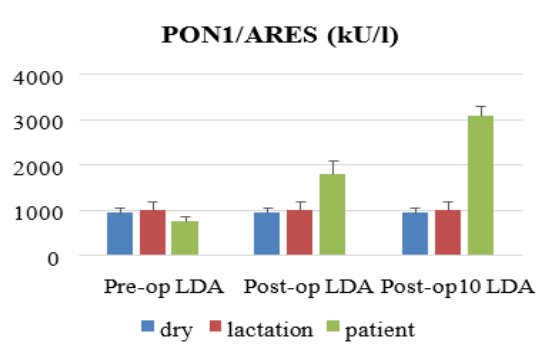

Figure 4. Changes in serum PON1/ARES activities between groups with LDA and control groups

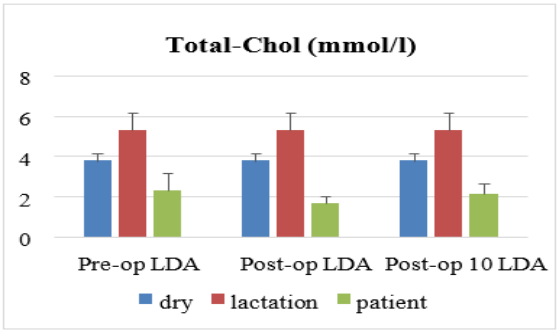

Figure 5. Changes in serum total cholesterol levels between groups with LDA and control groups

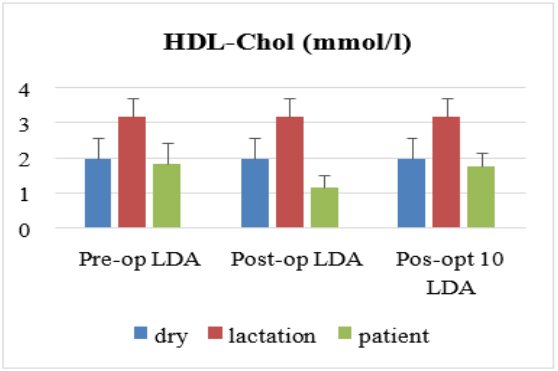

Figure 6. Changes in serum HDL cholesterol levels between groups with LDA and control groups

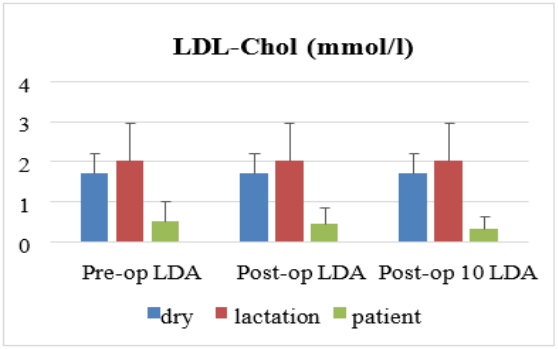

Figure 7. Changes in serum LDL cholesterol levels between groups with LDA and control groups

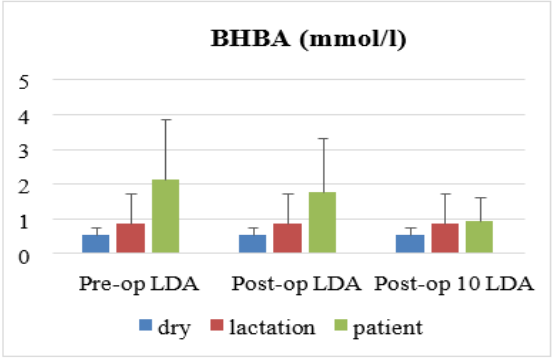

Figure 8. Changes in serum BHBA levels between groups with LDA and control groups

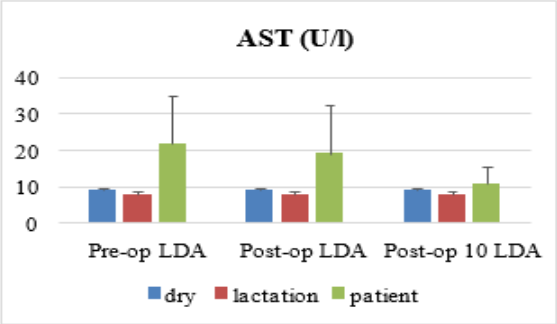

Figure 9. Changes in serum AST activity between groups with LDA and control groups

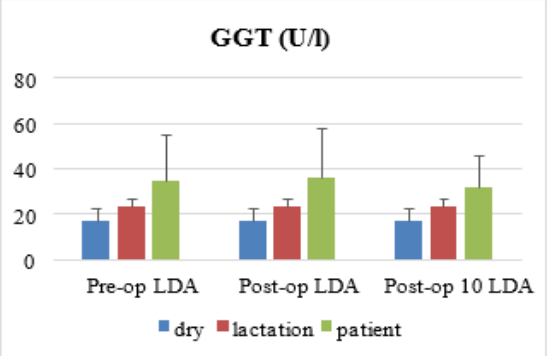

Figure 10. Changes in serum GGT activity between groups with LDA and control groups

Biochemical parameters related to lipid metabolism and fatty liver were presented in Table 2. Serum T-Chol levels in LDA groups were found significantly lower than in both control groups (p=0.0001). (Figure 5). Serum HDL-Chol level was determined significantly higher in control 2 (lactating cattle) than in control 1 (dry cows) (p=0.0001). Also, cattle with LDA were found significantly lower HDL-Chol levels than control groups (p=0.0001) (Figure 6). Serum LDL-Chol level of groups with LDA was detected significantly lower (p= 0.0001) than in control groups. However, for serum LDL-Chol levels was not found a significant statistical difference among groups with LDA (p>0.05) (Figure 7). Serum BHBA level was found significantly higher in the pre-op LDA group than in the control 1 (dry cows) (p=0.033) and post-op 10 LDA group (p=0.01) (Figure 8). Serum AST activity was assayed significantly higher in the pre-op LDA group compared to controls (p=0.0001) and to groups with post-op LDA (p=0.001) (Figure 9). Serum GGT activity was determined significantly higher in groups with LDA (p=0.036, p=0.046, p=0,036) than in the control 1 group (Figure 10).

DISCUSSION AND CONCLUSION

Abomasum displacement, especially LDA, is an economically important, multifactorial disease of high-yielding cows and occurs in 80%-90% of them within 3-4 weeks postpartum. Although diseases such as fatty liver, ketosis, and hypocalcemia are risk factors for AD, the cause of AD could not be clarified by etiology or physiopathology studies (Maden et al. 2012). Studies on clinical and laboratory findings of cattle affected by AD have an important role in controlling the disease and preventing complications. Since the stress factor is effective in the formation of AD, this situation is determined by oxidative activity and the evaluation of serum antioxidant status in cattle has special importance (Hasanpour et al. 2011). A few studies evaluating oxidant-antioxidant status in cattle with LDA are available (Hasanpour et al. 2011; Maden et al. 2012; Mamak et al. 2013; Aly et al. 2016; Durgut et al. 2016). Although these studies are promising, further research is required to use new diagnostic and therapeutic parameters for clinical and prognostic. The present study aimed to investigate some serum lipid parameters and oxidative stress markers before and after the operation in cattle with LDA by comparing them with healthy cattle.

Mudron et al. (1997) found a maximum increase in MDA levels in blood serum samples taken 60 minutes after the operation in Holstein cattle with LDA (n=10). They observed that MDA levels returned to preoperative levels at the 24th postoperative hour. Also, they determined a positive correlation between liver MDA and TG levels. It was shown that MDA was significantly increased in cattle with LDA (Maden et al. 2012; Aly et al. 2016). On the other hand, Mamak et al. (2013), could not detect a change in MDA when cattle with RDA and LDA were compared with healthy groups. In recent years, Durgut et al. (2016) stated that they first determined the TOS, TAS, and oxidative stress index (OSI) in cattle with AD according to the methods of Erel O (2005; 2004). In this study, they reported that TOS, TAS, and OSI values in cattle with LDA did not change when compared to the control group. In another study, it was reported that while reactive oxygen metabolites (ROMs) and OSI values were significantly higher in cows with LDA, biological antioxidant potential (BAP) decreased compared to healthy cows (Fiore et al. 2019). In our study, we found that serum TOS levels increased in groups with LDA, especially in the group with post-op10 LDA, compared to the control groups as reported by Durgut et al. (2016). We determined that MDA levels, another oxidation marker, increased significantly in cattle with pre-op LDA compared to the control groups (p=0.002) and decreased in the post-op groups and returned to the control group values. According to these results, it can be thought that LDA causes lipid peroxidation and ischemic damage.

PON1 is used as a biomarker in oxidative stress because it is protective against oxidation, in inflammation when it is considered a negative acute-phase protein, and in liver diseases, because it is synthesized in the liver. Although PON1 has been studied extensively in human medicine, it has been studied more limitedly in cattle in veterinary medicine, and studies are needed to elucidate the function of PON1. Ahmadi et al. (2016) reported that PON1 activity was decreased in cattle with fatty liver, but this decrease was not significant. In addition, Farid et al. (2013) showed that PON1 activity was lower in cattle with fatty liver than in control cattle. There is a decrease in PON1 activity in dairy cattle in late pregnancy and early lactation. This shows that oxidative stress can cause various disorders in the peripartum period. Therefore, it is suggested that serum PON1 activity can be used in the diagnosis of diseases during this period or as an indicator of serum antioxidant capacity (Turk et al. 2013, 2008, 2004; Antončić-Svetina et al. 2011; Folnožić et al. 2015; Kulka et al. 2016). As a result of our literature review, we could not find any article investigating PON1 activity in cattle with LDA. In our study, which is a first in this sense,

we observed that PON1/ARES activity in cattle with LDA decreased significantly (p=0.0001) in cattle with pre-op LDA compared to the control group. In the post-operative groups (post-op LDA and post-op 10 LDA), we determined that PON1/ARES activity gradually increased and even above the control values. In addition, it has been reported that the main cause of PON1 decrease in cattle with fatty liver is increased proinflammatory cytokines (TNF-α) in the liver and serum. Also, the decreased PON1 activity can be observed in increased free radical concentrations, inactivation of PON1 after hydrolysis of lipid peroxides, and occurred changes in the structure and composition of HDL (Ahmadi et al. 2016). Thus, our study predicts that the decrease in PON1 activity in cattle with LDA can be used in the diagnosis of fatty liver formation in cattle with LDA when evaluated together with liver function tests and lipid peroxidation parameters.

According to the methods of Erel O (2005; 2004), Durgut et al. (2016) stated that they could not find a difference in TAS concentration when compared with the control group in their study, which they stated was done for the first time in cattle with AD. In this sense, our study is the second study using the same method and kit. In our study, we determined that TAS concentration decreased significantly in cattle with pre-op LDA compared to control groups (dry and early lactation), and reached control group values in cattle with post-op10 LDA. Fürll et al. (2003) found higher TAS concentrations in cattle with LDA. They observed that the TAS concentration did not differ significantly after the correction of AD. It has been suggested that serum antioxidant levels (GPx and Se) in cows with LDA are lower than in healthy cattle, (Hasanpour et al. 2011) and that pre-and post-operative antioxidant supplementation can be used to support the treatment (Locher et al. 2011; Aly et al. 2016). According to our results, it was concluded that the determination of TAS in cattle with LDA may be an important parameter for the diagnosis of the disease and the evaluation of the effectiveness of the treatment.

In the dry period, increased FFA was associated with the risk of AD. It has been noted that the risk of AD is higher in cattle with increased FFA concentration after birth (postpartum, early lactation) than in cattle with post-partum normal FFA concentration. In addition, it was announced that increased BHBA concentration in dry period cattle increases the risk of AD formation by approximately 4 times. (LeBlanc S, 2010; McArt et al. 2013; Turk et al. 2013; Puppel and Kuczyńska, 2016; De Koster et al. 2018). In our study, we determined that the BHBA concentration increased in early lactation compared to the dry period in healthy cattle, while could not find a significant difference in FFA levels between all groups. Markiewicz et al. (2009) found a statistically insignificant increase in the FFA levels of cattle with AD compared to the control group in early lactation. Our results are in agreement with those. In this case, it can be concluded that FFA measurements are more variable depending on the methods and kits studied. Also, we observed that BHBA levels increased in cattle with pre-op LDA compared to the control group and gradually decreased in the post-operative groups. On the 10th postoperative day (post-op10 group), we observed that BHBA levels in cattle with LDA decreased to the control group levels. This can be explained by the increase in lipid mobilization from adipose tissue in response to NEB, which occurs as a result of the increased energy need for milk secretion and milk fat synthesis in cattle with LDA in the early lactation period. The return of BHBA to control group values in a group with post-op 10 LDA is also an important finding in terms of evaluating the effectiveness of the treatment. Similarly, Antanaitis et al. (2015) determined that BHBA concentrations increased in cattle with LDA compared to control cattle, and BHBA levels decreased on the 21st day after the operation. The importance of determining FFA concentrations in the first week before calving and BHBA concentrations in the first week after calving was emphasized in transitional herd management and especially against LDA risk (LeBlanc et al. 2005). The results of our study show that BHBA concentration, rather than FFA, can be used as an effective control parameter in transitional period and cattle with LDA.

Khalphallah et al. (2016) found to be T-Chol was significantly reduced in groups with AD before the operation. Durgut et al. (2016) found a significant decrease in serum T-Chol, HDL, and LDL- Chol levels, and an increase in serum TG levels in cattle with AD when compared to control groups. Sevinc et al. (2002), on the other hand, reported that HDL-Chol levels decreased in cattle with AD when compared to healthy cattle, while there was no significant change in LDL-Chol, VLDL-Chol, TG, and glucose levels. Other researchers showed that T-Chol decreased significantly in cattle with AD (Katoh 2002; Qu et al. 2013; Khalphallah et al. 2016). Sezer et al. (2012) determined serum T-Chol, LDL, and HDL-Chol levels below normal values in cattle with LDA before and after the operation (in 24. and 72. hours). Klevenhusen et al. (2015) reported that serum T-Chol levels did not change in cattle with LDA compared to healthy cattle. In our current study, we found a significant decrease in serum T-Chol, HDL-Chol, and LDL-Chol levels in cattle with pre-op LDA compared to control groups. This may be an indication of impaired lipoprotein metabolism. Serum TG levels are insignificantly increased in the group with pre-op LDA compared to the control groups. We also observed a significant decrease in TG levels in groups with the post-op 10 LDA, which can be attributed to a slight increase in serum FFA concentration.

In cattle with LDA AST activity increased compared to control cattle (Antanaitis et al. 2015; Mokhber Dezfouli et al. 2013) and decreased on the 21st day after the operation (Antanaitis et al. 2015). Guzelbektes et al. (2010) showed that GGT activity increased in cattle with LDA, while they could not detect a significant difference in serum AST activity of cattle with AD when compared with healthy cattle. Also, it has been reported that serum AST and GGT activities were significantly increased in cattle with AD when compared to healthy cattle (Sevinc et al. 2002; Klevenhusen et al. 2015; Puppel and Kuczyńska 2016). Maden et al. (2012) observed that AST activity in cattle with LDA increased compared to control cattle in early lactation, but there was no change in GGT activity. Increases in serum GGT activity may indicate liver cell damage in cattle with LDA, possibly leading to fatty liver disease. In addition, the increase in AST activity has been predicted to result from the mobilization of muscle proteins or degradation of proteins to release glucogenic amino acids, which are glucose precursors. This was supported by the determination of low milk protein concentration in cattle with LDA. Van Winden et al. (2003) emphasized that NEB-related BHBA and AST activities of postpartum cattle can be used to determine the development of LDA. Yildiz et al. (2019) observed that AST and GGT enzymes showing liver-related damage

started to increase in cases where the BHBA value was 1 mmol/L and above. In addition, it can be concluded that the increase in AST and GGT in cattle with LDA indicates hepatic damage, and the decrease in TG and cholesterol indicates liver dysfunction thus protein and lipid metabolism is damaged (Ghazy et al. 2016). Farid et al. (2013) reported that serum AST activity, FFA, BHBA, total bilirubin, and TG values increased in cattle with fatty liver, while T-Chol, HDL, VLDL, LDL, phospholipid, and albumin values decreased. In our current study, we observed that serum AST activity increased significantly in the pre-op LDA group compared to the control group, consistent with the above kinds of literature.

In our study, we observed that T-Chol and HDL-Chol levels decreased and MDA levels increased in cattle with LDA. This indicates that lipid peroxidation, which leads to cell death, increases as a result of increased uptake of FFAs by the liver. Increased lipid peroxidation may also be due to TG accumulation in the bovine liver. As a result, HDL-Chol and LDL-Chol are also reduced due to the lipoprotein metabolism disorder in the liver. It has been reported that BHBA significantly decreased the activities of antioxidant enzymes and increased lipid peroxidation. Thus, it was suggested that oxidative stress plays a role in apoptosis triggered by BHBA (Tian et al. 2014). In our study, similarly, we observed that while BHBA concentration increased in the pre-op LDA group, TAS level decreased significantly and TOS level increased. We also determined that PON1/ARES (antioxidant) decreased significantly while MDA (oxidant) increased significantly in the pre-op LDA group. Farid et al. (2013) emphasized that FFA, BHBA, AST, and lipid profile are convenient diagnostic parameters among fatty liver markers, and their combination with PON1 will provide high sensitivity and specificity.

In conclusion, in cattle with pre-op LDA we observed a decrease in PON1/ARES activity, an increase in AST activity, BHBA concentration, and a decrease T-Chol, HDL, and LDL-Chol levels as compared to the control groups. Therefore, we concluded that PON1/ARES is associated with lipid profile and liver enzymes and may be one of the supporting parameters in the diagnosis of fatty liver and associated LDA. According to these results, we determined that oxidative stress parameters such as TAS, TOS, and PON1/ARES can be used together with lipid parameters in the diagnosis, treatment, and prognosis of the disease in dairy cows with LDA. We think that our study will lead to more extensive research on these oxidative stress parameters, which are still new and open to research in the field of Veterinary Medicine. In addition, we think that antioxidant supplements both with feed and parenteral may be effective in treating and prognosis the disease for the transition period cattle.

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Conflict of Interest

The authors declare that they have no competing interests.

Authorship contributions

Concept: T.B., K.Y., Design: T.B., K.Y., Data Collection or Processing: T.B., K.Y., N.A., Analysis or Interpretation: T.B., N.A., Literature Search: T.B., N.A., Writing: T.B., N.A.

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