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Effect of Thyroxine Supplementation on Glomerular Filtration Rate in Hypothyroid Dogs

K. Gommeren*, I. van Hoek*, H.P. Lefebvre, G. Benchekroun, P. Smets, and S. Daminet

Background: Glomerular filtration rate (GFR) is decreased in humans with hypothyroidism, but information about kidney function in dogs with hypothyroidism is lacking.

Hypothesis: Hypothyroidism influences GFR in dogs. The objective of this study was to assess GFR in hypothyroid dogs before implementation of thyroxine supplementation and after re-establishing euthyroidism.

Animals: Fourteen hypothyroid dogs without abnormalities on renal ultrasound examination or urinalysis.

Methods: Blood pressure and GFR (measured by exogenous creatinine clearance) were measured before treatment (T0, n = 14) and at 1 month (T1, n = 14) and at 6 months (T6, n = 11) after beginning levothyroxine supplementation therapy (20 μg/kg/d, PO). The response to therapy was monitored at T1 by measuring serum total thyroxine and thyroid stimulating hormone concentrations. If needed, levothyroxine dosage was adjusted and reassessed after 1 month. Statistical analysis was performed using a general linear model. Results are expressed as mean ± standard deviation.

Results: At T0, the average age of dogs in the study group was 6.3 ± 1.4 years. Their average body weight decreased from 35 ± 18 kg at T0 to 27 ± 14 kg at T6 ($P < .05$). All dogs remained normotensive throughout the study. GFR increased significantly with levothyroxine supplementation; the corresponding results were 1.6 ± 0.4 mL/min/kg at T0, 2.1 ± 0.4 at T1, and 2.0 ± 0.4 at T6 ($P < .01$).

Conclusion: GFR was <2 mL/min/kg in untreated hypothyroid dogs. Re-establishment of a euthyroid state increased GFR significantly.

Key words: Canine; Hypothyroidism; Kidney function; Thyroid.

Hyper and hypothyroidism are known to alter kidney function in humans and experimental animals other than dogs.[1–7] These changes in kidney function are mediated indirectly by effects on the cardiovascular system and renal blood flow (RBF) and directly by effects on glomerular filtration rate (GFR), tubular secretory and absorptive capacities, and the structure of the kidney. Hyperthyroidism increases the rate of several physiologic processes, which is reflected in decreased systemic vascular resistance, increased cardiac output and increased RBF,[1] hypertrophic and hyperplastic tubules,[2] and increased GFR.[3] Most effects of hypothyroidism on kidney function are opposite those caused by hyperthyroidism. Intrarenal vasoconstriction,[4] decreased response to vasodilators in the kidney,[1] and decreased activity of the renin-angiotensin-aldosterone-system (RAAS)[5] all cause decreases in RBF. Together with the decreased cardiac output that occurs in hypothyroidism,[6] these processes lead to decreased GFR and increased serum creatinine concentration in experimental animals and humans.[3,7]

The correlation between the severity of thyroid dysfunction and renal function has been documented in humans with normal renal function. It has been established by Den Hollander et al[3] that treatment of hypothyroidism results in increased renal function, whereas treatment of hyperthyroidism results in decreased renal function. Strong correlations between

Abbreviations:

AUC	area under serum concentration versus time curve
BW	body weight
ECC	exogenous creatinine clearance
fT4	free T4
GFR	glomerular filtration rate
HPLC	high-performance liquid chromatography
RAAS	renin-angiotensin-aldosterone-system
RBF	renal blood flow
rhTSH	recombinant human TSH
SD	standard deviation
TSH	thyroid stimulating hormone
TT4	total thyroxine
UPC	urine protein/creatinine ratio
USG	urine specific gravity

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changes in thyroid status, serum creatinine concentration, and GFR also were noted by these authors.[3]

Naturally occurring hypothyroidism is caused by lymphocytic thyroiditis or idiopathic thyroid atrophy.[8] Currently, little information about the effect of hypothyroidism on kidney function in dogs is available in the literature. Therefore, the objective of this study was to evaluate kidney function, including GFR, in hypothyroid dogs before thyroxine supplementation therapy and after re-establishment of euthyroidism.

Materials and Methods

Animals

Fourteen client-owned dogs were included in this study. All owners provided written informed consent before enrollment. Inclusion criteria included a diagnosis of hypothyroidism based on serum total thyroxine (TT4) concentration below reference ranges confirmed by low serum free T4 (fT4) concentration and increased serum thyroid stimulating hormone (TSH) concentration. If serum TSH was not increased, the diagnosis was confirmed by either a positive titer for antithyroglobulin antibodies or an insufficient response to a recombinant human TSH (rhTSH) stimulation test. Dogs were considered hypothyroid if the absolute increase in serum TT4 post-rhTSH stimulation was <20 nmol/L or if the post-rhTSH stimulation TT4 concentration was <40 nmol/L.[9] The hypothyroid dogs were further assessed for inclusion by routine physical and laboratory examinations (CBC, biochemistry, and urinalysis) and renal ultrasonography. Dogs were excluded if they showed abnormalities on renal ultrasound examination or urinalysis. All urinalyses included sediment analysis. Dogs were also excluded if they had concurrent disease or had received medication that could possibly influence thyroid or kidney function within 2 months before inclusion in the study. Azotemia, however, was not a reason for exclusion.

Therapy for hypothyroidism consisted of oral levothyroxine (20 μg/kg/d; by tablet[a] q12h in the morning and evening or liquid[b] q24h in the morning). On days that a clearance test was performed, medication was administered at home in the morning before the patient was brought to the clinic. Therapy was assessed after 1 month (T1) by measuring serum TT4 and TSH. Therapy was adjusted as needed with 10–15 μg/kg/d levothyroxine and reassessed 1 month later. Dogs were re-evaluated at T1 after starting supplementing therapy and 5 months after establishing the optimal dose (ie, 6 months after the start of the treatment [T6]). At each visit, GFR, blood pressure (indirect Doppler method expressed as a mean of 5 consecutive measurements), serum creatinine concentration, urine specific gravity (USG), and urine protein/creatinine ratio (UPC) were determined.

GFR Measurement

Dogs were fasted for at least 10 hours before the start of the clearance test and fed immediately after the end of the sampling period. Water was offered ad libitum. Methods for assessing GFR by the exogenous creatinine clearance (ECC) test were similar to those previously described.[10,11,c] Briefly, animals received a bolus of 40 mg/kg creatinine dissolved in a 0.9% sodium chloride solution[d] through the cephalic vein. The dead space in the catheter was rinsed with 0.9% sodium chloride solution.[d] Blood samples (4 mL) were taken by jugular venipuncture immediately before creatinine administration and at 10 minutes and 1, 2, 6, and 10 hours after administration, placed in serum tubes, allowed to clot, and centrifuged. Aliquots of serum were stored at $-20\,^{\circ}C$ until analysis. Serum creatinine concentration was measured using a validated enzymatic method.[e] For a given dog, samples obtained during the 3 separate GFR measurements were assayed on the same day. Quality control samples were measured on each day that a run of assays was performed. The upper limit of quantification was 13.6 mg/dL. Within- and between-day coefficients of variation were $<3\%$ in the lower, middle, and upper ranges of concentration (1.2, 7.5, and 12.2 mg/dL), respectively, and there was a linear correlation between theoretical and measured concentration within quantification limits. A GFR result >2 mL/min/kg was considered normal and dogs with such values were considered to have normal renal function, whereas dogs with lower results were considered to have renal impairment, as previously defined.[12,13]

Pharmacokinetic Analysis

All analyses were performed using WinNonlin.[f] Serum concentrations were subjected to noncompartmental analysis using a statistical moment approach. The area under the serum concentration versus time curve (AUC) was calculated using the trapezoidal rule with extrapolation to infinity, as described by Watson et al.[10] Serum clearance of creatinine was determined by dividing the dose administered by the AUC, and indexed to body weight (BW) (mL/min/kg).

Statistical Analysis

A general linear model[g] was used to test the time effect on each variable. When a statistically significant effect was observed, a post-hoc multiple pair-wise comparison test was performed to compare values among various time points (T0, T1, and T6). Results are expressed as mean ± standard deviation (SD).

Results

The mean age of the dogs at the time of inclusion was 6.3 ± 1.4 years. No abnormalities on renal ultrasonography or urinalysis were identified. No dogs were excluded because of concurrent disease. Five dogs had serum creatinine concentrations above the reference range at inclusion, but none of these dogs had polyuria or polydipsia reported by the owner. Two dogs had superficial bacterial dermatitis that resolved rapidly with cefalosporin and levothyroxine treatment. The 14 dogs comprised 10 different breeds, 6 females (4 intact), and 8 males (5 intact). All 14 dogs received follow-up at T1; however, 3 dogs were lost for follow-up at T6 because of the owners' decision to withdraw their pets from the study for nonmedical reasons. Urinalysis was not performed for 2 of the 11 dogs at T6.

All dogs remained normotensive throughout the study and systolic blood pressure ranged from 100 to 160 mmHg. Results for BW, serum creatinine concentration, GFR, USG, and UPC before and 1 and 6 months after treatment are presented in Table 1. There was a significant decrease in the mean BW of the dogs between T0 and T6 ($P = .008$); however, there was no significant difference in BW between T0 and T1 or between T1 and T6.

There also was an increase in GFR with treatment, with a significant difference in GFR between T0 and T1 ($P = .001$) and between T0 and T6 ($P = .008$). However, there was no significant difference in GFR between T1 and T6. GFR was <2 mL/min/kg in 12 of the 14 dogs at T0, 6 of the 14 dogs at T1, and 5 of the 11 dogs at T6.

Table 1. Changes in clinical and laboratory variables before (T0) and 1 (T1) and 6 (T6) months after starting levothyroxine treatment.

	T0	T1	T6
BW	34.7 ± 17.5^{a}	33.3 ± 17.3^{a}	27.3 ± 14.3^{b}
	(6.9–63.0)	(6.1–67.0)	(4.5–45.3)
	N = 14	N = 14	N = 14
Serum creatinine	1.4 ± 0.4^{a}	1.1 ± 0.2^{b}	$1.2 \pm 0.3^{a,b}$
	(0.8–2.4)	(0.7–1.4)	(0.7–1.5)
	N = 14	N = 14	N = 11
GFR	1.6 ± 0.4^{a}	2.1 ± 0.4^{b}	2.0 ± 0.4^{b}
	(1.1–2.6)	(1.5–3.1)	(1.5–2.6)
	N = 14	N = 14	N = 11
USG	1.028 ± 0.015^{a}	1.027 ± 0.018^{a}	1.022 ± 0.015^{a}
	(1.007–1.050)	(1.006–1.050)	(1.006–1.035)
	N = 14	N = 14	N = 9
UPC	0.5 ± 0.9^{a}	0.5 ± 0.7^{a}	0.3 ± 0.3^{a}
	(0.07–3.28)	(0.07–2.37)	(0.05–1.07)
	N = 14	N = 14	N = 9

Results are reported as mean ± SD (range). N indicates the number of dogs evaluated. Different superscripts indicate a statistically significant difference between values. *P*-values are reported in the text.

BW, body weight; GFR, glomerular filtration rate; USG, urine specific gravity; UPC, urine protein/creatinine ratio.

Serum creatinine concentration decreased after treatment, with a significant difference between T0 and T1 ($P = .024$). No significant difference was noted between T0 and T6 or between T1 and T6. Observed GFR was <2 mL/min/kg in untreated hypothyroid dogs.

There were no significant changes in USG or UPC after treatment. USG was <1.030 in 9 of the 14 dogs at T0, 7 of the 14 dogs at T1, and 7 of the 9 dogs at T6. Proteinuria (UPC > 0.5) was present in 2 of the 14 dogs at T0, 2 of the 14 dogs at T1, and 1 of the 9 dogs at T6.

The relationships between pretreatment TT4, GFR, and serum creatinine concentration are shown in Figure 1A–1C. GFR appeared to have been influenced more by a low serum TT4 concentration than had serum creatinine concentration. Twelve of 14 dogs had GFR <2 mL/kg/min at T0 (Fig 1A). In contrast, the serum creatinine concentrations of 9 of the 14 dogs were within the reference range at T0 (Fig 1B). Of dogs with GFR <2 mL/min/kg, all but 5 had serum creatinine concentrations within the reference range at T0 (Fig 1C). In addition, Figure 1D illustrates how serum creatinine concentration remained poorly correlated with GFR after treatment for hypothyroidism, as many dogs with GFR <2 mL/min/kg still had serum creatinine concentrations within the reference range at T6.

Discussion

This study is the first to describe decreased GFR in hypothyroid dogs and an increase in GFR after re-establishment of euthyroidism. This study also showed that serum creatinine concentration was slightly increased or remained within the reference range in hypothyroid dogs, as previously described.[14] This observation confirms that serum creatinine concentration is an unreliable indicator of kidney function in hypothyroid dogs. Moreover, serum creatinine concentrate can be increased in hypothyroidism because of reduced GFR, but also may be increased because of creatinine generation from possible myopathy and rhabdomyolysis, as occurs in humans.[15,16] Creatine kinase concentration is increased in hypothyroid dogs, and this increase was suggested to be related to decreased metabolism or excretion, or associated with hypothyroid-related myopathy.[17] Nonetheless, a recent study showed that in hypothyroidism in humans, increased serum creatinine concentration was not related to impaired creatinine metabolism.[18]

There are at least 2 explanations for the lack of a statistical difference in serum creatinine concentrations between T0 and T6, even though a significantly increased GFR was observed. First, the lack of a significant difference could reflect an increase in muscle mass and, consequently, increased creatinine generation after correction of hypothyroidism. This mild increase in serum creatinine concentration could have resulted in a lack of statistical significance. Secondly, and more likely, it could be that serum creatinine concentration is not a very accurate indicator of renal function.

Decreases in GFR of 40 and 30% have been described in hypothyroid humans and rats, respectively.[3,7,18–20] A study performed more than half a century ago suggested that GFR was decreased in thyroidectomized dogs and increased after they were fed thyroid tissue.[21] In that study, hypothyroidism was not diagnosed according to current standards and GFR was not measured by a validated method. The decreased GFR seen in hypothyroidism could have several causes. First, hypothyroidism is associated with decreased renal perfusion,[3] which results from decreased cardiac output and circulating volume, impaired RAAS activity, and decreased atrial natriuretic peptide concentration.[20,22,23] Second, growth retardation in the parenchyma of the kidney, as described in mature rats with experimental hypothyroidism, can decrease glomerular surface area.[24] Third, filtrate overload caused by deficient sodium and water reabsorption in the proximal tubule could lead to adaptive preglomerular vasoconstriction.[25] Fourth, tubuloglomerular feedback decreases GFR when increased chloride load is sensed in the distal tubules, and renal expression of the chloride channel ClC-2 is decreased in hypothyroid rats.[26]

The clinical relevance of decreased GFR in hypothyroid dogs remains to be established. A GFR <2 mL/min/kg, as identified here in untreated hypothyroid dogs, is compatible with renal impairment but does not necessarily imply renal disease. There are no reports of acute or chronic renal failure in dogs secondary to hypothyroidism, but hypothyroidism-associated glomerulonephritis caused by lymphocytic-plasmacytic thyroiditis has been reported in a Boxer dog.[27] Hypothyroidism is a primary cause of acute renal failure in humans, but usually is reversed by treatment with levothyroxine.[28–30] Hypothyroidism-associated rhabdomyolysis has been implicated in development of acute renal failure.[29,30] However, independent of the issue regarding the development of chronic kidney disease in hypothyroid dogs, these

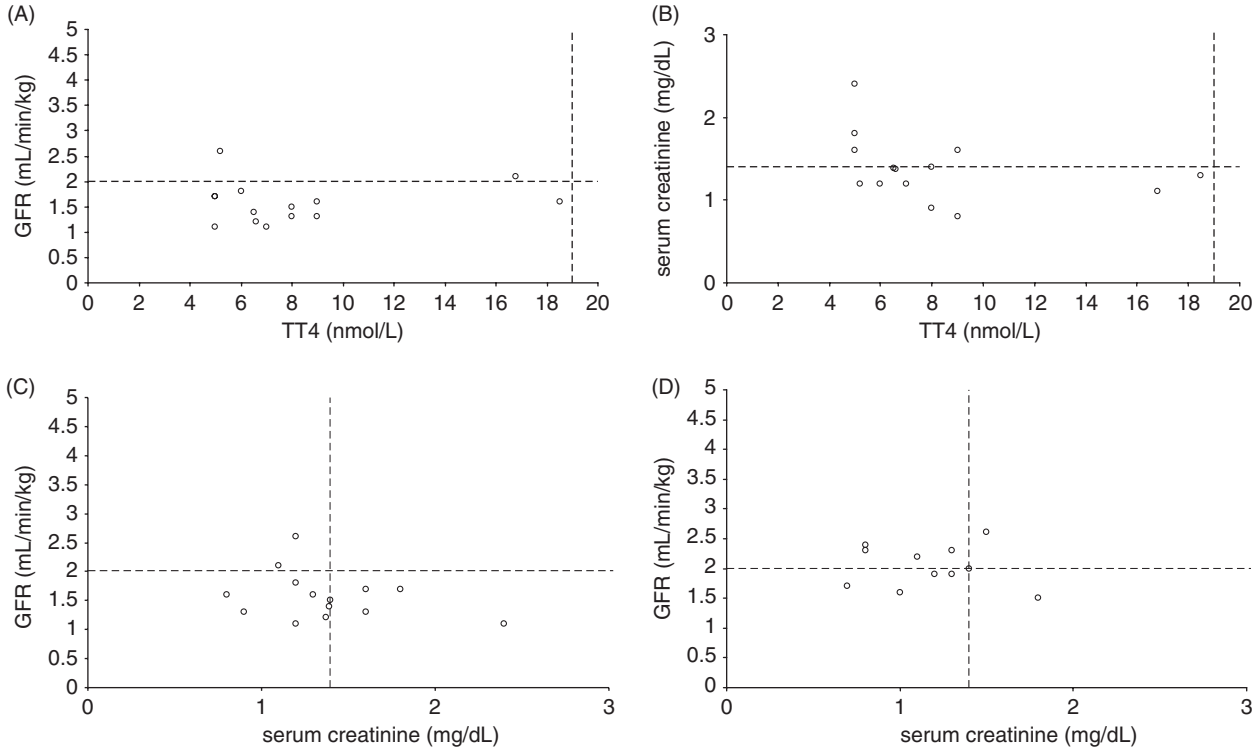

Fig 1. **(A)** Relationship between pretreatment serum total thyroxine (TT4) concentration (nmol/L) and glomerular filtration rate (GFR) (mL/min/kg) in 14 hypothyroid dogs. Horizontal dotted line represents the cut-off value for serum creatinine clearance (2.0 mL/min/kg). Vertical dotted line represents the lower reference range for serum TT4 concentration. **(B)** Relationship between pretreatment serum TT4 concentration (nmol/L) and serum creatinine concentration (mg/dL) in 14 hypothyroid dogs. Horizontal dotted line represents the cut-off value for renal azotemia (1.4 mg/dL). Vertical dotted line represents the lower reference range for serum TT4 concentration. **(C)** Relationship between pretreatment serum creatinine concentration (mg/dL) and pretreatment GFR (mL/min/kg) in 14 hypothyroid dogs. Vertical dotted line represents the cut-off value for renal azotemia (1.4 mg/dL). Horizontal dotted line represents the cut-off value for serum creatinine clearance (2.0 mL/min/kg). **(D)** Relationship between post-treatment (T6) serum creatinine concentration (mg/dL) and GFR (mL/min/kg) in 11 hypothyroid dogs. Vertical dotted line represents the cut-off value for renal azotemia (1.4 mg/dL). Horizontal dotted line represents the cut-off value for serum creatinine clearance (2.0 mL/min/kg).

patients could represent a population at high risk of renal injury in specific settings (eg, nephrotoxic drugs, general anesthesia, dehydration).

In the current study, GFR increased significantly after re-establishment of euthyroidism, but GFR remained <2 mL/min/kg in most of the dogs. In humans with hypothyroidism, decreased GFR is corrected after treatment with thyroid hormone, suggesting that the decrease in GFR was because of functional renal changes that did not cause permanent histologic damage.[3,18,31,32] Thus, the persistence of low GFR after re-establishing euthyroidism in the current study may suggest irreversible alterations in kidney function. However, our study design does not allow us to confirm the presence of renal injury or determine what the cause may have been. All dogs remained normotensive throughout the study, and thus changes in kidney function were unlikely to be caused by changes in systemic arterial pressure. At T6, euthyroidism may not have been re-established long enough to improve kidney function sufficiently. However, GFR did not change between T1 and T6, and a change in GFR after more than 6 months of therapy would not be expected. Reference ranges of GFR can differ among healthy dogs of different ages and breeds. Thus, comparing our data to those obtained from an age-matched control group would allow a more precise analysis of the increase in GFR after re-establishment of euthyroidism.[33,34]

All dogs responded to treatment, and euthyroidism was re-established in all dogs. Nonetheless, because the levothyroxine was administered orally, variations in pharmacokinetic parameters could complicate data interpretation. Because there appears to be no accumulation of thyroxine after repeated administration,[35] treatment timing could have affected our results. However, all dogs received levothyroxine at home in the morning before being brought to the clinic where the clearance test was performed. Hence, GFR testing was performed at approximately the same time after levothyroxine administration in all dogs, suggesting that all GFR determinations were performed under very similar conditions. Therefore, it is unlikely that treatment timing had a notable effect on our results.

Changes in serum TT4 concentration throughout the day can be expected and serum TT4 measurements are not reflective of a steady state. In addition, 2 different thyroxine formulations were used in this study, which could have further complicated pharmacokinetic

influences on our results. In contrast, GFR was measured over a 10-hour sampling period and the measured GFR is the result of more constant kidney function in a euthyroid state. Therefore, it is difficult to correlate GFR results to serum TT4 concentrations. This is in contrast to GFR results after treatment with radioiodine in hyperthyroid cats, where decreased GFR could be evaluated reliably over a range of serum TT4 concentrations.[36]

BW decreased after thyroxine supplementation. This decrease is expected because euthyroidism is associated with an increase in the metabolic rate and an increase in activity level of the patient relative to hypothyroidism. GFR can be affected by BW, but because the increase in GFR preceded the decrease BW, it is unlikely that the change in GFR was related to the change in BW.

Urine concentrating ability is impaired in hypothyroid rats but is reversible with thyroxine replacement.[37,38] The USG of dogs in our study ranged from hypo to hypersthenuric and did not change significantly after treatment. Moreover, USG varied greatly in our dogs, as occurs in healthy dogs.[39] Together, these findings illustrate the weakness of USG as a marker of renal function.

There are some limitations to the present study that should be addressed. First, this study evaluated GFR in only a small group of hypothyroid dogs and did not include age-, breed-, or BW-matched control groups. Hence, the cut-off GFR value was based on information contained in the literature.[12] This cut-off value was consistent with values obtained in Beagle dogs and other breeds using the same technique, as well as with published ranges for dogs.[10,40,c] This cut-off value also was recently used to screen another at-risk population: dogs with cardiac disease.[13] GFR measurements obtained using different methods of GFR estimation in healthy animals and patients with renal insufficiency have been reported, but, proper reference intervals are not yet available for any described method. Nonetheless, differences in GFR, serum creatinine concentration, and BW before and after treatment for hypothyroidism were statistically significant in this group of dogs. Second, this study provides no information on the development of renal dysfunction during progression of hypothyroidism because treatment was initiated immediately after diagnosis of hypothyroidism. However, this study does show that thyroxine supplementation induced a persistent increase in GFR. Lastly, the causes underlying the initial decrease in GFR in hypothyroid dogs remain unclear. Measuring RBF or renal biopsy analysis could tell us whether the GFR decrease was associated with decreased renal perfusion or hypothyroidism-associated renal lesions. Another limitation of the study was the use of creatinine clearance for measuring GFR. Urinary clearance of inulin, not creatinine clearance, is the gold standard method for measuring GFR. However, techniques for measuring urinary clearance can be laborious, difficult to propose to owners, tedious and time consuming for the staff, stressful (anesthesia may be required) and potentially harmful for the patient, and obtaining accurate measurements of urine volume can be difficult. ECC has been suggested as a reliable estimate of GFR.[10] The difference between serum and plasma creatinine concentrations is negligible (about 5%).[41] Therefore, the use of serum rather than plasma concentrations is unlikely to have influenced our findings. Moreover, measurements of ECC is reproducible in cats, with coefficients of variation $<22\%$.[42] The difference in GFR between 2 time points in our study exceeded 22% and can therefore be considered to reflect a clinically relevant increase, assuming the same reproducibility in dogs as in cats. In the present study, serum creatinine concentration was analyzed using an enzymatic method. The gold standard method for measuring creatinine is HPLC. However, the enzymatic method was validated before the study, is most frequently used in routine clinical laboratories, and has been proven a reliable alternative to HPLC in cats.[43]

This study suggests that GFR is decreased in hypothyroid dogs and that this decrease is at least partially reversible by re-establishing euthyroidism. Serum creatinine concentration appears to be less reliable than estimating GFR for screening kidney function in such patients. It would be interesting to establish an experimental model that could ascertain progressive alterations in renal function in which renal function and morphology could be compared between the initial euthyroid state, after induction of hypothyroidism, and after re-establishment of euthyroidism. Furthermore, postmortem evaluation of evidence of permanent kidney lesions in hypothyroid dogs could expand our knowledge about the impact of hypothyroidism on renal function.

Footnotes

[a] Forthyron Levothyroxine sodium 400 mg/tablet, Eurovet Animal Health BV, Bladel, the Netherlands

[b] Leventa Levothyroxine sodium 1 mg/mL, DPT Lakewood Inc, Lakewood, NJ

[c] Lefebvre HP, Jeunesse E, Concordet D, et al. Assessment of glomerular filtration rate using plasma exogenous creatinine clearance test: Preliminary results in a healthy canine population. J Vet Intern Med 2004: 18, 415 (abstract)

[d] 0.9% sodium chloride solution, B Braun Melsungen AG, Melsungen, Germany

[e] Vettest analyzer, Idexx Laboratories Europe BV, Amsterdam, the Netherlands

[f] WinNonlin Version 4.0.1, Scientific Consulting Inc, Apex, NC

[g] Systat version 8.0, SPSS Inc, Chicago, IL

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