Funduscopic findings following cataract extraction by means of phacoemulsification in diabetic dogs: 52 cases (1993–2003)

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Objective—To determine prevalence of retinal hemorrhages and microaneurysms in dogs with diabetes mellitus following cataract extraction by means of phacoemulsification and identify potential risk factors.

Design—Retrospective study.

Animals—52 dogs with diabetes mellitus and 174 dogs without.

Procedure—Medical records of dogs undergoing phacoemulsification between 1993 and 2003 were reviewed, and information was recorded on signalment, history, physical examination findings, ophthalmic examination findings, results of laboratory testing, electroretinographic findings, and surgical findings. Glycemic control was classified as poor, intermediate, or good on the basis of baseline blood glucose concentration, perioperative body weight loss, daily insulin dosage, and presence of glucosuria and ketonuria. Data from diabetic and nondiabetic dogs were analyzed to determine prevalence and risk factors for development of retinal hemorrhages or microaneurysms following phacoemulsification.

Results—11 of the 52 (21%) dogs with diabetes mellitus developed ophthalmoscopic signs of retinal hemorrhages or microaneurysms, compared with 1 of the 174 (0.6%) nondiabetic dogs. Median time from onset of diabetes mellitus to diagnosis of retinopathy was 1.4 years (range, 0.5 to 3.2 years). No risk factors for development of retinopathy were identified.

Conclusions and Clinical Relevance—Results suggest that retinal hemorrhages and microaneurysms may be more common and develop earlier in diabetic dogs than previously reported. This may affect treatment, as diabetic dogs survive longer with improved glycemic control. (*J Am Vet Med Assoc* 2004;225: 709–716)

Recognized ocular manifestations of diabetes mellitus in dogs include cataract formation,[1,2] corneal endothelial pleomorphism and polymegathism,[3] reduced corneal sensitivity,[4] and diabetic retinopathy.[5,6] Cataracts are common in diabetic dogs and often result in blindness.[1,2] In contrast, although diabetic retinopathy is common in humans and is a leading cause of blindness, it is reported to be rare and mild in dogs.[6,7]

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The cause of diabetic retinopathy has not been elucidated, but it is most likely multifactorial. Proposed etiologies include biochemical changes secondary to hyperglycemia and increased aldose reductase activity, advanced glycation end products, hemodynamic alterations, and vascular endothelial and pericyte loss.[6,8,9] The histologic appearance of diabetic retinopathy in dogs—microaneurysms, loss of mural cells, mural ghost cells, and retinal capillary dilation—is similar to that of the nonproliferative (background) form in humans.[10,11] Ophthalmoscopic findings in dogs with diabetic retinopathy include microaneurysms, retinal hemorrhages, dilatation and tortuosity of retinal venules, hyper-reflectivity of the tapetal portion of the retina, and chorioretinal exudates.[12,13] Microaneurysms and retinal hemorrhages are described as small red dots in the retina, with microaneurysms being slightly smaller and clearer and having sharper margins.[12,14] Small red lesions with irregular margins or uneven density are considered hemorrhages.[14] In dogs and humans, microaneurysms and retinal hemorrhages are sometimes difficult to differentiate ophthalmoscopically, and in humans, they are generally grouped under the term background diabetic retinopathy.[12,15] Similar histologic and ophthalmoscopic lesions have been described in dogs with experimentally induced galactosemia or diabetes mellitus.[16-18] Although diabetic retinopathy is not typically associated with vision loss in dogs,[7] 2 reports[12,19] have suggested that vision loss may occasionally occur.

The apparent low prevalence and mild severity of diabetic retinopathy in dogs has been attributed to the length of time it takes diabetic retinopathy to develop and the relatively shorter life span of dogs, compared with humans.[20] To the authors' knowledge, however, no studies have been performed to determine the prevalence of retinopathy in dogs with spontaneous diabetes mellitus. Ophthalmoscopically identifiable **retinal hemorrhages and microaneurysms (RH-MA)** can be considered a marker of diabetic retinopathy in dogs. The purposes of the study reported here, therefore, were to determine the prevalence of RH-MA in dogs with spontaneous diabetes mellitus following cataract extraction by means of phacoemulsification and identify risk factors for RH-MA.

Criteria for Selection of Cases

Medical records of all dogs referred to the Virginia-Maryland Regional College of Veterinary Medicine between January 1993 and January 2003 for cataract extraction by means of phacoemulsification were evaluated. Dogs were eligible for inclusion in the study if unilateral or bilateral phacoemulsification had been

done for the treatment of cataracts and at least 1 postsurgical follow-up ophthalmic examination had been performed at this hospital.

Procedures

Medical records of dogs included in the study were reviewed to determine prevalence of RH-MA among dogs with and without diabetes mellitus. Records of diabetic dogs were evaluated in greater detail to determine risk factors associated with development of RH-MA.

Data collected from the medical records of diabetic dogs included signalment; duration of diabetes mellitus; duration of cataracts; body weight at the time of surgery, as well as 3 weeks before and after surgery; and results of CBCs, serum biochemical profiles, and urinalyses. Ophthalmic information that was recorded included cataract classification, electroretinographic findings, aqueous flare, and intraocular pressure before and 1 and 3 weeks after surgery. In addition, if RH-MA were seen after surgery, their number and location were recorded. Surgical information that was recorded included whether surgery was unilateral or bilateral, surgeon, whether nonsteroidal anti-inflammatory medications were administered, and age of the dog at the time of surgery.

Electroretinography was performed when the fundus was not visible ophthalmoscopically. Two different electroretinographic machines[a,b] were used during the study period. For each machine, electroretinogram amplitudes for diabetic dogs were compared with amplitudes for nondiabetic dogs. However, results for the 2 machines were not compared.

Aqueous flare was assessed by means of slit-lamp biomicroscopy and graded subjectively on a scale from 0 to 4 (0 = absent, 0.5 = trace, 1 = mild, 2 = moderate, 3 = moderately severe, and 4 = severe). Intraocular pressure was measured with an applanation tonometer.[c] Severity of ketonuria and glucosuria at the time of surgery were both scored on a scale from 0 to 3.

Glycemic control was categorized as poor, intermediate, or good on the basis of a scoring system incorporating baseline blood glucose concentration, perioperative body weight loss, daily insulin dosage, and presence of glucosuria or ketonuria at the time of surgery. Baseline blood glucose concentration was determined after food had been withheld overnight and within 2 hours prior to insulin administration. A baseline blood glucose concentration between 100 and 300 mg/dL was assigned a score of 1, and a baseline blood glucose concentration outside this range was assigned a score of 0. Perioperative body weight loss was calculated as the percentage of body weight lost from 3 weeks before to 3 weeks after surgery. A perioperative body weight loss of ≤ 5% was assigned a score of 1, and a perioperative body weight loss of > 5% was assigned a score of zero. Daily insulin dosage was calculated as total units of insulin per day divided by body weight at the time of surgery. A daily insulin dosage of ≤ 2 U/kg was assigned a score of 1, and a daily insulin dosage of > 2 U/kg was assigned a score of 0. An absence of glucosuria at the time of surgery was assigned a score of 1, and the presence of glucosuria was assigned a score of 0. An absence of ketonuria at the time of surgery was assigned a score of 1, and the presence of ketonuria was assigned a score of 0. The highest potential score for any dog was 5. Good glycemic control was defined as a total score ≥ 4, intermediate glycemic control was defined as a score of 3, and poor glycemic control was defined as a score of ≤ 2. Glycemic control was scored only in those dogs for which information on all 5 variables was available.

Statistical analyses—The Fisher exact test was used to compare categoric variables between diabetic dogs with and without RH-MA. If a significant difference between the 2 groups was identified, a Jonckhere-Terpstra test was done to test for a trend. Scatterplots and histograms were used to compare distributions of continuous variables between diabetic dogs with and without RH-MA. A *t* test was used to compare continuous variables between diabetic dogs with and without RH-MA. For all analyses, values of $P < 0.05$ were considered significant.

Results

Two hundred thirty-one dogs underwent cataract extraction by means of phacoemulsification during the study period, of which 52 had diabetes mellitus and 179 did not. Five dogs without diabetes mellitus were excluded from the study because a postsurgical follow-up ophthalmic examination was not performed (n = 3) or postoperative ocular opacity precluded fundic examination. The percentage of diabetic dogs with RH-MA after surgery (11/52 [21%]) was significantly ($P < 0.001$) higher than the percentage of nondiabetic dogs with RH-MA after surgery (1/174 [0.6%]).

Twelve of the 52 (23%) diabetic dogs were of mixed breeding. The remaining diabetic dogs consisted of 11 Labrador Retrievers (21%), 3 Miniature Schnauzers (6%), 3 Pugs (6%), 2 Dachshunds (4%), 2 Pomeranians (4%), 2 Samoyeds (4%), 2 Yorkshire Terriers (4%), and 1 each of 15 other dog breeds. Twenty-four (46%) of the diabetic dogs were spayed females, 19 (37%) were castrated males, 6 (12%) were sexually intact males, and 3 (6%) were sexually intact females. Mean ± SD age of the 52 diabetic dogs at the time of surgery was 9.6 ± 2.1 years (range, 4.2 to 14.4 years). Mean ± SD age at the time diabetic retinopathy was diagnosed was 10.9 ± 1.2 years, whereas mean ± SD age at the time of the final follow-up examination in diabetic dogs without diabetic retinopathy was 10.0 ± 2.4 years. Median postsurgical follow-up time for the diabetic dogs was 61 weeks (range, 16 to 271 weeks).

Eighty-three (47.7%) of the nondiabetic dogs were spayed females, 48 (27.6%) were castrated males, 23 (13.2%) were sexually intact males, and 20 (11.5%) were sexually intact females. Mean ± SD age at the time of surgery was 7.2 ± 3.6 years (range, 0.1 to 17.6 years). Median postsurgical follow-up time was 24 weeks (range, 1 to 430 weeks).

Mean ± SD weight at the time of surgery for the diabetic dogs was 19.9 ± 12.3 kg (43.8 ± 27.1 lb; range, 5.1 to 45.9 kg [11.2 to 101 lb]). There was no significant ($P = 0.44$) difference between body weight at the time of surgery for diabetic dogs with RH-MA (17.3 ± 11.1 kg [38.1 ± 24.4 lb]) and those without (20.6 ±

12.6 kg [45.3 ± 27.7 lb]). Mean age at the time diabetes mellitus was diagnosed was also not significantly (P = 0.12) different between diabetic dogs with RH-MA (9.2 ± 0.9 years; range, 7.7 to 10.6 years) and those without (8.5 ± 2.2 years; range, 3.4 to 13.6 years). Phacoemulsification was performed by 5 different surgeons. Individual surgeons were not found to be significantly (P = 0.40) associated with whether dogs had RH-MA after surgery.

Of the 11 diabetic dogs with RH-MA after surgery, 5 were spayed females, 4 were castrated males, 1 was a sexually intact female, and 1 was a sexually intact male. Six of these 11 dogs were of mixed breeding, 1 was a Cairn Terrier, 1 was a Cocker Spaniel, 1 was a Dachshund, 1 was a Labrador Retriever, and 1 was a Lhasa Apso. Breed (P = 0.28) and sex (P = 0.95) were not significantly associated with whether dogs developed RH-MA after surgery. The 1 nondiabetic dog was a 7.7-year-old castrated male mixed-breed dog with a single red dot characteristic of RH-MA in each eye. The RH-MA in this dog was identified at only 1 of 8 follow-up ophthalmoscopic examinations (8 weeks after surgery) and was not documented again (follow-up time after surgery, 76 weeks).

Median time from diagnosis of diabetes mellitus to identification of RH-MA was 1.4 years (range, 0.5 to 3.2 years). Median time from diagnosis of diabetes mellitus to last follow-up examination in dogs without RH-MA was 1.0 year (range, 0.3 to 5.2 years). Duration of diabetes mellitus was not significantly (P = 0.90) associated with whether dogs developed RH-MA. In 4 of the 11 diabetic dogs with RH-MA, lesions were first identified during the final ophthalmic examination (13, 25, 32, and 89 weeks after surgery) and additional follow-up information was not available. All 7 of the other diabetic dogs with RH-MA had lesions evident during multiple follow-up examinations, including the last follow-up examination (median time from surgery to last follow-up examination, 55 weeks; range, 18 to 114 weeks). Three of these 7 dogs had bilateral retinal lesions identified initially, 2 had unilateral lesions initially but developed bilateral lesions, 1 had a cataract precluding evaluation of the contralateral fundus, and 1 had only unilateral lesions at the last follow-up examination. Six of the 7 diabetic dogs that underwent multiple follow-up examinations had progression of the disease, characterized by an increase in the number of lesions or a change from unilateral to bilateral involvement; lesions appeared to remain static in the remaining dog. Two of the 4 dogs with unilateral RH-MA had conditions precluding evaluation of the fundus of the contralateral eye (severe asteroid hyalosis in 1 and a cataract in the other), 1 had only unilateral lesions at multiple follow-up examinations, and 1 was lost to follow-up after identification of unilateral lesions. Median follow-up time after identification of diabetic retinopathy was 45 weeks (range, 6 to 112 weeks) in the 7 dogs that underwent multiple follow-up examinations following identification of retinopathy.

In all 11 dogs with RH-MA, lesions were located in the tapetal portion of the retina and were described in the medical records as multifocal pinpoint, petechial, dot, or blot lesions (**Figures 1 and 2**). Blot lesions were identified in only 1 dog. Ten dogs had multiple retinal lesions in affected eyes, and 1 dog had a single lesion in each eye.

There was no significant (P = 0.22) difference in mean intraocular pressure 1 week after surgery in diabetic dogs with RH-MA (15.3 ± 5.1 mm Hg) and those without (13.2 ± 4.6 mm Hg). Electroretinography was performed in 41 of the 52 diabetic dogs; in the remaining 11, the fundus was visible and electroretinography was not necessary. For 1 electroretinography machine,[a]

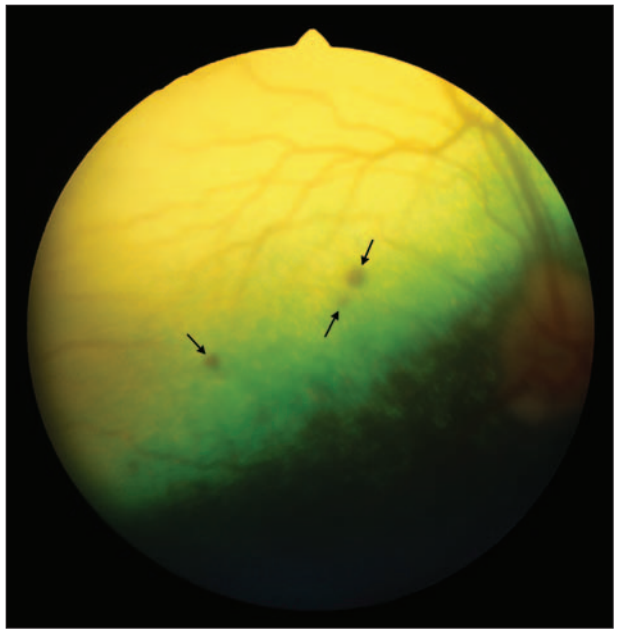

Figure 1—Retinal hemorrhages and microaneurysms (arrows) in the dorsolateral field of the tapetal portion of the retina in an 11-year-old mixed-breed dog with diabetes mellitus. Mild lens capsular fibrosis is present, resulting in diminished retinal detail.

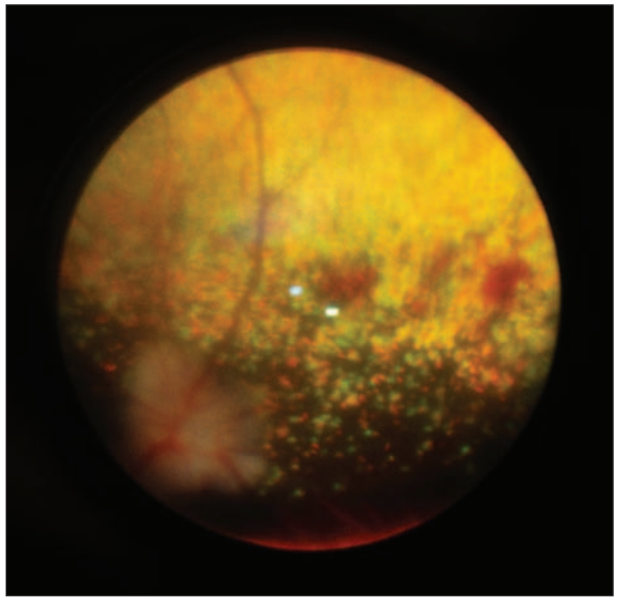

Figure 2—Multiple retinal blot hemorrhages in the dorsolateral field of the tapetal portion of the retina in a 14-year-old Dachshund with diabetes mellitus. Mild to moderate retinal vascular attenuation is also evident.

mean ± SD electroretinogram amplitude for diabetic dogs with RH-MA (225.9 ± 68.5 μV) was not significantly (P = 0.45) different from mean amplitude for diabetic dogs without RH-MA (287.2 ± 66.5 μV). Similarly, for the other electroretinography machine,[b] mean electroretinogram amplitude for diabetic dogs with RH-MA (215.8 ± 54.6 μV) was not significantly (P = 0.84) different from mean amplitude for diabetic dogs without RH-MA (211.0 ± 67.4 μV).

Mean ± SD aqueous flare score 1 week after surgery for diabetic dogs with RH-MA (0.9 ± 0.7; range, 0 to 2) was significantly (P = 0.042) different from mean score for diabetic dogs without RH-MA (1.0 ± 0.4; range, 0 to 1.5). However, the Jonckhere-Terpstra test did not identify a significant (P = 0.41) trend between aqueous flare score 1 week after surgery and development of RH-MA.

Complete data for calculation of a glycemic control score were available for 9 diabetic dogs with RH-MA and 25 diabetic dogs without. Of the 9 diabetic dogs with RH-MA, 5 had good glycemic control, 3 had intermediate control, and 1 had poor control. Of the 25 diabetics without RH-MA, 7 had good glycemic control, 9 had intermediate control, and 9 had poor control. The glycemic control score was not found to be significantly (P = 0.30) associated with whether dogs developed RH-MA.

Baseline blood glucose concentration, perioperative body weight loss, daily insulin dosage (U/kg), degree of glucosuria (0 to 3), and degree of ketonuria (0 to 3) were also evaluated individually to determine whether they were associated with development of RH-MA. Mean ± SD baseline blood glucose concentration for diabetic dogs with RH-MA (232.7 ± 93.2 mg/dL) was not significantly (P = 0.33) different from mean concentration for diabetic dogs without RH-MA (201.9 ± 92.4 mg/dL). Similarly, mean perioperative body weight losses for diabetic dogs with (1.2 ± 4.3%) and without (1.4 ± 7.2%) RH-MA were not significantly (P = 0.94) different. Mean daily insulin dosages for diabetic dogs with (1.8 ± 0.5 U/kg) and without (1.7 ± 0.7 U/kg) RH-MA were not significantly (P = 0.64) different. Mean degrees of glucosuria for diabetic dogs with (2 ± 1.3) and without (1.6 ± 1.2) RH-MA were not significantly (P = 0.40) different. Mean degrees of ketonuria for diabetic dogs with (0.1 ± 0.2) and without (0.1 ± 0.2) RH-MA were not significantly (P = 0.81) different.

Presurgical CBCs for the 11 diabetic dogs with RH-MA revealed that 4 of these dogs had mild thrombocytosis (570, 579, 589, and 684 × 10^3 platelets/μL; reference range, 220 to 539 × 10^3 platelets/μL) and 1 had mild anemia (Hct, 34.5%; reference range, 36% to 58%). Results of serum biochemical analyses and urinalyses performed on diabetic dogs with RH-MA were consistent with changes expected with diabetes mellitus, including hyperglycemia, hypercholesterolemia, high alanine transaminase and alkaline phosphatase activities, and glucosuria.

Ten of the 11 diabetic dogs with RH-MA received carprofen after surgery; the remaining dog did not receive any anti-inflammatory medications systemically after surgery. Mean ± SD dosage of carprofen in the 10 diabetic dogs with RH-MA was 2.2 ± 0.3 mg/kg (1 ± 0.1 mg/lb). Three of the 11 diabetic dogs were still receiving carprofen when RH-MA were documented. Median time diabetic dogs with RH-MA received carprofen after surgery was 21 days (range, 8 to 94 days). Of the 41 diabetic dogs without RH-MA, 25 (61%) received carprofen, 10 (24%) received aspirin, 3 (7%) received etodolac, and 2 (5%) received prednisone after surgery. The remaining dog (2%) did not receive any anti-inflammatory medications systemically after surgery.

One of the diabetic dogs with RH-MA was being treated concurrently for hyperadrenocorticism, and 1 was being treated for iatrogenic hypoadrenocorticism. Of the diabetic dogs without RH-MA, 6 were being treated concurrently for hypothyroidism, 1 was being treated for hyperadrenocorticism, and 1 had a high urine cortisol-to-creatinine ratio but was not being treated for hyperadrenocorticism. Systolic blood pressure was measured indirectly by means of Doppler ultrasonography[d] with a forelimb cuff in 2 dogs with RH-MA. Systolic arterial hypertension was diagnosed in 1 dog, in which systolic blood pressure was 200 to 240 mm Hg at the time RH-MA were identified (51 weeks after surgery). The dog was treated with enalapril (0.3 mg/kg [0.14 mg/lb], PO, q 24 h), and systolic blood pressure returned to the reference range. The number of RH-MA lesions in this dog increased from the time hypertension was identified until the last follow-up examination 42 weeks after the diagnosis of hypertension.

Discussion

In human patients, background diabetic retinopathy is diagnosed when a minimal to moderate number of RH-MA are identified during an ophthalmic examination and typically precedes development of proliferative retinal changes.[15] Similar lesions have previously been identified ophthalmoscopically in diabetic dogs,[6,7,12] but the early development of osmotic cataracts, which preclude fundic examination, has been a major impediment in longitudinal investigation of diabetic retinopathy in dogs. The prevalence (11/52 [21%]) of RH-MA among diabetic dogs in the present study was higher than that suggested by other reports[20-22] of diabetic retinopathy in dogs. For instance, 2 previous studies[20,21] found histologic evidence of diabetic retinopathy consisting of microaneurysms in only 3 of 29 (10%) and 2 of 12 (17%) diabetic dogs, and a previous study[22] of results of phacoemulsification in diabetic dogs reported that only 2 of 57 (3%) eyes had evidence of retinal hemorrhages. This latter study was limited by a short follow-up period, however, with a mean follow-up time of only 6 weeks (range, 2 to 12 weeks), and this short follow-up time likely accounts for the large difference in lesion prevalence between that study and the present study.

In the present study, RH-MA lesions were confined to the tapetal portion of the retina. In those dogs in which more specific localization was recorded, lesions tended to be seen most often in the dorsotemporal field. This is consistent with previous reports[18,23] of retinopathy lesion distribution in dogs with experimentally induced diabetes mellitus and galactosemia.

Diabetic retinopathy, manifested as RH-MA, was reported to first appear between 2 to 5 years after experimental induction of diabetes mellitus with alloxan and as early as 33 months after experimental induction of galactosemia in dogs.[16,18] In a case series[12] of dogs with spontaneous diabetes mellitus and retinopathy, it was suspected that dogs had been diabetic for 2 to 4 years prior to the development of retinopathy, although the duration of diabetes was not definitively established. In the present study, mean ± SD time from diagnosis of diabetes mellitus to development of RH-MA was 1.8 ± 0.8 years (median, 1.4 years; range, 0.5 to 3.2 years). One possible explanation for the difference between our findings and those in the literature could be the difference between actual disease onset and clinical diagnosis. Dogs with diabetes mellitus in our study may have had diabetes for variable periods before the diagnosis was made, whereas dogs with experimentally induced diabetes and galactosemia had a more definite time of onset. Additionally, there may be genetic or endocrine factors involved in the pathogenesis of retinopathy in dogs with spontaneous diabetes that were not present in dogs with experimentally induced disease.

One limitation of the present study was the use of a technique, indirect ophthalmoscopy, that was less sensitive than ideal for detection of RH-MA. In humans, the standard technique for determining the presence and severity of diabetic retinopathy is 7-field stereoscopic fundus photography.[24-26] Although there is fair to good agreement between results of ophthalmoscopy and fundus photography, approximately 50% of human patients with microaneurysms only may remain undetected with ophthalmoscopy.[27,28] Fluorescein angiography has been shown to increase sensitivity for detection of early retinopathy, compared with ophthalmoscopy[29,30] and fundus photography,[31,32] and results of fluorescein angiography in diabetic dogs are similar to those in human patients with diabetes.[33] In addition, fluorescein angiography allows objective differentiation of intraretinal hemorrhage and retinal microaneurysms, a distinction that can be difficult to make by means of ophthalmoscopic examination alone.[12,15] However, the present study was performed retrospectively, and RH-MA identified in this study were incidental findings identified during postsurgical ophthalmic examinations. In addition, the tapetum lucidum makes it more difficult to identify RH-MA in dogs, compared with humans.[12] Thus, prevalence reported in the present study may underestimate the true prevalence of postsurgical RH-MA. On the other hand, ophthalmologists who examined dogs in the present study were aware which dogs had diabetes mellitus, which may have led to a more critical evaluation of the fundus in diabetic dogs.

In dogs, retinal hemorrhage can occur secondary to multiple systemic diseases, including systemic hypertension, hyperviscosity syndrome, immune-mediated diseases, thrombocytopenia, coagulopathies, infectious diseases, and polycythemia.[34] However, these diseases typically result in other systemic or clinicopathologic signs or more rapid progression of the retinal lesions. None of the diabetic dogs in the present study had clinical findings consistent with these disorders, although they were not specifically evaluated for these problems. Only systemic hypertension and possibly hyperviscosity syndrome would be expected to be more common among diabetic than nondiabetic dogs. Increased blood viscosity secondary to increased serum α-globulin concentration, decreased serum albumin concentration, and changes in RBC membranes are known to occur in humans with diabetes and are some of the mechanisms believed to contribute to the development of diabetic retinopathy.[8] Mild increases in albumin and α_2-globulin concentrations have been documented in dogs with diabetes mellitus,[35] but these seem to be of insufficient magnitude to induce retinal hemorrhage.

Hypertension has been documented in dogs with spontaneous diabetes mellitus, with a prevalence of 46% in 1 study,[36] and systemic hypertension is known to increase the development and progression of diabetic retinopathy in humans.[24,26,37] Reported fundic manifestations of naturally occurring systemic hypertension in dogs include tortuosity of retinal arterioles, retinal edema, retinal and preretinal hemorrhage, retinal detachment, and papilledema.[38-41] The most consistent ophthalmoscopic sign in dogs with experimentally induced hypertension is retinal arteriolar tortuosity.[42] Although it is possible that petecchial retinal hemorrhage alone may be a manifestation of mild to moderate hypertension in dogs, such a correlation has not been previously established. In a study[43] of cats with hypertensive retinopathy secondary to renal failure and hyperthyroidism, the most common features were diffuse retinal edema and foci of intraretinal serous exudates. Systolic arterial hypertension was diagnosed by means of indirect blood pressure measurement in 1 dog in the present study following identification of RH-MA during a routine follow-up ophthalmic examination 51 weeks after surgery. Despite resolution of the hypertension with medical management, the number of RH-MA lesions progressed and hemorrhages did not reabsorb, suggesting that systemic hypertension was unlikely to have played a dominant role in the fundic changes in this dog. Other reported ocular manifestations of systemic hypertension in dogs were not identified in any dogs with RH-MA in this study. Unfortunately, because blood pressure measurements were not obtained consistently in dogs with RH-MA, definitive conclusions regarding the potential contribution of systemic hypertension to the retinal lesions cannot be made.

Ten of 11 diabetic dogs with RH-MA in the present study were treated with carprofen after surgery. Carprofen is a nonsteroidal anti-inflammatory drug that has analgesic, antipyretic, and anti-inflammatory properties.[44] In healthy dogs, carprofen has been shown to significantly reduce and delay platelet aggregation, although these changes are minor and unlikely to result in clinically important hemorrhage.[45] Carprofen administration in diabetic dogs in the present study could have led to thrombocytopathy, through inhibition of thromboxane A_2, causing decreased platelet aggregation and retinal hemorrhage. However, only 3 of the diabetic dogs with RH-MA were still receiving carprofen when RH-MA were first identified. Carprofen is also some-

what selective for cyclooxygenase-2 and should cause less inhibition of thromboxane A_2 production and less platelet dysfunction than less selective nonsteroidal anti-inflammatory drugs, such as aspirin and etodolac.[46] None of the diabetic dogs in the present study treated with aspirin or etodolac after surgery developed RH-MA. Although aspirin was purported to provide a protective effect against development of microaneurysms in humans in 1 study,[47] another study[48] found that aspirin did not have protective or detrimental effects on the course of diabetic retinopathy in human beings. A 5-year study[49] of aspirin treatment in dogs with experimentally induced diabetes mellitus showed significant inhibition of retinal hemorrhage and acellular capillary formation, but less effect on microaneurysm formation. On the whole, therefore, we believe it unlikely that carprofen contributed to the prevalence of diabetic retinopathy in the present study.

Risk factors for development of diabetic retinopathy have not been studied in dogs with spontaneous diabetes mellitus, but in humans, duration of diabetes mellitus is the most important risk factor for development of the disease.[50,51] Other reported risk factors in humans include high glycosylated hemoglobin concentration and other indicators of poor glycemic control, high blood pressure, age at diagnosis, and a family history of diabetes mellitus.[24,26,50-52] In the present study, duration of diabetes mellitus was not significantly associated with development of RH-MA. One possible reason for this is the duration of follow-up. In experimental models, lesions consistent with diabetic retinopathy can take 2 to 5 years to develop, whereas median follow-up time from the diagnosis of diabetes mellitus in the present study was 2.1 years (range, 0.9 to 5.1 years) for dogs that had RH-MA and 1.0 year (range, 0.3 to 5.2 years) for dogs that did not. The present study was also limited by the small number of diabetic dogs that underwent phacoemulsification. Study of a larger population may allow for detection of duration of diabetes mellitus as a risk factor for the development of RH-MA. Variability in glycemic control among diabetic dogs in the present study may also have contributed to the fact that duration of diabetes mellitus was not identified as a significant risk factor for development of diabetic retinopathy. Glycemic control was only assessed at the time of surgery, and poor glycemic control could have masked any effect duration of diabetes mellitus had on the development of RH-MA.

Glycemic control has been shown to be associated with progression of diabetic retinopathy in human beings.[51-54] Similarly, the importance of early establishment of good glycemic control has been shown in a study[17] evaluating glycemic control and progression of diabetic retinopathy in dogs. In that study, it was found that progression of diabetic retinopathy in dogs with experimentally induced diabetes mellitus was inhibited by establishment of good glycemic control within 2 months of disease onset. Dogs with poor glycemic control and dogs with good glycemic control after 2.5 years of poor control had progression of retinopathy. The lack of an association between glycemic control and development of RH-MA in the present study could have been a reflection of the limited information on which glycemic control scores were based. The glycemic control score was determined on the basis of factors measured at the time of surgery, and there was no information to determine how quickly euglycemia had been achieved following the initial diagnosis of diabetes or how well controlled the diabetes mellitus was following surgery. Because of the retrospective nature of the present study, there was no way to assess long-term glycemic control in the study population. Another limitation of the glycemic control score in the present study was the poor historical information in the medical records. Assessing historical information and physical examination findings has been shown to be a valid way to classify glycemic control in diabetic dogs.[55] Unfortunately, information on polyuria, polydipsia, polyphagia, lethargy, weakness, hepatomegaly, and hair coat changes was rarely documented in the medical records, and we were therefore unable to use historical information in classifying glycemic control.

The effect of phacoemulsification itself on the incidence or progression of diabetic retinopathy in dogs is unknown. Studies[56-59] in humans undergoing extracapsular cataract extraction have found an increased progression of diabetic retinopathy following surgery. However, more recent reports[60-63] of cataract extraction with phacoemulsification have suggested that progression of retinopathy is unaffected by this procedure. Other ocular factors, most notably intraocular pressure, have received attention with regard to progression of diabetic retinopathy in humans. Results of these studies[64-66] have been conflicting, with some showing reduced severity of retinopathy associated with high intraocular pressure[64,65] and others showing no effect of intraocular pressure on retinopathy.[66]

The significantly higher prevalence of RH-MA among diabetic dogs in the present study, compared with nondiabetic dogs, along with the lack of any clinical findings consistent with other systemic diseases, makes it likely that these dogs had background diabetic retinopathy. However, systemic hypertension was not definitively ruled out as a contributing factor in most affected dogs. A definitive diagnosis of diabetic retinopathy would require histologic examination of retinal tissue, which was not done in the present study. Importantly, retinal lesions in these dogs were mild, and findings consistent with more advanced retinopathy were not seen in any dogs in this study. Additionally, no evidence of vision loss attributable to retinopathy was noted in the medical records of affected dogs. Clearly, diabetic retinopathy is a complex disease and is likely influenced by several factors, including age, duration of diabetes, glycemic control, systemic blood pressure, and possibly genetic and endocrine factors. Risk factors reported in humans were not confirmed by findings for dogs in the present study, but the study design limited the conclusions that could be drawn. If the lesions reported in this study represent diabetic retinopathy, it would appear that the condition is of a higher prevalence and occurs earlier than previously reported in dogs. Further studies, including fluorescein angiography, retinal histology, blood pressure measurement, and better assessment of

glycemic control, are required to determine whether these retinal lesions are associated with diabetes mellitus and evaluate risk factors for their development.

[a]Epic-2000, version 3.03, LKC Technologies Inc, Gaithersburg, Md.
[b]Retinographics BPM-100 system, Retinographics Inc, Norwalk, Conn.
[c]Tonopen XL, Bio-Rad Inc, Santa Ana, Calif.
[d]Ultrasonic Doppler flow detector 811-AL, Parks Medical Electronics Inc, Aloha, Ore.

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