ORIGINAL ARTICLE

https://doi.org/10.21708/avb.2023.17.3.11128

Plasma fibrinogen and C-reactive protein in dogs

Fibrinogênio plasmático e proteína C-reativa em cães

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ABSTRACT: Complementary tests are essential for defining the diagnosis, prognosis, and treatment of diseases in animals. White blood count is the most common laboratory method for identifying and evaluating inflammatory processes in small animals. Therefore, this study aimed to evaluate plasma fibrinogen and C-reactive protein as supplementary tools for diagnosing inflammatory processes in dogs, correlating them with the results of the white blood count and the clinical condition of the animal. The sample size was calculated considering the estimated population of dogs living in the rural area of Curuçá, PA, Brazil. The sample included randomly selected healthy and unhealthy dogs. The animals underwent a clinical examination and complete blood count, fibrinogen, and C-reactive protein tests. Of a total of 149 animals, 17.4% (26/149) had hyperfibrinogenemia, 39.6% (59/149) were C-reactive protein positive, and 48.3% (72/149) had leukocytosis. Of the cases of leukocytosis, 63.8% (46/72) were due to neutrophilia. The analysis of the plasma protein: fibrinogen ratio in animals with hyperfibrinogenemia showed that the increased results were related to inflammatory processes in 84.6% (22/26) of these dogs. The results showed that fibrinogen and C-reactive protein are promising tools to identify inflammatory processes in dogs even before the presence of clinical signs; therefore, they are considered supplementary routine care methods to detect recent inflammatory processes not yet identified in the white blood count.

KEYWORDS: Acute phase protein, Hyperfibrinogenemia, Inflammatory response.

RESUMO: Os exames complementares são de suma importância para auxílio no diagnóstico, prognóstico e tratamento adequado dos animais. Em geral, na clínica de pequenos animais, o meio laboratorial mais utilizado para a identificação e avaliação de processos inflamatórios é o leucograma. Por isso, o objetivo do presente trabalho foi avaliar o fibrinogênio plasmático e a proteína C-reativa como ferramentas suplementares no diagnóstico de processos inflamatórios em cães, correlacionando-os ao leucograma e *status* clínico do animal. Para isso, após o cálculo de tamanho da amostra, considerando a população estimada de cães residentes na zona rural do município de Curuçá-PA, foram avaliados cães sadios e não sadios selecionados aleatoriamente. Realizou-se o exame clínico e coleta de sangue para o hemograma, fibrinogênio e proteína C-reativa. Do total de 149 animais, identificou-se que 17,4% (26/149) apresentaram hiperfibrinogenemia, 39,6% (59/149) reação positiva no teste de proteína C-reativa e 48,3% (72/149) leucocitose, sendo que em 63,8% (46/72) dos animais, a leucocitose era por neutrofilia. Quando avaliada a relação proteína plasmática:fibrinogênio dos animais com hiperfibrinogenemia, constatou-se que dos 26 cães, em 84,6% (22/26) o aumento estava relacionado a processos inflamatórios. Os resultados demonstram que o fibrinogênio e a proteína C-reativa são promissores para identificação de processo inflamatório em cães, antes mesmo da apresentação de sinais clínicos, portanto, podem ser considerados métodos suplementares na rotina de atendimentos, com o objetivo de detectar processos inflamatórios recentes e que ainda não foram identificados no leucograma.

PALAVRAS-CHAVE: Proteína de fase aguda, Hiperfibrinogenemia, Resposta inflamatória.

INTRODUCTION

The emotional bond between humans and companion animals has intensified in recent decades, resulting in exponentially increasing concerns about the health of these animals and increasing need and demand for veterinary care. Queiroz et al. (2016) state that the search for an early diagnosis directly influences treatment time, improving prognosis, and quality of life.

The laboratory test most requested in the clinical routine of dogs is the complete blood count (CBC) (BELLO et al., 2018), with the white blood cell count (WBC) used

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Received: 08/03/2023. Accepted: 28/08/2023

to identify inflammatory processes. Furthermore, some acute phase plasma proteins have been used for early identification of inflammatory processes to increase the chances of cure and regression of disease signs through specific and early treatments (QUEIROZ et al., 2016).

Plasma fibrinogen (FIB) and C-reactive protein (CRP) tests are rarely used in canine internal medicine, despite some authors showing their importance in the early diagnosis, prognosis, and follow-up of several subclinical diseases, e.g., uterine infections, enteropathies, and dermopathies (CÂMPELO et al., 2011; MEINERZ et al., 2012; VECINA; PATRÍCIO; CIARLINI, 2006). Therefore, this study aimed to evaluate plasma fibrinogen and CRP as additional tools to diagnose inflammatory processes in dogs, correlating them with the results of WBC and the clinical condition of the animal.

MATERIAL AND METHODS

The study was approved by the Animal Research Ethics Committee of the Federal University of Pará, under the number 6363180918.

The study was carried out in the rural area of Curuçá, PA, Brazil, located northwest of the Brazilian Amazon region, close to Belém, the capital city. To calculate the sample size, the canine population was estimated as 20% of the human population, in accordance with resolution no. 05/2013 of the Ministry of Health. Considering the size of the rural human population in the 2010 census (N = 22,154), the rural canine population was estimated at 4,431 animals. Statcalc tool from EpiInfo™ software v. 7.2.3.1 was used to calculate the sample with an expected frequency of 50%, acceptable error of 8%, and confidence level of 95%, reaching a minimum sample of 145 animals.

The dogs were selected using the random sampling method, in which the households were spatially drawn using the QGis 3.2.2 software. The MapIt Gis application was used to locate the drawn points geographically.

Tutors who accepted to participate signed an informed consent form and answered a semistructured questionnaire identifying the animals and their clinical complaints, morbid history, body condition score (BCS) according to Laflamme (1997), deworming, vaccination, estrous cycle, and castration. We preferably analyzed one animal per household. However, when requested by the owner, more than one animal was included, which led to a total of 149 dogs in the study.

Next, each animal was subjected to a general physical examination, according to Feitosa (2014), and the data were recorded in an individual clinical record.

The animals were free-roaming dogs, most of which were considered healthy by their tutors. The exclusion criteria were animals aged <6 months, pregnant, or who were medicated or vaccinated within a period of 10 days.

Blood samples were taken from the jugular and/or cephalic veins using a 5 ml disposable syringe and a 25 × 7 mm needle. Blood was stored in a tube with an anticoagulant (ethylenediaminetetraacetic acid, EDTA) for CBC and FIB and without an anticoagulant for CRP analysis. The samples were refrigerated at a temperature of 6–8°C for up to 3 h and sent to the Clinical Pathology Laboratory of the Veterinary Hospital of the Federal University of Pará.

CBC, FIB, and serum separation were performed within 24 h after collection, except for the blood smear prepared immediately after collection. After blood centrifugation, serum was aliquoted in 2 ml microtubes and frozen at -20°C for 7 days, with the serum thawed once for CRP testing.

CBC was performed on an automated counter for veterinary use (BC-2800, Mindray) to obtain red blood cell count, hemoglobin (Hb) level, mean corpuscular volume, mean corpuscular hemoglobin concentration, platelet count, and total WBC count. Hematocrit was analyzed according to Harvey (2012) and differential WBC was analyzed using a blood smear stained with a Rapid Panoptic Kit (two slides/animal) and an optical microscope (Olympus BX40). FIB was determined using the heat precipitation method following the recommendations of Jain (1993).

Serum CRP was analyzed using qualitative and semiquantitative methods, using a commercial latex agglutination kit and following the manufacturer's instructions (Labtest Diagnóstica S.A). The results were interpreted using the value set by the manufacturer as normal (0.5–1 mg/dl). The other reference ranges were based on the following authors: Kaneko; Harvey; Bruss (2008) for fibrinogen and Schalm (2000) for WBC.

Plasma protein: fibrinogen (PP: FIB) ratio was established using the PP-FIB/FIB formula to identify whether hyperfibrinogenemia was due to an inflammatory process or dehydration. Based on the data obtained, values >15 represented dehydration, and values <15 represented an inflammatory process (SUTTON; JOHNSTONE, 1977).

Clinical data were analyzed based on frequency distribution and their respective percentages. The Kappa test evaluates the agreement between laboratory methods, calculated using the Bioestat 5.3 software, at a significance level $\alpha = 5\%$. The Kappa value was interpreted by comparing the results with the estimates proposed by Landis; Koch (1977).

RESULTS AND DISCUSSION

Of the dogs evaluated, 53% (79/149) corresponded to males and 47% (70/149) to females, aged 1–19 years, most (75%) between 1–4 years, of an undefined breed (96.6%, 144/149). Caldin et al. (2009) reported no evidence that age and sex influence acute phase protein (AFP) levels.

None of the experimental animals were castrated. According to the tutors, anti-progestin medications were frequently used in females; however, they were unable to say how many times. A study by Squassoni et al. (2011) showed no significant differences in CRP values between the groups of dogs in diestrus, pregnant, or with pyometra, in contrast to

Carvalho et al. (2008), who reported higher mean CRP and FIB values in animals with pyometra than in healthy dogs. These variations may be related to the peak concentration of these proteins, which varies depending on the severity of the disease or the gestational hormonal phase.

Of the animals studied, 24% (36/149) could access the street, have contact with animals from the same household, other households, or live on the street. According to Brasil (2016), factors like these increase the spread of infectious and parasitic diseases among dogs, especially in stray or free-roaming animals.

The BCS of the animals ranged from 3 to 7, and 24.2% (36/149) of the animals had a BCS of 3 (thin) associated with clinical signs such as hypophagia, enlarged lymph nodes, pruritus, and alopecia. Therefore, it was not possible to identify whether BCS influenced the AFP results. Some studies showed that although the BCS, WBC, and FIB values differed significantly between the groups (CARNEIRO et al., 2013), they remained within the reference range proposed by Jain (1993). In a study by Mareze et al. (2016) that included obese dogs, CRP was not considered a significant component in the control and obese groups.

Clinical and laboratory changes were observed in 43.6% (65/149) of the animals (Table 1). The least frequent clinical signs were hyperkeratosis, scaling, oily skin, hyperpigmentation, small breast nodules (up to 2 cm), flank wound, vulvar mass, and muscle tremors.

The clinical-laboratory evaluation of animals with changes showed that 21.5% (14/65) of the dogs had clinical changes, 3% (2/65) had hyperfibrinogenemia, 9.2% (6/65) were CRP positive, and 13.8% (9/65) had WBC changes, characterized by leukocytosis with lymphocytosis and/or neutrophilia with or without left shift.

Laboratory analysis of healthy and unhealthy animals showed that 17.4% (26/149) had hyperfibrinogenemia, 39.6% (59/149) were CRP positive, and 48.3% (72/149) had leukocytosis (64% (46/72) due to neutrophilia, 33.3% (24/72) due to lymphocytosis, and 2.7% (2/72) due to eosinophilia). Of the animals with leukocytosis due to neutrophilia, 67.3% (31/46) had leukocytosis with a left shift. Junqueira and Carneiro (2004) reported that neutrophils are the most important cells of the leukocyte lineage in the pathogenesis of inflammation, predominant in the first 6–24 h of acute inflammation, which varies according to cause, intensity, inflammation site, species, and age.

In the present study, most of the animals were healthy and/or asymptomatic. Other authors studied FIB and CRP levels in unhealthy animals (TORRENTE et al., 2015; WATT; HORGAN; MICHILLAN, 2015). A study by Torrente et al. (2015) with dogs with systemic inflammatory response syndrome considered CRP analysis significantly relevant to detect the inflammatory response, with no normal values before the clinical condition of the animals improved, and reported that FIB levels were not affected by the severity of the disease, presenting a higher concentration, but remaining constant even with worsening of the patient's clinical condition. Similarly, the study by Watt; Horgan; Michillan (2015) that compared inflammation markers, such as body temperature, WBC, and CRP levels, concluded that CRP is the most sensitive method and a reliable marker of systemic inflammation. The correlation between severity progression and AFP levels was not the objective of the present study, which was carried out in a single moment. However, increased laboratory results in apparently healthy animals show the possibility of early disease before visible clinical signs.

In humans, serum CRP levels can increase 100–1,000 times within 24–48 h after inflammatory irritation (CÉRON; ECKERSALL; MARTINEZ SUBIELA, 2005). Of the dogs evaluated, 39.5% showed increased CRP levels (59/149); however, only 22% showed clinical signs. A significant percentage of dogs did not present clinical signs related to the evaluated proteins (FIB and CRP), highlighting their importance in the identification of subclinical inflammatory processes. Table 2 shows the means and standard deviations of FIB and CRP in healthy and unhealthy dogsIn the present study, dogs with hyperfibrinogenemia had almost twice the upper limit of the reference range and CRP levels were up to six times higher than normal, which may justify an acute inflammatory process

Table 1. Main clinical-laboratory changes in dogs from Curuçá, PA, in the northwest Brazilian Amazon region.

Clinical changes	N	LEUK.	HYPERFIB.	CRP
Hypophagia	2	2	w/c	w/c
Hypophagia and thinness	3	w/c	w/c	3
Alopecia, pruritus, pale mucous membranes, and enlarged lymph nodes	2	2	2	w/c
Apathy and pale mucous membranes	3	2	w/c	w/c
Thinness, pruritus, and alopecia	26	8	w/c	6
Enlarged lymph nodes	5	2	w/c	w/c
Total	41	16	2	9

*LEUK, leukocytosis due to neutrophilia with left shift; HYPERFIB, hyperfibrinogenemia; CRP+, C-reactive protein reagent; N, number of animals; w/c, without changes.

Table 2. FIB and CRP mean and standard deviation (x ± s) in dogs without clinical signs (G1) and with clinical signs (G2) from Curuçá, PA, in the northwest Brazilian Amazon region.

Protein (mg/dl)	G1	G2	Reference range (mg/dl)
Fibrinogen	620 ± 61.55	700 ± 109.54	200–400[1]
C-reactive protein	6.10 ± 2.56	3.13 ± 1.66	0.5–1[2]

Source: [1]Kaneko; Harvey; Bruss, 2008; [2]Labtest

before the onset of clinical signs. Carvalho et al. (2008) studied female dogs diagnosed with pyometra and reported that FIB levels increased up to three times the reference range in animals with hyperfibrinogenemia. Anziliero et al. (2013) analyzed CRP results in dogs with hematologic changes. The group experimentally inoculated with *M. luteus* showed peak levels, reaching 11 mg/dl in the first 48 h, which decreased rapidly in the subsequent days.

In the present study, the PP: FIB ratio was also evaluated in animals with hyperfibrinogenemia, and of the 26 dogs, 84.6% (22/26) presented this increase related to inflammatory processes, i.e., with a value <15; meanwhile, the other 15.4% (4/26) presented values >15, which are related to dehydration, according to Sutton; Johnstone (1977).

Of the animals with hyperfibrinogenemia associated with an inflammatory process (22/26), 54.5% also had leukocytosis due to neutrophilia (12/22), seven of them with a shift to the left, and five had an increase in other cell types (lymphocytes or eosinophils). Clinical changes were observed in 18% (4/22) of these animals, such as poor nutritional status, pale mucous membranes, enlarged lymph nodes, dehydration, capillary refill time of 3 s, presence of ectoparasites, alopecia, pruritus, or mammary neoplasia. Regarding animals with hyperfibrinogenemia due to dehydration (4/26), 50% had some clinical changes such as poor nutritional status, presence of ectoparasites, alopecia, or pruritus. Vecina; Patrício; Ciarlini (2006) reported that most dogs with WBC showing inflammation presented hyperfibrinogenemia associated with an inflammatory process; however, they did not analyze the clinical aspects of the patients. This highlights the importance of correlating laboratory and clinical findings for better interpretation of the results.

A study on experimental *Staphylococcus aureus* infection in dogs reported significantly increased FIB levels compared to baseline, which increased significantly between 6 h and 14 days after bacterial inoculation (ZAPRYANOVA; MIRCHEVA; DENEVI, 2013). Although it was not possible to follow up on the animals evaluated in the present study, 26 dogs presented hyperfibrinogenemia, with 84.6% of these cases possibly related to an inflammatory process, since an increase due to dehydration was ruled out based on the PP: FIB ratio.

Vecina; Patrício; Ciarlini (2006) observed hyperfibrinogenemia in 45.9% of dogs with normal WBC and 44.8% of these animals had PP: FIB ratio that showed an inflammatory process. They also stated that the identification of inflammation in a significant number of cases was only possible by determining FIB levels and that in dogs, hyperfibrinogenemia of inflammatory origin persists only for 24–72 h. These data show the importance of analyzing fibrinogen in the first days of the disease course, consistent with the present study, in which 35 animals had only hyperfibrinogenemia, which could indicate an acute inflammatory change presented before other parameters, including WBC, the main indicator used to evaluate inflammatory responses in the clinical routine.

The Kappa test did not show agreement between FIB and CRP (Kappa = -0.1955, p = 0.0027), FIB and leukocytosis (Kappa = 0.0120, p = 0.4253), or CRP and leukocytosis (Kappa = -0.0949, p = 0.1197), showing that despite the laboratory changes identified, the results of such tests did not agree with one another. Meanwhile, Anziliero et al. (2013) evaluated serum CRP levels in dogs with leukocyte changes and healthy dogs and tested their agreement, reporting a moderate Kappa value and showing that the latex agglutination method could be used as an alternative to monitor the inflammatory process and guide therapeutic procedures.

The present study does not intend to indicate the replacement of WBC, the laboratory method most commonly used in clinical routine to identify inflammatory processes in dogs, but rather to indicate that FIB and CRP levels can be alternative methods in the initial monitoring of inflammatory processes. Therefore, they would also be important screening tests at check-ups and/or elective surgeries, as the results obtained showed that asymptomatic animals can have hyperfibrinogenemia and increased CRP levels and should have their condition monitored by the veterinarian.

CONCLUSION

Plasma FIB and CRP were important indicators of an inflammatory reaction when evaluated separately. However, when the results were statistically treated, there was no agreement between the three parameters evaluated (FIB, CRP, and WBC), which may have been influenced by the stage of the inflammatory condition.

The results show that FIB and CRP are promising tools for identifying inflammatory processes in dogs, even before the onset of clinical signs; therefore, they are considered supplementary methods that should be included in the routine care of dogs for the early detection of inflammatory processes that have not yet affected WBC.

ACKNOWLEGMENTS

The authors thank the Coordination for the Improvement of Higher Education Personnel (CAPES) for granting a master's scholarship to Mário José Costa Carneiro and the Institute of Veterinary Medicine of the Federal University of Pará for providing the infrastructure to conduct the research. The authors also thank the PROPESP/UFPA (PAPQ) for their support in translating the article.

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