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ACUTE PHASE PROTEINS AS BIOMARKERS IN PERSPECTIVE TO ANIMAL DISEASES DIAGNOSIS

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ABSTRACT

When an infection, trauma or inflammation occurs due to any reason or disease, it causes acute phase response. A lot of pathophysiological responses occur due to it including pyrexia, pain, leukocytosis, removal of pathogen or causative agent to minimizing the tissue damage and increasing tissue repairing process. Acute phase proteins (APPs) are produced by hepatic or extrahepatic sources. Liver production of acute hepatic protein is regulated by pro-inflammatory cytokines. Liver produces positive and negative, both types of APPs. The acute phase protein that plays significant role in the activation of almost whole inflammation process and tissue recovery, starting from activation of complement system, binding cellular components, eliminating free radicles, neutralizing enzymes and controlling immune response are positive. APPs also play significant role in the diagnosis of different animals' diseases like bovine viral diarrhea, tuberculosis, bovine respiratory syncytial virus, mastitis, etc. These diseases are otherwise difficult to diagnose. Thus, APPs play a biomarker role in the early detection of chronic diseases. In this way, it become easy to diagnose and treat these diseases.

Keywords: Cytokines, Pro-inflammatory cytokines, Acute-phase protein, C-reactive protein, Diagnosis

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1. INTRODUCTION

Inflammation is major response when tissue injury or infection occurs. However, infection is not always connected with inflammation e.g., immune compromised individual. On the other hand, inflammation can also occur without infection. When a tissue is damaged or immune system is compromised, it produces cytokines that are pro-inflammatory in nature. Most of the functions played by cytokines are, to regulate immune response. Cytokines include interleukins (IL), interferons (INFs), tumor necrosis factor (TNF-α) and colony stimulating factors (CSF). Cytokines regulate apoptosis, cell growth, cell division, expression of adhesion molecule expression, chemotaxis and immunoglobulin production (Musolino et al. 2017). These pro-inflammatory cytokines produce vascular and cellular changes on the cite of injury or infection (Gruys et al. 2005). The changes include edema, redness, hotness, pain and loss of function (Calixto et al. 2003). The primarily function of all these changes is to recover the tissue to the normal stage. In case of chronic injury, substantial injury and recovery of injured tissue trigger a continuous inflammatory response (Chung et al. 2010). At the same time, another response is produced by the liver to produce plasma proteins known as acute phase proteins (APPs) (Cray et al. 2009; Lee et al. 2019).

The production of APPs contains a lot of reactions that causes different local and systemical effects. These effects include increase or decrease in the quantity of proteins that are produced by liver also called APP. Cytokines are the primary protein hormones that causes production of APPs by communicating between site of injury and liver. Almost all the cytokines have multiple sources from where they are produced and multiple targets on which they act to produce their response (Petersen et al. 2004; Musolino et al. 2017; Lee et al. 2019). Almost all the species produce them like mammals, fishes, and birds.

The concentration of APPs is largely affected by the change in their production by the hepatocytes in liver. The production of one protein that is serum amyloid A (SAA) and the other that is C-reactive protein is greatly affected up to 50% by the change in production from hepatocytes. Different pro-inflammatory cytokines influence and accelerate the production of different types of APPs that includes tumor necrosis factor-alpha (TNF-α) and interleukins for example IL-1, and IL-2 (Lee et al. 2016).

In chronic conditions like mastitis, continuous and repeatedly stimulus is present that is continuously provoking acute phase protein synthesis. In this condition serum concentration of APPs is generally increased than the normal values. This increase in APPs don't touches the level that is present in case of acute inflammation and always

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remain less than the acute inflammation. All the APPs show different increase in their value in case of chronic inflammation as compared to acute inflammation.

2. Acute Phase Proteins

2.1. Acute Phase Protein Synthesis (Fig. 1)

In the event of inflammation or infection, a critical phase response is triggered by the main symptoms of inflammation such as redness, fever, pain, loss of function, increased vascular flow, increased migration of neutrophils to the area of infection and peripheral leucocytes. It also causes increase in production of APPs from the hepatocytes in liver by signaling of cytokines for example IL-1, IL-6 and TNF-α. The three most important proteins are CRP (C-reactive protein), SAA (serum amyloid A) and SAP (serum amyloid protein).

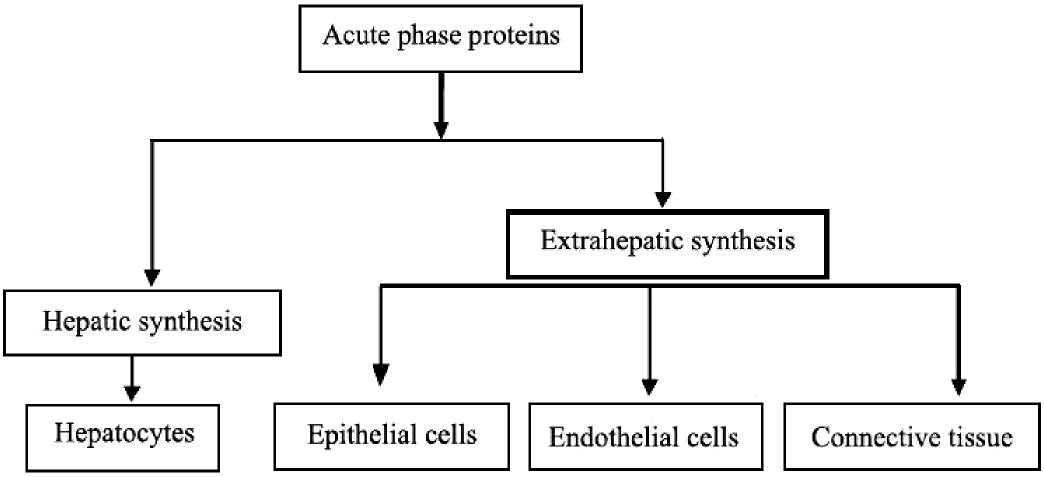

Fig. 1: Acute phase protein synthesis (Jain et al. 2011).

2.2. Classification of Acute-phase Proteins

There are different classifications of APPs based on concentration, mode of action and increase/decrease of concentration of APPs in different species.

2.2.1. On basis of Protein concentration

On the basis of concentration, there are two different types of APPs. These are called as positive and negative acute phase proteins (Czopowicz et al. 2017).

2.2.2. Concentration in Various Species

The level of acute phase proteins is variable according to the species (Merhan et al. 2017; Bazzano et al. 2022).

Cattle: In cattle, major APPs include Hp and SAA (Table 1). Minor APPs include alpha-antitrypsin, alpha-AGP, Cp and fibrinogen. SAA increases its concentration from 2 to 8-fold in acute phase protein response (APR). It acts faster than Hp (Merhan et al. 2017; Bazzano et al. 2022).
Dogs: The concentration of APPs shown by the dogs is almost same as in humans. The CRP concentration increases from normal level to 100-fold just after 24 hours of surgery and then decreases. After its other APPs like ceruloplasmin, Hp and alpha-AGP show moderate increases in their concentration up to two-fold. Alpha-antitrypsin doesn't show any change in its concentration (Jain et al. 2011). There are different major and minor acute phase proteins (Table 1) in different species (Cray 2012).
Pigs: Pigs shows high level of CRP serum concentration in comparison to show any sign of acute inflammation. The concentration of CRP increases up to 8 to 10 times. Hp plays a major role in pigs and its level increases up to 2-10 folds. Other major APP is SAA. Minor APP includes Cp. Negative APPs include transferring, fetuin and albumin, their concentration decreases from 20-40%.
Sheep and Goats: Major APP includes haptoglobin. The concentration of haptoglobin increases 100-fold when sheep in injected with yeast. Other APPs include Cp and fibrinogen. Concentration of these proteins increases up to four times. Value of SAA increases up to 10 times than normal in ewes in case of mastitis. Milk also show increase in SAA concentration in case of mastitis. Negative APP is mainly albumin that shows decrease in its concentration.

Similarly, just like of cattle and sheep in goats, Hp and SAA are considered as major APPs and a 20-fold increase has been reported in response to subcutaneous injections (Czopowicz et al. 2017). Another variation

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reported in literature is that in chronic conditions Hp increases, while in acute SAA is increased, however, many deviations has been observed to this rule (Rahman et al. 2010; Czopowicz et al. 2017).

Table 1: Species-wise major and minor acute phase proteins

Name of specie	Major Acute phase proteins	Minor Acute phase proteins
Cat	AGP, SAA	FIB, Hp
Chicken	None	AGP, Cp, FIB, Hp, SAA
Cow	Hp, SAA	AGP, Cp, CRP, FIB
Dog	CRP, SAA	AGP, Cp, Hp, FIB
Goat	Hp, SAA	AGP, FIB
Horse	SAA	AGP, Cp, FIB, Hp
Human	CRP, SAA	AGP, FIB, Hp
Mouse	Hp, SAA, SAP	CRP, FIB
Non-human primates	CRP	FIB, Hp, SAA
Pig	Hp, SAA, MAP	AGP, Cp, CRP, FIB
Rabbit	CRP, Hp, SAA	AGP, Cp, FIB
Rat	AGP, A2M	Cp, CRP, FIB, Hp
Sheep	Hp, SAA	AGP, Cp, CRP, FIB

Hp—haptoglobin, SAA—serum amyloid A, Fb—fibrinogen, Cp—ceruloplasmin, AGP—acid glycoprotein, CRP—C-reactive protein, SAP—serum amyloid protein, MAP—major acute protein, FIB—fibrinogen.

2.3. Positive Acute Phase Proteins

A large number of APPs are produced by liver in response to the APR (Table 2). The production of these proteins is enhanced during infection or the stage of inflammation. It includes CRP, alpha-1 antitrypsin, mannose-binding protein, D-dimer protein, alpha-1 anti-chymotrypsin, alpha 2 macroglobulin, complement factors, prothrombin, factor VIII, fibrinogen, von-Willebrand factor, SAA, SAP complement, plasminogen, ceruloplasmin (Cp), complement factors, and haptoglobin (Hp) (Eckersall and Bell 2010; Bazzano et al. 2022).

These powerful proteins play different roles in the immune system. Few destroy or stop the growth of microbial agents such as CAA and Hp. Some produce a negative response to an inflammatory response such as alpha 2 macroglobulin and serpins. Coagulation factors play an important role in coagulation. Positive phase proteins also produced during APR by anorexia and metabolic disorders.

2.4. Negative Acute Phase Proteins

During the injuries where liver response to APR by enhancing a large number of APPs, it also inhibits or decreases the synthesis of some proteins (Table 2). The production of these proteins is decreased, so they are called as negative acute phase proteins. Negative APPs include transferring, transthyretin, retinol binding protein, transcortin and albumin (Eckersall and Bell 2010; Bazzano et al. 2022).

2.5. On the basis of Mode of Action

Mode of action of APPs divide them in four major groups. Still, some of the APPs are undefined in any group.

Protease inhibitor: These inhibit the catalytic activity of proteases like alpha-1 antitrypsin, alpha-1 anti-chymotrypsin.

Complement proteins: It includes proteins that are C2, C3, C4, C5 etc.

Transport proteins: It includes Hp, hemopexin and Cp.

Coagulation protein: It includes fibrinogen and prothrombin

Other proteins: This group includes SAA, SAP, CRP and AGP.

Table 2: Negative and positive acute phase protein in different viral diseases

Disease	Virus	Family	Specie	Positive APP	Negative APP	Reference
SRLV	Caprine arthritis encephalitis	Retroviridae	Goat	Hp, SAA	Not Tested	Czopowicz et al. (2017)
BDV	Border disease	Flaviviridae	Goat	Hp, SAA	Not Tested	Balikci et al. (2013)
PPRV	Peste des petits ruminants	Paramyxoviridae	Sheep	Hp, SAA	Not Tested	Arslan et al. (2007)
BTV	Blue tongue disease	Reoviridae	Sheep	Hp, SAA	Albumins	Sánchez-Cordón et al. (2013) Aytekin et al. (2015)
BRSV	Bovine Respiratory Syncytial Virus	Paramyxoviridae	Cattle	Hp, SAA	Not Tested	Heegaard et al. (2000)
BVDV	Bovine viral diarrhea	Flaviviridae	Cattle	Hp, SAA, Fb	Not Tested	Burgstaller et al. (2016)
FMDV	Foot and mouth disease	Picornaviridae	Cattle	Hp, SAA, Fb, Cp	Albumin	Nazifi et al. (2011); Stenfeldt (2011); Stenfeldt and Arzt (2020)

2.6. Role of APPs in Animal Diseases Diagnosis

Role of APPs in disease diagnosis is very valuable. A lot of complex veterinary diseases can be diagnosed with the help of APPs level in blood (Cray et al. 2009; Eckersall and Bell 2010; Idoate et al. 2015; Reczyńska et al. 2018a). Some of the important diseases have been described below:

2.6.1. Bovine Respiratory Syncytial Virus (BRSV)

Bovine respiratory disease is mostly common in calves. It is life threatening condition which leads to heavy economic loss for both the dairy and beef sector. A number of factors and pathogens are involved. These includes gram-negative bacteria that is *Pasteurella multocida* and *Mannheimia haemolytica*, *Haemophilus somnus*. Gram-positive bacteria include *Mycoplasma bovis*. These all work with the syncytial viruses (BRSV). BRSV is from the genus Pneumovirus and family Paramyxoviridae (Reczyńska et al. 2018a).

In calves it infects small air passageways that leads to bronchiolitis or pneumonia. In young animals, its symptoms are closely related to cold. In case of young animals, the temperature reaches to 39.5°C, other signs include difficult and abdominal breathing. Breathing rate is also increased and nasal discharge is also present. This starts with the coughing and expiratory wheezing due to contracted air passageways and leads to shortness of breath, rapid breathing, forced breathing and cyanosis due to oxygen deficiency in body.

The virus has the affinity for lower respiratory tract epithelium. It attacks on the epithelium cells and activates mediators of inflammation. Due to inflammation the air passages become constricted. Virus also causes immune suppression in the body that paves the path for bacterial infection that is called secondary bacterial infection and difficult to diagnose (Reczyńska et al. 2018b).

2.6.1.1. Role of acute phase proteins in the Bovine Respiratory Syncytial Virus (BRSV)

The level of APPs is same as in bacterial infections leading to pneumonia. The level of SAA and Hp increases in the inflammation induced by BRSV. Level of haptoglobin depends upon the severity of disease and involvement of the lung. The level of serum amyloid A is high from the very beginning of inflammation (Larsen et al. 2001). Heegaard et al. (2000) reported that the concentration of Hp and SAA increases in BRSV. After one week of infection the concentration of SAA increases about 5-7 times the healthy animal along with the serum level of Hp.

2.6.2. Mastitis

Mastitis is a common inflammatory disease of udder in milking animals. It causes poor milk quality and decrease in milk production that leads to economic losses. It is caused by variety of bacteria which include both gram positive and negative bacteria. Mostly contagious bacteria like *Streptococcus agalactiae*, *Staphylococcus aureus* and Mycoplasma spp. are the causative agents. Environmental bacteria include *Enterococcus* spp. and *Escherichia coli*. In non-coagulase bacteria, important ones are *Streptococcus uberis* and *Staphylococcus* (Cheng and Han 2020). Mastitis has three types: chronic mastitis, clinical mastitis and subclinical mastitis on the basis of clinical examination. Clinical mastitis is easy to detect because of the visible evident signs like redness and swelling with elevated temperature of animal. During field test, flakes are present in the milk of the cow (Khan and Khan 2006; Du et al. 2022). Clinical form of mastitis is further divided on the basis of severity and inflammation into per-acute, acute and subacute forms. On the other hand, sub-clinical mastitis shows no clinical signs and judged by only high somatic cell count and low production of milk (Abebe et al. 2016). Chronic form is a prolonged inflammation that is difficult to cure and may lead to fibrosis of udder. There are many other risk factors that lead to onset and progression of disease like environmental sanitation, host immune system and pathogen's potential etc.

2.6.2.1. Role of acute phase proteins in Mastitis

Diagnosis of sub-clinical mastitis is the most difficult task. It is well identified and monitored with the level of N-acetyl-beta-D-glucosaminidase activity, electrical conductivity, lactose concentration in the milk. Others parameter like optical density and milk flow levels also prove good. From APPs, SAA and Hp serve as a good biological marker in diagnosis (Pyörälä 2003).

α-1 trypsin inhibitor and bovine serum albumin are the first APPs those were used as a diagnostic tool for mastitis. In other APPs, haptoglobin also increases its level in sub-clinical mastitis. Intra mammary infection can also be detected by the level of SAA and Hp present in milk. The level of SAA can be used to differentiate between moderate and mild mastitis. If the level of Hp and SAA is below the detection level, then it is confirmed that animal's udder is in good condition. A continues increase in the level of SAA and Hp indicates onset of chronic subclinical mastitis (Grönlund et al. 2005). CRP is not a good indicator in cattle, but its value also increases in case of mastitis in cattle. The level of Hp and SAA is more in the infected quarter of udder than the non- infected quarters. The detection of these APPs makes the detection easy and feasible because they can be easily detected from milk and there is no need for blood collection. If inflammation is present in the udder and milk APPs are increased due to this inflammation than they are regarded as sensitive and more reliable biomarker, then the somatic cell count (Ahmed et al. 2021; Gulshan et al. 2021; Bazzano et al. 2022).

2.6.3. Paratuberculosis (PTB) or Johne's disease

It is chronic state of diarrhea that is associated with malabsorption. It affects animals of all ages but calves are severely affected. It is one of the severe problems on the farms because it causes economic losses due to decrease in milk production, culling of animals, increases chances of mastitis, increases somatic cell count, reduces fertility and slaughter value of animal (Vázquez et al. 2012; Pinior and Köfer 2016). Bacterial and nutritional both factors play important role in the development of disease. It is the most important chronic intestinal disease with progressive granulomatous infection in ruminants and caused by *Mycobacterium avium subsp. paratuberculosis* (MAP) (Pillars et al. 2009). According to literature, paratuberculosis causes a huge loss in comparison to other diseases like enzootic bovine leukosis, bovine viral diarrhea and neosporosis (Chi et al. 2002; Rasmussen et al. 2021).

MAP can infect a number of species including wildlife, primates, humans, ruminants and non-ruminants' livestock. This disease shares its part in farm losses in different parts of the world. For example, losses due to Johne's disease in dairy cow's ranges from US$21-79 per cow annually. In Canada this loss is between US$35-57 per cow annually. Globally stated that it loses US$33 per cow annually in major milk producing countries. It becomes approximately 1% of the revenue generated from milk (Philip 2021).

2.6.3.1. Role of acute phase proteins in Paratuberculosis

A recent study has been conducted to confirm the role of serum proteins and acute phase proteins in the development of paratuberculosis. In this study, 44 animals those had the signs relative to the john's disease like diarrhea and seropositive for MAP were taken along 19 healthy animals that were seronegative for MAP. The level of different serum proteins, their fraction proteins and total protein was measured along different selected acute phase proteins like creative protein, haptoglobin and serum amyloid A (SAA) was checked in serum. In the cows, those had the signs of diarrhea showed low value of albumin, total protein and albumin/globulin ($P<0.001$). The concentration of α1-, β1- and γ-globulins was also low ($P<0.001$) and level of α2- and β2-globulins was higher. The level of haptoglobin and serum amyloid A was little higher. The level of CRP was little lower ($P<0.001$). The results showed that the lower value of albumin, albumin/globulin, total protein and serum protein was lower in sick animal. The concentration of other serum proteins like α1-, α2-, β1-, β2- and γ-globulins were elevated. Acute phase proteins like haptoglobin and serum amyloid A also showed increase in their level with decrease in CRP level in serum (Nagy et al. 2020).

2.6.4. Bovine viral diarrhea (BVD)

BVD causative agent belongs to family Flaviviridae and genus Pestivirus. Genus Pestivirus is the family of small positive strand RNA viruses. This genus contains four important viruses those cause diseases in different animals. These are Bovine viral diarrhea virus (BVDV) type 1 and type 2, border disease virus (BDV) and classical swine fever virus (CSFV) (Walz 2020). Some new species have also been discovered and classified as species of genus Pestivirus. It includes HoBi Pestivirus, isolated from calf serum, giraffe Pestivirus isolated from Kenyan giraffe, Bungowannah virus isolated from pigs in Australia and Pronghorn virus isolated from pronghorn in antelope in United states (Bielefeldt-Ohmann 2020).

The signs and symptoms include lethargy, fever, nasal and ocular discharge, decrease in appetite due to oral lesions and reduced milk production. In chronic cases it is likely to mucosal disease. Calves usually show cerebral hypoplasia. The signs shown in the calves are stumbling, tremors and wide stance. In most severe cases, death of calves occurs. In case of transient infection calf pneumonia, reproductive disorder, decreased milk production, diarrhea occur. It also increases the chance of other diseases to occur and causes death. In case of pregnant cows, it causes severe economic loss due to week and abnormal calves, congenital defects and abortion in infected pregnant animals. In case of bulls, it causes reproductive problem and secreted in semen for a prolonged period after recovery. This infected semen may cause spread of disease into female and cause abortion in second trimester.

BVD is endemic in many countries. Maximum 1-2% animals are persistently infected with the virus and 60-80% animals are tested positive for antibodies. Persistent infection is more dangerous because it plays a major role in spreading of virus. Acute infection can also have chances to spread virus horizontally. Transmission of virus from one animal to other is mostly direct but indirect way can also be there. The loses of BVD have been estimated 687.80 US dollars per animal (Mirosław and Polak 2019). It causes immunosuppression that can cause morbidity and mortality, decrease in reproductive performance (e.g., increased calving interval (CI) and increase in the time for first conception), abortion, still birth, malformation, reduced milk production, congenital deformities, decrease in growth and reduced weight gain (Richter et al. 2017).

2.6.4.1. Role of acute phase proteins in Bovine Viral diarrhea (BVD)

Acute phase responses once initiated causes increases in a number of proteins that are produced by the liver. On the other hand, it also causes reduction in the concentration of many acute phase proteins. After inflammation, proliferation of leukocytes and production of cytokines, positive and negative acute phase proteins cause the change in the concentration of serum proteins. So, the level of these acute phase proteins plays a very important role in the diagnosis of bovine diseases. From the positive phase acute proteins, serum amyloid A (SAA) and Haptoglobin (Hb) play very important role in the diagnosis of diseases because their concentration is greatly affected by the bacterial or viral persistent infections (Fig. 2). Specially, the level of SAA and haptoglobin protein is greatly

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affected by the viral infection like bovine respiratory syncytial virus and can be used as a good diagnosis or prognosis factor (Burgstaller et al. 2016). In another study, it was observed that the viral infection like bovine herpes virus infection or rinderpest virus, the acute phase proteins do not change its serum concentration and have no significant role in the diagnosis or prognosis of disease (Heegaard et al. 2000; Ulutas et al. 2011).

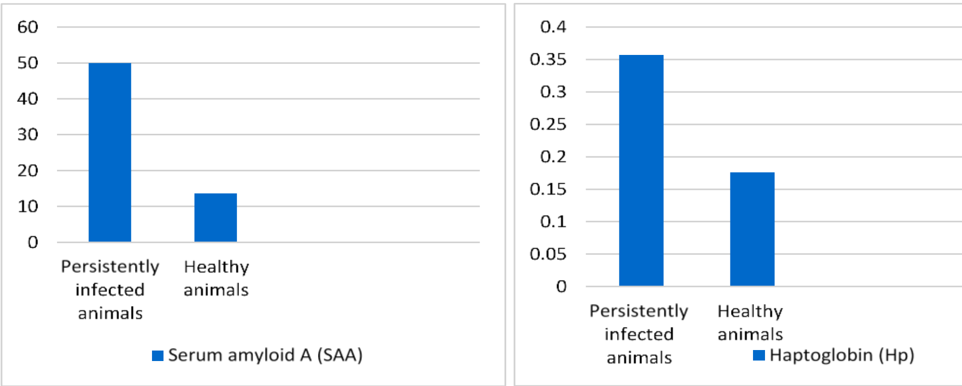

Fig. 2: APPs Concentration comparison of BVD infected and healthy animals (Ulutas et al. 2011).

2.6.5. Foot and mouth disease virus (FMDV)

The virus of this disease belongs to the Picornaviridae family and genus Aphthovirus. It contains a single standard RNA that is present in capsid. It causes foot and mouth disease in variety of farm animals and wild animals like sheep, goat, cow, buffalo and pigs (Alexandersen et al. 2003; Lee et al. 2019:). Control and prevention of FMD is very important because it causes decrease in the production of animals as well as affects the quality of products too. For this purpose, mass vaccination is crucial. Its vaccines are chemically inactivated vaccines (Chamberlain et al. 2015). The clinical symptoms include anorexia, high fever, depression, loss of appetite, dyspnea, intense salivation and lameness. FMD can be transferred both directly and indirect route. Direct route involves direct contact of healthy to infected animals. Indirect route involves barn equipment, wind and remaining feed and water of infected animal. The workers of the farm also spread virus from infected to healthy ones. FMD can easily spread by wind in the area around infected farm. So, it is very difficult to eradicate FMD in an area. Another problem that is more severe and adopted by the virus is that after the completion of acute phase, animal recovers itself. But it remains carrier with the virus and can spread the virus to other animals (Merhan et al. 2017). The virus replicates in many sites in the body of organism like pharyngeal mucosa, epithelial cells and rarely in lungs also.

2.6.5.1. Role of acute phase proteins in Foot and mouth disease (FMD)

In case of FMD, a lot of serum APPs show increase in their concentration including Cp, Fb, Hp and SAA. It has been observed that the concentration of SAA is eight time increased in diseased animal as compared to healthy one (Table 3). The concentration of HP rises up to five times as compared to healthy animals (Nazifi et al. 2011a). The concentration of APPs increases almost two-fold in diseased animal (Table 3) as reported in different research articles and shown in the following figures (Stenfeldt et al. 2011; Merhan et al. 2017). Similarly, the cattle and pigs infected experimentally with the virus have higher level of Hp, SAA, fibrinogen and ceruloplasmin as compared to healthy animals (Nazifi et al. 2011b; Lee et al. 2019). Another negative APPs known as albumin due to the anorexia in FMD that ultimately reduces its synthesis from liver (Merhan et al. 2017).

Table 3: Mean+SE of acute phase proteins in clinically healthy and FMD affected animals (Refs)

Acute Phase Proteins	Contro2l (n=10)	Moderately (n=10)	Severely (n=10)	P value
Hepatoglobin (g/L)	0.084+0.006a	0.308+0.043b	0.387+0.035c	<0.01
SAA (µg/mL)	4.86+0.30a	28.80+3.37b	45.44+8.77c	<0.01
Ceruloplasmin (m(g/dL)	7.76+0.59a	9.66+1.64a	15.98+2.19b	<0.01
Albumin (g/dL)	3.43+0.15a	3.39+0.25b	2.49+0.49	<0.05

a,b,c: The groups in the same row labelled different letters are statistically significant.

In another study, it has been observed that the concentration of SAA increases approximately 6-9-fold, the concentration of Hp increases 3-4 folds and increase in the concentration of Cp is twofold in early phase of the diseases, however in other chronic diseases of cattle it is decreased (Fig. 3). It has been reported that the serum

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concentration of albumin is decreased in the case of FMD infected animal (Stenfeldt et al. 2011; Stenfeldt and Arzt 2020).

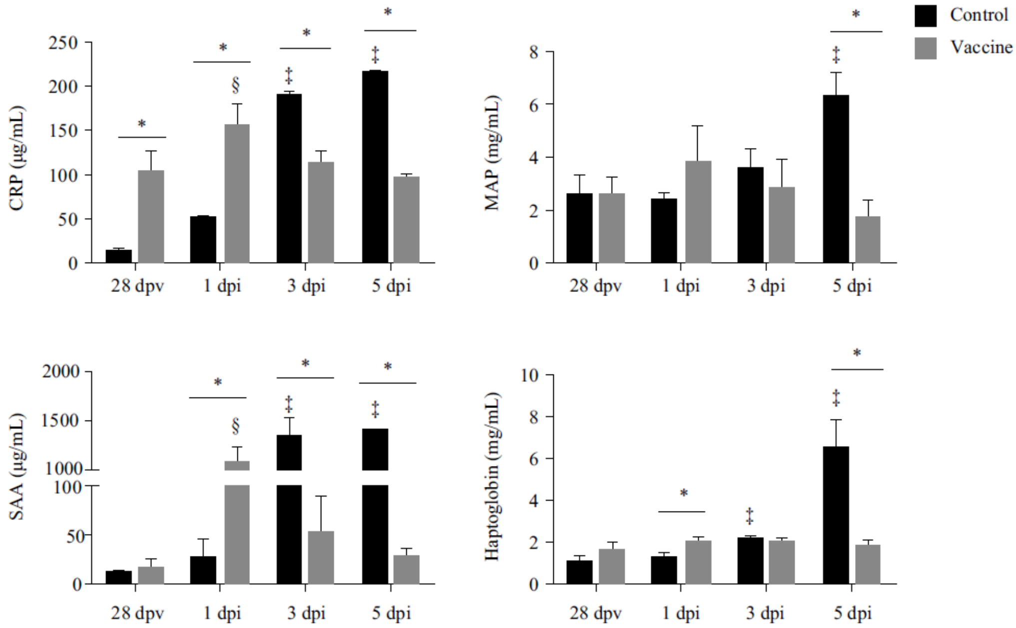

Fig. 3: Serum concentration of APPs in immunized pigs challenged against FMD virus serotype O (Lee et al. 2019). CRP - C-reactive protein; MAP - major acute phase protein; SAA - serum amyloid A; dpi - days post-infection; dpv - days post-vaccination. Asterisks (*) indicate significant differences between the control and vaccine groups at each time point; double daggers (‡) indicate significant change from 28 dpv in the control group; section marks (§) indicate significant change from 28 dpv in the vaccine group.

2.6.6. Small ruminant lentivirus (SRLV)

There are lot of viral diseases that affect small ruminants (sheep and goats). One of them is the severe disease that is small ruminant's lentivirus. It belongs to the Retroviridae family. The virus mostly infects the cells of immune system like monocytes, dendritic cells and other cells like macrophages. It also infects epithelial cells too. The virus is single standard RNA virus and is difficult to eliminate because it persists in the latent form in the infected animal for months to years (Jarczak et al. 2016; Górecka-Bruzda et al. 2019; Kurhaluk et al. 2021). It causes arthritis of different joints like mostly carpal and rarely tarsal joint in mature goats. It also leads to respiratory distress, neurological symptoms (due to progressive encephalomyelitis) and mammary induration in sheep. Other than this, in both species virus causes a special form of mastitis that is non-suppurative and indurative. In case of young kids, virus rarely causes leuko-encephalomyelitis (Blacklaws 2012; Kurhaluk et al. 2021). Virus can be transmitted both by vertical and horizontal pathways. Vertical pathway includes transmission from an infected mother via milk or colostrum due to shedding of virus in the secretions. Horizontal pathway includes direct contact with the infected animal or its secretions. Virus may also spread by sexual secretions of infected animal (Stonos et al. 2014). Economic losses due to decrease in milk production of lactating animals and culling of small, infected kids are there.

2.6.6.1. Role of acute phase proteins in Small ruminant lentivirus (SRLV)

Various researcher reported mixed type of results like Kaba et al. (2011) described that there is no change in the concentration of HP in case of infected animal when compared to the healthy goat. In contrast to this, Czopowicz et al. (2017) reported opposite results where a significant increase in the concentration of acute phase proteins was recorded. In three different groups of animals, control group (healthy one), CAE subclinical form or asymptomatic group and CAE clinal form or symptomatic group, the serum level of SAA has been increased five times and the level of Hp two times in CAE clinical form as compared to other two groups. The difference in the values of clinical form might be due to inflammation then that of the virus itself. However, another study by Reczyńska et al. (2018a) reported an elevated level of APPs (Serum amyloid A) in the serum of subclinical and asymptomatic groups infected with SRLV, while a decrease in the concentration of SAA and Cp (Fig. 4) in the milk of asymptomatic infected goat was evident (Kurhaluk et al. 2021).

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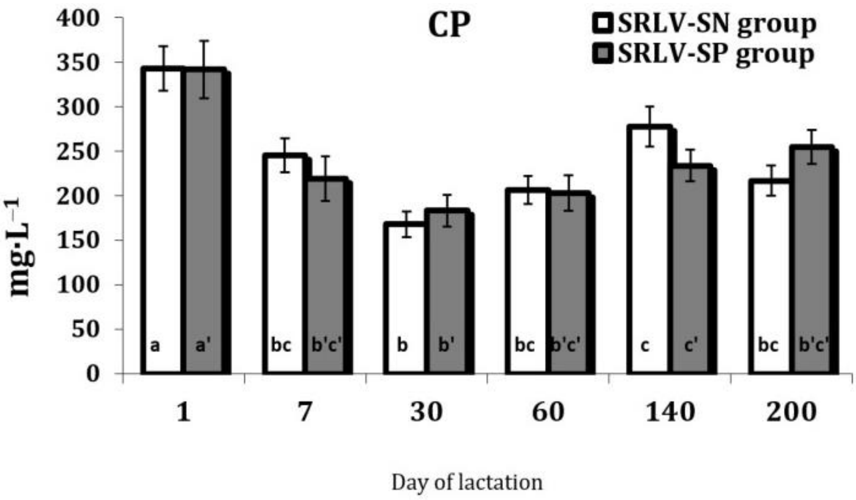

Fig. 4: Ceruloplasmin level (Cp, mg·L−1) in the serum of SRLV-SN and SRLV-SP goats during lactation. Values are expressed as means ± SEM; a, b, c—different letters indicate significant differences between stages of lactation within the SRLV-SN group at $p < 0.05$; a', b', c'—different letters indicate significant differences between stages of lactation within the SRLV-SP group at $p < 0.05$; SRLV-SP—small ruminant lentivirus seropositive goats; SRLV-SN—small ruminant lentivirus seronegative goats (Kurhaluk et al. 2021).

2.6.7. Border disease (BD)

It is a viral disease that is endemic in goat and sheep. It also affects other wild ruminants too. The disease is caused by single standard RNA (ssRNA) virus called as border disease virus (BDV). It belongs to family Flaviviridae and genus Pestivirus. Infection caused by virus is reported in many countries like China, Netherlands, Austria, Japan, Turkey and Spain. Transmission of infection occur by both horizontally and vertically. BVD causes many clinical symptoms in sheep and goat including reproductive disorders (stillbirth, infertility, abortion, offspring malformation and neonatal mortality). It causes damage to neuron muscular system causing locomotion dysfunction and body tremors (Oguzoglu et al. 2009). It causes hairy growth in lambs so also called as 'hairy-shaker' or 'fuzzy' lamb syndrome. In sheep, it causes lesions that resembles to the mucosal disease (Monies et al. 2004). It also causes digestive tract problems diarrhea and hemorrhages in different parts of digestive tract like stomach, small and large intestine (Li et al. 2013). The disease causes severe economic losses due to loss in the production and quality of animal products like meat, milk and wool (Valdazo-González et al. 2006).

2.6.7.1. Role of acute phase proteins in Border Disease (BD)

In literature it has been reported that the concentration of acute phase proteins is associated with border disease, serum concentration of SAA and Hp is higher in the BDV infected goat when compared to healthy one (Fig. 5). In a study, the serum values of SAA and Hp increases up to 7-8 folds in case of non-aborting infected goats when compared to healthy goats. In case of aborting infected goat, the serum concentrations of SAA and HP increases 11-15 folds as compared to healthy goats (Balikci et al. 2013).

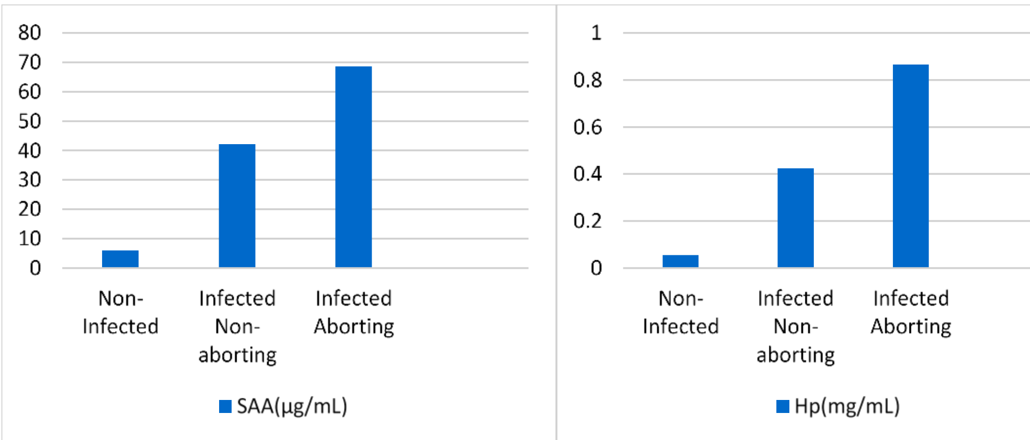

Fig. 5: SAA and Hp concentration in non-infected, BVD infected non-aborted and infected aborted goats (Balikci et al. 2013).

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2.6.8. Peste des petits ruminant's virus (PPRV)

It is a viral disease associated with Peste des petites ruminant virus (PPRV), belongs to the genus Morbillivirus, family Paramyxoviridae. Mainly infects the sheep and goat and causes heavy economic losses (Banyard et al. 2010; Khan et al. 2018), however, cattle and buffaloes remain asymptomatic, if infected. Many wild ruminants and camel are also suspectable showing clinical symptoms and sometime disease may prove fatal leading to death (Albina et al. 2013). This disease has two forms including mild and acute, mild form has little or some time with no significant signs. Acute form is more severe clinical form that can cause eventually death of infected animal. Body temperature rises about (40–41.3°C), animal become restless, coat become dull, dry and crusty muzzle, and mucous membrane becomes congested. Clinically, this disease is easily diagnosed by the ocular and nasal discharge, matting of eyelids due to pursues catarrhal conjunctivitis. Oral lesions, sloughing off of necrotic epithelium contribute in the inappetence of infected animal. There is bloody diarrhea in late stage of disease that causes animal emaciated and dehydrated. The virus also causes the immunosuppression that can contribute to the secondary infection. Other symptoms include bronchopneumonia, bronchospasm and fetal abortion in pregnant animal (Abubakar et al. 2012).

2.6.8.1. Role of acute phase proteins in Peste des petits ruminant's virus (PPRV)

Acute phase proteins are proved to be biomarker for the detection of a lot of viral diseases. PPR can also be diagnosed by the level of APPs. Studies reported that concentration of acute phase proteins are increased in PPR. The significant acute phase proteins like SAA and Hp are mainly increased. The level of SAA and Hp increases two-fold as compared to the normal level of AAPs in healthy animals (Arslan et al. 2007; Reczyńska et al. 2018b).

2.6.9. Bluetongue virus (BTV)

The blue tongue virus belongs to the Orbivirus genus and family Reoviridae. The virus a double standard DNA. The virus causes bluetongue disease in both wild and farm animals (Aytekin et al. 2015; Sobharani et al. 2019). BTV causes damage to immune cells like macrophages, lymphocytes, dendritic cells and endothelial cells also that are involved in the development of innate and adaptive immunity. In the last stage of disease, virus elimination by immune cells become impossible because virus adhere itself tightly to the surface of RBC's. This prolongs the time of virus infection and its removal from the body (Maclachlan et al. 2014). The infection is transmitted by vectors. Mostly vectors are blood sucking insects that belong to the genus Culicoides. The symptoms are associated with nasal discharge, lesions in oral mucosa, pulmonary and digestive tract hemorrhages, effusion in the lungs and high fever. It also causes the damage and necrosis to cardiac and skeletal muscles, coronitis and pericardial, abdominal and pleural effusions (Ganter 2014; Savini et al. 2014; Sobharani et al. 2019).

2.6.9.1. Role of acute phase proteins in Blue Tongue (BT)

A study reported that concentration of HP has almost 16 to 18-fold increased and that of SAA up to 3 to 5-fold in BTV infected animals when compared to the healthy one (Sánchez-Cordón et al. 2013). Aytekin et al. (2015) reported that the concentration of albumin remains constant during the course of blue tongue disease. It has been reported that BTV did not trigger the production of the Hp and SAA like that of BVD and BRSV that affects the cattle (Table 4). The reason for variation might be the severity of these diseases in cattle that is not evident in BTV in sheep, mostly asymptomatic or sub-clinical (Heegaard et al. 2000; Savini et al. 2014). Only increase in the fibrinogen has been reported (Sobharani et al. 2019).

Table 4: Concentration of different acute phase proteins in different diseases

Virus	Disease	Specie	Health state	SAA	Hp	Cp	Fb	Albumin	Reference
SRLV	Caprine arthritis encephalitis	Goat	Healthy	0.28-27.40	0.21–4.89	NT	NT	NT	Czopowicz et al. (2017)
			Infected	0.31-28.70mg/L	0.22–4.65g/L	NT	NT	NT	
BDV	Border disease	Goat	Healthy	6.06μg/mL	0.056	NT	NT	NT	Balikci et al. (2013)
			Infected	42.13–68.86 μg/mL	0.424–0.866 mg/mL	NT	NT	NT	
PPRV	Peste des petits ruminants	Sheep	Healthy	12.80[A]	1.54[A]	NT	NT	NT	Arslan et al. (2007)
			Infected	32.2[A]	3.13[A]	NT	NT	NT	
BTV	Blue tongue disease	Sheep	Healthy	ND	0.04g/L	41.53	NT	ND	Aytekin et al. (2015)
			Infected		1.58g/L	25.59mg/dL	NT	ND	
BRSV	Bovine Respiratory Syncytial Virus	Cattle	Healthy	<17μg/mL	<18μg/mL	NT	NT	NT	Heegaard et al. (2000)
			Infected	60–80μg/mL	8–10mg/mL	NT	NT	NT	
BVDV	Bovine viral diarrhea	Cattle	Healthy	25.6mg/L	0.13g/L	NT	6.45	NT	Burgstaller et al. (2016)
			Infected	77.7–375mg/L	0.89–1.87g/L	NT	6.5–10g/L	NT	
FMDV	Foot and mouth disease	Cattle	Healthy	4.50–4.86	0.084–0.09	0.06–0.08	0.06	3.43g/dL	Stenfeldt and Arzt (2020)
			Infected	28.8–45.44 μg/mL	0.308–0.41g/L	0.10–0.16 g/L	4.64g/L	2.49–3.39 g/dL	

ND-No Difference, NT-Not Tested, A—No information about units.

2.7. Hematological and neoplastic diseases of the dog

There are a lot of hematological neoplastic diseases in small animals like dogs. These include thrombocytopenia and anemia like diseases. These diseases are mostly associated with the cancer in the body. Such hematological and neoplastic diseases are well diagnosed by the level of APPs. Serum concentration of different APPs like SAA, CRP, Hp are helpful in diagnosis when compared with the normal animals' values (Tecles et al. 2005).

2.8. Acute phase index

For the detection of diseased animal from the healthy one, value of only one reactant is not significant for the detection of diseased animal. The enhanced response for a single patient can be calculated when we combine the values of positive APPs (fast and slow) with the negative APPs (fast and slow) to form an index. For example, in starvation, there is decrease in reactants.

$$\text{Nutritional and acute phase index (NAPI)} = \frac{\text{Concentration of rapid positive APP} \times \text{Concentration of slow positive APP}}{\text{Concentration of rapid negative APP} \times \text{Concentration of slow negative APP}}$$

In humans this index is used as prognostic inflammatory and nutritional index (PINI). In cattle it is used as acute phase index (API). NAPI significantly enhances the role of APPs in diagnosis of diseased patient to healthy one. It can help to monitor individual's and herd's health when many acute phase proteins are involved in a single infection (Gruys et al. 2005).

Conclusion

It is better to find a disease in sub clinical form for better treatment and management. Bio markers serve best for this purpose. There is always a need for new and better biomarkers for the early diagnosis, isolation and effective treatment of diseases. In most of the virus diseases, the blood serum level of two acute phase proteins SAA and Hp increases significantly. As, their level is increased in so many viral diseases, so it become difficult to differentiate one disease from other. But still some diseases can be diagnosed by acute phase proteins. For example, the blue tongue disease can be differentiated from other infection due to decrease in the blood serum level of Cp and albumin. The level of SAA in blood serum and milk is helpful for the detection of SRLV infection. These possibilities are too low to diagnose and differentiate a range of viral and bacterial infection. So, we conclude that APPs can serve as a role of auxiliary diagnostic tool in animal disease diagnosis.

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