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Prof. Dr. Bestami DALKILIÇ

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BÖLÜM 1

DERMATOSPARAXIS

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INTRODUCTION

Dermatosparaxis is a genetic disorder characterized by collagen dysplasia. In this disease, there is a decrease in the durability and integrity of the skin, delayed healing of skin lesions, and hyperextensibility. The disease is recessively associated with connective tissue disorder (Asherson et al., 2006; Aydemir, 1994; Azıroğlu and Milli, 1998; Erdoğan et al., 2018; Ermutlu et al., 2013; Gürel et al., 2005; Oderich et al., 2005; Odom et al., 2000; Pyeritz, 2012).

This rare disease is also known as elastic skin disease, Cutis hyperelastica, and is similar to Ehlers-Danlos Syndrome (EDS) in humans (Erdoğan et al., 2018; Gürel et al., 2005; Pyeritz, 2012). The disease was first described by Von Meekeran in 1682. Different clinical forms of the disease were described by Ehlers in 1902, and Danlos in 1908, and Ehlers-Danlos syndrome was named after them (Karakurumer et al., 1990). This disease is also known as Ehlers-Danlos syndrome and is found in ruminants (white-blue Hereford, Charolais, and Simmental cattle in Belgium), carnivores, horses, and humans (Colige et al., 2004; Ermutlu et al., 2013).

GENERAL INFORMATION

Epidemiology

This disease is found all over the World (Yılmaz et al., 1998). The disease is called cutaneous asthenia in animals (Erdoğan et al., 2018; Pyeritz, 2012). Studies have reported the disease in the USA, Norway, Finland, and Australia (Blood and Radostitis, 1990; Yılmaz et al., 1998). The disease has been observed in different animal species, such as horses (De Paepe and Malfait, 2012), cats (Germain, 2007; Lum et al., 2011), dogs (Busch et al., 2014), calves, sheep and rabbits (De Paepe and Malfait, 2012) (Asherson et al., 2006; Erdoğan et al., 2018).

Since it causes sensitivity and disruption in the integrity of the skin, it causes both animal welfare and economic loss in cattle and sheep breeding enterprises (Tim Van Damme et al., 2016). The disease can be linked to a dominant or recessive gene and chromosome X (Busch et al., 2014). Dog breeds such as Dachshunds, Boxers, St. Bernard dogs, German shepherds, Springer spaniels, Greyhounds, Irish setters and Poodles (Calatzis et al., 2003); in cats, Himalayan breeds (Pepin et al., 2000) and short-haired cats (Calatzis et al., 2003; Erdoğan et al., 2018; Germain, 2007) have been reported to be susceptible. It has been stated that the disease can also be seen in long-haired cats, and there is no gender predisposition (both male and female cats) (Erdoğan et al., 2018; Germain, 2007).

Symptoms

In the disease, there is a decrease in the durability of the skin and a delay in its healing with a deterioration in its integrity (Leipold et al., 1990; Yılmaz et al., 1998). In addition, hypermotility in the joints, arthritis, vasculitis, mitral valve problems, myopathy, myalgia, scoliosis, and osteoporosis are observed (Erdoğan et al., 2018). Clinical findings of the disease include increased skin elasticity and sensitivity, delayed healing of wounds in the body and failure to suture, formation of paper-shaped scar tissue, blueness of the sclera in the eyes, hypertelorism and exophthalmos, bat-type ear, diaphragmatic hernia, and aneurysm in the aorta. In addition, gingivitis, periodontitis, tooth fractures, and luxation in the temporomandibular joint are observed (Karakurumer et al., 1990). It was observed that there was a loose structure with pouches under the skin, accompanied by light-colored serous fluid, and calcifications and hematomas were observed at the pressure points on the extremities (Ermutlu et al., 2013). Ehler-Danlos Syndrome in humans and the form seen in domestic animals have similar pathogenesis, but there are also marked phenotypic differences. For example, the skin has less hyperextensibility and fragility in human clinical manifestations.

Human studies have reported that children with dermatosparaxis are stillborn, and those born alive die shortly after birth. In these patients, skin integrity in the area between the anus and the umbilical cord is disrupted; their abdomens are almost slit (Calatzis et al., 2003). Similarly, it has been reported that lambs diagnosed with dermatosporaxis died immediately after birth or within a few days due to sepsis as a result of secondary infection of the wounds on the skin.

It was reported that these lambs had wounds of different diameters and sizes on the body (especially on the neck and extremities), subcutaneous connective tissues were quickly detached, and hemorrhages were present. In small ruminants, the disease was recognized by the appearance of skin lesions during shearing. The skin was noted to be easily detached during the process (Yılmaz et al., 1998). Young animals are more prone to dermatosparaxis. It is characterized by loose skin that stretches too much when pulled and hangs around the joints of the extremities. The skin tears easily, and large open wounds occur with minor trauma. Despite intervention with sutures, these wounds do not close (Uri et al., 2015). Studies have reported ten different types of the disease, and clinical symptoms vary depending on the species (Busch et al., 2014; Erdoğan et al., 2018).

- **Type I (Gravis Type):** It is characterized by increased elasticity of the skin, hypermobility of the joints, hypersensitivity of the skin, and pseudo-tumoral formations. In addition, orthopedic

problems, vasculitis, abortion in females, and coagulation problems are observed.

- **Type II (Mitis type)** is a milder form of Type I.
- **Type III (Baning mipermobile type):** Orthopedic problems and mitral heart valve anomaly are seen.
- **Type IV (Ecchymotic type):** Even the simplest trauma can cause ecchymotic hemorrhages in the skin, aneurysms in the vessels, and death due to blood loss.
- **Type V (X chromosome-linked inheritance)**: Hyperelasticity of the skin, tumoral formations, and orthopedic problems are observed.
- **Type VII (the type with joint dislocations)**: It is characterized by dislocations of the joints, deformations of the jaw bones, gingivitis, and tooth loss.
- **Type VI (Eye type):** Scoliosis and kyphosis of the spine and eye lesions such as scleral bluing, microcornea, glaucoma, keratoconus, megalocornea, and ectopia lens.
- **Type VII (the type with joint dislocations)**: It is characterized by dislocations of the joints, deformations of the jaw bones, gingivitis, and tooth loss.
- **Type VIII** is characterized by increased skin elasticity, and joint and dental problems.
- **Type IX:** Occipital bony prominence, inguinal hernia, and diverticula in the vesica urinaria.
- **Type X:** Causes genetic damage to a protein called fibronectin, which plays a role in blood clotting, leading to prolonged blood clotting time.

Patogenesis

Dermatosparaxis has been encountered and described in domestic animals in various forms and with various clinical presentations. *Dermatosparaxis* is a connective tissue weakness caused by abnormalities in collagen biosynthesis or post-translational modifications and is a dominant collagen defect characterized by abnormally large, irregular, and bulging fibrils (Tim Van Damme et al., 2016).

Connective tissue provides the durability of the skin. Collagen is one of the essential elements of connective tissue. Typically, in the formation of collagen, the amino and carboxy-terminal parts of the molecule called

procollagen must be separated extracellularly by enzymes called peptidases. In dermatosparaxis disease, since the amino and carboxy-terminal parts of the procollagen molecule are not separated from each other due to the inadequacy in aminopeptidase enzyme activity, both inadequacy in collagen production and incomplete production of procollagen molecules are collected in the extracellular matrix and prevent collagen threads from coming together, causing disorders in skin integrity (Ermutlu et al., 2013; Yılmaz et al., 1998).

The disease is characterized by hyperflexibility of the skin and hypermobility of the joints. Collagen deficiency causes the Type III form of the disease. Molecular techniques (gel electrophoresis and scanning densitometer) have shown that mutation in the COL3A1 gene causes the fourth type of disease. Damage in collagen structure, factor XI and XIII deficiencies, and platelet dysfunctions are responsible for hemostatic disorders and hemorrhages observed in the disease. Therefore, there is a risk of operation in patients (Aşık et al., 1995).

Diagnosis

In the diagnosis of dermatosparaxis, clinical findings, skin biopsy, staining techniques (Van Gieson, Mallory, and Masson staining), cell culture, genetic tests, and histopathological examination are used (Erdoğan et al., 2018; Ermutlu et al., 2013). Collagenic formations are examined morphologically. Degenerations in fibrillar structures draw attention (Ermutlu et al., 2013).

The skin of sheep diagnosed with dermatosparaxis was examined histopathologically, and it was reported that the skin thickened with edema in the corium region, shortening and dissolution of collagen yarns, and loss of uniformity between the yarns (Yılmaz et al., 1998). The definitive diagnosis is made by electron microscopic examination (decrease in the diameter and number of collagen fibrils (Ermutlu et al. 2013) and differentiation, irregular distribution and fragmentation of collagen fibers in the dermis) (Asherson et al., 2006; Calatzis et al., 2003; De Felice et al., 2004; De Paepe and Malfait, 2012; Erdoğan et al., 2018; Lindsay et al., 2015; Pyeritz, 2012).

In the evaluation made by electron microscopy, it was observed that there were branches in the transverse sections of the threads in the corium layer of the skin, and collagen threads were more curved in the longitudinal sections (Yılmaz et al., 1998).

In the diagnosis of the disease, Van Gieson, Mallori, and Masson staining techniques reveal the structure of connective tissue (Calatzis et al., 2003; Erdoğan et al., 2018; Lindsay et al., 2015; Yenicesu et al., 2000).

It was found that collagen was stained paler than usual in staining with Van Gieson stain (Yılmaz et al., 1998). Abnormal collagen structures can be seen on examination with hematoxylin and eosin staining techniques, but this may not always be helpful in making the diagnosis. It has been reported that mason staining is generally more effective in the diagnosis (Fernandez et al., 1998).

When tissue samples taken from a calf with dermatosparaxis were fixed with 10% formalin, stained with the Hemotoxylene-Eosin staining technique, and examined under a light microscope, it was observed that the epidermis and dermis were separated from the subcutis and gelatinous exudate accumulation was observed in this region. Pink homogeneous collagen bundles were observed in sweat, sebaceous glands, and hair follicles in the dermis. The dermal layer had an oval-cylindrical appearance with blue-stained collagen bundles. Histopathological examination revealed granulation tissue growths, fibrinous effusion, diffuse hemorrhagic areas, neutrophils, and leukocytes between the subcutis and dermis. Eosinophil and leukocyte infiltration was detected around the vessels of the dermis, and it was observed that the epidermis became thinner than usual (Ermutlu et al., 2013).

Treatment

There is no treatment for the disease. The aim is to improve the animal's quality of life (Dokuzeylül et al., 2013; Oderich et al., 2005). Since no treatment method exists to eliminate the disease, the owner should be informed about this issue (Bergqvist et al., 2013; Erdoğan et al., 2018).

Animals diagnosed with dermatosparaxis should not be bred and should be removed from the herd. Since dermatosparaxis causes the skin to disrupt its integrity and heal late quickly, broad-spectrum antibiotic treatment must be performed to prevent secondary infections during the healing process of the wounds (Ermutlu et al., 2013). Current research on dermatosparaxis suggests that nutrition has an impact on disease symptoms and that nutritional supplements should be used to help restore normal tissue function. It is suggested that patients should be supported using nutritional supplements.

For this purpose, calcium, carnitine, coenzyme Q, glucosamine, magnesium, methyl sulfonyl methane, pnogynogen, silica, vitamin C, and vitamin K supplements have been stated to be beneficial (Bergqvist et al., 2013; Erdoğan et al., 2018).

When this disease is seen in pets, owners should be informed that they should keep the animal indoors and protect it from places with a risk of trauma. The animal's living space should be made safe. If necessary, the

animal should be dressed in protective clothing. Allergic conditions that may cause itching should be treated with antiallergic drugs, and the animal should be prevented from scratching itself. The nails of animals diagnosed with dermatosporaxis should be cut short and blunt. Wounds on the body for any reason should be treated with an appropriate suturing technique as soon as possible. Animals with dermatosporaxis have the chance to live under excellent care and feeding conditions. However, in severe cases, euthanasia is also an option (Bergqvist et al., 2013).

CONCLUSIONS AND RECOMMENDATIONS

Dermatosparaxis cases have been reported in different animal species in our country and various countries of the world. The leading underlying cause of this syndrome is a collagen disorder due to genetic factors. Since there is no known specific treatment for the disease, preventive and preventive medicine are more important.

To summarize dermatosparaxis briefly,

- There is no specific treatment for the disease.
- Supportive treatment should be applied,
- In order to minimize skin trauma, the animal's lifestyle should be appropriately regulated,
- Sick animals should not be used for breeding.

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BÖLÜM 2

DIABETES MELLITUS IN DOGS

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Introduction

Diabetes mellitus is a chronic, endocrine problem characterized by carbohydrate, protein and fat metabolism disorder, which is widely observed in humans and animals and is now known as diabetes (Güçlü and İmamoğlu, 2007; Surman and Fleeman, 2013; Rautray et al., 2014). The main cause is inadequate production of insulin, inability to produce insulin at all, or inability to use the normal amount of insulin produced by the tissues. It has been reported that the incidence of diabetes mellitus in dogs is around 0.5% (Guthrie and Guthrie, 2009) and is usually seen between the ages of 7-9 years (Greenbaum, 2002). Beagle, Poodle, Dachshund, Miniature schnauzer, Miniature pinscher, Cairn terrier, Keeshond and Puliks are genetically predisposed breeds. The gender factor is important for dogs and diabetes mellitus is twice as common in female dogs as in male dogs. In addition, in relation to the induction of growth hormone by progestagens; unspayed female dogs are more at risk than male dogs (Weese et al., 2019). The disease is classified as type 1, type 2, type 3 and type 4 diabetes mellitus. The most common form in dogs is type 1 diabetes mellitus (Şimşek and İçen, 2008). Diabetes mellitus may be asymptomatic or may cause retinopathy, nephropathy, cardiomyopathy, autonomic neuropathy and dysfunction in blood vessels by affecting many organs and systems with clinical symptoms such as polydipsia, polyuria, weight loss despite polyphagia (Tandoğan et al., 2022). In addition to clinical symptoms, hyperglycemia and glycosuria should also be considered in the diagnosis. In recent years, measurement of serum glycated hemoglobin and fuructosamine levels have also gained importance for diagnosis (Catchpole et al., 2005). The treatment protocol of diabetes mellitus mainly consists of diet, exercise and insulin therapy (Walsh et al., 2016).

Etiology

Along with genetic factors, factors such as obesity, high carbohydrate-fat amounts in the diet, physical inactivity and stress are involved in the formation of diabetes mellitus. In addition, trauma, inflammation, neoplasia, autoimmune diseases, infectious causes, insulin antagonist hormones and drugs are also effective in the formation of the disease (Topsakal and Özmen, 2016). Glucocorticoids, which are high in Cushing's Syndrome in dogs, show antagonist effect against insulin (Zanner et al., 2023). Glucocorticoids also cause insulin resistance by decreasing glucose transport to cells and increasing the amount of glucagon in circulation (Okumuş, 1999). Progesterones, which are released during diestrus periods and false pregnancies of dogs or used to maintain pregnancy and suppress estrus, cause the release of growth hormones by antagonizing insulin (Walsh et al., 2016). Growth hormone reduces the number of insulin receptors and

inhibits glycolysis. This leads to insulin resistance (Maden and Çuhadar, 2013; Okumuş, 1999). Some of the neoplastic formations seen in old dogs cause diabetes mellitus. While pancreatic adenocarcinomas cause damage to the organs, neoplasms such as pheochromocytoma and glucagonoma cause excessive release of glucagon and insulin resistance (Vichit et al., 2018). Diabetogenic hormones such as epinephrine, norepinephrine, glucagon, ACTH and growth hormone released together with glucocorticoids in stress situations stimulate gluconeogenesis and glycogenolysis (Ülgen and Kaymaz, 2013). Tissues cannot utilize glucose and insulin antagonism develops in insulin receptors, blood glucose concentration increases and subclinical diabetes mellitus develops (Vurkaç, 2017; Yagiyashi, 2023). In diabetic dogs, the attachment of neutrophils to antigens decreases due to high blood glucose levels. Therefore, susceptibility and risk against bacterial infections increase (Weese et al., 2019). In cases of uremia, the need for insulin increases and diabetes mellitus occurs (Şahinduran and Vurkaç, 2018). It has been revealed that agents such as streptozotocin, nicotinamide and alloxan, which are used to cause experimental diabetes, cause damage to beta cells, inhibit insulin release and cause diabetes (Erşan, 2008). Chronic malnutrition conditions cause an increase in the prevalence of diabetes. In addition, protein-deficient nutrition, especially in the fetal or neonatal periods, may lead to impaired glucose tolerance and gestational diabetes in female dogs (Topsakal and Özmen, 2016).

Pathogenesis

Insulin is a peptide, endocrine hormone secreted by the beta cells of the pancreas. Insulin allows glucose, amino acids and fats to be taken into the cell, used and stored. These events take place in the liver, muscle and adipose tissues (Umanath and Lewis, 2018). After food is consumed, it completes its absorption in the intestines, comes to the liver and is converted into glucose, which is an energy source. Glucose passes into the bloodstream and increases blood glucose levels. On the contrary, with the release of insulin from the pancreas, the glucose level in the blood decreases and blood glucose balance is achieved (Kahyaoğlu, 2011). Diabetes mellitus develops as a result of inability to produce, deficient production or inability to use insulin for any reason (Reusch et al., 2006).

In insulin deficiency, glucose cannot be transported to target cells or its utilization is restricted in insulin resistance. Therefore, the amount of glucose in the blood increases and hyperglycemia occurs (Tunalı et al., 2014). When the renal threshold value exceeds 180-220 mg/dL due to hyperglycemia, excess glucose cannot be reabsorbed from the renal tubules. In order to balance this situation, excess glucose is excreted in the urine, resulting in glycosuria. Since glucose is also an osmotic diuretic, it cau-

ses an increase in the osmotic pressure of the urine and a decrease in the reabsorption of water by the kidneys, resulting in polyuria. Dehydration occurs as a result of fluid and electrolyte loss due to polyuria (Taşkaldıran et al., 2021). With dehydration, the thirst center in the hypothalamus is stimulated and polydipsia occurs (Şimşek and İçen, 2008). Since glucose cannot be transported to the cells despite hyperglycemia, the energy needs of the neurons in the satiety center in the hypothalamus cannot be met and hunger is observed. Thus, polyphagia occurs (Surman and Fleeman, 2013). In cases of glycosuria, calorie loss increases and weight loss occurs due to the inability to utilize glucose and its excretion in the urine.

Another task of insulin with anabolic effect is to transport amino acids to muscle cells and use them for protein synthesis. In insulin deficiency, amino acids cannot be transported to cells (Steppan and Lazar, 2002). Amino acids that cannot be used in protein synthesis undergo catabolic effect and protein degradation occurs. As a result, muscle atrophy occurs and weight loss is observed (Şimşek and İçen, 2008).

When glucose cannot be utilized due to insulin deficiency, cells look for other sources of energy. In this case, insulin antagonist glucagon, cortisol, epinephrine and growth hormone increase. These hormones exert lipolytic effects, leading to increased lipase activity and accelerated lipolysis (Scudder and Roberts, 2023). As a result of lipolysis, excess fat stores are destroyed and free fatty acids increase in circulation. Free fatty acids accumulate in the liver and triglycerides are synthesized (Sertbaş, 2021). The liver increases very low density lipoprotein (VLDL) and cholesteryl ester synthesis to remove triglycerides. Very low-density lipoproteins transport triglycerides to tissues and then transform into low-density lipoprotein (LDL). Accumulation of triglycerides in the liver leads to hypertriglyceridemia and hepatic lipidosis (Shapiro et al., 2018; Son, 2012). On the other hand, atherosclerosis occurs as a result of vascular thickening and hardening due to the accumulation of small and dense LDL in the circulation, especially damaging the vascular endothelium. Gangrene may develop in areas where there is no blood flow due to impaired blood circulation (Noyan, 2011). This creates a basis for cardiovascular diseases. At the same time, weight loss is also observed as fat stores are emptied (Altıntaş, 2021).

While some of the free fatty acids turn into triglycerides, some of them form ketone bodies by oxidation (Rand, 2013). If acetoacetate, beta hydroxybutyrate and acetone, which are ketone bodies, are too much to be removed from the body by urine or respiration, it leads to metabolic acidosis and an increase in anion gap. Metabolic ketoacidosis may lead to dehydration, electrolyte losses, respiratory distress, depression, hypotension, coma and death (Rand et al., 2004).

In cases of hyperglycemia, osmotic effects of glucose cause a high amount of fluid to pass into the lens and edema develops in the lens. With damage to the lens optic fibers, proteins in the lens coalesce and light transmission is impaired. As a result, the opacity of the lens increases and cataract is formed (Okumuş, 1999).

Glucose in the urine allows bacteria to easily attach to the urinary bladder and this predisposes the animal to urinary system infections (Raskin and Cincotta, 2016).

Uveitis is a condition of inflammation in the uvea, the middle layer of the eyeball (Turan, 2022). Lens-induced uveitis is an inflammatory reaction of the uvea against lens proteins and is rarely seen in dogs with diabetes mellitus (Ergin and Çetin, 2022). Due to cataract, lens proteins are exposed to the local immune system and inflammation occurs. As a result, uveitis occurs (Li et al., 2014). Diabetic neuropathy is a rare complication in dogs (Munana, 1995; Rhew et al., 2021). Clinical findings include gait and posture disorders, muscle weakness, paralysis of the hind limbs and weakened reflexes in the legs (Kaeidi et al., 2011). Diabetic nephropathy is a structural and functional disorder that occurs in the kidneys of dogs that have diabetes mellitus for a long time and glycemic control cannot be achieved (Behrend et al., 2018). Diabetic nephropathy is caused by many factors such as hyperglycemia, proteinuria, systemic hypertension, and glycated hemoglobins (Bay, 2015; Çorakçı, 2003). Microalbuminuria formation is considered as an early indicator of diabetic nephropathy in dogs with diabetes mellitus. Therefore, it is recommended to monitor the urinary albumin: creatinine ratio in dogs with diabetes mellitus (Nelson and Couto, 2022). Systemic hypertension is a common complication of diabetes mellitus (Çayır et al., 2015). While diabetic nephropathy is responsible for the development of hypertension in dogs with Type 1 Diabetes mellitus, many factors such as obesity and cardiovascular diseases are responsible in dogs with Type 2 Diabetes mellitus (Rand et al., 2004; Ülgen and Kaymaz, 2013). In dogs with diabetes mellitus, reabsorption of sodium from the kidneys and fluid retention occur due to increased insulin and glucose levels (Lupsa and Inzucchi, 2018). With the increase in sodium concentration in the cell, calcium concentration also increases and the sympathetic nervous system is stimulated. With the decrease in the release of vasodilator prostoglandins, endothelin release increases. As a result, peripheral vascular resistance shaped by vascular smooth muscle contractions increases and hypertension occurs (Semlitsch, 2021).

Classification of diabetes mellitus

There are many types of diabetes mellitus and new information is constantly being added (Topsakal and Özmen, 2016). The disease is classified as type 1, type 2, type 3 and type 4 diabetes mellitus (Yagiyashi, 2023).

Type 1 Diabetes mellitus

Type 1 diabetes mellitus, the most common form in dogs, is defined as insulin-dependent diabetes (Şahinduran and Vurkaç, 2018). Although autoimmune factors are known to be more effective, genetic factors are also thought to play a role (Rhew et al., 2021). Type 1 diabetes mellitus is characterized by auto-immune destruction of all or some of the beta cells, pancreatitis or vascular damage and insulin production deficiency (Rautray et al., 2014). Since endogenous insulin release does not occur, the patient becomes insulin-dependent for life (Çelik and Bal, 2002).

Type 2 Diabetes mellitus

Type 2 diabetes mellitus is called non-insulin-dependent or adult diabetes (Ergün, 2003). Although it is rare in dogs, it usually occurs in elderly and obese dogs (Duh et al., 2017). It is a disease picture characterized by hyperglycemia caused by insulin resistance. Due to various environmental and genetic factors, the number and signaling of insulin receptors decrease and the response and sensitivity of target tissues to insulin decreases (Düdek, 2019). The inability of target cells to use insulin causes an increase in blood glucose levels (Fowler, 2008).Insulin resistance is defined as the inactivation of insulin with a reduced response to normal levels of insulin in the circulation (Flier, 1992; Savaş and Gültekin, 2017). It can develop in several different ways, such as decreased sensitivity of insulin receptors, a genetic defect in receptor production, or the formation of antireceptor antibodies (Ergün, 2003). Apart from the pancreas, insulin resistance can also be caused by disorders in the liver, muscle and adipose tissue (Li et al., 2017). Obesity, stress, insufficient physical activity, diets containing high amounts of carbohydrates, increased levels of progesterone, cortisol and thyroxine predispose to insulin resistance and Type 2 Diabetes mellitus. When carbohydrates that rapidly increase blood glucose levels are consumed in large amounts and frequently, the hormone insulin is constantly released. The short duration of the feeling of satiety causes frequent and excessive feeding and thus obesity (Kusuhara et al., 2018). In obesity states, increased free fatty acids accumulate as fat in the muscles (Czech, 2017; Ilıksu Gözü and Akçay, 2021). Increased adipose tissue mass plays a major role in insulin resistance. Adipose tissue not only stores triglycerides for energy needs but also secretes peptides such as adinopectin, leptin and cytokines that regulate insulin sensitivity and tumor necrosis

factor (TNF) alpha cytokine (McGarry, 2002). When insulin resistance is formed, lipolysis increases and free fatty acids are released into circulation (Li et al., 2017). Leptin is also known as satiety hormone and increases in obesity. It also increases the synthesis of interleukin-6 (IL-6) and TNF alpha and is involved in the formation of insulin resistance. Adinopectin has anti-atherosclerotic properties and its level decreases in obesity (Savaş and Gültekin, 2017). Resistin impairs glucose tolerance and is effective in the development of insulin resistance (Akçam, 2018).

Type 3 Diabetes mellitus (Gestational Diabetes)

Gestational diabetes is a type of diabetes that occurs during pregnancy and is also called gestational diabetes (Çelik and Bal, 2002). It is rarely seen in dogs and occurs mainly in middle-aged dogs in the second half of pregnancy (Gal and Odunayo, 2023). Blood glucose levels show continuous variability during pregnancy (Görgülü, 2019). With the increase in diabetogenic placental hormones during pregnancy, there is an increase in the release and sensitivity of insulin, which leads to insulin resistance (Oğuz, 2016). This type of diabetes resolves after birth (Dirar and Doupis, 2017). Abortion or congenital anomaly can be observed in gestational diabetes (German et al., 2009).

Type 4 Diabetes mellitus

It is a type of diabetes that develops due to diseases or factors with different etiologies, also called secondary diabetes (Hume et al., 2006). In dogs, it is frequently caused by endocrinopathies such as acromegaly, Cushing's Syndrome, insulinoma, pheochromastoma, glucagonoma, hypertroidism, exocrine pancreatic diseases such as pancreatotectomy, pancreatitis, pancreatic trauma, hormones such as long-term glucocorticoid, thyroid hormone, progesterone use, and the use of cytotoxic and diabetogenic drugs such as alloxan, streptozicin (Kıyıcı et al., 2019; Kuzi et al., 2022). In these cases, autoantibody formation is observed with a decrease in the number and affinity of insulin-sensitive receptors and insulin resistance is formed (Lee et al., 2022). When the secondary cause of diabetes is treated, glucose balance returns to normal and diabetes does not become permanent (Erşan, 2008).

Clinical Findings

Clinical findings in diabetes mellitus may vary according to insulin level, severity of hyperglycemia, presence of ketones and any concurrent disorder (Gündüz et al., 1993). The disease occurs in three different clinical forms; uncomplicated (non-ketotic), ketoacidotic and non-ketotic hyperosmolar (Kaymaz, 2013). The general and characteristic symptoms of

diabetes mellitus in dogs include polyuria, polydipsia, polyphagia and weight loss (Lurye, 2006). The main cause of glycosuria is exceeding the renal threshold due to hyperglycemia (Nelson and Couto, 2022). Blindness may occur in advanced cases where bilateral cataracts develop (Li et al., 2014). In obese dogs, significant weight loss is observed in the last period of the disease with both loss of muscle mass as a result of gluconeogenesis and reduction of adipose tissue as a result of lipolysis (Malerba et al., 2019). One of the other causes of weight loss is the loss of calories as a result of glucose not being utilized and excreted in the urine (Lust, 2002). Free fatty acids, which increase in circulation with the breakdown of fats, cause fatty liver. Hepatomegaly may be observed as a result of this fatty liver (Mattin et al., 2014). Some of the free fatty acids are converted into acetyl CoA and ketone bodies are synthesized. Metabolic acidosis occurs due to accumulation of ketone bodies in the blood (McGary, 2002). Diabetic ketoacidosis causes lethargy, depression, anorexia, dehydration, tachycardia, slow and deep breathing characterized as 'kussmaul breathing', acetone odor in respiration, coma and death as a result of circulatory collapse (Mazzi et al., 2008). In cases where the disease cannot be controlled, abdominal pain and vomiting are observed due to accompanying pancreatitis. In dogs with diabetes mellitus, the function of neutrophils is impaired and the patient becomes susceptible to bacterial or fungal diseases. Chronic cystitis, prostatitis, bronchopneumonia, bacterial or yeast dermatitis occur secondarily. Hypertension occurs in the patient with the accumulation of glucose in the endothelium (Aytuğ, 2019). Hyperglycemia in patients with diabetes mellitus may also lead to long-term complications such as retinopathy, nephropathy and neuropathy (Tandoğan et al., 2022).

Laboratory Findings

Laboratory findings in diabetes mellitus in dogs vary according to the clinical picture (Suzuki et al., 2016). In uncomplicated diabetes mellitus, complete blood count results are mostly within reference values. Hyperglycemia and consequently glycosuria occur due to blood glucose levels >200 mg/dL in dogs. Urine free weight can sometimes be low (>1.025). Alanine aminotransferase (ALT) and alkaline phosphatase (ALP) levels are elevated (<500 IU/L). Hypertriglyceridemia and hypercholesterolemia occur due to lipemia (Taşçene and Karagül, 2008).

In ketoacidotic diabetes mellitus, leukocytosis may occur in complete blood count (Suzuki et al., 2016). Blood glucose level in dogs is >200-250 mg/dL. Glycosuria is seen due to hyperglycemia. Hyperosmolarity occurs. Ketonuria is seen due to the increase in ketone bodies in the urine due to ketonemia. Blood pH decreases and acidosis develops. Loss of fluid and electrolytes leads to dehydration and prerenal azotemia. Therefore, hypo-

kalemia, hypochloremia and hyponatremia may be observed. Total protein, albumin and hematocrit values increase due to dehydration (Kumar et al., 2014; Şimşek and İçen, 2008).

In non-ketotic hyperosmolar diabetes mellitus, the blood glucose level in dogs is >600 mg/dL. Ketonemia and ketonuria are not seen (Nelson and Couto, 2022). Severe dehydration and hyperosmolarity (>350 mOsm/L) are present. Blood urea nitrogen (BUN) and creatinine values are increased as the kidneys are affected by severe dehydration. Metabolic acidosis occurs with increased plasma lactate concentration and total carbon dioxide content decreases (Qadri et al., 2015). Hyperglycemia, glycosuria, hypercholesterolemia, increased liver enzyme levels and hyperproteinemia are frequently encountered. Complications occur due to hyperglycemia and ketoacidosis (Scobie and Samaras, 2014). In dogs, hyperglycemia with clinical signs occurs with blood glucose levels reaching 200 mg/dL and glycosuria is observed when the renal threshold (>180 mg/dL) is exceeded. Serum insulin levels are <20 µU/mL in Type 1 diabetes mellitus and >26 µU/mL in Type 2 diabetes mellitus (Şimşek and İçen, 2008). Lipemia occurs with the breakdown of fats and hypercholesterolemia is observed.

Hypertriglyceridemia and hypercholesterolemia occur due to lipemia (Taşçene and Karagül, 2008). While the cholesterol level is 300 mg/dL in the early stages of the disease, it may be 900 mg/dL in the late stages (Sertbaş, 2021). ALT, AST, ALP levels increase due to hepatic lipidosis or pancreatitis (Sarıtaş and Göksel, 2013). In addition, amylase and lipase levels increase due to pancreatitis and renal failure (Scudder and Roberts, 2023). As a result of loss of pancreatic function, the amount of trypsin in feces decreases (Okumuş, 1999). Blood pH decreases due to ketonemia, which is characterized by an increase in ketone bodies in the circulation. Hyperglycemia decreases Ca absorption in the intestines and Ca and P are excreted in the urine. As a result, hypocalcemia and hypophosphatemia occur (Çelik and Bal, 2002). In urine analysis, glycosuria, ketonuria, bacteriuria and proteinuria may be observed (Shapiro et al., 2018). Specific gravity of urine increases and pH decreases (Son, 2012). In dogs with diabetes mellitus, bacteria easily adhere to the urinary bladder due to glucose in the urine. With the suppression of neutrophils and the growth of bacteria here, emphysematous cystitis is observed and bacteriuria is formed. Proteinuria may be observed due to glomerular damage caused by hyperglycemia and urinary infection (Semlitsch et al., 2021; Ülgen and Kaymaz, 2013). In the presence of ketonemia, ketonuria is observed with the removal of ketone bodies through urine (Ülgen and Kaymaz, 2013).

Diagnosis

The diagnosis of the disease is made by evaluating anamnesis, clinical and laboratory findings together (Erşan, 2008). For the diagnosis of diabetes mellitus in dogs, persistent fasting hyperglycemia and glycosuria despite polyuria, polydipsia and polyphagia among the characteristic clinical findings are sufficient (Zanner et al., 2023).

Fasting blood glucose is checked for the diagnosis of diabetes in line with the anamnesis and clinical signs. Fasting blood glucose value is accepted as 80-120 mg/dL (4.4-6.7 mmol/L) in healthy dogs (Scudder and Roberts, 2023). Fasting blood glucose is measured after at least 8 hours of fasting and dogs with >200 mg/dL (8 mmol/L) and above are considered diabetic. However, in cases where the fasting blood glucose value is 120-200 mg/dL (7.2-8 mmol/L), a definitive diagnosis cannot be made and patients are included in the prediabetes group. In cases with impaired fasting glycemia, oral or intravenous glucose tolerance test is used (Sarıtaş and Göksel, 2013). Oral glucose tolerance test is a frequently used and reliable test. Since this test can be affected by factors such as stress, medications and diet, attention should be paid to diet, exercise and medications used before the test. This test can be applied if there is no absorption problem in the digestive system (Sako et al., 2009). The application and interpretation of the test is as follows. Dogs fasted for at least 8 hours are given 1.75 g/kg glucose, 25% solution orally or by gastric catheter in the morning. Venous blood samples are taken once before the administration and at 30, 60, 90, 120, 180 minutes afterwards (Rudloff, 2017). Blood is taken in tubes with EDTA if the measurement is to be made immediately, and in tubes with sodium fluoride to prevent glycolysis if it is to be sent to the laboratory. In healthy dogs, blood glucose level reaches its highest level (<8.9 mmoL/L) at 30-60 minutes and decreases to fasting blood glucose level (<7 mmoL/L) at 120 minutes. In dogs with diabetes mellitus, the blood glucose level usually rises to >8.3 mmoL/L at 60 minutes and beyond and does not fall after 90 minutes, remaining above normal values. In another method, the intravenous glucose tolerance test, 0.5 g/kg glucose is administered intravenously as a 50% solution. Venous blood samples are taken at 15, 30, 60, 120, 180 minutes. In healthy dogs, the blood glucose level reaches its highest level (>16.6 mmoL/L) 15 minutes after infusion and starts to decrease to fasting blood glucose level within 60 minutes. In dogs with diabetes mellitus, blood glucose levels remain elevated until 120 minutes and fall to fasting blood glucose levels between 120-180 minutes (Ruckinsky et al., 2010).

Glucometers are also used to measure blood glucose levels in dogs at certain intervals. For this purpose, blood is taken from the outer surface of the ear, soles of the feet and gums (Bayrakal and İskefli, 2020). The auricle

is notched with a lancet and a drop of blood is brought into contact with the test stick. The path is followed according to the result on the glucometer (Bilal, 2013).

Hyperglycemia, which is seen in all types of diabetes mellitus, can also develop as a result of stress, fear, carbohydrate-rich diet, high doses of glucocorticoids, progesterone, adrenaline and insulin administration (Alberti and Zimmet, 2011). The distinction is made with glycated proteins. For this purpose, serum fructosamine and glycosylated hemoglobin are used and they are not affected by stress, exercise, nutrition and drug use (Abacı et al., 2007). Glycosylated hemoglobin (HbA1c) is formed by the irreversible binding of excess glucose in the blood to hemoglobin, a protein (Düdek, 2019). Glycated hemoglobins increase in hyperglycemia. HbA1c measurement provides information about blood glucose in the last 3 months. In healthy dogs, HbA1c level is accepted as 1.39 ± 0.70%. In dogs with diabetes mellitus, HbA1c concentration increases 2-3 times higher than normal (Taşçene and Karagül, 2008). For measurement, blood is taken in tubes with EDTA or heparin (Oğuz, 2015). With this parameter, early diagnosis of diabetes mellitus, differentiation of stress hyperglycemia and monitoring of blood glucose levels in diabetic patients are possible and easy (Mooney, 2003). Serum fructosamine is another parameter used to distinguish hyperglycemia caused by stress (Nabipour, 2003). It occurs as a result of glucose binding to serum proteins with an irreversible, non-enzymatic bond. Serum fructosamine measurement is measured from fresh or frozen serum and provides information about blood glucose for approximately 2-3 weeks (Nelson et al., 2023). Serum fructosamine value in healthy dogs is accepted as 100-400 μmoL/L. If conditions such as hypoproteinemia, hypoalbuminemia, and hemolysis are present, decreases in fructosamine levels may be observed (Niaz et al., 2018). Serum fructosamine concentration <400 mmoL/L indicates that glycemic balance is well maintained. Values >500 mmoL/L are evidence that the glycemic balance is not under control (Behrend et al., 2018).

Treatment

The treatment protocol of diabetes mellitus mainly consists of diet, exercise and insulin therapy (Yagiyashi, 2023). Purpose of treatment; It prevents the occurrence of clinical findings and complications by keeping blood glucose levels balanced. However, improving the patient's quality of life is among the main goals (Düdek, 2019). However, improving the patient's quality of life is among the main goals (Düdek, 2019). There are various forms of insulin, and their use varies depending on the patient's clinical and laboratory findings (Li et al., 2017). Since there is insulin re-

sistance in Type 2 Diabetes mellitus, treatment should be performed to first find and eliminate the cause of this condition (Metzger and Rebar, 2012).

We can examine treatment options under 4 main headings;

Insulin Applications

Insulin is a peptide hormone with a high molecular weight. Oral insulin is not used because peptides are digested in the intestines (Hulsebosch et al., 2022). Insulin treatment of Diabetes mellitus in dogs; Lente insulin (porcine zinc insulin suspension), PZI (human recombinant protamine zinc insulin), NPH (human recombinant neutral protamine hagedorn), detemir (human recombinant DNA) and glargine (human recombinant DNA) are frequently used (Şimşek and İçen, 2008). In terms of their effects, NPH and Lente intermediate-acting insulins; PZI, glargine and detemir insulin long-acting insulins; Regular insulin is classified as short-acting and fast-acting insulin. Information about insulin products and usage details is given in Table 1 (Behrend et al., 2018). In insulin applications, subcutaneous administration is generally preferred to ensure a long duration of action. The use of long-acting insulin preparations is not recommended in dogs with high degrees of dehydration and those that develop anorexia (Martin and Rand, 2000). Among these, the first insulin to be preferred in the treatment of dogs diagnosed with diabetes is lente insulin obtained from pigs (Vurkaç and Şahinduran, 2018). In cases where Lente insulin cannot be used, NPH should be used as an alternative. The starting dose is 0.5 U/kg for both lente and NPH insulin. It is applied subcutaneously, twice a day, at 12-hour intervals (Lee et al., 2022). Insulin detemir is the longest-acting insulin used in dogs and has a duration of action of at least 16 hours. It shows its effectiveness by binding to albumin after application. PZI has been used by clinicians in dogs since 2019. Although glargine is rapidly absorbed when the pH is 4, it is absorbed slowly by forming microparticles in the blood and subcutaneous tissues at neutral pH. High blood glucose levels need to be lowered slowly, not suddenly. The dose of insulin administered for this purpose can be increased by 1-4 IU in each administration, depending on body weight and blood glucose concentration (Behrend et al., 2018). The most important control of the response to treatment is the determination of fructosamine and glycated hemoglobin concentrations. Patients receiving insulin should undergo weekly check-ups. Routine checks should be performed every 4-6 months in dogs with diabetes mellitus whose clinical and laboratory findings are stable (Martin and Rand, 2000). In dogs that are just starting treatment, hospitalization for a few days is required to determine the insulin dose and type and to evaluate the glycemic response that will occur with the first insulin administration (Malerba et al., 2019). To find the appropriate insulin dose, a blood glucose curve should be drawn

by measuring the blood glucose level every 2 hours for at least 12-24 hours (Bayrakal and İskefli, 2020). Thus, overdosed insulin can prevent hypoglycemia or hyperglycemia due to under-administered insulin dose can be prevented (Bayrakal and İskefli, 2020).

Table 1. *Insulin preparations used for dogs (Behrend et al., 2018).*

Insulin Product	Commercial Preparation	Concentration	Starting Dose	Effect duration
Lente	Vetsulin	U-40	0.25-0.5 U/kg	24 h
Glargine	Lantus	U-100 U-300	0.3 U/kg	12-20 h
PZI	ProZinc	U-40	0.5-1 U/kg	24 h
NPH	Novolin Humulin	U-100	0.25-0.5 U/kg	12 h
Detemir	Levemir	U-100	0.1 U/kg	**12** h

Diet

Among the practices that support medical treatment in the treatment of diabetes mellitus in dogs, the most important is diet regulation. Carbohydrate, fat and protein metabolism is impaired in diabetic patients. The purpose of diet regulation; correcting obesity, stabilizing daily calorie intake and maintaining normal body weight (Kahyaoğlu, 2011). The ideal diet is high in fibre, high in complex carbohydrates and low in unsaturated fat. Fiber provides glycemic control and protects against obesity by reducing glucose absorption in the intestines (Kennerman, 2006). Rapid weight loss in obese animals is not recommended as it may lead to hepatic libidosis. The recommended period for weight loss is 2-4 months, but it should not exceed 1-2% of body weight per week. Obese animals are fed a diet high in fiber and low in fat and calories (Rand et al., 2004; Weaver et al., 2006).

Low-calorie improper feeding in lean animals; Normal body weight should first be gained with a low-fiber, high-calorie diet, as it may cause starvation, ketoacidosis and weakened immunity (Rand and Marshall, 2005). Soft and wet foods are not recommended as they may cause hyperglycemia immediately after consumption (Kıyıcı et al., 2019). The amount

of nutrition should be 28 g/kg per day and the meals should be divided into two and given at the same times every day. Dogs that will receive two doses of insulin should be fed every 12 hours during each injection, and dogs that will receive a single dose of insulin should be fed during the injection and 8 hours after the injection, when insulin activity is at its highest (Maden and Çuhadar, 2013). If there is a secondary disease accompanying diabetes, the diet should be rearranged. A low-protein food should be preferred for diabetic dogs with chronic renal failure, and a low-fat, low-fiber, vitamin K-containing food should be preferred for dogs with chronic pankeratitis. A low sodium, high fiber food should be used for a diabetic dog with hypertension, and a hypoallergenic food should be used for a dog with allergies (Kim et al., 2016). Some clinicians recommend that canned pumpkin, green beans, and commercial fiber supplements containing psyllium or wheat dextrin be included in the diet (Nerhagen et al., 2017).

Exercise

With exercise, blood flow accelerates and insulin is transported to the muscles. Insulin transported to the muscles reduces the amount of glucose there and ensures glycemic balance (Li et al., 2017). Exercise helps lose weight in obese animals and reduces or even eliminates insulin resistance. Just like diet regulation, exercise should be done at the same time every day and hours when insulin levels increase should not be chosen (Nelson et al., 2023). Strenuous exercises performed at irregular intervals cause hypoglycemia (Ömercioğlu, 2018).

Oral Antidiabetics

Oral antidiabetic drugs are used in the medical treatment of diabetes mellitus, especially in cases of insulin resistance (Dang et al., 2017). Since these drugs ensure glycemic balance, they are also known as oral antihyperglycemic or oral hypoglycemic drugs (Sertbaş, 2021). The choice of antidiabetic drug to be used in treatment should be specific to the patient (Güçlü and İmamoğlu, 2007). The patient's clinical and metabolic profile, the cost of the drug, and its side effects should be considered in treatment planning. Following these evaluations, the targeted blood glucose balance can be achieved with single or combined treatment (Longo, 2010).

Antidiabetic drugs used in the treatment of diabetes mellitus; Sulfonylureas, Alpha glucosidase inhibitors, Biguanides, Meglitinides, Dipeptidyl peptidase 4 inhibitors (DPP4-I), Thiazolidinediones, Sodium-glucose co-transporter 2 inhibitors (SGLT2-I), oral glucagon-like peptide-1 (GLP-1) receptor agonist, dopamine agonists and bile acid sequestrants (Sertbaş, 2021). These drugs act as insulin secretagogues, insulin sensitizers, slow

down the absorption of glucose from the digestive system, and incretin mimetics (Aytuğ, 2019).

The most commonly used agent in veterinary medicine is glipizide, which belongs to the sulfonylurea group. In dogs, glipizide is used twice a day at a dose of 0.25-0.5 mg/kg. The most common side effect is hypoglycemia and therefore the daily dose should not exceed 5 mg/kg. In order for it to be effective, there must be insulin release from beta cells (Aytuğ, 2019).

In conclusion, diabetes in dogs requires further study as it causes many complications and is life-threatening.

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BÖLÜM 3

ACUTE PHASE PROTEINS IN VETERINARY MEDICINE

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Introduction

The response of the organism to traumatic, infective and inflammatory conditions in animals is called acute phase response (APR) and the proteins produced as a result of this response are called acute phase proteins (AFP). Proteins are substances that play a role in many physiological events in the organism and are found in many and various types in living organisms. They form the basic building blocks of tissues and control many chemical reactions such as enzymes and hormones (Coşkun and Şen, 2011; Tiftik, 1996; Turgut, 2000).

Acute phase proteins are born in response to AFI usually synthesized by the liver. Today, there are acute phase proteins with very different known functions and properties. These proteins are present at negligible levels in healthy animals but their levels increase rapidly in unhealthy animals. Increased acute phase proteins in sick animals play a role as inflammation markers. The blood levels of these proteins, which play a decisive role in clinical importance, vary between animal species (Eckersall and Bell, 2010; Cray et al., 2009; Sevgisunar and Şahinduran, 2014).

Most of the acute phase proteins have been studied in detail human medicine and are now routinely used in disease prognosis. Recent studies have revealed that acute phase proteins have important areas of use in veterinary medicine. However, the presence of different acute phase proteins in each animal species and the lack of sufficient studies prevent the routine use of acute phase proteins in veterinary medicine (Gokce and Bozukluhan, 2009; Petersen et al., 2009).

Acute Phase Respons

Acute phase response (APR) is a response that occurs following inflammation, tissue injury, infection, neoplastic growth, parasitic, immunologic reactions in the organism. Following tissue injury, the secretion of cytokines, which are pro-inflammatory substances, from damaged tissues in response to this is called Acute phase respons. It is characterized by metabolic and systemic changes. It is a non-specific reaction that occurs after tissue damage occurs. Acute phase respons occurs in relation to the response of the organism and can be expressed as sudden changes in the blood concentration of many plasma proteins synthesized by the liver (Gokce and Bozukluhan, 2009; Kahyaoğlu, 2011; Sevgisunar and Şahinduran, 2004; Taşcene 2017).

The function of the acute phase response is protect the organs from further injury and damage to eliminate infectious agents, to clean molecules and residues that may cause harm to the organism, to initiate the repair

process to return the organism to normal functioning and to ensure homeostasis (Habif, 2005).

The acute phase response is a complex change characterized by local and systemic changes initiated by inflammatory mediators at the site of tissue destruction. Animals exhibit systemic inflammatory signs reflecting multiple endocrinological, hematological, immunological, metabolic and neurological changes. These signs include fever, anorexia, negative nitrogen balance, destruction of muscle cells, decreased levels of low and high-density cholesterol, anorexia, depression and hormone changes (Coşkun and Şen, 2011; Eckersall and Bell, 2010).

In local reactions that occur during the acute phase response, there is an increase in capillary permeability, the passage of leukocytes to the site of inflammation and the release of many chemical mediators. In systemic reactions there are increases or decreases in acute phase respons formed through mediators (Coşkun and Şen, 2011; Gokce and Bozukluhan, 2009).

Multisystemic reactions are initiated by many mediators. These mediators include cytokines, glucocorticoids and growth factors (Ceciliani et al., 2000; Habif, 2005). Other clinical changes include activation of the blood coagulation system, decrease in serum Ca, Zn, Fe, vitamin A and alpha tocopherol levels and changes in acute phase proteins (Alsemgeest et al., 1993; Sekin et al., 1999).

When tissue is damaged or affected by microorganisms, the organism initiates a series of responses on its own. Inflammatory cytokines are released, the vascular systems and inflammatory cells are activated. This can be considered as an early warning system informing the body of its current condition (Ceciliani et al., 2012; Sevgisunar and Şahinduran, 2014).

Acute phase protein production is a very complex reaction. While some mediators accelerate their production, others slow it down (Gokce and Bozukluhan, 2009). In acute inflammation, the levels of adrenocorticotropic hormone (ACTH) and hydrocortisone hormones increase following fever. In addition, the production of acute phase proteins is increased or decreased by some mediators. The main mediators are cytokines, interleukin 1β, tumor necrosis factor (TNF)-α, interleukin-6 (IL-6), interferon-γ (IFN), growth factor (TGF)-β and interleukin-8 (IL-8), which are stimulated by tissue macrophages (Kaneko, 1997). Acute phase protein production is accelerated by cytokines, mainly IL-6, and inhibited by insülin (Onat et al., 2002). Within a few hours after infection, a severe decrease in some blood proteins synthesized from the liver is observed. These are negative AFPs such as transthyretin (prealbumin) cortisol binding protein, transferrin and albumin (Nukina et al., 2001).

Cytokines such as interleukin-6 and IL-1 are initially released by macrophages and monocytes in the damaged tissue and travel to various tissues. Cytokines activate fibroblasts and endothelial cells at the site of local inflammation, causing them to secrete cytokines again and thus initiating a systemic inflammatory response with these secondary cytokines that enter the circulation. With the effect of systemic cytokine release, the circulating concentration of AFPs is increased to support changes in hepatocytes. The inflammatory response continues for 1-2 days and then gradually disappears. The presence of the stimulus causing AFI or chronicization of the case causes prolongation of this process (Eckersall, 2000; Hirvonen, 2000; Petersen et al., 2004).

Cytokines as Acute Phase Response Regulators

Cytokines are mediators of the acute phase response. Cytokine signals are transported into the cell through membrane-bound receptors. Different intracellular signaling pathways are activated by different cytokine-receptor interactions. Systemic inflammation elicits a systemic acute phase response. However, local inflammatory or traumatic processes also trigger an acute phase response (Moshage, 1997). No significant correlation was found between acute phase protein concentrations and cytokine levels and increased production of AFPs (Kushner et al., 1993). The production of specific cytokines is triggered by different pathophysiologic conditions in different animals. Therefore, although the concentrations of various AFPs usually increase or decrease together, they do not show a specific increase or decrease in all diseases or in all animal species. Cytokines can stimulate themselves and regulate the increase or decrease of other cytokines. Cytokine combinations can be additive, meaning that one cytokine can enhance the effect of another, inhibitory, meaning that one cytokine can suppress the effect of another, or synergistic, meaning that two cytokines can combine to exert a stronger effect. Cytokine effects may be affected by inhibitors, defective receptors, autoantibodies and binding to plasma proteins. The effects of cytokines can be influenced by other extracellular messengers (Kushner et al., 1993.)

Effects of Acute Phase Response on Physiological Functions

Acute phase response is clinically characterized by signs of systemic inflammation, fever, anorexia and depression. Feed and water intake decreases as a result of anorexia that develops in animals during AFI. Hypomotility and delayed emptying of digestive contents occur in these animals due to impaired gastrointestinal tract function (Gruys et al., 1994).

It is also reported that the hemostatic system is significantly affected during AFI. Some of the clinical signs of AFI include fever, anorexia and

stagnation. On the endocrine system; ACTH, cortisol, glucagon, insulin, growth hormone and adrenal catechelamines increase while thyroxine and gonadal steroids decrease. Metabolic changes; Protein metabolism, glucogenesis, hepatic production of AFP increases. In hematologic changes, serum zinc, iron, calcium and vitamin A levels decrease while copper levels increase. Leukocyte count first decreases and then increases, lymphocyte activity decreases while platelet activation increases, bactericidal capacity of neutrophils and phagocytosis capacity of macrophages decrease. Pain increases (Gokce and Bozukluhan, 2009).

Acute Phase Proteins

Acute phase proteins are synthesized mainly from the liver and most of them are glycoproteins. The secretion of acute phase proteins is regulated by proinflammatory cytokines. They are thought to be synthesized in response to mediators released from the site of tissue damage. Their turnover in serum is rapid. The period before the elevation of these proteins is called Lag phase. It has been shown that serum taken during the lag phase can transfer the ability to stimulate acute phase proteins in animals or organ cultures. This stimulation ability is realized by structures called cytokines (Aktepe, 2002).

The function of most AFPs has not been fully elucidated until recent years. The most general classification of acute phase proteins is positive and negative acute phase proteins. Apart from positive and negative AFP, it has been reported that there are proteins that are not associated with inflammatory reactions or whose amount in the blood is too low to be measured (Ceciliani et al., 2012; Gruys et al., 2014; Sevgisunar, 2014).

In the period following tissue damage, some acute phase proteins increase and are called positive acute phase proteins, while others decrease and are called negative acute phase proteins. Negative acute phase proteins include prealbumin, albumin (Alb), trasferrin, retinol binding protein and α2-glycoprotein. Positive acute phase proteins are serum amyloid A (SAA), haptoglobin (Hp), ceruloplasmin (Cp), α1-acid glycoprotein (α1-AGP), fibrinogen (Fb), C-reactive protein (CRP), protease inhibitors, lipopolysaccharide binding protein, transferrin, inter alpha trypsin inhibitor heavy chain 4 (ITIH 4), is a retinol binding protein (Gruys et al., 2005; Sevgisunar and Şahinduran, 2014).

Positive AFPs are mainly glycoprotein substances released from hepatocytes with the stimulation of inflammatory cytokines, while negative AFPs are structural plasma proteins commonly found in the blood (Murata et al., 2004). Positive acute phase proteins can be classified as major-moderate-minor according to the degree of their response to inflammatory

reactions. Major AFPs are found at low concentrations (<1μg/L) in the serum of healthy animals, increase significantly (100 to 1000-fold) within 24-48 hours after stimulation and show a rapid decrease during the recovery period. Moderate AFPs peak 2-3 days after activation, increase 5-10-fold and decline more slowly than the major response. Minor AFPs show a 50% or 100% increase from normal levels. The aim of this classification is to facilitate the identification of the factors involved in the etiology of AFI by revealing species-specific AFPs (Eckersall, 2010).

Recent studies describe AFPs as inflammatory response regulators that communicate with defense cells and pathogens (Ceciliani et al., 2012). Infection, trauma, surgery, burns, tissue infractures, immunological disorders and blood concentrations of AFPs vary depending on the balance between their production and degradation. Their concentrations are not affected by age, sex and genetic changes but increase rapidly in cases of infection and inflammation (Alsemgeest, 1993).

Some of the acute phase proteins are fetal proteins that are normally found very little in the serum of adults. Although the synthesis and concentrations of AFPs vary according to the animal species, they generally begin to increase within 8 hours after stimulation, reaching maximum blood concentrations within 24-48 hours. With recovery, it gradually decreases to normal levels within 4-7 days (Gruys et al., 1994; Gruys et al., 2005). In chronicized cases, serum levels remain high as the stimulation continues, but serum concentrations may differ in acute or chronic cases according to AFP type (Horadagoda et al., 1994; Gokce and Bozukluhan, 2009). Cases such as advanced cancer cause high changes in the plasma concentration of AFPs, while strenuous exercise, heat stroke and childbirth cause moderate changes (Habif, 2005).

Positive Acute Phase Proteins

Positive AFPs are basically proteins released by hepatocytes after cytokine stimulation and their serum levels increase. The main function of positive AFPs is opsonization, i.e. the presentation of microorganisms or antigens to phagocytes or macrophages by making compounds with the mentioned proteins. Apart from these, it has been reported that they have general functions such as binding and removal of microorganisms and their residues, complement activation, binding of residues such as cell nucleus remains as a result of cell destruction, enzyme neutralization, collection of free hemoglobin and radicals, and regulation of immune responses of the organism (Gruys et al., 2005).

Serum Amyloid A (SAA)

In its natural form, serum amyloid A has a molecular weight of around 11,700 Daltons because it forms complexes with lipoproteins and is therefore also called apolipoprotein. Three different isoforms have been identified in horses, four in humans and mice, and seven in cattle (Petersen et al., 2004). Although serum amyloid A is synthesized predominantly from the liver during inflammation, studies have reported that horses and cattle also have different isoforms such as milk amyloid A (MAA) synthesized outside the liver (Gokce and Bozukluhan, 2009; Petersen, 2004).

The serum concentration of SAA, an α globulin, is reported to be < 24μg/ml in healthy cattle (Çitil, 2003). In human medicine, SAA is used to determine the activity and prevalence of inflammatory events, to differentiate inflammatory diseases from non-inflammatory diseases, to monitor the course of diseases and to evaluate the success of treatment. In addition, it has been reported that high CRP and SAA levels may be considered as an indicator of latent infection or malignancy even in the absence of fever and neutrophilia (Batırel et al., 2003).

Although their functions are not known exactly, it is reported that they may have functions such as transport of cholesterol to hepatocytes, suppression of fever, inhibition of oxidative destruction of neutrophil granulocytes, stimulation of calcium mobilization by monocytes, endotoxin detoxification, inhibition of lymphocyte and endothelial cell proliferation, inhibition of platelet aggression and inhibition of adhesion of T-lymphocytes to extracellular matrix proteins (Ceciliani et al., 2012; Petersen et al., 2004).

Fibril depositing structures in tissues of patients with secondary amyloidosis are considered to be precursor molecules of amyloid A protein. Derived from patients with secondary amyloidosis. It is an α1-glycoprotein normally present in human plasma at less than 50μg/ml concentration. The plasma level of SAA, a polymorphic aprotein that forms a complex with HDL3 in the circulation, increases in infectious conditions and reaches a maximum value as high as 1.0 mg/ml within 24 hours. If treatment of bacterial infection with antibiotics is successful, plasma levels rapidly decrease (Lu et al., 2014).

Serum Amyloid A, a sensitive marker of acute phase response, is synthesized by liver cells in response to SAA stimulating factor, which is similar to interleukin 1 molecule released from macrophages. It is so named because its amino end resembles the major tissue protein formed by secondary amyloid deposits in chronic infectious conditions. SAA, a sensitive marker of acute phase response, is synthesized by liver cells in response

to SAA stimulating factor, which is similar to the IL-1 molecule released from macrophages (Schultz and Arnold, 1990; Taşcene, 2017).

SAA levels are quite low in healthy cattle. In cases of inflammation, its concentration can increase up to 10 times and therefore it is considered as a highly sensitive AFP against inflammation. Studies have shown that SAA increases in bacterial and viral infections, ketosis, during parturition, after operations, after fasting for more than 3 days and after endotoxin administration (Gokce and Bozukluhan, 2009). Its increase in milk can be detected in cows and sheep with mastitis. SAA level may also increase in cattle giving birth and exposed to physical stress. This shows that AFP can also increase in non-inflammatory conditions (Coşkun and Şen, 2011; Eckersall, 2000; Murata et al., 2004). Milk amyloid-A (MAA) is always at a certain level (0.5 mg/l and 0.6 mg/l) in healthy cows (Turgut, 2000).

In acute and chronic mastitis cases experimentally induced with Staphylococcus aerous, Hp and MAA levels in milk increased continuously, while only MAA levels increased during chronic subclinical mastitis. Very high SAA and MAA concentrations were detected in mastitis cases induced by E. coli. MAA level is a safe parameter in mastitis cases (Coşkun and Şen, 2011). Various studies on cattle have shown that stress has an effect on acute phase protein concentration (Lomborg et al., 2008). It was found that SAA level increased in calves under physical stress (floor, barn conditions) while Hp did not change (Alsemgeest et al., 1995).

In studies conducted in horses, it was found that the serum concentration of SAA increased in septicemia, local infection, enteritis and diarrhea cases and in *St. equi,* Equine herpes virus serotype 1, Equine influenza serotype A2 and Radococcus equi infections. In a study, it was reported that the serum concentration of SAA increased within the first 48 hours in horses infected with *Equine influenza virus* and decreased to normal levels within 11-22 days in uncomplicated cases. This study also revealed that there is a significant relationship between the serum concentration of SAA and the severity of respiratory symptoms (Eckersall, 2000).

In healthy horses, SAA is present in trace form, but the concentration increases rapidly after naturally and experimentally induced inflammation, infection or tissue injury (Hulten et al., 1999). In foals, the concentration of SAA is high during the first 1-2 weeks postpartum, but then decreases to normal levels. In mares, it has been reported that SAA level reaches its highest level 3 days after birth and remains high for 1 month (Gokce and Bozukluhan, 2009). Serum amyloid A has an important feature in terms of clinical use in dogs because it can increase in serum concentration in cases where a number of parameters indicating inflammation, such as CRP, do not increase. The normal serum concentration is 3.88±0.58 μg/ml. (Peter-

sen et al., 2004). Recent studies in animals have shown that elevated serum or plasma levels of SAA indicate the presence of inflammation or infection in the organism. SAA is the most commonly used acute phase protein in dogs after CRP. It has been reported that it can be used especially in the diagnosis of Canine parvovirus (Eckersall, 2000).

In a study conducted in calves, it was found that SAA concentrations increased in viral and bacterial infections. In this study, calves were inoculated with *Pasteurella multocida* and *BVD* agents and then SAA levels were examined. As a result, SAA was reported to be important parameters for these diseases (Taşçene, 2017).

As in many other species, SAA is considered to be a major AFP in cats and it is reported that it can increase over 1000-fold in the presence of inflammatory conditions compared to non-inflammatory conditions. Therefore, some researchers have indicated that SAA concentration may be a useful marker to detect the presence of an inflammatory condition in cats. The increase in the concentration of SAA in cats (approximately 10-50 fold) is lower than in other species (more than 100 fold in humans). While the normal serum concentration in cats is 42.5±26.6 μg/ml, it has been reported by researchers that it can increase to 121.3±29.3 μg/ml within 24 hours in case of acute inflammation (Hoshıya et al., 2001; Tuna, 2015).

Fibrinojen (Fb)

Fibrinogen consists of three pairs of polypeptide chains covalently linked by disulfide bonds. All three chains are synthesized from the liver. Its molecular weight is 340,000 daltons and it is the precursor of fibrin. It has an important role in blood clotting. Since plasma levels increase in inflammation, it is frequently used in the acute phase response for the diagnosis and treatment of the disease. Together with erythrocyte sedimentation rate, it is a non-specific marker in the follow-up of inflammation and tissue damage (Karagül et al., 2000).

During the acute phase response, there is a significant increase in the amount of hepatic mRNA. This increases the synthesis and secretion of the three polypeptide chains of fibrinogen. This molecule is a positive acute phase protein and its amount increases 3-4 fold during inflammation. It reaches a maximum level at the end of three days following inflammation. Cancer, burns, myocardial infarction, arthritis and bacterial infections, neoplastic diseases, traumatic cases have been reported among the reasons that increase fibrinogen. Soluble fibrinogen circulating in plasma is a glycoprotein consisting of three different polypeptide chains (Aa Bb g) covalently linked by disulfide bonds. All three chains are synthesized in the liver. The polypeptide chains are cross-linked by disulfide bonds. A

sudden change in hepatic mRNA structure results in increased synthesis and secretion of the 3 polypeptide chains of fibrinogen during the acute phase response (Dolitte, 1984; Taşcene, 2017).

In ruminants it is used specifically for the detection of inflammation in cattle. The normal serum concentration in ruminants ranges between 200-700 mg/dl. A total Fb concentration of 1000 mg/dl or higher is considered an indicator of poor prognosis. This protein is considered to be a reliable marker of inflammation and bacterial infection in cattle and sheep. Studies have shown that Fb concentration increases in acute mastitis, abscess, reticuloperitonitis traumatica, gastrointestinal inflammation, pyelonephritis, pericarditis, peritonitis and pneumonia (Bozukluhan, 2008; Gokce et al., 2007).

In dogs, fibrinogen is known as a moderately important acute phase protein. Normal serum concentration in dogs varies between 150-400 mg/dl. Total Fb concentration of 500 mg/dl or higher is an indicator of inflammation (Petersen et al., 2004). In a toxicologic study in 25 Beagle dogs, they reported that fibrinogen levels increased rapidly within a few days after administration (Hoshiya et al., 2001). In pregnant dogs, fibrinogen levels were reported to increase in the 5th and 6th weeks of pregnancy (Vannucchi et al., 2002).

Haptoglobins (Hp)

They are a group of proteins called α2 globulins and bind hemoglobin. Therefore, they are also known as hemoglobin-binding proteins. Once the haptoglobin-hemoglobin complex is formed, it is rapidly degraded in the lymphoreticular system. Its best known biological function is to bind free hemoglobin in the plasma formed by hemolysis of blood, preventing the body from losing iron and preventing free hemoglobin from precipitating in the renal tubules. Very few erythrocytes are destroyed intravascularly and the resulting hemoglobin binds to haptoglobin. This small amount maintains the body's iron stores. Uncomplexed hemoglobin has a melocell weight of 68,000 Daltons and can pass through the glomerular filter. However, the complex it forms by combining with haptoglobin cannot pass through the glomerular filter and thus some iron is returned to the circulation (Karagül, 2000; Kushner, 1993).

In hemolytic anemias, it prevents the intratissue accumulation of free hemoglobin. With decreased liver synthesis capacity, haptoglobin levels decrease. In the presence of hemolysis and acute phase reaction together, it is reported that it would be useful to measure changes in plasma levels of hemopexin, which is not an acute phase protein, instead of haptoglobin. Free heme-binding hemopexin is a β-globilin. By the liver The iron of the

heme group in the heme-hemopexin complex is given to ferritin and the rest of the heme is converted to bilirubin (Cray et al., 2009).

In humans, 16 different subtypes of Hp have been observed, making it a useful genetic marker. This protein is absent in healthy bovine serum. In studies in dogs, Hp is a structural serum protein and moderate AFP rather than an inflammatory protein. Hp is absent or present at very low levels (<0.1 mg/ml) in the serum of healthy cattle (Eckersall et al., 2000). The main function of haptoglobin is to prevent Fe loss by forming stable complexes with free Hb in the blood and clearing it from the circulation. By forming Hp-Hb complexes, it is transported to the liver by reticuloendothelial system cells and metabolized by Kuppfer star cells (Isaac et al., 2008). Since haptoglobin ensures the transport of free iron to the liver, it also prevents bacteria from utilizing free Fe and shows bacteriostatic effect (Bullen, 1981).

Haptoglobin hydrolyzes peroxides released from neutrophils at the site of inflammation and renders them harmless. In cattle, Hp acts as an immunomodulator in the regulation of lipid metabolism and lymphocyte functions. Because of this feature, it is reported that Hp concentration can be used to monitor the immune functions of calves (Bullen, 1981; Murata et al., 2004; Nakagawa et al., 1997). It has also been reported that Hp regulates prostoglandin synthesis (Nakagawa et al., 1997).

Haptoglobin serum concentration may be affected by factors other than AFI. In cases where the circulating free Hb level increases, Hb binds Hp and the complex formed is transported to the liver where it is eliminated. In this case, even if Hp production is stimulated by inflammation, the circulating level of Hp will be seen as low because Hb binds Hp. Therefore, the amount of Hp in serum decreases when free Hb concentration increases (Petersen et al., 2004). Haptogloin level has an important place in determining the prognosis of patients in calves (Kurt et al., 2019). It is the absence of Hp in the circulation during acute hemolytic crisis in babesiosis in cattle and in post-surgical hematoma in horses. In cases such as renal diseases and obstructive jaundice, Hp level in serum increases (Gokce and Bozukluhan, 2004; Petersen et al., 2004).

Serum or plasma Hp concentration increases in natural or experimentally induced inflammation, trauma and infections in cattle. It was determined that Hp levels increased during parturition, after castration, traumatic retucilitis and peritonitis, after rumenotomy operation, respiratory tract infections and mastitis (Alsemgeest et al., 1994). Studies have shown that bovine Hp is a very important finding in bacterial and viral diseases and plasma levels increase significantly in these diseases (Gokce and Bozukluhan, 2004). It was determined that Hp levels in cattle increased in animals

infected with pasteurellosis, pneumonia, fatty liver syndrome, mastitis, difficult labor in sheep, *Bovine respiratory syncytial virus* and foot and mouth virus, *Herpes virus 1* and *P. hemolytica* serotype A1 and *P. multocida* . There was a correlation between this increase and the severity of clinical symptoms, duration of symptoms and fever, and it was found that Hp levels decreased in animals treated with antibiotics (Conner and Eckersall, 1988; Petersen et al., 2004).

It has been reported that Hp concentration, which is at normal levels in dogs, reaches a peak level on the 5th day after surgical intervention or trauma (Conner and Eckersall, 1988). Hp levels in dogs with parvo viral enteritis were reported to be higher than in healthy dogs (Kocatürk et al., 2010). In dogs with babesiosis, Hp level before treatment was found to be lower than after treatment, this was reported to be related to hemolysis occurring in babesiosis (Erkılıç, 2019).

Hp rates in cats are AFP and their temperature increases 2-10 times after a fire stimulation. They found that the Hp temperature increased in the provinces with FIP, and the serum Hp capacity, which was found to be 0.04-3.84 g/L in healthy vessels, was 0.29-8.65 g/L in the vessels with FIP, and the difference was reported to be significant (Duthie et al., 1997). Hp is also important in pigs. Serum Hp levels increase especially in Toxoplasma gondii and Mycoplasma hyorhinis coffeehouses (Eckersall, 2000).

Ceruloplasmin

It is an α-2 globulin consisting of a single polypeptide chain. Its molecular weight is around 132,000 Daltons. It binds six copper atoms per molecule. The sialic acid part of ceruloplasmin connected to the polypeptide chain contains 10% carbohydrate. Although serum levels vary due to genetic polymorphism, no specific phenotype-related disorder has been identified. Discovered many years ago, ceruloplasmin was soon shown to have oxidase activity for many polyamine and polyphenol substrates and was named copper oxidase. It has been shown that the ferrooxidase activity of ceruloplasmin is necessary for the oxidation of the Fe+2 structure to the Fe+3 form, which is the first step in the binding of iron to transferrin (Dowton and Colten, 1988).

Ceruloplasmin, an acute phase protein whose concentration increases by 50% during the acute phase response, is thought to prevent lipid peroxidation and free radical formation. Plasma levels of ceruloplasmin increase in cases of infection, malignancy, trauma, obstruction and infection of the biliary tract; The increase is more evident in RES diseases such as Hodgkin. It has been shown that substances called leukocyte endogenous mediators mediate the synthesis of ceruloplasmin. It is known that the increase

in ceruloplasmin concentration in diseases enables the release of copper from the liver stores into the plasma. While serum ceruloplasmin levels are low at birth, they are between 20-40 mg/dl in normal adults. A two-fold increase is observed in cases of oral contraceptive therapy, pregnancy and acute phase reactant. The oxidase activity of ceruloplasmin can be used in a colorimetric assay using p-phenylenediamine as the substrate (Dowton and Colten, 1988).

It has been stated that Cp measurement can be used to monitor the disease and determine its severity in experimentally induced S. aureus infections in obese and normal weight rabbits (Georgieva et al., 2102). In horses, Cp is considered an AFP that occurs in the middle or advanced stages of acute infections (Okumura et al., 1991). It is stated that in salmonellosis infection in calves, the Cp level increases in the first three days and reaches its highest level on the fourth day (Murata et al., 2004). In a study conducted on calves with omphalitis, it was revealed that the Cp level in healthy animals is lower than in calves with omphalitis and that the Cp level can be used as an indicator and has an important place in prognosis (Kurt et al., 2019).

C-reactive protein(CRP)

C reactive protein has a molecular weight of 115 kDa and consists of 5 noncovalent subunits. This protein was found during the acute phase of pneumococcal pneumonia and was named C reactive protein due to its ability to bind to pneumococcal C polysaccharin. AFP is a widely used AFP in human medicine and is used to distinguish viral meningitis from bacterial meningitis, to screen for the presence of an organic disease, and to monitor septicemia and meningitis in newborns. Known functions of CRP include disrupting the nuclear structure by binding to the C polysaccharide in the membranes of microorganisms during AFR (Gokce and Bozukluhan, 2004).

It has been reported that there is a relationship between the increase in cattle CRP during naturally occurring diseases and the health status of the herd. It has been reported that CRP level is related to body condition score, lactation status and animal health, and increases rapidly in case of infection, but CRP is not considered an acute phase protein in cattle. Some studies reported that CRP can be used to distinguish bacterial, viral, or acute or chronic diseases (Ceciliani et al., 2012). There is information that CRP concentration can also be used as a criterion in determining the stress level in herds (Gokce and Bozukluhan, 2004).

CRP, a moderately important AFP in horses, is increased in many cases of inflammation and infection. In studies conducted in these animals, it

was found that this protein increased significantly in aseptic inflammation caused by intramuscular turpentine injection and in birth has been determined. Additionally, serum CRP concentration increases significantly in castration, arthritis, enteritis and pneumonia in horses (Yamashita et al., 1991). Among acute phase proteins, CRP is reported to be the most important acute phase protein in dogs. The normal level in healthy dogs varies between 0.8 and 14.0 μg/ml (Gruys et al., 1994). Serum CRP levels; In dogs, it increases in many conditions such as pregnancy, surgical trauma, polyarthritis, leptospirosis, bacterial or hemorrhagic enteritis, paroviral enteritis, ehrlichiosis and leishmaniasis (Conner and Eckersall, 1988).

Serum CRP level can increase up to 115 times in different inflammatory conditions in dogs. While this level is 500-1000 times higher in humans, such dramatic increases are not observed in dogs (Yamamoto et al., 1993). No significant increase in CRP is observed after any inflammatory stimulus in cats (Tuna, 2015). The amount of serum CRP was measured in experimental Staphylococcus intermedius infection in obese and non-obese dogs and it was observed that it increased approximately 80-fold 1 day after the infection. It has been shown that obese dogs respond faster to the inflammatory reaction (Slavov, 2011). In another study conducted in dogs, CRP measurement from cerebrospinal fluid (SS) and its comparison with serum CRP values were conducted, and it was stated that it could be used as an effective method in inflammatory situations in animals. However, in cases of steroid-induced meningitis and arthritis, they reported that serum CRP data and CRP measurement from SS are not useful in the current disease (Lowrie et al., 2009; Sevgisunar and Şahinduran, 2014).

Negative Acute Phase Proteins

These AFPs are negative AFPs that show decreased synthesis of hepatic mRNA regulation and consist of normal blood proteins transthyretin (TTR, or prealbumin), retinol binding protein (RBP), cortisol binding globulin, transferrin (Tf) and albumin (Alb). There is no detailed information about cortisol binding globulin in veterinary medicine (Murata et al., 2004).

Along with the decrease in negative AFPs, a decrease in serum zinc and iron amounts was also observed. The decrease in these metals indicates a temporary increase in free hormones that bind to negative AFP. Therefore, negative AFPs are defined as “acute potentiating reactants” by some authors (Gruys et al., 1994).

Albumin

The average weight of the album is 69 kDa. It is a plasma protein consisting of 585 amino acids and is synthesized only by the liver. It is the main source of amino acids that the animal body can use when necessary (Sevgisunar and Şahinduran, 2014). Albumin concentration is a very important protein that ensures and balances plasma oncotic pressure. It is found in plasma at the highest rate (35-50%). Since it is a small molecule, extravascular concentration changes are an important indicator in determining membrane integrity. In addition, since it is produced only by the liver, the decrease in its blood concentration is considered an important finding indicating liver failure (Gruys et al., 1994).

Its main biological functions include binding and transport, serving as a source for endogenous amino acids, and maintaining plasma pressure. It has been reported that its concentration decreases in liver diseases, starvation, AFY, kidney and intestinal diseases, and malabsorption syndrome (Gruys et al., 1994). Serum albumin level is often used to evaluate nutritional status and determine the severity of the disease (Kaneko, 1980).

It is reported that the half-life of albumin varies according to species and the values are 8.2 days in dogs, 16.5 days in cattle and 19.4 days in horses (Jain, 1993).

Increases in albumin levels are observed with dehydration. Hypoalbuminemia; It indicates loss of albumin (nephrotic syndrome or glomerulonephritis), movement into extravascular spaces (effusions in body cavities, vasculopathy) or decreased production (liver failure, malnutrition, malabsorption, maldigestion, acute phase response associated with increased globulin production). If the patient does not have any of these conditions, the cause of the low albumin level is probably inflammation (Kaneko, 1980).

Albumin catabolism increases in tissue damage and inflammatory conditions. With destruction, serum albumin level may decrease by 20-50%. During the acute phase reaction, the increase in the synthesis of positive acute phase proteins from hepatic mRNAs is accompanied by a decrease in the serum concentration of albumin (Gruys et al., 1994). Serum albumin levels in calves inoculated with Pasteurella haemolytica decreased after infection (Walker et al., 1994). It has been reported that serum albumin concentration in sheep injected with intrathoracic yeast decreases following infection and increases from the 10th day after infection (Pfeffer et al., 1993).

Transferrin (Tf)

Transferrin, a glycoprotein, is the plasma protein that has the most important role in transporting iron. It consists of 687 amino acids and its molecular weight is 79,550 Daltons. It is a polypeptide chain, 6% of which is carbohydrate, and its isoelectric point is between 5.5-5.9 (Karagül et al., 2000).

Transferrin, a major β-globulin, transports iron ions from mucosal and intracellular iron stores to the bone marrow, which contains erythrocytes and other cell precursors with receptors for the ions. In order for iron to be transferred from transferrin to the cell, iron-loaded transferrin must bind to its receptor on the membrane, and for this binding, pH must be neutral. Following binding, the transferrin-receptor complex is taken into the cell in the form of a vesicle (Tiftik, 1996).

After iron is removed from this vesicle, the vesicle binds to the membrane via exocytosis and iron-free transferrin is separated from the receptor. Transferrin levels decrease during the acute phase response due to unbalanced nutrition in terms of protein and energy, infection, neoplastic diseases and chronic liver diseases (Tiftik, 1996). Transferrin is the most important plasma protein involved in the transport of iron. Although it is mainly produced in the liver, it is also produced to a lesser extent in reticulo endothelial system cells (RES) (Murata et al., 2004). Studies have shown that its concentration decreases in acutely infected cattle. Transferrin is an important acute phase protein, especially for birds (Gokce et al., 2009; Murata et al., 2004).

Transthyretin (prealbumin)

The half-life of transthyretin, also known as prealbumin, in plasma is approximately 2 days, which is much shorter than the half-life of albumin. Therefore, prealbumin is more sensitive to changes in protein-energy status than albumin, and its concentration largely reflects that obtained from available food rather than all other nutritional factors. A low prealbumin level can primarily be used as a marker to identify patients at risk who require careful evaluation and follow-up, but it can also be used in patients who need nutritional support as part of the treatment plan (Sevgisunar and Şahinduran, 2014).

Structure of Acute Phase Proteins

The structures of acute phase proteins vary. Most of the acute phase proteins have a glycoprotein structure. Glycoproteins are proteins that contain oligosaccharide (glycan) chains covalently linked to polypeptide skeletons. Glycoproteins are a class of glycoconjugates or mixed carbo-

hydrates. These are synonymous terms used to indicate molecules containing one or more carbohydrate chains covalently bonded to proteins or lipids (Hugles, 2010; Taşçene, 2017).

In human and veterinary medicine, measuring acute phase protein levels and monitoring the glycosylation profile in diseases are of great importance in choosing the path to be followed in diagnosis and treatment. For this reason, acute phase proteins with glycoprotein structure are of special importance (Nakano et al., 1998). Major acute phase proteins with glycoprotein structure; serum amyloid A (SAA), α1-Acid Glycoprotein (α 1-AG, AGP), fibrinogen, haptoglobulin (Hp), α 1-antitrypsin (α 1-Protease Inhibitor), α 2-macroglobulin, ceruloplasmin and transferrin (Eckersall, 2000).

Functions of Acute Phase Proteins

The acute phase response is a nonspecific response to tissue destruction, infection and trauma, and its function is to protect the organism from further destruction. AFPs produced during this response can generally directly destroy inflammatory agents and contribute to the healing and regeneration of tissue (Gruys et al., 1994; Petersen et al., 2004; Gokce and Bozukluhan, 2004).

While some AFPs take part in clearing the residues released as a result of the effects of phagocytic cells and proteolytic enzymes, others (such as CRP) protect the organism from their harmful effects by binding to phosphocholine or nuclear residues in the destroyed cell membrane. There are also AFPs that function in the recovery of useful molecules. The best example of this is Hp, which prevents iron (Fe) loss by binding free hemoglobin (Hb). In addition, Serum Amyloid A ensures the use of cholesterol in tissue repair and the removal of excess, while ceruloplasmin prevents further damage from tissues by collecting oxygen radicals (Gokce and Bozukluhan, 2004; Gruys et al., 1994; Petersen et al., 2004).

In summary, the functions of AFPs include preventing iron loss by binding Hb, scavenging free radicals, preventing oxidation of lipids, binding bacterial components, transporting cholesterol, activating components and preventing microbial growth (Gokce and Bozukluhan, 2004; Gruys et al., 1994; Petersen et al., 2004).

Conclusions and Recommendations

As a result, many more studies are needed to better understand the functions and clinical uses of these proteins. Although measurement methods, AFP value ranges according to animal species and specific ELISA kits are not clearly established, there are no other parameters that can help us in

subclinical determination of the existing disease state, other than the proteins mentioned so far. As a result of DNA and RNA analyses, it has been revealed that not only the receptors or stimulations but also the synthesis processes in the cell nucleus and cytoplasm are important in the formation and release of these proteins, and therefore the studies to be done on this subject should be concerned not only with the general aspect of the work but also with the molecular dimension. When examined from this perspective, this concept is called “proteomics”, which is a combination of the words “protein” and “genome”, based on the fact that AFPs form complex and incompletely understood structures with all other cellular organelles in all inflammatory processes. The emergence of the concept of proteomics will not only provide a better understanding of AFPs, but also will explain how the concept of disease occurs at the molecular level by getting to the bottom of all the complex mechanisms involved in the subject, and will better explain the importance of multidisciplinary studies against diseases in the future.

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