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Research Article

Evaluation of iron, iron binding capacity, transferrin, some oxidative stress markers and hematological parameters in foot and mouth disease in cattle

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ABSTRACT

This study aimed to investigate the changes in serum iron, iron binding capacity, transferrin, some oxidative stress markers, and hematological and biochemical parameters in cattle infected with foot-and-mouth disease and to reveal their importance. The animal material of the study was composed of 20 Simmental cattle between 6 and 12 months of age, which were diagnosed with foot-and-mouth disease based on the results of the clinical and laboratory examinations (patient group), and the control group was composed of 10 animals selected from a different herd, with the same age group and breed characteristics and fed with the same ration. Among the hematological parameters examined in the study, the total leukocyte count (WBC (x103/μL)) was found to be higher in the patient group with statistical significance compared to the control group ($P<0.05$). Among the biochemical parameters, iron (Fe (μg/dL)), total iron binding capacity (TIBC (μg/dL)), phosphorus (P (mg/dl)), magnesium (Mg (mg/dl)), and glucose (mg/dl)) levels were found to be significantly lower ($P<0.001$); the transferrin saturation (TS (%)), reduced glutathione (GSH (mg/dL)), and alkaline phosphatase (ALP (U/L)) were found to be significantly lower ($P<0.05$); and Malondialdehyde (MDA (μmol/L)), creatine kinase (CK ((U/L)), and creatinine (Crea (mg/dl)) were found to be significantly higher ($P<0.05$) in the patient group compared to the control group. Consequently among the biochemical parameters examined in the study, the changes in the Fe (μg/dL), TIBC (μg/dL), TS (%), GSH (mg/dL), and MDA (μmol/L) levels were observed.

INTRODUCTION

Foot and Mouth Disease (FMD) is a contagious vesicular disease (Wong et al., 2020). It is a highly contagious viral disease that affects ungulates in particular (Gökce et al., 2004). The morbidity rate of the disease is 100% among susceptible animals and between 80-100% among the offspring (Gakuya et al., 2011). The agent that causes the disease is Aphthovirus, a single-stranded RNA virus from the Picornaviridae family (Gokce et al., 2004). The agent has 7 main stereotypes, which are O, A, C, SAT 1, SAT 2, SAT 3, and Asia 1, and these stereotypes have various subtypes (more than 60 strains) (Uzlu et al., 2016; Wong et al., 2020).

Serum Fe concentration is considered an inflammatory biomarker in domestic animals, and iron metabolism is impaired in many systemic diseases (Gozzelino and Arosio, 2016). Transferrin (Tf) is an important protein for the binding and transfer of iron (Gomme et al., 2005). Transferrin is a negative acute-phase protein; therefore, it decreases in inflammatory cases (Asif et al., 2016).

Iron binding capacity is an important test used in the diagnosis of iron metabolism disorders and is defined as the iron binding capacity of transferrin. There are two types of iron-binding capacity: total iron-binding capacity (TIBC) and unsaturated iron-binding capacity (UIBC). Transferrin saturation (TS) is expressed as a percentage and indicates the amount of serum Fe bound to Tf (Elsayed et al., 2016).

The pathogenesis of many diseases involves oxidative stress. Oxidative stress develops due to the impairment of the balance between oxidants and antioxidants (Ozcan et al., 2015) and leads to cellular damage (Marreiro et al., 2017). The activation of protective antioxidant defense mechanisms in cells with the stimulation of lipid peroxidation causes some changes in malondialdehyde (MDA) and reduced glutathione (GSH) levels (Uzlu et al., 2016). For this reason, reduced glutathione (GSH) and malondialdehyde (MDA) concentrations are measured to determine oxidative stress in diseases (Uzlu et al., 2016; Bozukluhan et al., 2021).

This study aimed to investigate the changes in iron, total iron-binding capacity, transferrin saturation, some oxidative stress markers, and hematological parameters in foot and mouth disease in cattle and reveal their importance.

MATERIALS and METHODS

This study was initiated after obtaining approval from the Kafkas University Local Ethics Committee of Animal Exper-

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iments (KAU-HADYEK/2022-032) and the Kars Provincial Directorate of Agriculture.

Animal material

The animal material of this study was composed of 20 Simmental cattle between 6-12 months of age, which were raised in the villages of Kars where FMD was diagnosed by the Kars Provincial Directorate of Agriculture and showed FMD symptoms (patient group), and the control group was composed of 10 animals selected from a different herd, with the same age group and breed characteristics and fed with the same ration. The clinical examinations were performed on the animals in the patient and control groups, and the T (rectal body temperature (°C)), P (pulsation (n/min)), and R (respiration (n/min)) counts were noted.

Taking blood samples

Blood samples were obtained from the infected cattle before treatment (hour 0) and from healthy cattle once, using a 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). Serum samples were obtained by centrifuging the blood samples in vacuum tubes at 3000 rpm for 10 minutes (Hettich Rotina 380R®, Hettich, Germany).

Biochemical and hematological measurements

Total leukocyte count (WBC x10^3/µL), erythrocyte count (RBC x10^6/µL), percentage of hematocrit (Hct %), hemoglobin concentration (Hb g/dL), and platelet count (Thr x10^3/µL) were measured from whole blood samples using a complete blood count device (VG-MS4e®, Melet Schloesing, France). Alanine aminotransferase [ALT (IU/L)], aspartate aminotransferase [AST (IU/L)], glucose (mg/dL), creatinine [CREA (mg/dL)], urea [UREA (mg/dL)], total protein [TP (g/dL)], lipase (U/L), creatine kinase [CK (IU/L)], calcium [Ca (mg/dl)], phosphorus [(P (mg/dl)], magnesium [Mg (mg/dl)], amylase ((U/L), 25-Hydroxy Vitamin D (ug/L), gamma-glutamyl transferase [GGT (U/L)], alkaline phosphatase [ALP (U/L)], and total bilirubin [TBIL (mg/dl)] enzyme activities were measured in the serum samples using a fully automatic biochemistry device (Mindray BS120®, Mindray Medikal Teknoloji Istanbul, Turkiye).

Malondialdehyde (MDA) was measured according to the method reported by Yoshoiko et al., (1979), and reduced glutathione (GSH) was measured according to the method reported by Beutler et al., (1963). Iron (Fe) and unsaturated iron binding capacity (UIBC) were measured with a commercial testing kit (Biolabo, France) colorimetrically (Epoch, Biotek, USA). Total iron binding capacity (TIBC) was obtained by adding serum iron (Fe) and unsaturated iron binding capacity (UIBC) levels. Serum transferrin saturation (TS) was calculated over serum Fe and TIBC levels using the formula [TS (%)=Fe/ TIBC x 100] (Merhan and Ozcan, 2010).

Statistical analysis

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

RESULTS

In the clinical examination of the cattle included in the study, symptoms such as anorexia, excessive salivation, weight loss, high fever, vesicular lesions in the foot and mouth mucosa, lameness, and nail shedding were observed. The rectal body temperatures (°C), pulsation (n/min), and respiration (n/min) counts of the infected and healthy cattle were evaluated and presented in Table 1. Among the vital parameters, body temperature and respiratory rate were determined to be higher in the patient group with statistical significance compared to the control group ($P<0.05$). There was no statistically significant difference between the patient and control groups in terms of pulsation rate ($P>0.05$). Hematological results of the infected and healthy cattle were presented in Table 1. Among the hema-

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

Parameters	Patient (n: 20) Mean ± SEM	Control (n: 10) Mean ± SEM	P
WBC (x10^3/µL)	14.32±1.00	7.71 ±0.37	<0.001
RBC (x10^6/µL)	9.42 ±0.49	8.64 ±0.23	0.160
HCT (%)	35.70 ±1.46	31.31 ±1.89	0.085
Hb (g/dl)	9.68 ±0.37	10.73 ±0.43	0.095
THR (x10^3/µL)	504.50±25.34	416.60 ±63.88	0.225
T (°C)	39.59 ±0.19	38.68 ±0.20	0.006
P (sayı/dk)	81.00 ±3.61	68.60 ±7.51	0.102
R (sayı/dk)	34.40±2.65	24.50 ±2.46	0.024

WBC: Total leukocyte count, RBC: Erythrocyte count, HCT: Hematocrit, Hb: Hemoglobin, THR: Platelet 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 cattle.

Parameters	Patient (n: 20) Mean ± SEM	Control (n: 10) Mean ± SEM	P
Fe (µg/dL)	78.91±1.85	99.72±3.10	<0.001
TIBC (µg/dL))	212.62±3.06	237.28±3.95	<0.001
TS (%)	37.34±1.16	42.08±1.33	0.018
MDA (µmol/L)	3.70±0.19	2.52±0.14	<0.001
GSH (mg/dL)	52.32±2.90	64.34±3.47	0.018
Lipase (U/L)	30.70±0.60	29.26±0.74	0.161
Ca (mg/dl)	8.90±0.12	8.14±1.04	0.484
P (mg/dl)	5.82±0.34	7.94±0.22	<0.001
Mg (mg/dl)	1.81±0.07	2.22±0.05	<0.001
Amylase (U/L)	26.40 ±1.97	28.70 ±1.98	0.469
25-Hydroxy Vitamin D (ug/L)	35.53±3.71	31.91 ±2.98	0.529
ALT (U/L)	30.88 ±4.48	31.22 ±5.46	0.963
AST (U/L)	92.28 ±8.03	95.79 ±9.52	0.792
GGT (U/L)	21.28 ±1.79	20.54 ±1.17	0.784
ALP (U/L)	115.90 ±8.64	186.98 ±30.15	0.046
CREA (mg/dl)	1.55 ±0.14	0.91 ±0.05	<0.001
UREA (mg/dl)	105.24 ±3.98	118.87 ±5.33	0.054
TBİL (mg/dl)	0.35 ±0.15	0.11 ±0.03	0.289
TP (gr/dl)	6.86 ±0.25	6.31 ±0.31	0.203
CK (U/L)	553.16 ±112.61	279.32 ±38.29	0.031
Glucose (mg/dl)	41.40±2.65	98.10±5.82	<0.001

Fe: Iron, TIBC: Total iron binding capacity, TS: Transferrin saturation, MDA: Malondialdehyde, GSH: Reduced glutathione, Ca: Calcium, P: Phosphorus, Mg: Magnesium, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma glutamyl transferase ALP: Alkaline phosphatase, Crea: Creatinine, UREA: Urea, TBIL: Total bilirubin, TP: Total protein, CK: Creatine kinase. P<0.05 indicates statistical significance. SEM: Standard error of mean.

tological parameters, WBC ($x10^3/\mu L$) was found to be higher in the patient group with statistical significance compared to the control group (P<0.05). In addition, no statistically significant difference was found between the patient and control groups in other hematological parameters (P>0.05). Biochemical values of the infected and healthy cattle were presented in Table 2. Among the biochemical parameters, the Fe (µg/dL), TIBC (µg/dL), P (mg/dl), Mg (mg/dl), and glucose (mg/dl) levels were lower with statistical significance (P< 0.001) while TS (%), GSH (mg/dL), and ALP (U/L) were found to be significantly lower (P<0.05) in the patient group compared to the control group. In addition, MDA (µmol/L), CK ((U/L), and Crea (mg/dl) were determined to be significantly higher in the patient group compared to the control group. (P<0.05). Despite the presence of differences between the patient and control groups, no statistically significant difference was found in lipase (U/L), Ca (mg/dl), amylase ((U/L), 25-Hydroxy Vitamin D (ug/L), ALT (U/L), AST (U/L), GGT (U/L), UREA (mg/dl), TBIL (mg/dl), and TP (gr/dl) levels (P>0.05).

DISCUSSION

Clinical findings of the disease include high fever, tachypnea, and vesicular lesions in foot and mouth mucosa and various parts of the body, loss of weight, anorexia, excessive salivation, lameness, nail shed due to lesions in the feet are common in infected animals (Gakuya et al., 2011, Uzlu et al., 2016). Similar symptoms were observed during the clinical examination of the infected cattle in the present study.

In living beings, an acute phase response occurs in tumoral and immunological diseases due to inflammation and tissue damage related to infection. This response leads to local reactions, and the defense cells are activated (Yilmaz and Gokce 2017). Consequently, WBC increases (Yilmaz and Gokce 2017, Akyuz et al., 2022a). In this study, we observed that WBC was significantly higher in the patient group compared to the control group. We think that the increased number of WBCs in animals infected with FMD was a reaction of the immune system against severe inflammation and tissue damage, which occurred in many systems due to primary and secondary pathogenic factors. However, there are also studies stating that WBC does not change in FMD disease (Kar et al., 2015).

Iron has important roles as the building block of many proteins in the body, especially hemoglobin (Tapiero et al., 2001). Fe metabolism is affected by many pathological conditions such as inflammation, anemia, and renal failure that develop in living beings for various reasons (Baydar and Dabak 2014). There is a direct correlation between the incidence of diseases and Fe deficiency. Therefore, the level of Fe is frequently examined in the evaluation of inflammatory conditions. Fe level decreases rapidly in cases of severe inflammation and endotoxemia (Tsukano et al., 2020). The most important reason for the decrase in Fe level is the increased use of it by pathogenic agents (Ganz and Nemeth, 2009). In addition, the disruption of the enzyme activities that involve defense cells (Tapiero et al., 2001) and hypoferremia mediated by interleukin-6 (IL-6) are considered to be responsible (Ganz and Nemeth, 2009).

In this study, the total iron binding capacity was low ($P<0.001$) in the patient group. It was reported to be caused by the decrease in total iron binding capacity in cases of severe disease (Asif et al., 2016).

Transferrin saturation indicates the amount of serum Fe bound to transferrin. The most important reason for the decreased transferrin saturation is iron deficiency. The low level of iron in the blood indicates the use of a smaller transferrin binding area and low saturation in these binding areas (Elsayed et al., 2016). In this study, serum transferrin saturation was found to be lower in the patient group compared to the control group. The possible reason for this is the increase in the use of Fe by the pathogenic agents due to the severe course of the disease in animals with foot and mouth disease and the decrease in serum iron levels due to nutritional deficiency.

Stress factors and pathogenic agents, which play an important role in the pathogenesis of diseases, lead to an increase in the production of free radicals, weakening the antioxidant defense capacity and causing oxidative stress (Talukder et al., 2015). Lipid peroxidation is an indicator of oxidative stress that causes impairment in the structure and function of cells. Malondialdehyde (MDA), which originates from polyunsaturated fatty acids and is one of the decomposition products of lipid peroxides, is a parameter used for detecting both the degree of cellular damage (Sezer and Keskin 2014) and oxidative stress (Khoshvaghtı et al., 2014). There is an increase, particularly in the MDA level under oxidative stress (Akyuz et al., 2021). Oxidative stress plays a role in the pathogenesis of many diseases, including foot and mouth disease (Uzlu et al., 2016). It was believed that the serum MDA level increased in the patient group as a result of stress factors and cellular degeneration due to oxidative damage caused by aphthovirus.

One of the important antioxidants that prevent lipid peroxidation and the accumulation of free radicals is glutathione (GSH) (Mates, 2000). GSH is one of the nonenzymatic antioxidant defense systems. GSH is frequently measured to determine oxidative stress in the blood (Cenesiz, 2020). The level of GSH decreases during oxidative stress (Yurdakul and Saritas, 2013). Studies on foot and mouth disease have reported that GSH levels decreased in the patient groups (Uzlu et al., 2016, Cenesiz 2020). In the current study, we think that the GSH level decreased as a result of pathological changes in tissues and organs due to cellular damage caused by the increase in oxidants. One of the main reasons for this finding is the increase in free radicals and lipid peroxidation due to foot and mouth disease.

Creatinine is a toxic substance and one of the end products of muscle metabolism. Serum creatinine levels increase as a result of protein catabolism due to infectious conditions, hunger, and high fever. Blood pressure is observed to decrease in cases of fluid loss in the body. Consequently, prerenal azotemia develops due to the decrease in glomerular filtration rate, and renal functions are impaired. Therefore, serum creatinine levels increase (Sezer and Gokce, 2021). In foot and mouth disease, serum creatinine level increases depending on the damage to soft tissues such as the liver, heart, and kidney (Salim et al., 2019). In this study, serum creatinine levels were found to be higher compared to the control group because kidney damage may have been formed in the animals infected with foot and mouth disease. Studies have reported that serum magnesium levels decrease significantly as a result of impaired immune system function in acute viral infections (Yoruk et al., 2014). In this study, it was determined that serum magnesium levels decreased in animals infected with foot and mouth disease. One of the most apparent symptoms of diseases in animals is loss of appetite. In severe disease cases, a decrease in phosphorus level is observed in the body due to anorexia (Akyuz and Aydin, 2022). Another reason for the decrease in phosphorus levels is malabsorption due to enteritis (Sezer and Gokce, 2021, Akyuz et al., 2022b). In this study, it was determined that the serum phosphorus level decreased in the patient group compared to the control group. The possible cause of this is the severe course of the infection and the nutrition deficiency in the animal. In addition, serum phosphorus levels decreased due to malabsorption secondary to enteritis in the patient group infected with foot and mouth disease. Alkaline phosphatase (ALP) is an isoenzyme group located in the outer layer of the cell membrane. One of its most important tasks is to catalyze the hydrolysis of organic phosphate esters in the extracellular space. Alkaline phosphatase levels generally decrease due to nutritional deficiency (Krupaa et al., 2020). In this study, serum ALP enzyme activity was found to be lower in the patient group compared to the control group. We think that the main reason for this may be the lack of magnesium, protein, and phosphorus in the patient group due to nutritional deficiency (Coskun and Sen, 2012). One of the causes of hypoglycemia in severe infectious diseases is the decrease in glycogen due to impaired glucose metabolism in the liver (Sen et al., 2009) along with lack of appetite and hunger (Sezer and Gokce, 2021). In this study, it was determined that the blood glucose level decreased in the patient group compared to the control group. In foot and mouth disease, soft tissue damage develops especially in vital organs such as the liver and heart (Salim et al., 2019). Due to the damage to the liver, glucose metabolism is impaired, and the level of glycogen stores decreases. Furthermore, it was believed that loss of appetite and hunger due to lesions in the mouth and secondary infections in animals infected with foot and mouth disease are among the main causes of hypoglycemia. In severe inflammatory diseases, the regeneration time in soft tissues is prolonged in living organisms due to the impairment of the balance between

anabolic and catabolic activities. One of the most important reasons is the impairment of energy metabolism due to mitochondrial changes (Lepper et al., 2011) and proteolysis resulting from the impairment of transmission in cell membranes (Sezer and Gokce, 2021). Serum creatine kinase enzyme activity increases as a result of myopathy (Sezer and Gokce, 2021, Akyuz and Gokce, 2021). In this study, it was determined that serum creatine kinase enzyme activity was higher in the patient group compared to the control group.

CONCLUSION

Consequently, foot and mouth disease is an important viral infectious disease that has a severe clinical course and causes oxidative stress in cattle. Among the hematological parameters measured in the study, the number of WBCs was determined to have increased. Among the biochemical parameters, a decrease was found in Fe, TIBC, TS, GSH, P, Mg, ALP, and glucose levels while the MDA, Crea, and CK enzyme activities were found to have increased.

DECLARATIONS

Ethics Approval

Kafkas University Local Ethics Committee of Animal Experiments (KAU-HADYEK/2022-032)

Conflict of Interest

There is no conflict of interest.

Consent for Publication

All authors have permission to publish.

Author contribution

Idea, concept and design: MS, TG, OM, EA, KB, GG

Data collection and analysis: MS, TG, OM, EA, KB, GG

Drafting of the manuscript: MS, TG, OM, EA, KB, GG

Critical review: MS, TG, OM, EA, KB, GG

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request

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