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Symmetric Dimethyl Arginine: A Prognostic Marker in Early Diagnosis of Canine Chronic Kidney Disease

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Kidney diseases are most common clinical problems, occurring in dogs (Katoch *et al*., 2018) and considered as the third leading cause of death. Indiscriminate use of certain antimicrobial, non-steroidal, anti-inflammatory or analgesics and anti-neoplastic drugs have been reported to cause renal damage in dogs (Legatti *et al.*, 2018). The emergence of several infectious (*Ehrlichia canis, Babesia gibsoni, Leptospira*,etc.) and metabolic diseases (diabetes) have further aggravated the incidence rate of renal disorders among dogs in India. Early diagnosis of kidney diseases is essential to stabilise renal function and prevent the rapid progression of the disease. In general, the markers of renal disease recognized from haematological and serum biochemical evaluations, urinalysis, or imaging or pathology studies (Polzin, 2011) have low sensitivity and specificity in the early stages which limit their use in screening of renal diseases. Biomarkers that are capable of early detection, risk stratification and prognostication such as SDMA would represent a tremendous focus (Hall *et al*., 2016). Symmetric dimethyl arginine (SDMA) is primarily removed from the body by the kidneys, and unlike creatinine it is not influenced by muscle mass, age and breed (Yerramilli *et al.,* 2016). The key to successful management of patients with renal disease lies in the early detection of varied etiology and initiate aggressive therapy. Timely intervention and systematic approach will slow down the progress of disease process in kidneys. Therefore, the present study was conducted for early detection of chronic kidney disease in dogs with SDMA biomarker and to see its association with other serum biochemical parameters.

In the present study, a total of 9,347 dogs of different breeds, age groups of either sex were screened for kidney diseases. A total of 103 dogs were selected based on history, clinical signs and diagnosis of CKD was confirmation by estimation of SDMA. The study also included apparently healthy dogs (n=10) as control. Apart from imaging studies, quantitative estimation of canine symmetric dimethyl arginine (SDMA) was done using sandwich ELISA method as described by manufacturer using the kits supplied by M/s. Bioassay Technology Laboratory, Shanghai and expressed in µg/dL. The other serum biochemical parameters estimated using assay kits and standard procedures were BUN, creatinine, total protein, albumin, globulin, ALT and ALP. The dogs with CKD were categorized into 4 stages based on SDMA, viz., stage I, II, III and IV according to IRIS guidelines. The data was subjected to statistical analysis by using SPSS (SPSS 20.0, Chicago, IL, USA). Tukey's multiple comparison post hoc test was also used to find the differences between groups. All the data was presented as Mean±SE and $P < 0.05$ was considered significant (Snedecor and Cochran, 1994).

In the present study, the means ± SEs of SDMA in dogs with stage I, II, III and IV CKD were 16.59±0.53 µg/dL, 25.07±1.30 µg/dL, 46.89±1.09 µg/dL and 87.51±3.11 µg/dL, respectively and these were compared with other biochemical parameters in healthy dogs and dogs with CKD (Table 1).

Majority of the dogs (44.67 %) in the current study were found to be in stage IV and their values range from 54-146 mg/dL with Mean± SE as 87.51±3.11mg/dL. These findings were in agreement with those of Sharma *et al*. (2015), who graded affected dogs into different stages and recorded that majority of the dogs were in stage III and IV. It is evident from this study that the mean serum creatinine level in stage I of CKD dogs was 0.84 ± 0.07 mg/dl, in stage II 1.83±0.09, in stage III 2.85±0.15 and in stage IV 8.93 ± 0.51mg/dL. Though serum SDMA was above 14 µg/ dL, serum creatinine was below 1.4 mg/dL in 13 dogs of CKD stage I and 3 dogs of stage II (Table 1), which was in agreement with Yerramilli *et al.* (2016) who reported creatinine as insensitive for the detection of early renal disorders and also opined that SDMA was more sensitive biomarker for early detection of renal dysfunction even in non-azotemic dogs that are not influenced by muscle mass, age and breed (Hall *et al.*, 2016). SDMA, a new biomarker for the early detection of

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Table 1: Serum biochemical parameter in healthy and dogs with different stages of CKD (Mean± SE)

Sr. No	Parameter	Healthy (n=10)	CKD-I (n=17)	CKD-II (n=15)	CKD-III (n=25)	CKD-IV (n=46)
1.	SDMA (µg/dL)	9.12± 0.89^{a}	16.59±0.53^{b}	25.07±1.30^{c}	46.89±1.09^{d}	87.51±3.11^{e}
2.	Creatinine (mg/dL)	0.69±0.10^{a}	0.84±0.07^{a}	1.83±0.09^{b}	2.85±0.15^{c}	8.93±0.51^{e}
2.	Blood Urea Nitrogen (mg/dL)	16.36±1.07^{a}	14.9±0.39^{a}	37.76±3.75^{ab}	55.87±6.01^{b}	127.25±16.4^{d}
3.	Total Protein(g/dL)	7.83±0.66^{d}	6.49±0.29^{d}	6.93±0.33^{cd}	5.60±0.28^{a}	5.54±0.23^{a}
4.	Albumin (g/dL)	3.25±0.07^{c}	2.86±0.04^{b}	2.85±0.30^{b}	2.54±0.24^{a}	3.11±0.12^{c}
5.	Globulin(g/dl)	3.71±0.68^{d}	3.73±0.31^{d}	4.08±0.28^{d}	3.06±0.19^{b}	2.43±0.21^{a}
6.	A/G ratio	0.87±0.23^{a}	1.32±0.07^{a}	0.79±0.13^{a}	0.97±0.12^{a}	1.27±0.87^{b}
7.	Alanine amino-transferase (U/L)	17.81±3.92^{a}	19.24±0.28^{a}	22.63±3.69^{a}	30.18±3.35^{b}	27.98±1.49^{b}
8.	Alkaline phosphatise (U/L)	48.37±5.77^{a}	51.88±0.77^{a}	61.28±8.38^{ab}	87.22±7.91^{b}	145.52±20.3^{c}

Means bearing different superscripts within a row differed significantly (P<0.05)

kidney dysfunction, is an endogenous methylated form of the arginine that is released into circulation during normal protein catabolism. Dahlem *et al.* (2017) stated that SDMA is excreted by the kidneys into urine in an unchanged form and hence, this metabolite accumulates in the course of renal dysfunction, which increases earlier than serum creatinine in animals with progressing kidney dysfunction. Pelander *et al.* (2015) also stated that SDMA estimation in addition to creatinine might improve the diagnostic value and avoid false positives as with estimation of serum creatinine alone which was in agreement with present study.

Significant elevation of BUN and creatinine values in dogs with CKD were recorded in this study similar to earlier observations (Sonu *et al*., 2019). Elevated levels of creatinine and blood urea nitrogen could be due to diminished renal excretion and enhanced tubular absorption of urea which would be elevated only when there was loss of up to 75 % of functional renal mass, whereas SDMA would be elevated even with loss of 10 % functional nephrons (Dahlem *et al.*, 2017).

Significantly lower (P<0.05) mean values of serum total protein (g/dL) were recorded in dogs with chronic kidney disease stage III (5.60±0.28) and stage IV (5.54±0.23) as compared to Stage II, I and healthy control group. Similar was the trend for globulin and inverse trend for A/G ration in dogs with CKD (Table 1). These findings were in accordance with the reports of Kandula and Karlapudi (2015), who opined that hypoproteinemia might be due to gastrointestinal bleeding and proteinuria.

Significant elevation of alanine amino transferase and alkaline phosphatase in CKD stage III and IV was recorded in the present study. Elevated alkaline phosphatase in CKD might be due to secondary renal hyperparathyroidism and was associated with increased mortality (Beddhu *et al.*, 2009).

Although novel markers like SDMA provide exciting clues into the pathophysiology of diseases and enable us to improve diagnostic capabilities, the high cost involved is still prohibitive for widespread clinical application.

Our study demonstrated that SDMA is a sensitive biomarker in early detection of kidney diseases, which further helps in slowing down the progression of disease.

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