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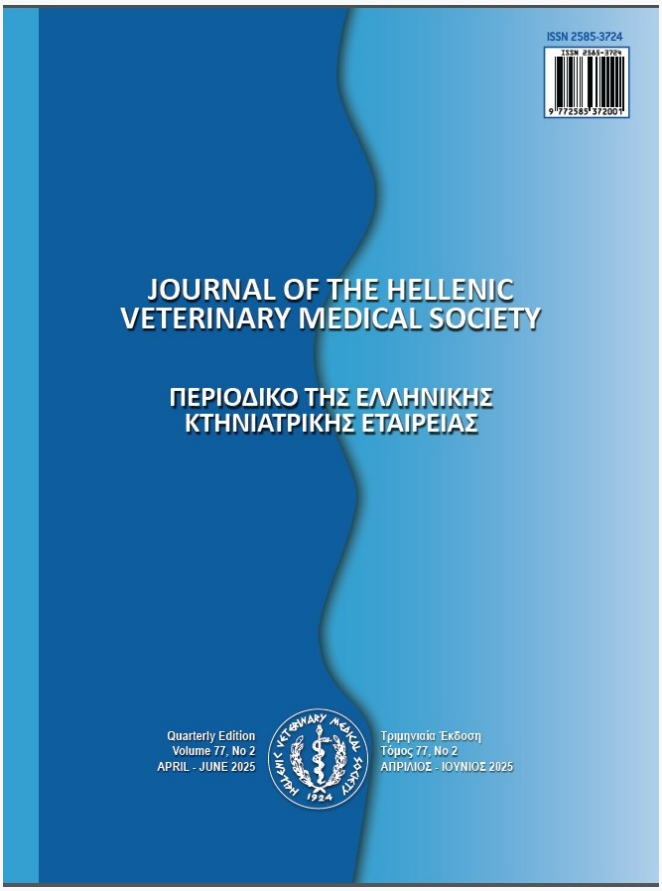

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Investigation of Oxidative Stress Levels in Cats with Chronic Kidney Disease

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ABSTRACT: This study aimed to examine the oxidative stress levels and several biochemical parameters of cats diagnosed with CKD and evaluate their potential roles in disease monitoring and prognosis determination. Thirty cats diagnosed with CKD formed the CKD group, and 10 healthy cats formed the control group. For biochemical analyses, blood samples taken from the Vena cephalica antebrachii of cats were centrifuged. The serum was removed, and analyses were carried out. Among these analyses, biochemical parameters such as symmetric dimethylarginine (SDMA), malondialdehyde (MDA), total antioxidant status (TAS), total oxidant status (TOS), and the oxidative stress index (OSI) and urea, creatinine, ALT, AST, and ALP levels were examined. According to the findings of the present study, while TAS levels were found to be low in cats diagnosed with CKD ($P<0.05$), TOS, OSI, MDA, and SDMA levels were found to be high ($P<0.05$). In addition, urea and creatinine levels and ALP and AST activities were greater in cats diagnosed with CKD than in healthy cats ($P<0.05$), whereas ALT activity did not change ($P>0.05$). These findings indicate that CKD is associated with increased oxidative stress in cats and that certain biochemical parameters can be used in the diagnosis of CKD. Therefore, oxidative stress is important in the pathophysiology of CKD, and the progression of this disease can be controlled by playing an important role in the diagnosis, monitoring, and treatment planning of kidney disease.

Keyword: Cat; Chronic kidney disease; Oxidative stress; Symmetric dimethylarginine.

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INTRODUCTION

Chronic kidney disease (CKD) is defined as a structural or functional disorder of the kidney that can range from a small lesion in a single kidney to severe nephron loss affecting both kidneys over a period of three months or more. It is an irreversible and typically progressive disease (Polzin, 2011). To compensate for kidney damage, active nephrons dilate the glomerular arteries, increasing intraglomerular pressure, renal plasma flow, and the glomerular filtration rate (GFR). This condition is called hyperfiltration. While hyperfiltration increases the excretion of nitrogenous substances in healthy nephrons, increasing intraglomerular capillary pressure gradually leads to mechanical damage to capillaries and glomerular-derived protein loss. Excessive amounts of filtered protein are absorbed from the proximal tubule, broken down by cellular lysosomal mechanisms, and returned to the bloodstream. During the breakdown of proteins, reactive oxygen species are released, which stimulates the release of inflammatory cytokines. In this inflammatory process, epithelial cells are damaged, and increased intraglomerular capillary pressure causes scar formation and ultimately blockage of glomerular capillaries. Capillary damage that begins at the glomerular level spreads to tubular epithelial cells and causes tubular interstitial fibrosis, which is characteristic of CKD. As a result, homeostatic responses that begin as a compensation process turn into progressive kidney damage and result in CKD (Maden et al., 2022). CKD is common in cats, with an estimated prevalence between 1.6% and 20% (O'Neill et al., 2015). Although CKD occurs at all ages, its prevalence increases with age (Bartges, 2012; DiBartola et al., 1987) and affects 80% of cats over 15 years of age (Boyd et al., 2008; Marino et al., 2014; Syme et al., 2006). For this reason, it is considered the leading cause of death in geriatric cats. Tubulointerstitial inflammation is the most common histopathological feature of CKD in cats, and fibrotic changes indicate a worse prognosis (Paepe and Daminet, 2013). Various factors, such as breed, hypertension, age, vaccination, proteinuria, and acute kidney injury (AKI), also play a role in the pathogenesis of CKD (Brown et al., 2016; Cowgill et al., 2016; Greene et al., 2014). Owing to the lack of early diagnostic markers of renal dysfunction, CKD in cats is often diagnosed late in the disease stage and after irreversible damage to the renal parenchyma has developed (Yerramilli et al., 2016). Clinically, CKD in cats is always recognized at a late phase on the basis of a combination of coherent clinical signs, azotemia, and inappropriate urine specific gravity (USG) (Paepe and Daminet, 2013). Serum creatinine and urea, indirect markers of the glomerular filtration rate, are used in diagnosis, and each has its own limitations (Kerl and Cook, 2005). Urine specific gravity, blood pressure and the urine protein/creatinine ratio can be used in the recognition, staging and prognosis of CKD. In recent years, SDMA, a new biomarker, has begun to be used for indirect measurement of the GFR. SDMA, which is freely filtered by the kidneys, is a product of intranuclear protein metabolism. Therefore, serum levels of SDMA inversely correlate with measurements of the glomerular filtration rate in humans, rats, mice, dogs, and cats. SDMA has been investigated as a clinical renal biomarker for approximately 10 years. A reference range has been established for SDMA measured by LC–MS in healthy cats and dogs. SDMA is a delicate and specific biomarker for renal function. Longitudinal studies on dogs and cats with chronic kidney disease have shown an average decrease of 40% in the glomerular filtration rate, with SDMA levels increasing months before serum creatinine levels. Additionally, it has been observed that serum creatinine levels increase only in the later stages, even when there is up to a 75% decrease in the glomerular filtration rate (Relford et al., 2016). Available studies to date suggest that plasma or serum SDMA concentrations increase with decreasing GFR and are unaffected by extrarenal factors (Braff et al., 2014).

Recently, the significant role of oxidative stress in the development of CKD has been increasingly emphasized (Nakanishi et al., 2019; Sung et al., 2013; Sureshbabu et al., 2015). Oxidative stress is a condition that damages cell constituents (such as proteins, lipids, and nucleic acids) and disrupts cell metabolism, leading to cell death through apoptosis (Sureshbabu et al., 2015). Oxidative stress results from both increased production of reactive oxygen species (ROS) and impairment of antioxidant defense mechanisms (Maciejczyk et al., 2017). In CKD patients, activation of the renin–angiotensin–aldosterone system has been shown to reduce nitric oxide (NO) production and increase NADPH oxidase activity. This leads to the formation of free radicals and may contribute to the progression of renal fibrosis (Borys et al., 2017). In addition, oxidative stress biomarkers are recommended for the diagnosis of CKD patients because of changes in enzymatic and nonenzymatic antioxidant systems, including the accumulation of protein and lipid oxidation products

in the renal parenchyma of CKD patients (Borys et al., 2017; Sureshbabu et al., 2015). TAS, TOS and MDA were selected among the markers of oxidative stress in our study to provide a broad perspective on systemic oxidative balance and lipid peroxidation in CKD. In particular, TAS and TOS reflect the cumulative activity of all antioxidants and oxidants, while MDA is a well-known indicator of lipid oxidative damage. These parameters are also more applicable in veterinary clinical practice due to the availability of validated commercial assay kits. This study aims to contribute to the diagnostic process by examining oxidative stress biomarkers and renal parameters associated with chronic kidney disease in cats and to evaluate their potential role in disease monitoring and prognosis.

MATERIALS AND METHODS

The animal material used in the study was from different sexes who were brought to the Internal Medicine Clinic of Ondokuz Mayıs University Faculty of Veterinary Medicine Training, Research and Practice Hospital, with complaints of weakness, weight loss, vomiting, polyuria and polydipsia; who had not previously received any treatment; and who were diagnosed with chronic kidney disease. CKD was diagnosed by complete blood count; ultrasonographic examination; and high urea, creatinine and SDMA levels. Additionally, staging was performed according to the IRIS Staging guidelines of 2019. Disease can be differentiated by performing blood chemistry tests, such as ALT, AST, ALP, GGT, UREA, CREA, TP, ALB, TBIL and CBC (complete blood count) tests. Cats with comorbid diseases were excluded from the study. The sample consisted of 30 cats between the ages of 3 and 13. In addition, 10 cats that were diagnosed as healthy after clinical examination constituted our control group. Specifically, cats were evaluated for the presence of comorbidities such as diabetes mellitus and hypertension through physical examination, blood glucose analysis, blood pressure measurements, and review of medical history. Cats with persistent hyperglycemia, systolic blood pressure >160 mmHg, or other concurrent systemic illnesses were excluded. The sample size was determined via power analysis using GPower 3.1.9.4 to ensure sufficient statistical power (effect size = 0.40, $\alpha = 0.05$, power = 0.80) for detecting significant differences between groups. All cats in the study and control groups were brought to the hospital for disease and control reasons, blood samples were taken during conventional clinical procedures, and blood samples were stored for the study following the indicated analysis. Blood samples were taken from *Vena cephalica antebrachii* for routine examinations of the cats. The blood samples were centrifuged at 3500 rpm for 10 minutes, and the serum samples were removed. Serum samples were stored at -20 °C after routine clinical biochemical analyses were performed.

Symmetric dimethylarginine (SDMA) levels were measured using a feline-specific ELISA kit (MyBioSource, MBS1602667; sensitivity: 3.68 nmol/L; intra-assay CV <8%; inter-assay CV <10%) on a microplate reader (Tecan Infinite F50, Austria). The total oxidant status (TOS) (Rel Assay) and total antioxidant status (TAS) (Rel Assay) were analysed on an ELISA plate reader with the procedure recommended in the kit containing the colorimetric test kits. The oxidative stress index (OSI) was calculated from the TAS and TOS values. Serum biochemistry measurements, such as those of urea, creatinine, ALT, AST, and ALP, were made on a Mindray BS 120 Vet biochemistry device.

The SPSS statisticts 27 program was used for statistical analysis. The normal distribution of the data was evaluated by examining the skewness, kurtosis values and Kolmogorov–Smirnov test results. Since the data were normally distributed, the parametric t test was used to determine the differences between the groups. Data with $P<0.05$ were considered significant. The Pearson correlation test was used to determine the correlation between the data.

RESULTS

In this study, the TAS, TOS, OSI, MDA and SDMA values were determined in blood samples taken from cats diagnosed with chronic kidney disease and healthy cats. In addition, urea and creatinine levels and ALT, ALP, and AST activities were determined.

When the oxidative stress levels of the healthy group and the CKD diagnosis group were compared, the TOS, OSI, and MDA levels were determined to be high in the patient group, whereas the TAS levels were determined to be low in the patient group. Serum SDMA levels were also determined to be higher in the patient group than in the healthy group. While serum biochemistry parameters such as urea and creatinine levels and ALP and AST activities were high in the patient group, ALT activity did not change.

Our TAS data were significantly negatively correlated with the OSI ($P<0.01$) and MDA ($P<0.05$), whereas our TOS data were significantly positively

correlated with the OSI (P<0.01) and MDA (P<0.05). A positive significant correlation was also found between our OSI and MDA data (P<0.01). While there was a positive significant correlation between our SDMA data and the urea and creatinine data, a positive significant correlation was also found between the creatinine and urea data (P<0.01) (Table 1).

Serum TAS (P<0.001), TOS (P<0.001), OSI (P=0.004), and MDA (P=0.029) levels in the healthy and CKD patient groups are shown in Figure 1.

The serum SDMA (P<0.001), creatinine (P<0.001), and urea (P<0.001) levels of the healthy and CKD patients are shown in Figure 2.

Table 1. Correlation values between serum TAS, TOS, OSI, MDA, SDMA, creatinine, and urea levels and AST, ALT, and ALP activity

		TAS	TOS	OSI	MDA	SDMA	Urea	Creatinin	AST	ALT	ALP
TAS	Pearson Correlation	1	-0.245	-.465**	-.350*	.510**	.506**	.609**	.313*	-0.189	0.07
	Sig. (2-tailed)		0.127	0.003	0.027	0.001	0.001	.000	0.05	0.243	0.668
	N	40	40	40	40	40	40	40	40	40	40
TOS	Pearson Correlation	-0.245	1	.676**	.333*	-.338*	-0.299	-0.226	-.364*	0.03	-.315*
	Sig. (2-tailed)	0.127		.000	0.036	0.033	0.061	0.161	0.021	0.853	0.048
	N	40	40	40	40	40	40	40	40	40	40
OSI	Pearson Correlation	-.465**	.676**	1	.408**	-.523**	-.450**	-.453**	-0.289	0.198	-0.19
	Sig. (2-tailed)	0.003	.000		0.009	0.001	0.004	0.003		0.22	0.241
	N	40	40	40	40	40	40	40	40	40	40
MDA	Pearson Correlation	-.350*	.333*	.408**	1	-.458**	-.389*	-.342*	-0.158	.375*	-0.022
	Sig. (2-tailed)	0.027	0.036	0.009		0.003	0.013	0.031	0.331	0.017	0.893
	N	40	40	40	40	40	40	40	40	40	40
SDMA	Pearson Correlation	.510**	-.338*	-.523**	-.458**	1	.587**	.652**	0.256	-0.245	0.094
	Sig. (2-tailed)	0.001	0.033	0.001	0.003		.000	.000	0.11	0.128	0.563
	N	40	40	40	40	40	40	40	40	40	40
Creatinin	Pearson Correlation	.609**	-0.226	-.453**	-.342*	.652**	.805**	1	0.157	-0.084	0.236
	Sig. (2-tailed)	.000	0.161	0.003	0.031	.000	.000		0.333	0.607	0.143
	N	40	40	40	40	40	40	40	40	40	40
Urea	Pearson Correlation	.506**	-0.299	-.450**	-.389*	.587**	1	.805**	0.204	-0.079	0.277
	Sig. (2-tailed)	0.001	0.061	0.004	0.013	.000		.000	0.207	0.629	0.084
	N	40	40	40	40	40	40	40	40	40	40
AST	Pearson Correlation	0.07	-.315*	-0.19	-0.022	0.094	0.277	0.236	-0.048	0.174	1
	Sig. (2-tailed)	0.668	0.048	0.241	0.893	0.563	0.084	0.143	0.77	0.282	
	N	40	40	40	40	40	40	40	40	40	40
ALT	Pearson Correlation	-0.189	0.03	0.198	.375*	-0.245	-0.079	-0.084	-0.112	1	0.174
	Sig. (2-tailed)	0.243	0.853	0.22	0.017	0.128	0.629	0.607	0.492		0.282
	N	40	40	40	40	40	40	40	40	40	40
ALP	Pearson Correlation	.313*	-.364*	-0.289	-0.158	0.256	0.204	0.157	1	-0.112	-0.048
	Sig. (2-tailed)	0.05	0.021	0.071	0.331	0.11	0.207	0.333		0.492	0.77
	N	40	40	40	40	40	40	40	40	40	40

*Correlation is significant at the 0.05 level (2-tailed).

**Correlation is significant at the 0.01 level (2-tailed).

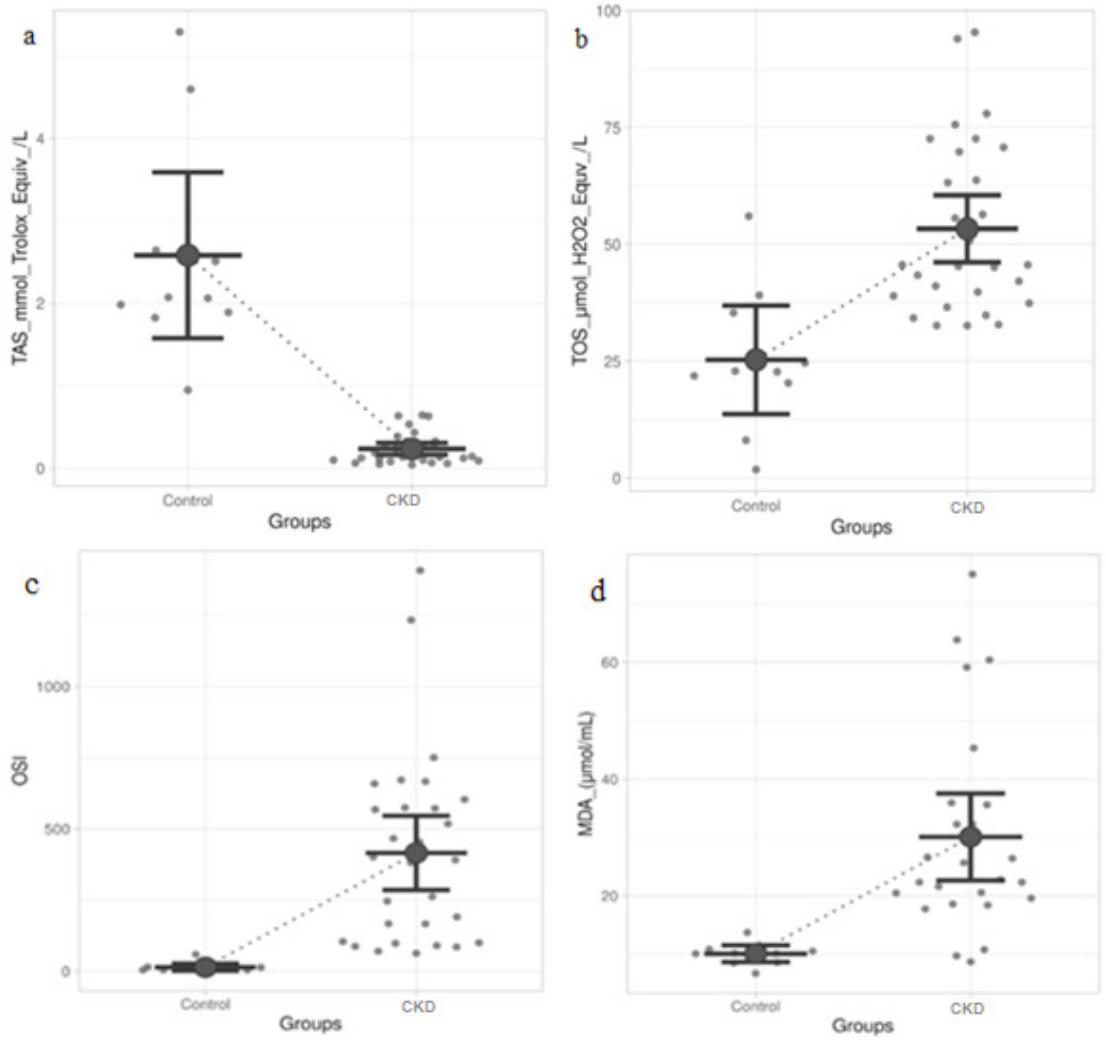

Figure 1. Serum TAS levels (a), serum TOS levels (b), serum OSI levels (c) and serum MDA levels (d).

The serum AST (P=0.036), ALT (P=0.160), and ALP (P<0.001) levels of the healthy and CKD patients are shown in Figure 3.

DISCUSSION

CKD is one of the most common progressive diseases in aging cats and significantly impacts their quality of life. While its general prevalence in the feline population is estimated to be approximately 2% to 4%, this rate increases to 30% to 40% in cats older than 10 years (Jepson et al., 2009; Marino et al., 2014; O'Neill et al., 2015). Despite extensive research on CKD, studies evaluating the relationship between oxidative stress and disease progression in cats are limited. Our study aims to contribute to this gap by analysing oxidative stress biomarkers and their potential role in monitoring disease severity. The progression of CKD is influenced by various pathophysiological factors that contribute to renal damage over time (Cowgill et al., 2016). Deterioration of kidney function is closely associated with the severity of clinical manifestations, with common signs including polyuria, polydipsia, muscle wasting, weight loss, lethargy, and weakness. While current treatment options cannot reverse renal damage, symptomatic management can help mitigate clinical and biochemical imbalances, thereby improving the quality of life of affected cats. Additionally, early therapeutic interventions may slow disease progression and delay the onset of advanced renal dysfunction (Relford et al., 2016).

This study aimed to determine the levels of oxidative stress parameters, SDMA, and several biochemical parameters in cats diagnosed with CKD, considering that these parameters may be useful in the diagnosis and prognosis of this disease.

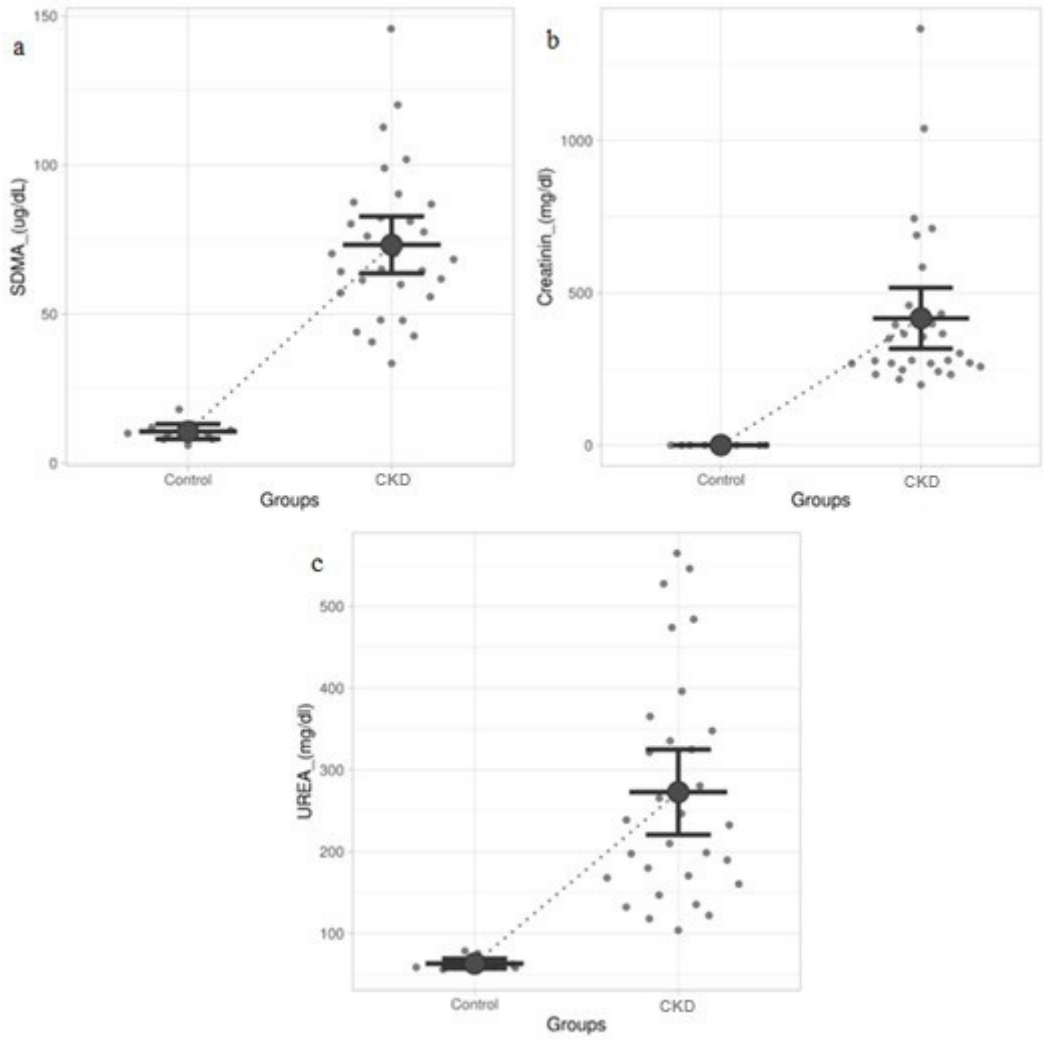

Figure 2. Serum SDMA levels (a), serum creatinine levels (b), and serum urea levels (c).

Chronic kidney disease (CKD) is a pathological condition characterized by the accumulation of toxic substances in the body due to impaired excretory function resulting from nephron loss. As kidney function decreases, waste products that are normally excreted in the urine accumulate in the body, leading to the formation of uremic toxins (Vanholder et al., 2008). Many of these toxins contribute to the development of chronic inflammation and oxidative stress, which play crucial roles in the progression of CKD and its associated complications.

Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defense mechanisms. While ROS play essential physiological roles as signalling molecules, excessive ROS production or insufficient antioxidant capacity leads to oxidative stress, resulting in oxidative damage to nucleic acids, lipids, and proteins (Pizzino et al., 2017; Sugeçti, 2021). Studies have demonstrated that oxidative stress is closely linked to CKD progression, with significantly elevated levels of oxidative stress markers detected in lipid and DNA samples from CKD patients (Gastaldello et al., 2000).

Several studies have examined oxidative stress parameters in cats with CKD. In a study by Yu and Paetau-Robinson (2006), ten cats with spontaneous renal failure and ten control cats were fed a standard diet for four weeks, followed by a diet supplemented with vitamins E, C, and β-carotene (Yu and Paetau-Robinson, 2006). The results indicated that cats with CKD were more prone to oxidative stress than healthy cats were. Furthermore, antioxidant supplementation reduced 8-OHdG, a marker of DNA damage, in CKD-affected cats. However, although malondialdehyde (MDA) levels are elevated in CKD cats, antioxidant supplementation did not significantly alter these levels. Similarly, Valle

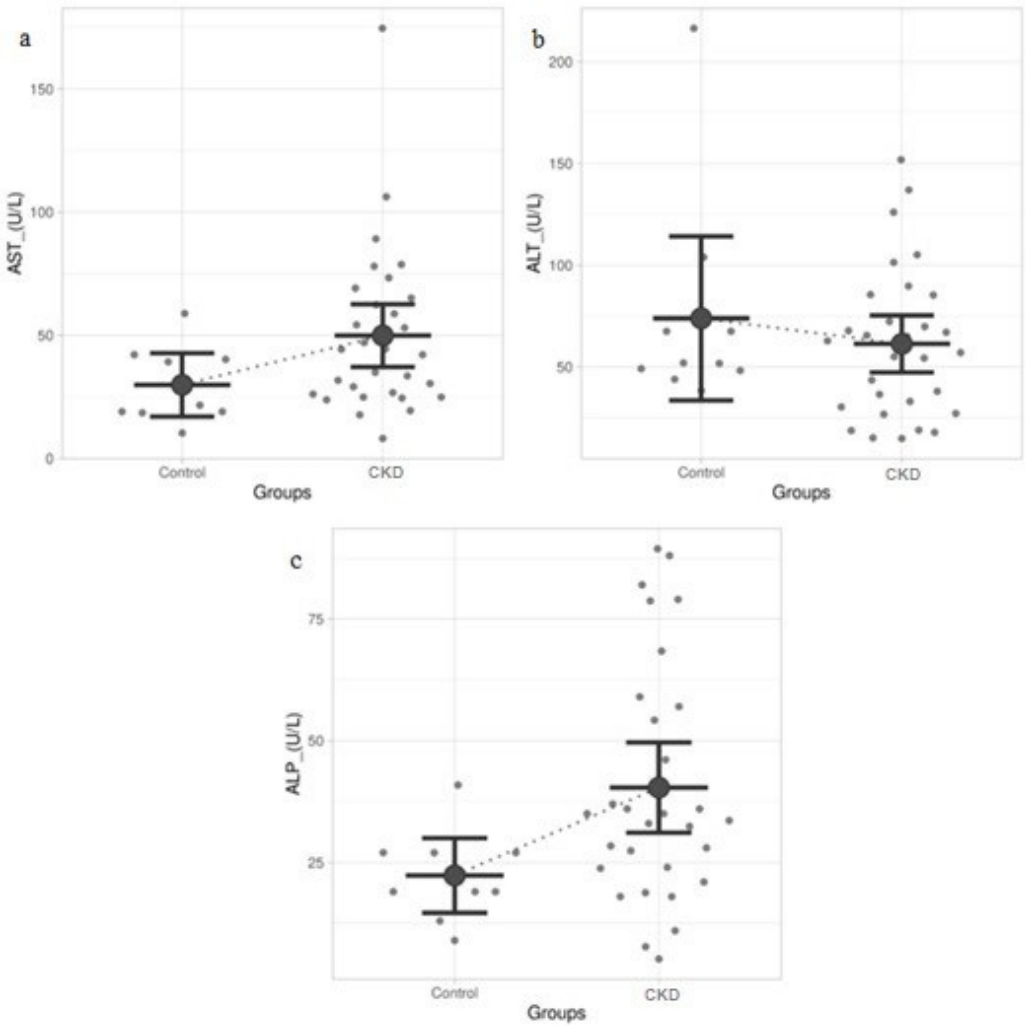

Figure 3. Serum AST levels (a), serum ALT levels (b) and serum ALP levels (c).

et al. (2019) reported that serum MDA levels were significantly greater in CKD cats than in controls (Valle et al., 2019). Another study by Keegan and Webb (2010) revealed that plasma antioxidant capacity was significantly lower in CKD-affected cats than in healthy cats (Keegan and Webb, 2010).

The findings of our study align with those of previous studies, which revealed that total oxidative status (TOS), MDA, and oxidative stress index (OSI) levels were significantly greater in CKD cats than in control cats, whereas total antioxidant status (TAS) levels were significantly lower. These results suggest that oxidative stress plays a major role in the pathophysiology of CKD in cats.

The pathophysiology of oxidative stress in CKD involves multiple mechanisms. The kidneys play a crucial role in detoxification, and as renal function declines, the clearance of oxidative stress-inducing toxins is impaired, leading to increased free radical accumulation. This imbalance weakens the antioxidant defense system, exacerbating oxidative stress. Additionally, inflammatory cytokines and proteins that are elevated in CKD, such as IL-1β and IL-8, further contribute to oxidative stress by activating immune system components (Sánchez-Lozada et al., 2008).

Another important mechanism in oxidative stress progression in CKD involves the renin–angiotensin–aldosterone system (RAAS). In CKD, RAAS activation leads to increased levels of angiotensin II (Ang II), which impairs nitric oxide (NO) synthesis in endothelial cells (Borys et al., 2017). This disruption contributes to oxidative stress-mediated vascular and kidney damage. Additionally, NADPH oxidase activity increases due to RAAS activation, leading to excessive ROS production and further oxidative damage in kidney tissues. Given these mech-

anisms, it is reasonable to suggest that the increase in oxidative stress in CKD-affected cats observed in our study may be linked to these underlying processes. These findings highlight the importance of further exploration of oxidative stress biomarkers in feline CKD to develop targeted therapeutic strategies aimed at mitigating oxidative damage and improving disease management.

In cats, SDMA is a biomarker that can be used for the early diagnosis of CKD. The use of SDMA is more advantageous for early detection than the use of urea or creatinine (Hall et al., 2014; Relford et al., 2016). SDMA is produced during protein breakdown through the methylation of L-arginine within the cell nucleus. When proteins are broken down, the remaining SDMA molecules are released into the bloodstream (Tain and Hsu, 2017). Symmetric dimethylarginine is not attached to proteins in the blood plasma; it is primarily eliminated through the kidneys (over 90%). Passes freely through the kidney filtration system before being absorbed by the tubules (Kielstein et al., 2006; Relford et al., 2016). In cats, as kidney function decreases (as measured by the GFR), SDMA levels increase in a manner (Braff et al., 2014), making it a valuable indicator of kidney function. Research has demonstrated a correlation between the levels of SDMA and creatinine in the blood (Braff et al., 2014). Compared with that of creatinine, the concentration of SDMA becomes elevated when kidney function decreases by 40% earlier than expected on the basis of traditional measures that require a 75% decline in kidney function (Polzin, 2011). Furthermore, unlike changes in creatinine, changes in diet or body muscle mass do not significantly affect SDMA levels. This process involves factors other than creatinine, which can be influenced by factors outside of kidney health, such as diet and muscle mass composition (Braun et al., 2003; Butani et al., 2002). The reference range for serum or plasma urea levels in cats is 42.8–64.2 mg/dL; the creatinine value is reported as 0.5–1.5 mg/dL or 0.8–1.8 mg/dL (Altıntaş and Fidancı, 1993). In the present study, the urea values in the control group of cats were 63.28 mg/dL, and the creatinine values were 0.47 mg/dL. The values found for urea and creatinine were within the reference values. In this study, the urea and creatinine values of the patients were found to be abnormally high and compatible with kidney disease. In a study conducted on cats diagnosed with CKD, Altıntaş et al. (2006) reported that the serum urea and creatinine values in all sick animals were significantly greater than those in controls (Altıntaş et al., 2006). Grelova et al. (2022) reported that the serum SDMA and creatinine levels were significantly higher in cats with CKD than in control cats (Grelová et al., 2022). In a study by Hal et al. (2014), SDMA and creatinine levels were significantly greater in cats diagnosed with CKD than in healthy individuals (Hall et al., 2014). In another study, when the mean urea and creatinine levels of cats with CKD and healthy cats were compared, these values were greater in cats with chronic kidney disease than in healthy cats (Uren et al., 2009). In a study conducted by Valle et al. (2019) in a total of twenty-two cats diagnosed with CKD between the ages of 4–14 years, the serum urea and creatinine values were significantly greater in cats with CKD than in the control group (Valle et al., 2019). In a study conducted by Granick et al. (2021) in cats staged as CKD stage 1 and stage 2, the serum creatinine and SDMA levels were significantly greater in all CKD stages than in the control group (Granick et al., 2021). In another study by Peterson et al. (2018) on chronic kidney disease in cats with hyperthyroidism, the serum SDMA, urea, and creatinine values were greater in the preazotemic group than in the nonazotemic group (Peterson et al., 2018). In a study conducted by Loane et al. (2022) in 15 control cats, 15 acute kidney injury cats, and 19 chronic kidney disease cats, the serum SDMA, urea, and creatinine values were found to be greater in the CKD and ABH groups than in the control group (Loane et al., 2022). In this study, SDMA, urea, and creatinine values and ALP and AST activities were significantly greater in cats diagnosed with CKD than in those in the control group, whereas ALT activity did not change. SDMA is a metabolite formed in the kidneys and excreted in the urine. However, when chronic kidney disease occurs, renal function weakens as a result of kidney damage, and the glomerular filtration rate decreases. Thus, the kidneys cannot clear SDMA quickly enough and excrete it in the urine, and the level of SDMA in the blood increases. This situation may also lead to increased levels of waste products such as urea and creatinine in the blood as a result of decreased urinary excretion. In our study, the high values of SDMA, urea, and creatinine in the group with CKD are thought to be due to this situation.

CONCLUSION

In conclusion, the TAS, TOS, OSI, MDA, SDMA, urea, creatinine, AST, and ALP activities increased, the TAS values decreased, and ALT activity did not change in cats diagnosed with CKD. These findings

indicate that the antioxidant defense mechanism is weakened as a result of renal dysfunction, which is an indicator of renal tissue damage in CKD patients, and that oxidative stress is increased by disruption of the oxidative balance. In addition, elevated biochemical markers such as SDMA, urea, and creatinine are commonly associated with decreased renal function in cats with CKD. Therefore, monitoring these values may help in assessing renal impairment in affected cats. The regular monitoring of these markers by veterinarians can help them assess the condition of patients accurately and determine appropriate treatment strategies. In addition, the parameters measured in our study may play a significant role in the diagnosis, monitoring, and treatment planning of kidney disease. They may be significant in controlling the progression of the disease. We recommend studies in which appropriate antioxidants can be used in the treatment process in cats with CKD. In addition, since our study was conducted with a limited number of cats, our findings provide important conclusions regarding the relationship between oxidative stress and CKD, but a larger sample size may increase the generalizability of the results. Future studies with larger populations may also strengthen the reliability and applicability of these findings.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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