The Pharma Innovation Journal 2018; 7(1): 104-108

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2018; 7(1): 104-108

www.thepharmajournal.com
Received: 18-11-2017
Accepted: 19-12-2017

Imtiyaz Ahmad Bhat
Ph. D Scholar Department of Veterinary Clinical Medicine, Sher-e-Kashmir Institute of Agriculture Sciences and Technology SKUAST-K, Jammu and Kashmir, India

Shahnaz Bashir
Assistant Professor Department of Veterinary Epidemiology and Preventive Medicine Sher-e-Kashmir Institute of Agriculture Sciences and Technology SKUAST-K, Jammu and Kashmir, India

Waseem Rather
M. V. Sc Scholar Department of Veterinary Clinical Medicine, Sher-e-Kashmir Institute of Agriculture Sciences and Technology SKUAST-K, Jammu and Kashmir, India

Zaffar Iqbal
Ph.D Scholar Department of Animal Genetics and Breeding Sher-e-Kashmir Institute of Agriculture Sciences and Technology SKUAST-K, Jammu and Kashmir, India

MA Kawa
M.V.Sc Scholar Department of Veterinary Epidemiology and Preventive Medicine Sher-e-Kashmir Institute of Agriculture Sciences and Technology SKUAST-K, Jammu and Kashmir, India

Ajaz Quadir
Ph.D Scholar Department of Veterinary Anatomy, Sher-e-Kashmir Institute of Agriculture Sciences and Technology SKUAST-K, Jammu and Kashmir, India

Syed Ashiq Hussain
Assistant Professor Department of Veterinary Clinical Medicine, Sher-e-Kashmir Institute of Agriculture Sciences and Technology SKUAST-K, Jammu and Kashmir, India

Shifiat Ahmad Beigh
Assistant Professor Department of Veterinary Clinical Medicine, Sher-e-Kashmir Institute of Agriculture Sciences and Technology SKUAST-K, Jammu and Kashmir, India

Showket Nabi
Assistant Professor Department of Veterinary Clinical Medicine, Sher-e-Kashmir Institute of Agriculture Sciences and Technology SKUAST-K, Jammu and Kashmir, India

Ajaz Ahmad Dar
Assistant Professor Department of Veterinary Epidemiology and Preventive Medicine Sher-e-Kashmir Institute of Agriculture Sciences and Technology SKUAST-K, Jammu and Kashmir, India

Correspondence
Imtiyaz Ahmad Bhat
Ph. D Scholar Department of Veterinary Clinical Medicine, Sher-e-Kashmir Institute of Agriculture Sciences and Technology SKUAST-K, Jammu and Kashmir, India

Acute Phase Proteins and their Clinical Significance in Veterinary Medicine: An Overview

Imtiyaz Ahmad Bhat, Shahnaz Bashir, Waseem Rather, Zaffar Iqbal, MA Kawa, Ajaz Quadir, Syed Ashiq Hussain, Shifiat Ahmad Beigh, Showket Nabi and Ajaz Ahmad Dar

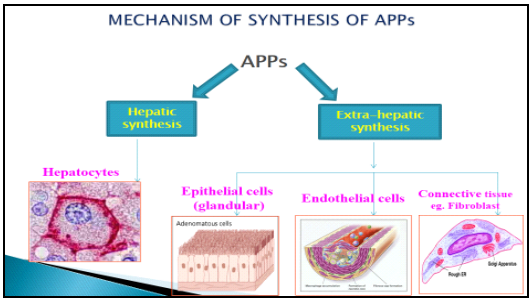
Abstract
Acute phase proteins are a group of non-specific innate immune components whose concentration changes with respect to a challenge, and a reaction of the host to pathophysiological insults (infection, inflammation, trauma etc) is collectively known as the acute-phase response. It begins within inflammatory sites where a vast number of inflammatory mediators are released by cells like macrophages and monocytes. The process involves a wide range of pathophysiological responses like pyrexia, leukocytosis, hormone alterations, and minimizing tissue damage while enhancing the repair process. The positive acute phase proteins (APPs) are considered very important due to their involvement in functions like activating the complement system, in binding cellular remnants like nuclear fractions, optimization and trapping of microorganisms and their products, in neutralizing enzymes, scavenging free hemoglobin and radicals, and in modulating the host's immune response. APP can be used as diagnostic tool in diseases like mastitis, bovine respiratory syncytial virus, leptospirosis, prostate cancer, babesiosis, bronchopneumonia, reproductive tract infection. Thus, APPs act as indicators of animal health status.

Keywords: Acute phase proteins, acute phase response, disease diagnosis

Introduction
Acute phase proteins (APPs) are defined as a group of blood proteins, non-specific innate immune components whose concentration changes with respect to external or internal challenges such as infection, inflammation, surgical trauma and stress [1]. (Buaumann and Gauldie, 1994). The concentration of these proteins increases during the early phase of reaction of the host (Acute phase response) to the insult. APPs help to determine the presence of infections and inflammatory conditions very quickly and accurately depending upon the sampling technique and time [2] and act as diagnostic and prognostic indicators of animal health [3]. The circulating concentration of these proteins is related to severity of the disorder and the extent of tissue damage in affected host.

Mechanism of synthesis of APPs
There are two ways of synthesis of APPs
1. Hepatic synthesis
2. Extra Hepatic synthesis

In hepatic mode, the hepatocytes of liver are involved while as in extra hepatic mode epithelial cells, endothelial cells and connective tissue are involved [4].



(Adapted from Jensen and Whitehead, 1998)

Acute Phase Response (APR)

It is a non-specific and a complex reaction of an organism against any stimulus- physical or biological (injury, trauma, infection, stress, inflammation and neoplasia). It begins within inflammatory sites where a vast number of inflammatory mediators - (IL-1, IL-6 & TNF-α) are released by macrophages and monocytes [5].

Classification of APPs

On the basis of concentration

The response of the host to the stimulus may either decrease the concentration of APPs (called as Negative APPs e.g. Albumin, pre-albumin, transthyretin, transferrin etc) or increase their concentration (called as positive APPs e.g. serum amyloid A, haptoglobin, ceruloplasmin, C reactive protein etc). Among the positive APPs, the serum level of some APPs increases 10 to 100 or even1000 folds within few hours after injury, and are called as major APPs. Proteins whose levels increase 2-10 times and then return to normal after longer period are known as moderate APPs and those with slight increase in serum level (approximately 2 times or lesser) are known as minor APPs [6].

On the basis of mode of action

Based on their mechanism of action the APPs are classified as Protease Inhibitors (e.g. alpha-1 antitrypsin, Coagulation Proteins (e.g. Fibrinogen), Complement Proteins (e.g. C2, C3 and C4) Transport Proteins (e.g. Transferrin) and other Proteins (e.g. alpha-1 acid glycoproteins)

Biological activity and diagnostic utility of APPs

Positive acute phase proteins

Haptoglobin

Haptoglobin (Hp) consists of two α and two β chains which are connected by disulfide bridges [7]. Hp is highly polymerized and exists as a polymer associated with albumin in the blood circulation with a molecular weight of approximately 1000–2000 kDa [8]. The main function of Hp is to inhibit the oxidative activity of free hemoglobin released from erythrocytes by forming Hp-hemoglobin complex with it [9]. This binding also reduces the availability of haem residue for the growth of bacteria [10]. Hp has its significance in that it is used clinically as a useful parameter for measuring the occurrence and severity of inflammatory responses in cattle with various diseases like mastitis, endocarditis, endometritis [2].

Serum amyloid A

Serum amyloid A (SAA) is an apolipoprotein and is associated with high density lipoprotein [11] (Uhlar *et al*..., 1994). Different isoforms of SAA are SAA1, SAA2, SAA3, M-SAA3 and SAA4. In response to inflammatory stimuli, these are expressed constitutively at different levels [4]. SAA1 and SAA2 are expressed during inflammation principally in the liver whereas SAA3 is expressed in many distinct tissues like the mammary gland [12]. SAA4 shows no response with respect to external stimuli [13]. The main functions of SAA are the inhibition of phagocyte oxidative bursts, reverse transport of cholesterol from tissue to hepatocytes, platelet activation, and opsonization [14].

Fibrinogen

Fibrinogen (Fbg) is a precursor of fibrin and plays an important role in the coagulation process. It helps in the conversion of a clot to its insoluble fibrin form [15]. It is a β-globulin composed of three polypeptide chains linked by disulfide bridges and a glycoprotein [16]. It is present in plasma and the main role is in homeostasis, tissue repair and provides substrate for fibrin formation. Its level can increase two to three fold during an inflammatory reaction which may cause red blood cell aggregation and significantly increase blood viscosity [17]. Studies in humans have shown an association between fibrinogen concentrations and subsequent cardiovascular disease risk, atherosclerosis and acute thrombosis [18]. In cattle, fibrinogen concentration increases during infection, inflammation and traumatic diseases [19].

Ceruloplasmin

Ceruloplasmin (Cp) is an acute phase protein of the α-2 globulin fraction. It plays a role in iron metabolism as it is a component of ferroxidase enzyme [20]. It also plays a role in Cu homeostasis in humans as it carries about 70% of the total Cu in human plasma. It acts as a marker of animal health and welfare [21]. In cattle it has been evaluated as a good indicator in many disease conditions [22]. In dairy cows it acts as a reliable indicator of early mastitis cases and in young animals its concentration in serum increases during induced pneumonic pasteurellosis [23].

Alpha-1 acid glycoprotein

Alpha-1 acid glycoprotein (AGP) is a glycosylated protein with about 45% carbohydrate. It is also called as orosomucoid in which the composition of the glycan residues alters during an acute phase response [24]. AGP is considered to be immunomodulator and natural anti-inflammatory agent. In addition it is required to maintain capillary permeability [24]. It is considered to be associated with chronic conditions. The serum concentration of AGP helps in the identification of infectious peritonitis [25].

Alpha-1 antitrypsin

Alpha-1 antitrypsin (AAT) acts as an acute phase protease and serine protease inhibitor (serpin).As serine protease inhibitor it inhibits neutrophil elastase and proteinase-3 [26]. AAT is elevated in certain acute phase inflammatory reactions to limit the damage caused by activated neutrophil granulocytes and their enzymes like protease, elastase [27]. AAT deficiency in patients, a hereditary disorder can lead to severe tissue breakdown during inflammation [28] which may result in pulmonary emphysema, chronic obstructive lung disease, liver diseases and liver cirrhosis in severe cases.

Lactoferrin

Lactoferrin (Lf), also known as lactotransferrin is a globular glycoprotein with a molecular weight of about 80 kDa. Lactoferrin is a multifunctional transferrin protein capable of binding and transferring Fe^{3+} ions [29]. The structure of lactoferrin is very similar to that of transferrin and the only difference is in their relative affinities for Fe and the propensity for release of Fe [30]. The affinity of lactoferrin to bind iron is two times higher than that of transferrin [31]. The lactoferrin-iron bond is very strong and can resist pH values of as low as 4 [32]. Lactoferrin has ability to keep iron bound at low pH even at the sites of infection and inflammation where the pH may fall under 4.5 due to metabolic activity of bacteria [33]. It has the ability to bind with iron hence limits the growth of Fe-requiring pathogenic bacteria including enteropathogenic *Escherichia coli* as these bacterial

pathogens are dependent on Fe for their metabolic activities, growth, and proliferation [34].

Negative acute phase proteins

Albumin

Serum albumin is the major negative acute phase globular protein with a molecular weight of 69 kDa. It makes a large contribution to plasma colloid osmotic pressure due to its small size and abundance and also serves as a carrier protein for many insoluble organic substances. Albumin contributes about 75% of the osmotic pressure of plasma and can be utilized as a major source of amino acids by an animal when necessary. Due to its relatively long half-life of about 14-20 days, it has been used as a marker of chronic nutritional status. It also acts as an indicator of morbidity and mortality [35].

Transferrin

Transferrin (Tf) is an iron-binding protein of serum and is a powerful chelator. It is capable of binding iron tightly and reversibly. One molecule of transferrin can bind two atoms of ferric iron (Fe^{3+}) with high affinity. This affinity is higher in the extracellular pH of 7.4 and decreases in acidified endosomes resulting in the dissociation of Fe^{3+} [36]. The role of transferrin is to transport iron safely in the bodyand to supply it to growing cells [37], to render iron soluble under physiological conditions, to prevent iron-mediated free radical toxicity, and to facilitate transport into cells [38]. Transferrin like lactoferrin inhibits multiplication and growth of certain viral, bacterial and fungal organisms by binding with iron and thus limiting the growth of such organisms.

Transferrin concentrations in cattle play an important role in determining various physiological states, energy-deficient (ketotic) condition in cows, several acute and chronic infections [39]. The concentrations of Tf ranges from 2.0 and 6.6 g/l in healthy cattle as compared with 1.5 and 8.5 g/l and < 2.0g/l in Ketotic and Johne's disease affected cattle. Chronic infectious diseases (such as Para tuberculosis) were characterized by relatively low values (below 2 g/l). Further, Tf concentration in adult cattle was lower compared to young stock [39].

Transthyretin

Transthyretin (TTR) is a serum protein with a molecular mass of 55 kDa. It is also known as thyroxin-binding protein and belongs to the homotetrameric transport protein family [40]. It is involved in the transport of thyroid hormones and also indirectly aids in transport of vitamin A in plasma by forming a complex with retinol-binding protein [41]. It was previously called as pre-albumin and is the precursor proteins commonly found in amyloid deposits.

Species-Wise Significance of Apps

Dog: C reactive protein (CRP) is the major APP which is used as a marker for systemic inflammation/infection in canines. Its concentration in healthy canines ranges from 0.08-2.26 mg/dl [42] and rises within 4-6 hours of infection. Serum CRP level > 3.5 mg/dl indicates systemic inflammation. The concentration of CRP increases in lymphoma in canines[43], pyometra, panniculitis, acute pancreatitis, polyarthritis, leptospirosis, babesiosis, parvo infection, glomerulonephritis, immune mediated diseases and malignant neoplasia [44]. In canine babesiosis the serum CRP concentration has been found significantly higher and that of haptoglobin significantly lower compared to healthy dogs [45]. A negative APP albumin is a significant biomarker for bacterial infection. The serum concentration of fibrinogen, a positive APP, is more reliable than albumin owing to persistently higher concentration (up to 21 days) post inoculation with *Staphylococcus aureus* [46].

Cat: The main APPs of cat are SAA, AGP and Hp. However, their concentration in healthy cat is not yet well established. Generally APP concentration in healthy cats increases with age and there is gender variation as well. Pathological conditions in cats where the concentration of SAA, AGP and Hp has been found to increase include infections, injuries, renal failure, and neoplasms [47]. In feline immunodeficiency diseases, chlamydiosis, non symptomatic corona virus infections, carcinoma, sarcoma and round cell tumour the concentration of AGP increases while as in malignant mesothelioma, renal failure and pancreatitis SAA concentration increases [48] and in inflammations, infectious peritonitis and splenectomy the concentration of Hp increases.

Cattle: In cattle SAA, Hp and fibrinogen are the major positive APPs, and albumin and PON (Paraoxanase) are negative APPs of diagnostic significance. Various studies have been made on their concentration and significance with respect to different physiological status (parturition, lactation) and/or health condition. Calves generally show higher concentration of APPs than adult cattle due to various physiological needs and challenges faced by the calves during their growing stage. Tothova *et al*... (2011) [5] observed 6.8 mg/dl and 5.9 mg/dl concentration of Hp and SAA respectively in one month old healthy calves which later on dropped to 2.1 mg/dl and 1.9 mg/dl respectively at the age of six months. SAA and Hp are useful APPs are used to differentiate acute and chronic inflammation in cattle. Among seven different isoforms of SAA noticed in chronic inflammation of cow only three (SAA 1, SAA 2 and SAA 3) are elevated in acute phase response. Hp has highest serum specificity while SAA has maximum clinical sensitivity [49]. SAA concentration rises rapidly in bronchopneumonia and that of Hp increases with severity of the disease [50]. Both SAA (13.4 mg/dl) and Hp (20.3 mg/dl) concentrations increased significantly in *Anaplasma marginale* infected cows [51]. However, only SAA but not Hp concentration increased significantly in *Brucella abortus* infected cows [52]. SAA in serum and milk increases in mastitic cows and the increase in milk is much earlier than in serum and precede increased milk somatic cell count [53]. Hp concentration in mastitic cows increases in both serum and milk. Both Hp and SAA have a good sensitivity for the diagnosis of mastitis by using a threshold value of 0.02 mg/ml for milk Hp and 0.55 g/ml for milk SAA with no false positive results. Concentration of Hp in cows with mastitis caused by Gram-negative bacteria has been found approximately twice compared to cows infected by Gram-positive bacteria (1,126 vs 575 mg/ml, respectively) [54]. High level of APPs occurs in cows suffering from fatty liver [55], and SAA concentration increases in grain fed cows [56]. Concentration of both SAA (> 6.6 mg/dl) and Hp (> 13 mg/dl) increases after parturition, attaining highest level within 3 days post-partum. Cows with post-partum metritis exhibit high levels (> 8.5 mg/dl) of SAA [57]. Immediately post-partum high blood Hp concentration (> 80 mg/dl) acts as marker for reproductive disorders [58]. SAA, Hp and fibrinogen concentration increases significantly in cows affected with foot diseases like sole ulcers [59]

Pigs: CRP, SAA, Hp, pig-MAP and albumin are the APPs of significance. Except pig MAP all the above APPs have been found elevated in porcine reproductive and respiratory syndrome virus (PRRSV). Hp level has been found increased in Aujeszky's disease virus (ADV) infection. The APP of highest sensitivity in pigs is Hp [60] when compared to others. The serum concentration of both Hp and CRP have been found high in fattening pigs with clinical disease than apparently healthy pigs [61].

Conclusion

Acute phase proteins serve as reliable biomarkers for assessment of health status in animals. They act as a useful tool for understanding the patho-physiology of animal diseases, spread of infection and efficacy of therapeutic regimens, thus act as important diagnostic and/or prognostic indicators of disease in animals.

References

1. Baumann HJ, Gauldie J. The acute phase response. Immunolol Today. 1994; 15:74-88.
2. Eckersall PD, Young FJ, McComb C, Hogarth CJ, Safi S, Weber A *et al*. Acute phase proteins in serum and milk from dairy cows with clinical mastitis, 2000.
3. Gruys E, Toussaint MJM, Niewold TA, Koopmans SJ. Acute phase reaction and acute phase proteins. Journal of Zhejiang University Science. 2005; 6B:1045-1056.
4. Jensen LE, Whitehead AS. Regulation of serum amyloid A protein expression during the acute phase response. Biochemical Journal. 1998; 334:489-503.
5. Tothova CS, Nagy O, Seidel H, Paulikova I, Kovac G. The influence of hoof diseases on the concentrations of some acute phase proteins and other variables of the protein profile in heifers. Acta Veterinaria (Beograd). 2011; 61:141-150.
6. Kaneko JJ, Harvey JW, Bruss ML. Clinical biochemistry of domestic animals. 5th edition. San Diego (CA): Academic Press. 1997, 117-138.
7. Morata H, Miyamoto T. Bovine haptoglobin as a possible immunomodulator in the sera of transported calves. British Veterinary Journal. 1993; 149:277-283.
8. Godson DL, Campos M, Attah-Poku SK, Redmond MJ, Cordeiro DM, Sethi MS *et al*. Serum haptoglobin as an indicator of the acute phase response in bovine respiratory disease, 1996.
9. Yang FM, Haile DJ, Berger FG, Herbert DC, Van Beveren E, Ghio AJ. Haptoglobin reduces lung injury associated with exposure to blood. American Journal of Physiology and Lung Cell Molecular Physiology. 2003; 284:402-409.
10. Murata H, Shimada N, Yoshioka M. Current research on acute phase proteins in veterinary diagnosis, an overview. Veterinary Journal. 2004; 168:28-40.
11. Uhlar CM, Burgess CJ, Sharp PM, Whitehead AS. Evolution of the serum amyloid A (SAA) protein superfamily. Genomics. 1994; 19:228-235.
12. Weber A, Weber AT, McDonald TL, Larson MA. *Staphylococcus aureus* lipotechoic acid induces differential expression of bovine serum amyloid A3 (SAA3) by mammary epithelial cells: Implications of early diagnosis of mastitis. Veterinary Immunology and Immunopathology. 2006; 109:79-83.
13. De Beer MC, Yuan T, Kindy MS, Asztalos BF, Roheim PS, de Beer FC. Characterization of constitutive human serum amyloid A protein (SAA4) as an apolipoprotein. Journal of Lipid Research. 1995; 36:526-534.
14. Petersen HH, Nielsen JP, Heegaard PM. Review: Application of acute phase protein measurements in veterinary clinical chemistry. Veterinary Research. 2004; 35:163-87.
15. Davalos D, Akassoglou K. Fibrinogen as a key regulator of inflammation in disease. Seminars in Immunopathology. 2012; 34:43-62.
16. Gentry PA. Acute phase proteins. In: Loeb WF, Quimby FW (eds.): Clinical Chemistry of Laboratory Animals. Taylor & Francis, Philadelphia. 1999; 336-398.
17. Medcalf RL. Fibrinolysis, inflammation and regulation of the plasminogen activating system. Journal of Thrombosis and Haemostasis. 2007; 5:132-142.
18. Eidelman RS, Hennekens CH. Fibrinogen: a predictor of stroke and marker of atherosclerosis. European Heart Journal. 2003; 24:499-500.
19. Hirvonen J, Pyorala S. Acute-phase response in dairy cows with surgically treated abdominal disorders. Veterinary Journal. 1998; 155:53-61.
20. Lovstad RA. A kinetic study on the phenothiazine dependent oxidation of NADH by bovine ceruloplasmin. Biometals. 2006; 19:1-5.
21. Skinner JG, Brown RAL, Roberts L. Bovine haptoglobin response in clinically defined field conditions. Veterinary Record. 191; 128:147-149.
22. Sheldon IM, Noakes DE, Rycroft AN, Dobson H. Effect of pospartum manual examination of the vagina on uterine bacterial contamination in cows. Veterinary Record. 2002; 151:531-534.
23. Fagliari JJ, Weiss DJ, McClenanhan D, Evanson. Serum protein concentrations in calves with experimentally induced pneumonic pasteurellosis. Arquivo Brasileiro de Medicina Veterinaria e Zootecnia. 2003; 55: 4.
24. Fournier T, Medjoubi N, Porquet D. Alpha-1-acid glycoprotein. Biochimicaet Biophysica Acta. 2000; 1482: 306-311.
25. Bence LM, Addie DD, Eckersall PD. An immunoturbidimetric assay for rapid quantitative measurement of feline alpha-1-acid glycoprotein in serum and peritoneal fluid. Veterinary Clinical Pathology. 2005; 34:335-340.
26. Lomas DA. The selective advantage of α1- antitrypsin deficiency. American Journal of Respiratory Critical Care Medicine. 2006; 173:1072-1077.
27. Janciauskiene SM, Bals R, Koczulla R, Vogelmeier C, Köhnlein T, Welte. The discovery of α1- antitrypsin and its role in health and disease. Respiratory Medicine. 2011; 105:1129-1139.
28. Tuder RM, Janciauskiene SM, Petrache I. Lung disease associated with α1-antitrypsin deficiency. Proceedings of the American Thoracic Society. 2010; 7:381–386.
29. Metz-Boutigue MH, Jolles J, Mazurier J, Schoentgen F, Legrand D, Spik G, Montreuil J, Jolles P. Human lacto transferrin: amino acid sequence and structural comparisons with other transferrins. European Journal of Biochemistry. 1984; 145:659-676.
30. Moore SA, Anderson BF, Groom CR, Haridas M, Baker EN. Three-dimensional structure of diferric bovine lactoferrin at 2.8 A resolution. Journal of Molecular Biology. 1997; 274:222-236.
31. Adlerova L, Bartoskova A, Faldyna M. Lactoferrin, a review. Veterinarni Medicina. 2008; 53: 457–468.

32. Mazurier J, Spik G. Comparative study of the iron-binding properties of human transferrins. Complete and sequential iron saturation and desaturation of the lactotransferrin. Biochimicaet Biophysica Acta. 1980; 629: 399-408.
33. Valenti P, Antonini G. Lactoferrin an important host defense against microbial and viral attack. Cellular and Molecular Life Sciences. 2005; 62:2576-2587.
34. Brock JH. Lactoferrin in human milk: Its role in iron absorption and protection against enteric infection in the newborn infant. Archives of Disease in Childhood. 1980; 55:417-421.
35. Don BR, Kaysen G. Serum albumin: Relationship to inflammation and nutrition. Seminars in Dialysis 2004; 17:432-437.
36. Gomme PT, McCann KB. Transferrin: structure, function and potential therapeutic actions, 2005.
37. Huebers HA, Finch CA. The physiology of transferrin and transferring receptors. Physiological Reviews. 1987; 67:520-582.
38. Kaplan J, Jordan I, Sturrock A. Regulation of the transferrin – independent iron transport system in cultured cells. Journal of Biological Chemistry. 1991; 266:2997-3004.
39. Moser M, Pfister H, Bruckmaier RM, Rehage J, Blum JW. Blood serum transferrin concentration in cattle in various physiological states, in veal calves fed different amounts of iron, and in cattle affected by infectious and non-infectious diseases. Zentralblatt fur Veterinarmedizin A. 1994; 41:413-420.
40. Foss TR, Wiseman RL, Kelly JW. The pathway by which the tetrameric protein transthyretin dissociates. Biochemistry. 2005; 44:15525-15533.
41. Ingenbleek Y, Young V. Transthyretin (prealbumin) in health and disease: nutritional implications. Annual Review of Nutrition. 1994; 14:495-533.
42. Otabe K, Sugimoto T, Jinbo T, Honda M, Kitao S, Hayashi S *et al.* Physiological levels of C-reactive protein in normal canine sera. Veterinary Research Communications. 1998; 22:77-85.
43. Joans, FS. The role of C-reactive protein as a biomarker in dogs with lymphosarcoma. MSc thesis, University of Glasgow, 2013.
44. Nakamura M, Takahashi M, Ohno K, Koshino A, Nakashima K, Setoguchi A *et al.* C-reactive protein concentration in dogs with various diseases. Journal of Veterinary Medical Science. 2008; 70:127-131.
45. Ulutas B, Bayramli G, Ulutas PA, Karagenc T, Serum. Concentration of some acute phase proteins in naturally occurring canine babesiosis: a preliminary study. Clinical Pathology. 2005; 34:144-147.
46. Zapryanova, Mircheva T, Denev SA. Plasma protein profiles and fibrinogen concentrations in dogs with experimentally induced *Staphylococcus aureus* infection. Revue de Medecine Veterinaire. 2013; 64:150-155
47. Paltrinieri S. The feline acute phase reaction. The Veterinary Journal. 2008; 177:26-35.
48. Tamamoto T, Ohno K, Ohmi A, Sek I, Tsujimoto H. Time- course monitoring of serum amyloid A in a cat with pancreatitis. Veterinary Clinical Pathology. 2009; 38:83-86.
49. Horadagoda NU, Knox KM, Gibbs HA, Reid SW, Horadagoda A, Edwards SE *et al.* Acute phase proteins in cattle, Discrimination between acute and chronic inflammation. Veterinary Record. 1999; 144:437-441.
50. Heegaard PMH, Godson DL, Toussaint MJM, Tjornehoj K, Larsen LE, Viuff B *et al.* The acute phase response of haptoglobin and serum amyloid A (SAA) in cattle undergoing experimental infection with bovine respiratory syncytial virus. Veterinary Immunology and Immunopathology. 2000; 77:151-159.
51. Coskun A, Ekicio D, Güzelbektes H, Aydoŏdu U, and Sen I. Acute Phase Proteins, Clinical, Hematological and Biochemical Parameters in Dairy Cows Naturally Infected with Anaplasma marginale. Kafkas Universities Veteriner Fakultesi Dergisi. 2012; 18:497-502.
52. Sharifiyazdia H, Nazifi S, Nikseresht K, Shahriari R. Evaluation of Serum Amyloid A and haptoglobin in dairy cows naturally infected with Brucellosis. Journal of Bacteriology Parasitology. 2012, 3:157.
53. Pedersen LH, Aalbaek B, Rontved CM, Ingvartsen KL, Sorensen NS, Heegaard PM *et al.* Early pathogenesis and inflammatory response in experimental bovine mastitis due to *Streptococcus uberis*. Journal of Comparative Pathology. 2003; 128:156-164.
54. Wenz JR, Fox LK, Muller FJ, Rinaldi M, Zeng R, Bannerman DD. Factors associated with concentrations of select cytokine and acute phase proteins in dairy cows with naturally occurring clinical mastitis. Journal of Dairy Science. 2010; 93:2458-2470.
55. Ametaj BN, Bradford BJ, Bobe G, Nafikov RA, Lu Y, Young JW *et al*. Strong Relationships between Mediators of the Acute Phase Response and Fatty Liver in Dairy Cows. Canadian Journal of Animal Science. 2005; 85:165-175.
56. Emmanuel DGV, Dunn SM, Ametaj BN. Feeding High Proportions of Barley Grain Stimulates an Inflammatory Response in Dairy Cows. Journal of Dairy Science. 2008; 91:606-614.
57. Chan JP, Chang CC, Hsu WL, Liu WB, Chen TH. Association of increased serum acute phase protein concentrations with reproductive performance in dairy cows with postparturient metritis. Veterinary Clinical Pathology. 2010; 39:72-78.
58. Dubuc J, Duffield TF, Leslie KE, Walton JS, LeBlanc SJ. Risk factors for postpartum uterine diseases in dairy cows. Journal of Dairy Science. 2010; 93:5764-5771.
59. Kujala M, Orro T, Soveri T. Serum Acute Phase Proteins as a Marker of Inflammation in Dairy Cattle with Hoof Diseases. The Veterinary Record. 2010; 166:240-241.
60. Parra MD, Fuentes P, Tecles F, Martínez- Subiela S, Martínez JS, Muñoz A *et al.* Porcine Acute Phase Protein Concentrations in Different Diseases in Field Conditions. Journal of Veterinary Medicine. 2006; 53:488-493.
61. Pallares FJ, Martinez-Subiela S, Seva J, Ramis G, Fuentes P, Bernabe A *et al.* Relationship between serum acute phase protein concentrations and lesions in finishing pigs. The Veterinary Journal. 2008; 177:369-373.