The Effect of Contact Lens Coefficient of Friction on the Development of Lid Wiper Epitheliopathy and Tear Film Matrix Metalloproteinase Levels

by
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ABSTRACT

Purpose:

Contact lens discomfort (CLD) is a significant factor in patient discontinuation. Factors suggested in CLD include inflammatory and mechanical factors. Coefficient of Friction (CoF) is a contact lens property negatively correlated with contact lens comfort. Lid Wiper Epitheliopathy (LWE), a clinical sign, may demonstrate the impact of CoF on CLD. Matrix metalloproteinases (MMPS) are zinc proteases that break down extracellular matrix and are markers of inflammation. Little is known about LWE development and MMPs levels in new contact lens fits. We investigated the development of LWE and tear film MMP concentration in new contact lens fits over a one-week period.

Methods:

Twenty subjects without LWE staining were fit with a high CoF contact lens in one eye and a low CoF contact lens in the contralateral eye based on microtribometry data from Roba et al (2011). Lens/eye assignment was randomized. Two 20 microliter drops of Lissamine green were instilled in the lower conjunctival cul-de-sac. Digital images were taken and LWE graded. Ten microliters of tears were collected at baseline (BL), 2 hours (2H), and 7 days (7D) post-contact lens fit. Samples were analyzed for MMP-9, MMP-10, and MMP-13. Non-parametric statistics were performed when appropriate.

Results:

A difference in LWE was observed for all eyelids ($P = .0004$). A significant change was observed in the upper eyelids ($P < .0001$) but not the lower eyelids ($P = .137$). A difference in LWE from BL to 2H ($P = .00006$) and BL to 7D ($P = .00004$) was observed, but not between 2H and 7D ($P = .437$). A difference in LWE was observed from BL to 2H and BL to 7D for upper eyelids for each lens (Acuvue Oasys: BL-2H $P = .003$, BL-7D $P = .002$; Air Optix Night and

Day: BL-2H $P = .005$, BL-7D $P = .005$). No difference was observed between the 2 eyelids at 2H or 7D post fit ($P = .495$ and $P = .968$). No changes in MMP-9, MMP-10 and MMP-13 were noted during the study period.

Conclusion:

LWE staining of the upper eyelid changed between BL and 1) 2H and 2) 7D post contact lens fit, but not between 2H and 7D. There was no difference in superior LWE staining between the lenses, suggesting that differing CoFs may not lead to different amounts of LWE. Contact lens wear in the early fitting period does not appear to alter tear film concentrations of MMP-9, MMP-10 or MMP-13.

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Chapter 1: Introduction

This thesis addresses two main goals. The first goal was to determine if the grade of Lid Wiper Epitheliopathy (LWE) development, over the course of one week after contact lens fitting, differs between a high and low coefficient of friction (CoF) contact lens. The second goal was to determine if the concentration of tear film MMP-9, MMP-10, and MMP-13 differs between the high and low CoF contact lens.

1.1 Contact Lens Comfort and Dropout

Contact lenses can improve many aspects of vision, such as expanding field of view, minimizing retinal image size differences in anisometropic patients, and reducing peripheral distortions. Because of these advantages, the demand for contact lenses remains high, with an estimated 140 million contact lens wearers worldwide driving a $9 billion dollar global contact lens market that is growing approximately 5 to 6% per year.(Nichols et al. 2013; "Contact Lens Spectrum - Contact Lenses 2019" n.d.) While the contact lens market continues to display growth, loss of patients to discontinuation of contact lens use, referred to clinically as contact lens dropout, remains a significant issue with up to 23% of patients dropping out of contact lens wear within one year of initial fitting (Sulley et al. 2017, Dumbleton et al. 2013).

Subjective end of day discomfort and ocular dryness has been demonstrated as a key factor in contact lens discontinuation in previous studies (Sulley et al. 2017, Dumbleton et al. 2013, Richdale et al. 2007, Stapleton et al. 2017, Stahl et al. 2018). While dryness is often cited as the main reason for dropout, several signs of dry eye such as non-invasive tear break-up time (NIKBUT), tear meniscus height (TMH), and severity of blepharitis are often not predictive for contact lens dropout (Pucker et al. 2019). Since contact lenses can have such a profound effect on visual performance compared to spectacle wear, minimizing the potential for patient contact lens discontinuation is an important goal for eyecare practitioners. However, despite continuous

advances in contact lens design and materials, contact lens discomfort and the potential for future dropout can be difficult to predict with current contact lens clinical metrics and the underlying etiology of contact lens discomfort in patients with a healthy ocular surface remains poorly understood (Stahl et al. 2018). Thus, there is a need to identify clinical signs that could predict contact lens discomfort and the potential for dropout in order to streamline the contact lens fitting process.

1.2 Contact Lens Properties and Comfort

Physical characteristics of soft contact lenses have been proposed as affecting contact lens comfort, including corneal coverage, contact lens centration, lens movement, lens diameter, base curve, edge design, lens material, modulus, water content, and oxygen transmissibility. It is useful to consider these factors in two general categories: 1) factors of lens design and 2) factors intrinsic to the lens material, or bulk factors. Factors of lens design include overall lens diameter and corneal coverage, contact lens base curvature, contact lens centration, contact lens movement, and edge design. Information on contact lens designs is not readily available to the public as this information is considered trade secrets by contact lens companies. Although lens designs are not public, it is commonly known that contact lens manufacturers design lens parameters to improve comfort. The combination of overall lens diameter and base curve affects contact lens centration, movement and corneal coverage. Modern contact lens designs rarely offer more than one lens diameter option and limit base curve to 1 or 2 choices for mass produced planned replacement and daily disposable contact lenses.

The decision to limit available contact lens parameters by manufacturers is most likely due to the limited effect contact lens coverage, centration and movement have on contact lens comfort with modern contact lens designs. Contact lens coverage and centration does not appear

to have a significant effect on comfort for clinically acceptable fits with modern contact lenses (i.e. contact lenses that provide paralimbal corneal coverage). While a contact lens with excessive movement may induce ocular irritation, multiple studies have failed to find a link between lens movement and comfort, while one study noted that less movement may improve comfort (Stapleton et al. 2017). Contact lens edge design does appear to affect comfort, with thinner edge profiles providing better comfort compared to round, blunt edges; however, while round, blunt contact lens edges were common with lathe cut contact lenses, cast-molded contact lenses provide thinner edge profiles. Combined, modern contact lenses have been design to avoid issues known to induce ocular discomfort.

Bulk factors, such as lens material, modulus, water content, and oxygen transmissibility have also been examined in relationship to contact lens comfort. Overall, bulk factors do not play a large role in comfort for modern contact lens designs. Most of the contemporary literature has examined whether silicone hydrogels contact lenses provide superior comfort over older hydrogel designs, with the belief that the increased oxygen permeability could change contact lens comfort. Guillon et al. (2013) examined the published literature and concluded that studies examining the topic suffered from serious methodological flaws; however, Guillon concluded that silicone hydrogel lenses did not display superior comfort to hydrogel lenses. Additionally, water content and lens modulus have not been shown to affect contact lens comfort with silicone hydrogel lenses.

1.3 Coefficient of Friction

While soft contact lenses are fit primarily based on the relationship of the contact lens base curve and overall diameter to the cornea, future discomfort and dropout is difficult to predict based on these parameters alone. Although loose-fitting lenses (greater than 1 mm post-

blink movement) and smaller lenses providing inadequate corneal coverage have been shown to decrease soft contact lens success rates, when a clinically acceptable fit is achieved based on these parameters, it may be difficult to predict the potential for future dropout (Sulley et al. 2017, Stapleton et al. 2017).

Because of the inability to predict successful contact lens comfort based on lens design parameters and bulk factors such as the lens material, contact lens surface properties have drawn interest for their effect on comfort. Coefficient of friction (CoF), a material property describing the surface lubricity of contact lenses, has recently been of interest in relation to contact lens comfort. In a retrospective review, Brennan et al. (2009) examined the relationship between contact lens comfort, reported using visual analogue scales, to the reported coefficient of friction from peer reviewed literature for commercially available contact lenses. Brennen reported a strong negative correlation between end of day contact lens comfort and lens modulus ($r = –0.75$, $p < 0.05$) and the CoF of the lens material ($r = 0.90$, $p < 0.01$, data from Ross 2005), but not with oxygen transmissibility (Dk/t) ($r = –0.32$, NS). Kern et al. (2013) reported a similar strong inverse correlation between CoF and contact lens discomfort.

The measurement of the coefficient of friction for contact lenses is an *in vitro* process. Coefficient of friction is measured using a microtribometer that slides a sensor across the surface of a contact lens with a set force and number of stroke cycles while using a fluid lubrication layer to mimic the tear film (Pult 2015). While studies have attempted to imitate the force and lubrication composition during a blink while measuring the CoF of commercially available soft contact lenses, CoF does not fully describe an individual's lid interaction with a specific contact lens. While CoF is a useful laboratory metric, CoF is not measureable in a clinical setting. Thus,

a clinically observable corollary of CoF would be useful as a predictor of contact lens discomfort.

Roba et al. (2011) reported the CoF of several commercially available contact lenses at 0, 50, and 100 cycles given a sliding speed of 0.1 mm/s, shown in table 1. Of particular interest were Acuvue Oasys, which had a CoF of 0.018 at 100 cycles, and Air Optix Night & Day Aqua, which had a CoF of 0.166 at 100 cycles. Because both lenses are commercially available, widely prescribed, and differ in their CoF approximately ten-fold, they were of particular interest for evaluating differences between high and low CoF lenses. A comparison of other parameters between these two lenses is shown in table 2.

Because the CoF of a material varies based on test conditions such as the normal force, sliding speed, and lubrication viscosity applied, it is not feasible to compare measures of CoF for contact lenses between different studies where the above variables are not held constant (Dunn et al. 2013, Roba et al. 2011, Sterner et al. 2016). The choice of lubricant used during testing and the addition of wetting agents can also decrease CoF, as shown in table 1. The Acuvue® Oasys™ contact lens used an internal wetting agent marketed as Hydraclear® Plus Technology, which is high molecular weight polyvinylpyrrolidone (PVP) incorporated into the matrix of the contact lens (Johnson & Johnson Vision 2017, Contact Lens Spectrum 2009). The Air Optix® Night & Day® Aqua contact lens utilizes 1% copolymer 845 wetting agent, a combination of polyethylene glycol (PEG) and PVP added to the lens packaging solution. This wetting agent releases during contact lens wear to improve contact lens comfort.

Contact Lens	CoF 0 cycles	CoF 50 cycles	CoF 100 cycles
Acuvue® Oasys™	0.016 ± 0.014	0.024 ± 0.018	0.018 ± 0.015
Clariti™	0.034 ± 0.014	0.023 ± 0.005	0.022 ± 0.009
Acuvue® Advance™ Plus$^{\alpha}$	0.022 ± 0.005	0.021 ± 0.001	0.024 ± 0.004
Acuvue® Advance™$^{\alpha}$	0.029 ± 0.002	0.028 ± 0.002	0.042 ± 0.010
Biofinity®	0.033 ± 0.009	0.057 ± 0.004	0.050 ± 0.002
Acuvue®	0.093 ± 0.023	0.069 ± 0.010	0.090 ± 0.10
Air Optix® Night & Day® Aqua$^{\beta}$	0.108 ± 0.051	0.110 ± 0.093	0.166 ± 0.058
Air Optix®Aqua$^{\gamma}$	0.178 ± 0.061	0.187 ± 0.045	0.222 ± 0.073
Air Optix®$^{\gamma}$	0.343 ± 0.038	0.361 ± 0.048	0.292 ± 0.031
Night & Day®$^{\beta}$	0.391 ± 0.081	0.394 ± 0.040	0.382 ±0.27
Pure Vision®	0.415 ± 0.037	0.443 ± 0.041	0.423 ± 0.032
Optima™ 38	0.203 ± 0.045	0.587 ± 0.010	0.551 ± 0.017

Table 1: Coefficient of friction (CoF) data for commercially available soft contact lenses for a sliding speed of 0.1 mm/s. Symbols α, β, and γ notes contact lenses made from the same material but produced with and without the addition of surface wetting agents. Note that the addition of surface wetting agents reduced the measured coefficient of friction for each lens (Modified from Roba et al. (2011)).

Because the CoF of a material varies based on test conditions such as the normal force, sliding speed, and lubrication viscosity applied, it is not feasible to compare measures of CoF for contact lenses between different studies where the above variables are not held constant (Dunn et al. 2013, Roba et al. 2011, Sterner et al. 2016). The choice of lubricant used during testing and the addition of wetting agents can also decrease CoF, as shown in table 1. The Acuvue® Oasys™ contact lens used an internal wetting agent marketed as Hydraclear® Plus Technology, which is high molecular weight polyvinylpyrrolidone (PVP) incorporated into the matrix of the

contact lens (Johnson & Johnson Vision 2017, Contact Lens Spectrum 2009). The Air Optix® Night & Day® Aqua contact lens utilizes 1% copolymer 845 wetting agent, a combination of polyethylene glycol (PEG) and PVP added to the lens packaging solution. This wetting agent releases during contact lens wear to improve contact lens comfort.

	Material	Water Content	Base Curve	Center Thickness @ -3.00D	Wetting Agent
Acuvue® Oasys™	Senofilcon A	38%	8.4, 8.8	0.07 mm	PVP
Air Optix® Night & Day® Aqua	Lotrafilcon A	24%	8.4, 8.6	0.08 mm	PEG+PVP

Table 2: Comparison of parameters for Acuvue Oasys and Air Optix Night & Day Aqua

1.3 Lid Wiper Epitheliopathy

1.3.1 Lid Wiper Epithelium and Defining LWE

The margin of the eyelid is a region where there is a transition from keratinized epithelium to lid wiper epithelium. Lid wiper epithelium spreads tears during blinking and is located just posterior to the lid margin between the mucocutaneous junction (Marx line) and the subtarsal fold on both the superior and inferior eyelid. The lid wiper runs horizontally from the lateral canthus to the medial punctum. It is thought that the lid wiper region is the only area in close apposition to the globe during blinking, as it is histologically different from the rest of the palpebral conjunctiva, being composed of non-keratinized stratified squamous epithelium (Ehlers et al. 1965). This type of tissue is also found in other areas of the body that experience frequent mechanical wear, such as the cornea and the epithelial lining of the oral cavity, providing further evidence of the lid wiper's role during blinking (Gray et al. 2005). The lid wiper region is typically approximately 100 microns in width. Although identification of the anterior border of the lid wiper epithelium can typically be observed by staining Marx line, lid wiper epithelium width can be difficult to define as the border of the posterior lid wiper epithelium and the

anterior portion of the subtarsal fold is poorly defined (Knop et al. 2011). The sensitivity of the lid wiper region was found to be greater than the lid margin and the palpebral conjunctiva, but less than the cornea, using the Cochet-Bonnet aesthesiometer (Navascues-Cornago et al. 2015). For this reason, it is reasonable to assume that damage to this region could lead to subjective complaints of discomfort, grittiness, or dryness.

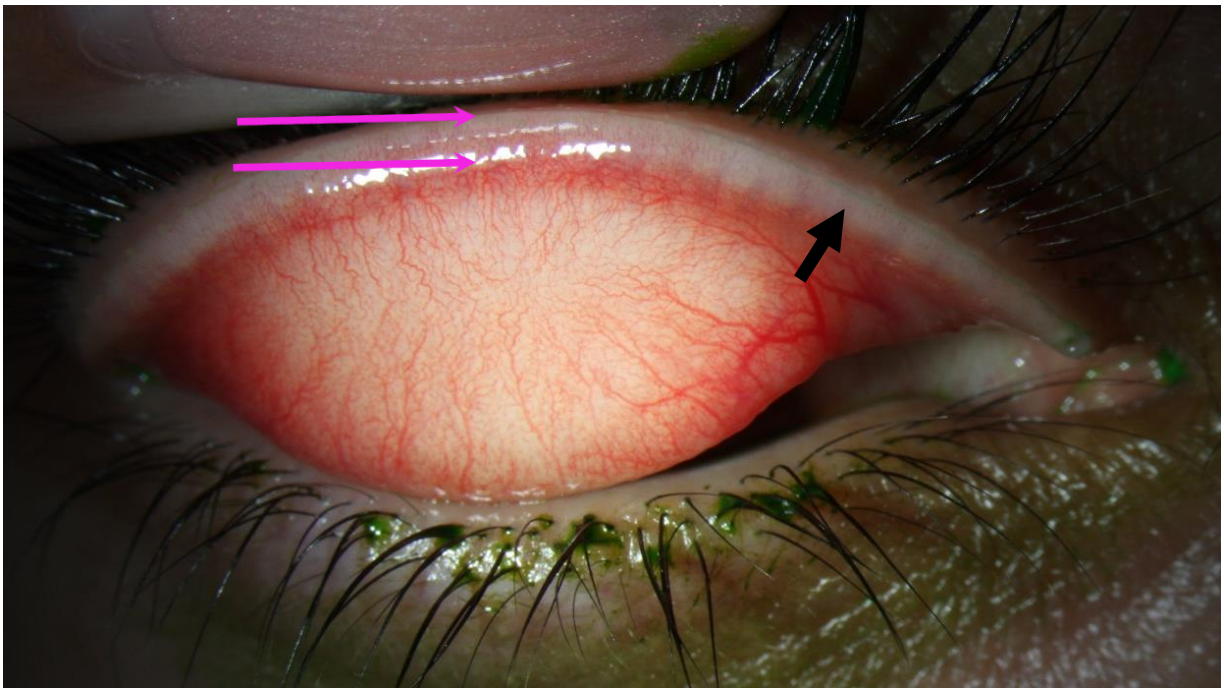

Figure 1: Photo of the lid wiper region. The anterior and poster borders of the region are demonstrated (purple arrows). The mucocutanous junction, i.e. Marx line, is observed using Lissamine green (black arrow). Average lid wiper region is approximately 100 microns in width.

Lid wiper epitheliopathy (LWE) is defined by damage to epithelial cells in the lid wiper region and was first described by Korb in 2002. It can be a sign of underlying ocular surface disease and is thought to develop due to inadequate ocular surface lubrication (Efron et al. 2016). Lid wiper epitheliopathy can be visualized using lissamine green, sodium fluorescein, rose bengal, or a combination of two or more dyes to stain the lid wiper region. However, recent

studies have used lissamine green or a combination of lissamine green and sodium fluorescein due to stinging upon instillation of rose bengal (Efron et al. 2016).

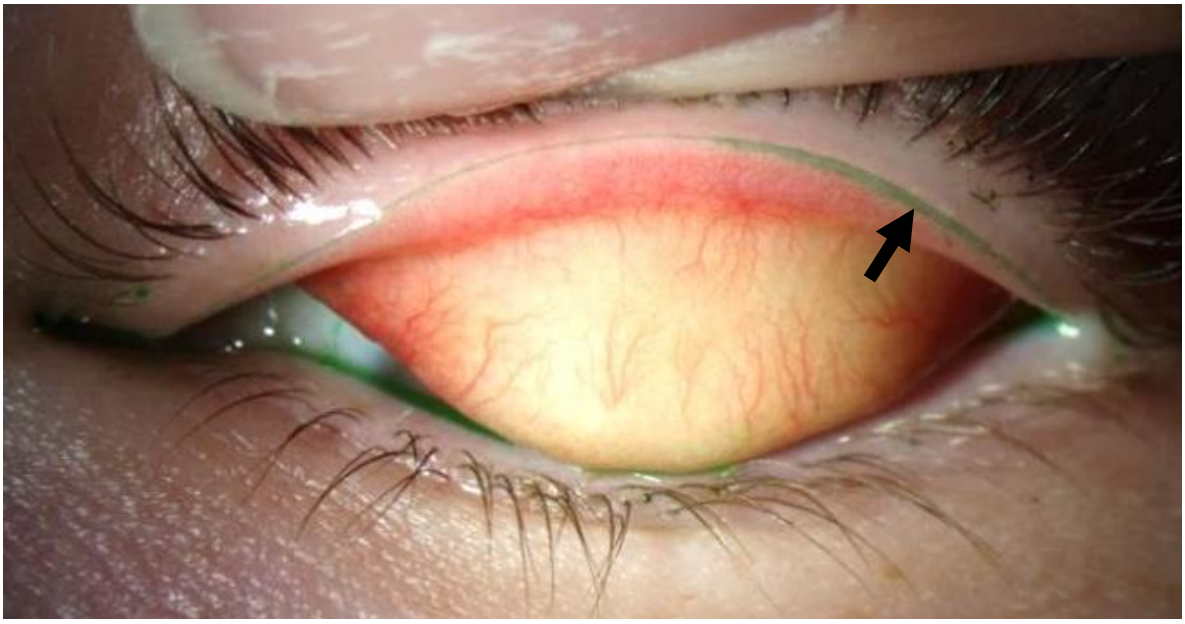

Figure 2: Photo of LWE stained with Lissamine green (black arrow).

1.3.2 Grading LWE

Lid wiper epitheliopathy is graded by the horizontal width of staining in millimeters and the average sagittal height of staining based on the percentage of vertical lid wiper epithelium involvement. These grades are then averaged for a final clinical grade of LWE.

LWE Grade	Description	Height (%)	Width (mm)	Final LWE Grade: $(\frac{H+W}{2})$
0	No LWE	<25	<2	<0.25
1	Mild LWE	25-50	2-4	0.25-1.00
2	Moderate LWE	50-75	5-9	1.25-2.00
3	Severe LWE	>75	>10	2.25-3.00

Table 3: LWE clinical grading scale developed by Korb et al. (2002). The final LWE score for a patient is determined by taking the average of the LWE Height and Width scores and assigning a 0-3 score based on the criteria outlined in the right-hand column.

While the grading scale proposed by Korb et al. is adequate for clinical grading of LWE, there are disadvantages to the approach. The 2 dimensions of LWE staining grades in the Korb approach are graded using different scales, horizontal physical length and vertical percentage of LWE staining observed. This can be challenging to perform while examining a patient during lid eversion. An additional limitation is the averaging of the width and height scores to calculate a final LWE score limits the ability to detect changes in LWE staining over time. To better standardize subjective LWE grading uniformly across subjects in clinical research, grading photographic images in controlled sessions with trained examiners, rather than at the time of the exam, is preferred. True LWE staining extends beyond and should be differentiated from the normal staining of the mucocutaneous junction. It has been noted in previous studies that touching the lid wiper region during lid eversion can induce staining and repeated lid eversion can increase LWE scores. Therefore, care should be taken not to touch the lid wiper epithelium during lid eversion to more accurately assess LWE (Efron et al. 2016, Shaw et al. 2019).

1.3.3 LWE and Dry Eye

LWE has been previously associated with dry eye disease and is thought to be caused by increased friction during blinking due to insufficient ocular surface lubrication (Korb et al. 2002, Korb et al. 2005, Korb et al. 2010, Best et al. 2013). In 2005, Korb et al. divided 100 age-matched subjects who had not worn contact lenses in the past six months into symptomatic vs. asymptomatic groups based on the SPEED questionnaire and evaluated the subjects for LWE. This study found that LWE was present six times more in the symptomatic group versus the asymptomatic group. Moderate to severe staining (Grade 2-3) was eight times more common in the symptomatic group versus the asymptomatic group. In 2010, Korb et al. conducted a similar study on subjects that had been diagnosed with dry eye. Fifty subjects were included in both the

dry eye and the non-dry eye group. The study concluded that LWE was much more common in the dry eye group (88%) versus the non-dry eye group (16%). Additionally, moderate to severe staining was noted much more often in the dry eye group (46% G2, 20% G3) versus the non-dry eye group (2% G2, 0% G3).

The presence of LWE in dry eye disease has been confirmed by other investigators. Yeniad et al. assessed LWE in a dry eye and a control group determined by a questionnaire, Schirmer I, NaFl TBUT, and NaFl corneal staining (2010). LWE was more prevalent in the dry eye group compared to the control group; however, it did not correlate with the fluorescein TBUT or Schirmer I tests. Yeniad concluded that LWE can be used to aid in the diagnosis of dry eye in conjunction with other tests. Sonomura et al. examined 76 dry eye patients divided into dry eye versus non-dry eye groups based on the Schirmer I test (2014). Group A consisted of subjects with < or = 5 mm wetting, while group B consisted of > or = 6 mm wetting. Group A was shown to have significantly higher grades of LWE compared to group B on both the upper and lower eyelids. Liu et al. examined LWE, conjunctival staining, and conjunctival impression cytology in 350 subjects with dry eye disease (2020). This study found that LWE was strongly correlated with average non-invasive keratograph break-up time (NIKBUT) and ocular surface staining. This indicated that abnormal friction factors due to disrupted ocular surface lubrication seemed to affect the presence and severity of LWE staining. Wang et al. (2018) compared the efficacy of LWE versus corneal staining in predicting dry eye disease. This study found that LWE was more accurate in diagnosing dry eye disease compared to corneal staining, and concluded that LWE staining should be routinely performed for dry eye examinations.

1.3.4 Superior vs. Inferior LWE

While some have suggested that inferior LWE is an equal indicator of dry eye disease compared to superior LWE, differences exist in the blinking motion between the upper and lower lids that could lead to different staining mechanisms. While the upper lid moves from 10-12 mm vertically during blinking, the lower lid moves primarily horizontally (Sun et al. 1997). For this reason, it is possible that differences could exist between horizontal and vertical staining patterns between the upper and lower lid that could skew the average grade of LWE. Additionally, the tear meniscus is adjacent to the lower lid wiper region, and the hyperosmolarity of the tear meniscus may play a role in the development of inferior LWE staining (McMonnies et al. 2015, Golebiowski et al. 2012).

1.3.5 LWE and Contact Lens Wear

Several studies have examined the relationship of LWE to symptomatic habitual contact lens wear in presenting populations. Korb et al. (2002) conducted a study of 105 soft contact lens wearers, divided into symptomatic and asymptomatic groups based on subjective reporting of symptoms. Eighty percent of the symptomatic group had LWE while 13% of the asymptomatic group had LWE. This study led Korb et al. to propose that LWE can explain contact lens discomfort in patients with no other observable signs.

In 2008, Berry et al. separated 50 hydrogel contact lens wearers into a symptomatic and an asymptomatic group based on the Contact Lens Dry Eye Questionnaire (CLDEQ). This study found that upper LWE scores were higher in the symptomatic group versus the asymptomatic group, but findings were not significant for lower LWE scores. Pult et al. conducted a similar study classifying subjects as symptomatic or asymptomatic based on the CLDEQ (2008). LWE scores were found to be significantly higher in the symptomatic group versus the asymptomatic group. Another study by Pult et al. in 2009 examined LWE in new contact lens fits. Subjects

were classified as symptomatic or asymptomatic based on the Ocular Surface Disease Index (OSDI). LWE significantly increased after contact lens fitting over the study period, but it was not found to sufficiently predict contact lens induced dry eye, where other factors such as NITBUT and OSDI scores had more predictive ability. Siddireddy et al. (2018) evaluated 30 habitual daily disposable soft contact lens wearers for LWE. Subjects were divided into symptomatic and asymptomatic groups based on the CLDEQ questionnaire. LWE staining of the superior lid was significantly correlated with comfort scores in both the symptomatic and asymptomatic groups.

Several studies have found that while contact lens wear increases LWE, there was no difference between asymptomatic and symptomatic wearers. Best et al. (2013) used the OSDI to determine subject symptoms and found that upper LWE increased significantly after 6 months of soft lens wear; however, LWE grades did not significantly differ between those that dropped out of lens wear and those that did not discontinue lens wear. Read et al. (2014) assessed LWE in 10 non-contact lens wearers, 10 symptomatic wearers, and 10 asymptomatic wearers based on 0-100 visual analogue comfort scores. While LWE was significantly increased in contact lens wearers versus non-contact lens wearers, there was no difference in LWE grades between the symptomatic and asymptomatic groups. Schulze et al. assessed LWE in 253 habitual soft contact lens wearers (2016). LWE staining was found to be present in 85% of subjects, but it was not found to be associated with contact lens comfort assessed with the Contact Lens User Experience (CLUE) questionnaire. No differences in LWE staining with habitual lens wear was observed by race, gender or age; however, differences in LWE staining were observed for different lens materials. Stahl et al. studied the relationship between subjective comfort and upper LWE, tear stability and production, and tear osmolarity with two different types of soft contact lenses

(2017). While LWE increased with contact lens wear, it was not affected by lens type, and not associated with comfort scores. They proposed that a wider range of comfort scores would be helpful in further studying the role LWE has in contact lens discomfort.

1.3.6 LWE and Inflammation

Although LWE is thought to develop secondary to inadequate ocular surface lubrication, it has been suggested that LWE is associated with sub-clinical inflammation of the ocular surface (Efron 2016). Alzahrani et al (2016) investigated Langerhans cell density in 46 habitual contact lens wearers. Subjects in the study were divided into normal and contact lens-induced dry eye (CLIDE) groups. The CLIDE group was found to have greater Langerhans cell density in the lid wiper region using confocal microscopy, indicating inflammatory involvement in LWE. Korb et al. (2002) anecdotally reported increased lid wiper hyperemia in patients with LWE. However, another study found no link between lid wiper hyperemia and LWE (Read et al. 2014).

1.4 Matrix Metalloproteinases (MMPs)

1.4.1 Role of MMPs on the Ocular Surface

While there is some evidence suggesting that LWE is related to ocular surface inflammation, it is currently unknown if tear film inflammatory mediators contribute to the development of LWE. Studying the association between LWE and tear film inflammatory markers could provide insight into the underlying etiology of LWE.

Matrix metalloproteinases (MMPs) are a family of zinc proteases that function in breaking down extracellular matrix. They are regulators of inflammation, tissue remodeling, and pathogenic processes. MMPs are produced by keratocytes and speed up the extracellular matrix destructive process to remodel the stroma. It is thought that MMPs may also be produced by corneal epithelial cells in response to physiological

stress, such as increased tear osmolarity (Pflugfelder et al. 2017). Targets of MMP-9 include occludin, a tight junction protein, and galectin-3, a component of extracellular matrix (Pflugfelder et al. 2017). Increased concentration of tear film MMP-9 has previously been observed in tears and corneal tissue in dry eye disease, keratoconus, keratoconjunctivitis, and corneal wound healing (Shen et al. 2015, Jamerson et al. 2020, Leonardi et al. 2003, Mulholland et al. 2005, Schargus et al. 2015, Shetty et al. 2015, Fu et al. 2020).

Matrix metalloproteinase-10, or MMP-10, is referred to as stromelysin and also functions in the breakdown of extracellular matrix. It has been shown to be increased in the tear film with scleral lens wear (Walker et al. 2020). Matrix metalloproteinase-13 is also referred to as collagenase 3, and is involved in the breakdown of epithelial basement membrane. It has been associated with corneal neovascularization and fibrosis (Wolf et al. 2019). Little is known about the role of MMP-10 and MMP-13 on the ocular surface during the early contact lens fitting period.

1.4.2 MMPs and Dry Eye Disease

Previous studies have found that MMP-9 is an accurate clinical marker of dry eye disease. Messmer et al. (2016) measured the presence of MMP-9 in tears using the InflammaDry test (Rapid Pathogen Screening, Inc, Sarasota, FL) in healthy subjects and those with dry eyes. A positive InflammaDry test correlated with other signs of dry eye disease such as OSDI scores, TBUT of less than 5 seconds, Schirmer test results, number of capped Meibomian glands, and conjunctival and corneal staining. They concluded that a positive InflammaDry test correlated well with other well-accepted diagnostic criteria for dry eye disease. Another study compared tear film MMP-9 concentration between 46

subjects with dry eye disease based on OSDI scores greater than 20 with 18 healthy controls. Tear film MMP-9 activity was increased in the dry eye disease group and corresponded to the severity of ocular surface disease (Chotikavanich et al. 2009). Additionally, tear film MMP-9 concentration has also been shown to be elevated in ocular surface inflammatory conditions associated with dry eye such as ocular rosacea and blepharitis (Afonso et al. 1999, Acera et al. 2008). While MMPs have been associated with ocular surface inflammation and the use of contact lenses may be inherently inflammatory to the ocular surface, it is unknown if MMPs play a role in the development of LWE in contact lens wearers (Efron 2017).

1.4.3 Effect of Topical Medications on Tear Film MMPs

As tear film MMPs have been associated with ocular surface inflammation, the use of anti-inflammatory topical medications to decrease MMPs levels has been of interest. Pinto-Fraga et al. (2018) studied the effect of 0.1% fluorometholone ophthalmic solution (FML) on tear film inflammatory markers in subjects with dry eye disease. This group found that the use of 4 drops of FML daily for 22 days significantly decreased MMP-9. Sambursky et al. (2017) found that subjects with a positive InflammaDry test were more likely to have a reduction in dry eye disease symptoms of at least 50% compared to subjects with a negative InflammaDry test after being treated with topical 0.05% cyclosporine. These studies show promise for treatment options to reduce tear film MMPs and decrease ocular surface disease symptoms; however, concomitant use of ophthalmic steroids with contact lens wear is contraindicated and may limit the utility of such treatments for chronic management of contact lens-induced LWE.

1.4.4 MMPs and Contact Lens Wear

Several studies have assessed the effects of contact lens wear on tear film MMP concentration; however, this literature has focused more on the use of rigid contact lenses rather than soft contact lenses. Alghamdi et al. (2020) conducted a study in which subjects were grouped into healthy non-contact lens wearers, previous soft contact lens wearers that had dropped out of lens wear for six months, and habitual soft contact lens wearers of short (2 years), moderate (5 years) or long (10 years) duration. MMP-9 tear film concentration and activity was significantly higher in contact lens wearers with short wear experience compared to non-wearers (23.1 ± 17.9 ng/ml and 4.1 ± 4.1 ng/ml) and subjects with moderate wear experience. This study concluded that the early years of contact lens wear increase expression of MMP-9 compared to its inhibitor TIMP, indicating increased MMP-9 activity. Carracedo et al. (2016) studied the effects of short-term scleral lens wear on tear film MMP-9 in patients with keratoconus. After 6-9 hours of lens wear, there was a significant rise of tear film concentrations of MMP-9 and lower tear osmolarity. They concluded that this may have been due to tear film stagnation under the scleral lens. Walker et al. (2020) evaluated the presence of tear film inflammatory markers present in the fluid reservoir underneath scleral lenses after eight hours and four days of lens wear. The study found that MMP-9 concentration was significantly increased from baseline (15.2 ng/ml) to eight hours of wear (62.7 ng/ml). MMP-10 concentration was greater in fluid reservoir tears compared to basal ocular surface tears at both time points. Gonzales-Perez et al. (2012) studied the concentration of tear film inflammatory mediators in CRT wearers and contact lens wearers 12 months after initial fitting. They found that MMP-9 only significantly increased in CRT wearers and was related to the amount of myopia corrected and the amount of corneal staining.

1.5 Significance

LWE can be quickly and easily assessed by instilling lissamine green dye into the lower conjunctival sac and then everting the upper eyelid. If LWE is found to be predictive of contact lens discomfort and dropout, LWE staining could easily be incorporated into standard contact lens fit and follow-up examinations. If the magnitude of LWE development is related to the CoF of a contact lens, LWE would have the potential to improve the efficiency of the contact lens fitting process by giving eye care practitioners a tool to predict which patients will experience contact lens discomfort early in the fitting process. Previous studies correlating LWE with contact lens wear and dry eye disease have been primarily cross-sectional and have not controlled for the material properties, solution use, or disposal schedule of the contact lens. Previous studies relating LWE to symptomatic contact lens wear have focused on subjective comfort scores at the beginning of the study and have not focused on changes in subjective comfort over time. While previous studies have determined the prevalence and grade of LWE present in habitual contact lens wearers and non-contact lens patients, it is currently unknown how quickly LWE may develop in patients after contact lens fitting. Development of LWE in the post-contact lens fitting period may allow clinicians to predict the potential for contact lens discomfort and future dropout.

While tear film MMPs have been related to dry eye disease, ocular surface inflammation, and corneal wound healing, it is unknown if they are affected by the CoF of contact lenses or are related to the development of LWE. If tear film MMP concentration is associated with CoF, it could provide insight for the underlying etiology of contact lens discomfort. Furthermore, if tear film MMP concentration is associated with LWE development, it could provide further evidence of an inflammatory etiology for contact lens wear.

The InflammaDry test is used in clinical settings to identify the presence of MMP-9 in ocular surface tears, where a concentration of MMP-9 above 40 ng/ml considered a positive finding (Lanza et al. 2016). If MMP-9 is found to significantly increase in contact lens wearers during the study period, InflammaDry testing could easily be incorporated into contact lens follow up visits in order to assess whether the contact lens is inducing ocular surface inflammation. Additionally, if tear film MMPs other than MMP-9 are found to increase during contact lens wear, this could potentially indicate the need for a clinical test to include different MMPs. The presence of a positive InflammaDry test has also been associated with significant ocular surface symptom improvement, indicating potential treatment aims for dryness and discomfort (Sambursky et al. 2017).

The specific aims of this thesis are as follows:

1. Determine if the grade of LWE development, over the course of one week, differs between a high and low CoF lens
2. Determine if the concentration of tear film MMP-9, -10, and -13 differs between a high and low CoF contact lens

Chapter 2: The Effect of Contact Lens Coefficient of Friction on Lid Wiper Epitheliopathy & tear film MMPs in the Early Contact Lens Fitting Period

2.1 Background

Contact lenses improve many aspects of vision, such as expanded field of view, minimizing retinal image size differences, and reducing peripheral distortions. Additionally, contact lens use has been associated with improved quality of life metrics. As such, minimizing the potential for contact lens discontinuation is an important goal for eye care practitioners. Although contact lens wear is extremely common, contact lens dropout remains a significant problem. Studies have estimated that up to 23% of patients stop contact lens wear within a year of fitting (Sulley et al. 2017, Dumbleton, et al. 2013). Discomfort and dryness has been demonstrated as a key factor in contact lens discontinuation (Sulley et al. 2017, Dumbleton et al. 2013). However, predicting future contact lens discomfort in healthy patients is difficult based on contact lens fit observation such as corneal coverage, lens centration and lens movement (Stapleton 2017).

One potential predictor of contact lens comfort that has been proposed is the Coefficient of Friction (CoF) of a lens material. CoF is a unitless value describing the ratio of the force of friction between two objects, with higher coefficient of friction scores indicating more frictional force (Sivamani et al. 2003). In contact lenses, coefficient of friction is an *in vitro* measurement that describes the surface lubricity of the lens surface and has been inversely correlated with patient reported outcomes of contact lens comfort, with increasing coefficient of friction leading to decreased contact lens comfort (Kern et al. 2013). CoF is a useful laboratory metric to provide some insight on the lubricity of a contact lens surface; however, a uniform testing procedure has not been adopted by the contact lens community and CoF values may vary depending on the experimental setup employed. Regardless of the test methodology, CoF is not directly

measureable in a clinical setting, thus an observable corollary clinical sign of the CoF of a contact lens could be useful as a predictor of subsequent contact lens discomfort.

One potential clinical finding that may act as an observable corollary clinical sign is Lid Wiper Epitheliopathy (LWE). The term Lid Wiper Epitheliopathy was initially reported by Korb et al. as damage to epithelial cells of the posterior eyelid in what he described as "the lid wiper region". The lid wiper region is a small area of non-keratonized epithelium posterior to the orifices of the Meibomian glands on the upper and lower eyelids. On the upper eyelid, the anterior border of the lid wiper region is defined by Marx's line, which marks the mucocutaneous junction of the eyelid, and the posterior border is defined by the subtarsal fold. Previous studies have found associations between the severity of LWE grading and dry eye symptoms in both contact lens wearers and non-contact lens wearers (Korb et al. 2002, Korb et al. 2005, Korb et al. 2010, Best et al. 2013, Pult et al. 2008).

While there is cross-sectional data pertaining to LWE, this data reflects established contact lens use. Little work has been done regarding the development of LWE in eyelids without LWE staining post initial contact lens fit. Given the relationship between coefficient of friction and contact lens comfort, a potentially interesting clinical question is whether contact lenses with different coefficient of friction values generate different amounts of LWE during contact lens fitting. Knowledge regarding the development of LWE in the post-contact lens fitting period may allow clinicians to predict the potential for contact lens discomfort and future dropout.

Another consideration is the role that matrix metalloproteinases (MMPs) may play in contact lens fitting. Matrix metalloproteinases are a family of zinc proteases that function in breaking down extracellular matrix. They are regulators of inflammation,

tissue remodeling, and pathogenic processes (Shen et al. 2015, Jamerson et al. 2020, Leonardi et al. 2003, Mulholland et al. 2005, Schargus et al. 2015, Shetty et al. 2015, Fu et al. 2020). MMPs are produced by keratocytes, epithelial cells, and neutrophils and speed up the extracellular matrix destructive process in order to remodel the corneal stroma (Pflugfelder et al. 2017).

Previous work has suggested the MMP concentration can change in the tear film in response to contact lens wear. Alghamdi et al. (2020) examined healthy non-contact lens wearers, previous soft contact lens wearers that had dropped out of lens wear for six months, and habitual soft extended wear contact lens wearers of short (2 years), moderate (5 years) or long (10 years) duration and found that MMP-9 tear concentration was significantly higher in contact lens wearers with short wear experience (23.1 ± 17.9 ng/ml) compared to non-wearers (4.1 ± 9.1 ng/ml). This study also found that the early years of contact lens wear increase expression of MMP-9 compared to its inhibitor TIMP. Gas permeable contact lens wear may also alter tear MMP levels. Gonzales-Perez et al (2012) studied the concentration of tear film inflammatory mediators in CRT wearers and contact lens wearers 12 months after initial fitting. They found that MMP-9 only significantly increased in CRT wearers and was related to the amount of myopia corrected and the amount of corneal staining.

The objective of this study was to examine the role contact lens coefficient of friction plays in the development of LWE in contact lens fitting and the potential of contact lenses with differing coefficients of friction to alter matrix metalloproteinases concentrations in the tear film. We hypothesize that high coefficient of friction contact

lenses may induce higher grades of LWE and increased levels of MMPs in the tear film, potentially leading to contact lens discomfort.

2.2 Methods

2.2.1 Inclusion and Exclusion Criteria

The study was conducted in concordance with the tenets of the Declaration of Helsinki and was registered on Clinicaltrials.gov. Patients were informed of the risks and benefits of the study and signed an informed consent document prior to study participation. Subject demographics, medical and ocular history, medications, and habitual contact lens information were collected. Eligible subjects were between 18 and 46 years of age, had a spherical equivalent refractive error between –0.75 and –6.50 D at the spectacle plane, had not worn contact lenses for a minimum of 7 days prior to the first study visit or were a contact lens neophyte. Subjects were excluded if they had significant ocular surface disease, LWE staining of the upper eyelid at the first study visit, symptoms of ocular irritation as evaluated by the OSDI questionnaire (defined as an OSDI score >23 at screening), a history of significant ocular inflammatory disease, a history of refractive or eyelid surgery, greater than 1.00 D of anisometropia or refractive cylinder, or had taken part in another contact lens or solution trial in the 7 days prior to the first study visit.

2.2.2 Study design

The study was a prospective contralateral eye comparison study. Subjects were examined over 3 study visits within a 1-week period: Visit 1.1 (baseline evaluation and contact lens fitting), Visit 1.2 (2 hour post lens fitting evaluation) and Visit 2 (1 week post contact lens fit evaluation). At baseline, NIKBUT, tear meniscus height (TMH), and LWE staining were collected. Prior to contact lens fitting, subjects were assessed with slit

lamp biomicroscopy to confirm acceptable ocular surface health and to exclude subjects with current LWE staining of the upper lid.

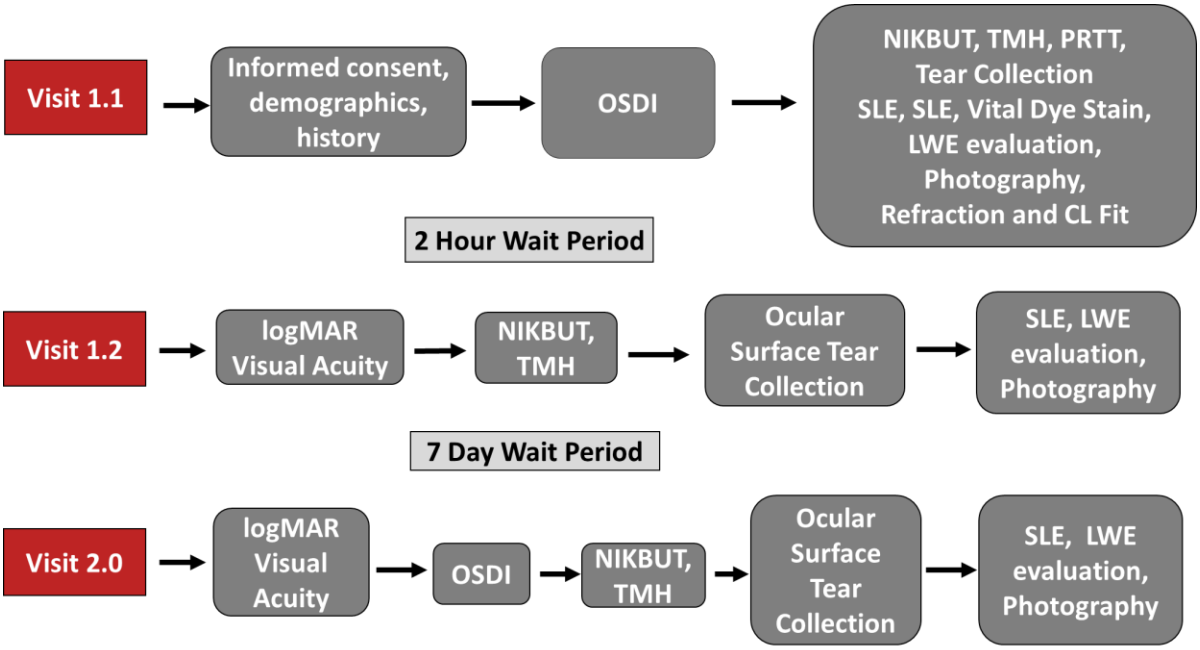

Figure 3: Sequence of events for the one-week study period.

2.2.3 Contact Lens Fitting

Contact lens selection per eye was determined based on the study randomization schedule. Subjects were fit with in one eye with the Acuvue Oasys with Hydraclear Plus (i.e. Acuvue Oasys; Johnson and Johnson Vision) and the other eye with Alcon Air Optix Night & Day Aqua (i.e. Air Optix Night & Day; Alcon Laboratories). The Acuvue Oasys is a planned replacement silicone hydrogel contact lens made of senofilcon A material (38% water) with base curves of 8.4 and 8.8mm, an overall diameter of 14.0mm, a center thickness of 0.07mm for a –3.00D power and polyvinylpyrrolidone wetting agent (PVP; aka Hydraclear Plus). The Air Optix Night & Day is a planned replacement silicone hydrogel contact lens made of lotrafilcon A material (24% water) with base curves of 8.4 and 8.6mm, an overall diameter of 13.8mm, a center thickness of 0.08mm for a –3.00D

power and 1% copolymer 845 wetting agent (polyethylene glycol and polyvinylpyrrolidone; a.k.a. Aqua). The CoF value of the Acuvue Oasys with Hydroclear Plus reported by Roba et al. (2011) was 0.018 after 100 test cycles and was selected as a representative low CoF contact lens surface. The CoF value for the Air Optix Night & Day reported by Roba et al. was 0.166 after 100 test cycles and was selected as a representative high CoF contact lens surface.

Initial base curve selection was determined per the respective contact lens fitting guides based on corneal curvature measurements obtained at the baseline visit (V1.1). Manifest refraction, using maximum plus to maximum visual acuity was performed and initial contact lens power was selected using the spherical equivalent of the manifest refraction. After initial contact lens selection, contact lens fit and vision were evaluated. Contact lenses were modified based upon improvement in visual acuity (3 or more letters Snellen acuity) with spherical over-refraction. Base curve modification was performed if the contact lens fit was inadequate. Upon successful fit and minimum BCVA greater than or equal to 20/30, the lenses were dispensed to the subject. Subjects were asked to wear the study contact lenses in the prescribed eyes every day for at least eight hours per day. Subjects were trained on contact lens cleaning and dispensed a 3% hydrogen peroxide contact lens disinfecting solution (ClearCare; Alcon laboratories) for disinfection and storage, with a minimum six hour neutralization.

2.2.4 Contact Lens Assessment

Contact lens centration was determined by measurement of contact lens corneal overlap from the corneal limbus to contact lens edge measured to the nearest 0.1 mm, using a Haag-Streit slit lamp reticule under 10X magnification. Horizontal contact lens decentration was calculated

as the difference between temporal and nasal overlap (i.e., temporal overlap – nasal overlap), with positive values representing temporal contact lens decentration and negative values representing nasal contact lens decentration. Vertical contact lens decentration was calculated as the difference between superior and inferior overlap (i.e., superior overlap – inferior overlap), with positive values representing superior contact lens decentration and negative values representing inferior contact lens decentration.

Contact lens movement in primary gaze was assessed using the Haag-Streit slit lamp reticule. Post-blink contact lens movement was evaluated by placing the zero point of the reticule at the visible edge of the contact lens and the patient was instructed to blink. Vertical displacement of the lens edge was recorded to the nearest 0.1mm. Contact lens lag in primary gaze was assessed by placing the zero point of the reticule at the visible edge of the contact lens and pulling the lid margin out. The amount the lens dropped was recorded to the nearest 0.1 mm.

2.2.5 Tear film quality

Tear film quality was assessed using phenol red thread testing, Non-invasive Tear Break Up Time (NITBUT) and inferior tear meniscus height (TMH). Phenol red thread testing was performed at baseline (V1.1) to evaluate basal tear secretion prior to contact lens fitting. To assess the stability of the tear film, 1st and Average Non-invasive Tear Break Up Time was measured using the Oculus Keratograph 5 (Oculus, Wetzlar, Germany). To reflect how the tear film/lid wiper epithelium interface may influence the development of LWE, NITBUT was performed prior to lens fitting at V1.1 and performed over the contact lens at visits 1.2 and 2.0. Tear break up time was performed three times for each eye at each visit and averaged prior to statistical analysis. Tear

meniscus height was measured temporally, centrally, and nasally in each eye at 4, 6 and 8 clock hours at all visits. TMH was measured prior to contact lens fitting at V1.1 and over the lens at V1.2 and V2.0. Ten microliters of basal ocular surface tears were collected at each study visit using microcapillary tubes and were stored in a –80 degree Celsius freezer until protein analysis. Tear samples were analyzed using the Luminex Multiplex Assay with according to manufacturer guidelines. Samples were run in duplicate and test volumes were diluted to be run with 10 ug of total protein according to manufacturer recommendations.

2.2.6 Subject Comfort Evaluation

The OSDI was administered to assess subjects for dry eye symptoms at V1.1 prior to contact lens fitting and V2.0, 1 week post-contact lens fitting. At the baseline visit, the subjects were instructed to complete the survey regarding symptoms during the previous week of no lens wear. At V2.0, subjects were instructed to complete the survey regarding symptoms during the study period of lens wear.

2.2.7 LWE Staining Protocol

LWE staining and lid photography were performed at V1.1, V1.2, and V2.0. Ophthalmic dyes were prepared by placing ophthalmic test strips in sterile saline (Purilens, Lifestyle Co, Freehold, NJ). A 1 mg sodium fluorescein test strip (BioGlo, Hub Pharmaceuticals, Plymouth MI) was placed in a 1.5 mL Eppendorf tube with 100 microliters sterile saline for one minute. Lissamine green was prepared placing a 1.5 mg lissamine green test strip (GreenGlo, Hub Pharmaceuticals, Plymouth MI) in a 1.5 mL Eppendorf tube with 150 microliters of sterile saline for one minute. A combined test solution for corneal and lid wiper staining was created by combining 100 microliters of

the sodium fluorescein solution and 100 microliters of the lissamine green solution. A 20-microliter drop was instilled into the lower conjunctival cul-de-sac of each eye using a micro-pipette followed by assessment of corneal staining with a Wratten filter. A second 20-microliter drop was instilled into both eyes five minutes after the first drop instillation. One minute after the second drop instillation, the superior and inferior eyelids were assessed for LWE staining with lissamine green and photographed using a digital camera.

2.2.8 LWE Grading

Lid wiper photographs were randomized and subjectively graded by two trained, masked observers according to the scale created by Korb in 2002. Images were graded by both observers independently from the same computer monitor to avoid differences in screen lighting and contrast. The height and width scores from each observer were averaged to provide one overall score for each eyelid.

2.2.9 Statistical analysis

Statistical analyses were performed in SPSS v26 (IBM) and GraphPad. When data were not significantly different from a normal distribution (non-invasive tear break up time, tear meniscus height), statistical analyses were conducted using paired t-tests and repeated-measures analyses of variance (RM-ANOVA), with adjusted post-hoc t-tests, when appropriate. For NITBUT and TMH, the RM-ANOVA included two repeated factors—lens type (Acuvue Oasys and Air Optix Night and Day) and time (baseline, 2 hours post-fitting and 7 days after lens fitting). For data that was not normally distributed (LWE staining), Friedman and Mann-Whitney non-parametric statistics were performed. MMP concentrations were adjusted by multiplying raw values by the dilution factor. Tear film MMP concentrations under the level of detection (LOD) were divided by $\sqrt{2}$

(Croghan et al. 2003). Outliers in MMP data sets were analyzed using the ROUT function in Graphpad Prism 8.4.1 and were removed prior to analysis.

2.3 Results

2.3.1 Subject Demographics

Twenty subjects were included in this study. The mean age for the study subjects was 23.95 ±2.31. Subjects were majority female, white, and non-Hispanic or Latino. The mean spherical equivalent refractive error for the right eye and left eye, respectively, were –2.19 ± 1.46 D and –1.94 ± 1.75 D.

n	20		
Age (mean ± SD)	23.95 ± 2.31years. Range 22 to 33 years		
Sex	Male: 5 (25%) Female: 15 (75%)		
Refraction OD (mean ± SD)	–2.19 ± 1.46 DS.		
Refraction OS (mean ± SD)	–1.94 ± 1.75 DS.		
Race			
White	14 (70%)	**African American**	1 (5%)
Asian	4 (20%)	**Other**	1 (5%)
Ethnicity			
Hispanic or Latino	14 (70%)	**Non-Hispanic or Latino**	6 (30%)

Table 4: Subject Demographics.

2.3.2 Contact Lens Fit

Horizontal and vertical contact lens decentration were evaluated. Both contact lenses displayed slight mean temporal decentration, with no significant difference in horizontal decentration (paired t-test; $P = .51$). A statistically significant, but clinically insignificant, difference in vertical contact lens decentration was observed ($P = 0.03$). No

differences in post-blink contact lens movement (P = .81) or contact lens lag (P = .86) were observed between the two lens designs.

	AO lateral decentration (mm)	**ND lateral decentration (mm)**	**AO vertical decentration (mm)**	**ND vertical decentration (mm)**
Mean ± SD	0.21 ±0.47	0.13 ± 0.28	0.23 ± 0.34	0.035 ± 0.11
P value	0.51		0.031	
	AO post blink movement (mm)	**ND post blink movement (mm)**	**AO primary gaze lag (mm)**	**ND primary gaze lag (mm)**
Mean ± SD	0.415 ± 0.12	0.425 ± 0.10	0.245 ± 0.08	0.25 ± 0.08
P value	0.80		0.86	

Table 5: Contact lens fitting characteristics for Acuvue Oasys (AO) and Air Optix Night & Day Aqua (ND).

2.3.3 Tear Film Quality

There was no effect for lens (repeated measures ANOVA; P = .23) or time (P = 0.17) and there were no differences in first NIKBUT for any time point. The average NIKBUT had no main effect for lens (P = .99) but there was a significant main effect for time (P = .008). There was a significant difference in average NIKBUT between baseline and 2 hours (P = .02), but no significant difference between baseline and one week (P = .91) or between two hours and one week (P = 1.00). There was no effect of lens on TMH (P = .68), but there was a significant main effect for time (P < .01). There was a significant decrease in TMH between baseline and two hours (P < .01) and baseline and one week (P < .01), but no significant difference between two hours and one week (P= 1.00). There was no significant change in OSDI scores over the study period (paired t-test, P = .19).

2.3.4 LWE

A significant increase in LWE was noted for all eyelids over the course of one week ($P < .01$). When selecting for just lower eyelids, a significant change in LWE was not noted over the course of the study period ($P = .14$). When selecting for all upper eyelids, regardless of contact lens type, a significant increase in LWE was noted between V1.1 and V1.2 ($P < .01$) and between V1.1 and V2.0 ($P < .01$), but not between V1.2 and V2.0 ($P = .44$). When selecting for upper eyelids by contact lens, eyes wearing Acuvue Oasys had a significant increase in LWE was noted between V1.1 and V1.2 ($P = .003$) and between V1.1 and V2.0 ($P < .01$), but not between V1.2 and V2.0 ($P = .50$). Eyes wearing Air Optix Night & Day Aqua had a significant increase in LWE between V1.1 and V1.2 ($P < .01$) and between V1.1 and V2.0 ($P < .01$), but not between V1.2 and V2.0 ($P = .97$). There was no significant difference in LWE between the two study contact lenses.

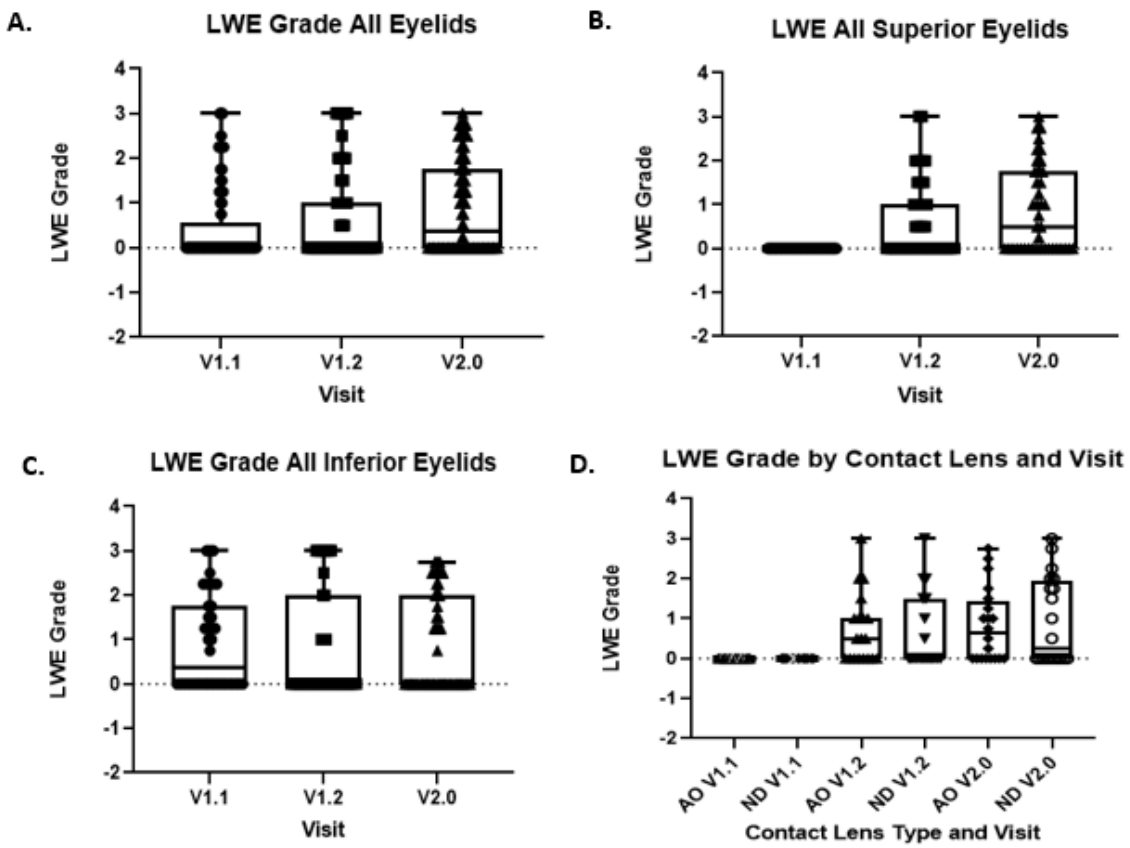

Figure 4: Boxplots of LWE grades for all eyelids (A), all superior eyelids (B), all inferior eyelids (C), and superior eyelids by contact lens (D).

2.3.5 MMPs

No significant changes in MMP-9 (repeated measures ANOVA; P = .18 AO, P = .14 ND), MMP-10 (P = .63 AO, P = .16), or MMP-13 (P = .25 AO, P = .91 ND) were noted for either contact lens over the study period. There were no differences in MMP-9 concentration between the two lenses at V1.1 (paired T test; P = .63), V1.2 (P = .79) or V2.0 (P = .36).

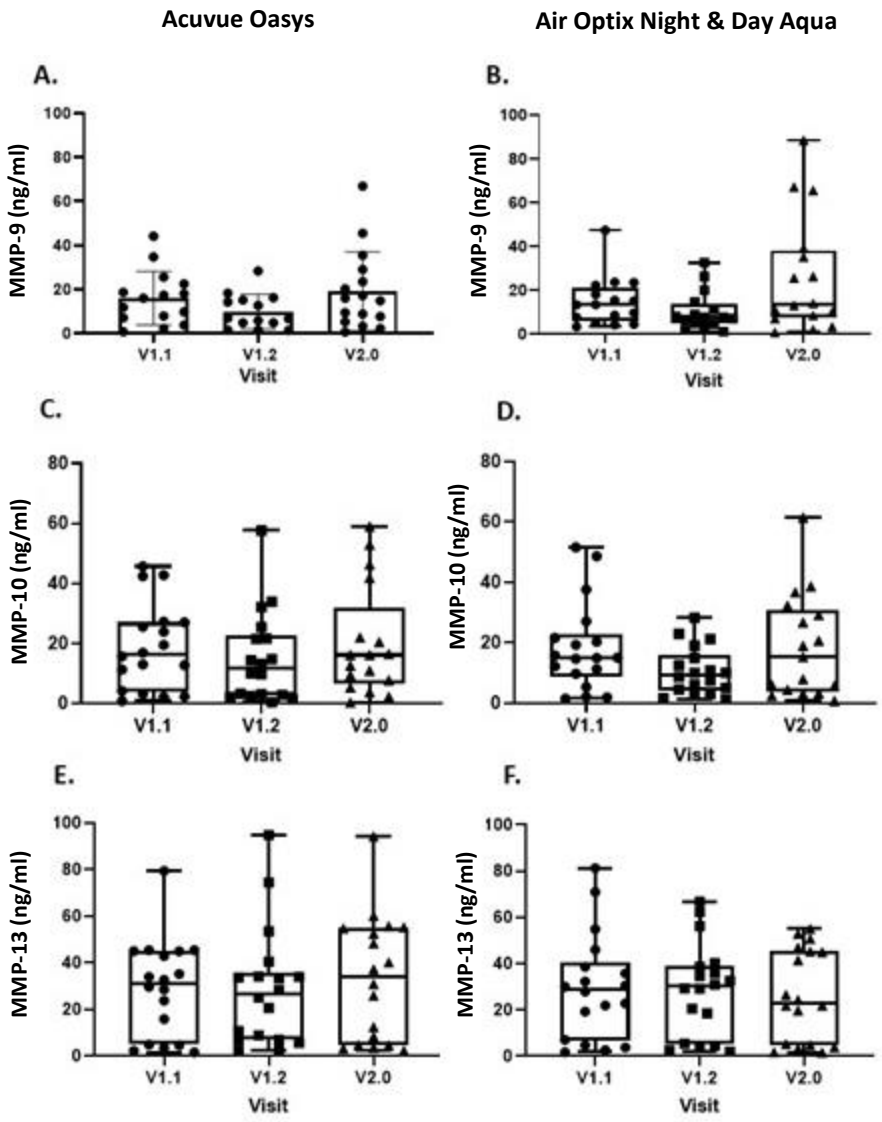

Figure 5: Boxplots for MMP-9 (A&B), MMP-10 (C&D), and MMP-13 (E&F) concentration (pg/ml) for Acuvue Oasys (AO) and Air Optix Night & Day Aqua (ND).

2.4 Conclusions

More than forty years after introduction of the first commercially available soft contact lenses, projecting contact lens comfort continues to be a challenge for eye care practitioners. Contact lens manufacturers have introduced continual innovations to improve patient comfort, from formulation of new materials, improvement in contact lens edge profiles and the incorporation of contact lens wetting agents. Despite these improvements, contact lens

dropout remains a significant issue. While multiple contact lens properties have been examined for an association with contact lens comfort, the coefficient of friction of contact lens materials has emerged as the leading indicator of contact lens comfort. Because the coefficient of friction value for a contact lens may change based on the test paradigm and the fact that there is no unified testing procedure for determining coefficient of friction, comparison of the surface lubricity values for different contact lens brands is challenging (Stapleton et al. 2017, Efron et al. 2016). Additionally, coefficient of friction is not a clinically observable contact lens parameter. The impact of contact lens coefficient of friction on individual patients is challenging to assess because it is a laboratory metric that is not readily observable clinically. This has led to recent interest in the contact lens community on the role contact lenses play in the development of lid wiper epitheliopathy. Despite this interest, very little is known on how quickly LWE will develop once a patient begins contact lens wear. In our study, LWE was observed as early as 2 hours after contact lens fitting. There was a significant increase in LWE between baseline to 2 hours and baseline to 1 week for both the Acuvue Oasys and the Air Optix Night and Day, but no difference between 2 hours and 1 week for either lens design, suggesting that LWE does not vary greatly in the early contact lens fitting period. In our sample, the amount of LWE observed over the course of 1 week, suggesting that the difference in the coefficient of friction between the lens designs was a significant factor in LWE development when the lens are properly fit using the manufactures fitting guidelines.

We did not detect a change in tear film MMP-9, MMP-10, or MMP-13 concentration over the study period. MMP-9 remained within the reported normal range of 3-40 ng/ml for most of the subjects during the study period (InflammaDry bulletin). Alghamdi et al. (2020) investigated MMP-9 tear film concentrations in habitual contact lens wearers. Alghamdi found

an increase in MMP-9 concentration in habitual soft contact lens wearers after 1-3 years of wear compared to non-contact lens wearers (23.1 ± 17.9 ng/ml and 4.1 ± 4.1 ng/ml); however, they found no increase in MMP-9 concentration for habitual contact lens wearers after 4-6 years or 8-12 years of wear. The median MMP-9 concentration observed in our study at baseline (17.7 ng/ml, Interquartile Range 7.8-37.1) was consistent with the findings of Walker et al, but was higher than the value reported by Alghamdi for non-contact lens subjects. The median observed MMP-9 concentration at 2 hours and 1 week post contact lens fitting in our study was less than that reported by Alghamdi after 1-3 years of lens wear. Additionally, we observed no difference in MMP-9 tear film concentration between the study visits. Based upon our observation, and the work of Alghamdi, MMP-9 levels in contact lens wear are not elevated early in the fitting process, but may increase over the first few years of contact lens wear.

There are some limitations and strengths to the approach used in the study that should be acknowledged. One consideration is the differences in design between commercially available contact lenses. The use of commercially available lenses did not isolate coefficient of friction of the material as a test variable and did not control of parameters such as overall diameter and edge design, making it possible that other factors influenced LWE development. Although the study did not control physical parameters of the contact lens design, the nominal difference in center thickness between the lenses for a –3.00D power is 1 micron (Acuvue Oasys 0.07mm vs. 0.08mm) and the difference in overall diameter is 0.2mm (Acuvue Oasys 14.0mm vs. Air Optix Night & Day 13.8mm). Because of the proprietary nature of contact lens designs and the lack of literature on the edge design of the Air Optix Night and Day, it is impossible to know the exact differences in the lens edge profile for the study contact lenses. Maissa et al. (2012) examined the development of conjunctival staining with various commercially available contact lenses,

including the Acuvue Oasys and the Alcon Air Optix Aqua contact lens, a different product in the Air Optix family. Maissa displayed that the Acuvue Oasys "Infinity Edge" had a knife edge profile while the Air Optix Aqua had a more chisel shaped edge design. Given potential similarities in manufacturing for contact lens products, the profile of the Air Optix Aqua suggests that the edge design of the Air Optix Night and Day is most likely be more chisel shaped compared to the Acuvue Oasys. While the contact lenses used in the study have different design parameters, contact lens comfort is poorly predicted by lens parameters such as overall diameter in modern contact lens designs when properly fit while CoF has been shown to have a strong negative correlation with contact lens comfort. As such, contact lens CoF may be the property most influential in LWE development.

A second consideration is the question of what constitutes a significant difference in CoF values between contact lens materials. Contact lens companies have attempted to reduce the coefficient of friction in their contact lens offering to improve comfort. This is observed in the Night and Day contact lens design, where Roba reported a CoF for the initial product offering of 0.382 ±0.27, while the current Night and Day Aqua lens has a reported CoF of 0.166 ± 0.058. Because of these attempts at continual improvement of contact lens products, previous generation contact lens designs have been discontinued and replaced with improved product offerings. For this study, the lenses were chosen was based on the difference in reported CoF by Roba et al. (2011) for lenses that were commercially available, with the Air Optic Night and Day having a reported CoF that is approximately 10 fold greater than the Acuvue Oasys. Despite this difference in CoF, we did not observe a significant difference in the amount of LWE that developed early in the contact lens fitting period.

Contact lens solution manufactures are increasingly incorporating wetting agents in their products to improve comfort with planned replacement contact lenses. With planned replacement contact lens use, wetting agents incorporated in the lens matrix or included in the packing solution can diminish prior to the end of the recommended replacement schedule. Use of daily disposable contact lenses allows for continual patient exposure to the intended wetting agent. In our study, we used planned replacement contact lenses disinfected with a formulation of the ClearCare hydrogen peroxide solution that does not include an additional wetting agent to avoid the potential of the wetting agent to impact LWE development. Using this solution also avoids any potential interaction of the disinfectant present in a multipurpose solution affecting LWE development. Future work should focus on the effect of multipurpose solutions and contact lens solutions with wetting agents additives on LWE development and whether LWE development differs with daily disposable contact lens use.

An additional consideration is the subject population and study duration. The study population consisted of young, healthy myopic patients without dry eye symptoms and with no upper lid LWE at the baseline visit who were either contact lens neophytes or habitual contact lens wearers who had discontinued lens wear for 1 week prior to enrollment. In the study, the majority of subjects were habitual contact lens wearers. A potential question is whether previous contact lens wear would make individuals more prone to increased LWE development. Conversely, are eyes that have never worn contact lenses more vulnerable to LWE development? Schulze reported that 85% of habitual contact lens wearers displayed LWE. In our population, one week of contact lens discontinuation led to upper eyelids without LWE staining, suggesting that LWE is a transient condition that resolves relatively quickly when contact lenses are discontinued in young healthy individuals. Due to the limited number of contact lens neophytes

in our sample, no statistical comparison of LWE staining between neophytes and habitual contact lens wearers could be performed. Additionally, the study only followed subjects for a 1 week period. While some subjects in the study did not develop LWE staining during the 1 week study period, the report by Schulze suggests that contact lens wearers will most likely exhibit some LWE at some point during contact lens wear, suggesting that LWE may develop with prolonged lens wear beyond the initial fitting period. To avoid any effect from diurnal fluctuation of both LWE and MMPs (Ritchey et al. 2017, Markoulli et al. 2013), we required study subjects to return for follow up visits at the same time of day ± two hours. Future work regarding LWE development should focus on recruiting contact lens neophytes to help determine if differences in early LWE development are observed with new contact lens wearers.

Despite the reported difference in contact lens CoF values for the two contact lenses, no significant difference in corneal staining occurred during the one-week study period. No study subject developed greater than grade 2 corneal staining (Brian Holden Vision Institute). The lack of significant corneal staining and no difference observed with tear film MMP levels may be attributed to enrollment of relatively asymptomatic subjects at baseline. Subjects with corneal staining or significant symptoms of ocular discomfort may display different tear film MMP levels. While our study examined potential change in tear film MMP concentrations over the study period, it did not evaluate MMP activity. Further studies could focus on tear film MMP activity by assessing the relative concentration of MMPs and TIMPs in order to better understand of the role of MMPs in LWE development and contact lens wear.

In summary, LWE staining can be observed in some subjects as soon as 2 hours after the initiation of contact lens wear. LWE staining did not appear to differ between contact lenses

of differing coefficient of friction in the early contact lens fitting period. Future work should examine other aspects of contact lens wear that may influence LWE development.

Chapter 3: Conclusions:

While we hypothesized that the higher CoF contact lens used in this study would cause higher grades of LWE to develop, there was no difference in the grade of LWE staining between the higher CoF contact lens and the lower CoF contact lens used in this study. While no differences existed for this study period, this study cannot predict what would happen later in the contact lens fitting period. As the typical adaptive period for soft contact lens fitting is between one and two months, it would be reasonable to study the effects of CoF on the grade of LWE development later in the contact lens fitting period but still within the adaptive period. Future research should explore the relationship between coefficient of friction and LWE staining later in the soft contact lens fitting period in order to reassess LWE as a sign of contact lens discomfort.

While there were no differences in the grade of LWE development between the two lenses used, there was a statistically significant amount of LWE that developed regardless of contact lens type over the course of the study period. While a significant amount of LWE developed between baseline and two hours and baseline and seven days, there was no difference between two hours and seven days. This shows that LWE can develop early in the contact lens fitting period, however, the relationship of LWE staining to contact lens discomfort is unclear due to no significant change in OSDI scores over the study period.

It is currently unknown if previous contact lens wear could affect LWE development. While the results show promise that LWE staining can develop in an acute time frame, previous contact lens wearers were included in this study. We attempted to negate the effects of previous lens wear by mandating a one week minimum contact lens washout period before subjects were

enrolled in this study, however, it is unknown if chronic contact lens wear could predispose subjects to develop LWE. Because this study did not specifically select for contact lens neophytes, previous lens wear may have affected the grade of LWE development. Future studies could focus on LWE development in new contact lens fits to prevent this from confounding the results.

Because no change in MMP-9, MMP-10, or MMP-13 was detected over the study period, this did not appear to be related to LWE development over the study period, as LWE significantly increased for both lenses. Little has been reported on MMP concentration in the tear film of contact lens wearers. Tear film MMP-9 levels at baseline were consistent with the findings of Walker; however, these values are higher than the value reported by Alghamdi for non-contact lens wearers. The observed level of tear film MMP-9 in our study after contact lens wear was less than that reported by Alghamdi for 1-3 years of lens wear. This difference may be due to the method of tear film MMP collection. The collection method used in this study and the work of Walker el al. was to draw basal tear fluid directly from the inferior tear meniscus using capillary tubes, where the method used by Alghamdi was to collect tear film MMPs using a flush tear collection method, potentially explaining the reported differences in MMP-9 concentration.

Since we excluded severely symptomatic subjects at the onset of the study based on baseline OSDI scores, this could have affected the predisposition of the subjects to develop LWE. Subjects with less ocular surface dryness symptoms after one week minimum of contact lens washout may be less likely to develop symptoms after continuing lens wear.

Because of the lack of data regarding the development of LWE in the early contact lens fitting process, there was no data to perform an a priori sample size calculation and a sample size of 20 was selected for the pilot study. Based on the mean LWE grade observed at 1 week for the

eye wearing the Night & Day contact lens, a sample size of 11 eyes would be required to detect a change in LWE staining from zero for an alpha of 0.05 and 80% statistical power. To design a study with an alpha of 0.05 and 80% statistical power that could detect a difference in LWE staining between the two contact lens designs, a sample size of 661 would be required.

The main findings of this thesis are as follows:

- LWE staining was detected as early as 2 hours after contact lens fitting in some subjects. There was a significant increase in LWE between V1.1 and V1.2 and between V1.1 and V2.0, but not between V1.2 and V2.0. There was no significant difference in LWE between the two study contact lenses over the study period.
- There was no significant change in OSDI scores over the study period. Additionally, there was no significant change in corneal staining during the study period.
- There was no significant increase in tear film MMP-9, MMP-10, or MMP-13 concentration for either lens during the study period. There was no difference in MMP-9 levels between the two lenses for any time point.
- There was no significant difference in horizontal decentration, post-blink movement, or primary gaze lag for the study contact lenses. There was a significant difference in vertical decentration between the study contact lenses with Acuvue Oasys showing slight superior decentration on average. However, the mean decentration was 0.23 mm, which is likely not clinically meaningful.
- There was no effect for lens or time on NIKBUT. There were no differences in first NIKBUT for any time point. The average NIKBUT had no significant effect for lens but there was a significant effect for time.

There was a significant difference between V1.1and V1.2, but no significant difference between V1.1 and V2.0 or between V1.2 and V2.0.

- There was no effect of lens on TMH, but there was a significant effect for time. There was a significant decrease in TMH between V1.1 and V1.2 and V1.1 and V2., but no significant difference between V1.2 and V2.0.

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