Chapter

Clinical Significance of Some Acute Phase Proteins in Cattle

Kadir Bozukluhan and Oguz Merhan

Abstract

Acute phase proteins are proteins synthesized by the liver in response to the acute phase response. While these proteins are insignificant in healthy animals, their concentrations increase rapidly during infection, inflammation, or tissue damage and are used as an indicator of inflammation. Since the blood concentrations and importance levels of these clinically important proteins differ according to the animal species, they are evaluated separately for each animal species. Most of the acute phase proteins have been studied in detail in the field of human medicine and are routinely used in the diagnosis and prognosis of diseases. In the field of veterinary medicine, it has not been used sufficiently. In this book chapter, we will provide up-to-date information about acute phase proteins that are important for cattle, as well as explain that acute phase proteins can be used in the early diagnosis of diseases, in the differentiation of viral and bacterial infections, in guiding the treatment of sick animals and in determining their prognosis.

Keywords: cattle, ceruloplasmin, clinical significance, haptoglobin, serum amyloid A

1. Introduction

Acute phase response (APR) is a response following inflammation, tissue injury, infection, neoplastic growth, or immunological disorders, and this response is characterized by metabolic and systemic changes [1]. APR can be briefly expressed as changes in the concentrations of many plasma proteins that occur in relation to the response of the organism [2]. The function of APR is to protect organs from further injury, to eliminate infectious agents, to clear harmful molecules and residues for the organism, and to restore homeostasis by activating the repair process necessary for the organism to return to its normal function [3]. APR emerges as a complex reaction initiated by inflammatory mediators in the area where tissue destruction occurs and is characterized by local and systemic changes [2, 4]. Increase in capillary permeability, leukocyte migration to the inflammation site, and release of various chemical mediators take place among the local reactions occurring during APR [2]. Among the systemic reactions created by APR, there are changes in the level of acute phase proteins (APP) formed by mediators. Systemic reactions are initiated by mediators such as cytokines, glucocorticoids, and growth factors. Cytokines, which act as intracellular and intercellular signaling molecules and are soluble biological mediators, are in peptide or glycoprotein structure [5–8]. Macrophages and neutrophils arriving

at the inflammation site together with endothelial cells secrete pro-inflammatory cytokines (Interleukin "IL"-6, IL-1β, tumor necrosis factor "TNF"-α, interferon γ, IL-8, and macrophage inhibitor protein-1) [9]. While the production of APPs is accelerated by many cytokines (especially IL-6), it is inhibited by insulin and okadaic acid [10]. Cytokines, which have many different effects such as gene expression, metabolic process, and regulation of oxidation-reduction potential in the cell and ion flow in the cell membrane [9], generally stimulate APP synthesis and corticosteroids regulate cytokine activity. Pro-inflammatory cytokines such as IL-6 and IL-1 activate fibroblast and endothelial cells in the local inflammation area and allow cytokines to be secreted again. Thus, APP is synthesized from the liver as a result of the systemic inflammatory response initiated by the cytokines that enter the circulation [3, 7]. In addition to giving information about the formation of the inflammatory process and being a good marker in the diagnosis of the disease, the use of fast and sensitive measurement methods has made the measurement of APP popular [3, 11].

2. Acute phase proteins

Acute phase proteins are known as proteins whose concentrations change in the blood in cases of inflammation, infection, tissue damage, neoplastic developments, etc. [2, 12]. APPs are species specific and their diagnostic importance varies according to animal species [13, 14]. APPs whose levels change in the case of infection and inflammation are accepted as a nonspecific indicator of the tissue damage [3, 15]. In general, APPs, which can directly destroy inflammatory agents, also contribute to the tissue healing and regeneration. In addition, they have functions such as restoring useful molecules, cleaning residues, transporting cholesterol, preventing oxidation, and activating complement [12, 16].

3. Some acute phase proteins important for cattle

Haptoglobin with positive APP, serum amyloid A (SAA), ceruloplasmin, α1-acid glycoprotein, and albumin with negative APP take place among APPs that are important for cattle [2, 12, 17].

Haptoglobin: Haptoglobin, with a molecular weight of about 125 kDa, got its name from its ability to form a stable complex (haptein = binding) with hemoglobin [18]. In cattle, haptoglobin is found together with albumin as a polymer with a molecular weight of 1000–2000 kDa. It is captured by the reticuloendothelial system when bound with hemoglobin [2, 3, 19]. Haptoglobin is absent or very low (<0.1 mg/mL) in the serum of healthy cattle [20]. As soon as the immune system is stimulated for various reasons, its level in the serum increases up to 100 times [13, 21]. Haptoglobin concentration, which starts to increase within 24 hours after the onset of the inflammation, peaks on the 3–5th day and then decreases and reduces to its normal limits on the 8–21st day [20]. It has been reported that the prognosis is good when the level of haptoglobin used to determine the prognosis in cattle is between 0.1 and 1 g/L, and if this level is >1 g/L, the prognosis is poor and it is necessary to start treatment. In addition, the haptoglobin level can be used to determine the severity of the disease, and a level of 0.2–0.4 g/L is defined as mild infection, while a level of 1–2 g/L is defined as severe infection [20, 22].

Although haptoglobin has many functions, its main function is to prevent iron loss by forming stable complexes with free hemoglobin in the blood [23]. Haptoglobin

binds hemoglobin and the formed haptoglobin hemoglobin complex is transported to the liver and metabolized. The binding of haptoglobin to hemoglobin is very important in terms of the anti-inflammatory property of haptoglobin [24]. However, haptoglobin hydrolyzes the peroxides released from neutrophils in the inflamed region and renders them harmless. It has been reported that haptoglobin, which acts as an immunomodulator in the regulation of lipid metabolism and lymphocyte functions, will be able to be used to monitor the immune functions of cattle [14]. Although haptoglobin is an important APP studied in many species, its serum concentration can be also affected by factors other than APR. For example, in cases where the level of free hemoglobin in the circulation increases, even if haptoglobin synthesis is stimulated by inflammation, its circulating level will be seen as low because hemoglobin binds the existing haptoglobin. Therefore, in cases where the concentration of free hemoglobin in the serum increases, the amount of haptoglobin decreases. The best example of this is the absence of haptoglobin from circulation in acute hemolysis in cattle babesiosis [2].

Measurement of APP levels gives accurate and clear results in the diagnosis of inflammatory diseases in ruminants compared with hematological findings. It has been reported that it can be a helpful parameter in the diagnosis in the diseases such as neonatal diarrhea [25–27], omphalitis [28, 29], pneumonia [30], ascaridiosis [31], besnoitiosis [32], *Trypanosoma evansi* [33], anaplasmosis [34–36], hypodermosis [37], in the bacterial and viral diseases such as brucellosis [38], tuberculosis [39], reticuloperitonitis traumatica [40, 41], foot-and-mouth disease [42], as well as in fatty liver [43] including dystocia [44] and subclinical ketosis (**Table 1**) [45, 46]. In addition, in another study conducted in cattle with endometritis, it has been reported that haptoglobin and TNF-α levels decreased significantly after the treatment compared to the pre-treatment values [47] and that progesterone-releasing intravaginal device (PRID) administration increases haptoglobin and ceruloplasmin levels, but decreases albumin levels in another study conducted by Kuru et al. [48] in cattle.

Serum amyloid A: SAA has a molecular weight of approximately 180 kDa and exists in a complex with lipoprotein. Although SAA is synthesized by the liver with the effect of SAA-stimulating factor during inflammation, it is also synthesized locally in the udder ("milk SAA," MAA) outside the liver [2, 49]. The serum concentration of SAA, which is α globulin, is reported as <24 μg/mL [14] in healthy cattle. SAA, which rises within 2–5 hours after inflammatory stimulation and reaches a peak level within 24 hours, can be used for earlier diagnosis of acute cases [12]. SAA is used to determine the prevalence as well as the activity of inflammatory events, to monitor the course of the diseases and to evaluate the success of the treatment applied [50]. The functions of SAA include transport of cholesterol to hepatocytes, inhibition of oxidative degradation of neutrophil granulocytes, stimulation of calcium mobilization by monocytes, endotoxin detoxification, inhibition of lymphocyte and endothelial cell proliferation, prevention of platelet aggregation, and adhesion of T lymphocytes to extracellular matrix proteins [2, 13]. It has been reported that determining the haptoglobin/SAA ratio will be able to be also used in the differential diagnosis of acute and chronic cases [12]. SAA, one of the important APPs in cattle, has been reported to increase in nonfed for more than 3 days [51] in the infections such as foot-and-mouth disease [42], coryza gangrenosa bovum [52], hypomagnesemic tetany [53], enzootic bovine leukosis [54], subclinical ketosis [46], postpartum [55], mastitis [56–58], subclinical endometritis [59], and pneumonia (**Table 1**) [60, 61]. In addition, it has been reported that it increases in relation to the severity of clinical symptoms in viral respiratory system diseases [2]. It has been reported that there was no significant difference in the levels of APPs between double-infected animals and single-infected

Diseases	APP investigated	Findings of the study
Neonatal diarrhea Hypodermosis Tuberculosis	Haptoglobin, albumin	Infected animals had higher concentrations of haptoglobin, and the level of albumin was lower.
Pneumonia Foot-and-mouth disease	Haptoglobin, SAA, albumin	Infected animals had higher concentrations of haptoglobin, SAA; the level of albumin was lower.
Omphalitis, Ascaridiosis, Besnoitiosis, *Trypanosoma evansi*, Anaplasmosis, Brucellosis, Fatty liver Dystocia	Haptoglobin	Haptoglobin was higher.
Reticuloperitonitis traumatica	Haptoglobin, Ceruloplasmin, α1-Acid glycoprotein	Haptoglobin, ceruloplasmin, and α1-acid glycoprotein levels were higher in diseased animals.
Subclinical ketosis	Haptoglobin, SAA	Haptoglobin and SAA levels were higher in diseased animals.
Nonfed for more than 3 days, Coryza gangrenosa bovum, Hypomagnesemic tetany, Enzootic bovine leukosis, postpartum	SAA	SAA was higher.
Mastitis, Endometritis	SAA, Ceruloplasmin	SAA and ceruloplasmin levels were higher in diseased animals.
Hepatic abscess and leukosis, *Pasteurella haemolytica*, digestive system disease	α1-Acid glycoprotein	α1-Acid glycoprotein was higher.

Table 1.
A brief summary of APPs-related studies on cattle.

animals in a study conducted in dual- and single-infected cattle [62]. In another study conducted in cattle with bovine respiratory disease complex, it has been reported that haptoglobin and SAA levels increased compared to healthy animals, and the level of APPs decreased with the treatment [63].

Ceruloplasmin: Ceruloplasmin, which consists of a single polypeptide chain, is a copper-binding α-2 globulin. The functions of ceruloplasmin is (i) lipid peroxidation, (ii) oxidation of toxic ferrous iron to nontoxic ferric form, (iii) obtainment of increasing immune function by acting on various enzyme levels, (iv) mediation of copper transporting to enzymes such as lysyl oxidase and copper-zinc superoxide dismutase involved in tissue repair, (v) role in the antioxidant system, and (vi) regulation of phagocytosis and antimicrobial activity [13, 64, 65].

It has been reported that ceruloplasmin is very useful in monitoring the inflammatory process in cattle [66]. The studies conducted have reported that APP levels increase in cattle with reticuloperitonitis traumatica [41], endometritis [67], and subclinical mastitis (**Table 1**) [68]. In addition, it has been reported that the level of APPs increases in cattle infected with foot-and-mouth disease and can be used in the diagnosis of the disease [42].

α1-Acid glycoprotein: α1-Acid glycoprotein is a sialoprotein synthesized from hepatocytes, containing 180 amino acids and released at a molecular weight of

41 kDa [69]. This protein has two important functions: drug binding and immunomodulation. α1-Acid glycoprotein, a natural anti-inflammatory agent, increases IL-1 receptor antagonist release by macrophages by inhibiting neutrophil activation. It also inhibits lymphocyte proliferation and natural killer cell activity [2, 13]. When the albumin concentration formed during APR decreases, α1-acid glycoprotein, which has good drug binding properties, helps to maintain the total drug-binding level [13]. α1-Acid glycoprotein, whose concentration in the blood increases moderately and slowly [2], increases in chronic cases rather than acute inflammation [18]. It has been reported that α1-acid glycoprotein, which is of moderate importance for cattle, will be able to be used especially in monitoring the inflammatory process [12]. The studies conducted have reported that its concentration increased in cattle with hepatic abscess and leukosis [12, 20] in traumatic pericarditis [40], *Pasteurella haemolytica* [12], and digestive system disease (**Table 1**) [70].

Albumin: Cattle albumin, a negative APP, is synthesized by the liver and its molecular weight is 67 kDa and consists of 583 amino acids [71, 72]. Albumin is a very important protein that maintains and stabilizes the plasma oncotic pressure. Because it is a small molecule, its extravascular concentration changes are an important indicator of membrane integrity [73, 74]. In addition, the decrease in blood concentration due to the fact that it is produced only by the liver is accepted as an important finding indicating liver failure [75]. Binding and transport, acting as a source for endogenous amino acids, and maintaining plasma pressure take place among its main biological functions. It is reported that its concentration decreases in liver diseases, anorexia during APR, kidney and intestinal diseases, and malabsorption syndrome [8, 76]. It has been reported in the studies conducted that albumin levels decrease in neonatal diarrhea [26], pneumonia [30], hypodermosis [37], tuberculosis [39], and foot-and-mouth disease (**Table 1**) [42].

4. Conclusion

Acute phase proteins, which are nonspecific markers synthesized by the liver as a result of APR in cattle, are very useful in terms of diagnosis and monitoring of diseases, as well as determining the prognosis of patients. In particular, the measurement of APPs is important in terms of distinguishing bacterial or viral infection and guiding the treatment to be applied. When used for this purpose, it strengthens the diagnosis and provides more accurate information in determining the prognosis of sick animals.

Author details

Kadir Bozukluhan[1*] and Oguz Merhan[2]

1 Kars School of Higher Vocational Education, Kafkas University, Kars, Turkey

2 Faculty of Veterinary, Department of Biochemistry, Kafkas University, Kars, Turkey

*Address all correspondence to: kbozukluhan@hotmail.com

IntechOpen

References

[1] Dhama K, Mahendran M, Chauhan RS, Tomar S. Cytokines: Their functional roles and prospective applications in veterinary practice: A review. Journal of Immunology and Immunopathology. 2008;**10**:79-89

[2] Petersen HH, Nielsen JP, Heegaard PMH. Application of acute phase protein measurements in veterinary clinical chemistry. Veterinary Research. 2004;**35**:163-187. DOI: 10.1051/vetres:2004002

[3] Merhan O, Bozukluhan K. Acute phase response and some acute phase proteins in animals. In: Yıldız G, Baran MS, Kaplan O, Durna Aydın Ö, editors. Current Multidisciplinary Studies in Veterinary Medicine I. Ankara: Iksad Publishing House; 2022. pp. 3-33

[4] Tothova C, Nagy O, Kovac G. Acute phase proteins and their use in the diagnosis of diseases in ruminants: A review. Veterinární Medicína. 2014;**59**:163-180. DOI: 10.17221/7478-VETMED

[5] Ramadori G, Christ B. Cytokines and the hepatic acute-phase response. Seminars in Liver Disease. 1999;**19**:141-155. DOI: 10.1055/s-2007-1007106

[6] Suffredini AF, Fantuzzi G, Badolato R, Oppenheim JJ, O'Grady NP. New insights into the biology of the acute phase response. Journal of Clinical Immunology. 1999;**19**:203-214. DOI: 10.1023/a:1020563913045

[7] Ceciliani F, Giordano A, Spagnolo V. The systemic reaction during inflammation: The acute phase proteins. Protein and Peptide Letters. 2002;**9**:211-223. DOI: 10.2174/0929866023408779

[8] Gruys E, Toussaint MJM, Niewold TA, Koopmans SJ. Acute phase reactant and acute phase proteins. Journal of Zhejiang University Science B. 2005;**6**:1045-1056. DOI: 10.1631/jzus.2005.B1045

[9] Garcia Moran GA, Parra-Medina R, Cardona AG, Quintero-Ronderos P, Garavito RE. Cytokines, chemokines and growth factors. In: Anaya JM, Shoenfeld Y, Rojas-Villarraga A, Levy RA, Cervera R, editors. Autoimmunity: From Bench to Bedside. Bogota: El Rosario University Press; 2013. pp. 133-168

[10] Panichi V, Migliori M, De Pietro S, Taccola D, Andreini B, Metelli MR, et al. The link of biocompatibility to cytokine production. Kidney International Supplement. 2000;**76**:S96-S103. DOI: 10.1046/j.1523-1755.2000.07612.x

[11] Whicher T, Bienvenu J, Price CP. Molecular biology, measurement and clinical utility of the acute phase proteins. Pure and Applied Chemistry. 1991;**63**:1111-1116. DOI: 10.1351/pac199163081111

[12] Gruys E, Obwolo MJ, Toussaint MJM. Diagnostic significance of the major acute phase proteins in veterinary clinical chemistry: A review. Veterinary Bulletin. 1994;**64**:1009-1018

[13] Murata H, Shimada N, Yoshioka M. Current research on acute phase proteins in veterinary diagnosis: An overview. The Veterinary Journal. 2004;**168**:28-40. DOI: 10.1016/S1090-0233(03)00119-9

[14] Gökçe Hİ, Bozukluhan K. Important acute phase proteins in farm animals and their usage in veterinary practice. Dicle University Journal of Faculty of Veterinary Medicine. 2009;**1**:1-14

[15] Bazzano M, Marchegiani A, Troisi A, McLean A, Laus F. Serum

amyloid A as a promising biomarker in domestic animals reproduction: Current knowledge and future perspective. Animals. 2022;**12**:589-599. DOI: 10.3390/ani12050589

[16] Grover HS, Saini R, Bhardwaj P, Bhardwaj A. Acute-phase reactants. Journal of Oral Research and Review. 2016;**8**:32-35. DOI: 10.4103/2249-4987.182491

[17] Gul ST, Mahmood S, Bilal M, Saleemi MK, Imran M, Zubair M. Acute phase proteins as biomarkers in perspective to animal diseases diagnosis. Agrobiological Records. 2022;**9**:45-57. DOI: 10.47278/journal.abr/2022.013

[18] Safi S. Acute phase proteins - analysis, clinical applications and potentials. In: Khatami M, editor. Inflammatory Diseases - Immunopathology, Clinical and Pharmacological Bases. London: InTechOpen; 2012. pp. 351-380. DOI: 10.5772/19375

[19] Naryzhny SN, Legina OK. Haptoglobin as a biomarker. Biochemistry (Moscow) Supplement. Series B, biomedical. Chemistry. 2021;**15**:184-198. DOI: 10.1134/S1990750821030069

[20] Eckersall PD, Conner JG. Bovine and canine acute phase proteins. Veterinary Research Communications. 1988;**12**:169-178. DOI: 10.1007/BF00362798

[21] Eckersall PD. Recent advances and future prospects for the use of acute phase proteins as markers of disease in animals. Revue de Médecine Vétérinaire. 2000;**151**:577-584

[22] Skinner JG, Brown RA, Roberts L. Bovine haptoglobin response in clinically defined field conditions. The Veterinary Record. 1991;**128**:147-149. DOI: 10.1136/vr.128.7.147

[23] Quaye IK. Haptoglobin, inflammation and disease. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2008;**102**:735-742. DOI: 10.1016/j.trstmh.2008.04.010

[24] Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. The New England Journal of Medicine. 1999;**340**:448-454. DOI: 10.1056/NEJM 199902113400607

[25] Albayrak H, Kabu M. Determining serum haptoglobin and cytokine concentrations in diarrheic calves. Fırat University Veterinary Journal of Health Sciences. 2016;**30**:113-117

[26] Merhan O, Bozukluhan K, Gökçe G, Yılmaz O. Investigation on the levels of haptoglobin, ceruloplasmin and some biochemical parameters levels in calves with diarrhea. Fırat University Veterinary Journal of Health Sciences. 2016;**30**:195-198

[27] Erkılıç EE, Merhan O, Kırmızıgül AH, Öğün M, Akyüz E, Çitil M. Salivary and serum levels of serum amyloid A, haptoglobin, ceruloplasmin and albumin in neonatal calves with diarrhoea. Kafkas Universitesi Veteriner Fakültesi Dergisi. 2019;**25**:583-586. DOI: 10.9775/kvfd.2018.21424

[28] Bozukluhan K, Merhan O, Ogun M, Kurt B, Cihan M, Erkilic EE, et al. Investigation of haptoglobin, serum amyloid A, and some biochemical parameters in calves with omphalitis. Veterinary World. 2018;**11**:1055-1058. DOI: 10.14202/vetworld. 2018.1055-1058

[29] Kurt B, Erkilic EE, Merhan O, Aydin U, Akyuz E, Sezer M, et al. The determination of levels of acute-phase proteins, inducible nitric oxide synthase and endothelial nitric oxide synthase in calves with omphalophlebitis.

Fresenius Environmental Bulletin. 2019;**28**:8601-8605

[30] Bozukluhan K, Merhan O, Kiziltepe S, Ergin Egritag H, Akyuz E, Gokce HI. Determination of haptoglobin, some biochemical and oxidative stress parameters in calves with pneumonia. Fresenius Environmental Bulletin. 2021;**30**:9485-9489

[31] Bozukluhan K, Merhan O, Özcan A, Gökçe Hİ, Gökce G. Investigation of the levels of serum haptoglobin, oxidative indicators and some biochemical parameters in calves naturally infected with *Toxocara vitulorum*. Ankara Universitesi Veteriner Fakültesi Dergisi. 2017;**64**:75-79. DOI: 10.1501/Vetfak_0000002778

[32] Gonzalez-Barrio D, Huertas-Lopez A, Diezma-Diaz C, Ferre I, Ceron JJ, Ortega-Mora LM, et al. Changes in serum biomarkers of inflammation in bovine besnoitiosis. Parasites and Vectors. 2021;**14**:488. DOI: 10.1186/s13071-021-04991-0

[33] Alsaad KM, Jarad A, Lafta MH. *Trypanosomiasis evansi* of buffalo at Basrah, Iraq -clinico- hematobiochemical and diagnostic studies. Biochemical and Cellular Archives. 2021;**21**:2035-2042

[34] Nazifi S, Razavi SM, Kaviani F, Rakhshandehroo E. Acute phase response in cattle infected with *Anaplasma marginale*. Veterinary Microbiology. 2012;**155**:267-271. DOI: 10.1016/j.vetmic.2011.08.024

[35] Coşkun A, Derinbay Ekici Ö, Güzelbekteş H, Aydoğdu U, Şen İ. Acute phase proteins, clinical, hematological and biochemical parameters in dairy cows naturally infected with *Anaplasma marginale*. Kafkas Universitesi Veteriner Fakültesi Dergisi. 2012;**18**:497-502. DOI: 10.9775/kvfd.2011.5822

[36] Bozukluhan K, Gökçe G, Merhan O, Öğün M, Erkılıç EE. Investigation of acute phase proteins and some biochemical parameters in cattle infected with *Anaplasma marginale*. In: 10. National Veterinary Internal Diseases Congress; 27-30 June 2013; Nevşehir. Kayseri: Erciyes University Press; 2013. p. 105

[37] Merhan O, Bozukluhan K, Gokce HI. Acute phase proteins and biochemical and oxidative stress parameters in *Hypoderma spp*. infested cattle. Journal of the Hellenic Veterinary Medical Society. 2017;**68**:535-540. DOI: 10.12681/jhvms.16049

[38] Bozukluhan K, Merhan O, Büyük F, Çelebi Ö, Gökçe G. Determination of some acute phase proteins level in cattle with brucellosis. Ankara Universitesi Veteriner Fakültesi Dergisi. 2016;**63**:13-16. DOI: 10.1501/Vetfak_0000002703

[39] Merhan O, Bozukluhan K, Çelebi Ö, Öğün M, Atakişi E, Büyük F. Levels of acute phase protein and some biochemical parameter in cattle infected with *Mycobacterium bovis*. Journal of Faculty of Veterinary Medicine, Erciyes University. 2017;**14**:101-105

[40] Bozukluhan K, Gökçe Hİ. Investigations of some acute phase proteins in cattle with traumatic reticuloperitonitis or with traumatic pericarditis. Journal of Faculty of Veterinary Medicine, Erciyes University. 2007;**4**:107-113

[41] Akyüz E, Aydın U. Prognostic value of haptoglobin and ceruloplasmin levels determined in cows with adhesive and non-adhesive traumatic reticuloperitonitis. Kafkas Universitesi Veteriner Fakültesi Dergisi. 2022;**28**:337-344. DOI: 10.9775/kvfd.2021.27040

[42] Merhan O, Bozukluhan K, Kiziltepe S, Gokce HI. Investigation of

levels of haptoglobin, serum amyloid A, ceruloplasmin and albumin in cattle with foot-and-mouth disease. Israel Journal of Veterinary Medicine. 2017;**72**:14-17

[43] Nakagawa H, Yamamoto O, Oikawa S, Higuchi H, Watanabe A, Katoh N. Detection of serum haptoglobin by enzyme-linked immunosorbent assay in cows with fatty liver. Research in Veterinary Science. 1997;**62**:137-141. DOI: 10.1016/s0034-5288(97)90135-1

[44] Bayyit E, Merhan O. Some acute phase proteins and oxidative stress level in cows with normal parturition and dystocia. Atatürk University Journal of Veterinary Sciences. 2022;**15**:145-150. DOI: 10.17094/ataunivbd.688400

[45] Merhan O, Öğün M, Bozukluhan K, Maraşlı Ş. Investigation of levels of haptoglobin, ceruloplasmin and albumin in cattle with subclinical ketosis. In: III. International Eurasian Agriculture and Natural Sciences Congress; 17-20 October, 2019; Antalya. Konya: Medya Plaza; 2019. p. 193

[46] Brodzki P, Marczuk J, Lisiecka U, Szczubial M, Brodzki A, Gorzkos H, et al. Comparative evaluation of cytokine and acute-phase protein concentrations in sera of dairy cows with subclinical and clinical ketosis as a different view of the causes of the disease. Veterinary World. 2021;**14**:1572-1578. DOI: 10.14202/vetworld.2021.1572-1578

[47] Kaya S, Kaçar C, Merhan O, Demir MC, Arı UÇ, Zonturlu AK. The effect of intrauterine thyme essential oil and dimethyl sulfoxide infusion on clinical recovery and serum haptoglobin, tumor necrosis factor and nitric oxide levels in cows with clinical endometritis. Kocatepe Veterinary Journal. 2021;**14**:45-50. DOI: 10.30607/kvj.772613

[48] Kuru M, Merhan O, Kaya S, Oral H, Kükürt S. The effect of short term progesterone-releasing intravaginal device treatment on acute inflamation markers for Holstein heifers. Revue de Médecine Vétérinaire. 2015;**166**:336-340

[49] Trela M, Domanska D, Witkowska-Pilaszewicz O. Diagnostic use of serum amyloid A in dairy cattle. Agriculture. 2022;**12**:459-468. DOI: 10.3390/agriculture12040459

[50] Witkowska-Pilaszewicz OD, Zmigrodzka M, Winnicka A, Miskiewicz A, Strzelec K, Cywinska A. Serum amyloid A in equine health and disease. Equine Veterinary Journal. 2019;**51**:293-298. DOI: 10.1111/evj.13062

[51] Katoh N, Oikawa S, Oohashi T, Takahashi Y, Itoh F. Decreases of apolipoprotein B-100 and A-I concentrations and induction of haptoglobin and serum amyloid A in nonfed calves. Journal of Veterinary Medical Science. 2002;**64**:51-55. DOI: 10.1292/jvms.64.51

[52] Issi M, Gül Y, Başbuğ O, Ulutaş PA. Haptoglobin, serum amyloid A and ceruloplasmin concentrations in cattle with suspicion of coryza gangrenosa bovum. Veterinarski Arhiv. 2017;**87**:703-712. DOI: 10.24099/vet.arhiv.160801a

[53] Ali MA, Gomaa NA. Some serum biochemical parameters and acute phase proteins in response to hypomagnesaemic tetany in lactating cattle. Alexandria Journal of Veterinary Sciences. 2016;**49**:1-5. DOI: 10.5455/ajvs.225967

[54] Guzel M, Tutuncu M, Albayrak H, Ozan E, Koc R, Kadi H. Acute phase response in enzootic bovine leukosis. The Journal of the Hellenic Veterinary Medical Society. 2017;**68**:155-159. DOI: 10.12681/jhvms.17924

[55] Varol K, Ergin Eğritağ H, Merhan O, Bozukluhan K. Evaluation of acute phase response in blood and milk samples of healthy Holstein breed cattle in the postpartum period. Kafkas Universitesi Veteriner Fakültesi Dergisi. 2022;**28**:59-65. DOI: 10.9775/kvfd.2021.26421

[56] Nazifi S, Haghkhah M, Asadi Z, Ansari-Lari M, Tabandeh MR, Esmailnezhad Z, et al. Evaluation of sialic acid and acute phase proteins (haptoglobin and serum amyloid A) in clinical and subclinical bovine mastitis. Pakistan Veterinary Journal. 2011;**31**:55-59

[57] Çenesiz S, Gürler H, Fındık A, Çiftci G, Ertekin A, Çenesiz M. Acute phase proteins in *Staphylococcus aureus* positive milks. Journal of Etlik Veterinary Microbiology. 2018;**29**:111-115

[58] Armağan Aydın T, Emre B. Evaluation of amyloid A and C-reactive protein levels in the diagnosis of subclinic mastitis in cows. Dicle University Journal of Faculty of Veterinary Medicine. 2021;**14**:131-135. DOI: 10.47027/duvetfd.991646

[59] Salah N, Khudhair NY, Rasheed Y, Mahmood MY. Comparison of serum acute phase proteins and inflammatory cytokines between healthy and subclinically endometritic postpartum buffaloes. The Journal of Animal & Plant Sciences. 2021;**31**:671-680. DOI: 10.36899/JAPS.2021.3.0257

[60] Joshi V, Gupta VK, Bhanuprakash AG, Mandal RSK, Dimri U, Ajith Y. Haptoglobin and serum amyloid A as putative biomarker candidates of naturally occurring bovine respiratory disease in dairy calves. Microbial Pathogenesis. 2018;**116**:33-37. DOI: 10.1016/j.micpath.2018.01.001

[61] Akgul O, Kozat S, Ozkan C, Kaya A, Akgul Y. Evaluation of acute phase protein levels and some cytokine levels in pneumonic calves. Medycyna Weterynaryjna. 2019;**75**:152-157. DOI: 10.21521/mw.6184

[62] Sahinduran S, Kale M, Kıyıcı R, Sevgisunar NS. Some acute phase proteins and hepcidin levels in single and dual infection with BVD and BHV-1. Mehmet Akif Ersoy University, Journal of Health Sciences Institute. 2017;**5**:115-123

[63] Yılmaz O, Gökçe G. Investigations on clinic, haematology, biochemistry, oxidative stress, acute phase proteins in infectious respiratory disease complex (BRDC) in cattle. Atatürk University Journal of Veterinary Sciences. 2017;**12**:34-44. DOI: 10.17094/ataunivbd.309771

[64] Cerone SI, Sansinanea AS, Streitenberger SA, Garcia MC, Auza NJ. Cytochrome c oxidase, Cu, Zn-superoxide dismutase, and ceruloplasmin activities in copper-deficient bovines. Biological Trace Element Research. 2000;**73**:269-278. DOI: 10.1385/BTER:73:3:269

[65] Hellman NE, Gitlin JD. Ceruloplasmin metabolism and function. Annual Review of Nutrition. 2002;**22**:439-458. DOI: 10.1146/annurev.nutr.22.012502.114457

[66] Szczubial M, Dabrowski R, Kankofer M, Bochniarz M, Albera E. Concentration of serum amyloid A and activity of ceruloplasmin in milk from cows with clinical and subclinical mastitis. Bulletin of the Veterinary Institute Pulawy. 2008;**52**:391-395

[67] Kaya S, Merhan O, Kacar C, Colak A, Bozukluhan K. Determination of ceruloplasmin, some other acute phase proteins, and biochemical parameters in cows with endometritis. Veterinary

World. 2016;**9**:1056-1062. DOI: 10.14202/vetworld.2016.1056-1062

[68] Szczubial M, Dabrowski R, Kankofer M, Bochniarz M, Komar M. Concentration of serum amyloid A and ceruloplasmin activity in milk from cows with subclinical mastitis caused by different pathogens. Polish Journal of Veterinary Sciences. 2012;**15**:291-296. DOI: 10.2478/v10181-011-0149-x

[69] Albani JR. Tertiary structure of human α1-acid glycoprotein (orosomucoid). Straightforward fluorescence experiments revealing the presence of a binding pocket. Carbohydrate Research. 2004;**339**:607-612. DOI: 10.1016/j.carres.2003.10.016

[70] Santos JFD, Rego ROD, Afonso JAB, Fagliari JJ, Silva PC, Soares PC, et al. Hematologic response and serum and peritoneal fluid proteinogram of cattle affected by intestinal diseases and traumatic reticuloperitonitis. Semina-Ciencias Agrarias. 2021;**42**:209-228. DOI: 10.5433/1679-0359.2021v42n1p209

[71] Jachimska B, Wasilewska M, Adamczyk Z. Characterization of globular protein solutions by dynamic light scattering, electrophoretic mobility, and viscosity measurements. Langmuir. 2008;**24**:6866-6872. DOI: 10.1021/la800548p

[72] Majorek KA, Porebski PJ, Dayal A, Zimmerman MD, Jablonska K, Stewart AJ, et al. Structural and immunologic characterization of bovine, horse, and rabbit serum albumins. Molecular Immunology. 2012;**52**:174-182. DOI: 10.1016/j.molimm. 2012.05.011

[73] Evans TW. Review article: Albumin as a drug-biological effects of albumin unrelated to oncotic pressure. Alimentary Pharmacology and Therapeutics. 2002;**16**(Suppl. 5):6-11. DOI: 10.1046/j.1365-2036.16.s5.2.x

[74] van de Wouw J, Joles JA. Albumin is an interface between blood plasma and cell membrane, and not just a sponge. Clinical Kidney Journal. 2022;**15**:624-634. DOI: 10.1093/ckj/sfab194

[75] Don BR, Kaysen G. Serum albumin: Relationship to inflammation and nutrition. Seminars in Dialysis. 2004;**17**:432-437. DOI: 10.1111/j.0894-0959.2004.17603.x

[76] Tennant BC, Center SA. Hepatic function. In: Kaneko JJ, Harvey JW, Bruss ML, editors. Clinical Biochemistry of Domestic Animals. New York: Academic Press; 2008. pp. 379-412