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Positive kidney profile of dogs with *Leishmania* sp. and treated with miltefosine

Perfil renal de cães positivos para *Leishmania* sp. e tratados com Miltefosina

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Highlights

Treatment with miltefosine did not change function and renal vascularization.
Renal ultrasound detected alterations before changes in other parameters.
Collor Doppler showed hypo-vascularization in intrarenal vessels of positive dogs.

Abstract

Canine leishmaniasis has a wide variety of clinical signs, and, depending on the stage of the disease, the kidneys are the organs most affected. To stage the disease and carry out treatment, kidney assessment is of great importance, along with drug interactions and the deposition of immune complexes. In this study, we evaluated the renal morphology and function by means of B-mode ultrasonography and vascular Doppler, biochemical, urinalysis, and blood pressure tests, correlating the findings in dogs positive for leishmaniasis and treated with miltefosine. For this, 38 dogs were used, 12 healthy (G1) ones and 26 naturally infected with *Leishmania* sp.; of these, 12 animals were not treated (G2), and 14 were treated with miltefosine (G3). Evaluations were performed twice, with an interval of 30 days, before and after treatment with miltefosine. The average values of blood pressure as well as biochemical and urinary parameters were within the normal ranges for the species. In the volumetric Doppler measurement, no statistical differences were observed for systolic velocity, diastolic velocity, and resistivity index between the kidneys and the treated and untreated groups. According to the results obtained, treatment with miltefosine does not influence the renal parameters evaluated.

Key words: Leishmaniasis. Doppler. Kidneys. Miltefosine.

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Resumo

A leishmaniose canina possui uma ampla variedade de sinais clínicos, tendo os rins como os órgãos mais afetados. Para o estadiamento da doença e realização do tratamento, a avaliação renal é de grande importância, além das interações medicamentosa podem ocasionar com a deposição de imunocomplexos. O presente trabalho, teve como objetivo avaliar a morfologia e função renal por meio da ultrassonografia modo B e Doppler vascular, exames bioquímicos, urinálise e de pressão arterial, correlacionando seus achados de cães positivos para leishmaniose e tratados com miltefosina. Para tanto, foram utilizados 38 cães, 12 hígidos (G1), 26 naturalmente infectados por Leishmania sp, destes, 12 animais que não foram tratados (G2) e 14 tratados com miltefosina (G3). As avaliações foram feitas em dois momentos, com intervalo 30 dias, para contemplar as avaliações antes e após o tratamento com miltefosina. Os valores médios de pressão arterial, parâmetros bioquímicos e urinários, encontravam-se dentro da normalidade para a espécie, na mensuração Doppler volumétrica não foi observado diferença estatística entre as variáveis de velocidade sistólica, velocidade diastólica e índice de resistividade entre os rins e os grupos tratados e não tratados. De acordo com os resultados obtidos, o tratamento com miltefosina não influencia nos parâmetros renais avaliados.
Palavras-chave: Leishmaniose. Doppler. Rins. Miltefosina.

Introduction

Canine leishmaniasis (CL) is a chronic and zoonotic disease that can cause a wide variety of clinical signs, being subdivided into cutaneous, visceral, and mucocutaneous forms, which can lead to death (Alvarenga et al., 2010; Solano-Gallego et al., 2011; Godoy et al., 2016; World Health Organization [WHO], 2022). It is caused by protozoa of the species Leishmania sp., which are transmitted by the bite of sandflies; Lutzomyia longipalpis is the species of greatest epidemiological importance (Harhay et al., 2011). In Brazil, domestic dogs are the main reservoirs in urban areas.

Control is based on the reduction of the sand fly population, the elimination of reservoirs, and health education (C. H. N. Costa, 2011). In areas where such control measures are employed, the incidence and lethality rates of the disease are decreasing (Quinnell & Courtenay, 2009; Barreto et al., 2011). With this practice, thousands of dogs have been euthanized, with little or no impact on the spread of the disease (Dantas-Torres, 2007; Quinnell & Courtenay, 2009; Passantino et al., 2010; C. H. N. Costa, 2011). The treatment of dogs reduces the parasite load and infectivity for sandflies (Alvar et al., 1994; Ribeiro et al., 2008; Miró et al., 2011; Silva et al., 2012; Dantas-Torres et al., 2020; S. N. Melo et al., 2018). In 2016, in a joint Technical Note, No. 001/2016, the Ministries of Agriculture, Livestock and Supply (MAPA) and Health (MS) authorized the registration of the product Milteforan® (miltefosine), the main drug used in the treatment of CL in Europe; it is not used in the treatment of humans in Brazil.

Canine leishmaniosis causes various clinical signs secondary to the inflammation promoted by the multiplication of the parasite in different tissues, with kidney lesions being commonly observed (Genaro, 1993; Ferrer, 1999; Feitosa et al., 2000; Paltrinieri et al.,

2016; Leite et al., 2015; Baneth et al., 2022). The evolution of the disease is linked to the immune competence of the host (Ciaramella et al., 1997; Alexandre-Pires et al., 2010; Andrade et al., 2014), which can cause the development of circulating immune complexes that will be deposited in blood vessels and organ tissues, causing vasculitis and systemic complications (Ferrer, 1999; F. A. Costa et al., 2003).

The deposition of immune complexes in renal glomeruli results in the progressive loss of nephrons and reduced glomerular filtration, causing elevations of various substances that would normally be excreted. The evaluation of serum urea and creatinine concentrations is commonly used to assess the glomerular filtration rate (Nelson & Couto, 2015; A. F. L. R. Dias et al., 2021; Baneth et al., 2022).

For renal evaluation, ultrasonography is the most commonly used imaging method in veterinary medicine and can provide information that may influence the management of the case (Mattoon & Nyland, 2002; Feeney et al., 2008). The color and spectral Doppler ultrasound modalities with B-mode examination increase the specificity and sensitivity of the sonographic diagnosis of alterations since they allow the evaluation of hemodynamics, dimensions, and organ parenchyma (Machado et al., 2004). Based on the biochemical profile, we can detect alterations in glomerular filtration, using the dosages of urea (U) and creatinine (C). In cases of pre-renal, renal, or post-renal azotemia, both may be increased. The C level is the main indicator of the glomerular filtration rate (GFR) and may be altered in the majority of patients with chronic kidney disease (CKD) (Castro, 2005; Lopes et al., 2007). Therefore, serum determinations of U and C, as well as hematological, biochemical, and urinary evaluation help to determine the GFR through an indirect evaluation; an increase in non-protein nitrogenous compounds due to uremic toxins goes along with higher levels of these parameters (Polzin, 2011).

Considering the importance of CL, with its great zoonotic potential and the scarcity of data in the literature involving renal ultrasonographic evaluation of dogs affected by this disease and after undergoing the treatment recommended by the Ministries of Agriculture, Livestock and Supply (MAPA) and Health (MS), we describe the B-mode and Doppler ultrasonographic findings of the kidneys of these naturally infected animals treated with miltefosine.

Material and Methods

The study was carried out in the city of São Luís, state of Maranhão, Brazil, in accordance with the guidelines of the Ethics and Animal Experimentation Committee of Universidade Estadual do Maranhão (CEEA), São Luís, MA, under protocol number 01/2021. We used 38 dogs, older than 1 year, of different breeds and sexes. The serological evaluation of these animals for the diagnosis of visceral leishmaniasis was performed as established by the Ministry of Health (technical note 01/2011), using the rapid immunochromatographic test (ALERE®) as a screening test and the enzyme-linked immunosorbent assay (ELISA) as a confirmatory test (Secretaria de Estado da Saúde, [2015]). Blood was collected from all dogs and submitted to the Snap 4DX immunochromatographic test (IDEXX ®); animals that tested positive were excluded

from the study. Animals with a history of previous kidney disease and treated with nephrotoxic drugs were also excluded.

The animals were divided into three groups according to the treatment performed. Group I: control group, consisting of 12 dogs without renal changes and not carrying canine visceral leishmaniasis. Group II: control group, composed of 12 untreated dogs with canine visceral leishmaniasis. Group III: 14 dogs with canine visceral leishmaniasis and treated with miltefosine. Evaluations were made twice, with an interval of 30 days, before and after treatment with miltefosine (Figure 1).

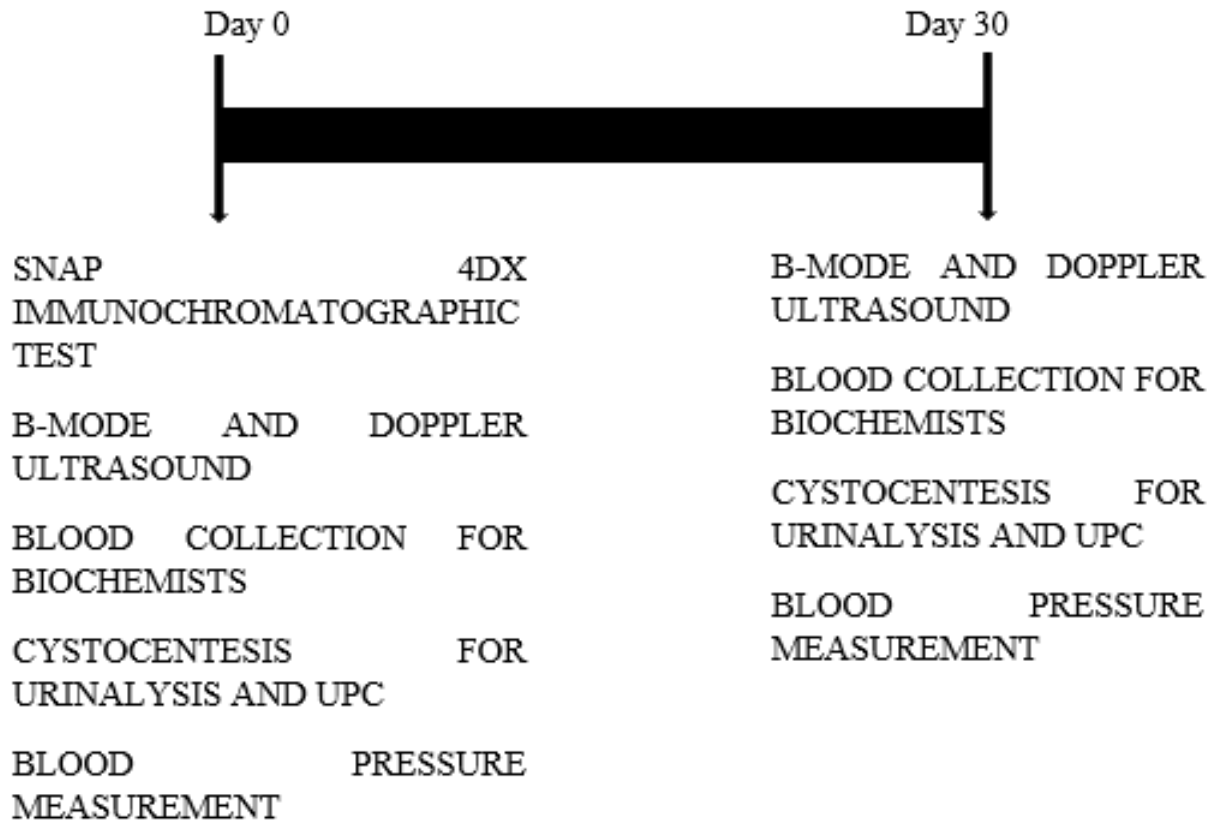

Figure 1. Timeline diagram showing the timing of ultrasound examinations, laboratory tests, and cystocentesis and blood pressure measurement. The laboratory study included assessments of urea, creatinine, urinalysis, and urinary protein/creatinine ratio.

A GE Logic E ultrasound device with a linear and a micro-convex transducer was used. A B-mode total abdominal evaluation was performed, evaluating the organs with longitudinal, dorsal, and transversal scans. In the scans, the length, width, height, and cortico-medullary ratio were measured, and the renal contour and parenchyma were observed. Subsequently, a Doppler examination of the renal arteries was performed on the same days as the B-mode ultrasound. Initially, the renal arteries were mapped using the color Doppler mode. A transducer was positioned on the blood vessel, in the region of the renal hilum in transverse plane, to obtain the spectral tracing with pulsed Doppler, observing the renal, interlobar, arcuate, and interlobular arteries.

The resistivity index (RI) was calculated according to Rivers et al. (1997). To obtain uniform measurements, three consecutive waves of similar appearance were analyzed in the tracing of each region observed (M. B. Melo et al., 2006). The RI was obtained after obtaining the peak of the systolic velocity and the end of the diastolic velocity, using the ultrasound device software (Novellas et al., 2007; Bigé et al., 2012). The insonation angle was below 60º, and measurements were performed when the spectrum remained with at least three constant waves, obtaining the average values.

For the biochemical tests, blood samples were collected on the days of the ultrasound evaluations. The blood was stored in silicon vacuum tubes with and without anticoagulant and sent to the clinical pathology laboratory for a complete blood count as well as U and C dosages. The reference values of Kaneko et al. (2008) were considered. During the ultrasonography, a guided cystocentesis was performed, which was later stored in everything proper and conditioned at cooling temperature, later sent to the laboratory and the analysis was performed freshly, evaluating the parameters urine protein creatinine ratio (UPC) and urinalysis. Blood pressure was measured using vascular Doppler, as described by Mucha and Camacho (2003), employing a DV-3001 model device. The measurements were performed on 2 days (the same days as the ultrasonography exams). Three pressure measurements were made during a 10-minute period, discarding the value of the first measurement and determining the arithmetic means of the others. Animals with mean arterial pressure ≥ 180 mmHg were considered hypertensive (Brown et al., 2007).

The variables (C, U, blood pressure, UPC, density, SV, DV, and RI) were statistically analyzed using analysis of variance (ANOVA) after meeting the assumptions of normality of errors and homogeneity of variances using the Cramer von Mises and Brown and Forstyles tests, respectively. The means were compared using the Tukey test. Pearson's correlation was used to identify the relationships between the variables. A significance level of 95% ($p < 0.05$) was considered for all tests.

Results and Discussion

The average blood pressure values were 118 to 140 mg, with G1 having the lowest values (118 to 128 mg) and G2 having the highest values (135 to 140 mg); there was a statistically significant difference among the other groups. The UPC values ranged from 0.3 to 2.2, where the highest values were observed in G3, during treatment with milteforan, albeit without a significant difference among groups. The average values of urinary density ranged from 1,024 to 1,030, with no statistical difference among the means of the groups. The serum creatinine (C) levels ranged from 0.66 to 1.2 mg/dL, with an average of 0.66 mg/dL in G1, 1.2 mg/dL in G2, 0.99 mg/dL in G3; the values for G1 and G2 were significantly different. The serum urea levels (U) ranged from 37 to 43.8 mg/dL, with no statistical difference among the groups (Table 1).

Table 1
Comparison of average values (± standard deviation) of systolic pressure (mmHg), UPC, density, creatinine, and urea evaluated at two time points (1 - 1st evaluation; 2 - 2nd evaluation) in negative, positive dogs without treatment (POSITIVE) and *Leishmania*-positive dogs with treatment (TREATED)

VARIABLES	NEGATIVES		POSITIVES		TREATED	
	EVALUATION		EVALUATION		EVALUATION	
	1	2	1	2	1	2
PRESSURE	128 ^{ab} ± 9	118 ^{b} ± 8	135 ^{a} ± 21	140 ^{a} ± 20	128 ^{ab} ± 14	125 ^{ab} ± 10
UPC	0.3 ± 0.2	0.3 ± 0.2	0.33 ± 0.4	0.4 ± 0.6	1.8 ± 5	2.2 ± 6
DENSITY	1,030 ± 9	1,029 ± 7	1,024 ± 15	1,024 ± 13	1,025 ± 13	1,024 ± 10
CREATININE	0.66 ^{a} ± 0.2	0.66 ^{a} ± 0.2	1.2 ^{b} ± 0.6	1.1 ^{b} ± 0.4	1.0 ^{b} ± 0.7	0.9 ^{ab} ± 0.5
UREA	38.4 ± 17.5	37 ± 16	38.9 ± 19.5	39.3 ± 19	41.3 ± 23.6	43.8 ± 17

*Averages followed by similar letters within rows do not differ by the SNK test ($p > 0.05$). Averages with normal distribution and homogeneity of variances, respectively, by Cramer-von Mises and Brown and Forsythe tests ($p > 0.05$). Urine protein creatinine ratio (UPC).
Reference values: Blood pressure 100 to 150 mmHg (International Renal Interest Society [IRIS], 2019); UPC < 0.2; Density: 1,025 to 1,035; Creatinine 0.5 to 1.6 mg/dL; Urea: 10 to 54 mg/dL (Kaneko et al., 2008).

None of the dogs evaluated had arterial hypertension, with SBP values lower than 180 mmHg. Although for canines, the threshold for kidney tissue damage to occur is unknown, it is assumed to be approximately 160 mmHg since renal damage in dogs with SBP below 180 mmHg has already been described by Reusch et al. (2010).

The values for dogs with CKD are divided as follows: systolic blood pressure from 130 to 150 mmHg is classified as minimal risk, from 150 to 160 mmHg, it is classified as low risk, from 160 to 180 mmHg, it is classified as moderate risk, and values greater than 180 mmHg represent a high risk (Brown et al., 2007; Cortadellas, 2012; IRIS,

2023). According to Paltrinieri et al. (2016) and Rebelo et al. (2021), urinary density may decrease in leishmaniasis-positive dogs, emphasizing the need for follow-up through urinalysis. The density values observed in this study are similar to those reported by Martín et al. (2017), who obtained a mean value of 1,030 in dogs submitted to CT scanning and under anesthesia. There is an important correlation with the evaluation of sediment, pH, and UPC, verifying proteinuria rates, which is a risk factor for the progression of nephropathies. The urine must be collected aseptically, by cystocentesis, to avoid contamination and alterations from the lower urinary tract. The UPC has an important function in the classification of proteinuria and must be performed during all treatments (Rebelo et al., 2021).

In this study, G3 presented a UPC value above normal values, indicating proteinuria. However, persistent proteinuria of renal origin is determined when verified in three or more repetitions of the test, performed within a minimum interval of 15 days and excluding pre- and post-renal causes of proteinuria (Lees et al., 2005; Brown, 2013; Harley & Cathy, 2012; Vaden & Elliott, 2016). The magnitude of the UPC values is related to the type and evolution of the renal injury. Generally, UPC values > 2.0 are highly suggestive of glomerular injury, and lower values occur in tubulointerstitial injuries (Less et al., 2005; Grauer, 2011; Littman et al., 2013; Vaden & Elliott, 2016).

The isolated interpretation of the UPC values impedes the distinguishing between glomerular protein loss and proteinuria associated with inflammation or hemorrhage of the lower urinary tract (Grauer, 2011). It is therefore necessary to evaluate the urinary sediment and the clinical history to obtain a differential diagnosis (Grauer, 2011; Littman et al., 2013; Vaden & Elliott, 2016).

The average concentrations of C and U in positive animals were higher than those in negative animals, but within the standard values found in healthy dogs according to Kaneko et al. (2008). This shows that even during treatment with miltefosine, the urea and creatinine values were within the normal ranges. The present results differ from those reported by Kiral et al. (2004), who experimentally infected 10 dogs with Leishmania infantum and showed that the U levels were not altered; however, there was a significant increase in the C values, indicating renal impairment. The urea and creatinine levels obtained in the present study differ from those reported by Nieto et al. (1992), who stated that it is more common to observe increased levels of U than C in dogs with leishmaniasis. In another study, E. L. Dias et al. (2008) observed increased levels of U and no C when evaluating 28 dogs seroreagent for leishmaniasis. The present results differ from those obtained in a survey performed by Rebelo et al. (2021), who reported that, based on laboratory tests, 24.14% of the animals had kidney lesions. The differences between our findings and those of other authors may be due to the method of selecting the animals and to the fact that veterinary clinicians are currently better prepared to maintain the staging of patients with stable parameters. However, the use of laboratory tests for the renal evaluation of dogs with CL should be complete since the incidence of dogs with azotemia is low in relation to the identification of alterations by ultrasonographic methods,

which demonstrates that even without an increase in serum U and C levels, these animals are susceptible to renal injury (F. A. Costa et al., 2003).

According to Ciaramella et al. (1997), renal impairment is a natural after-effect in dogs affected by leishmaniasis, a fact that was not observed in the biochemical tests performed, probably caused by the method of selecting the patients, where dogs with no previous renal alterations were selected after renal staging. This alteration is characterized by the deposition of immune complexes that may cause glomerulonephritis and interstitial nephritis, resulting in renal failure, according to Feitosa et al. (2000), and potentially leading to proteinuria, hematuria, and increased serum levels of U and C (Ettinger & Feldman, 1998). In more advanced stages of the disease, this increase may occur, albeit with a low number of cases (Amusategui et al., 2003; Rebelo et al., 2021).

In a study conducted by Santos et al. (2020), during the staging of dogs being treated with miltefosine, the C and U values were normal, which is in agreement with our findings.

Miltefosine has no nephrotoxic action, although some effects cannot be completely ruled out. The renal parameters have prognostic values and are considered reserved when the levels of U and C are persistently elevated, even post-treatment (Vischer et al., 2007). The renal changes caused by leishmaniasis are secondary to the deposition of immune complexes in the glomeruli, which can lead to interstitial nephritis and membranoproliferative glomerulonephritis, generating function impairment and often being the main cause of death in dogs with leishmaniasis. Renal failure may be present in dogs without systemic clinical signs of leishmaniasis (Ciaramella et al., 2005), caused by cellular infiltration in the glomerular and interstitial regions of the kidneys (C. H. N. Costa, 2011).

In the present study, the B-mode ultrasonographic evaluation did not demonstrate any sonographic alterations originating from the urinary tract in G1 that could have compromised the participation of the dogs in the study. Some animals of G2 showed the changes reported by Baltazar et al. (2016) and Oliveira et al. (2018) for patients positive for leishmaniasis, such as splenomegaly, nephropathy, points of renal mineralization, and the presence of echogenic punctiform content in the urinary bladder. In G3, we observed splenomegaly in all patients, glomerulonephritis in one patient, and hepatopathy and points of mineralization in the kidneys in some animals (Figure 2).

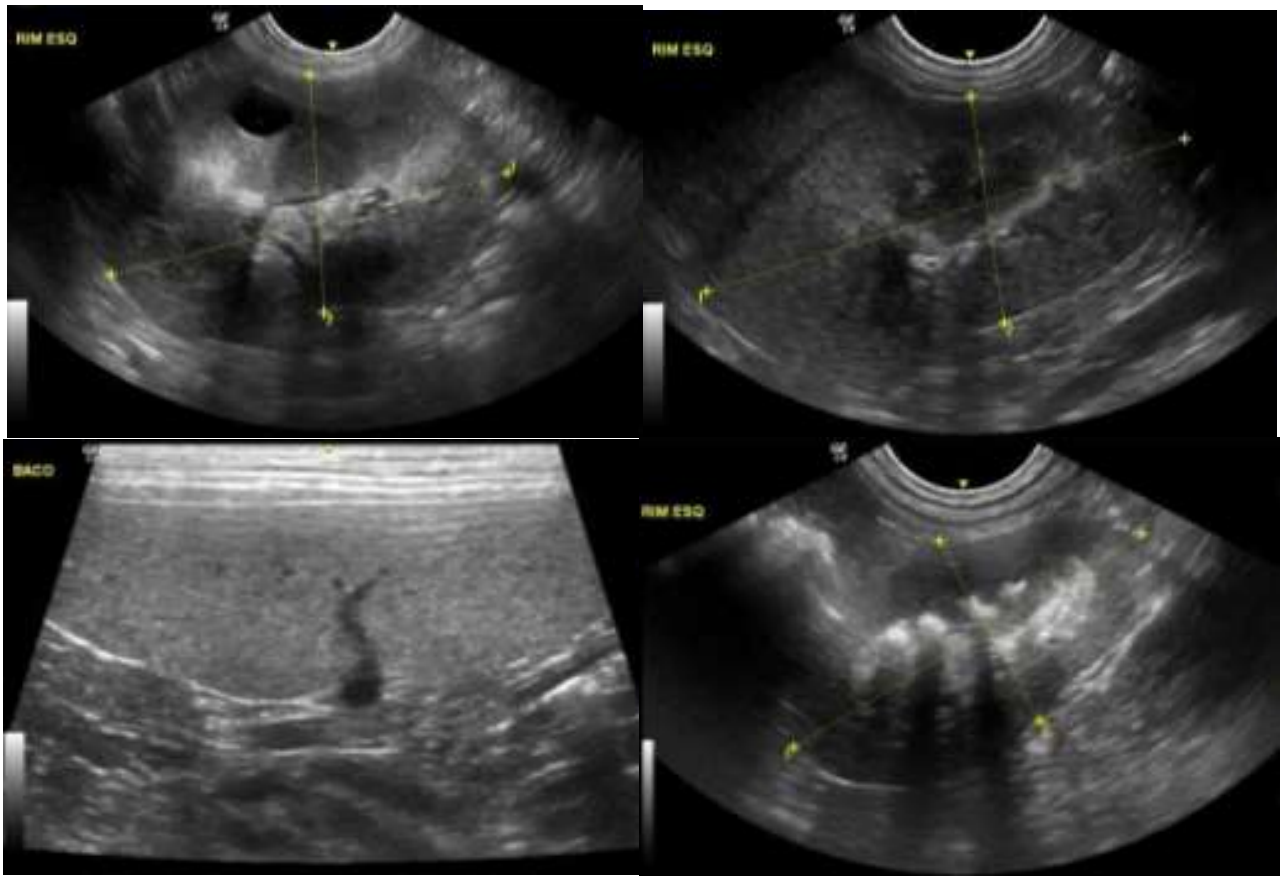

Figure 2. A - Image referring to the left kidney of a G2 patient, with morphological changes and the presence of a cyst. B - Image referring to the left kidney of a G1 patient, without sonographic alterations. C - Image referring to the spleen of a G3 patient, with splenomegaly. D - Image referring to the left kidney of a G4 patient, with morphological alterations and the presence of mineralization points.

Renal Doppler evaluation was performed in all patients. The small intra-renal vessels could not be evaluated in all patients because it was impossible to isolate and evaluate them during respiratory movement and because of overlapping of the abdominal content. The dogs belonging to G2 and G3 showed signs of hypo-vascularization in the intrarenal vessels when assessed using Collor Doppler.

The increase in the echogenicity of the renal cortex and the loss of corticomedullary delimitation, also observed in studies of dogs with leishmaniasis, are changes related to chronic diseases such as interstitial nephritis and/or glomerulonephritis, corroborating with previous findings (Greene, 2013; Nyland et al., 2002; Lamb et al., 2018; Oliveira et al., 2018). Renal ultrasound images of dogs with leishmaniasis show heterogeneous

echotexture, reduced vascular flow, less visible arched arteries, and high IR values (Baltazar et al., 2016; Rebelo et al., 2021). According to Mamprim et al. (2018), conventional ultrasonographic evaluation is one of the most important diagnostic procedures for renal evaluation, but only with Doppler, information of intrarenal blood flow alteration by means of the resistivity index can be obtained. This can facilitate the diagnosis of nephropathies because acute renal alterations do not promote numerous alterations to B-mode ultrasound.

In the volumetric Doppler measurement, the systolic velocity (SV) values ranged from 42.4 to 60.2 cm/s for the right kidney and 45.4 to 60.1 cm/s for the left one. Diastolic velocity (DV) ranged from 14.5 to 21.3 cm/s in the right kidney and 15.8 to 19.8 cm/s in the left one. No statistical difference was observed for the SV and RV variables between kidneys and among groups. Regarding the resistivity index (RI), values of 0.67 to 0.68 were observed for the right kidney and 0.65 to 0.68 for the left kidney, with no statistical difference between among the groups and evaluations (Table 2).

Table 2
Comparison of mean values (± standard deviation) of SV, VD, and IR in kidneys (R - right; L - left) evaluated at two moments (1 - 1st evaluation; 2 - 2nd evaluation) in negative, positive dogs without treatment (POSITIVE) and *Leishmania*-positive dogs with treatment (TREATED)

GROUP	KIDNEY	EVAL	PARAMETER		
			SV	DV	RI
NEGATIVE	R	1	47 ± 15.6	15.3 ± 5.7	0.68 ± 0.06
	R	2	53.8 ± 22.3	16.6 ± 6.9	0.67 ± 0.07
	L	1	45.8 ± 13.3	15.8 ± 4.6	0.65 ± 0.06
	L	2	50.8 ± 18.8	16.1 ± 5.5	0.65 ± 0.06
POSITIVE	R	1	44.5 ± 18.2	14.5 ± 5.5	0.66 ± 0.08
	R	2	42.4 ± 16.7	16.8 ± 9.7	0.66 ± 0.08
	L	1	46.1 ± 18.8	16.1 ± 8.5	0.66 ± 0.07
	L	2	46.2 ± 16.7	17.5 ± 7.5	0.67 ± 0.04
TREATED	R	1	54.2 ± 17.8	18.5 ± 7	0.67 ± 0.06
	R	2	60.2 ± 32.4	21.3 ± 16.1	0.67 ± 0.07
	L	1	53.1 ± 16.7	18.4 ± 7.2	0.68 ± 0.04
	L	2	60.1 ± 27.8	19.8 ± 11.1	0.67 ± 0.06

*Averages different within groups by the SNK test ($p<0.05$); § Averages between groups by Tukey´s test ($p < 0.05$). Averages with normal distribution and homogeneity of variances, respectively, by Cramer-von Mises and Brown and Forsythe tests ($p > 0.05$). Systolic velocity (SV); Diastolic velocity (DV); Resistivity index (RI).
Reference values: VS: 79.96 cm/s; VD: 28.86 cm/s (M. B. Melo et al., 2006). IR: < 0.7 (Koch et al., 1997).

The RI values obtained in this study were within the normal range for the species according to Novellas et al. (2007), 0.72, Zubarev (2001), 0.71, Baltazar et al. (2016), 1.1, and Agut et al. (2020), 0.66. These animals had no Doppler flux metric abnormalities of the renal arteries, conforming that the Doppler technique is relevant in the early evaluation of renal diseases by allowing the identification of abnormal perfusion patterns, However, in a comparative study between RI values and renal biopsy findings, the author reported that in some cases, kidneys with purely glomerular disease may have RI values within normal limits and alterations in echogenicity (Platt, 1997). The average values of peak systolic velocity obtained in this study were lower than the 79.96 cm/s reported by M. B. Melo et al. (2006); the normal values reported for humans range from 60 to 100 cm/s (Zubarev, 2001).

In the final RV, we observed lower results than those reported by M. B. Melo et al. (2006), who obtained an average of 28.86 ± 8.82 cm/s. However, the difference between the groups is notable since changes in flow velocity, both systolic (42.4 to 60.2 cm/s) and diastolic (14.5 to 21.3 cm/s), may have some clinical significance. Koch et al. (1997) considered 0.70 as the upper limit for RI in normal dogs, a value also proposed by Agut et al. (2020) as being normal for dogs. We use no sedative protocol and therefore avoided any interference with heart and respiratory rates, which remained within normal physiological limits; the arterial branches evaluated were exclusively the right and left renal arteries. Novellas et al. (2007) determined normality references in the intrarenal artery resistivity index in non-sedated dogs and cats because these values can facilitate the detection of changes in blood flow in the renal bed. Increased resistivity levels may be related to end-stage renal disease, showing intrarenal parenchymal lesions, although some systemic parameters, such as heart rate, may influence these levels (Radermacher et al., 2002, 2003; Rebelo et al., 2021). These influences were not observed in this study, where the RI presented within normal levels, demonstrating that the animals evaluated had no intra-renal parenchymal lesions.

In a study performed in dogs with leishmaniasis, evaluating the kidney by means of B-mode and Doppler ultrasound, Baltazar et al. (2016) and Oliveira et al. (2018) obtained high RI values (1.1 and 0.67, respectively) and a positive correlation between with the creatinine and resistivity index (C/RI). Ostrowska et al. (2016), when evaluating the RI of healthy dogs with an average age of 6 years, obtained values of 0.64. Lotério (2018), when evaluating dogs with heart disease and pyometra, obtained values of 0.73 to 0.85, indicating that pre-existing changes caused renal changes. When evaluating animals from the age of 1 day up to adulthood, Agut et al. (2020) observed that the RI values of puppies up to 20 weeks (0.64 to 0.89) were higher than those of adults (0.66) and that after 1 year, the values stabilized. The data obtained by Agut et al. (2020) and Ostrowska et al. (2016) are similar to those of the present study, where the RI values, although without oscillation among the evaluated parameters (IR 0.62 to 0.69), are lower than those reported by Baltazar et al. (2016) and Lotério (2018). The lower values are most likely a result of the inclusion of dogs with morphological, histological, and biochemical alterations, in contrast to the dogs used in the present study.

In the veterinary literature, the normal values of renal RI largely differ among different studies (Morrow et al., 1996). When comparing the RI values of normal and nephropathic dogs, Morrow et al. (1996) concluded that an RI greater than 0.70 was considered abnormal, and the sensitivity and specificity values of this index in determining normal versus abnormal kidneys were 38% and 96%, respectively. Further, the authors concluded that the combination of an unaltered B-mode ultrasound examination and an RI > 0.70 is suggestive of active renal disease of the tubulointerstitial and vascular compartments.

The parameters evaluated in the present study are within the normal ranges for canines. This corroborates the results of Lotério (2018), who reported a positive correlation between the RI and C level. According to Lotério (2018), the most severe RI alterations happen in the distal arterial branches.

Lotério (2018) justified the C/RI correlation with the four stages of acute renal failure (ARF). The first or initial phase may occur soon after the renal insult, followed by the extension phase (second stage), during which ischemia, hypoxia, inflammation, and tubular injury lead to apoptosis or necrosis (Ross, 2011). In the extension stage, the initial insult is amplified by ongoing renal inflammation and worsening ischemia and hypoxia. Toxins disrupt adenosine triphosphate (ATP)-generating metabolic pathways, and ischemia can deplete cellular ATP stores. Consequently, there is a loss of energy and failure of the sodium-potassium pump, culminating in edema, cell death, and nephron dysfunction. Nephron dysfunction leads to a decreased glomerular filtration rate (GFR), and azotemia will become evident only in the third stage of ARF (Ware, 2006; Ross, 2011). The increase in RI can be revealed as early as in the second stage, where changes in vascular impedance are observed (Platt et al., 1991), whereas the increase in C is only observed in the third stage with the decline in the GFR (Lotério, 2018). The positive correlation between C and renal artery RI values supports the link of the indices and the GFR since increased arterial resistance is associated with worsening renal function (Espada et al., 2006; Lotério, 2018).

The normality of biochemical and ultrasonographic parameters, even in the face of the challenges imposed by the treatment, demonstrates the feasibility of the Doppler examination for the staging of leishmaniasis treatment. This is in agreement with Dadalto (2020), who concluded that Doppler ultrasonography is a viable technique with hemodynamic information of the renal perfusion impairment as the resistivity index was higher in relation to the normality values previously described. These findings precede the alteration of the symmetric dimethylarginine biomarker (SDMA), since they had histological proof of the lesion.

Conclusion

Via renal ultrasonography, we evaluated the morphological changes preceding biochemical and urinary alterations. Our results enable a precise prognosis and the establishment of adequate treatment strategies. The association of ultrasonographic and biochemical evaluations proved to be efficient in

determining nephropathies without clinical or laboratory alterations. The treatment of leishmaniasis with miltefosine did not lead to changes in renal function and vascularization in dogs.

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