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Clinical Features and Prognosis of Corneal Ulcers in Dogs with Chronic Kidney Disease

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Abstract This study was designed to investigate the characteristics of corneal ulcers in dogs with chronic kidney disease (CKD). Medical records of dogs that had been diagnosed with corneal ulcers and chronic kidney disease at Haemaru Referral Animal Hospital between April 1, 2011 and March 31, 2016 were investigated. A control group was randomly selected during the same time period. This group included patients with corneal ulcers but no evidence of systemic disease. The mean healing time of superficial corneal ulcers in the CKD group was 21.0 ± 15.0 days. This was a significantly longer healing time than was observed in the control group (11.0 ± 6.6 days, $p = 0.019$). The incidence rates of uveitis and keratoconjunctivitis sicca in the CKD group were significantly higher than in the control group ($p = 0.000$ and $p = 0.026$, respectively). Additionally, non-healing ulcers had significantly elevated white blood cell counts, while those with healing ulcers had WBC counts within the normal range in CKD group ($p = 0.000$). This study revealed that corneal ulcers in CKD patients would be delayed epithelial healing process and accompanied by ocular disease which affected to corneal healing compared to non-CKD patients.

Key words chronic kidney disease, corneal ulcer, dog, keratoconjunctivitis sicca, uveitis.

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Introduction

Corneal ulcers are caused by inadequate corneal epithelial protection or excessive corneal epithelial loss. Each component of the cornea heals at a different rate, and simple corneal ulcer should resolve within 7 days without progression into the stroma (7). Delayed corneal healing could lead to complications such as corneal vascularization and uveitis. Insufficient stromal regeneration could result in a weak corneal structure to maintain the globe (6).

Healing of corneal ulcers could be delayed due to concurrent ophthalmic problems such as eyelid dysfunction, chronic irritation (e.g. distichiasis, eyelid tumors), and tear film deficiencies (e.g. keratoconjunctivitis sicca, meibomianitis). In these cases, concurrent problems must also be controlled or the ulcer could become complicated.

Healing of the cornea could also be affected by the presence of systemic disease. It is well known that hyperadrenocorticism and diabetes mellitus delay the healing of corneal ulcers (2,4). In practice, chronic kidney disease (CKD) is one of the more common systemic diseases seen in patients with corneal ulcers. This study was designed to identify the clinical characteristics of corneal ulcers in canine CKD patients and to demonstrate the correlation between CKD and healing time for corneal ulcers in dogs.

Materials and Methods

Patient selection

Medical records of 192 dogs that had been diagnosed with corneal ulcers and chronic kidney disease at Haemaru Referral Animal Hospital between April 1, 2011 and March 31, 2016 were investigated. The CKD patients were divided into 4 groups according to the International Renal Interest Society (IRIS) guidelines (10). Stage 1 CKD patients were excluded from this study because they were not azotemic. Possible abnormalities present in stage 1 CKD patients include inadequate urinary concentrating ability, abnormal renal imaging findings, proteinuria, and increasing blood creatinine concentrations over time. Complete medical records for the time between the development of the ulcer and its ultimate healing were required for patients included in the CKD group (34 patients, 38 eyes).

The control group (31 patients, 37 eyes) consisted of patients with corneal ulcers who had been randomly selected from the same hospital during the same time period. Patients in the control group were more than 10 years old with no evidence of kidney disease or hyperadrenocorticism. They had not been treated with long-term steroid therapy, which is reported to have a negative effect on corneal healing (3,6).

Data selection

Medical records including signalment, the date of diagnosis of the corneal ulcer, the date of healing, concurrent eye disease, white blood cell count, type of corneal ulcer, surgical treatment, prognosis, and concurrent systemic disease were analyzed. Corneal ulcers were diagnosed via fluorescein staining and slit lamp biomicroscopy. Routine topical treatments were performed depending on the severity of the ulcer; these included antibiotics, artificial tears, 1% EDTA, 4% acetylcysteine, and autologous serum eye drops. The corneal ulcers were allocated to one of four categories: superficial (uncomplicated, simple or erosive, loss of less than one-third of the stroma), deep (stromal or exposing Descemet's membrane (descemetocele), complicated, loss of more than two-thirds of the stroma), melting, and perforated (5).

Statistical analyses

The age of the patients and the healing time for the ulcers were expressed as mean ± standard deviation (SD) for each group. Statistical analyses were performed using a commercial software program (SPSS 21.0, SPSS Inc., Chicago, IL, USA). The Kruskal-Wallis test was employed to compare the distribution of the type of corneal ulcer and the incidence of concurrent disease between the CKD and control groups. Correlation between corneal status and severity of uveitis was assessed using a Pearson's correlation coefficient. The effect of surgical intervention on healing of the ulcer was evaluated using Kendall's tau method. To compare the mean age of the patients and the healing time for the ulcers, Student's t-test was used. p values of less than 0.05 were considered statistically significant.

Results

The CKD group included 34 patients (38 eyes) with IRIS CKD stage 2 to 4 and corneal ulcers. The control group consisted of 31 dogs (37 eyes). The mean ages of the patients in the CKD and control groups were 13.5 ± 2.5 and 12.6 ± 1.8 years old, respectively, and there was no significant difference between the groups ($p > 0.05$). The predominant breed in both groups was the Shih-tzu (Table 1). The concurrent ophthalmic diseases in order of prevalence were uveitis, keratoconjunctivitis sicca (KCS), and glaucoma in both groups (Fig. 1). However, the incidence of uveitis and KCS was significantly higher in the CKD group than in the control group ($p = 0.000$ and $p = 0.026$, respectively). Correlation of corneal status with severity of uveitis was statistically significant ($r =$

0.284, p = 0.0482).

The CKD group contained of 17 eyes with superficial ulcers (45%), 8 eyes with stromal ulcers (21%), 6 eyes with melting ulcers (16%), and 7 eyes with perforated ulcers (18%). The control group contained 20 eyes with superficial ulcers (52.6%), 16 eyes with stromal ulcers (43.2%), and 2 eyes with perforated ulcers (5.4%). The grade of corneal ulcer did not differ significantly different between the two groups ($p > 0.05$). In the CKD group, 11 out of 17 eyes (64.7%) with superficial ulcers healed, whereas all eyes with superficial ulcers in the control group healed. The mean healing time for superficial ulcers in the CKD group was 21.0 ± 15.0 days, which was significantly longer than the mean healing time for the same category of ulcer in the control group (11.0 ± 6.6 days, p = 0.019). Only two eyes (25%) with stromal ulcers in the CKD group healed and the mean healing time was 38 days, while 14 eyes (87.5%) with the same category of ulcer in the control group healed over an average of 17.1 ± 10.4 days. No eyes with melting ulcers healed and only one eye with a perforated ulcer (50%) healed in CKD group; the perforating ulcer took 92 days to heal. In control group, there were no eyes with melting ulcers. Only one of the eyes with a perforating ulcer (50%) in the control group healed, this took 64 days. Stromal, melting, and perforating ulcers could not be statistically analyzed because of too few of the eyes healed to determine statistical significance.

In the CKD group, 28 dogs (32 eyes) had WBC counts measured on the day the ulcer was diagnosed. Among these patients, those with non-healing ulcers had markedly elevated WBC counts, while those with healing ulcers had WBC counts within the normal range (Fig. 2, p = 0.000). Surgical intervention was performed in 11 eyes in the CKD group. This included temporary tarsorrhaphy, conjunctival graft, and direct corneal suture. However, surgical intervention did not significantly affect corneal healing time in the CKD group ($p > 0.05$).

Table 1. Breed predisposition of corneal ulcer patients

	CKD[a] group (n = 34)	Control group (n = 31)
Shih-tzu	12	18
Yorkshire terrier	6	-
Maltese	5	4
Pekingese	3	1
Mixed breed	3	2
Miniature schnauzer	2	1
Pomeranian	1	1
Cocker spaniel	1	1
Poodle	1	-
Miniature pinscher	-	1
Chow chow	-	1
Dachshund	-	1

[a]CKD, chronic kidney disease.

Discussion

Many articles in human medicine refer to the relationship between CKD and ocular disease. One human study evaluating corneal and conjunctival calcification in CKD patients reported that calcification and reduced tear production were the reasons for the red eye seen in these patients (11). Another study investigating ocular surface disorders reported that CKD patients showed significantly abnormal tear film pro-

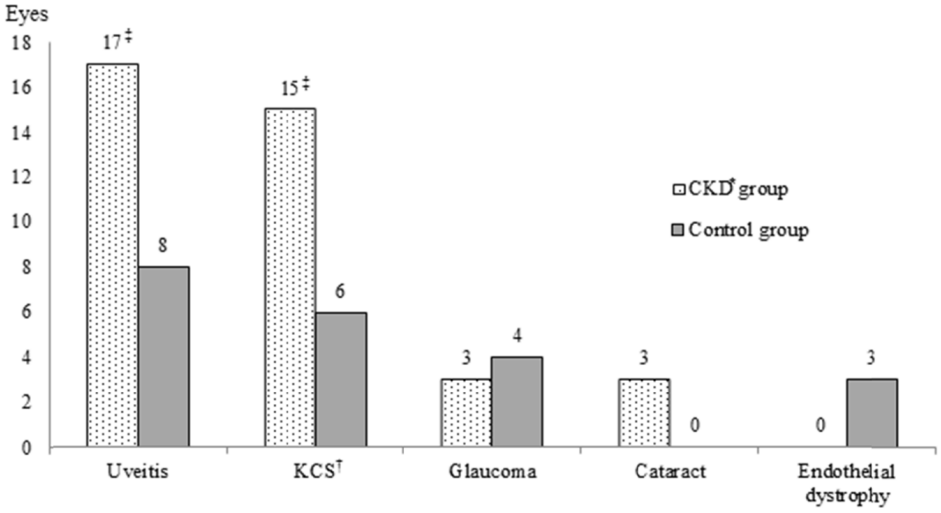

Fig. 1. Concurrent ophthalmic diseases of CKD* and control groups. (Statistical significancies between CKD and control groups were only compared in uveitis and KCS†) *CKD, chronic kidney disease; †KCS, keratoconjunctivitis sicca; ‡significantly different compared to the control group.

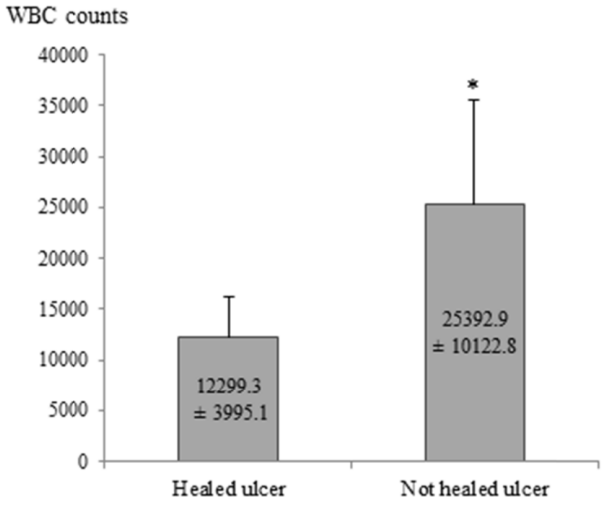

Fig. 2. White blood cell counts in chronic kidney diseases patients with healed vs. non-healed corneal ulcers. *Significantly different compared to healed corneal ulcer patients.

duction (9). A report on ocular changes in children with CKD revealed that dry eye syndromes were more common among these children (1). Despite the fact that a number of these studies exist in humans, to the best of our knowledge there have been no studies evaluating the relationship between ocular changes and CKD in dogs.

In practice, many clinicians have noted that corneal ulcers in dogs with CKD are often complicated or do not heal and have considered that the presence of KCS could be one of the reasons as it is in humans. In this study, retrospective evaluation was performed to identify characteristic differences between corneal ulcers in dogs with CKD and healthy dogs. The incidence of corneal ulcers in dogs with CKD in this study was 4.2% (34/814). Similar to a previous study that reported that brachycephalic breeds were prone to corneal ulcers, Shih-tzu was the predominant breed with corneal ulcers in both the control and CKD groups in this study (5). The most common ocular disease was uveitis (44.7% in the CKD group, 21.6% in the control group). The correlation between category of corneal ulcer and severity of uveitis was statistically significant ($r = 0.284$, $p = 0.0482$). The incidence of uveitis was significantly higher in the CKD group than in the control group ($p = 0.000$). Uveitis might be followed by the development of a corneal ulcer, and it might negatively affect healing of the ulcer.

In this study, all dogs in the CKD group with non-healing ulcers had elevated WBC counts. Chronic kidney disease might lead to metabolic changes that result in acute or chronic systemic inflammatory changes in the organs. A previous study showed that inflammatory biomarkers including C-reactive protein (CRP) and interleukin-6 were significantly elevated in CKD patients. Oxidative stress biomarkers including plasma protein carbonyl groups, plasma free F_2-isoprostane, and plasma protein reduced thiols were also significantly elevated in these patients (8). Unfortunately, these markers were not analyzed in this study. The elevated WBC counts and high incidence of uveitis in the CKD group might reflect the systemic inflammatory status of the CKD dogs in this study and might affect the corneal healing process.

KCS was the second most common concurrent ocular disorder in both groups and was thought to be the main cause of the corneal ulcers. The incidence rate of KCS was significantly higher in the CKD group (36.8%) than in the control group (16.2%, $p = 0.026$). The mechanism behind the development of KCS in CKD has been described in humans as squamous metaplasia of conjunctival epithelium and transformation of secretory conjunctival epithelium into non-secretory keratinized epithelium. This, in addition to dehydration caused by a decreased ability to concentrate urine and anorexia, leads to KCS (11). It has not yet been proven that this metaplasia occurs in the dog conjunctival epithelium as well, and further study is required.

Severity of corneal ulcers did not differ significantly between the two groups in this study ($p = 0.093$). However, eyes with superficial ulcers in the CKD group took significantly longer to heal than those in the control group ($p = 0.019$). Healing times of stromal ulcers, melting ulcers, and perforating ulcers could not be compared statistically because the most failed to heal.

There was no significant difference in this study on corneal healing time whether the surgical intervention, which was reported taken shorter healing times on corneal ulcer (5). This result might be influenced by the high mortality rate the patients requiring surgical intervention. Healing time could not be properly evaluated in 12 dogs (15 eyes) because they died of CKD complications within one month of the diagnosis of a corneal ulcer.

In conclusion, dogs with corneal ulcers and CKD showed a high incidence of concurrent uveitis and KCS, evidence of systemic inflammation (elevated WBC count), and had a delayed healing time. Therefore, it would be suggested that CKD patients with corneal ulcers should be treated aggressively in the early stages of corneal ulcer considering delayed healing time.

Conflicts of Interest

The authors have no conflicting interests.

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