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A comparative review of evaporative dry eye disease and meibomian gland dysfunction in dogs and humans

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Abstract

Dry eye disease is a complex ophthalmic disorder that consists of two main subtypes, aqueous deficient dry eye (ADDE) and evaporative dry eye disease (EDED). Due to the complex underlying physiology, human dry eye disease can be difficult to model in laboratory animal species. Thus, the identification and characterization of a spontaneous large animal model of dry eye disease is desirable. Dogs have been described as an ideal spontaneous model of ADDE due to the similar pathophysiology between dogs and humans. Recently, EDED and meibomian gland dysfunction (MGD) have been increasingly recognized and reported in dogs. These reports on EDED and MGD in dogs have identified similarities in pathophysiology, clinical presentations, and diagnostic parameters to humans with the comparable disorders. Additionally, the tests that are used to diagnose EDED and MGD in humans are more easily applicable to dogs than to laboratory species due to the comparable globe sizes between dogs and humans. The reported response of dogs to EDED and MGD therapies are similar to humans, suggesting that they would be a valuable preclinical model for the development of additional therapeutics. Further research and clinical awareness of EDED and MGD in dogs would increase their ability to be utilized as a preclinical model, improving the positive predictive value of therapeutics for EDED and MGD in both humans and dogs.

1 | INTRODUCTION

Dry eye disease is a broad class of ophthalmic disorders defined as a loss of tear film homeostasis due to tear film instability and hyperosmolarity, which induce symptoms

such as ocular surface inflammation and damage.[1] There are two main subtypes of dry eye disease described in both humans and dogs: evaporative dry eye disease (EDED) and aqueous deficient dry eye (ADDE) (Figure 1). The study of and treatment of canine ADDE have led to major advancements in our treatment of ADDE in humans. Specifically, the use of cyclosporine for the treatment of ADDE in dogs paved the way for its use in human patients,[2,3] thus highlighting the role of the dog as an important spontaneous preclinical model of human ophthalmic disease. This review will focus on comparing and contrasting the causes and clinical signs of EDED in humans and dogs to highlight the applicability of canine patients as spontaneous models of disease. Additionally, this review will highlight the tear film diagnostic testing and therapeutic strategies between humans and dogs, drawing parallels that can translate to the development of improved diagnostics and mechanism-derived therapeutic approaches.

2 | MECHANISM OF DISEASE

2.1 | Evaporative dry eye disease

In humans, EDED is caused by tear film instability due to a loss of the tear film evaporative barrier without a decrease in aqueous tear production.[4] This is typically associated with the decreased synthesis or secretion of the lipids that compose the evaporative barrier. However, not all patients with a decrease in lipid synthesis, or lipid layer thickness, have tear film instability and thus clinical signs of EDED.[5] Additionally, there are ocular surface and adnexal abnormalities, including pterygium in humans and trichiasis in dogs, that also lead to tear film instability and EDED. However, this review will focus on EDED due to lipid derangements. These lipids are predominantly produced by the meibomian glands, thus any insult that decreases their function can cause EDED. Meibomian gland dysfunction (MGD) is also a multifactorial condition most commonly described as meibomian gland orifice obstruction and metaplasia, reduced and altered meibum lipid profile, cystic dilation of the central duct, and acinar atrophy seen as meibomian gland dropout.[4,6] However, the described clinical characteristics of MGD vary widely in the literature with reports including a mixture of meibomian gland and eyelid pathologies including posterior blepharitis,[7] eyelid thickening (Figure 2),[8] and increased eyelid vascularity[9] in their definition of MGD, though these are less widely accepted. In dogs, the definitions of EDED and MGD are similar, but the associated alterations in the tear film lipid layer are not fully described.[10]

2.1.1 | Causes of meibomian gland dysfunction

Primary: Obstructive MGD is the main form of primary MGD and the most common cause of EDED.[11] It has been proposed that obstructive MGD occurs due to hyperkeratinization and hypertrophy of the meibomian duct epithelium and subsequent damming of lipid secretions leading to upstream cystic dilation of the ducts and acini.[4,11] This decrease in lipid secretion leads to disuse atrophy of the acini.[11] Increased pressure within the gland can also lead to acinar atrophy due to the inhibition of lipid secretion. Another theory of the underlying mechanism of MGD is that meibocyte progenitors undergo senescence leading to acinar atrophy.[12] Regardless of the underlying cause, loss of acini ultimately occurs, which is seen clinically as meibomian gland dropout. The theories presented here are not an exhaustive list of the existing theories on the development of MGD. Additional information

on the other theories of MGD development in humans can be found in a recent review by Chhadva et al.[13]

Secondary: Secondary MGD can occur as a result of diseases or clinical interventions that affect the meibomian glands. For example, in humans and dogs demodex infections of the eyelash follicles and meibomian glands can lead to blepharitis and MGD.[14,15] In humans, periocular radiotherapy for the treatment of conjunctival or orbital lymphoma can induce MGD and EDED.[16] Additionally, chronic inflammatory diseases of the ocular surface, such as graft-versus-host disease and Stevens–Johnson syndrome, can cause the development of MGD in humans.[17,18] In dogs, the clinical excision of meibomian gland adenomas,[19,20] epitheliomas,[21,22] and distichiae[23] have been reported to affect the meibomian glands. Some of these studies investigated the impacts of the procedures on the tear film reporting no effect on the tear film[19] or a decrease in tear film breakup time (TFBUT, see Section 4.1.1).[23] Thus, additional studies are needed to determine the impact of therapeutic interventions, such as meibomian gland excision, cryoinjury, or thermal cautery on the development of secondary MGD in dogs. These findings indicate that a variety of insults to the meibomian glands can lead to the development of MGD and EDED.

2.1.2 | Asymptomatic meibomian gland dysfunction—Age-related changes to the meibomian gland, such as dropout and decreased meibum quality, may not always lead to clinical signs of MGD.[24] One study demonstrated that human patients with an abnormal tear film and impaired meibum secretion do not always present with clinical symptoms of MGD and that asymptomatic MGD may be more common than symptomatic disease.[25] Additionally, studies performed in children have identified meibomian gland dropout without identifying corresponding symptoms,[26] however, it is possible that these children could develop symptoms in the future due to the early absence of glandular tissue.[27] This phenomenon has been identified in dogs as well. For example, meibomian gland dropout and shortening has been identified in Shih Tzus without clinical signs of EDED (see Section 3).[28] The presence of asymptomatic individuals with meibomian gland changes highlights the complexities in interpreting meibomian gland morphology and its impact on ocular surface health.

2.2 | Aqueous deficient dry eye

In humans and dogs, ADDE is caused by a decrease in lacrimal gland function leading to decreased aqueous tear production characterized by a decreased Schirmer tear test (STT, see Section 4.2).[4,29] This is typically due to an immune-mediated attack on the lacrimal gland.[2,4] In dogs, this syndrome is well characterized and commonly referred to as keratoconjunctivitis sicca, yet more recent literature has utilized the term ADDE to highlight the similarities with human disease.[30] Additional causes of ADDE in humans and/or dogs include disrupted neuronal stimulation of the lacrimal gland,[31,32] drug-induced (e.g., atropine, sulfa-containing oral antibiotics),[33,34] hypothyroidism,[35,36] diabetes mellitus,[35,37] trauma, congenital alacrima,[38,39] historical infection (e.g., distemper virus),[40] and surgical excision of the gland of the third eyelid.[41]

2.3 | Mixed dry eye disease

The diagnosis of EDED or ADDE alone can be complicated by inconsistencies in clinical signs, diagnostic results, and patient symptoms. Additionally, the diagnosis can be further complicated by the fact that one form of dry eye disease can predispose patients to developing the other type. For example, in patients with EDED, the chronic damage to the ocular surface from decreased tear stability can lead to a decrease in corneal sensation, dampening the neurological stimulus for lacrimal secretion, and, thus, secondary ADDE.[4] In ADDE, the decreased aqueous layer could prevent the adequate spreading of the tear film lipid layer, thus leading to a functional EDED.[4] Additionally, chronic ocular surface inflammation in patients with ADDE could induce the formation of neutrophil extracellular traps, which can clog the meibomian glands leading to their dysfunction.[42] These mixed forms of dry eye disease are well described in the literature. For example, one study on human patients identified that 12.8% of patients with ADDE also had MGD.[43] Additionally, the ADDE group in this study had a significantly shorter TFBUT compared to healthy human patients,[43] suggesting a functional EDED. Similarly, one study in dogs determined that a cohort of animals with MGD also had decreased STT values,[44] consistent with a mixed dry eye disease in dogs.

3 | CLINICAL PRESENTATION

In humans, patients with dry eye disease can present with decreased vision, foreign body sensation, dryness, irritation, itchiness, or burning sensation.[4,45] However, these signs are not specific for EDED or ADDE. Patients with EDED also tend to present with eye fatigue and eyelid heaviness,[43] but additional diagnostic tests are required to differentiate between EDED and ADDE. In dogs, the initial clinical features that lead to a diagnosis of EDED and MGD include inspissation or doming of the meibomian gland orifices, marginal blepharitis, and excessive serous ocular discharge (epiphora). However, these more subtle features are not always apparent to owners, thus dogs typically present with more advanced stages of disease with severe clinical signs, including hyperemia, mucopurulent discharge, and secondary corneal disease, such as fibrosis, neovascularization, and pigmentation (Figure 2).[46,47]

3.1 | Risk factors

3.1.1 | Age—Increasing age is a risk factor for the development of MGD and EDED in both human[48] and canine[49] patients. As mentioned in Section 2.1.2, meibomian gland changes increase with age, but these are not always associated with clinical signs.[24] There is increasing evidence that these alterations in the meibomian glands may occur early in life, as they can be identified in children, yet they do not exhibit clinical signs of disease until later in life.[26,27] However, it is still unclear what factors cause these previously asymptomatic patients to develop symptoms of EDED over time. There is a paucity of literature correlating age and MGD in dogs; however, one retrospective study on ocular surface disease demonstrated that increasing age was a risk factor for the development of MGD.[49] Specifically, increasing age in Shih Tzus has been associated with a significant decrease in TFBUT leading to ocular surface pathologies including corneal opacification,

pigmentation, fibrosis, and neovascularization.[50] These findings further underscore the effect of EDED and its contributions to ocular surface disease in dogs.

3.1.2 | Sex—The effect of sex on the risk of EDED development varies between humans and dogs. For example, one study comparing human EDED with other forms of dry eye disease identified that female patients are more at risk of developing EDED.[43] This is likely due to the importance of androgens in meibomian lipid synthesis, which is further supported by the finding that androgen deficiency in males and females can lead to MGD and subsequent EDED in humans.[51] However, in dogs, the predisposition for developing MGD appears to be toward male dogs.[49] This finding was identified in a single study of 150 dogs, thus additional prevalence studies over a longer time course are needed to confirm this association between sex with EDED and MGD in dogs.

Ethnicity: In humans, individuals of Asian descent appear to be predisposed toward EDED. This finding was presented in a systematic review comparing dry eye disease in people of Asian and Caucasian descent.[27] The authors of this systematic review proposed that the anatomical increase in eyelid tension seen in Asian patients could lead to this predisposition.[27] An independent study also identified that East and South Asian individuals are predisposed to EDED,[48] supporting this association. However, this finding has only been identified in a subset of epidemiological studies on EDED.

Canine breed: In dogs, it has been proposed that brachycephalic breeds are predisposed to both EDED and ADDE, though the literature more firmly supports their predisposition for ADDE. In Shih Tzus, 16 of 28 eyes of clinically healthy animals showed meibomian gland abnormalities, such as gland shortening and dropout.[28] An additional study identified that meibomian gland atrophy and dropout was correlated with age with older Shih Tzus experiencing more abnormalities.[52] A more recent study identified a negative correlation with age and TFBUT in Shih Tzus,[50] suggesting that with increasing age, the meibomian glands begin to shorten and dropout, leading to a decrease in tear film quality and EDED. Additionally, Pekingese dogs were found to have surface lipid abnormalities including a granular or curdled appearance or the presence of dark globular structures with polarized light biomicroscopy.[53] These findings suggest that there are abnormalities in the tear film lipids which could be leading to decreased tear film stability, predisposing these animals to EDED.[53] Brachycephalic dogs have also been shown to be more predisposed to corneal or adnexal diseases.[54,55] This predisposition is likely correlated with their decreased tear production[56] and corneal sensation due to a decreased corneal nerve density[56,57] combined with anatomical challenges such as macroblepharon,[58] or excessive eyelid tissue, lagophthalmos, an inability to completely close their eyelids, exophthalmos, or protrusion of the globes,[53] all of which lead to decreased protection of the ocular surface. The exophthalmos seen in brachycephalic dogs can also lead to incomplete blinking. In humans, it has been shown that the act of blinking leads to the expression of meibum lipids. Forceful blinking increases the amount of meibum released onto the ocular surface whereas incomplete blinking leads to decreased meibum expression, decreased TFBUT, and, subsequently, an increased incidence of MGD.[59–61] Thus, a similar phenomenon may be occurring in brachycephalic animals with an incomplete blink.

Additionally, one study identified that Miniature Schnauzers have decreased meibum production compared with other breeds.[62] This study was focused on healthy animals, and it is uncertain if the decrease in meibum production will predispose these animals to developing EDED later in life or if this represents a breed-specific difference in healthy meibum production.

3.1.3 | Miscellaneous—Additional risk factors of EDED in humans include comorbidities, such as ocular rosacea,[59] local hypersensitivity reactions to or the toxic effects of medications, such as retinoic acid,[60] and marginal blepharitis. However, to date, no studies have identified these additional factors to cause EDED in dogs, thus additional work is needed to investigate their potential role. In dogs, it appears that fungal or staphylococcal infections of the periocular skin and/or eyelids or atopic dermatitis can lead to severe blepharitis, resulting in tear film abnormalities and EDED. However, further studies are needed to establish these causal relationships with EDED.[14]

4 | DIAGNOSTIC TECHNIQUES

There is a diverse array of techniques that are available for the diagnosis of EDED. These tests range from assessing tear film quality and quantity to imaging the tear film on the ocular surface all with the goal of determining the adequacy of the tear film. This section will describe the diagnostic testing strategies used in both humans and dogs (Table 1).

4.1 | Tear film quality assessment

As a hallmark cause of EDED is a decrease in tear film quality, techniques that identify these deficits are crucial for the diagnosis of EDED.

4.1.1 | Tear film breakup time—Tear film breakup time is the most commonly utilized diagnostic measure of tear film stability. TFBUT is classically described as the time from eyelid opening to the appearance of the first dry spot on the corneal surface.[63] The visualization of this process is aided by the addition of a fluorescent dye, such as fluorescein, magnification, and cobalt blue light. However, fluorescein can also decrease tear film stability, decreasing the accuracy of this method.[64] In humans, it has been shown that using <2 μL of 5% fluorescein solution confers more reliable TFBUT results.[65] This is likely because the volume of tears present on the human ocular surface is approximately 7–12 μL,[66,67] thus larger volumes of fluorescein would overwhelm the native tear film dynamics. By contrast, the normal tear volume of dogs is approximately 65 μL,[68] thus larger volumes of stain could theoretically be used without diluting out the native features of the tear film. Additional considerations for the interpretation of this test include the volume and concentration of the dye applied to the ocular surface, the time between administration and measurement, and the technique of the examiner.[63] An important feature to note in canine patients is the presence of a nictitating membrane that can interfere with this test even when the eyelids are being held open, altering the results. Overall, TFBUT is a powerful diagnostic tool, but the results need to be interpreted carefully in light of its limitations.

4.1.2 | Noninvasive tear film breakup time—The measurement of noninvasive tear film breakup time (NIBUT) is an additional method to assess the stability of the tear film.

This method differs from traditional TFBUT in that it does not use a stain, but rather a light is shone onto the ocular surface with a grid insert and the time it takes for the projected lines to become distorted is determined (Figure 3).[20] This technique avoids the potential influences of exogenous dye on tear film stability.

This technique has been well characterized in human medicine, but its use in canine patients has been reported rarely. In humans, the first reported use of NIBUT as a diagnostic method was in 1985.[69] Since then, this technique has been increasingly utilized in human patients. The few studies that have utilized NIBUT to diagnose EDED in dogs used different parameters to define and classify animals with reduced tear film stability. One study utilized a cutoff of 5 s as their determination of an unstable tear film without validation of this value.[70] A different study subclassified NIBUTs from their canine patients that were under 20 seconds into different categories.[44] This study did identify that NIBUT grades for patients with MGD were significantly lower than animals without MGD,[44] suggesting that this method could be a valid diagnostic tool in veterinary medicine. However, additional work is necessary to verify these categories and better correlate canine NIBUTs with clinical signs and significance. Despite these limitations, NIBUT represents a valuable diagnostic technique that would increase our ability to diagnose EDED in dogs.

4.1.3 | Tear osmolarity—Tear osmolarity tests measure the amount of solutes in the tear film either through determining the tear freezing point depression or electrical impedance.[71] Human patients with EDED tend to have an increased tear osmolarity compared with healthy individuals,[71,72] but not all patients with obstructed meibomian glands and a high osmolarity present with symptoms of dry eye disease.[73] Additionally, the exact mechanism of the increased osmolarity in patients with EDED is still unknown. One proposed mechanism is that the decreased stability of the tear film can lead to transient increases in osmolarity adjacent to regions about to undergo or that recently underwent breakup.[74–76] However, other studies have identified an increase in osmolarity in conjunction with a decrease in STT values,[71,77] suggesting this increase in osmolarity is due to the decreased aqueous tear volume in patients with mixed DED. In dogs, less is understood about the alterations in tear osmolarity in animals with EDED as there have been no studies investigating the impact on tear osmolarity in dogs with EDED or MGD. Normative osmolarity values have been published in dogs and there have been a few studies that identified an increase in osmolarity in dogs with ADDE.[30,78–80] The thick, tenacious mucoid discharge associated with ADDE in dogs has the tendency to obstruct the osmometer, thus presenting a major limitation that decreases the clinical utility of tear osmolarity as a diagnostic tool in dogs.[78] However, there are no reports on the assessment of tear film osmolarity in dogs with qualitative tear deficiencies, which may prove a key diagnostic for dogs with EDED.

4.2 | Tear film quantity assessment

In addition to the quality of the tears, it is clinically important to determine the quantity of tears present in a patient presumed to have dry eye disease to determine which subtype is/are present. There are a myriad of diagnostic tests available to quantitate aqueous tear production, including STT, endodontic paper point tests,[56] phenol red thread test,[61,81]

strip meniscometry test,[82–84] and many others. For the purposes of this review, we will compare and contrast the STT-1, the most commonly performed measurement of aqueous tear production.

In humans, the STT strip is placed into the lower conjunctival fornix for 5 minutes before the results are determined by reading the tear collection on the millimeter scale printed on the strip.[85] However, in dogs, the STT is performed by placing the tip of the test strip for 1 min and then reading the result.[86] This difference is likely due to the differences in patient compliance and in tear volumes between dogs and humans as mentioned in Section 4.1.1. The STT is the gold standard diagnostic technique for the diagnosis of ADDE in both humans and dogs, in which affected patients will present with decreased STT values. However, in human and canine[49] patients with EDED, these values should be within normal limits. Thus, this diagnostic test represents a simple method to differentiate patients suffering from either ADDE or EDED.

4.3 | Imaging

4.3.1 | Interferometry—Interferometry is a technique in which the interference patterns of reflected light off the lipid-aqueous interface is measured to determine the lipid layer quantity and quality (Figure 4).[85] This technique is commonly referenced in the literature; however, the interpretation of its results is variable. The most commonly utilized grading scheme for interferometry in humans was initially proposed by Yokoi et al.[87] In this scheme, there are five grades, (1) somewhat gray in color with a uniform distribution (2) somewhat gray color with a nonuniform distribution, (3) a few colors with a nonuniform distribution, (4) many colors with a nonuniform distribution, and (5) corneal surface partially exposed.[87] In this scheme, the higher grades represent an abnormal tear film. Others have utilized alternative strategies to diagnose abnormalities in the tear film lipids using this technique. For example, one study identified a Jupiter-interferomic pattern as being indicative of ADDE due to the correlated increased lipid layer thickness and longer TFBUT in these patients compared to patients with a crystal-interferometric pattern, which the authors determined was characteristic of EDED.[88] In the canine literature, there are also discrepancies in the clinical interpretations of interferometric grades. For example, in one study, low interferometric grades were interpreted as being indicative of an abnormal tear film lipid layer.[44] However, the lower grades in this canine study correspond to the uniform and nonuniform gray patterns that had been previously described as healthy in human patients.[44,87] A different canine study utilized a similar scale in which they report that their lowest grade corresponded to a complete lack of the aqueous phase.[49] Thus, in both of these studies, canine patients with the lowest scores were determined to have EDED,[44,49] whereas in the human literature, higher scores were determined to have an abnormal tear film lipid layer.[87] These findings suggest that more consistency in grading and interpretation between studies and across species is needed.

4.3.2 | Non-contact infrared meibography—Non-contact meibography is a technique in which the eyelid is everted and imaged using a slit lamp equipped with an infrared light or using a handheld imager with infrared capabilities (Figure 5).[89,90] With both methods, meibomian gland dropout, dilation, ductal distortion, and shortening can be

identified in humans with MGD.[90] Non-contact infrared meibography has also been utilized in the characterization and diagnosis of MGD in canine patients. For example, one study used this technique as a diagnostic criteria in their retrospective analysis on MGD in dogs, though it was only used to rule in or out MGD based on the appearance of the meibomian glands.[49] Additionally, this technique has been utilized to identify meibomian gland dropout and shortening in case reports.[91,92] Thus, this method represents a versatile and clinically informative method to assess meibomian gland health in both human and veterinary patients.

4.4 | Miscellaneous

4.4.1 | Meibometry

—Meibometry is a technique that quantifies meibum production. This technique utilizes a plastic tape placed along the inner margin of the eyelid to collect the lipids secreted by the meibomian glands.[93] The lipids collected on the tape are then detected using a photometer. In humans, meibometry values correlate with TFBUT,[93] suggesting that meibometry can be used for the diagnosis of EDED through the identification of abnormal meibum production. Meibometry has been performed in healthy dogs[62,94] and dogs with ADDE.[30] However, the results of the meibometry evaluations showed high variability within the same healthy dogs.[94] Thus, additional work is necessary to increase the test–retest repeatability of this technique prior to its widespread use in veterinary clinics.

4.4.2 | Ocular surface staining

Fluorescein: Fluorescein staining can be utilized to evaluate the health of the ocular surface by assessing the staining pattern obtained after application. Multifocal punctate staining is seen when fluorescein dye adheres in the spaces that are left when corneal epithelial cells are desquamated (Figure 6).[95] This punctate staining can be identified in human patients with EDED when their ocular surface is damaged by the unstable tear film. In dogs, punctate staining has been identified in animals with ADDE,[96] though this method would also be applicable to patients with EDED induced corneal epithelial damage.

Rose bengal: Rose bengal stain is thought to bind to degenerate corneal epithelial cells due to a loss of the protective mucin layer.[97,98] However, the coloration of rose bengal is difficult to visualize on the corneal surface but has been utilized to identify conjunctival epithelial cell loss in humans with EDED.[99] In dogs, the degree of rose bengal staining correlated with signs of ADDE,[100] however, this has not been investigated in dogs with EDED. The main limitation of this technique is the ocular irritation and cytotoxic effects associated with its administration, which are exacerbated by exposure to light.[98]

Lissamine green: Lissamine green is a synthetic organic acid that can stain devitalized corneal epithelium without causing ocular surface irritation in humans or dogs.[101,102] Lissamine green staining scores in people with EDED correlated with a shortened TFBUT[103] and was significantly increased compared with healthy controls.[43] In veterinary medicine, lissamine green has been used to assess the health of the corneal and conjunctival epithelial surfaces. In the conjunctiva, increased lissamine green staining score was significantly associated with a decreased TFBUT.[101] However, the diagnostic capabilities of lissamine green for EDED are uncertain as the dogs in this study also had a shortened

STT, thus representing mixed disease.[101] Based on the safety and staining characteristics, lissamine green staining could be used as a diagnostic test in veterinary medicine to identify ocular surface damage due to EDED.

5 | THERAPEUTICS

5.1 | Immunomodulatory/anti-inflammatory medications

Immunomodulation is the main treatment modality for ADDE as it is typically caused by an immune-mediated disorder, however, it also has clinical efficacy in patients with EDED and MGD. For example, treatment with topical cyclosporine has been shown to decrease ocular surface and meibomian gland inflammation in human patients with EDED and MGD.[104] In dogs, the use of anti-inflammatory medications for the treatment of MGD has only been reported once in a case report. This report described the use of tobramycin and dexamethasone, which successfully treated the dog's blepharitis and MGD.[91] Importantly, the use of cyclosporine has been widely used in canine medicine as a treatment for ADDE.[105–108] Other topical immunomodulatory agents, such as tacrolimus,[109] sirolimus,[110] and pimecrolimus,[111] have been utilized in canine patients with ADDE as well. These formulations are of special interest because they were dissolved in oils or formulated as a liposome, thus they might be of more clinical interest in dogs with EDED as they could potentially address multiple mechanisms of disease, namely the ocular surface inflammation and the lipid deficiencies in those patients. However, investigations into the ability of these immunomodulatory agents to aid in tear film stabilization have not been performed.

5.2 | Lipid replacement

As patients with EDED typically have a deficiency in tear film lipids, one potential therapeutic strategy is focused on augmenting the lipid component of the tear film. This has mainly been done through increasing fatty acids in the diet. Some clinical trials in humans have shown that dietary supplementation with omega-3 fatty acids improve clinical symptoms of EDED by prolonging TFBUT and tear film stability.[112,113] However, the Dry Eye Assessment and Management (DREAM) study, a large scale randomized trial in humans, failed to replicate those results.[114] In dogs, there has been one study investigating the effect of dietary omega-3 supplementation for the treatment of dry eye disease, which identified a significant increase in TFBUT at all timepoints.[115] This study was performed in dogs with ADDE, so the translatability to dogs with EDED is uncertain, therefore additional studies are required to determine the therapeutic efficacy of dietary omega-3 fatty acid supplementation for the treatment of EDED in dogs.

Omega-3 fatty acid eye drops have also been studied as a therapy for patients with EDED (e.g., NovaTears + Omega-3). One study in human patients with EDED found that the use of these drops significantly increased TFBUT, decreased MGD scores and increased patient comfort.[116] These results were further supported by an additional study on artificial tears that contained omega-3 fatty acids that identified increased lipid layer thickness for at least one hour after application.[117] However, the only enrollment criteria utilized in this study was a decreased lipid layer thickness.[117] In dogs, there are few studies investigating the use of topical lipid replacement for the treatment of dry eye disease. One study in dogs

applied a fatty acid cream to the ocular surface for the treatment of ADDE and identified an increase in STT values and a decrease in ocular surface inflammation scores.[118] This study represented the first use of this therapeutic for the treatment of dry eye disease and its positive results suggest that this fatty acid therapeutic could also be used in canine and human patients with EDED, thus highlighting the potential of dogs with spontaneous disease to serve as a model to test novel therapeutics. Overall, these positive results suggest that lipid-based topical therapies could be effective in the treatment of EDED.

By contrast, topical formulations containing mineral oil seem to have minimal efficacy in patients with EDED. One study in humans on a mineral oil-based artificial tear product found only mild increases in TFBUT after treatment.[119] Though, the inclusion criteria for this study included a decreased STT value, thus these patients likely represent a mixed EDED/ADDE sample. In dogs, mineral oil was assessed as a topical ointment for the treatment of ADDE, but its use did not increase STT values.[120] As this study did not assess the effect on TFBUT, the applicability to dogs with EDED is unknown. Despite the apparent clinical benefits of lipid replacement therapies, mineral oil-based topical therapeutics do not appear to be viable treatment strategy.

5.3 | Antibiotics

A complication of MGD is the over proliferation of bacteria in the damaged meibomian glands,[121] thus antibiotics like azithromycin and doxycycline have been utilized for the treatment of MGD and EDED in humans. Additionally, it has been shown that azithromycin, but not tetracyclines, has a direct impact on meibocyte differentiation in vitro, a feature that likely contributes to its beneficial effects in patients with MGD.[122] Oral doxycycline and topical and oral azithromycin have been used to treat MGD in humans, though the most significant effects on TFBUT and meibum quality are from doxycycline and topical azithromycin.[123–125] Oral doxycycline has been utilized in one case report for the treatment of one dog with MGD, which successfully decreased the animal's blepharitis, though the impact on tear film stability is unknown.[91] Additional studies on the impact of azithromycin and doxycycline treatment in dogs with MGD are warranted.

5.4 | Heat therapy

As patients with EDED and MGD often have inspissated meibomian glands, heat therapy is commonly recommended to melt the concretions of meibum, facilitating its release onto the ocular surface. In humans, the LipiFlow System is commonly utilized and functions by applying heat to the upper and lower eyelids while simultaneously exerting pressure to express the meibomian glands when the meibum is more fluid.[126] The use of this system has improved TFBUT, meibomian gland secretions and clinical signs in several studies in humans.[126–128] The use of warm compresses and palpebral massage have been reported in dogs,[91] but the use of a specific device to apply heat and pressure has not been reported. This represents an area of potential development for the care of our canine patients and an opportunity to study more effective therapeutic strategies.

Intense pulsed light therapy (IPL) is an additional therapeutic option that has been utilized for the treatment of MGD and EDED in humans. In this therapy, pulsed light is applied

to the periocular skin. There are several mechanisms that have been proposed for the efficacy of IPL for MGD including decreasing inflammatory mediators,[129] increasing anti-inflammatory mediators,[130] limiting cellular turnover,[121] and heat transfer to the eyelids and meibomian glands[72]; however, the exact mechanism is still not well understood. This therapy can be used in conjunction with low light therapy[131] and meibomian gland expression,[6] which induces similar effects as the pressure therapy described above in which the melted meibum is forced out of the gland. Intense pulsed light therapy has not been attempted in dogs; however, it is unlikely to be successful in canine patients due to the impaired ability of the light to penetrate their haired periocular skin.

6 | DOGS AS A MODEL OF HUMAN EDED

6.1 | Benefits

Despite a paucity of reports describing EDED in dogs, more recent studies have combined traditional tear film staining diagnostics with advanced imaging to further characterize the qualitative tear abnormalities in dogs. Current studies demonstrate the clinical similarities between dogs and humans; thus, dogs represent an appealing spontaneous animal model of disease. The main benefits of using dogs as a model of disease include the presence of spontaneous disease and the potential for shared environment and lifestyle risk factors seen in human patients. Additionally, the size of the eyelids and ocular surface of dogs is more similar to humans than laboratory animals (e.g., rabbits and rodents), easing the collection of meibum from the eyelids and performing the diagnostic tests used in humans. This is in contrast with the diagnostic techniques that can be used in laboratory animal species, such as mice and rats, which must be modified or not employed due to the substantially smaller size of their eyelids and ocular surface. Additionally, both humans and dogs have similar reference ranges for the diagnostic tests reported in Table 1. They also have similar physiological parameters, such as blink and tear turnover rates, highlighting their similarities in ocular surface physiology.[132] Importantly, the lipid composition of the canine meibum is both structurally and quantitatively comparable to humans, whereas rabbits, a commonly used large animal model for ocular drug development, has a markedly different lipid composition compared to humans and dogs.[133] Additionally, the composition of the ocular surface mucins, known to play a key role in tear film stabilization, are more similar between dogs and humans than other species that have been examined.[134] Given the similarities in clinical parameters as well as meibum and ocular surface biochemical composition, spontaneous EDED in dogs can serve as a model of human disease, translating to an improved positive predictive value in the assessment of novel therapeutics for EDED.

6.2 | Challenges

There are limitations to the use of dogs, especially client-owned animals, in clinical research. A main limitation is the identification of canine cases with more mild disease as is seen in human patients, likely due to the inability of canine patients to communicate initial symptoms reported in humans including itchiness or a foreign body sensation. Thus, dog owners typically identify clinical signs of moderate to severe disease prior to presenting to a veterinarian for evaluation. Additionally, the clinical course of EDED may be variable in both human and canine patients, therefore standardizing results and determining the

broader applicability of treatment strategies can be limited in both species. Once patients are identified, they would need to be enrolled in a trial, which clients may be adverse to due to their personal beliefs about the use of animals in research, especially their own pet. Finally, once animals are enrolled in the trials, it can be challenging to maintain their enrollment and ensure client compliance if a treatment regimen is implemented. Furthermore, the doses required to provide clinical effect in humans and dogs may differ. As mentioned in Section 2.2, cyclosporine was initially used in dogs for the treatment of ADDE, however, the concentration necessary for the treatment of ADDE in dogs is much higher than is required for human patients, suggesting such differences might be necessary in the treatment of canine EDED. An additional limitation is that not all therapeutic options will be efficacious in canine patients. As mentioned in Section 5.4, IPL therapy is unlikely to work in canine patients due to species differences, thus they would not be a good model to study the effectiveness of this therapeutic intervention.

7 | CONCLUSIONS

Humans and dogs both spontaneously develop EDED and ADDE. Much of the literature on dry eye disease in dogs is focused on ADDE, though few studies have described the ability of dogs with EDED and MGD to model human disease. This review highlights the similar pathophysiology and clinical presentations of dogs and humans with EDED and MGD. Additionally, the diagnostic tests that are available and clinically useful between the two species are similar, thus better enabling clinicians to compare the diseases across these two species, compared with traditional laboratory species. Finally, the therapeutics that have proven successful in canine and human patients with EDED and MGD are similar, suggesting that dogs could be a valuable preclinical model for the development of therapeutics for the treatment of these disorders. Overall, dogs represent a viable spontaneous model of EDED seen in humans, though, like any animal model, they are not without their limitations. The main limitation currently is the small number of studies describing MGD and EDED in dogs, though this number is growing. Thus, an increase in studies investigating EDED and MGD in dogs will increase the awareness of these diseases, enabling the identification of more cases for future preclinical studies.

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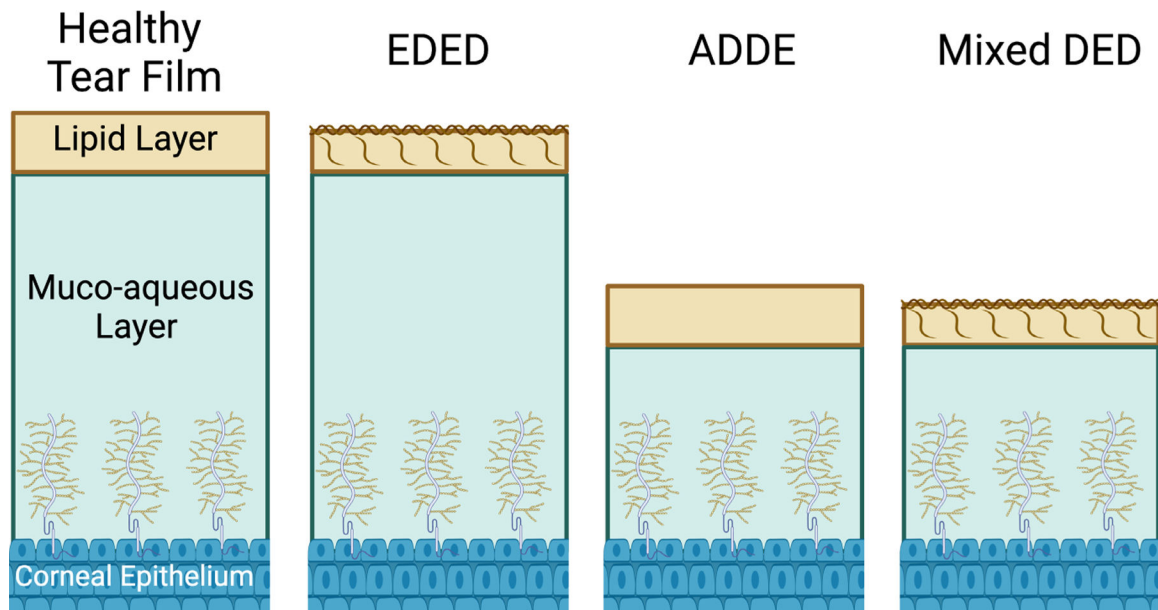
FIGURE 1.

Schematic representation of the changes to the tear film in EDED and ADDE. The healthy tear film is represented with approximations for the thicknesses of the layers of the tear film, the muco-aqueous layer, and the lipid layer. Patients with EDED typically have a heterogenous lipid layer, leading to decreased tear film stability (depicted by the waves in the diagram), which may be thinner. However, a thin tear film in the absence of lipid abnormalities that induce tear film instability does not necessarily lead to clinical signs of EDED.[5] In patients with ADDE, the aqueous component of the tear film is severely depleted, leading to clinical signs of disease. Additionally, patients can have mixed conditions in which they have a lipid layer with an altered composition and a decrease in the aqueous component, further confounding the diagnosis.
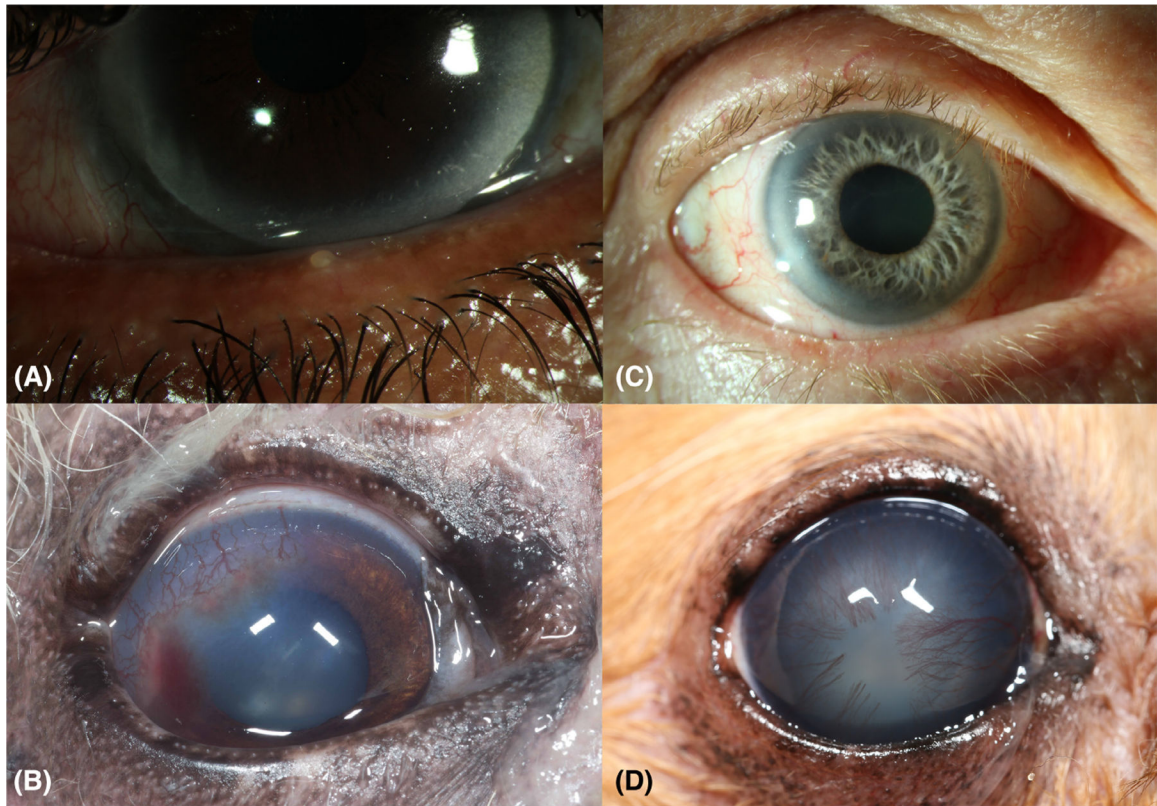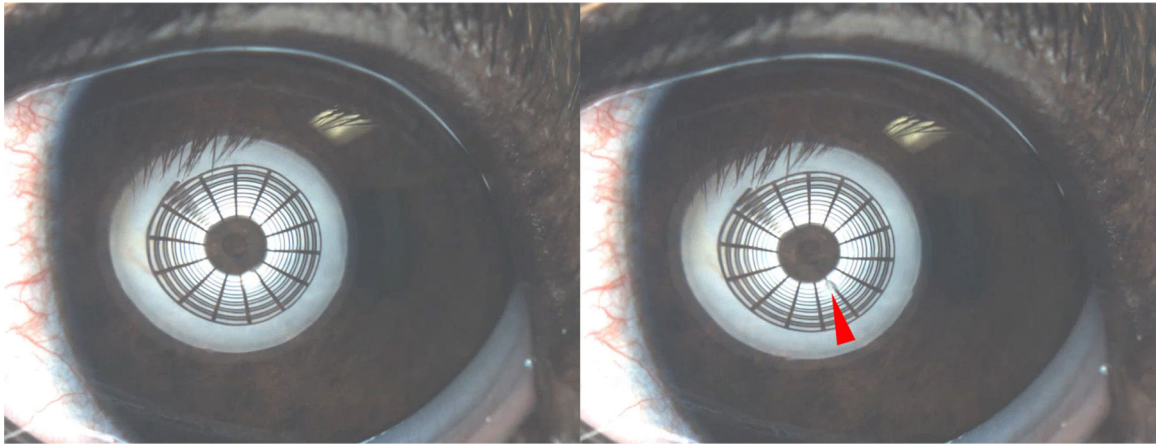
FIGURE 2.

Comparison of meibomian gland and eyelid pathologies between human and canine patients. Abnormal meibum quality can lead to meibomian gland plugging in humans (A) and dogs (B). Eyelid thickening in humans (C) and dogs (D) has been utilized as diagnostic criteria for MGD,[8] though this criteria is less widely accepted than other diagnostic findings. The canine eyes in image B and D demonstrate corneal neovascularization and edema due to the ocular surface damage induced by the poor-quality tear film. The human eye in image C also demonstrates telangiectasias.

FIGURE 3.
Noninvasive tear film breakup in dogs. In the noninvasive tear film breakup test, a grid is projected onto the ocular surface and the time it takes for distortions to form in the grid is determined. The time to the initial distortions is considered the tear film breakup time. A normal grid (A) and a mild distortion (B, red arrow) are shown in a healthy canine patient.
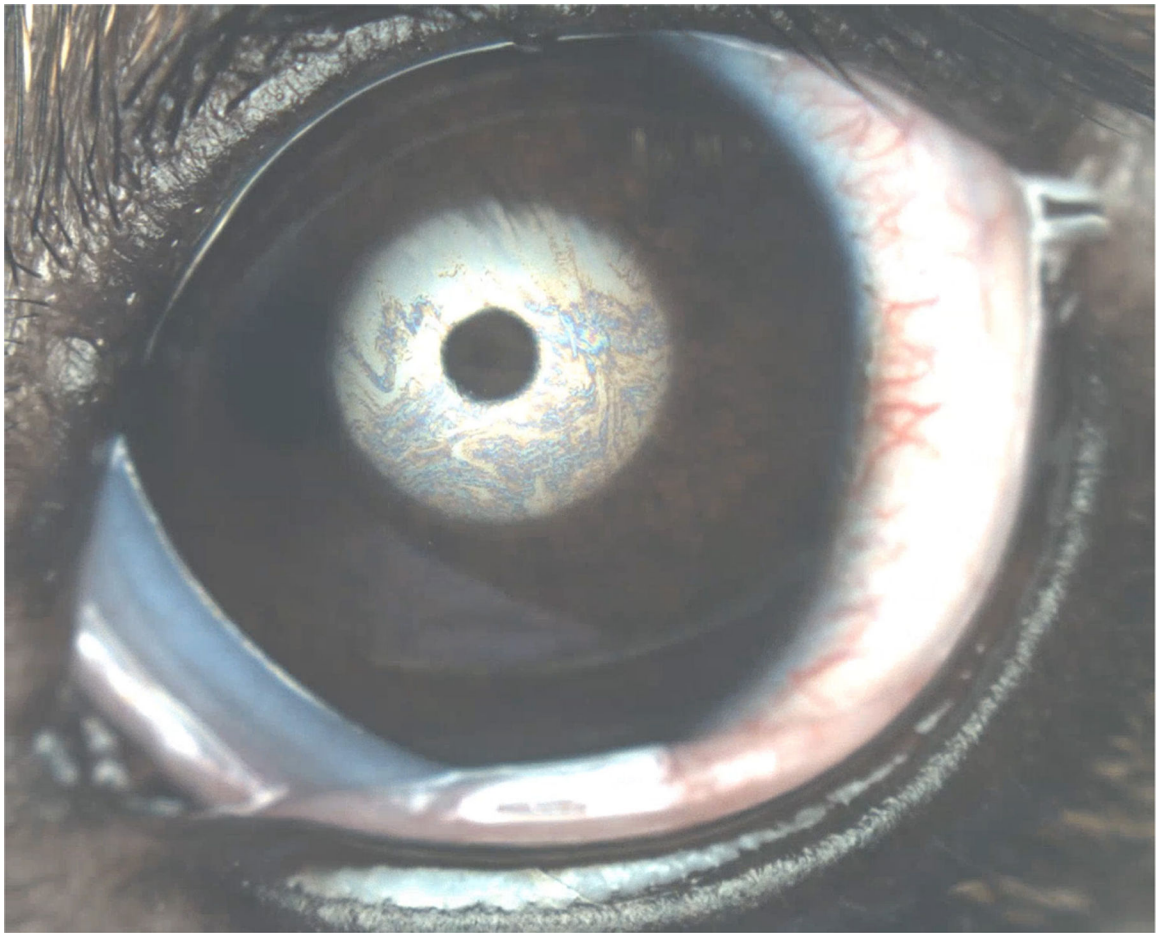
FIGURE 4.
Interferometry in a healthy dog. The interferometric pattern displayed in this normal canine patient corresponds with a grade 4 or 5 according to the scales utilized in canine patients.[44,49]
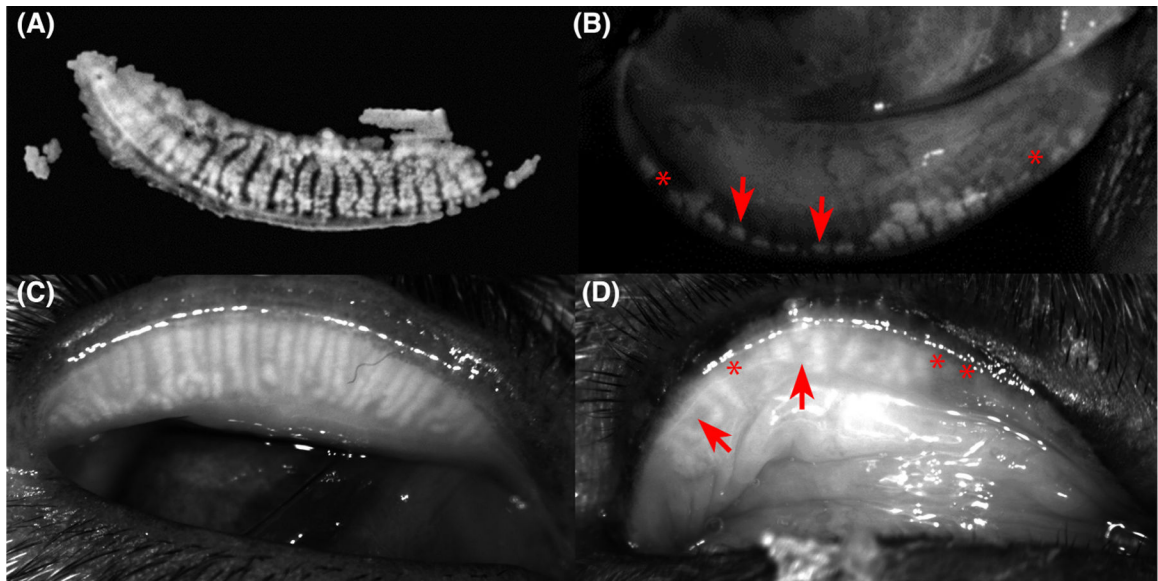
FIGURE 5.
Meibography in humans and dogs. Noncontact infrared meibography images from a clinically healthy human patient (A) and dog (C) showing rows of meibomian glands (white cigar-shaped structures) that appear to cover most of the interior aspect of the eyelid. Human (B) and canine (D) patients with meibomian gland dropout express blunted or absent meibomian glands along the interior aspect of the eyelid. Red asterisks identify regions of meibomian gland dropout and arrows highlight shortened meibomian glands.
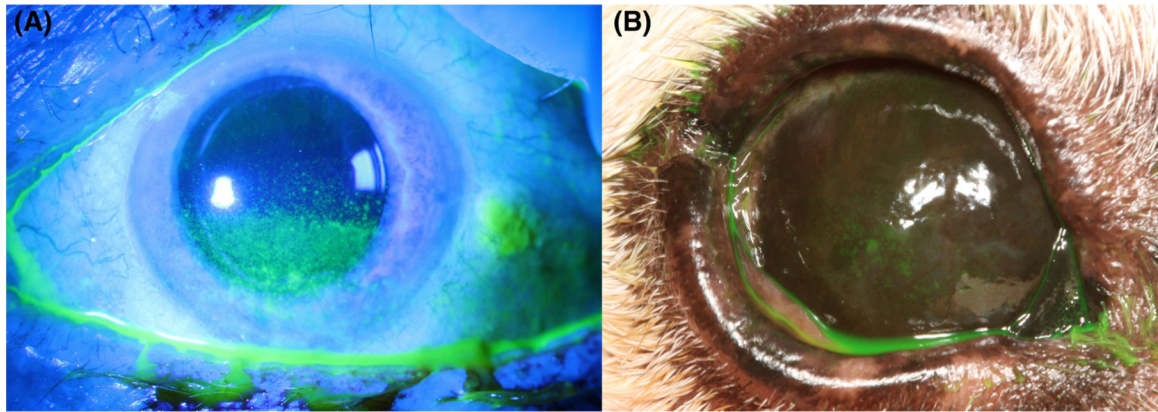
FIGURE 6.
Multifocal punctate fluorescein staining in humans and dogs. Punctate staining can be seen when there is damage to the ocular surface that does not lead to a complete epithelial defect, but rather multifocal epithelial cell loss. Multifocal punctate staining can be seen in the inferior aspect, but the superior aspect is relatively normal in these examples from human (A) and canine (B) patients.

TABLE 1

Comparison of diagnostic test values of healthy human and canine patients with patients with EDED

Diagnostic test	Healthy humans	Humans with EDED	Healthy dogs	Dogs with EDED
TFBUT	13.1 s[43]	3.7 s[43]	21 s[61]	<5 s[135]
NIBUT	24.2 s[136]	14.9 s[136]	20 s[137]	<5 s[70]
STT	27.5 mm/5 mins[43]	20.5 mm/5 mins[43]	22.8 mm/min[82]	22.7 mm/min[49]
Lipid layer thickness	100 nm[88]	83.9 nm[88]	30–80 nm[137]	15–30 nm[49]

Abbreviations: EDED, evaporative dry eye disease; NIBUT, noninvasive tear film breakup; STT, Schirmer tear test; TFBUT, tear film breakup time.