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Approach to Acute Phase Reactions in the Aspects of Pathology and General Situation in Turkey

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Abstract: This review evaluates the importance of acute phase proteins (APP) and acute phase reaction (APR), which are accepted as sensitive biomarkers in diagnosing of animal diseases, both in general and pathological terms, with a particular emphasis on the situation in Turkey. Pathological examinations have been extensively used in studies investigating the APP and APR in veterinary medicine globally. In contrast, the number of studies and pathology involvement is limited in Turkey. For this reason, we conducted a qualitative and quantitative analysis of the studies in the world and in Turkey to emphasize the importance of the subject and increase awareness among the clinicians. The review is the first comprehensive report on the subject in Turkey and is supported by a regional map of the distribution of performed studies.
Keywords: *Acute phase protein, Acute phase reaction, C-reactive protein, Haptoglobin, Secondary amyloidosis, Serum amyloid-A.*

Akut Faz Reaksiyonlarına Patoloji Açısından Yaklaşım ve Türkiye'deki Genel Durum

Özet: Bu derleme, hayvanlarda hastalıkların teşhisinde duyarlı biyobelirteçler olarak kabul edilen akut faz proteinleri (AFP) ve akut faz reaksiyonunun (AFY) hem genel hem de patolojik açıdan önemini Türkiye'deki duruma özel bir vurgu yaparak değerlendirmektedir. Patolojik incelemeler, dünya çapında veteriner hekimlik alanında AFP'leri ve AFY'yi araştıran çalışmalarda yaygın olarak kullanılmaktadır. Buna karşılık Türkiye'de, hem çalışma sayısı hem de patolojinin katılımı sınırlıdır. Bu nedenle konunun önemini vurgulamak ve klinisyenlerin farkındalığını arttırmak için dünyada ve Türkiye'de yapılan çalışmaların nitel ve nicel bir analizini yaptık. Bu derleme, Türkiye'de konuyla ilgili yapılan ilk kapsamlı çalışmadır ve yapılan çalışmaların dağılımının bölgesel bir haritası ile desteklenmektedir.
Anahtar Kelimeler: *Akut faz protein, Akut faz yanıt, C-reaktif protein, Haptoglobin, Sekonder amiloidozis, Serum amiloid A.*

Introduction

Acute phase reaction (APR) is a complex reaction induced by stimuli such as tissue damage, infection, trauma, neoplasia, or immunological disorders. This response includes many pathophysiological changes (Bochler & Slauson, 2002), is nonspecific, and can be observed in many conditions that cause tissue damage (Ceron et al., 2005). The most critical changes in APR are the synthesis and release of acute phase proteins (APP) (Ceciliani et al., 2002). Acute phase proteins are a group of blood proteins synthesized primarily by the liver during APR. Since their concentrations change during the APR, these proteins have been proposed as essential biomarkers for monitoring and protecting animal health (Ceron et al., 2005).

The primary purpose of our work was to evaluate APR both clinically and pathologically in the field of veterinary medicine in Turkey, give insight to researchers for new studies, and provide relevant information to veterinary practitioners. To emphasize the importance of the subject, a review of the studies carried out in the world and Turkey, with their regional distributions, are presented. The references used in this study consisted of studies found by searching the terms "acute phase proteins in animals" and "acute phase proteins in Turkey" in PubMed and Google Scholar electronic databases between 2000-2022. The search for the former terms revealed 21,263 publications in PubMed and 17,900 publications in Google Scholar. A total of 169 animal studies were published in Turkey in the same period.

1. Acute Phase Response

Local inflammation is the first response of the immune system to noxious stimuli. If the inflammatory reaction progresses, the organism activates a wide-ranging systemic response known as APR (Bochler & Slauson, 2002). Innate immunity is an effective system for preventing infections and initiating inflammatory reactions. Acute phase reaction, which is considered part of this immunity, covers all inflammation-related events, including metabolic, hematopoietic, neuroendocrine, and hepatic changes (Ceciliani et al., 2002).

1.1. Acute Phase Reaction and the Inflammatory Process

Acute phase reaction, which occurs during acute and chronic inflammatory reactions involving many organs, denotes numerous metabolic changes (Murata et al., 2004). Ensuring the continuity of the APR depends on the recruitment of neutrophils, lymphocytes, and macrophages to the inflamed area and the secretion of cytokines by activated endothelial cells and innate immunity cells (Bochler & Slauson, 2002; Ceciliani et al., 2002).

Cytokines, which act as intracellular and intercellular signaling molecules, are synthesized in increasing amounts in cells during the inflammatory reaction, and have numerous and complex effects such as activating APR and regulating APP synthesis in the body (Bochler & Slauson, 2002). The cytokines that regulate the synthesis and release of APP from the liver are called proinflammatory cytokines. These proinflammatory cytokines, which have numerous effects on the body, are interleukin-1 (IL-1), IL-6, and tumor necrosis factor-α (TNF-α) (Bochler & Slauson, 2002). Various clinical and pathological changes, aiming to eliminate the harmful stimulus, maintain homeostasis, and support the healing process, occur during the APR (Kumar et al., 2014). Some of these changes are summarized below:

Synthesis of proinflammatory cytokines: Tumor necrosis factor-α, IL-1, and IL-6 are synthesized and secreted by monocytes, macrophages, and other cells in the inflamed area. These cytokines can enter the circulation to initiate APR, which accompanying infection and inflammation (Kumar et al., 2014).

Fever: Pyrogenic substances stimulate leukocytes and other cells to produce cytokines, and ensure the release of proinflammatory cytokines. These cytokines increase the level of cyclooxygenase enzyme by stimulating the hypothalamus. Hypothalamus then induces the production of prostaglandins and neurotransmitters, and increases the body temperature (Kumar et al., 2014).

Synthesis of APP: Proinflammatory cytokines such as IL-1, TNF-α, and particularly IL-6 plays essential roles in the synthesis and increase of plasma APP concentrations (Kumar et al., 2014).

Leukocytosis: Leukocytosis is one of the significant manifestations of the APR (Ceciliani et al., 2002). Cytokines such as TNF-α and IL-1 increase the release of leukocytes from the bone marrow. Additionally, these cytokines, activate the endothelium and increase the expression of adhesion molecules which promotes leukocyte adhesion and migration (Kumar et al., 2014).

2. Acute Phase Proteins: Acute phase proteins are a group of blood proteins identified in the early 1900s as early reactants for diagnosing infectious diseases and are considered essential biomarkers (Murata et al., 2004). These proteins regulate inflammation via either their proinflammatory or antiinflammatory features (Ceron et al., 2005). The synthesized APPs and their concentrations during the APR vary according to the type of noxious stimulus and animal species (Ceciliani et al., 2012). With the formation of the inflammatory reaction, APPs rapidly enter the bloodstream. These proteins are generally absent or present only at deficient levels in plasma. During the APR, their synthesis in the liver increases, and they enter the circulation (Kumar et al., 2014).

2.1. Some Major Acute Phase Proteins

2.1.1. Serum Amyloid A: Serum amyloid A (SAA), with a molecular weight of 15 kDa, is a high-density lipoprotein-associated apolipoprotein (Ceron et al., 2005). High expression of SAA is thought to have a vital role in the pathogenesis of secondary amyloidosis (Bochler & Slauson, 2002). Conditions increasing the SAA concentration are presented in Table 1. As seen in the table 1, most studies investigating the SAA were performed in large ruminants, and increased SAA concentrations were observed mainly due to viral and parasitic infections.

2.1.2. Haptoglobin: Haptoglobin (Hp) is an α2 globulin component capable of binding hemoglobin. With a molecular weight of 125kDa, Hp is one of the most critical APPs in ruminants (Eckersall, 2000). Trigger conditions leading to an increase in Hp concentration have mainly been detected in viral and bacterial infections of large ruminants and are summarized in Table 2.

2.1.3 C-Reactive Protein: C-reactive protein (CRP) is an APP that has been identified for the first time in the blood of people suffering from pneumonia (Kumar et al., 2014). C-reactive protein, a prominent APP in dogs, can facilitate diagnosis by demonstrating the presence and extent of inflammation (Nakamura et al., 2008). The conditions that lead to increased CRP concentration, which is used as an effective marker, especially in systemic inflammations, are presented in Table 3. As seen in this table, an increase in CRP concentration has been observed in various animal species, especially in dogs, in many triggering conditions such as infections and neoplasia.

2.2. The Importance of Acute Phase Proteins in Veterinary Medicine in Turkey

The search carried out with the “acute phase proteins in Turkey” revealed 5,930 publications in the Google Scholar database and 2,974 publications in the PubMed database. A total of 169 of these studies were performed on animals. The distribution of these studies by region is given in Figure 1. It was determined that five of these studies were reviews,

Table 1. Summary of triggering events leading to increased serum amyloid A concentration.

Animal	Triggering Event	Reference
Cat	FCoV/Kidney failure/Diabetes mellitus	(Tuna, 2015)
Dog	Parvovirus	(Sahinduran et al., 2016)
	Sarcoptes canis	(Arslan and Kırmızıgül, 2020)
Cattle	*Escherichia coli* F5/Rotavirus/Coronavirus/*Eimeria* spp.	(Balikci and Al, 2014)
	BVDV/BHV 1	(Sahinduran et al., 2017)
	CGB	(Issi et al., 2017)
	FMD	(Mallick et al., 2021)
	Babesia bigemina	(Mohammadi et al., 2021)
	Trichostrongylus spp.	(Sevimli et al., 2015)
	Hydatid cysts	(Sevimli et al., 2015)
Sheep	*Cryptosporidium parvum*	(Dinler et al., 2017)
	Fasciola hepatica	(Denizhan et al., 2019)
Goat	*Trichuris* spp.**+***Trichostrongylidae* spp.**+***Fasciola* spp.	(Ulutaş et al., 2008)
Horse	Endometritis	(Hedia et al., 2021)
Chicken	Amyloid arthropathy*	(Sevimli et al; 2013)
Mice	*T. gondii**	(Atmaca et al., 2019)

Bovine herpes virus 1-BHV 1; Bovine viral diarrhea virus-BVDV; Coryza gangrenosa bovum-CGB; Feline corona virus-FCoV; Foot and mouth disease-FMD; *-Experimental.

Table 2. Summary of triggering events leading to increased Haptoglobin concentration.

Animal	Triggering Event	Reference
Dog	Parvovirus	(Kocaturk et al., 2010)
	S. canis	(Arslan and Kırmızıgül, 2020)
	Neospora caninum	(Ferreira et al., 2021)
Cattle	*E. coli* F5/Rotavirus/Coronavirus/ *Eimeria* spp.	(Balikci and Al, 2014)
	Brucellosis	(Bozukluhan et al., 2016)
	BRSV/BHV-1/BVDV/BPI 3	(Dörtkardeş and Şahinduran, 2020)
	BVDV**+**BHV-1	(Sahinduran et al., 2017)
	CGB	(Issi et al., 2017)
	FMD	(Mallick et al., 2021)
	B. bigemina	(Mohammadi et al., 2021)
Sheep	Sheeppox virus	(Bozukluhan et al., 2018)
	*C. parvum**	(Dinler et al., 2017)
	F hepatica	(Denizhan et al., 2019)
Goat	*Corynebacterium pseudotuberculosis*	(Akgul et al., 2018)
	Trichuris spp.**+***Trichostrongylidae* spp.**+***Fasciola* spp.	(Ulutaş et al., 2008)
Mice	*T. gondii**	(Atmaca et al., 2019)

Bovine parainfluenza virus 3-BPI 3; Bovine respiratory syncytial virus-BRSV.

Table 3. Summary of triggering events leading to increased C-reactive protein concentration.

Animal	Triggering Event	Reference
Dog	Demodicosis	(Salem et al., 2020)
	Parvovirus	(Kocaturk et al., 2010)
	IBD/Hemangiosarcoma/Lymphoma/Malignant mesothelioma	(Nakamura et al., 2008)
	Pyometra	(Enginler et al., 2014)
	Gastric mucosal injury*	(Bayramli and Ulutas, 2008)
Sheep	Pneumoania	(Halıgur and Ozmen, 2011)
Goat	*C. pseudotuberculosis*	(Akgul et al., 2018)

Inflammatory bowel disease-IBD.

Table 4. Some acute phase reaction studies performed on animals in Turkey.

Animal	Case	Measured APP's	Reference
Cat	Haemobartonellosis/*İsospora* spp./Dermatitis/ Renal failure/Diabetus mellitus	SAA+Hp+Cp+AGP	(Tuna, 2015)
Dog	Parvovirus	SAA+Hp+CRP^{X}	(Sahinduran et al., 2016)
	Chronic heart failure	CRP	(Saril et al., 2022)
	Pyometra+Cystic endometrial hyperplasia/Mucometra	SAA+CRP+Fb^{X}	(Enginler et al., 2014)
	Gastric mucosal injury*	SAA+Hp+CRP+Fb+ALB	(Bayramli and Ulutas, 2008)
Cattle	Brucellosis	Hp+Cp+ALB	(Bozukluhan et al., 2016)
	BHV-1/BVDV/BRSV/BPI-3/BAV-3	SAA+Hp	(Dörtkardeş and Şahinduran, 2020)
	CGB	SAA+Hp+Cp	(Issi et al., 2017)
	Hydatid cysts+*Trichostrongylus* spp.	SAA+Hp^{X}	(Sevimli et al., 2015)
Sheep	Sheeppox virus	Hp+Cp+ALB	(Bozukluhan et al., 2018)
	*C. parvum**	SAA+Hp	(Dinler et al., 2017)
Goat	Pneumonia	SAA+CRP+SAP^{X}	(Halıgur and Ozmen, 2011)
Chicken	Amyloid arthropathy*	SAA^{X}	(Sevimli et al., 2008; Sevimli et al., 2012)
Mice	*T. gondii* *	SAA+Hp^{X}	(Atmaca et al., 2019)
Rat	Effects of agomelatine on endothelial+cardiac damage*	Hp^{X}	(Asci et al., 2019)

α1 acid glycoprotein-AGP; Albumin-ALB; Ceruloplasmin-Cp; C-reactive protein-CRP; Fibrinogen-Fb; Haptoglobin-Hp; Serum amyloid A-SAA; Serum amyloid P-SAP; ^{X}-Studies with Pathological Evaluation

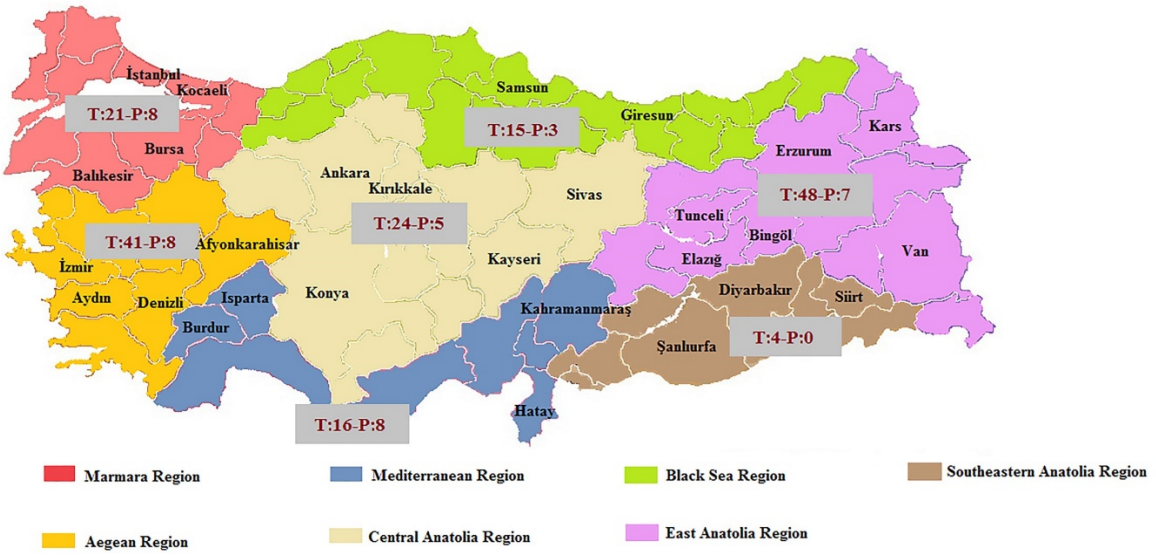

Figure 1. Number of studies on acute phase proteins in animals by regions in Turkey, T: Total number of studies, P: Number of studies with pathological evaluation.

five were case reports, four were thesis dissertations, two were short communications, and 153 were research articles. Approximately 32.5% of the APR studies conducted in Turkey were in large ruminants, 21.3% in laboratory animals, 17.1% in small ruminants, 14.2% in dogs, 8.8% in poultry, 2.3% in fish, and 1.7% in cats and horses. It was noted that only 39 of these studies included pathological evaluation. Some studies performed on APR in various animal species in Turkey are presented in Table 4.

2.3. Some Pathology Studies Evaluating Acute Phase Proteins in Turkey

Considering that APPs are sensitive biomarkers in pathophysiological changes, it is critical to evaluate APR both in general terms and pathologically (Bochler & Slauson, 2002). In an experimentally induced *Toxoplasma gondii* infection study in mice, the histopathological evaluation revealed severe tissue damage and perivascular mononuclear cell infiltrations in brain tissue and meninges (Atmaca et al., 2019). In that study, serum APP levels were also measured. It was suggested that significantly increased SAA and Hp levels were indicative of a remarkable role in tissue repair by inducing the activation of leukocytes. In their experimental study on rats Asci et al. (2019), induced endothelial and cardiac damage with lipopolysaccharide (LPS) administration. These researchers observed myofibrillar vacuolar degeneration and neutrophil leukocyte infiltration in the myocardium, and increased Hp expression immunohistochemically. Enginler et al. (2014) detected higher CRP levels in dogs with pyometra than with cystic endometrial hyperplasia. They suggested that serum CRP level can be used as a diagnostic marker to differentiate between these two pathological conditions. In another study (Halıgur & Ozmen, 2011), a correlation was found between the expression levels of SAA and TNF-α, and the severity of pneumonia in sheep and goats; these two APPs were proposed as biomarkers to evaluate the severity of pneumonia. Sevimli et al. (2015) found increased SAA and IL-6 levels in cattle with hydatid cysts, necrosis, and inflammation in their lungs and livers. They suggested that SAA was a more sensitive indicator than other APPs in hydatid cyst infections.

Conclusion

Much information has been gained about the APR and APPs in the last decade, but the relationship between the structure and function of APPs is still not fully elucidated (Ceciliani et al., 2012). The APR is known as the adaptive response of the host to the noxious stimulus (Bochler & Slauson, 2002). It is generally a fast-forming response and develops before the clinical findings appear and the immune response forms. Therefore, it can be considered an early marker of pathological conditions. The induction of APR and changes in the concentrations of APPs can be detected on the first day of the noxious stimulus. Thus, APPs have a very high sensitivity to detecting subclinical infections (Ceron et al., 2005). Circulating concentrations of APPs are correlated with the degree of tissue damage in the affected animal. Therefore, the measurement of APP concentrations is a powerful marker for assessing the presence and extent of the disease process and the effectiveness of disease management in veterinary medicine (Eckersall, 2000). However, the correct timing for sampling is a prerequisite for diagnostic and prognostic values (Murata et al., 2004). More emphasis has been given to the follow-up of APR in animals for clinical and experimental purposes in the last ten years (Eckersall, 2000). However, this rate is meager in Turkey compared to the studies conducted in the world. It has been noted that APR studies conducted worldwide are primarily on ruminants and pet animals, whereas the studies conducted in Turkey mainly focused on ruminants. According to the 2021 data of the Turkish Statistical Institute (2021), the number of studies and the pathological evaluations in these studies are insufficient in regions where animal husbandry is intense, such as the Southeastern Anatolia Region and the Black Sea Region. The use of APPs for the diagnosis and prognosis is also insufficient in pet animals. In the clinical environment, blood samples can be tested for APPs and also APR can be evaluated in addition to histopathology for the diagnosis postmortem.

This review is the first to evaluate studies on APR in terms of both general and pathological aspects in veterinary medicine in Turkey. We hope that this review may contribute to the research on APPs, which are sensitive biomarkers in diagnosing diseases.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Ethical Approval

This study is not subject to HADYEK's permission in accordance with Article 8 (k) of the "Regulation on Working Procedures and Principles of Animal Experiments Ethics Committees". ("Ethical Declaration Form" has been filled and uploaded to the system.)

Similarity Rate

We declare that the similarity rate of the article is 7% as stated in the report uploaded to the system.

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