DOI : 10.5958/2277-8934.2020.00023.5 Vol 27 No 2, p 159-163

BIOMARKERS OF INFECTION AND INFLAMMATION IN CAMELS (*Camelus dromedarius*)

Mohamed Tharwat[1,2]
[1]Department of Veterinary Medicine, College of Agriculture and Veterinary Medicine,
Qassim University, P.O. Box 6622, Buraidah, 51452, Saudi Arabia
[2]Department of Animal Medicine, Faculty of Veterinary Medicine, Zagazig University, Zagazig, Egypt

ABSTRACT

Inflammation and infection biomarkers or acute phase proteins (APPs) can be used in diagnosis, prognosis and in monitoring response to therapy, as well as in general health screening. It has also been suggested that APPs may be useful in the assessment of animal welfare. Acute phase reaction or response (APR) is a positive (increase) or negative (decrease) response of APPs to infection, inflammation, trauma or other causes and it might be a physiological protective mechanism during inflammatory events. The APPs have received attention as biomarkers for APR due to its low physiological levels, a fast incline, marked rise in concentration during APR that eases detection and a fast decline after cessation of a stimulus. In ruminants, the major APPs are haptoglobin (Hp) and serum amyloid A (SAA), and have been proposed as sensitive and rapid indicators of inflammatory disturbances. Hp is a major APP in numerous species of livestock and domesticated animals as well as in camels. Elevated Hp concentrations occur not only with inflammation, but also with some conditions not generally associated with inflammation or tissue damage. SAA is considered also as one of the major acute-phase reactants in vertebrates. Elevated serum SAA levels are found following inflammation and also under conditions unrelated to inflammation such as physical stress and parturition. In camels, it was found that chronic infections as well as non-inflammatory stressors following parasitic infections, at parturition, following stimulation by electroejaculation and following race stimulate APPs production. This review describes the commonly used biomarkers in camel medicine as indicators of infection and inflammation.

Key words: Acute phase proteins, biomarkers, camels, haptoglobin, serum amyloid A

Biomarkers of infection and inflammation or acute-phase proteins (APPs) are a class of proteins whose blood concentrations increase (positive APPs) or decrease (negative APPs) in response to infection, inflammation or trauma (Murata *et al,* 2004; Petersen *et al,* 2004; Ceron *et al,* 2005; Tharwat *et al,* 2014; Tharwat and Al-Sobayil, 2015; Tharwat and Al-Sobayil, 2015, 2018a,b). This response is called the acute-phase reaction or acute-phase response (APR). The APR is a rapid, nonspecific, systemic response occurring secondary to many types of tissue injury and might be a physiological protective mechanism during inflammatory events (Yazwinski *et al,* 2013). The origin of APR can be attributed to infection, inflammation, surgical trauma, or other causes (Petersen *et al,* 2004; Ceron *et al,* 2005), and the purpose of the response is to restore homeostasis and to remove its disturbance (Ebersole and Cappelli, 2000; Ceron *et al,* 2005). The APR is induced by the pro-inflammatory cytokines IL-1, TNF-α and especially IL-6 (Tizard, 2009). These cytokines activate receptors on various target cells and promote hormonal and metabolic changes leading to local and systemic effects, including APP synthesis in the liver (Petersen *et al,* 2004; Tizard, 2009).

In response to injury, local inflammatory cells (neutrophil granulocytes and macrophages) secrete a number of cytokines into the bloodstream. The liver responds by producing a large number of APPs (Petersen *et al,* 2004). The negative APPs include albumin, the most abundant constitutive plasma protein, and transferrin. The positive APPs include Haptoglobin (Hp), C-reactive protein, serum amyloid A (SAA), ceruloplasmin, fibrinogen and alpha 1-acid glycoprotein (Eckersall and Bell, 2010).

In domestic animals, a critical mass of knowledge on the use of APPs as biomarkers of inflammatory conditions has accumulated over recent years, so there is now sufficient understanding of the pathophysiology of the response to support the use of these compounds as diagnostic tools in clinical settings (Eckersall and Bell, 2010; Tharwat *et al,* 2014; Tharwat and Al-Sobayil, 2015; Tharwat and Al-Sobayil, 2018a,b). In ruminants, the APPs have

SEND REPRINT REQUEST TO MOHAMED THARWAT email: mohamedtharwat129@gmail.com

been proposed as sensitive and rapid indicators of inflammatory disturbances (Eckersall, 2000; Eckersall and Bell, 2010; Schneider *et al,* 2013).

In veterinary medicine, the APPs can be used in diagnosis, prognosis and in monitoring response to therapy, as well as in general health screening (Eckersall and Bell, 2010). In ruminants, the major APPs are Hp and SAA (Murata *et al,* 2004). In cattle, Hp and SAA are effective in the diagnosis and prognosis of mastitis, enteritis, peritonitis, pneumonia, endocarditis, and endometritis (Gronlund *et al,* 2003; Murata *et al,* 2004; Petersen *et al,* 2004). Elevations in this protein have also been reported in cows with fatty liver syndrome, at parturition, and during periods of starvation and transport stress (Uchida *et al,* 1993; Nakagawa *et al,* 1997; Katoh and Nakagawa, 1999). It has also been suggested that APPs may be useful in the assessment of animal welfare (Eckersall, 2000; Murata *et al,* 2004; Murata, 2007; Baghshani *et al,* 2010). Six-fold increases in Hp concentration were found in dairy cows with infectious and metabolic disease at slaughter compared to animals with minor lesions (Hirvonen *et al,* 1997), and 40-fold and 7-fold increases in HP and SAA, respectively were found in culled dairy cattle with acute lesions, relative to healthy beef-type animals (Tourlomousis *et al,* 2004).

Although not studied to the same extent, the APR in camels appear similar to that in cattle and chronic infections continue to stimulate APPs production (Tharwat and Al-Sobayil, 2015; Tharwat and Al-Sobayil, 2018a,b). The changes in APPs due to various inflammatory and non-inflammatory conditions have been studied intensively in many animal species (Murata *et al,* 2004; Murata, 2007). The APPs have received attention as biomarkers for APR due to its low physiological levels, a fast incline, marked rise in concentration during APR that eases detection and a fast decline after cessation of a stimulus (Ceron *et al,* 2005). This review describes the commonly used biomarkers in camel medicine as indicators of infection and inflammation; and to the best of the author's knowledge, this review is the first to discuss such title.

Application of inflammation biomarkers in camel medicine

Hp and SAA are the common used APPs in camel medicine. Haptoglobin is an α2-globulin synthesised in the liver (Eckersall and Bell, 2010) and is a major APP in numerous species of livestock and domesticated animals as well as in camels (Baghshani *et al,* 2010; Nazifi *et al,* 2012). Elevated Hp concentrations occur not only with inflammation, but also with some conditions not generally associated with inflammation or tissue damage (Murata *et al,* 2004; Baghshani *et al,* 2010). Another APP that is considered one of the major acute-phase reactants in vertebrates is SAA. Elevated serum SAA levels are found following inflammation and also under conditions unrelated to inflammation such as physical stress and parturition (Murata *et al,* 2004; Baghshani *et al,* 2010).

APR manifested by significant increases in Hp, SAA, fibrinogen and interleukins were reported in camels naturally infected with *Trypanosoma evansi* (El-Bahr and El-Deeb, 2016). From another study, it was also concluded that APPs could be used as diagnostic and prognostic biomarkers in camels with urinary tract infection (El-Deeb and Buczinski, 2015). Similarly, Hp and SAA were markedly elevated in camels naturally infected with *Toxoplasma gondii* (Azma *et al,* 2015). APR occurred in female

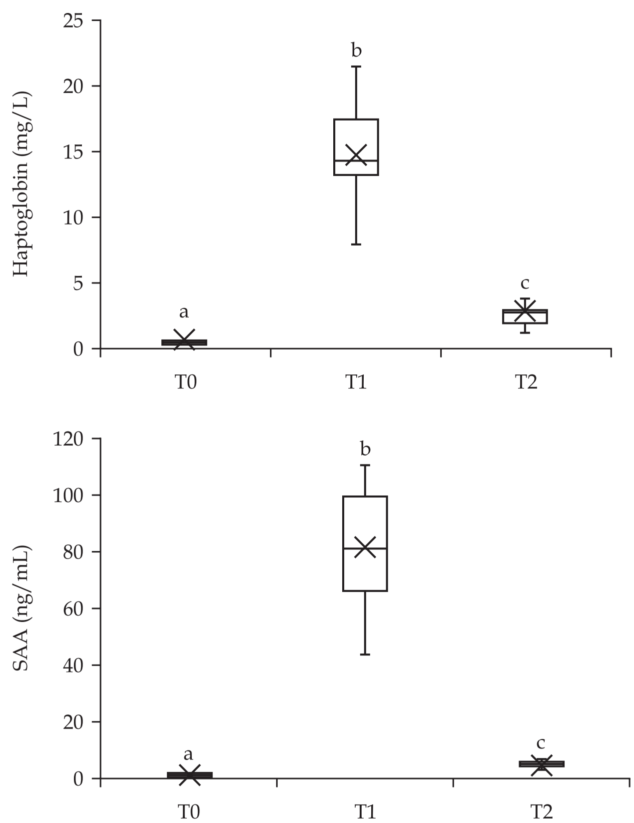

Fig 1. Box and whiskers plots of serum haptoglobin and serum amyloid A (SAA) in camels during the periparturient period. Box represents the 75^{th} and 25^{th} percentiles while whiskers extend to the 95^{th} and 5^{th} percentiles. T0, 3 wk before expected parturition; T1, within 12h of parturition; T2, 3 wk after parturition. Values with different letters differ significantly (P<0.5) (Tharwat and Al-Sobayil, 2015).

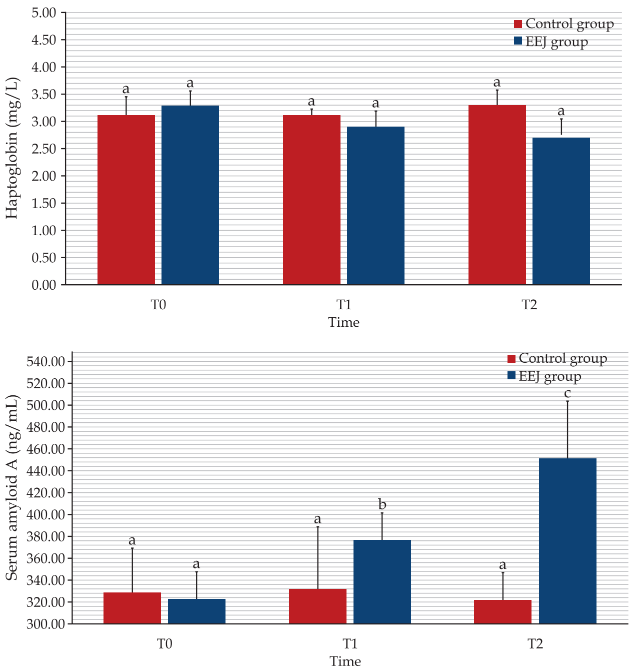

Fig 2. Effect of stimulation by electroejaculation (EEJ) on concentrations of haptoglobin and serum amyloid A in male dromedary camels (mean ± SD, n=20) compared to control group (n=10). T0: just before EEJ; T1: directly after EEJ; T2: 24h after EEJ. [a,b,c] Values differ significantly. (Tharwat and Al-Sobayil, 2018a).

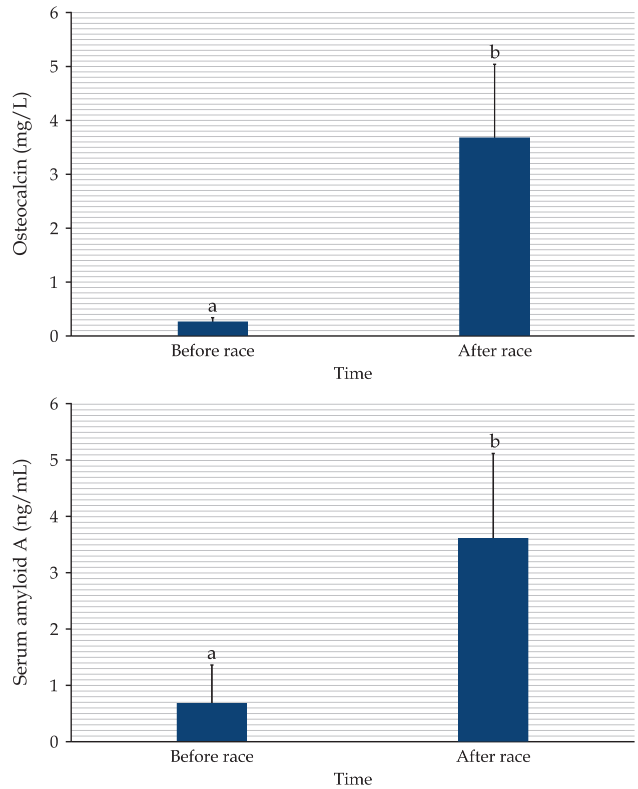

Fig 3. Mean serum concentrations of serum amyloid A in racing camels before and after a 5 km race. [a,b] Differ significantly at P< 0.05. (Tharwat and Al-Sobayil, 2018b).

dromedary camels at parturition that was manifested by significant increases in Hp and SAA as compared to values before or after parturition (Fig 1) (Tharwat and Al-Sobayil, 2015).

Generally, the APPs are secreted during the inflammatory response (Eckersall and Bell, 2010). However, in our recent study (Tharwat and Al-Sobayil, 2015), significant increases of Hp and SAA at parturition was found. These elevation detected at parturition were not attributed to pathological conditions, as the WBCs did not change significantly at that time, thus confirming the absence of pathological conditions. These elevations could be due to cortisol and hormone release and to stress resulting in numerous changes (Huzzey *et al,* 2011). Parturition, often considered as a physical stress, represents a variety of physical and psychological stimuli that alter homeostasis and metabolism (Trevisi *et al,* 2012). The mechanism behind the stress-induced APPs release at parturition is not known, but a hypothesis based on a neuroendocrine-immune network concept has recently been put forward, indicating that non-inflammatory and psychophysical stressors activate the combined action of the sympatho-adrenal axis and the hypothalamic–pituitary–adrenal axis. This would affect both the immunity-related cells and the release of glucocorticoids, and would ultimately lead to the production and release of APPs. Therefore the elevations in APPs or inflammation biomarkers clearly differentiate the physiological response to parturition versus the inflammation related to pathologies during the periparturient period.

APR manifested by significant increases of SAA has also been reported in camels subjected to electroejaculation (EEJ) (Fig 2) (Tharwat and Al-Sobayil, 2018a). It was not attributed to pathological conditions, as the WBCs did not change significantly, thus confirming the absence of pathological conditions. Therefore, these elevations, together with the cortisol increases, could be due to a physical "stress" resulting in the numerous changes (Huzzey *et al,* 2011; Bauer *et al,* 2012). EEJ, often considered as a physical stress, represents a variety of physical and psychological stimuli that alter homeostasis and metabolism (Tharwat and Al-Sobayil, 2018a).

As a result of stress, APR manifested by significant increases of Hp and SAA was also reported in camels after race (Fig 3) (Tharwat and Al-Sobayil, 2018b). In this study, the significant increases of Hp and SAA after racing cannot be associated with pathological conditions as WBCs did not change significantly after racing, thus confirming the absence of pathological conditions. Therefore, these elevations, together with the cortisol increase, could be due to a physical "stress" resulting in the numerous changes that occur during racing (Bauer *et al,* 2012). Exercise, often considered as a physical stress, represents a variety of physical and psychological stimuli that alter the homeostasis and metabolism of animal organisms (Mastorakos *et al,* 2005).

The mechanism behind the stress-induced SAA release after EEJ and race is not known, but a hypothesis based on a neuroendocrine-immune network concept has recently been reported (Murata, 2007). This indicates that the non-inflammatory and psychophysical stressors activate the combined action of the sympatho-adrenal axis and the hypothalamic–pituitary–adrenal axis. This would affect both the immunity-related cells and the release of glucocorticoids, and would ultimately lead to the production and release of APPs (Murata, 2007). In addition, glucocorticoids have been shown to induce or facilitate hepatic synthesis of APPs *in vitro* (Alsemgeest *et al,* 1995).

Conclusions

This mini review sheds light on the commonly used inflammation biomarkers or APPs (Hp and SAA) in camel medicine. These biomarkers are elevated in camels following non-inflammatory stressors as parasitic infections, at parturition, following stimulation by electroejaculation and following race stimulate APPs prsoduction. It is expected that APPs might be used in facilitating the diagnosis and prognosis of camel diseases.

References

Alsemgeest SPM, Lambooy IE, Wierenga HK, Dieleman SJ, Meerkerk B, van Ederen AM and Niewold, TA (1995). Influence of physical stress on the plasma concentrations of serum amyloid A (SAA) and haptoglobin (Hp) in calves. Veterinary Quaternary 17:9–12.

Azma F, Razavi SM, Nazifi S, Rakhshandehroo E and Sanati AR (2015). A study on the status of inflammatory systems in camels naturally infected with *Toxoplasma gondii*. Tropical Animal Health and Production 47:909-914.

Baghshani H, Nazifi S, Saeb M and Saeb S (2010). Influence of road transportation on plasma concentrations of acute phase proteins, including fibrinogen, haptoglobin, serum amyloid A, and ceruloplasmin, in dromedary camels (*Camelus dromedarius*). Comparative Clinical Pathology 19:193–198.

Bauer NB, Er E and Moritz A (2012). Effect of submaximal aerobic exercise on platelet function, platelet activation, and secondary and tertiary hemostasis in dogs. American Journal of Veterinary Research 73:125-133.

Ceron JJ, Eckersall PD and Martinez-Subiela S (2005). Acute phase proteins in dogs and cats; current knowledge and future perspectives. Veterinary Clinical Pathology 34:85-99.

Ebersole JL and Cappelli D (2000). Acute-phase reactants in infections and inflammatory diseases. Periodontology 23:19-49.

Eckersall PD and Bell R (2010). Acute phase proteins: biomarkers of infection and inflammation in veterinary medicine. Veterinary Journal 185:23-27.

Eckersall PD (2000). Acute phase proteins as markers of infection and inflammation: monitoring animal health, animal welfare and food safety. Irish Veterinary Journal 53:307-311.

El-Bahr SM and El-Deeb WM (2016). *Trypanosoma evansi* in naturally infected dromedary camels: lipid profile, oxidative stress parameters, acute phase proteins and proinflammatory cytokines. Parasitology 143:518-522.

El-Deeb WM and Buczinski S (2015). The diagnostic and prognostic importance of oxidative stress biomarkers and acute phase proteins in Urinary Tract Infection (UTI) in camels. PeerJ. 3:e1363.

Gronlund U, Hulten C, Eckersall PD, Hogarth C and Waller KP (2003). Haptoglobin and serum amyloid A in milk and serum during acute and chronic experimentally induced Staphylococcus aureus mastitis. Journal of Dairy Research 70:379-386.

Hirvonen J, Hietarkopi S, Saloniemi H (1997). Acute phase response in emergency slaughtered cows. Meat Science 3:249-257.

Huzzey JM, Nydam DV, Grant RJ and Overton TR (2011). Associations of prepartum plasma cortisol, haptoglobin, fecal cortisol metabolites, and nonesterified fatty acids with postpartum health status in Holstein dairy cows. Journal of Dairy Science 94:5878-5889.

Katoh N and Nakagawa H (1999). Detection of haptoglobin in the high-density lipoprotein and the very high-density lipoprotein fractions from sera of calves with experimental pneumonia and cows with naturally occurring fatty liver. Journal of Veterinary Medical Science 61:119-124.

Mastorakos G, Pavlatou M, Diamanti-Kandarakis E and Chrousos GP (2005). Exercise and the stress system. Hormones (Athens) 4:73-89.

Murata H, Shimada N, Yoshioka M (2004). Current research on acute phase proteins in veterinary diagnosis: an overview. Veterinary Journal 168:28-40.

Murata H (2007). Stress and acute phase protein response: an inconspicuous but essential linkage. Veterinary Journal 173:473-474.

Nakagawa H, Yamamoto O, Oikawa S, Higuchi H, Watanabe A and Katoh N (1997). Detection of serum haptoglobin by enzyme-linked immunosorbent assay in cows with fatty liver. Research in Veterinary Science 62:137-141.

Nazifi S, Oryan AM, Ansari-Lari M, Tabandeh MR, Mohammadalipour A and Gowharnia M (2012). Evaluation of sialic acids and their correlation with acute-phase proteins (haptoglobin and serum amyloid A) in clinically healthy Iranian camels (*Camelus dromedarius*). Comparative Clinical Pathology 21:383-387.

Petersen HH, Nielsen JP, Heegaard PMH (2004). Application of acute phase protein measurement in veterinary clinical chemistry. Veterinary Research. 35:163-187.

Schneider A, Corrêa MN, Butler WR (2013). Acute phase proteins in Holstein cows diagnosed with uterine infection. Research in Veterinary Science 95:269-271.

Tharwat M and Al-Sobayil F (2018a). Influence of electro-ejaculator on serum concentrations of acute phase proteins and bone metabolism biomarkers in male dromedary camels (*Camelus dromedarius*). Journal of Applied Animal Research 46:1226-1232.

Tharwat M and Al-Sobayil F (2018b). The impact of racing on serum concentrations of bone metabolism biomarkers in racing Arabian camels. Journal of Camel Practice and Research 25:59-63.

Tharwat M, Al-Sobayil F and Buczinski S (2014). Influence of racing on the serum concentrations of acute phase proteins and bone metabolism biomarkers in racing greyhounds. Veterinary Journal 202:372-377.

Tharwat M, and Al-Sobayil F (2015). Serum concentrations of acute phase proteins and bone biomarkers in female dromedary camels during the periparturient period. Journal of Camel Practice and Research 22:271-278.

Tizard IR (2009). Veterinary Immunology. An Introduction, 8th ed. Saunders Elsevier, St. Louis, Missouri.

Tourlomousis P, Eckersall PD, Waterston M and Buncic S (2004). A comparison of acute phase protein measurements and meat inspection findings in cattle. Foodborne Pathogens and Disease 1:281-290.

Trevisi E, Amadori M, Cogrossi S, Razzuoli E and Bertoni G (2012). Metabolic stress and inflammatory response in high-yielding, periparturient dairy cows. Research in Veterinary Science 93:695-704.

Uchida E, Katoh N and Takahashi K (1993). Appearance of haptoglobin in serum from cows at parturition. Journal of Veterinary Medical Science 55:893-894.

Yazwinsk M, Milizio JG and Wakshlag JJ (2013). Assessment of serum myokines and markers of inflammation associated with exercise in endurance racing sled dogs. Journal of Veterinary Internal Medicine 27:371-376.