The response of the pituitary-adrenal and pituitary-thyroidal axes to the plasma glucose perturbations in *Babesia canis rossi* babesiosis

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ABSTRACT

This prospective, cross-sectional, interventional study was designed to determine the association between the hormones of the pituitary-adrenal and pituitary-thyroid axes and other clinical parameters with the blood glucose perturbations in dogs with naturally occurring *Babesia canis rossi* babesiosis. Thirty-six dogs with canine babesiosis were studied. Blood samples were obtained from the jugular vein in each dog prior to treatment at admission to hospital and serum endogenous adrenocorticotrophic hormone (ACTH), pre-ACTH cortisol, thyroxine, free thyroxine and TSH concentrations were measured. Immediately thereafter each dog was injected intravenously with 5 μg/kg of ACTH (tetracosactrin). A 2nd blood sample was taken 1 hour later for serum post-ACTH cortisol measurement. Three patient groups were recruited: hypoglycaemic dogs (glucose < 3.3 mmol/ℓ, n = 12); normoglycaemic dogs (glucose 3.3–5.5 mmol/ℓ, n = 12); hyperglycaemic dogs (glucose > 5.5 mmol/ℓ, n = 12). Basal and post-ACTH serum cortisol concentrations were significantly higher in hypoglycaemic dogs, whereas body temperature, serum thyroxine and free thyroxine were significantly lower in hypoglycaemic dogs. Haematocrit was significantly lower in both hypo-and hyperglycaemic dogs compared with normoglycaemic dogs. Low blood glucose concentrations were significantly associated with high basal and post-ACTH cortisol concentrations and with low serum thyroxine and free thyroxine concentrations in dogs suffering from *B. canis rossi* babesiosis.

Key words: ACTH, *Babesia canis rossi,* body temperature, cortisol, free thyroxine, glucose, post-ACTH cortisol, thyroxine, TSH, haematocrit.

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INTRODUCTION

The blood glucose perturbations in virulent canine babesiosis have been highlighted recently and 1 study identified hypoglycaemia in 20 % of canine babesiosis cases admitted to a veterinary hospital[11]. Apart from its association with hyperlactataemia and poor outcome[15], little is known regarding the pathophysiology of hypoglycaemia in this disease.

Human falciparum malaria is a disease in which pathophysiology similar to that of virulent canine babesiosis has been postulated[4,8,18]. In malaria, increased insulin concentrations was a cause of hypoglycaemia in adults and children and inadequate gluconeogenesis, compounded by increased glucose demand and prolonged fasting were contributing factors in children[7,23,25,27]. Owing to the instrumental role of cortisol in plasma glucose counterregulation, pituitary-adrenal axis dysfunction has been postulated as a cause of hypoglycaemia in malaria. Conflicting studies have shown either no evidence of pituitary-adrenal dysfunction[3,17,21,23,29] or evidence of impaired cortisol secretion for the degree of hypoglycaemia in some patients[28], as well as data suggesting that there is a pituitary contribution to the relative adrenal insufficiency documented in malaria[6]. Another study has shown no difference in the concentrations of counter-regulatory hormone concentrations between malaria patients and controls, apart from a markedly increased cortisol and lactate concentrations in patients[24]. This has been taken as additional evidence of the major role of cortisol in the stimulation of gluconeogenesis in malaria patients. Increased serum cortisol concentrations have also been associated with an increased susceptibility to *Plasmodium falciparum* infection, especially in primigravid women[2] and serum cortisol concentrations were found to be significantly higher on day 0 *versus* day 7 of uncomplicated *P. falciparum* malaria in Brazil[13]. One study on thyroid function in falciparum malaria did find evidence of depressed thyroid hormone concentrations[5].

Endocrine studies performed so far in canine babesiosis, have shown a significantly positive association between pituitary-adrenal hormones and outcome, whereas thyroid hormones showed a negative association with outcome[20]. The pituitary-adrenal and thyroidal responses to the plasma glucose changes seen in canine babesiosis are currently unknown. The aim of this study was to describe the pituitary-adrenal and pituitary-thyroidal response to hypoglycaemia and to verify the association of previously described parameters such as low haematocrit, collapse and icterus with hypoglycaemia[11] in virulent canine babesiosis caused by *Babesia canis rossi.* To limit the confounding effect of the previously described hypoglycaemia, hypercortisolaemia and hypothyroxinaemia on poor outcome, this study was limited to dogs that survived the illness.

MATERIALS AND METHODS

This prospective study was performed on dogs with canine babesiosis presented to the Onderstepoort Veterinary Academic Hospital, University of Pretoria, South Africa, between January 2006 and February 2006. Initial diagnosis was made based on the detection of large *Babesia* spp. parasites on stained thin capillary blood smears. Only dogs that survived to hospital discharge were eligible for the study. Dogs were not included in the study if they had a history of previous exogenous corticosteroid therapy, known malignancies which might have involved the adrenal or thyroid glands, known concurrent disease, or if *Ehrlichia canis* morulae were detected on blood smear. After the dogs had been sampled, they were excluded if concurrent disease was identified during their hospital stay or if

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Table 1: **Summary of the historical, signalment and clinical data in the three plasma glucose groups of dogs with *Babesia canis rossi* babesiosis.**

Parameter	Hypoglycaemic group Median (IQR)	Normoglycaemic group Median (IQR)	Hyperglycaemic group Median (IQR)
Age	11.5 months (5–24)	24 months (8–36)	8 months (4–13.5)
Body weight	6 kg (2.4–17.5)	10 kg (7.7–16)	8 kg (5.4–17.8)
Duration of illness	3 days (1.25–3.75)	2 days (2–3)	2 days (2–6)
Time since last meal	36 hours (12–72)	22 hours (12–24)	18 hours (12–24)
Length of hospital stay	3.5 days (1.5–4.75)	1 day (1–2)	2.5 day (1–5)
Body temperature	*37.2 °C (36.2–39)	40 °C (39.4–40.5)	39.6 °C (38.4–40)
Pulse rate	123 bpm (101–154)	131 bpm (105–160)	147 bpm (129–160)
Respiratory rate	44 bpm (33–60)	44 bpm (26–60)	45 bpm (40–81)
Haematocrit	0.09 ℓ/ℓ (0.09–0.12)	*0.27 ℓ/ℓ (0.14–0.40)	0.13 ℓ/ℓ (0.07–0.21)
	Number of cases	**Number of cases**	**Number of cases**
Collapsed	*10	2	2
Weak	2	5	6
Alert	0	5	4
Icterus present	4	1	4
Icterus absent	8	11	8

Key: IQR = interquartile range; bpm = beats/breaths per minute; * = significantly different.

their blood samples were positive for *B. canis vogeli* or *Ehrlichia canis* by polymerase chain reaction (PCR) and reverse line blot (RLB) as previously described[14]. The membrane used for RLB included probes for *B. c. vogeli, B. c. rossi, B. c. canis* and *Ehrlichia canis.* The study was approved by the Animal Use and Care Committee of the University of Pretoria.

Study design

History, including duration of illness prior to presentation and time since last meal were determined. Signalment, including patient age, sex and weight, was recorded. Upon clinical examination, habitus (collapsed, weak, alert) and icterus (absent or present), body temperature, pulse and respiratory rate were also determined. Blood samples were obtained prior to treatment on the day of admission. Blood was taken from the jugular vein by needle venipuncture with pre-cooled syringes and needles in all cases and placed into serum tubes, fluoride oxalate tubes and pre-cooled plastic EDTA tubes. EDTA tubes were kept on ice and spun down within 10 minutes in a refrigerated centrifuge at 4 °C. Immediately thereafter, all patients were injected intravenously with 5 μg/kg of ACTH (tetracosactrin, Synacthen®, Alliance pharmaceuticals). Another serum sample for post-ACTH cortisol determination was taken 1 hour later. Serum samples were allowed to clot and the tubes were spun down within 1 hour. The serum and plasma were harvested from their respective tubes, placed in dedicated plastic storage tubes and stored at –80 °C until analysis. Three patient groups were defined as previously described[11]: hypoglycaemic dogs (glucose < 3.3 mmol/ℓ); normoglycaemic dogs (glucose 3.3–5.5 mmol/ℓ); hyperglycaemic dogs (glucose > 5.5 mmol/ℓ). Dogs were followed up to determine their length of hospital stay and outcome in order to exclude dogs that died.

EDTA plasma was submitted for haematology and ACTH analysis. Fluoride oxalate plasma was submitted for glucose determination using the hexokinase method (Technicon R A 1000 system, Miles Inc., Diagnostic Division, Tarrytown, NY). Hormones were assayed in a single batch. ACTH (IMMULITE 1000 ACTH, chemiluminescent immunometric assay, Diagnostic Products Corp, USA), Cortisol (Radioimmunoassay cortisol, Coat-A-Count, Diagnostic Products Corp, USA), thyrotropin (Immunoradiometric canine TSH, Coat-A-Count, Diagnostic Products Corp, USA), free thyroxine (Radioimmunoassay free T4, Coat-A-Count, Diagnostic Products Corp, USA) and thyroxine (Radioimmunoassay canine T4, Coat-A-Count, Diagnostic Products Corp, USA) assays were performed in duplicate with kits previously validated for dogs. Sensitivity of the ACTH, cortisol and thyrotropin, free thyroxine and thyroxine assays were 10 pg/mℓ, 5.5 nmol/ℓ, 0.03 ng/dℓ, 0.13 pmol/ℓ and 2.8 nmol/ℓ, respectively. For statistical purposes, values below the limit of detection were taken as 9 pg/mℓ, 5.4 nmol/ℓ, 0.03 ng/dℓ, 0.12 pmol/ℓ and 2.7 nmol/ℓ, respectively. Owing to limited serum availability, 1 hyperglycaemic dog did not have endogenous ACTH performed and 1 normoglycaemic dog did not have serum TSH performed. All the other hormone analyses were performed on all 36 dogs.

Statistical analysis

Parameters were tested for normal distribution using the 1-sample Kolmogorov-Smirnov test. Differences in the median hormone concentrations between the 3 blood glucose groups (multiple comparisons) were analysed for non-parametric data with the Kruskal-Wallis test on ranks. Only variables that showed significant difference were subjected to subsequent pairwise comparisons using the Mann-Whitney *U*-test to compare each of the groups separately with one another. Contingency tables were constructed with habitus as an ordinal variable (1 = collapse, 2 = weak, 3 = alert) and icterus (0 = absent, 1 = present) as a dichotomous variable, in order to compare observed *versus* expected frequencies within the 3 blood glucose groups using the chi-square test. For all comparisons, differences were considered significant when $P < 0.05$. Values in the text are given as median and interquartile range (IQR). Statistical analysis was performed using a commercial software package (SPSS 14.0, 2005, SPSS Inc., Chicago, Illinois, USA).

RESULTS

Twelve dogs were recruited within each blood glucose group. All historical, signalment and clinical data for the 3 groups of dogs are given in Table 1. Twenty-two dogs (61 %) were male and 14 dogs (39 %) were female. The overall median patient age was 11.5 months (IQR 6–33 months), which did not differ significantly

Table 2: **Summary of the results of the serum ACTH, basal cortisol, post-ACTH cortisol, delta cortisol, TT4, fT4 and TSH concentrations in the three plasma glucose groups of dogs with *Babesia canis rossi* babesiosis.**

Analyte	Hypoglycaemic group	Normoglycaemic group	Hyperglycaemic group
ACTH: median (IQR)	15.75 pg/mℓ (11–33)	11.9 pg/mℓ (9–22)	11.9 pg/mℓ (10.7–16)
Basal cortisol: median (IQR)	*371 nmol/ℓ (195–522)	122 nmol/ℓ (73–274)	103 nmol/ℓ (61–167)
Post-ACTH cortisol: median (IQR)	*444 nmol/ℓ (337–807)	329 nmol/ℓ (273–381)	345 nmol/ℓ (245–400)
TT4: median (IQR)	*2.7 nmol/ℓ (2.7–4.4)	11.9 nmol/ℓ (7–18)	8.9 nmol/ℓ (3–14)
fT4: median (IQR)	*0.12 pmol/ℓ (0.12–0.12)	2.18 pmol/ℓ (0.28–3)	1.27 pmol/L (0.37–2.34)
TSH: median (IQR)	0.03 ng/mℓ (0.03–0.1)	0.09 ng/mℓ (0.06–0.37)	0.11 ng/mℓ (0.03–0.13)

Key: IQR = interquartile range; * = significantly different.

between the 3 groups ($P = 0.12$). The median duration of illness prior to presentation was 2 days (IQR 2–3.25 days), which did not differ between the 3 groups ($P = 0.63$). Body weight, time since last meal and ultimate length of hospital stay did not differ significantly between the groups ($P = 0.15$, $P = 0.289$, $P = 0.092$, respectively).

Ten of 12 dogs in the hypoglycaemic group collapsed, compared to 2/12 in each of the other groups. The chi-square test showed that there was a significant association between clinical collapse and hypoglycaemia ($\chi^2 = 15.8$, df = 4, $P < 0.01$). Four of 12 dogs were icteric in each of the hypo- and hyperglycaemic groups compared to 1/12 in the normoglycaemic group. The chi-square test failed to show any association between icterus and glycaemic status ($\chi^2 = 2.67$, df = 2, $P = 0.264$).

Median body temperature of the dogs in the hypoglycaemic group was significantly lower than that of the normoglycaemic group ($P < 0.001$) and than that of the hyperglycaemic group ($P < 0.05$). The body temperatures of the normo- and hyperglycaemic groups did not differ significantly ($P = 0.14$). By contrast, the median haematocrit of both the hypo- and hyperglycaemic dogs were significantly lower than that of the normoglycaemic group ($P < 0.01$, $P < 0.05$, respectively). Pulse rates and respiratory rates did not differ significantly between the groups ($P = 0.275$, $P = 0.635$, respectively).

Pituitary-adrenal axis hormone concentrations

Details of all the hormone results are given in Table 2.

Endogenous ACTH concentrations

Basal ACTH concentrations were not significantly different between groups ($P = 0.4$).

Basal cortisol concentrations

Median serum cortisol concentrations were significantly higher in the hypoglycaemic compared to the normoglycaemic ($P < 0.01$) and compared to hyperglycaemic dogs ($P < 0.001$). The serum cortisol concentrations were not significantly different between the normo- and hyperglycaemic dogs ($P = 0.4$) (Fig. 1).

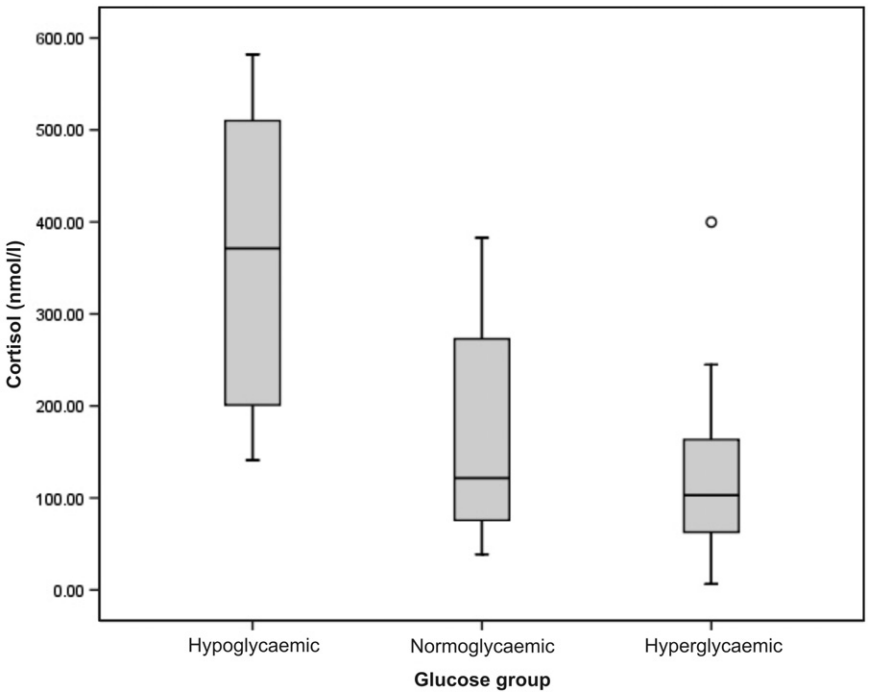

Fig. 1: **Box plots of the admission serum cortisol concentrations of the three plasma glucose groups in 36 dogs with canine babesiosis. For each box plot the box represents the interquartile range (*i.e.* the 25th to 75th percentile range or the middle half of the data). The horizontal bar in the box is the median and the T bars represent the main body of the data, which in most instances is equal to the range. Outliers are indicated by open circles.**

Post-ACTH cortisol

Median post-ACTH serum cortisol concentrations were significantly higher in the hypoglycaemic compared with the normoglycaemic ($P < 0.05$) and with the hyperglycaemic dogs ($P < 0.05$). The post-ACTH serum cortisol concentrations were not significantly different between the normo- and hyperglycaemic dogs ($P = 0.93$) (Fig. 2).

Pituitary-thyroidal axis hormone concentrations

Basal serum thyroxine concentrations

Serum thyroxine concentrations were significantly lower in the hypoglycaemic compared with the normoglycaemic ($P < 0.001$) and compared with hyperglycaemic dogs ($P < 0.01$). The serum thyroxine concentrations were not significantly different between the normo- and hyperglycaemic dogs ($P = 0.48$) (Fig. 3).

Basal serum free thyroxine concentrations

Serum free thyroxine concentrations were significantly lower in the hypoglycaemic compared with the normoglycaemic ($P < 0.01$) and with the hyperglycaemic dogs ($P < 0.01$). The serum free thyroxine concentrations were not significantly different between the normo- and hyperglycaemic dogs ($P = 0.713$) (Fig. 4).

Serum TSH concentrations

Serum TSH concentrations were not significantly different between groups ($P = 0.06$).

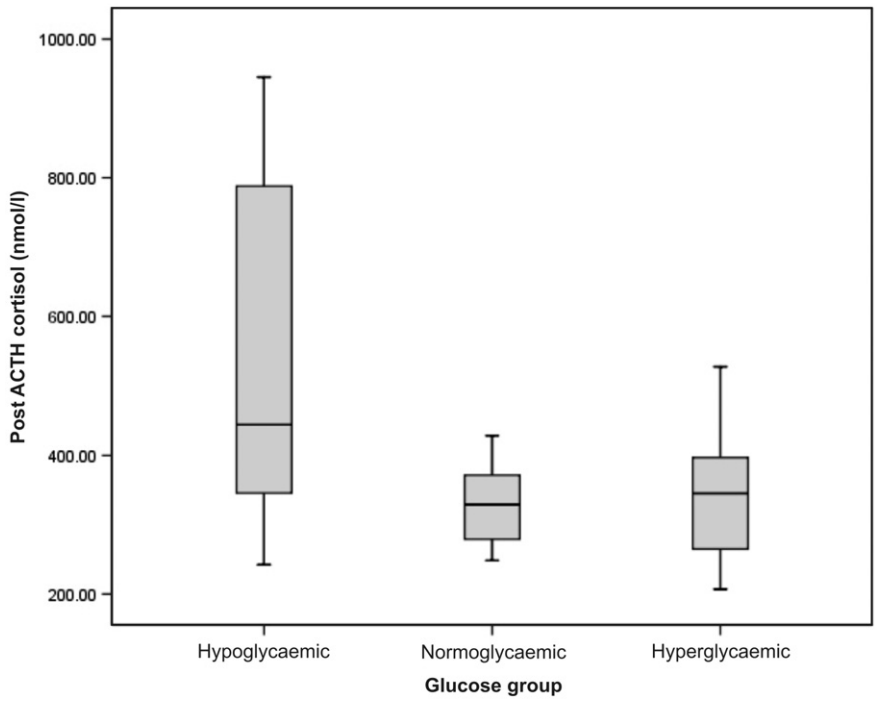

Fig. 2: **Box plots of the admission serum post-ACTH cortisol concentrations of the three plasma glucose groups in 36 dogs with canine babesiosis. For each box plot the box represents the interquartile range (***i.e.* the 25th to 75th percentile range or the middle half of the data). **The horizontal bar in the box is the median and the T bars represent the main body of the data, which in most instances is equal to the range.**

DISCUSSION

Only canine babesiosis cases that were admitted and discharged alive were used in this study. Mildly affected dogs treated as outpatients, as well as more severely affected dogs that died, were excluded. This was done in an attempt to assure that the groups were as similar as possible in all respects, apart for their blood glucose concentrations, to limit the confounding effect of the previously described high death rate (in the hypoglycaemic group) on the cortisol, T4 and fT4 concentrations[11,20]. The similar ages, body weights, duration of illness prior to presentation, time since last meal and days hospitalised of the 3 groups attest to the optimal achievement of this goal.

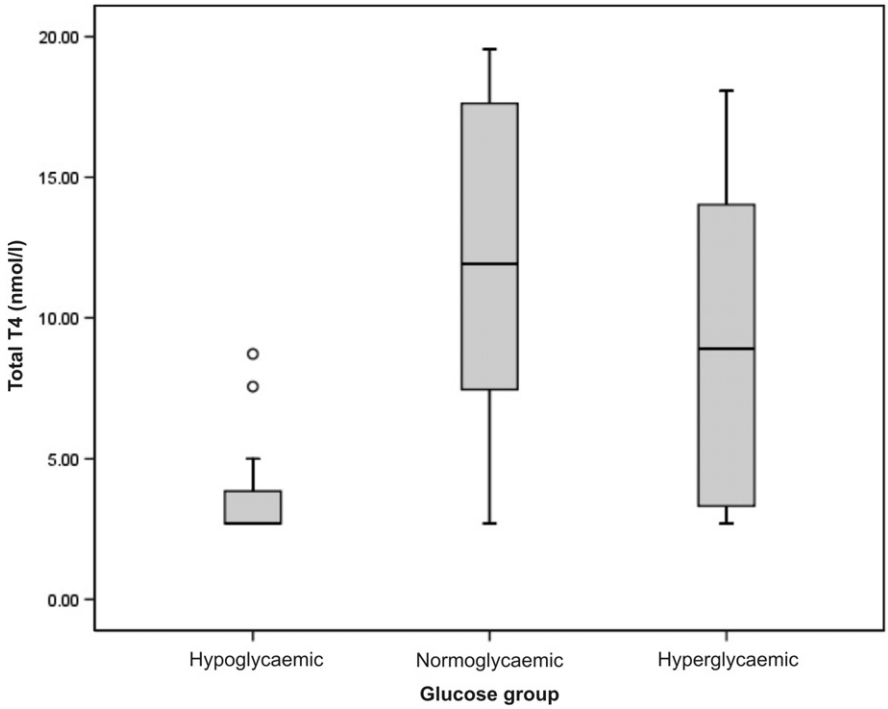

Fig. 3: **Box plots of the admission serum total T4 concentrations of the three plasma glucose groups in 36 dogs with canine babesiosis. For each box plot the box represents the interquartile range (***i.e.* the 25th to 75th percentile range or the middle half of the data). **The horizontal bar in the box is the median and the T bars represent the main body of the data, which in most instances is equal to the range. Outliers are indicated by open circles.**

Significant hypoglycaemia and attendant risk factors such as clinical collapse, low haematocrit, icterus and young age have previously been described in virulent *B. canis rossi* babesiosis[11]. Clinical collapse and low haematocrit were also significantly associated with hypoglycaemia in our study, corroborating the findings of the earlier study. Collapsed dogs, in addition to being prone to hypoglycaemia, have also been shown to be much more likely to die of virulent canine babesiosis[1]. We found, however, that low haematocrit was also associated with hyperglycaemia. Icterus and young age was not clearly associated with hypoglycaemia in our study; however, the median age of the hypo- and hyperglycaemic groups were markedly lower than that of the normoglycaemic group and showed a trend towards significance. Icterus was also more prevalent in the hypoglycaemic group and it is believed that a larger sample size would probably have led to our study's results concurring with earlier studies. In addition, this study found a significantly lower body temperature in hypoglycaemic dogs. Low body temperature has not previously been associated with hypoglycaemia in canine babesiosis. It is well known that young puppies suffer from hypothermia and hypoglycaemia and that the 2 phenomena are inter-related[9,22]. In small-breed dogs this inability to maintain temperature and glucose concentrations can persist till a year of age and our results are thus in agreement with other studies in that the hypoglycaemic group was younger and smaller in size than the other groups[12,26].

This study found significantly higher basal and post-ACTH stimulated serum cortisol concentrations in hypoglycaemic dogs with *B. canis. rossi* babesiosis. We initially postulated that adrenal failure (indicated by a low basal or post-ACTH serum cortisol) could be a plausible cause of hypoglycaemia in this acute haemoparasitic disease. This does not seem to be the case, because the pituitary-adrenal axis responded appropriately under conditions of hypoglycaemia and low haematocrit. Our findings thus concur with most of the malaria studies which showed increased cortisol secretion and no indication of adrenal insufficiency[3,13,16,21,24,29].

The response of the pituitary-thyroidal axis is similar to that described in acute malarial disease in humans[5] as well as in animals with non-thyroidal illness[10,19].

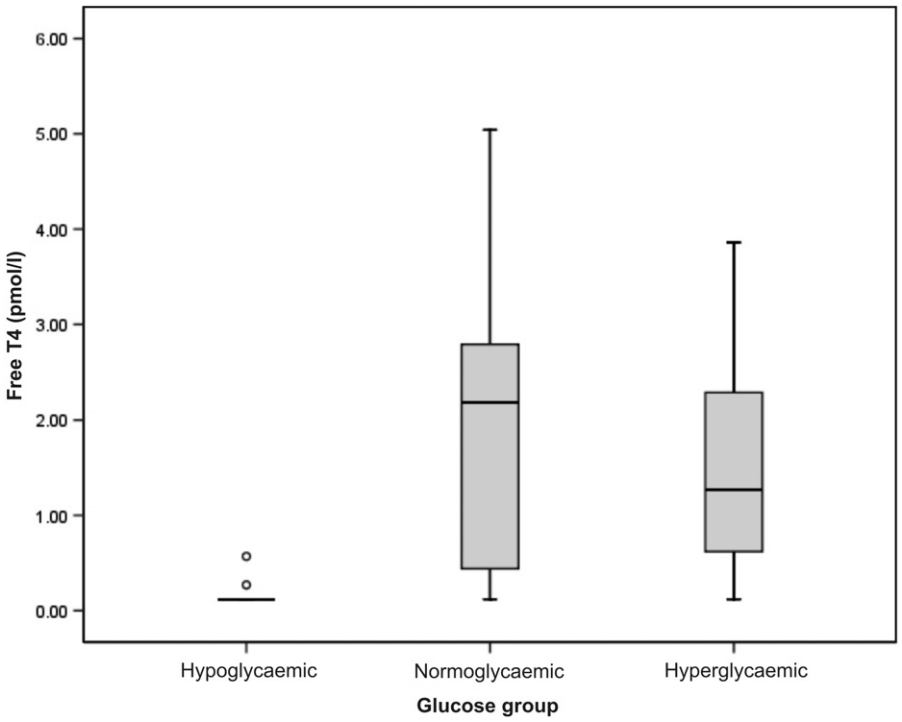

Fig. 4: **Box plots of the admission serum free T4 concentrations of the three plasma glucose groups in 36 dogs with canine babesiosis. For each box plot the box represents the interquartile range (***i.e.* the 25th to 75th percentile range or the middle half of the data). **The horizontal bar in the box is the median and the T bars represent the main body of the data, which in most instances is equal to the range. Outliers are indicated by open circles.**

The significantly lower T4 and fT4 in the hypoglycaemia dogs is probably a contributing factor to the significantly lower body temperature observed in the hypoglycaemic group.

We conclude from this study that the adrenal and thyroidal hormones respond in opposite ways to the insult of hypoglycaemia and that the responses in the normo- and hyperglycaemic groups are essentially no different from one another. Hypoglycaemia is a significant complication of both human falciparum malaria and *B. c. rossi* babesiosis and much research remains to be done to elucidate its pathophysiology.

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