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Serum cortisol and insulin concentrations in dogs naturally infected with *Babesia canis*

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ABSTRACT

Babesiosis is an emerging tick-transmitted infectious disease of vertebrates that occurs worldwide. In Europe the predominant cause of canine babesiosis is *Babesia canis*. The disease can be clinically classified into uncomplicated and complicated forms. Both uncomplicated and complicated babesiosis due to *Babesia canis* appear to be the result of host inflammatory responses. The main aim of this study was to investigate the endocrine anti-inflammatory response in dogs naturally infected with *Babesia canis*. It was demonstrated that a marked endocrine response occurs in dogs naturally infected with *Babesia canis*, with significant increases in the concentration of cortisol and insulin. Statistically significant differences were found between the studied groups for all variables (cortisol, insulin and glucose) before the antibabesial treatment. The day after treatment a statistically significant difference was found between healthy dogs and the dogs that survived, as well as the dogs that died, for cortisol and glucose, but not for insulin. In all of the studied dog groups the median value of glucose was within the reference range, but one animal within the group of dogs that survived was hypoglycemic before the antibabesial treatment. After the antibabesial treatment all the studied animals had glucose values within the reference range. A statistically significant positive correlation was found between cortisol and insulin. The results of this study showed that concentrations of cortisol and insulin can be used to predict mortality in canine babesiosis caused by *B. canis*.

Key words: endocrine response, compensatory anti-inflammatory response syndrome, dogs, babesiosis, insulin, cortisol

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Introduction

Babesiosis is an emerging tick-transmitted infectious disease of vertebrates that occurs worldwide. For a long time it was considered that canine babesiosis is caused by two species of babesia, classified either as large (*Babesia canis*) or small (*Babesia gibsoni*) babesia. The large *Babesia canis* was divided into three different species, namely, *Babesia canis* (*B. canis*), *Babesia rossi* (*B. rossi*) and *Babesia vogeli* (*B. vogeli*) (UILENBERG et al., 1989; SCHETTERS, 2005). Recently, a new large babesia species, *Babesia* sp. (Coco) was discovered (BIRKENHEUER et al., 2004; LEHTINEN et al., 2008). In the last two decades, several additional small babesia species have been detected in dogs: *Babesia conradae* (*B. conradae*), *Babesia microti*-like species provisionally classified as *Theileria annae* (*T. annae*), and *Theileria equi* (*T. equi*) (ZÄHLER et al., 2000; CAMACHO et al., 2001; CRIADO-FORNELIO et al., 2003; KJEMTRUP et al., 2006; BECK et al., 2009).

In Europe the predominant cause of canine babesiosis is *B. canis* (BECK et al., 2009; BRKLJAČIĆ et al., 2010).

Canine babesiosis caused by *B. canis* is a very common cause of morbidity and mortality of dogs in Croatia, especially in the area of the City of Zagreb (CACCIÒ et al., 2002; BRKLJAČIĆ et al., 2010).

The disease can be clinically classified into uncomplicated and complicated forms. For some time uncomplicated babesiosis has been suggested to be a consequence of haemolysis (JACOBSON and CLARK, 1994) while complicated canine babesiosis has been suggested to be a consequence of the development of systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS), both of which are cytokine-mediated phenomena (JACOBSON and CLARK, 1994; WELZL et al., 2001). Recent publications show that both uncomplicated and complicated babesiosis due to *B. canis* appear to be the result of host inflammatory responses (MATIJATKO et al., 2007; SCHETTERS et al., 2009). It is clinically important to understand that the pro-inflammatory state of the acute phase response (SIRS) also initiates anti-inflammatory mediators (compensatory anti-inflammatory response syndrome - CARS) (MATIJATKO et al., 2012).

The initial metabolic response to sepsis is closely regulated by specific endocrine changes, which inactivate anabolic pathways and increase anterior pituitary activity (KARGA et al., 2000; VAN DEN BERGHE, 2000). The early events in inflammatory response also induce the production of cortisol and insulin potent anti-inflammatory mediators (VAN DEN BERGHE, 2000).

The anti-inflammatory effects of insulin are twofold: it suppresses pro-inflammatory mediator action, and decreases glucose concentration thus decreasing the pro-inflammatory effects of glucose (DAS, 2002; GUZIK et al., 2002).

It has been proven that some cytokines, namely IL-1, IL-6, and TNF- α , are responsible for cortisol release into the circulation, for example in human malaria as well as in other models of nonspecific immune system activation (DAVIS et al., 1997).

Little is known about the specific endocrine perturbations in canine babesiosis (REES and SCHOEMAN, 2008), especially in the cases of canine babesiosis caused by *B. canis*. In recent studies of canine babesiosis caused by *B. rossi* negative outcome factors have been discovered. Namely, dogs with the highest degree of parasitaemia, as well as dogs with high concentrations of cortisol and low concentrations of thyroxin had unfavourable prognosis (SCHOEMAN et al., 2007). Also, differences in the basal cortisol concentrations between the survivor and non-survivor dogs infected with *B. rossi* have been identified, but not between the healthy dogs and infected dogs that survived (SCHOEMAN and HERRTAGE, 2008). Furthermore, studies of canine babesiosis caused by *B. rossi* have demonstrated that the insulin concentrations in sick dogs are mostly low, and that as such they can be regarded as a normal finding in anorexic animals invaded with the aforementioned piroplasm (REES and SCHOEMAN, 2008).

The principal limitation of the aforementioned studies is that the research was carried out on different samples (patients) so interpretation of their interaction and correlation is not possible. The final limitation is that this study was carried out on dogs with canine babesiosis caused by *B. rossi*, which is considered to be a different disease from babesiosis caused by *B. canis*. Therefore the aim of this study was to investigate endocrine anti-inflammatory response in dogs naturally infected with *B. canis*.

Materials and methods

Animals. The study was performed on three groups of animals: a group of healthy animals (group 0), a group of dogs naturally infected with *B. canis* that survived (group 1), and a group of dogs naturally infected with *B. canis* that died (group 2).

Group 0 consisted of 30 healthy dogs, which had no signs of any disease. Imidocarb dipropionate was administered in the same dose to all of them as a preventive measure against babesiosis at the request of their owners.

Group 1 consisted of 26 dogs naturally infected with *B. canis*, admitted to the Clinic for Internal Diseases, Faculty of Veterinary Medicine, University of Zagreb, Croatia, with clinical signs of acute babesiosis. The diagnosis was confirmed by demonstration of the parasites within the infected erythrocytes in Romanowsky-stained thin blood smears. All the infected dogs were included in a larger study by BECK et al., (2009), in which the babesia were characterized by the polymerase chain reaction method (PCR). All the dogs included in this study were infected by *B. canis*. A single dose (6 mg/kg of body weight) of imidocarb dipropionate (Imizol® 12%, Schering-Plough) was administered to all the dogs, with confirmed babesiosis, subcutaneously, on the day of admission.

Group 3 consisted of 4 dogs naturally infected with *B. canis* that died despite the antibabesial and supportive treatment.

Samples. The blood samples for analysis were collected from the cephalic vein on the day of admission, and the day after the administration of imidocarb dipropionate. The samples were placed in tubes with EDTA for haematological analysis and tubes with no anticoagulant, which were centrifuged at 1,200 g for biochemical analysis.

Haematological and biochemical analysis. White blood cell count (WBC), platelet count and haematocrit (HCT) were determined using an automatic haematology analyser (Horiba ABX; Diagnostics, Montpellier) while serum creatinine, alanine aminotransferase (ALT), alkaline phosphatase (AP), creatine phosphokinase (CPK), glucose and serum bilirubin were determined using biochemical autoanalyser Olympus AU 600 (Olympus Diagnostica, Hamburg). Analyses were performed using standard methods and the original reagents from the manufacturer (Olympus Diagnostica, Hamburg).

Cortisol and insulin determination. Cortisol concentration was determined by the radioimmunoassay method, on a gamma-scintillation counter (CompuGamma 1282 LKB, Finland) using the diagnostic kit RIA CORTISOL (CT).

Insulin concentration was determined by non-competitive chemiluminescence immunoanalysis, using the analytical system ADVIA Centaur XP (Siemens Healthcare Diagnostics Inc.).

Statistical analysis. Descriptive statistics were drawn up according to the usual statistical methods and normality was tested by the means of the Kolmogorov-Smirnov test. No distributions were normal so we used the Sign test to test differences between the same animals on two consequent days and the Kruskal-Wallis test to test differences within the same variable but between different groups, according to the severity of disease (healthy - 0, sick survived - 1 and sick died - 2). Correlations between parameters were tested by means of the Pearson correlations test. Values for all the tests were considered statistically significant for $P < 0.05$.

Results

Thirty cases fulfilled the selection criteria for acute canine babesiosis and were included in the study. Twenty-six dogs with babesiosis showed improvement in their clinical symptoms within twenty-four hours after antibabesial treatment (group 1), while four dogs developed MODS and, despite the treatment and intensive care, died within seven days (group 2).

We found statistically significant ($P < 0.05$) differences between the studied groups for all variables (cortisol, insulin and glucose) before the antibabesial treatment (Fig. 1, 3 and 5). The day after the treatment a statistically significant difference was found between healthy dogs and dogs that survived, as well as dogs that died, for cortisol and glucose, but not for insulin (Fig. 2, 4 and 6).

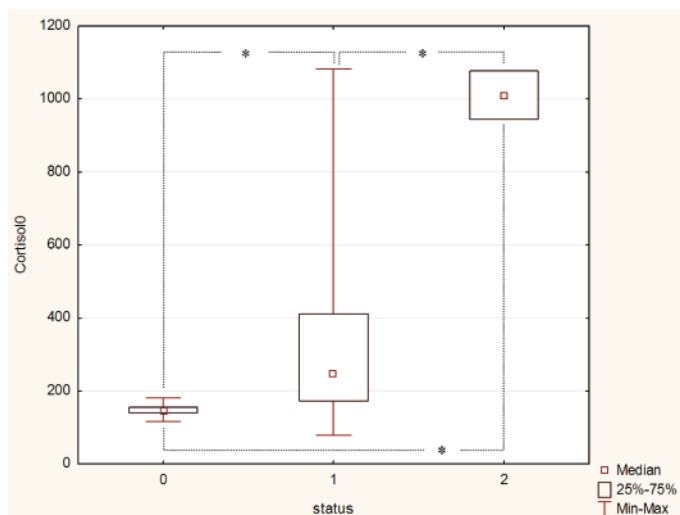


Fig. 1. Cortisol on day 0 according to disease severity groups. * Indicates a significant difference ($P < 0.05$) between group of healthy dogs (0), dogs that survived babesiosis (1) and dogs that died from babesiosis (2) by Kruskal-Wallis test. The plots show the median (square within box), 25th and 75th percentiles (box), minimum and maximum values (whiskers).

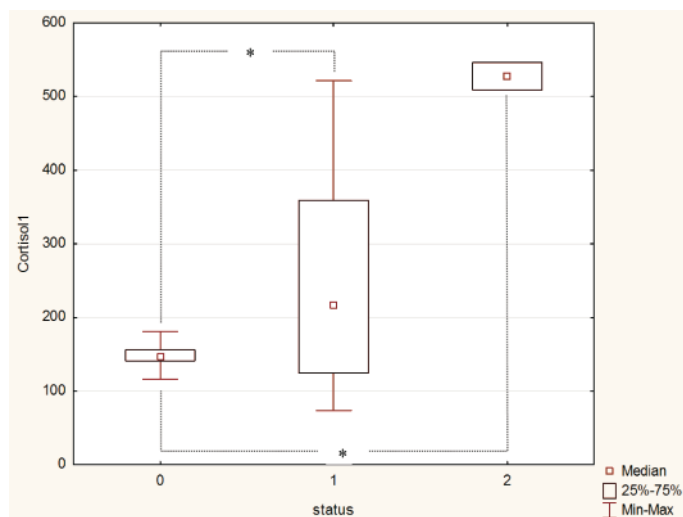


Fig. 2. Cortisol on day 1 according to disease severity groups. * Indicates a significant difference ($P < 0.05$) between group of healthy dogs (0), dogs that survived babesiosis (1) and dogs that died from babesiosis (2) by Kruskal-Wallis test. The plots show the median (square within box), 25th and 75th percentiles (box), minimum and maximum values (whiskers).

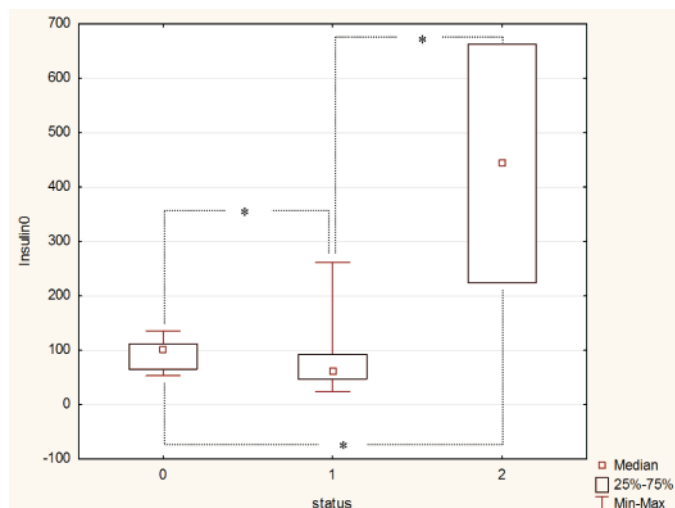


Fig. 3. Insulin on day 0 according to disease severity groups. * Indicates a significant difference ($P<0,05$) between group of healthy dogs (0), dogs that survived babesiosis (1) and dogs that died from babesiosis (2) by Kruskal-Wallis test. The plots show the median (square within box), 25th and 75th percentiles (box), minimum and maximum values (whiskers).

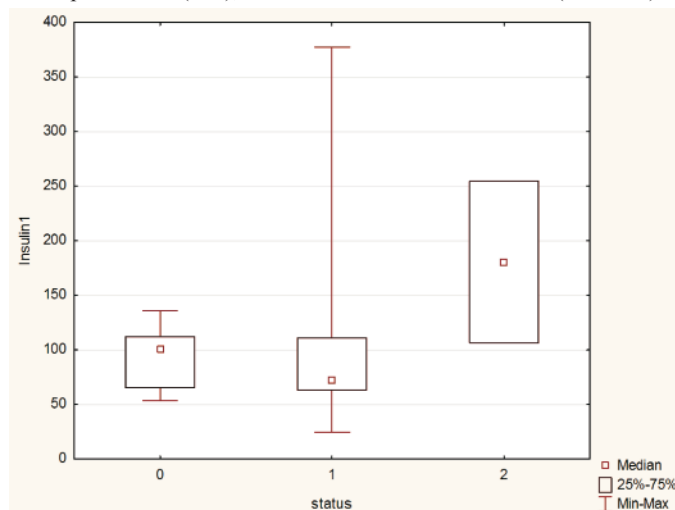


Fig. 4. Insulin on day 1 according to disease severity groups. * Indicates a significant difference ($P<0.05$) between group of healthy dogs (0), dogs that survived babesiosis (1) and dogs that died from babesiosis (2) by Kruskal-Wallis test. The plots show the median (square within box), 25th and 75th percentiles (box), minimum and maximum values (whiskers).

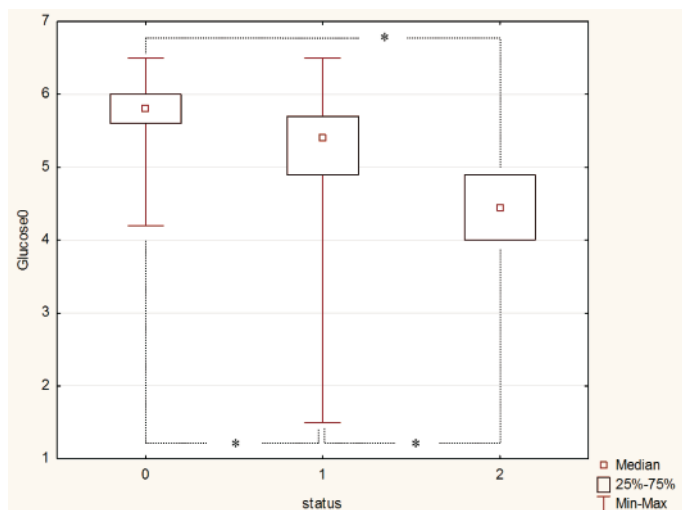


Fig. 5. Glucose on day 0 according to disease severity groups. * Indicates a significant difference ($P<0.05$) between group of healthy dogs (0), dogs that survived babesiosis (1) and dogs that died from babesiosis (2) by Kruskal-Wallis test. The plots show the median (square within box), 25th and 75th percentiles (box), minimum and maximum values (whiskers).

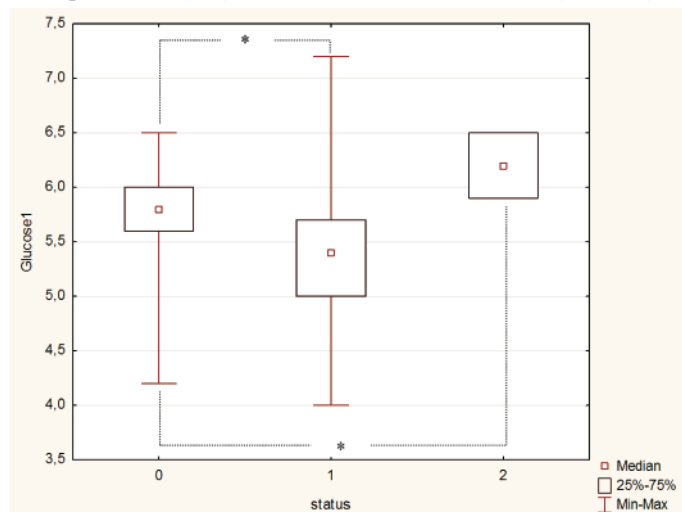


Fig. 6. Glucose on day 1 according to disease severity groups. * Indicates a significant difference ($P<0.05$) between group of healthy dogs (0), dogs that survived babesiosis (1) and dogs that died from babesiosis (2) by Kruskal-Wallis test. The plots show the median (square within box), 25th and 75th percentiles (box), minimum and maximum values (whiskers).

All the dogs that died (group 2) had extremely high values of cortisol in comparison to the reference values (20-250 nmol/L) (MOONEY and PETERSON, 2004), before the antibabesial treatment, while dogs that survived babesiosis (group 1) had a median value of cortisol concentration within the reference range, with the upper value of almost 1100 nmol/L (Fig. 1). After antibabesial treatment the cortisol value decreased by half in both groups of dogs with babesiosis (Fig. 2). In healthy dogs cortisol values were within the reference range before and after application of the antibabesial drug (Fig. 1 and 2).

Before the antibabesial treatment all the dogs that died had insulin values above the reference range (35-140 pmol/L) (MOONEY and PETERSON, 2004) while the dogs that survived had median values within the reference range, with the value in some dogs above the reference range (Fig. 3). After the antibabesial treatment, the median values of insulin decreased significantly in the group of dogs that died, while in the group of dogs that survived they stayed the same (Fig. 4). All the healthy dogs had insulin values within the reference range before and after application of the antibabesial drug (Fig. 3 and 4).

In all the studied dog groups, the median value of glucose was within the reference range (3.6-6.5 mmol/L). In only one animal (within the group of dogs that survived) hypoglycaemia was present before the antibabesial treatment (Fig. 5). After the antibabesial treatment all the studied animals had glucose values within the reference range.

In our study we found a statistically significant positive correlation between cortisol and insulin ($P < 0.01$).

Discussion

It has been established that severe trauma, disease, infection, and surgery can result in major metabolic stresses. Survival of animals with such insults depends greatly upon a functioning neuroendocrine system. As a result, endocrine changes associated with glucocorticoids, thyroid hormones, glucose/insulin and growth hormone have been extensively studied in human medicine.

The hormonal changes associated with sepsis appear to be important compensatory responses directed towards (1) increasing the availability of fuel (glucose, fatty acids, and amino acids) for the greatly accelerated needs of the cellular metabolic machinery and (2) maintaining an adequate blood volume, blood pressure, and tissue perfusion (WILSON, 1976).

The acute response in such states is directed toward energy conservation, immunomodulation, decrease in anabolic processes, and is in general terms adaptive and appropriate (VAN DEN BERGHE et al., 1998; LALOGA, 2001). The acute, adaptive adrenal response to stress is a shift away from mineralocorticoid production to an up to six-fold increase in glucocorticoid production (NYLEN and MULLER, 2004). Insulin together

with cortisol, is an important part of CARS, and acts primarily anti-inflammatory by suppressing the effects of pro-inflammatory mediators and, by decreasing the glucose concentrations, diminishes its pro-inflammatory effect. The results of our study confirm this, as cortisol and insulin concentrations were statistically significantly higher in dogs with babesiosis compared to healthy dogs. An explanation of this is that early in sepsis there is an increase in corticosteroid concentrations, which is later followed by an increase in insulin concentrations (VAN DEN BERGHE, 2000). This timeline is evident in our study, because cortisol concentrations were higher on the first than the second day and the concentrations of insulin were higher second compared to the first day of the study. Increased corticosteroid concentrations cause insulin resistance. Also, it is important to highlight the fact that cortisol and insulin concentrations were higher in the dogs that died, compared to the dogs that survived. These results indicate that the dogs that died had a more pronounced anti-inflammatory response. Previous studies have shown that in dogs with complicated babesiosis, concentrations of pro-inflammatory mediators were increased (MATIJATKO et al., 2007), therefore we can hypothesize that a stronger pro-inflammatory response triggers stronger anti-inflammatory response as well. The normal values of blood glucose levels in the vast majority of dogs (only one dog was hypoglycaemic), despite the hyperinsulinaemic state (especially in the dogs that died), confirm the presence of insulin resistance, which is contrary to the findings of the study of canine babesiosis caused by *B. canis rossi* by REES and SCHOEMAN (2008). These authors state that insulin secretion was inhibited in normoglycaemic dogs, and concluded that an appropriate physiological relationship between glucose and insulin was preserved. Furthermore, our results show that both cortisol and insulin are predictors of mortality in canine babesiosis caused by *B. canis*, because the dogs that died of babesiosis had statistically significantly higher concentrations of cortisol and insulin compared to dogs that survived canine babesiosis. Our findings are partially supported by the study of SCHOEMAN et al. (2007), which demonstrated significantly higher cortisol levels in dogs that died from canine babesiosis caused by *B. rossi*. The significant positive correlation between cortisol and insulin can be explained by the fact that both hormones are, in essence, anti-inflammatory mediators, so their concentrations change side-by-side. Similar findings have been documented in human medicine, namely in the study of MAITRA et al. (2000).

One limitation of our study is that only the anti-inflammatory component of the inflammatory response has been studied, so we can only hypothesise about the extent of pro-inflammatory response, based on the results of previous studies.

Finally, when analysing the results of this study, it can be concluded that canine babesiosis triggers a marked endocrine response, which is part of the CARS. Also, hyperinsulinaemia in the setting of normoglycaemia, indicates that insulin resistance develops. Furthermore, it was established that concentrations of cortisol and insulin

can be used to predict mortality in canine babesiosis caused by *B. canis*. In the light of these results, it would be prudent to research further the role of other hormones in canine babesiosis caused by *B. canis*, especially the role of pituitary hormones.

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SAŽETAK

Babezioza predstavlja prijeteću zaraznu bolest kralježnjaka koju prenose krpelji, a proširena je diljem svijeta. Glavni uzročnik bolesti u pasa u Europi je vrsta *Babesia canis*, a bolest se javlja u dva osnovna oblika: nekomplicirana i komplicirana babezioza. Oba oblika su u osnovi posljedica upalnog odgovora nositelja. Glavni je cilj istraživanja bio odrediti endokrini protuupalni odgovor pasa prirodno inficiranih vrstom *Babesia canis*. Ustanovljen je značajan endokrini protuupalni odgovor, praćen značajnim porastom koncentracije kortizola i inzulina. Utvrđene su statistički značajne razlike među istraživanim skupinama pasa za sve istraživane pokazatelje (kortizol, inzulin i glukoza) prije primjene antibabezijskog lijeka. Dan nakon primjene antibabezijskog lijeka utvrđene su statistički značajne razlike između skupina zdravih pasa, pasa koji su preživjeli babeziozu i pasa koji su uginuli od babezioze za kortizol i glukozu, dok za inzulin nije bilo statistički značajne razlike između navedenih skupina pasa. U svih istraživanih skupina medijan vrijednosti koncentracije glukoze nalazio se unutar referentnog raspona, osim za jednog psa iz skupine koji su preživjeli babeziozu, a koji je bio hipoglikemičan prije primjene antibabezijskog lijeka. U svih istraživanih skupina koncentracija glukoze je bila unutar referentnog raspona dan nakon primjene antibabezijskog lijeka. Utvrđena je statistički značajna pozitivna korelacija između kortizola i inzulina. Rezultati istraživanja su pokazali da se koncentracije kortizola i inzulina mogu koristiti kao pretskazatelji smrtnosti babezioze pasa uzrokovane vrstom *Babesia canis*.

Ključne riječi: endokrini odgovor, kompenzacijski protuupalni odgovor, psi, babezioza, inzulin, kortizol
