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Ultrasonographic Evaluation of Renal Cortex and Outer Medulla Thickness in Dogs with Chronic Kidney Disease

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Abstract : This study was performed to retrospectively pursue any correlation between renal cortex thickness (RCT), outer medulla thickness (OMT) on ultrasonography (US) and chronic kidney disease (CKD) with International Renal Interest Society (IRIS) stage. Medical records and US findings of the dogs diagnosed CKD were reviewed for comparing to those of the clinically healthy dogs from March. 2015 through June. 2016. To evaluate the correlation about normal and CKD patients, RCT and the OMT were measured on US images. RCT and OMT were adjusted by dividing body surface area for standardization (RCTS, OMTS). Also the ratio of RCT/OMT were calculated and these indices were evaluated to investigate any tendency between 5 groups (normal and 4 IRIS stages) using Jonckheere-Terpstra trend test (J-T test). The RCTS showed a declining tendency ($p < 0.02$) and the OMTS showed an inclining tendency from normal through each IRIS stage ($p < 0.01$). The RCT/OMT showed also declining tendency ($p < 0.01$). Although the gold standard for renal function including GFR is lack, it is thought that differentiation between normal and CKD patients could be possible on US measurement of renal cortex and outer medulla thickness, which could be an alternative index for kidney function in diagnostic imaging.

***Key words* :** dog, CKD, IRIS stage, cortex, outer medulla, ultrasonography.

Introduction

Chronic kidney disease (CKD) is defined as the presence of functional or structural disorders in kidneys. In general, these abnormalities can be evaluated by clinical pathologic approach such as symmetric dimethylarginine assay (SDMA), serum BUN and creatinine level (4,5). Also in diagnostic imaging, the ultrasonographic (US) findings of renal length, margin and echogenicity could be assessed. However, diagnostic imaging approach cannot be a quantitative analysis.

In human medicine, diagnostic imaging indices such as the thickness or volume of the cortex and medulla measured by US or computed tomography are developed as indicator of renal function. In studies of the relationship between renal cortex thickness on US and the degree of renal impairment in CKD using estimated glomerular filtration rate (eGFR), there was a statistically significant relationship between eGFR and cortical thickness (1,12,17). There are also several studies evaluating kidney function by measuring the volume of kidney parenchyma using CT or MRI (3,16).

This study is to investigate whether these indices can be applied to canine CKD patients and whether these indicators can represent renal function. The purposes of this retrospective study are to determine whether there are significant differences in renal cortical thickness (RCT) and outer medulla thickness (OMT) between normal and CKD patients and to pursue any correlation between US measurements of RCT, OMT with each IRIS stage in canine CKD patients.

Materials and Methods

Patient selection

Canine patients that were diagnosed with CKD for the first time at the Veterinary Medical Teaching Hospital, Seoul National University between March 2015 and June 2016 were recruited. Patients without serum chemistry results or abdominal US or difficult in identifying kidney structure due to progression of CKD were excluded. As a result, 26 CKD patients were selected for the study. All these patients, serum chemistry to measure BUN, creatinine and abdominal US were performed on the day at admission. Nineteen healthy canine patients without any abnormality in renal function confirmed by laboratory tests such as urine specific gravity, dip stick test, urine sediments and serum BUN, creatinine were also included in this study to compare with these CKD patients.

Ultrasonographic evaluation of renal cortex and outer medulla

Based on a study that discussed the outer medulla of normal canine kidney on US, we were able to establish the measuring criteria of RCT and OMT. According to this study, the hyperechoic outer medulla, which can be misinterpreted as a medullary rim sign in normal dogs without renal dysfunction, is particularly well visualized in small-breeds on US

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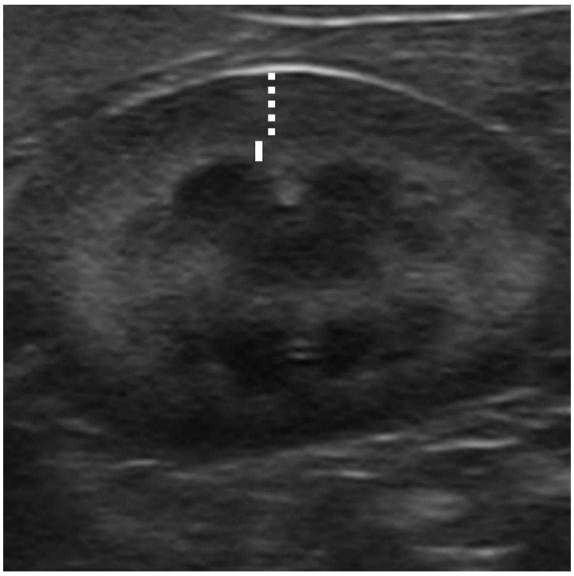

Fig 1. Ultrasonographic measurements of RCT (dash line) and OMT (full line) on sagittal section.

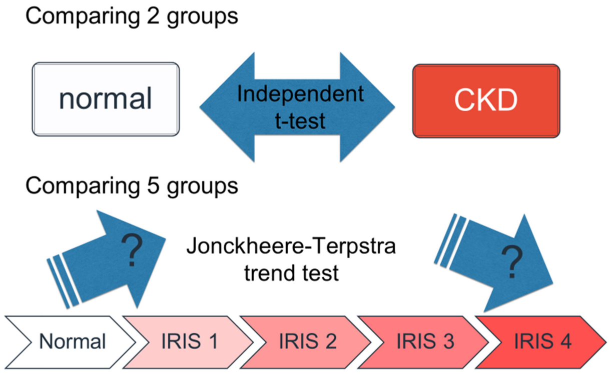

Fig 2. A summary of the statistical analysis used in this study. Comparing the indices (RCT, OMT, RCT/OMT) between normal and CKD patients using an independent t-test and then tried to figure out the trend of these indices between the five groups of the normal and the IRIS stages using the J-T trend test.

images. And this study concluded the outer medulla and the actual renal cortex on US should be distinguished (6).

The US images were obtained using 4-9 or 4-10MHz microconvex and 5-12 or 5-13 MHz linear probes (SA-9900, Medison, Seoul, Korea; and Aloka Prosound 7, Hitachi Aloka Medical Ltd., Tokyo, Japan). And the images were evaluated with a DICOM workstation (INFINITT PACS, INFINITT Healthcare Co., Ltd., Seoul, Korea) using electronic calipers. In US images, the RCT and OMT were measured at the middle point of the kidney in the sagittal or dorsal section. RCT was made in the uppermost hypoechoic part of the renal parenchyma and OMT was performed in the hyperechoic parenchyma region below the cortex (Fig 1). RCT and OMT were adjusted by dividing body surface area for standardization (RCTS, OMTS). To ensure objectivity, the RCT and OMT were measured each three observers (S.L., S.H., S.C.) and observer measured three times independently. By comparing each of the three measurements, the intra-observer agreement of each observer was evaluated and the inter-observer agreement was evaluated by comparing the average values of the three measurements of each observer.

Statistical analysis

The data were analyzed 2 different ways. First, the RCTS, OMTS and RCT/OMT were compared between normal and CKD patients by independent *t*-test. And these indices were evaluated to investigate any tendency between 5 groups (normal and 4 IRIS stages) using Jonckheere-Terpstra trend test (J-T test) which is a test for verify the hypothesis that the medians of data are ordered (increase or decrease) among groups (7). The statistical analysis used in this study is illustrated schematically in (Fig 2). Intra- and inter-observer agreement were assessed using the Intraclass correlation coefficient (ICC). All statistical analysis was performed using SPSS (IBM SPSS Statistics for Windows, Version 23.0, IBM Corp., Armonk, NY, U.S.A.). A *p*- value < 0.05 was considered to represent statistically significant differences.

Results

Nineteen normal patients without clinical evidence of renal dysfunction and 26 CKD patients were included. The normal patients consisted of Maltese (n = 10), Yorkshire terrier (n = 2), Chihuahua (n = 1), Dachshund (n = 1), Pekingese (n = 1), Pomeranian (n = 1) and Cocker spaniel (n = 1), poodle (n = 2). The mean age was 3.63 years and average weight was 3.82 kg. They visited the hospital for G.I tract disease (n = 8), neurological disorder (n = 4) such as disc disease and seizure, dermatological disorder (n = 2), endocrine disease (n = 1), ophthalmic disorder (n = 1), etc. (n = 3) and no abnormality in the kidney function except the corresponding disease.

Table 1. Intra-observer agreement evaluation of normal and CKD patients

Normal	US index	ICC	CI	CKD	US index	ICC	CI
Observer 1	RCT	0.969	[0.853; 0.950]	Observer 1	RCT	0.985	[0.977; 0.991]
	OMT	0.989	[0.982; 0.994]		OMT	0.994	[0.990; 0.996]
Observer 2	RCT	0.987	[0.977; 0.993]	Observer 2	RCT	0.994	[0.990; 0.996]
	OMT	0.988	[0.980; 0.994]		OMT	0.973	[0.957; 0.984]
Observer 3	RCT	0.994	[0.990; 0.997]	Observer 3	RCT	0.99	[0.984; 0.994]
	OMT	0.994	[0.990; 0.997]		OMT	0.997	[0.995; 0.998]

ICC: intraclass correlation coefficient, CI: confidence interval.

Table 2. Inter-observer agreement evaluation of normal and CKD patients. ICC: intraclass correlation coefficient, CI: confidence interval

	US index	ICC	CI
Normal	RCT	0.904	[0.834; 0.947]
	OMT	0.968	[0.944; 0.982]
CKD	RCT	0.796	[0.677; 0.876]
	OMT	0.823	[0.738; 0.887]

CKD patients consisted of Maltese (n = 8), Shihtzu (n = 7), Yorkshire terrier (n = 4), other small-sized breed (n = 2), medium-sized breed (n = 4), and large-sized breed (n = 1). The mean age was 12.08 years and average weight was 5.72 kg. The IRIS stage, defined as serum creatinine level, showed the following distribution; IRIS stage 1 (n = 6), IRIS stage 2 (n = 1), IRIS stage 3 (n = 14), IRIS stage 4 (n = 5).

The RCT and OMT is measured in US images by 3 observers (S.L., S.H., S.C.). Each observer measured 3 times and the mean value was used as a data. To secure objectivity, ICC was evaluate. A high agreement was found in the analysis of intra-observer agreement of RCT and OMT measurements on ultrasound in 19 normal patients. And intra-observer agreement in 26 CKD patients was also highly agreeable (Table 1). In the inter-observer agreement analysis, both RCT and OMT showed higher agreement in normal patients than CKD patients. RCT measurements in CKD patients showed slightly lower agreement than normal (Table 2). The measurements in patients with CKD were somewhat less consistent than normal patient. However, the ICC was higher than 0.75 in CKD patients and this could be interpreted as a good correlation between observers (2).

The RCT and OMT were compared by standardized values divided by the body surface area of the patients (RCTS, OMTS). The distribution of the measured RCTS, OMTS, and RCT/OMT values is shown in (Fig 3). The results of independent *t*-test for 19 normal and 26 CKD patients were shown in (Table 3). The RCTS was higher in normal group and the OMTS was higher in CKD group. The ratio of RCT to OMT (RCT/OMT) was smaller in patients with CKD. There were significant differences in RCTS, OMTS, and RCT/OMT between the two groups ($p < 0.05$).

Table 3. The mean values of RCTS, OMTS, and RCT/OMT in normal and CKD patients

	RCTS	OMTS	RCT/OMT
Normal	10.72 ± 0.38	5.55 ± 0.25	2.03 ± 0.86
CKD	9.19 ± 0.42	8.41 ± 0.41	1.12 ± 0.39
p-value	< 0.007**	< 0.05*	< 0.04*

Table 4. The results of J-T test in the 5 groups. The RCTS and OMTS, RCT/OMT

	RCTS	OMTS	RCT/OMT
St. J-T Statistic	−2.412	5.518	−7.797
p-value	< 0.016*	< 0.01**	< 0.01**

These indices were also significantly correlated with each IRIS stage. The RCTS showed a declining tendency ($p < 0.02$) and the OMTS showed an inclining tendency from normal through each IRIS stage ($p < 0.01$). The RCT/OMT showed also declining tendency ($p < 0.01$). The results of J-T test are shown in (Table 4). Fig 4 is a diagram interpreting the J-T test.

Discussion

Assessment of kidney in patients with CKD on US has been based on the cortical and medullary echo, length of kidney, and irregularity of margin. These are useful parameter in diagnosing CKD but cannot be quantitative analysis for kidney function (14). Therefore, this study was aimed to quantitatively evaluate the structural changes of kidneys on US with changes in kidney function. The most obvious indicator of kidney function is glomerular filtration rate (GFR). However, it is difficult to measure patient GFR in a clinical setting. Although serum creatinine levels do not increase until 75% of nephrons are damaged, or rise due to other causes

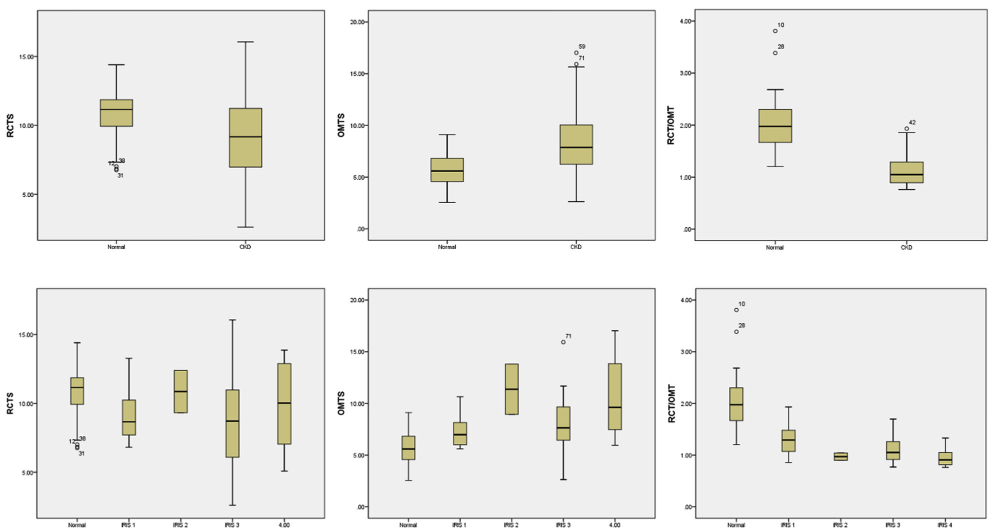

Fig 3. Boxplot of the RCTS, OMTS, RCT/OMT in normal and CKD patients and each IRIS stage groups.

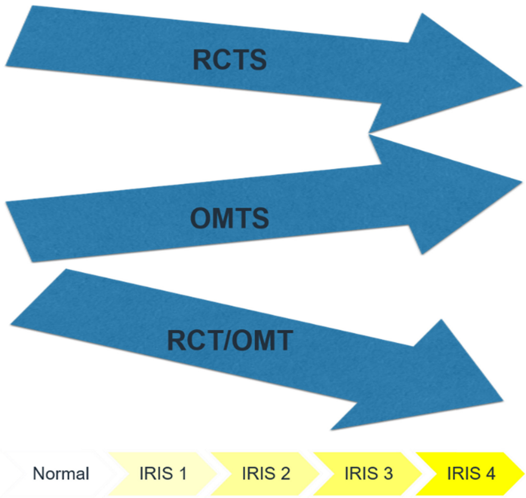

Fig 4. The tendency of the indices confirmed in this study by J-T trend test.

other than renal function, they replace GFR measurements in most clinical settings (15). In humans, various methods of obtaining estimate GFR (eGFR) that can predict GFR using only simple patient information such as body weight, age, sex and ethnicity based on the patient's serum creatinine concentration have been studied. In addition, studies have been actively carried out to obtain more accurate eGFR in CKD patients with renal dysfunction so that a more clinical approach can be achieved (8,9,11,13,19). In addition, this study found that SDMA, which is known to have a strong correlation with GFR and detect kidney dysfunction more earlier than serum creatinine, was not available due to lack of cases. (5,10). However, as the indices used in this study, there was a statistically significant difference between normal and CKD patients. Also we confirmed the tendency of each index according to IRIS stages. As the IRIS stage increased, that is, as the CKD progressed, the RCTS tended to decrease and the OMTS tended to increase, and thus the RCT/OMT statistically confirmed a tendency to be more markedly decreased (Fig 4).

The evaluation of outer medulla mentioned in this study has not been studied so far in veterinary research, especially diagnostic imaging. Also, OMT measurement was easier on US images than the whole medulla evaluation.

Decreased RCT in CKD is pathologically associated with glomerulosclerosis and tubular atrophy (18). The increase in OMT can be explained as follows: In humans, a study showed that GFR declines with normal aging and total kidney volume remains stable through about age 50 years due to declining cortical volume and a compensatory medullary volume increases (3). Further research will be necessary in canine patients about medullary thickness or volume moreover outer medulla with pathological approach.

The limitation of this study is that as the IRIS stage increases in CKD patients, the distinction between the two structures of kidney becomes vague. The kidney cortex and outer medulla were more clearly identified in younger patients and in those who had no renal dysfunction (Fig 5). Indeed, 11 cases were excluded from this study because of the difficulty in distinguishing between the two structures especially in CKD patients group. Also the indices were not compared with clear indicator representative of renal function. And the number of samples used in this study is small.

Therefore, future studies will be conducted prospectively with a larger number of samples and based on the criteria that can represent the renal function such as SDMA. In addition, studies on the relationship between age related changes in kidney structure and renal function will be studied as in human studies.

In conclusion, the US assessment of the renal cortex and outer medulla is distinctly identified. Although the gold standard for renal function including GFR is lack, it is thought that differentiation between normal and CKD patients could be possible on US measurement of RCT and OMT, which could be an alternative index for kidney function in diagnostic imaging.

References

1. Beland MD, Walle NL, Machan JT, Cronan JJ. Renal

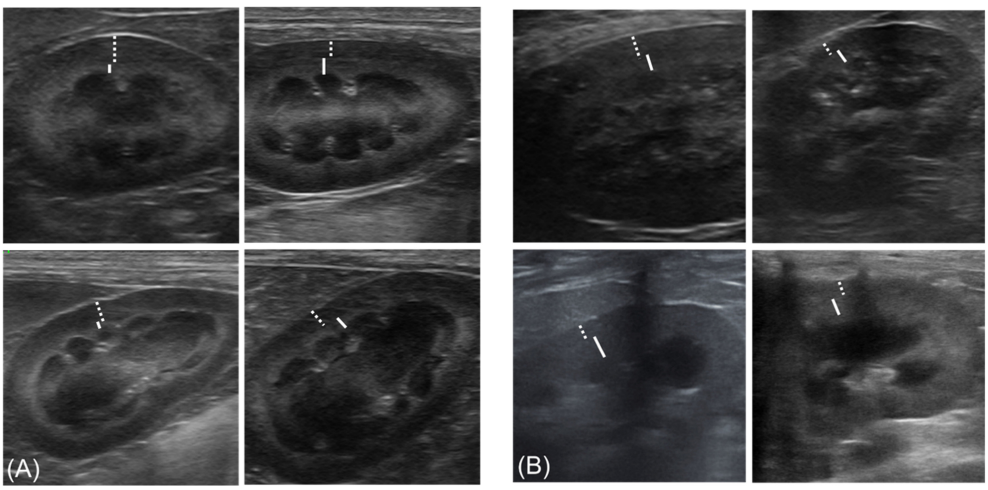

Fig 5. The RCT and OMT identified in normal patients (A) and RCT and in CKD patients (B). The structural difference between the cortex and the outer medulla is clearly shown in (A).

cortical thickness measured at ultrasound: is it better than renal length as an indicator of renal function in chronic kidney disease? AJR Am J Roentgenol 2010; 195: 146-149.
2. Burdock EI, Fleiss JL, Hardesty AS. A New View of Inter-Observer Agreement. Personnel Psychology 1963; 16: 373-384.
3. Denic A, Glassock RJ, Rule AD. Structural and Functional Changes With the Aging Kidney. Adv Chronic Kidney Dis 2016; 23: 19-28.
4. Finco DR, Duncan JR. Evaluation of blood urea nitrogen and serum creatinine concentrations as indicators of renal dysfunction: a study of 111 cases and a review of related literature. J Am Vet Med Assoc 1976; 168: 593-601.
5. Hall JA, Yerramilli M, Obare E, Yerramilli M, Almes K, Jewell DE. Serum Concentrations of Symmetric Dimethylarginine and Creatinine in Dogs with Naturally Occurring Chronic Kidney Disease. J Vet Intern Med 2016; 30: 794-802.
6. Hart DV, Winter MD, Conway J, Berry CR. Ultrasound appearance of the outer medulla in dogs without renal dysfunction. Vet Radiol Ultrasound 2013; 54: 652-658.
7. Jonckheere A. A Distribution-Free k-Sample Test Against Ordered Alternatives. Biometrika 1954; 41: 133-145.
8. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006; 145: 247-254.
9. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 2009; 53: 982-992.
10. Nabity MB, Lees GE, Boggess MM, Yerramilli M, Obare E, Yerramilli M, Rakitin A, Aguiar J, Relford R. Symmetric Dimethylarginine Assay Validation, Stability, and Evaluation as a Marker for the Early Detection of Chronic Kidney Disease in Dogs. J Vet Intern Med 2015; 29: 1036-1044.
11. Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, Furth SL. New equations to estimate GFR in children with CKD. J Am Soc Nephrol 2009; 20: 629-637.
12. Takata T, Koda M, Sugihara T, Sugihara S, Okamoto T, Miyoshi K, Hodotsuka M, Fujise Y, Matono T, Okano J, Hosho K, Iyama T, Fukui T, Fukuda S, Munemura C, Isomoto H. Left Renal Cortical Thickness Measured by Ultrasound Can Predict Early Progression of Chronic Kidney Disease. Nephron 2016; 132: 25-32.
13. Teo BW, Xu H, Wang D, Li J, Sinha AK, Shuter B, Sethi S, Lee EJ. GFR estimating equations in a multiethnic Asian population. Am J Kidney Dis 2011; 58: 56-63.
14. Seiler GS. The Abdominal Cavity: Canine and Feline, The kidneys and Ureters. In: Textbook of Veterinary Diagnostic Radiology, 6th ed. St. Louis: Elsevier. 2013: 705-723.
15. Von Hendy-Willson VE, Pressler BM. An overview of glomerular filtration rate testing in dogs and cats. Vet J 2011; 188: 156-165.
16. Wang X, Vrtiska TJ, Avula RT, Walters LR, Chakkera HA, Kremers WK, Lerman LO, Rule AD. Age, kidney function, and risk factors associate differently with cortical and medullary volumes of the kidney. Kidney Int 2014; 85: 677-685.
17. Yamashita SR, von Atzingen AC, Iared W, Bezerra AS, Ammirati AL, Canziani ME, D'Ippolito G. Value of renal cortical thickness as a predictor of renal function impairment in chronic renal disease patients. Radiol Bras 2015; 48: 12-16.
18. Breshears MA, Confer AW. Pathology of Organ Systems, The Urinary System. In: Pathology Basis of Veterinary Disease, 6th ed. St. Louis: Elsevier. 2017: 617-681
19. Zuo L, Ma YC, Zhou YH, Wang M, Xu GB, Wang HY. Application of GFR-estimating equations in Chinese patients with chronic kidney disease. Am J Kidney Dis 2005; 45: 463-472.