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Effect of oral antioxidants on the progression of canine senile cataracts: a retrospective study

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ABSTRACT

Background: Cataracts are the leading cause of impaired vision or blindness in dogs. There are many antioxidants that can prevent cataract progression, but whether they are clinically effective in dogs has not been established.
Objectives: To analyze the delaying or preventing effect of oral antioxidants on canine senile cataracts through retrospective analysis.
Methods: Medical records of dogs from January 1, 2015 to July 10, 2020 were reviewed. Dogs that were 8 yr of age or older with senile cataracts were included in this study. The dogs were divided into two treatment groups (dogs administered with Ocu-GLO supplement and dogs administered with Meni-One Eye R/C supplement) and a control group (dogs that were not administered any supplement). Dogs with incipient and immature cataracts were included in this study. Altogether, 112 dogs (156 eyes) with incipient cataracts and 60 dogs (77 eyes) with immature cataracts were included. The period of time that cataracts progressed from incipient to immature, and from immature to mature was recorded for each dog.
Results: There was no significant delaying effect on the progression of incipient cataracts. However, both Ocu-GLO (hazard ratio = 0.265, $p = 0.026$) and Meni-One (hazard ratio = 0.246, $p = 0.005$) significantly delayed the progression of immature cataracts compared to the control group.
Conclusions: Although there was no significant delaying effect of oral antioxidants on incipient cataract progression, antioxidants could be used to delay the progression of senile immature cataract.

Keywords: Antioxidant; cataract; dog; prevention; supplement

INTRODUCTION

Cataracts are the leading cause of impaired vision or blindness in dogs [1]. There are several classification schemes for canine cataracts [2]. Canine cataracts are classified by specific etiology, age at which cataracts develop (congenital, juvenile, and senile cataract), anatomical location of the cataract within the lens (capsular, subcapsular, zonular, cortical, nuclear, sutorial, axial, and equatorial), and the stage of cataract progression (incipient, immature, mature, and hypermature) [2]. Although cataract surgery is considered the only definite

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Conflict of Interest
The authors declare no conflicts of interest.

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treatment for cataracts, preventing cataract formation or delaying cataract progression would be beneficial [3].

Senile cataracts in dogs are known to be caused by oxidative stress by various factors, including ultraviolet radiation, lipid peroxidation, and protein peroxidation [4-6]. Commercially available oral antioxidant supplements and antioxidant eye drops are publicized to prevent or delay cataract formation in dogs and humans. Lipid peroxidation and protein peroxidation have also been confirmed in the lens of canine senile cataracts [7].

Several antioxidants that have been reported to delay cataract progression include vitamin C, vitamin E, β-carotene, alpha-lipoic acid, astaxanthin, grape seed extract (GSE), and zinc [4, 6-15]. Currently, Ocu-GLO (Animal HealthQuest, USA) and Meni-One Eye R/C (Meni-One, Japan) have been widely used as oral antioxidant supplements in veterinary ophthalmology. No studies have evaluated the effect of commercially available oral antioxidants on senile cataract progression in dogs, and only the effects of alpha-lipoic acid and astaxanthin, which are ingredients of Ocu-GLO and Meni-One Eye R/C, respectively, have been evaluated in dogs with diabetic cataracts [16,17]. Although various antioxidant products for delaying or preventing cataracts have been introduced, there have been a few clinical trials and were only conducted for vitamin C, vitamin E, and β-carotene in humans [11,18], and no clinical trials have been conducted in dogs. This retrospective study aimed to analyze whether senile cataract progression was delayed in dogs that were administered oral antioxidants (Ocu-GLO or Meni-One Eye R/C) when compared with the control group.

MATERIALS AND METHODS

Antioxidant products

Ocu-GLO (Animal HealthQuest) and Meni-One Eye R/C (Meni-One) were prescribed in dogs with incipient and immature cataracts if the owners complied with administering supplements to their dogs. Both products contain several ingredients that have antioxidant effects. Both supplements contain grape seed extract (GSE) and vitamin E, and each supplement contains various other antioxidants. Ocu-GLO contains antioxidants such as alpha-lipoic acid and vitamin C, while Meni-One Eye R/C contains astaxanthin and curcuminoid (**Supplementary Table 1**). All dogs included in this study were administered a supplement at the dosage recommended by the manufacturer.

Animals

Medical records of dogs that presented to the Division of Ophthalmology, Veterinary Medical Teaching Hospital, College of Veterinary Medicine, Seoul National University in Seoul, Korea from January 1, 2015 through July 10, 2020 were evaluated retrospectively. To assess the effectiveness of antioxidant products on canine senile cataract progression, the following inclusion criteria were established: (1) dogs with incipient or immature cataracts that were 8 yr of age or older and (2) dogs that were consistently administered supplements according to the study protocol. Dogs with congenital cataracts and those with other concurrent ocular diseases or systemic co-morbidities that could promote cataractogenesis (uveitis, hyphema, retinal detachment, progressive retinal atrophy, sudden acquired retinal degeneration syndrome, diabetes mellitus, and trauma) were excluded. Ophthalmic examinations were performed for all dogs prior to the study initiation. Neuro-ophthalmic examinations included menace response and dazzle reflex assessment. Tear volumes were quantified by

Schirmer tear test 1 (Schirmer tear test; MSD, USA) and intraocular pressures (IOP) had been estimated (TONOVET; Finland Oy, Finland) for all eyes. The eyes of the dogs were examined and pictures were made using a slit lamp biomicroscope (Topcon - Model SL-D7; Topcon Corp., Japan). The fundus was evaluated using indirect ophthalmoscopy (Keeler Vantage Plus; Keeler Ltd., UK). Several eyes could be evaluated for cataracts without instillation of mydriatic drugs, but cataracts located in the equatorial region of the lens had been evaluated after mydriasis using a Finoff transilluminator (Welch Allyn Medical Product, USA). One of the two diplomates of the Asian College of Veterinary Ophthalmologist evaluated and recorded the stage of maturation, anatomical location within the lens, and shape of cataracts. The stages of cataract were classified into incipient, immature, mature, and hypermature. Cataracts with minor or localized opacification involving less than 15% of the lens volume were classified as incipient cataracts. Immature cataract was defined as a stage in which opacification was greater than 15% of the lens volume, the tapetal reflection could be observed through lens opacity, and there was no clinically evident resorption of lens material or capsular wrinkling. Mature cataract was defined as a stage in which the tapetal reflection disappeared due to total opacification. Hypermature cataract was defined as the stage at which proteolysis had progressed with clinically evident resorption of lens material and the lens appeared to be shrunken (**Supplementary Fig. 1**) [2,19]. In the retroillumination view, several shots were taken with the light of the weakest intensity as possible, and a picture suitable for evaluation had been selected and saved. Cataract was evaluated by considering not only the retroillumination views and slit lamp biomicroscopy views, but also the equator evaluation with a Finoff transilluminator after dark adaptation. Then, a board-certified ophthalmologist evaluated the cataract. Incipient and immature cataracts were analyzed to evaluate the delaying effect of antioxidant supplements on senile cataracts.

Incipient cataract progression analysis

Dogs that had incipient cataracts were divided into three groups: dogs that were administered Ocu-GLO (group O_1), Meni-One Eye R/C (group M_1) and dogs that were not administered any supplement (group C_1). In the C_1 group, the time from the date of diagnosis of incipient cataracts to the date of diagnosis of immature cataracts was recorded. In the O_1 and M_1 groups, the time from the date of supplement administration in the incipient cataract stage to the date of further advancement of cataract and diagnosis of immature cataract was recorded. If the date of supplement administration was earlier than the date of diagnosis of the incipient cataract, the time was calculated in a manner similar to that in the C_1 group. To match the degree of cataract progression at the beginning of follow-up, the slit lamp biomicroscopy images of all dogs were reviewed, and dogs were excluded if the cataract stages were close to immature. The follow-up period was established until a maximum of 800 days was reached in all groups.

Immature cataract progression analysis

Dogs with immature cataracts were also divided into the Ocu-GLO group (O_2 group), the Meni-One Eye R/C group (M_2 group), and the control group (C_2 group). The time from the date diagnosed with immature cataract to the date diagnosed with mature cataract was recorded. To match the degree of cataract progression at the beginning of follow-up, the slit lamp biomicroscopy images of all dogs were reviewed, and dogs were excluded if the cataract stages were close to mature. The follow-up period was established until a maximum of 800 days was reached in all groups.

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Statistical analyses

The Kruskal-Wallis test was used to determine the difference in the age variables among the groups. In addition, the χ^2 test was used for the cross-analysis to determine whether there was a difference in sex and species variables among the groups. Fisher's exact test was performed for accurate verification. Kaplan-Meier survival analysis was used for each group to determine the cataract-delaying effect of each antioxidant. The log-rank test was used to evaluate the significance of the differences between the survival curves of the different groups. If there were significant differences in the cross-analysis of age, sex, and breed among the three groups, this could have affected the results. Therefore, the analysis was performed using Cox proportional hazards models that could correct for the effects of variables.

IBM SPSS Statistics version 25.0 (IBM Corp., USA) was used for the statistical analyses, and it was considered statistically significant when $p < 0.05$.

RESULTS

Analysis of incipient cataract progression

In total, 156 eyes of 112 dogs were included in the incipient cataract group. Among these, 93 eyes of 72 dogs were included in the C_1 group, 29 eyes of 18 dogs were included in the O_1 group, and 34 eyes of 22 dogs were included in the M_1 group. In the present study, each eye was evaluated independently.

The mean age of all dogs with incipient cataracts was 11.5 ± 2.5 yr. The mean ages were 11.9 ± 2.7, 11.1 ± 1.7, and 10.9 ± 2.3 yr in the C_1, O_1, and M_1 groups, respectively. No significant difference was observed in the age variables among the three groups (p = 0.139) (**Table 1**).

There was no significant difference in the sex ratios among the three groups. No significant difference was observed in the sex variables in the cross-analysis performed using the χ^2 test and Fisher's exact test (p = 0.559) (**Table 2**).

There were 17 breeds included in the incipient cataract group. Maltese (n = 47, 30.1%) was the most common breed, followed by Poodle (n = 20, 12.8%), and Cocker Spaniel (n = 19, 12.2%). There was a significant difference in breed variables in the cross-analysis performed using the χ^2 test and Fisher's exact test (p = 0.006) (**Table 3**).

Table 1. Mean ages of the three groups in dogs with incipient or immature cataract

Groups	Mean age (yr)	SD	*p*
C_1	11.9	2.7	0.139
O_1	11.1	1.7	
M_1	10.9	2.3	
Total	11.5	2.5	
C_2	12.0	2.6	0.093
O_2	12.5	2.6	
M_2	10.8	2.3	
Total	11.8	2.6	

C_1, dogs with incipient cataracts administered no supplements; O_1, dogs with incipient cataracts administered Ocu-GLO; M_1, dogs with incipient cataracts administered Meni-One Eye R/C; C_2, dogs with incipient cataracts administered no supplements; O_2, dogs with incipient cataracts administered Ocu-GLO; M_2, dogs with incipient cataracts administered Meni-One Eye R/C; SD, standard deviation.

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Table 2. Sex distribution of the three groups in dogs with incipient or immature cataract

Groups	Sex			
	F	FS	M	MC
C_1	12 (7.7%)	39 (25.0%)	5 (3.2%)	37 (23.7%)
O_1	1 (0.6%)	13 (8.3%)	0 (0.0%)	15 (9.6%)
M_1	3 (1.9%)	13 (8.3%)	3 (1.9%)	15 (9.6%)
Total	16 (10.3%)	65 (41.7%)	8 (5.1%)	67 (42.9%)
p	0.559			
C_2	2 (2.6%)	17 (22.1%)	3 (3.9%)	19 (24.7%)
O_2	4 (5.2%)	10 (13.0%)	0 (0.0%)	6 (7.8%)
M_2	0 (0.0%)	11 (14.3%)	0 (0.0%)	5 (6.5%)
Total	6 (7.8%)	38 (49.4%)	3 (3.9%)	30 (30.0%)
p	0.145			

C_1, dogs with incipient cataracts administered no supplements; O_1, dogs with incipient cataracts administered Ocu-GLO; M_1, dogs with incipient cataracts administered Meni-One Eye R/C; C_2, dogs with incipient cataracts administered no supplements; O_2, dogs with incipient cataracts administered Ocu-GLO; M_2, dogs with incipient cataracts administered Meni-One Eye R/C; F, female; FS, female spayed; M, male; MC, male castrated.

Table 3. Breed distribution of the three groups in dogs with incipient cataract

Breeds	Groups			Total	*p*
	C_1	O_1	M_1		
Maltese	25 (16.0%)	12 (7.7%)	10 (6.4%)	47 (30.1%)	
Poodle	8 (5.1%)	5 (3.2%)	7 (4.5%)	20 (12.8%)	
Cocker Spaniel	17 (10.9%)	0 (0.0%)	2 (1.3%)	19 (12.2%)	
Shih-tzu	9 (5.8%)	1 (0.6%)	6 (3.8%)	16 (10.3%)	
Yorkshire Terrier	8 (5.1%)	2 (1.3%)	4 (2.6%)	14 (9.0%)	
Mixed	8 (5.1%)	3 (1.9%)	1 (0.6%)	12 (7.7%)	
Pomeranian	4 (2.6%)	0 (0.0%)	1 (0.6%)	5 (3.2%)	
Schnauzer	1 (0.6%)	3 (1.9%)	0 (0.0%)	4 (2.6%)	
Miniature Pinscher	4 (2.6%)	0 (0.0%)	0 (0.0%)	4 (2.6%)	0.006*
Beagle	2 (1.3%)	0 (0.0%)	0 (0.0%)	2 (1.3%)	
Bichon Frise	0 (0.0%)	0 (0.0%)	2 (1.3%)	2 (1.3%)	
Boston Terrier	2 (1.3%)	0 (0.0%)	0 (0.0%)	2 (1.3%)	
Chihuahua	2 (1.3%)	0 (0.0%)	0 (0.0%)	2 (1.3%)	
Labrador Retriever	0 (0.0%)	2 (1.3%)	0 (0.0%)	2 (1.3%)	
Weimaraner	2 (1.3%)	0 (0.0%)	0 (0.0%)	2 (1.3%)	
Dachshund	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	
Pekingese	0 (0.0%)	1 (0.6%)	0 (0.0%)	1 (0.6%)	

C_1, dogs with incipient cataracts administered no supplements; O_1, dogs with incipient cataracts administered Ocu-GLO; M_1, dogs with incipient cataracts administered Meni-One Eye R/C.
*There was significant difference in breed variables in the cross-analysis performed using the χ^2 test and Fisher's exact test ($p < 0.05$).

The difference in rates of cataract progression for each group was confirmed through representative retroillumination images (**Supplementary Fig. 2**). Based on the results of the Kaplan-Meier survival curves for the three groups, the survival rates of the O_1 and M_1 groups were higher until 400 days. However, there was no significant difference among the survival rates of the three groups according to the log-rank test ($C_1 - O_1$ groups, $p = 0.161$; $C_1 - M_1$ groups, $p = 0.450$; $O_1 - M_1$ groups, $p = 0.459$) (**Fig. 1**). The progression of cataract was analyzed using the Kaplan-Meier survival curves, and the survival rate means the rate at which the cataract did not progress. Data whose follow-up was stopped during the 800 days, which is the total follow-up period, were classified as 'censored data'. Censored data also included cases where cataracts had not progressed until the follow-up period was completed.

As the distribution of breeds was significantly different among the three groups, the analysis was performed using the Cox proportional hazards models. The hazard ratio (HR) is the value obtained by dividing the risk rate in the experimental group by the risk rate in the control group. That is, if the HR is 1, the experimental group and the control group have

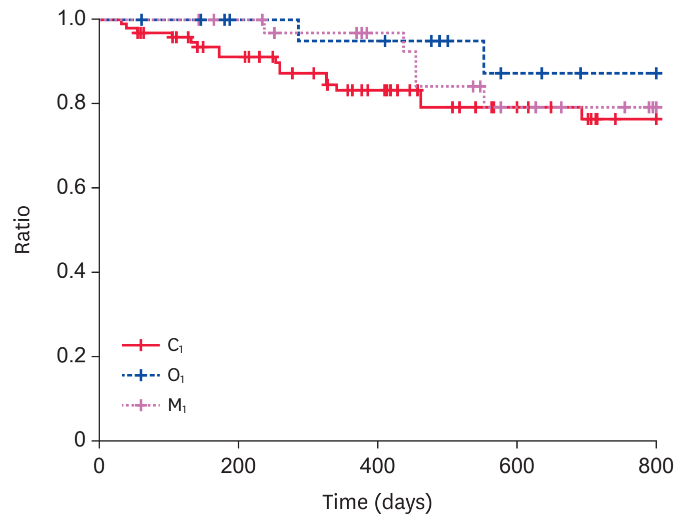

Fig. 1. Kaplan-Meier survival curves in dogs with incipient cataracts.
There was no significant difference among the survival curves of the three groups.
C_1, dogs with incipient cataracts administered no supplements; O_1, dogs with incipient cataracts administered Ocu-GLO; M_1, dogs with incipient cataracts administered Meni-One Eye R/C.

the same risk rate, and if the HR is greater than 1, it menas that the risk of the experimental group increases. Also, if the HR is less than 1, it means that the risk in the experimental group decreases. The HR of the cataract progression compared to Maltese was significant in Shih-Tzu (HR = 6.316, p = 0.010) (**Table 4**). The variable due to the difference in breed distribution was corrected using Cox proportional hazards models. However, even though the variable was corrected, the group administered supplements did not show a significant difference in HR compared to the control group ($C_1 - O_1$ groups, HR = 0.460, p = 0.143; $C_1 - M_1$ groups, HR= 0.320, p = 0.133) (**Table 5**).

Table 4. The HR of each breeds compared to Maltese under the Cox proportional hazard model in dogs with incipient cataract

Breeds	HR (95% CI)	*p*
Maltese	1	
Poodle	4.060 (0.966–17.056)	0.056
Cocker Spaniel	2.159 (0.430–10.853)	0.350
Shih-Tzu	6.316 (1.543–25.857)	0.010*
Yorkshire Terrier	4.266 (0.858–21.211)	0.076
Mixed	Unable to measure	-
Pomeranian	Unable to measure	-
Schnauzer	6.626 (0.685–64.111)	0.102
Miniature Pinscher	Unable to measure	-
Other breeds†	5.014 (0.993–25.308)	0.051

HR, hazard ratio; CI, confidence interval.
*The hazard ratio of the cataract progression was significant compared to the Maltese ($p < 0.05$).
†If there were two or fewer dogs in one breed, they were classified as 'Other breeds' (Beagle [n = 2], Bichon Frise [n = 2], Boston Terrier [n = 2], Chihuahua [n = 2], Labrador Retriever [n = 2], Weimaraner [n =2], Dachshund [n = 1], Pekingese [n = 1]).

Table 5. The HR and *p*-value under the Cox proportional hazards model compared to the C_1 group

Groups	HR (95% CI)	*p*
O_1	0.460 (0.163–1.299)	0.143
M_1	0.320 (0.072–1.414)	0.133

C_1, dogs with incipient cataracts administered no supplements; O_1, dogs with incipient cataracts administered Ocu-GLO; M_1, dogs with incipient cataracts administered Meni-One Eye R/C; HR, hazard ratio; CI, confidence interval.

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Analysis of immature cataract progression

There were 77 eyes of 60 dogs from the immature cataract group that were analyzed including 41 eyes of 34 dogs in the C_2 group, 20 eyes of 13 dogs in the O_2 group, and 16 eyes of 13 dogs in the M_2 group. Each eye was evaluated independently.

The mean age of all dogs with immature cataracts was 11.8 ± 2.6 yr. The mean ages of the C_2, O_2, and M_2 group were 12.0 ± 2.6 yr, 12.5 ± 2.6 yr, and 10.8 ± 2.3 yr, respectively. No significant difference was observed in the mean age among the three groups (p = 0.093) (**Table 1**).

The difference in sex distribution among the three groups was not statistically significant (χ^2 test and Fisher's exact test, p = 0.145) (**Table 2**).

There were 12 breeds included in the immature cataract group. The Yorkshire Terrier (19.5%) was the most common in the immature cataract group, followed by Maltese and Poodle (18.2%), and Cocker Spaniel (15.6%). There was a significant difference in breed variables in the cross-analysis performed using the χ^2 test and Fisher's exact test (p = 0.002) (**Table 6**).

The difference in the rate of cataract progression in each group could be confirmed through representative retroillumination images (**Supplementary Fig. 3**). Based on the Kaplan-Meier survival curve, the survival rate of the O_2 and M_2 groups was higher than that of the C_2 group. However, there was no significant difference between the Kaplan-Meier survival curves of the M_2 and C_2 groups in the log-rank test, whereas there was a significant difference between the survival curves of the O_2 and C_2 ($C_2 - O_2$ groups, p = 0.032; $C_2 - M_2$ groups, p = 0.067; $O_2 - M_2$ groups, p = 0.979) (**Fig. 2**).

As the distribution of breeds was significantly different among the three groups, the analysis was performed using the Cox proportional hazards models. The HR of cataract progression compared to Yorkshire Terrier was significant in the Poodle (HR = 0.288, p = 0.045), Cocker Spaniel (HR = 0.239, p = 0.019), and Shih-Tzu (HR = 0.133, p = 0.021) (**Table 7**). The variable due to the difference in breed distribution was corrected using Cox proportional hazards models. As a result, the HRs of the O_2 and M_2 groups were significantly lower than those of the C_2 group. ($C_2 - O_2$ groups, HR = 0.265, p = 0.026; $C_2 - M_2$ groups, HR= 0.246, p = 0.005) (**Table 8**).

Table 6. Breed distribution of the three groups in dogs with immature cataract

Breeds	Groups			Total	p
	C_2	O_2	M_2		
Yorkshire Terrier	6 (7.8%)	9 (11.7%)	0 (0.0%)	15 (19.5%)	0.002*
Maltese	5 (6.5%)	2 (2.6%)	7 (9.1%)	14 (18.2%)	
Poodle	12 (15.6%)	1 (1.3%)	1 (1.3%)	14 (18.2%)	
Cocker Spaniel	5 (6.5%)	6 (7.8%)	1 (1.3%)	12 (15.6%)	
Shih-Tzu	6 (7.8%)	0 (0.0%)	2 (2.6%)	8 (10.4%)	
Chihuahua	1 (1.3%)	2 (2.6%)	4 (5.2%)	7 (9.1%)	
Beagle	2 (2.6%)	0 (0.0%)	0 (0.0%)	2 (2.6%)	
Bichon Frise	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	
Boston Terrier	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	
Malamute	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	
Miniature Pinscher	0 (0.0%)	0 (0.0%)	1 (1.3%)	1 (1.3%)	
Pomeranian	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	

C_2, dogs with incipient cataracts administered no supplements; O_2, dogs with incipient cataracts administered Ocu-GLO; M_2, dogs with incipient cataracts administered Meni-One Eye R/C.
*There was a significant difference in breed variables in the cross-analysis performed using the χ^2 test and Fisher's exact test (p < 0.05).

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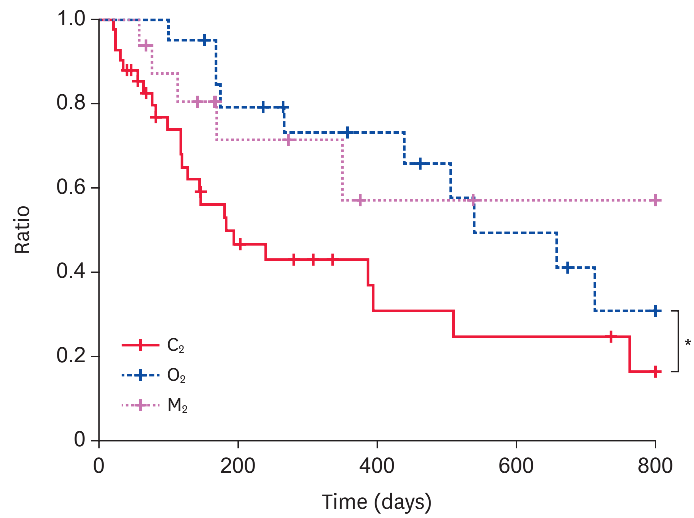

Fig. 2. Kaplan-Meier survival curves in dogs with immature cataracts.
C_2, dogs with incipient cataracts administered no supplements; O_2, dogs with incipient cataracts administered Ocu-GLO; M_2, dogs with incipient cataracts administered Meni-One Eye R/C.
*There was significant different between O_2 and C_2 groups (p = 0.032).

Table 7. The HR of each breeds compared to Yorkshire Terrier under the Cox proportional hazard model in dogs with immature cataract

Breeds	HR (95% CI)	*p*
Yorkshire Terrier	1	
Maltese	0.374 (0.112–1.244)	0.109
Poodle	0.288 (0.085–0.973)	0.045*
Cocker Spaniel	0.239 (0.072–0.790)	0.019*
Shih-Tzu	0.133 (0.024–0.736)	0.021*
Chihuahua	1.046 (0.284–3.856)	0.947
Other breeds†	0.536 (0.146–1.965)	0.347

HR, hazard ratio; CI, confidence interval.
*The hazard ratio of cataract progression was significant compared to the Yorkshire Terrier ($p < 0.05$).
†If there were two or fewer dogs in one breed, they were classified as 'Other breeds' (Beagle [n = 2], Bichon Frise [n = 1], Boston Terrier [n = 1], Malamute [n = 1], Miniature Pinscher [n = 1], Pomeranian [n = 1]).

Table 8. The HR and *p*-value under the Cox proportional hazards model compared to the C_2 group

Groups	HR (95% CI)	*p*
O_2	0.265 (0.082–0.853)	0.026*
M_2	0.246 (0.093–0.650)	0.005*

C_2, dogs with incipient cataracts administered no supplements; O_2, dogs with incipient cataracts administered Ocu-GLO; M_2, dogs with incipient cataracts administered Meni-One Eye R/C; HR, hazard ratio; CI, confidence interval.
*The HR was significantly lower than that of the control group ($p < 0.05$).

DISCUSSION

Cataracts are responsible for the reduced vision in a large number of aged dogs [1,2]. A previous study including 2,000 dogs in the United Kingdom reported that half of the dogs had cataracts at 9.4 ± 3.3 yr of age [1]. It was also reported that all dogs over 13.5 yr of age had some degree of cataracts [1]. In the study reported here, the mean age of onset of incipient and immature cataracts was 11.2 ± 2.3 yr and 11.4 ± 2.5 yr, respectively. In the present study, dogs over 8 yr of age were analyzed for senile cataracts. In veterinary medicine, the age of onset of senile cataract has not been clearly defined [2]. It was reported that if cataracts develop in dogs above 7 yr of age, a hereditary basis would be unlikely [2]. As each owner might have a different way of counting the age of their dog, dogs over 8 yr of age were included to decrease the likelihood of a hereditary basis for cataracts substantially in the present study. The onset of senile cataracts occurs after 10 yr of age in small breed dogs and after 6 yr of age in large breed dogs [19]. In addition, senile cataracts tended to be more common in large breeds than in small breeds from the same age group [20]. As most of the dogs in the present study were small breed dogs, the age criteria for senile cataracts were not established according to their size.

The causes of senile cataracts vary and have not been clearly elucidated in dogs and humans [13]. However, oxidative damage has been considered as one of the primary factors in cataractogenesis [4,6,8,13]. Factors involved in the mechanism of cataractogenesis in humans and mice include reactive oxygen which induces oxidation of lens proteins, DNA damage, and lipid peroxidation [4,5,13,14]. Peroxidation of lipids and proteins has also been reported in the lens of dogs with senile cataracts *in vitro* [7].

Recently, several dogs have been administered various antioxidant products to delay the progression of cataracts. Previous studies have shown that age-related cataracts are associated with oxidative stress [4-6,11,13,21]. A previous study reported that glutathione was a critical substance for maintaining the homeostasis of the lens, and vitamin C, vitamin E, β-carotene, and acetyl-salicylic acid could prevent the cataractogenesis and the aging of the lens *in vitro* [6]. It was reported that vitamin C could prevent cataract formation *in vitro*, and vitamin E also partially inhibited lipid peroxidation and cataract formation *in vitro* experiment using the lens of rats [13]. In addition, it had been shown that glutathione and vitamin C, endogenous antioxidants, play important roles in the lens of humans and rats with senile cataracts [4, 12]. Grape seed extract (GSE), one of the antioxidant components of Ocu-GLO and Meni-One Eye R/C, was reported to have antioxidant effects on canine lens epithelial cells *in vitro* [8, 22]. In addition, it was reported that GSE and Zincovit tablet (nutritional food supplement) were effective in delaying or preventing selenite-induced rat cataracts in a rat model [10]. However, no clinical trials have analyzed the delaying effects of GSE in senile cataract in humans or dogs. Alpha-lipoic acid and astaxanthin, which are components of Ocu-GLO and Meni-One Eye R/C, respectively, were found to have a reversal effect on lens opacification and a delaying effect on canine diabetic cataracts [16,17]. The delaying effect of astaxanthin on cataract progression was also reported in selenite-induced rat cataract model [23]. However, the effects of alpha-lipoic acid and astaxanthin on senile cataracts have not been elucidated. Despite several positive results of antioxidants, the effect of oral antioxidants on the development and progression of senile cataracts is controversial in human clinical trials. Conflicting studies have reported that vitamin C, vitamin E, and β-carotene may delay the increase in opacity of senile cataracts in human clinical trial [15], whereas other clinical trials reported that these supplements were ineffective in delaying or preventing senile cataracts [11,14,18,24]. In addition, there have been no clinical trials to determine the effect of antioxidants on senile cataracts in dogs.

In the study reported here, the effect of Ocu-GLO and Meni-One Eye R/C on delaying the progression of incipient and immature cataracts was investigated. There was no significant delaying effect on the incipient cataract progression in either the Kaplan-Meier survival analysis or the Cox proportional hazards model. However, in the analysis of immature cataract progression, Kaplan-Meier survival curves of the O_2 and M_2 groups decreased more slowly than that of the C_2 group, and there was a significant difference between the survival curves of the O_2 and C_2 groups. Although there was no significant difference

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between the survival curves of the M_2 and C_2 groups, the survival curves of the M_2 groups showed a tendency to decrease more slowly than that of the control group. In addition, the Cox proportional hazards model, which corrected the differences in breed distribution, confirmed that the cataract progression of the O_2 and M_2 groups was significantly delayed.

There was no significant effect of the antioxidant supplements in several human clinical trials [14,18,24], and it was not effective in delaying the progression of incipient cataracts in this study. A previous study reported that 70.1% of age-related cataracts did not progress and 29.9% progressed slowly, and the proportion in which cataracts did not progress was higher in incipient cataracts than in immature cataracts in dogs [25]. Because incipient cataracts did not progress or progressed very slowly, the significant delaying effect of the supplement on incipient cataracts might not have been identified in this study and human clinical trials. Therefore, to analyze the progression of the incipient cataract, it is necessary to follow up for a sufficient time or devise a method to quantify the cataract area. In human clinical trials, retroillumination images were analyzed, visual acuity was evaluated, and questionnaires were conducted to analyze microscopic changes [14,15,18,24]. However, as tapetum exists in dogs, the area of the cataract may vary depending on the direction in which the retroillumination view is taken. It would be important to find a method to quantify the cataract area in dogs reliably.

In this study, it was found that antioxidants effectively inhibit the progression of immature cataracts. The immature cataract tends to progress in 72.7% and progresses faster than other cataracts [25]. Because of these features, immature cataracts might have more significant results than incipient cataracts in this study, which evaluated whether the cataract progressed to the next stage. In addition, unlike the human clinical trial, which investigated supplements containing only vitamin C, vitamin E, and β-carotene, the two supplements compared in this study contained several other major antioxidants. This may be due to the effects of other antioxidants.

Senile cataracts in humans are associated with several biochemical changes, such as ionic imbalance (high sodium, calcium and low potassium), enzymatic modification (thiol transferase, glutathione reductase, endopeptidases, and aldose reductase), and non-enzymatic or post-translational modification (conformation changes, denaturation, cross-linking, aggregation, deamidation, and glycation) [4]. Similarly, as the development and progression of senile cataracts might be associated with various mechanisms in dogs, there is no conclusive evidence that antioxidants are not effective in preventing or delaying senile cataracts.

Eye drops containing antioxidants, as well as oral antioxidants, have been widely used in humans and dogs. Pirenoxine antioxidant eye drops were reported to suppress the progression of presbyopia in rats and also reduce lens opacity and delayed cataract progression in dogs [26-28]. Additionally, the instillation of eye drops containing N-acetyl carnosine, another antioxidant, resulted in the delayed progression of senile cataracts and subtle reduction in the opacification of the lens in humans and dogs [3,21,29-32]. Therefore, further studies comparing the delaying effects of oral and topical antioxidants on senile cataracts are needed.

There are several limitations to this retrospective study. Re-evaluation intervals varied among the dogs or groups. Long-term re-evaluations might have led to an erroneous conclusion that cataract progression was delayed in dogs with progressive cataracts. Conversely, analysis of dogs with short-term re-evaluations might have led to an inaccurate conclusion of rapid cataract progression. However, because the incipient cataract rarely progresses or progresses very slowly, the re-evaluation interval would not have a significant effect on the results. Dogs with immature cataracts were usually re-evaluated regularly to prevent lens-induced uveitis or to plan surgery. Most of the dogs were re-evaluated at regular intervals, and only few dogs were re-evaluated at short or long-term intervals.

Image analysis programs have been used in the previous studies [3,29] to quantify cataract progression, but were not used in the present study as progression to the next stage of cataract maturation was established as a criterion that did not require documentation of subtle changes in lens opacification. If the degree of cataract opacity had been analyzed and quantified in 2D or 3D, it would have been possible to analyze subtle changes, such as the progression of incipient cataracts. However, as there is a tapetum in dogs, it could make and artifacts and errors when measuring the cataract area using the retroillumination view. There is a need for a method of calculating the cataract area or volume without these artifacts or errors.

The locations of the cataracts were not discussed in the present study and the tests were performed without instillation of the mydriatic agent each time. Capsular and subcapsular cataracts typically do not progress or progress very slowly over time, whereas cataracts located in the anterior, posterior, and equatorial cortex typically progress [33]. Progression of the cataract varies by location within the lens [34,35]. Documenting the specific detailed location of cataracts within the lens may have revealed correlations regarding cataract progression based on location. Although every examination focused on the location of the previous cataract and determining whether it progressed, this study did not analyze the subtle changes of cataracts, but evaluated whether they had progressed to the next stage. The progression of the cataract to immature or mature cataracts could be assessed even if mydriatic agents had not been instilled.

Factors that can affect cataract progression include the dog's diet and living environment. Some dogs may have ingested antioxidants due to dietary differences, and UV light may have caused oxidative damage to the lens of dogs who had spent a long time outdoors. Because this study is retrospective study, there is a limitation in not being able to completely control these factors. However, most dogs were small dogs that live indoors, so the impact on the living environment would not have been significant.

In this study, the number of dogs that were administered supplements was low. Analysis of a larger number of dogs may have yielded more accurate and significant results. A controlled prospective clinical trial considering these factors would be beneficial.

In conclusion, despite its limitations, the present study could be meaningful, as it clinically analyzed the effect of antioxidants on senile cataract progression in dogs for the first time. Although there was no significant difference in incipient cataract progression, Ocu-GLO and Meni-One Eye R/C might have delayed the progression of immature cataract in this study. Considering these results, antioxidant supplements could be beneficial in delaying the progression of immature cataracts in canine senile cataracts and could be prescribed to delay the progression of cataracts in dogs that could not undergo cataract surgery for several reasons.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Ingredients of two oral antioxidants, Ocu-GLO and Meni-One Eye R/C

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Supplementary Fig. 1

Stages of cataract in this study. (A) Incipient, (B) immature, (C) mature, and (D) hypermature cataract.

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Supplementary Fig. 2

Representative retroillumination images of incipient cataract progression in three groups: C_1, O_1, and M_1.

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Supplementary Fig. 3

Representative retroillumination images of immature cataract progression in three groups: C_2, O_2, and M_2.

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