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Abstract
Background: Although ocular findings in diabetic patients are well described, prevalence data for those is unknown.
Aim: To describe the prevalence of ocular findings and their association with glycemia in dogs with diabetes mellitus.
Methods: Medical records from diabetic dogs assessed by the ophthalmology and the internal medicine services at the Veterinary Teaching Hospital of the Autonomous University of Barcelona were reviewed (2009–2019).
Results: Seventy-five dogs (150 eyes) of both genders (51/75 females; 68% and 24/75 males; 32%) and a mean age of 9.37 ± 2.43 years, were included. The most common ocular findings were cataracts (146/150; 97.3%), vitreous degeneration (45/98; 45.9%), anterior uveitis (47/150; 31.3%), aqueous deficiency dry eye (ADDE) (33/150; 22%), diffuse corneal edema (31/150; 20.7%), non-proliferative retinopathy (13/98; 13.3%), and lipid keratopathy (9/150; 6%). The most prevalent type of cataracts observed (78/146; 53.4%) was intumescent, which was commonly accompanied by non-proliferative retinopathy (p = 0.003). Among the diabetic dogs, blood glucose levels were statistically higher in dogs with non-proliferative retinopathy or anterior uveitis (p < 0.005).
Conclusions: Ocular complications of diabetes mellitus in dogs are numerous, being the most frequent intumescent cataracts, vitreous degeneration, anterior uveitis, ADDE, diffuse corneal edema, and non-proliferative retinopathy. This high prevalence warrants a more detailed ophthalmic evaluation in diabetic dogs especially for those undergoing cataract surgery. Furthermore, a predisposition for anterior segment inflammation and non-proliferative retinopathy is suggested when fasting plasma glucose is higher than 600 mg/dl.
Keywords: Cataracts, Glucose, Intumescent, Phacoemulsification, Retinopathy.

Introduction
Diabetes mellitus (DM) is a common endocrine disorder characterized by chronic hyperglycemia resulting from a deficit in insulin production, action, or both (Fracassi, 2017). The prevalence of DM in dogs has been estimated from 0.3% in first-opinion practices to 1% in referral institutions (Guptill et al., 2003; Fracassi et al., 2004; Davison et al., 2005; Mattin et al., 2014). Two clinical forms are recognized in dogs: insulin-dependent and non-insulin-dependent. The former is the most common, being characterized by permanent hypoinsulinemia and, thereby, necessitating regular exogenous insulin to maintain glycemic regulation (Fracassi, 2017). Unfortunately, glycemic control can be difficult to attain in some insulin-dependent dogs, resulting in chronic exposure to high blood levels of glucose and ketoacidosis that can lead to systemic complications. Eyes are particularly vulnerable to the pathophysiological changes that occur because of chronic hyperglycemia, and consequently, ocular complications are a common finding in DM. Ocular findings being historically associated with DM in dogs are as follows: keratoconjunctivitis sicca (Cullen et al., 2005; Williams et al., 2007; Gemensky-Metzler et al., 2015), polymegathism and pleomorphism in corneal endothelial cells (Yee et al., 1985), corneal hypesthesia (MacRae et al., 1982), non-healing corneal ulcers (Good et al., 2003), lipid keratopathy (Crispin, 2002), corneal xanthogranulomas (Harvey et al., 2020), corneal abscesses (Michau, 2020), intracorneal stromal hemorrhages (Matas et al., 2012; Violette and Ledbetter, 2017), lipid-laden aqueous humor (Violette and Ledbetter, 2019; Schechtmann et al., 2020), cataracts (Miller and Brines, 2018), lens-induced uveitis (Paulsen et al., 1985), phacomorphic glaucoma (Williams, 2004), vitreous degeneration (West et al., 2020), non-proliferative retinopathy (Landry et al., 2004), and peripheral neuropathies (Katherman and Braund, 1983). Unfortunately, until now, there are no studies reporting the prevalence of ocular findings in diabetic canine patients nor the association between those and glucose blood levels. Thus, the present study

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was conducted to describe the prevalence of the most common ocular findings in diabetic dogs, as well as to establish if there is a correlation between ophthalmic findings and blood glucose levels.

**Materials and Methods**

**Inclusion criteria**
Medical records of dogs evaluated by the ophthalmology service at the Veterinary Teaching Hospital of the Autonomous University of Barcelona between 2009 and 2019 were retrospectively reviewed. Dogs were included in the study if diagnosed with DM by a board-certified specialist in small animal internal medicine or a resident-in-training under direct supervision. DM was diagnosed by means of three findings as follows: appropriate clinical signs (polyuria, polydipsia, polyphagia, and weight loss), persistent fasting hyperglycemia (>200 mg/dl), and glycosuria. Animals with systemic hypertension were excluded from the study because of the important co-morbidity that those patients could have with the ocular findings. Blood pressure measurement was performed during internal medicine evaluation or during preanesthetic examination, and in all cases animals were excluded if systolic readings were over 160 mmHg. In all dogs, ophthalmic examination included neuro-ophthalmic examination, Schirmer tear test I (STT-1) (MSD Animal Health, Madison, NJ), slit-lamp biomicroscopy (Kowa SL-15 and -17®; Kowa Company Ltd., Tokyo, Japan), rebound tonometry (TonoVet® using “d” setting; Icare Finland Oy, Helsinki, Finland), and fluorescein stain (FluoroTouch®; Madhu Instruments, New Delhi, India). In addition, binocular indirect ophthalmoscopy (Heine Omega 500®; Heine, Herrsching, Germany), gonioscopy, and B-mode ultrasonography were performed when applicable. Animals were excluded if primary glaucoma, evidence of trauma, or infectious diseases were detected.

**Data retrieval**
Data collected and reviewed from the medical records included signalment (breed, age, and gender), levels of fasting glycemia at the time of the ocular examination, eye/s affected, ophthalmic findings, whether or not cataract surgery was performed and post-phacoemulsification ocular fundus findings.

**Ophthalmic findings: diagnosis and grading system**
Aqueous deficiency dry eye (ADDE) was considered when STT-1 readings were under 15 mm/minute and no signs of corneal or conjunctival inflammation were observed. Cataract classification was established according to what was previously reported (Leiva and Peña, 2020): incipient, when lens opacity extended from 1% to 15%; immature when opacity covered between 16%–99% and fundic reflection was still able to be visualized; mature, when the whole lens was affected and no fundic reflection was visible after maximal mydriasis; hypermature, when cortex resorption, capsule wrinkling, capsule plaques, or deposition of pigment on the anterior capsule were present; and intumescent, when the size of the lens was bigger than normal, lens sutures were broken, and/or liquid was seen within the lens. Similarly, the degree of anterior uveitis was also graded semiquantitatively (on a scale from trace to +4) based on conjunctival congestion, aqueous flare (0 to +4), ocular hypotony, and miosis or resistance to mydriasis after tropicamide application. Non-exudative uveitis was considered when previous signs were present, but no visible aqueous flare was observed. Phacomorphic glaucoma was diagnosed when intraocular pressure (IOP) increased over 25 mmHg, the anterior chamber depth was diminished and no alterations were observed on gonioscopy. Vitreous degeneration was diagnosed by B-mode ultrasound examination and graded using a previously reported scheme whereby the vitreous degeneration is classified into four grades (0–III), depending on the number of echoes seen on ultrasonography (Labruyère et al., 2008). Non-proliferative diabetic retinopathy was considered if retinal petechia or subretinal hemorrhages were present and no systemic hypertension was detected.

**Statistical analysis**
Quantitative results were reported by the mean and standard deviation (SD) or median and range for normally or non-normally distributed data, respectively (as assessed by the Kolmogorov-Smirnov test). Qualitative results were described by absolute and relative frequencies. Fisher’s exact test was used for qualitative variables, and unpaired t-test and Mann-Whitney U test for quantitative variables. For all statistical analyses, a commercial software (SPSS 25.0®, IBM, Chicago, IL) was used, and a significance threshold of p < 0.05 was set.

**Ethical approval**
This paper refers to a retrospective study with no animals involved in the experimental process, so no consent of ethics is needed for this study.

**Results**
Medical records of 75 diabetic dogs met the inclusion criteria (150 eyes). The mean (±SD) age of the study population at first ophthalmic examination was 9.37 years (±2.43 years). There were 12 castrated males (16%), 12 intact males (16%), 27 spayed females (36%), and 24 intact females (32%). Twenty-nine dog breeds were identified in the study population, including mix breed (27/75 dogs; 36%), Yorkshire Terrier (4/75; 9.3%), West Highland White Terrier (4/75; 5.3%), English Cocker Spaniel (4/75; 5.3%), Golden Retriever (3/75; 4%), and one or two dogs from 24 other different breeds.

**Ophthalmic findings**
Ocular lesions and their prevalence are summarized in Figures 1 and 2, and shown in Figure 3. All dogs had bilateral, although not always symmetrical, clinical findings. Cataract was the most common
ocular finding (146/150 eyes; 97.3%), being bilateral in all the affected dogs. Intumescent cataracts were seen in 78 eyes (78/146; 53.4%), mature cataracts in 24 eyes (24/146; 16.4%), hypermature and immature in 21 eyes each (21/146; 14.4%), and incipient in 2 eyes (2/146; 1.4%) (Fig. 2). Vitreous degeneration was the second most common ocular finding (45/98 eyes; 45.9%), being bilateral in 21 dogs (21/24; 87.5%), and unilateral in 3 (3/24; 12.5%). According to Labruyere’s scoring system, grade I vitreous degeneration was
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Discussion

The present work provides new information on the ophthalmic findings associated with DM in dogs that could be helpful in the prevention and management of diabetic ocular disease. Also, shows a direct association between blood glucose levels and some of the most commonly identified ocular findings concomitant with the disease. This suggests that 600 mg/dl may be established as a cut-off value from which some ocular clinical signs, such as non-proliferative retinopathy and anterior uveitis, may be more frequently seen.

Different epidemiologic studies suggest that some canine breeds are at higher risk of developing DM (Guptill et al., 2003; Fracassi et al., 2004; Cullen et al., 2005). To the authors’ knowledge, there are no reports on whether there is a breed predisposition to develop secondary ocular signs. In the present study, mix breed dogs were clearly overrepresented, but this fact could indicate regional differences in breed distribution, rather than a true predisposition for ocular complications of DM. According to previous reports (Guptill et al., 2003; Fall et al., 2007), middle-aged to older females were the most commonly affected by DM, with a similar incidence of ocular findings. Although neutering status has been associated with better glycemic control (Guptill et al., 2003), the findings herein suggest that neutering status may not influence the prevalence of ocular complications associated with DM.

Cataract was the most prevalent finding in this population of diabetic dogs with ophthalmic clinical signs (97.3%), intumescent cataract being the most common. This agrees with previous studies in which cataracts were consistently found as the main ophthalmic complaint in diabetic animals (Ling et al., 1977). In fact, Beam et al. (1999) stated that 75% of the canine population diagnosed with DM will develop cataracts by approximately 12 months after the first diagnosis of
diabetes. It is well-known that intumescent cataracts develop due to an osmotic imbalance secondary to intralenticular sorbitol accumulation. The speed of development depends on sugar concentration and endogenous activity of aldose reductase, which very often ends with an acute onset cataract (Engerman et al., 1982). This acute onset is often the main complaint for requesting an ophthalmologic examination, which could explain why intumescent was the most common type of cataracts seen in the present study.

Vitreous degeneration is an age-related ocular condition in dogs, with a higher prevalence in female dogs (Krishnan et al., 2020). In fact, it is described that dogs have 24 times more likelihood of developing vitreous degeneration per year of age (Krishnan et al., 2020). In the present study, due to the impossibility of fully evaluating and grading the condition by biomicroscopy, a B-mode ultrasound was performed for this purpose. This technique has been reported to have high sensitivity and specificity when diagnosing vitreous diseases (Labruyère et al., 2008). Vitreous degeneration was surprisingly the second most common ocular finding (45.9%) in the present study. Most of the affected eyes displayed a mild degree of the condition (77.7%), not showing a statistical correlation with the type of cataracts (p > 0.05). This agrees with Park et al. (2015) who found an increased degree of vitreous degeneration when associated with chronic cataracts (mature or hypermature), but not with acute, intumescent, incipient, or immature cataracts. Similarly, Krishnan et al. (2020) ruled out a possible correlation between vitreous degeneration and other ocular comorbidities, such as cataracts, lens luxation, glaucoma, and/or retinal detachment.

Tear film dysfunction, both aqueous and evaporative, has been documented in dogs (Cullen et al., 2005; Williams et al., 2007) and humans (Manaviat et al., 2008) with DM. Human medicine studies have demonstrated

### Table 1. Statistical correlation between ophthalmic findings (in absolute frequencies) and type of cataracts in diabetic dogs.
Statistically significant p-values are underlined and in italics. A significance threshold of p < 0.05.

<table>
<thead>
<tr>
<th>Ocular signs</th>
<th>Cataracts (n = 146)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incipient (n = 2)</td>
<td>Immature (n = 21)</td>
</tr>
<tr>
<td>ADDE (n = 31)</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Lipid keratopathy (n = 9)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Diffuse corneal edema (n = 31)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Anterior uveitis (n = 40)</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Vitreous degeneration (n = 44)</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Non-proliferative retinopathy (n = 12)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Phacomorphic glaucoma (n = 2)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

### Table 2. Glycemia levels are shown as mean ± SD in diabetic dogs with ocular findings. For each ocular finding, the statistical results of the evaluation between affected and non-affected eyes are shown, establishing a significance threshold of p < 0.05. Significant p-values are underlined and in italics.

<table>
<thead>
<tr>
<th>Ocular signs</th>
<th>Glycemia (mg/dl)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>ADDE (n = 31)</td>
<td>430.20 ± 84.20</td>
<td>0.623</td>
</tr>
<tr>
<td>Diffuse corneal edema (n = 31)</td>
<td>477.11 ± 119.91</td>
<td>0.617</td>
</tr>
<tr>
<td>Lipid keratopathy (n = 9)</td>
<td>522.25 ± 147.10</td>
<td>0.147</td>
</tr>
<tr>
<td>Anterior uveitis (n = 47)</td>
<td>494.78 ± 110.48</td>
<td>0.013</td>
</tr>
<tr>
<td>Phacomorphic glaucoma (n = 2)</td>
<td>507.56 ± 122.71</td>
<td>0.936</td>
</tr>
<tr>
<td>Cataract (n = 146)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incipient (n = 2)</td>
<td>538.50 ± 168.99</td>
<td>0.590</td>
</tr>
<tr>
<td>Immature (n = 21)</td>
<td>467.54 ± 98.98</td>
<td>0.844</td>
</tr>
<tr>
<td>Mature (n = 24)</td>
<td>505.93 ± 153.33</td>
<td>0.483</td>
</tr>
<tr>
<td>Hypermature (n = 21)</td>
<td>418.50 ± 136.69</td>
<td>0.526</td>
</tr>
<tr>
<td>Intumescent (n = 78)</td>
<td>454.38 ± 92.75</td>
<td>0.827</td>
</tr>
<tr>
<td>Vitreous degeneration (n = 44)</td>
<td>486.63 ± 137.44</td>
<td>0.501</td>
</tr>
<tr>
<td>Non-proliferative retinopathy (n = 12)</td>
<td>645.88 ± 41.94</td>
<td>0.000</td>
</tr>
</tbody>
</table>
that while basal rates of aqueous tear secretion were equivocal between diabetic and nondiabetic patients, STT values were lower in diabetics (Goebbels, 2000). In the present study, ADDE was found in 22% of the dogs. Surprisingly, many of these animals had no obvious clinical signs at diagnosis, making it possible to go undetected if no STT-1 had been performed. Duration of diabetic disease has been considered a risk factor for ADDE, as it negatively influences STT-1 values in diabetic dogs (Williams et al., 2007). Diabetic dogs undergoing phacoemulsification have been reported to be almost twice as likely to develop dry eye within the first 2-week postoperative period, compared to nondiabetic dogs. Tear supplementation rather than an institution of a stimulant tear product may be considered to protect the cornea during the anesthetic and surgery recovery period as tear values may improve after the 2-week postoperative period (Gemensky-Metzler et al., 2015). Furthermore, small diabetic dogs (<10 kg) have been reported as 1.7 times more likely to be diagnosed with dry eye postoperatively rather than small nondiabetic dogs (Gemensky-Metzler et al., 2015). It is unclear as to whether poor DM control is an important factor in the manifestation of dry eye diseases in diabetic canines as has been documented in humans (Ozdemir et al., 2003). Some canine studies suggest no significant correlation between poor DM control and low STT (Cullen et al., 2005; Williams et al., 2007); however, no complete cohort observational studies evaluating this factor have been published to date.

Anterior uveitis was the third most common clinical finding in the study (31.3%). It has been reported that 71% of patients with cataracts will show lens-induced uveitis (LIU) elicited by an inflammatory response that occurs secondary to protein leakage from the lens capsule occurs (also known as phacoalytic uveitis) (Paulsen et al., 1985). The degree of inflammation depends on the amount of soluble and insoluble proteins within the lens (Wilcock and Peiffer, 1987). Taking this into consideration, it is expected that LIU secondary to DM would be more severe in young patients than in older ones, as albuminoid proteins inside the lens increase with age (Orterwerth and Olesen, 1989). Young animals have a higher number of soluble proteins that can diffuse through intact lens capsules when an intumescent cataract develops quickly in diabetic patients. Although no correlation was found between the degree of uveitis and the type of cataract, it was more commonly diagnosed in dogs with intumescent cataracts. Another mechanism for LIU in diabetic dogs is associated with the rapid increase in the size of intumescent cataracts, thus leading to tears in the lens capsule at the equator (phacoelastic uveitis) (Wilkie et al., 2006). This type of uveitis tends to be more aggressive and to have a more acute onset. Wilkie et al. (2006) reported that dogs affected with spontaneous lens capsule rupture had, based on their histories, been diabetic for an average of 123 days and had cataracts for an average of 39 days. In the present study, no cases of phacoelastic uveitis were diagnosed. Based on the low amount of aqueous flare, the majority of the uveitis cases were classified as mild anterior phacoalytic exudative uveitis (75.6%).

Diabetic corneal endothelial changes have been widely described in the human literature, but in veterinary medicine, they are scarcely reported (Yee et al., 1985). Conversely to what has been described in human medicine (Shenoy et al., 2008; El-Agamy and Alsubaie, 2017; Liaboe et al., 2017), diabetic dogs exhibit pleomorphism and polymegathism but no changes in endothelial density (Yee et al., 1985). These changes appeared to be indirectly correlated with the level of diabetic control (Yee et al., 1985). This should be taken into consideration when assessing patients for phacoemulsification surgery, as it may predispose diabetic dogs to more severe postoperative corneal edema. Furthermore, preoperative specular microscopy could help in presurgical decision making, such as viscoelastic selection, phacoemulsification machine settings, or postoperative use of topical hyperosmotic drugs.

Punctate retinal hemorrhages were found in 13.3% of the eyes examined (out of 98 eyes assessed by indirect ophthalmoscopy). This prevalence markedly differs from reports in human medicine, in which the prevalence is much higher (Herring et al., 2014). Conversely to the proliferative changes seen commonly in humans (Manaviat et al., 2008), canine diabetic retinopathy is characterized by microvascular changes including capillary microaneurysms and hemorrhages (Braga-Śá et al., 2018). The pathogenesis of diabetic retinopathy has been hypothesized to be the same as for cataract formation (Muhiana, 1995). In one retrospective study, retinal hemorrhages following cataract surgery in dogs occurred in 21% of diabetic patients with only 0.6% of nondiabetics having these lesions (Landry et al., 2004). While the median time from diagnosis of diabetes to the onset of non-proliferative retinopathy in dogs has been reported as 1.4 years (Landry et al., 2004), the proliferative retinopathy commonly seen in humans has been associated with longer periods of time. The lower incidence of proliferative changes in dogs might be explained by the age of onset of DM and the shorter life span of dogs, yielding a shorter duration of disease during their lifetime (Miller and Brines, 2018). Furthermore, differences in the presence of vascular endothelial growth factor in the aqueous humor of diabetic patients with retinopathy (Funatsu et al., 2005) could explain these interspecies disparities. Dr. Williams found that diabetic cataracts had significantly increased axial thickness compared to non-diabetic cataracts as demonstrated by B-mode ultrasonography (Williams, 2004). This reinforces the recommendation for performing early phacoemulsification to reduce the risk of phacomorphic
glaucoma. In the present study, a very low incidence of phacomorphic glaucoma was documented which can be explained by the short time between DM diagnosis and the ophthalmic examination.

Phacoemulsification is the gold standard treatment for cataracts in dogs. Although the success rate in diabetic dogs is approximately the same as that for cataract extraction in nondiabetic patients (Bagley and Lavach, 1994), postoperative complications such as corneal ulcers, diffuse corneal edema, lipemic aqueous humor, and ocular neuropathies have been reported to be more likely to develop in diabetic dogs (MacRae et al., 1982; Ledbetter et al., 2006; Klein et al., 2011; Foote et al., 2019). Based on the prevalence of ocular signs observed in the present study, and the incidence of postoperative complications reported, a more complete ocular preoperative assessment is recommended in diabetic dogs undergoing cataract surgery. Specular microscopy, Tear Film Break-up Time (TFBUT), STT-1, gonioscopy, and corneal esthesiometry could be helpful for anticipating surgical and postoperative complications, and therefore, helping with their management.

In the dog, hyperglycemia does not cause symptoms until glucose values are persistently elevated, usually above 180–220 mg/dl (Fracassi, 2017). Although ocular findings are a well-known complication for diabetic dogs, no glycemic threshold values have been previously established for any of the more common ophthalmic presentations. In the present study, a statistical association between fasting glycemia levels, non-proliferative retinopathy, and anterior uveitis was seen, suggesting that diabetic dogs with glycemic values higher than 600 mg/dl could be predisposed to anterior segment inflammation and non-proliferative retinopathy.

Limitations of this study include those inherent to the retrospective nature, the lack of homogeneity in data assessment, incomplete medical records, and variations in clinical approach.

**Conclusion**

Ocular complications of DM in dogs are numerous. This high prevalence warrants a more detailed preoperative evaluation in diabetic dogs undergoing cataract surgery. Furthermore, the positive correlation between cataracts and retinopathy suggests an early surgical treatment as the most appropriate approach. Moreover, a predisposition for anterior segment inflammation and non-proliferative retinopathy is suggested when fasting plasma glucose is higher than 600 mg/dl. Data from this study can help ophthalmologists to better understand the disease and provide more effective treatments and surgical approaches to canine patients.

**Conflict of interest**

The authors declare that there is no conflict of interest. **Authors contribution**

All authors contributed to making the completion of this manuscript possible. Francisco Cantero, Marta Leiva, and Teresa Peña designed the study and had direct patient contact. Francisco Cantero obtained all data supervised by Marta Leiva and Teresa Peña. Angel Ortillès analyzed the data and gave statistical conclusions. Francisco Cantero, Angel Ortillès, and Marta Leiva wrote the paper. Teresa Peña, Marta Leiva, and Angel Ortillès critically reviewed the manuscript for important intellectual content.

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