EVAPORATIVE TEAR FILM AND CONTACT LENS FACTORS ASSOCIATED WITH DRY EYE SYMPTOMS IN CONTACT LENS WEARERS

DISSERTATION

Presented in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in the Graduate School of the Ohio State University

By

Jason J. Nichols, OD MS MPH

*****

The Ohio State University
2004

Dissertation Committee:
Professor Karla Zadnik, OD PhD, Advisor
Professor Joseph T. Barr, OD MS
Professor P. Ewen King-Smith, PhD

Approved By

Karla Zadnik
Advisor
Vision Science Graduate Program
Contact lens-related dry eye is a significant problem, experienced by about one-half of all contact lens wearers. Generally, contact lens-related dry eye is termed “evaporative,” compared with other aqueous deficient dry eye diseases. However, few studies have confirmed indicators of evaporation relative to contact lens wear. The Contact Lens and Dry Eye Study (CLADES) is a cross-sectional/nested case-control study designed to study tear film, contact lens, ocular surface, and patient-related factors associated with self-reported dry eye disease in contact lens wearers. Although the study is not complete, the data and analyses presented in this dissertation are being used to guide the direction of further patient testing. Thus, the data presented here are strictly confidential.

Data from 325 patients in the CLADES database were used for these analyses. Initial analyses were conducted using 274 patients who completed the Contact Lens Dry Eye Questionnaire (CLDEQ) on two occasions in order to determine reliability and classification issues relating to this screening instrument. Two datasets were then assembled in order to determine tear film, contact lens, and patient-related factors associated with self-reported dry eye. The full dataset (n = 325) includes all patients in the original dataset, and patients are classified based on their initial responses on the CLDEQ. The clean dataset (n = 216) includes only patients who completed the CLDEQ.
on two occasions (n = 274), and patients who do not misclassify their disease status upon re-administration of the survey (n = 58, 21.2%, p = < 0.0001). Logistic regression was used to determine patient-related factors that might be used to predict misclassification (i.e., change in classification), and this analysis revealed that women less than 45 years of age tended to be those that misclassified their disease status (odds ratio = 2.50, 95% confidence interval = 1.20, 5.20).

Primary factors evaluated for a relation to disease status in these analyses included meibomian gland structural alterations, pre-lens tear film lipid layer thickness, non-invasive tear breakup time, hydrogel dehydration, and the use of a nominally characterized high water content lens. Secondary factors evaluated for a relation to disease status included things like socio-demographic information, U.S. Food and Drug Administration (FDA) hydrogel classification, hydrogel ionicity and material, phenol red thread testing, fluorescein corneal staining, and lissamine green conjunctival staining. Following univariate logistic regression analyses, multivariate models were built in order to determine significant factors associated with disease status. Factors that contributed significantly to the prediction of disease status across both the full and clean datasets included gender (p < 0.0001 and 0.006, respectively) and meibomian gland count (p = 0.02 and 0.03, respectively). However, the result for meibomian gland count was opposite of what was expected (e.g., more whole glands counted was associated with dry eye disease). Other factors that showed significance in the analysis of the clean dataset
included osmolarity \((p = 0.02)\), nominal water content \((p = 0.03)\), and pre-lens tear film noninvasive breakup time \((p = 0.03)\). No analyses showed a relation between measured dehydration and dry eye status, either when grouped together, or for specific contact lens types.

In summary, classification issues relating to contact lens-related dry eye studies significantly impact the internal validity of the sample, and these data provide some initial insight into these issues. Several factors were found to be associated with contact lens-related dry eye including gender (females), increased osmolarity, and decreased pre-lens non-invasive breakup time. The data are not consistent with the hypothesis that contact lens wear leads to alterations of meibomian gland structure. Yet, contact lens wear seems to alter the pre-lens lipid layer in a way that was not measured by the outcomes of this study. Future studies will need to address alternative hypotheses as they relate to the pre-lens tear film and dry eye during contact lens wear.
ACKNOWLEDGMENTS

I sincerely wish to thank those who have helped me successfully pursue this road to a career in academia, and in particular, in completing this PhD. In some regard, the journey has really just begun, but the roots that were planted are now firmly established. There are many people who have helped encourage and support me along the way. My advisor, Karla Zadnik, is truly an inspiration to in all facets of her career, and I appreciate all of the mentoring that she has provided me along this journey. My wife Kelly is also an inspiration, and I appreciated all of the knowledge, support, advice, and encouragement she has provided me not only in studying the tear film and dry eye disease, but also as a life-long partner.

I have also had the opportunity to work with several other mentors, colleagues, and friends along this journey including Joe Barr, Greg Good, Ewen King-Smith, Gil Pierce, Michael Twa, and Jeff Walline. Each has helped mold and shape my career in very unique ways. A special thank you goes to Lynn Mitchell for her tireless efforts in working with me, and to David Berntsen for his assistance on the project.

This work was supported by NIH/NEI EY13766.
January 19, 1973 ........................................... Born – Flint, Michigan

1991............................................................... Graduate-Waterford Kettering High School.

1995............................................................... B.A. Biology, Hope College.

1999............................................................... O.D. Optometry, The Ohio State University.

2000............................................................... M.S. Physiological Optics, The Ohio State University.

2000............................................................... Fellowship, American Academy of Optometry

2001............................................................... Cornea and Contact Lens Advanced Practice Fellowship, The Ohio State University

2002............................................................... Fellowship, Clinical Research Curriculum program at The Ohio State University

2002............................................................... M.P.H. Public Health (Epidemiology), The Ohio State University.

1999-2002...................................................... Graduate Teaching and Research Associate, The Ohio State University.

2002-present .................................................. Senior Research Associate, The Ohio State University.

2003-present .................................................. Diplomate, The American Academy of Optometry Public Health Section.


**FIELDS OF STUDY**

Major Field: Vision Science
TABLE OF CONTENTS

Abstract ........................................................................................................................ ii
Acknowledgments........................................................................................................ v
Vita............................................................................................................................... vi
List of Tables................................................................................................................ xi
List of Figures .............................................................................................................. xiii

Chapters

1. Introduction .............................................................................................................. 1
   The Tear Film ........................................................................................................ 1
   The Lipid Layer ...................................................................................................... 1
   The Aqueous Layer .............................................................................................. 2
   The Mucin Layer ................................................................................................. 5
   The Tear Film: Some General Characteristics and Functions .................... 6
   Contact Lens Materials ..................................................................................... 8
   Hydrogel Lens Groups .................................................................................... 10
   Water Content and Refractive Index ............................................................. 11
   Deposition .......................................................................................................... 14
   Contact Lens-Related Symptoms of Ocular Irritation .................................. 15
   Contact Lens, Tear Film, and Ocular Surface Interactions ......................... 20
   The Pre- and Post-Lens Tear Film: General Considerations .................... 20
   Contact Lens and Lipid Layer Interactions .................................................... 24
   Contact Lens Utilization and Public Health Significance ............................ 30
   An Evaporative Model of Contact Lens-Related Dry Eye ......................... 32
   Specific Aims ...................................................................................................... 35

2. Methods .................................................................................................................... 36
   Study Design Overview .................................................................................... 36
   Phase I—Entry Criteria, Recruitment, and Subject Selection .................... 37
   Phase II—Examination Phase Primary Outcomes ........................................ 37
       Pre-Lens Lipid Layer Thickness ................................................................. 39
       Pre-Lens Tear Film Noninvasive Breakup Time ........................................ 40
       Water Content and Refractive Index ......................................................... 40
   Material Type .................................................................................................... 42
   Meibography ..................................................................................................... 44

 ix
LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 1. Studies of dry eye symptoms during contact lens wear.</td>
<td>96</td>
</tr>
<tr>
<td>Table 2. Meibomium gland lipid components found in the lipid layer of the tear film.</td>
<td>97</td>
</tr>
<tr>
<td>Table 3. Procedures performed in the Phase II Clinical Examination.</td>
<td>98</td>
</tr>
<tr>
<td>Table 4. Sample size estimates need for analyses associated with Phase II of CLADES.</td>
<td>99</td>
</tr>
<tr>
<td>Table 5. Test-retest data associated with the CLDEQ classification scheme. Numbers in parentheses represent percentages.</td>
<td>100</td>
</tr>
<tr>
<td>Table 6. Association between univariate patient-related factors and dry eye misclassification.</td>
<td>101</td>
</tr>
<tr>
<td>Table 7. Table of continuous tear film and contact lens descriptive factors by dry eye group.</td>
<td>102</td>
</tr>
<tr>
<td>Table 8. Table of meibography gestalt grading by dry eye group.</td>
<td>103</td>
</tr>
<tr>
<td>Table 9. Table of pre-lens tear film lipid layer thickness by dry eye group.</td>
<td>104</td>
</tr>
<tr>
<td>Table 10. Table of soft vs. RGP lens wear by dry eye group.</td>
<td>105</td>
</tr>
<tr>
<td>Table 11. Table of hydrogel FDA classification by dry eye group.</td>
<td>106</td>
</tr>
<tr>
<td>Table 12. Table of hydrogel nominal ionicity by dry eye group.</td>
<td>107</td>
</tr>
</tbody>
</table>
Table 13. Table of hydrogel nominal water content by dry eye group. ....................... 108

Table 14. Table of measured hydrogel dehydration by nominal water content. ......................................................................................................................... 109

Table 15. Table of measured hydrogel dehydration (refractive index) by nominal water content. ............................................................................................................ 110

Table 16. Analysis of etafilcon A usage relative to dry eye status and dehydration. .................................................................................................................................. 111

Table 17. Analysis of lotrafilcon A usage relative to dry eye status and dehydration. .................................................................................................................................. 112

Table 18. Table of gender by dry eye group. ........................................................................ 113

Table 19. Table of educational status by dry eye group. ................................................. 114

Table 20. Table of total household income by dry eye group. ..................................... 115

Table 21. Table of smoking status by dry eye group for the full dataset (n = 325). ................................................................................................................................. 116

Table 22. Multivariate logistic regression analyses of tear film and patient-related factors associated with hydrogel contact lens-related dry eye status for the full and clean datasets. .......................................................... 117
LIST OF FIGURES

Figure Page

Figure 1. Contact Lens and Dry Eye Study design. ..................................................... 118

Figure 2. Sample images associated with the meibography gestalt grading scale. ................................................................. 119

Figure 3. Distribution of surveyed CLADES patients ................................................. 120

Figure 4. Distribution of test-retest differences associated with CLDEQ Index. ......................................................................... 121

Figure 5. Bland-Altman plot of difference vs. mean for CLDEQ Index. ..................... 122
CHAPTER 1

INTRODUCTION

The Tear Film

The Lipid Layer

Traditionally, the tear film is described as a three-layer solution covering the anterior ocular surface. A more recent model of the tear film suggests more of a two-layer structure, with a superficial lipid layer and an underlying aqueous layer with dissolved mucus concentrated to a greater extent at the glycocalyx. The superficial lipid layer is the anterior most portion of the tear film and is produced primarily by the meibomian glands in the upper and lower tarsal plates. There are thought to be about 20 meibomian glands in the lower lid and 30 in the upper lid (Tiffany, 1995). Lipids are released from the meibomian glands through the holocrine mechanism. Although the regulation of the meibomian gland is not fully understood, recent studies have shown definite hormonal control of the glands. Specifically, the meibomian gland is an androgen target organ, and androgen metabolizing enzymes (5alpha-reductase mRNA) are located in the gland tissue (Rocha, Wickham et al., 2000; and Sullivan, Sullivan et al., 2000). Although not as well understood, the meibomian glands are also thought to have nervous innervation; up to seven different nerve fiber types have been identified including sympathetic and mostly...
parasympathetic types (Chung, Tigges et al., 1996; Kirch, Horneber et al., 1996; and Seifert and Spitznas, 1996). Lipids are thought to be produced also by the glands of Moll and the lash follicle glands of Zeis.

Classically, interference techniques have placed the lipid layer thickness between 40 and 80nm (Olsen, 1985). The lipids of the tear film include polar and nonpolar types: (in decreasing order) hydrocarbons, sterol esters, waxy ester, triacylglycerols, free cholesterol, free fatty acids, and polar lipids (Mathers and Lane, 1998; Shine and McCulley, 1998; and McCulley and Shine, 2003). The melting range of the lipids of the tear film is 19 to 32°C, and the refractive index of human lipids is about 1.482 (Tiffany, 1986). Lipocalin, a protein found in the aqueous tears, is thought to aid in lipid spreading over the aqueous film (Glasgow, Marshall et al., 1999). The specific functions of the lipid layer are to reduce aqueous evaporation (Mishima, 1965; and Iwata, Lemp et al., 1969), reduce epiphora (Norn, 1966), decrease contamination (Norn, 1966), seal the lid margins (Norn, 1966), and decrease the surface tension of tears (Tiffany, 1985; and Nagyova and Tiffany, 1999).

The Aqueous Layer

The aqueous layer maintains the bulk of the tear film, and is produced primarily by the lacrimal gland but also by the accessory glands of Kraus and Wolfring. The glands of Krause are located in the upper and lower conjunctival fornices, whereas the glands of Wolfring are located in the tarsal plates. The lacrimal gland is a compound tubulo-
alveolar gland (like the salivary gland) that is divided into the orbital and palpebral lobes. The orbital lobe is the larger portion, which empties through up to eight ducts into the conjunctival sac. The ducts of the orbital portion run through the palpebral portion, which has up to 10 ducts. The gland is controlled through nervous and hormonal regulatory mechanisms. Nervous innervation to the gland includes the trigeminal nerve (principal afferent pathway), the facial nerve (principal efferent pathway), and cervical sympathetic nerve fibers. Parasympathetic fibers line the gland acinar and myoepithelial cells, controlling water/electrolyte secretion through acetylcholine and vasoactive intestinal peptide (VIP). Sympathetic fibers (and norepinephrine release) innervate lacrimal gland blood vessels.

The aqueous tear film is composed primarily of water, electrolytes (sodium, chloride, potassium, bicarbonate, magnesium, phosphate, and calcium), serum proteins (albumin, transferrin, IgG, IgM) and lacrimal gland proteins (lysozyme, lactoferrin, beta-lactasin, tear lipocalin, secretory IgA), enzymes (lactate dehydrogenase, pyruvate kinase, malate dehydrogenase, amylase), and metabolites (glucose and urea released by serum). The electrolytic concentration of the tears relates to its osmolality which is approximately 300 to 310 mOsm/liter (Gilbard, Farris et al., 1978; and Craig, Simmons et al., 1995). The electrolytes in the tears aid in maintaining corneal integrity. Some have suggested that osmolality is an indicator of dry eye disease as an increase in tear film evaporation or decrease in aqueous production may lead to a more concentrated tear film. The pH is also
related to the electrolytic balance in the tear film (specifically, bicarbonate) and it ranges from about 7.3-7.7 (Norn, 1977; and Hill and Carney, 1978).

The total protein content of the tear film is about 0.136 to 4.5 gm/100ml (Adler and Hart, 1992). The exact role of many of the proteins has not been established. Tear lipocalin is thought to bind and transport lipids to the aqueous phase of the tears (Glasgow, Marshall et al., 1999). This protein may play a key role, therefore, in tear film stability. The immunoglobulin fractions (antibodies) are associated with humoral aspects of immunity. Lysozyme is found in higher concentrations in the tears than any other part of the body and is a glycolytic enzyme produced by lysosomes. It possesses antibacterial properties as it dissolves bacterial cell walls. Beta-lysin is another antibacterial protein found in the tears that acts on the cell membrane of bacteria and is produced by platelets. Lactoferrin is an iron-binding protein produced by the lacrimal gland that removes iron from the tear film inhibiting bacterial replication (Broekhuyse, 1974; Arnold, Cole et al., 1977; and Stuchell, Farris et al., 1981). As lactoferrin is produced by the lacrimal gland, damage of the gland may lead to a reduction in its concentration in the tear film; thus, some have suggested this may be an indicator of “aqueous-deficient” dry eye disease (Boersma and van Bijsterveld, 1987; and Yolton, Mende et al., 1991).

“Text-book” estimates associated with the thickness of the tear film usually state values around 7 to 10µm (with negligible components from the lipid and mucus), although values from about 2.7 to 40µm have been reported in the literature (Adler and
Hart, 1992; Prydal, Artal et al., 1992; and King-Smith, Fink et al., 2000). The temperature of the tears is about 35°C, while the overall refractive index is about 1.3369 (Patel, Anderson et al., 1994; and Craig, Simmons et al., 1995). The surface tension of the tears is about 45 dynes/cm (Tiffany, Winter et al., 1989).

*The Mucus Layer*

Finally, the mucus layer is the posterior most portion of the tear film and is produced primarily by the goblet cells of the bulbar conjunctiva but also by the epithelial cells of the ocular surface (which contain mucus secretory vesicles) and crypts of Henle in the fornices. The goblet cells are specialized apocrine cells that number about 1.5 million on the ocular surface, and are most concentrated over the nasal conjunctiva (Ralph, 1975; and Nelson and Wright, 1984). Mucus secretion is not well understood but probably is controlled neurally (Kessler and Dartt, 1994; Paz, Tisdale et al., 2003; and Shatos, Rios et al., 2003). Newer studies are showing that P2Y₂ (a purine derivative neuromodulator) stimulates the goblet cell (which has such P2Y₂ receptors) leading to mucus production (Cowlen, Zhang et al., 2003; and Nichols, Yerxa et al., 2004). The mucus layer of the tear film is composed of various glycosylated proteins that are about 50% carbohydrate by mass. Human mucins have been designated as MUC1 (ocular), MUC2, MUC3, MUC4(ocular), MUC5AC (ocular), MUC5B, and MUCs6-8. MUC5AC is though to be the major “mucus gel” of the tear film, while MUC1 is thought to aid in the spreading of MUC5AC (Tiffany, Winter et al., 1989). The function of MUC4 in
relation to the ocular surface is not presently known. The mucus layer of the tear film is thought to be primarily responsible for lubrication of the ocular surface, although it also serves a protective role. Both dry eye disease and contact lens wear have been shown to be associated with a reduction in goblet cell density and thus, potentially an alteration to this layer (Adar, Kanpolat et al., 1997; Albietz, 2001; Pisella, Malet et al., 2001; and Cakmak, Unlu et al., 2003).

The Tear Film: Some General Characteristics and Functions

There are several purposes associated with the overall tear film. In no particular order, one of these functions is optical, whereby the tear film is spread by the eyelids over the rough ocular surface to form a uniform surface for refraction of light that is to focus on the retina. Studies have shown the importance of the tear film in relation to maintaining good vision (Rieger, 1992; Chen and Wang, 1999; and Tutt, Bradley et al., 2000).

A second important function of the tear film is that it is protective of the ocular surface mechanically and bacteriostatically. Mechanical debris and metabolic wastes are flushed from the ocular surface by the tears, and foreign bodies result in increased tear secretion to aid with this process. The aqueous tears contain bacteriostatic substances (lysozyme, lactoferrin, beta-lysin), antiviral immunoglobulins (secretory IgA), and complement which aid in protection, while the mucus system traps and carriers away fine particulate matter. The tears protect the surface of the eye from the external environment
by responding to constant, varying challenges, such as desiccation, bright light, cold, mechanical stimulation, and noxious chemicals. There is exquisite control of tear volume, composition, and structure in response to these challenges.

A third function of the tear film is to provide lubrication to the ocular surface. The conjunctival and corneal surfaces are lubricated by the tears so that they slide over each other during blinking. Lubrication provided by the tear film is also important for successful contact lens wear in terms of both the pre-lens and post-lens tear film. A fourth function of the tear film is osmotic, as appropriate corneal hydration levels are maintained partly through the osmotic properties of the tears. A final function of the tear film is to aid in maintaining a nutritional balance of the ocular surface. This is true as oxygen passes through the tears and across the anterior surface of the eye.

Contact lens wear potentially changes the normal homeostasis of the tear film and ocular surface. This is potentially true for all layers of the tear film and may relate to the materials properties of the lens. The basal (aqueous) tear film is thought to be produced at a rate of about 1 to 2 µL per minute (Mishima, 1965; and Puffer, Neault et al., 1980). The stability of the tear film is related to each of the relative constituents, both in terms of quantity and quality. It is unclear how contact lens wear leads to alterations in the production rate of the tear film, although one might suggest that because contact lenses lead to a corneal hyposensitivity, they might lead to a decrease in aqueous secretion (Gilbard, Gray et al., 1986; and Murphy, Patel et al., 2001). Elimination of the tear film
occurs through the drainage portions of the lacrimal system, evaporation, and conjunctival absorption. Contact lens wear could alter each of these mechanisms. For instance, contact lens wear leads to alterations in the blink reflex, which in turn, could lead to alterations in the tears heading through the excretory portion of the lacrimal system (Stewart, 1968; Stewart, 1976; Conway and Richman, 1982; Conway and Knoll, 1986; and Collins, Heron et al., 1987). An alteration in the blink reflex may also be associated with an increase in tear film evaporation, especially if the inter-blink period is prolonged (Tsubota and Nakamori, 1995). The nature of a contact lens material may lead to interactions with the lipid layer (through deposition), which may reduce the stability of the lipid layer of the pre-lens tear film, which may lead to increased tear film evaporation and contact lens dehydration. Although likely, these issues remain debatable.

**Contact Lens Materials**

Contact lens polymers can generally be classified into four categories including 1) thermoplastics, 2) synthetic elastomers, 3) rigid gas permeable (RGP) copolymers, and 4) hydrogels. The basic idea in terms of chemical composition for most polymers is the idea of a polymer backbone with suspended chemical groups (i.e., the “washing line” of monomers) (Tighe, 1997). Thermoplastics are polymers that are shaped with heat and pressure but at room temperature are fairly rigid. An example of a thermoplastic is polymethyl methacrylate (PMMA). Although the material is optically pure, easy to work with, and quite wettable, its major disadvantage is its lack of oxygen permeability.
Synthetic elastomers, such as silicone, are polymers that are extremely flexible, showing rubber-like behavior. They can be stretched to extremes and will return to their original shape, and they have extremely high oxygen permeabilities (i.e., 7 to 8 times that of a hydrogel material of about 80% water). However, these polymers have surfaces that are extremely hydrophobic and therefore require surface treatments before use on the eye. Silicone elastomer lenses are also prone to adhering to the cornea, caused by a “suction cup” effect of the lens (Refojo and Leong, 1981). A third group, rigid gas permeables (RGP), have chemical side-groups branching off the polymer backbone that are fastened together using carbon-to-carbon double bonds. The major advantage of RGP materials is their high oxygen permeabilities, although their primary disadvantage is initial discomfort for the patient (Bennett, Smythe et al., 1998; and Bennett, Stulc et al., 1998). Finally, hydrogel materials are similar to other polymers in that they maintain a “washing line” structure with a long backbone (the line) and suspended chemical groups (the laundry). Polymerization of hydrophilic monomers and cross-linking leads to hydrogel materials. Hydrogels have modest oxygen permeabilities and generally allow for comfortable contact lens wear. The vast majority of contact lenses used today are of hydrogel material. However, a new breed of material (the silicone hydrogel) will likely become the primary material used for contact lens fitting over the next 10 years.

The first hydrogel developed was the polyhydroxyethyl methacrylate (PHEMA) material, developed by Otto Wichterle in the early 1960s. This is a non-ionic
homopolymer of 2-hydroxyethyl methacrylate (HEMA) that has cross-linking chains of ethyleneglycol dimethacrylate (EGDMA). A polymer contains more than one type of a repeating monomer unit (a copolymer contains two different monomers polymerized together). Typically, soft lens materials start with either HEMA as the principal monomer. HEMA materials (38% water content) depend mainly on the electronegativity of carbon-oxygen within the matrix to attract water. Another monomer can be added to hydrophilic materials (i.e., N-vinyl 2 pyrrolidone), and this monomer depends on the polarity of the carbon-nitrogen bonds to attract water. The pyrrolidone monomers are generally used in Food and Drug Administration (FDA) Group II materials. A third group contains methacrylic acid, which is found in FDA Group IV materials. These two monomers are known to be highly attractive to water, which is why Group II and IV lenses are of high water content. Cross-linking agents are used to provide structural stability to the monomers.

*Hydrogel Lens Groupings*

Some believe water content is the most important property of hydrogels, as this property plays a role in the oxygen transmission of the material, in addition to providing comfort relative to rigid materials (Refojo, 1973; Hill and Andrasko, 1981; and Tighe, 1997). A second important but related property of the material is its ionicity. The FDA defines a high water content lens as one that is over 50% water and an ionic material as one that contains more than 0.2% ionic material. Typically, hydrogel materials are named
in the US through the United States Adopted Name (USAN) system (e.g., balafilcon A) and then classified by the FDA into one of four groups. The USAN is typically given for a material of a specific composition, although the same USAN has been aberrantly given to two or more different ratios of the same monomers in the past.

**Water Content and Refractive Index**

The water content of a hydrogel material is associated with the number of hydrophilic sites in the polymer. The hydrophilic nature of hydrogel materials is derived from the ability of carboxyl groups (negatively charged) to share an electron with a molecule of water and inversely related to the number of crosslinks (McCarey and Wilson, 1982). The water contents of hydrogel polymers can be decreased by increasing the amount of hydrophobic monomers (i.e., methyl methacrylate) and increased by copolymerizing with increasing amounts of hydrophilic monomers (i.e., HEMA and vinyl pyrrolidone). The resultant water content in a hydrogel is always a product of the proportions of these two factors—hydrophilic sites and cross-linking. The number of hydrophilic sites (water attracting centers) within the polymer give rise to what is known as “bound” water, while the polymer-polymer interactions give rise to what is known as “free” water within the matrix (i.e., free water occupies polymer free areas rather than binding with polar sites). Both bound and free water are concentrated in “pores” which are about 20-30Å in diameter (a water molecule is about 3Å in diameter, although it is not symmetrical) (McCarey and Wilson, 1982). There is generally less free water in the
HEMA derivatives as compared to the pyrrolidone derivatives because the electronegativity of oxygen (HEMA) is greater than nitrogen (pyrrolidone); therefore, water bound to sites with nitrogen centers will be weaker than water bound to sites with oxygen centers.

One of the most elusive material characteristics potentially associated with patient dryness symptoms has been initial (or nominal) water content of a lens. All hydrogel lenses have the potential to lose water when taken from a vial or blister pack both in-vitro and in-vivo. Generally, low water content lenses may lose about 1% of water content, high water content lenses may lose about 5%, and no lenses have ever been shown to completely dehydrate during lens wear (dehydration levels are at most 15%). The mechanism of greater water loss in higher water content lenses is not fully understood. Some suggest that the difference in dehydration rates between low and high water content lenses may be related to the ratio of free-to-bound water associated with the plastic (Brennan and Efron, 1987; and Efron, Brennan et al., 1987). There is more free than bound water in the matrix of high water content lenses, so these lenses are thought to dehydrate more. Martin (1995) has shown that the evaporation of water from the anterior surface of a contact lens is greater for contact lenses of high water content (Martin, 1995).

For traditional HEMA-based hydrogel lenses, there is a direct relation between water content and refractive index (Nichols and Berntsen, 2003; and Nichols, Mitchell et
The refractive index of water ($n = 1.33$) is lower than the refractive index of PHEMA (1.405), so the refractive index of a low water content contact lens is higher than that of a high water content lens. For example, the typical refractive index range for a polymer material at 20% water content is 1.46-1.48, while the refractive index range for a polymer at 75% water content is 1.37-1.38. Fatt and Chaston (1980, 1982) have previously fitted laboratory data from contact lenses to determine the water content from the refractive index. There are several methods of measuring hydrogel lens water content including gravimetric methods, nuclear magnetic resonance imaging, and refractometry. The recommended techniques of the International Organization for Standardization (ISO) for measuring hydrogel water content are refractometry and gravimetric methods. (1997) These methods are somewhat costly and time consuming. (Galas and Enns, 1993) Refractometry is a feasible method for measuring the water content of a soft lens clinically. This method is possible due to the fact that the refractive index of a soft lens is dependent on its water content (Fatt and Chaston, 1980; Mousa, Callander et al., 1983; Nichols and Berntsen, 2003; and Nichols, Mitchell et al., 2003). In refractometry, the water content is determined by measuring the refractive index of the contact lens relative to the refractive index of the prism used in the refractometer (Brennan, 1983; Nichols and Berntsen, 2003; and Nichols, Mitchell et al., 2003) The difference determines the angle of refraction of the limiting ray and the extent of illumination of the internal scale of the
refractometer (percent water or solid content depending on the refractometer). (Brennan, 1983; and Efron and Brennan, 1987)

Deposition

Another important material characteristic associated with hydrogel lenses that may impact comfort (although not necessarily the typical “dryness” symptom) is the potential for the material to deposit. It has been reported that all lenses form a “coating” within the first minute of lens wear. This pellicle is primarily composed of mucus, and it is about one micron thick. Most of the time this coating is related to aiding the lens in terms of ocular surface biocompatibility (Klotz, Butrus et al., 1989; and Hart, Plociniak et al., 1998). However, this biocompatibility is not always true, as some deposits may not be beneficial.

Hydrogel lenses are generally termed “ionic” and “nonionic,” based on the amount of ionic material within a lens (> 0.2% is termed ionic). Lysozyme is the principal deposit associated with lens spoilage, particularly as lysozyme is attracted to group IV lenses (Garrett, Garrett et al., 1999; and Jones, Senchyna et al., 2003). Although many clinicians and textbooks suggest a relation between deposits and patient-reported discomfort, few such scientific reports exist. In fact, one report showed no relation between deposits and symptoms (Gellatly, Brennan et al., 1988). A variety of substances have been implicated as a deposit including lysozyme, lactoferrin, globulin fractions,
mucins, lipid, amino acids, calcium, microorganisms, carbohydrates, and other organic and nonorganic debris (Brennan and Coles, 2000).

Lipid deposits are generally prone to develop on nonionic higher water content hydrogel lenses and hydrophobic RGP lenses (which are also lipophilic) (Bontempo and Rapp, 1994; and Jones, Franklin et al., 1996). Lysozyme is positively charged and has been implicated as the most prominent and quickly adhered substance to ionic lenses, which tend to have a negative charge (Sack, Jones et al., 1987; Garrett, Garrett et al., 1999; and Jones, Senchyna et al., 2003). Brennan and Coles (2002) state that “proof linking a specific component with a specific biocompatibility issue remains lacking,” although many issues with deposits and tolerability of lens wear have been resolved with the introduction of disposable lenses (Brennan and Coles, 2000). Thus, it is unlikely that contact lens deposition and spoilage are associated with the contact lens-related dryness symptoms addressed by this work. However, ionic lens utilization is being assessed in this study so that it can be evaluated in terms of its relation to contact lens-related dry eye symptoms.

**Contact Lens-Related Symptoms of Ocular Irritation**

Surprisingly, there have been only a handful of studies that have evaluated symptoms of ocular irritation experienced by contact lens wearers (Brennan and Efron, 1989; Doughty, Fonn et al., 1997; Guillon, Styles et al., 1997; Begley, Caffery et al., 2000; and Begley, Chalmers et al., 2001). Table 1 outlines several characteristics of those
studies. Up to 75% of contact lens wearers have symptoms of ocular irritation, and “dryness” is the most commonly-reported symptom across studies. Dryness generally means “marked by the absence of natural or normal moisture,” which a lens wearer experiences as a sensation. Charles McMonnies led the ophthalmic community in many regards in terms of a characterization of symptoms of ocular irritation, both in contact lens wearers and non-lens wearers. In “McMonnies Questionnaire,” five such symptoms are addressed in terms of their frequency of occurrence including dryness, grittiness, burning, soreness, and scratchiness. In their first reported study, McMonnies and Ho (1986) assessed 63 hydrogel lens wearers and 160 hard lens wearers, but did not report individual scores (McMonnies and Ho, 1986). Rather, they report “for both contact lens wearing groups dryness was the most common primary symptom”. They also report that contact lens wearers report these symptoms to occur more frequently than non-lens wearers (p < 0.0001), and that soft lens wearers report them to occur more frequently than hard lens wearers (p < 0.01). This was really the first systematic report of symptoms of ocular irritation in contact lens wearers.

Brennan and Efron (1989) were among the first to report on the symptoms of ocular irritation during contact lens wear (Brennan and Efron, 1989). One hundred four patients wearing HEMA contact lenses were asked how often their eyes felt “scratchy,” “dry,” or “watery” while wearing their lenses. They reported that “dryness” was reported to occur significantly more frequently than the other two symptoms. Twenty-five percent
of patients reported “never” experiencing this sensation and about 19% reported experiencing this symptom “often.” They also reported that these symptoms of ocular irritation were more commonly reported by females using oral contraceptives and by patients wearing toric lenses and lenses older than six months.

Doughty and coworkers (1997) also attempted to evaluate the problem of symptoms of dryness during contact lens wear (Doughty, Fonn et al., 1997). They surveyed 86,160 Canadian individuals by mail, and 13,517 responded to the survey (15.7% response rate). Of those responding, 3,285 were contact lens wearers, and of the lens wearers, 50.1% responded that they had “dry eye symptoms.” The percent of symptomatic contact lens wearers was significantly greater than the percent of symptomatic non-contact lens wearers (21.7%, p < 0.001). No individual symptoms were reported.

Vajdic and coworkers (1999) administered a questionnaire of ocular symptoms to 664 spectacle, 171 hydrogel and 48 rigid gas permeable (RGP) lens wearers who were volunteers for various clinical trials between 1989 and 1995 (Vajdic, Holden et al., 1999). Overall, there were no differences in symptom profiles when comparing hydrogel and RGP lens wearers, although contact lens wearers in general reported significantly more dryness, redness, and grittiness than spectacle lens wearers. The most commonly reported symptom (occurring at least sometimes) for hydrogel lens wearers was again dryness (73%) followed by redness (66%). Thirteen percent of hydrogel lens wearers reported
dryness “often or constantly.” They concluded that “The mechanism that induces the principal ocular sensation of contact lens wearers, dryness, remains unknown.”

Begley and coworkers (2000) have shown that the dryness symptom generally increases significantly over the course of the day, such that the symptom is about two times more intense in the evening compared with the morning (Begley, Caffery et al., 2000). They also showed that contact lens wearers report significantly more “dryness” while wearing their lenses than while not wearing their lenses. The etiology of these symptoms of ocular irritation during contact lens wear are unknown, in particular, the cause of the morning-to-evening differential in symptom-reporting. Begley and coworkers (2000) speculate “It may be because of deposit formation over the course of a day, which renders the lens surface increasingly hydrophobic.”

In a follow-up study using a refined “Contact Lens Dry Eye Questionnaire,” Begley and coworkers (2001) administered this instrument at six clinical centers across North America (Begley, Chalmers et al., 2001). This instrument evaluates nine specific symptoms, both in terms of frequency and diurnal intensity. The symptoms evaluated include discomfort, dryness, visual changes, sore/irritated eyes, gritty/scratchy eyes, foreign body sensation, burning/stinging, light sensitivity, and itching, in addition to a self-perception question (e.g., do you think you have dry eyes while wearing your contact lenses?). Three hundred sixty-seven contact lens wearers completed the survey. The results showed that discomfort was the most commonly reported symptom (79% of
contact lens wearers), followed by dryness (77%) and visual changes (67%). About twice the number of lens wearers reported significant dryness compared to non-lens wearers. There was a definite trend toward increasing symptom intensity throughout the day for lens wearers, as 19% of the sample reported moderate-to-intense discomfort in the morning that increased to 56% for the evening. About 18% of lens wearers indicated they felt that had dry eye disease, and 13% of those not diagnosed with dry eye and 38% of those diagnosed with dry eye reported needing to remove their lenses more often than once per week.

Guillon and coworkers (2002) mailed McMonnies’s questionnaire to 502 soft contact lens wearers and 309 non-contact lens wearers (Guillon, Cooper et al., 2002). They report that there was a significantly higher percentage of “dry eye symptomatic patients” who were contact lens wearers compared with non-lens wearers (p < 0.001). They also showed that symptomatic lens wearers report significantly more problems with air conditioning/central heating and smoky environments than asymptomatic patients. They report that “the symptom of ocular dryness was the best detector of the symptomatology,” and suggest that these findings “…support the hypothesis of the evaporative etiology of contact lens-related dry eye.”

There are several interesting points worth discussing in relation to the issue of symptoms during lens wear. First, although several larger-scale symptom surveys have been conducted in lens wearers, there has been no attempt to examine relations between
tests of tear film function and symptoms of ocular irritation in this group. If tests of tear film function are of any clinical value, they must be inherently related to patient-reports of symptoms. Second, much of the focus on patient-reported symptoms in contact lens wearers has been on the perceived frequency of symptom occurrence, rather than on the intensity or severity of the symptom. It would seem as though the intensity of a symptom might dictate the prognosis for continued lens wear more than the frequency of occurrence of the symptom.

Contact Lens, Tear Film, and Ocular Surface Interactions

The Pre- and Post-Lens Tear Film: General Considerations

A contact lens divides the tear film into two layers—the pre- and post-lens tear films. Although it is clear that the lipid layer maintains the superficial aspect of the pre-lens tear film with an aqueous component behind it, the constituents of these layers are not otherwise clear. Studies have shown that a mucus coating forms over the anterior surface of hydrogel lens after about 30 minutes of lens wear, and we know that a lens “settles” in terms of its impact on the thickness of the tears during this same period (Fowler and Allansmith, 1980; and Nichols and King-Smith, 2004). The exact tear constituents of the post-lens tear film are not known. Most would, however, agree that successful contact lens wear depends on a stable tear film, including the production and maintenance of the constituents in each of these layers. Environmental conditions, lens parameters, tear film factors, or wearing schedules may impact the tear film structure.
during contact lens wear. This may have clinical consequences such as contact lens-related dry eye symptoms, lens adherence, reduced tear exchange, contact lens dehydration, corneal desiccation, inflammatory events, and potentially sight-threatening infections (Willcox, Morris et al., 1997; Willcox, Power et al., 1997; Fonn, Situ et al., 1999; Chang and Chang, 2001; Creech, Chauhan et al., 2001; Dejaco-Ruhswurm, Scholz et al., 2001; Rattanatam, Heng et al., 2001; Chauhan and Radke, 2002; and Nichols and King-Smith, 2003). What is not understood is the nature of the frequent symptoms that contact lens patients experience in terms of tear film and contact lens variables.

For successful contact lens wear, the pre-lens tear film is important for several reasons. First, this outer layer of the tears provides a uniform coating over the contact lens making it a smooth optical surface. If this outer layer becomes rough or irregular, as it may during tear drying and break-up, this will lead to light scatter and reductions in image quality (Timberlake, Doane et al., 1992; and Tutt, Bradley et al., 2000). Another function of the pre-lens tear film during contact lens wear is to provide comfort and lubrication to the palpebral conjunctiva, especially during the blink. Additionally, the superficial lipid layer of the tear film reduces evaporation of the tear film, maintaining contact lens hydration (Mishima and Maurice, 1961; and Guillon, 1986). If the lipid layer is altered by the presence of a contact lens, increased evaporation of the pre-lens tear film (PLTF) probably occurs followed by contact lens dehydration and depletion of the post-
lens tear film by absorption into the contact lens (Sharma and Ruckenstein, 1985). This may be the mechanism of contact lens-related dry eye.

Just as the pre-lens tear film is important during contact lens wear, so too is the post-lens tear film (PoLTF). Along with oxygen permeability properties of the lens material itself, oxygen transmission to the cornea depends on the PoLTF thickness (Wagner, Polse et al., 1980). The PoLTF also provides ocular comfort during contact lens wear, cushioning the lens on the corneal and conjunctival epithelium while the lens moves (Little and Bruce, 1994; Little and Bruce, 1995; and Bruce and Mainstone, 1996). The PoLTF, via tear exchange, removes cellular and inflammatory debris from this layer and further lubricates the epithelial layers (Hayashi and Fatt, 1976). If the PoLTF is diminished, as it might be during contact lens-related dry eye or the overnight wear of contact lenses (i.e., lens adherence), the accumulation of debris and inflammatory mediators may pose a significant threat to the ocular surface in terms of ocular infection, inflammation, or mechanical desiccation (Josephson and Caffery, 1989; Little and Bruce, 1994; and Little and Bruce, 1995). In fact, depletion of the PoLTF is could be the mechanism of inferior arcuate staining seen in soft contact lens wearers (Zadnik and Mutti, 1985; and Little and Bruce, 1995).

Although experts and clinicians would logically agree that there are changes in the tear film associated with the wear of contact lenses, these changes are not well understood or documented, especially in relation to symptoms during lens wear. Using
the search terms “contact lens” and “tears” in the MEDLINE database title field yields 22 published articles to date (3/25/04). All are more “basic” studies that have evaluated the concentration of various proteins or other inflammatory mediators in the tears of contact lens wearers, but these studies have not addressed any relation to comfort (although they may related to other complications associated with contact lens wear). For example, there have been several studies that have evaluated IgA and/or lysozyme changes in the tear film during lens wear, but these documented changes do not explain alterations in patient comfort or other symptoms of ocular irritation. A study by Vinding and workers (1987) showed a significant decrease in IgA in tears of contact lens wearers compared to non-wearers, but there was no difference in lysozyme concentrations between the two groups (Vinding, Eriksen et al., 1987). This was confirmed by a more recent study in soft lens wearers that showed a decrease in IgA in the tears of contact lens wearers (Willcox and Lan, 1999). Another study showed that in RGP lens wearers, there again is a decrease in IgA (especially during the first few months of lens wear) and a significant increase in lysozyme, but lactoferrin levels remained unchanged (Vinding, Eriksen et al., 1987). Another study evaluated the relative concentration of fibronectin, albumin, and total protein in the tear film of contact lens wearers compared to non-contact lens wearers and found a significant increase in fibronectin but no difference in albumin or total tear protein between the groups (Baleriola-Lucas, Fukuda et al., 1997). Yet another study has showed that interleukin-6 (IL-6—an inflammatory mediator) is present in the tears of
contact lens wearers but not present in the tears of non-lens wearers suggesting that a contact lens may lead to a low-grade inflammatory response of the ocular surface (Schultz and Kunert, 2000). Although each of these studies is important in understanding some of the potential mechanisms of an increased risk of infection during lens wear or other inflammatory complications, they do not provide insight into the mechanism of dry eye or comfort during contact lens wear.

Contact Lens and Lipid Layer Interactions

Another way to think about the tear film in relation to contact lens wear is by studying the characteristics of each layer rather than the total tear film. For instance, the superficial lipid layer of the tear film is found anterior to the PLTF. Table 2 lists the specific components of the tear film lipid layer in humans and their relative contributions. It is important for the contact lens to remain “wetted” with a coherent tear film over its surface in order to provide good comfort, vision, lubrication, prevent surface drying, remove debris and particulate matter, and counter contamination and infection during lens wear. However, the hydrophobic nature of some materials (particularly rigid gas permeable (RGP) materials) may inhibit the formation of a smooth lipid layer leading to instability of the PLTF. Obviously, hydrogel lenses are inherently more wettable than RGP materials, although water content alone does not make a lens wettable.

In theory, the polar lipids could serve as wetting agents in that their nonpolar groups could bind to a hydrophobic surface and the polar groups would interface with the
watery layer. In this way, they might act as surfactants reducing the surface tension of the tears allowing for them to spread. This is not true of nonpolar lipids, which act as a water barrier (prevent evaporation) and lubricant. Because only about 15% of the lipid layer is polar lipids, the lipid layer as a whole would probably not be a good wetting agent in terms of contact lenses (Nicolaides, 1986). However, both the polar and nonpolar lipids are essential in that each plays a different role in terms of normal tear film function. Holly (1981) suggested that a contact lens must have a thick coat of continuous mucus with a superficial lipid layer resting over the top to aid with wetting in this regard (Holly, 1981).

Bruce and coworkers (1995) hypothesized that tear break-up time and lens deposits were the mechanisms for the dryness symptom associated with contact lens wear. In their study, two groups were classified based on the symptoms (24 cases and 26 controls), and pre-lens thinning times (a.k.a., pre-lens NITBUT) were measured and compared between the groups. The median pre-lens NITBUT for the symptomatic group was 3 seconds and was 3.5 seconds for the asymptomatic group (p = 0.93). The authors concluded that pre-lens tear stability was not associated with patient comfort.

Chui and coworkers (1999) attempted to determine if NITBUT and measures of aqueous tears (e.g., the phenol red thread test) were predictive of “successful” contact lens wear (determined through number of hours of wear) (Chui, Cho et al., 2000). They found that hydrogel lens wear was associated with a significant initial decrease in
NITBUT but no change in tear volume as assessed by the phenol red thread (PRT) test. After 28 weeks, the NITBUT and PRT tests were unable to predict the length of soft contact lens wear. As an individual’s symptoms during lens wear probably relates to his or her wearing time, this draws into question the ability of the NITBUT and PRT tests to predict symptoms. However, as with other studies by other investigators related to the issue of symptoms, tear film, and contact lens wear, no sample size or power calculations were performed. Thus, the absence of evidence here does not necessarily support the lack of a relation.

Fonn and coworkers performed a similar study but used two groups of patients—one with symptoms of dryness and the other without such symptoms (Fonn, Situ et al., 1999). This was a contralateral eye study in which patients were asked to wear lenses of etafilcon A and omafilcon A material for a period of seven hours. Lens water content was measured with an Atago CL-1, and patients recorded their dryness and comfort over several periods throughout the day. The study showed significantly more dryness, decreased comfort, and reduced pre-lens NITBUT in the symptomatic group compared to the asymptomatic group. No relation was found between lens dehydration and dryness, comfort, or NITBUT for either lens type for either group. Not surprisingly, changes in comfort were significantly associated with dryness over the wear period for both lens types. Given the previous discussion about the mechanism of hydrogel lens dehydration (i.e., a break in the tear film leads to evaporation and dehydration), this study could have
supported this theory as both lens dehydration and pre-lens NITBUT were measured. However, once again the study was inappropriately powered to find this relation in that there were only 20 patients tested and these clinical measures are notoriously variable. The correlation coefficients between lens dehydration and dryness were 0.09 and 0.23 for the etafilcon A and omafilcon A material lenses respectively; however, the investigators only had 7% and 16% power to have found a true relation if indeed it existed. Thus, this study really cannot confirm or deny the relation between NITBUT, lens dehydration, and comfort and these questions still remain in debate.

Maissa and coworkers (2002) sampled the tear film of hydrogel lens wearers and non-lens wearers and determined lipid layer profiles using high pressure liquid chromatography (HPLC) (Maissa, Guillon et al., 2002). They found that hydrogel lens wearers had a significant decrease in the phospholipids, triglycerides, and monoglycerides compared to non-lens wearers, but lens wearers had significantly higher levels of cholesterol than non-lens wearers. There was no attempt to correlate these findings with meibomian gland structure, interference patterns associated with the lipid layer, or patient-reported symptoms during lens wear.

Guillon and coworkers (2002) have also used the method of “thickness dependent fringes” to view the lipid layer of contact lens wearers wearing three different material lenses (Guillon, Morris et al., 2002). Nine subjects each wore lenses of omafilcon A (FDA Group 2), alphafilcon A (FDA Group 2), and etafilcon A (FDA Group 4), and the
lipid layer structure was assessed prior to application, during lens wear, and after removal.
The authors showed that overall hydrogel lens wear leads to a reduction in lipid coverage
and thickness in the PLTF. Further, omafilcon A showed the best lipid coverage,
followed by alphafilcon A and etafilcon A materials. The authors conclude that this
finding suggests that omafilcon A material lenses should be used in patients with a poor
lipid layer to prevent evaporation of the tear film.

Another study of potential relevance to patient-reported comfort during lens wear
was recently conducted by Thai and coworkers (2004) who evaluated four different
classifications of hydrogel materials on outcomes associated with the PLTF (Thai,
Tomlinson et al., 2004). Twenty subjects each wore lenses made from polymacon (Group
1), omafilcon A (Group 2), phemfilcon A (Group 3), balafilcon A (Group 3), and
etafilcon A (Group 4) at five different times. The objective of this study was to
characterize differences between the precorneal and PLTF (thinning time, evaporation
rate, lipid layer stability) that might relate to lenses with different material properties in
these subjects. The authors showed that all hydrogel lenses were associated with an
increase in the PLTF evaporation rate (which increased 34% compared to measures of
precorneal tear film evaporation) and a decrease in tear thinning time (which was reduced
by 65% overall when comparing the PLTF and precorneal tear film). Interferometric
measures showed significant difference when comparing PLTF and precorneal tear film
lipid layers, but no differences were shown among the different classes of materials. The
authors conclude that the presence of a contact lens alone significantly alters precorneal tear physiology, regardless of the material property. Although this study is an important one, it lacks any sort of assessment of subjective comfort in relation to the outcomes.

In another similar study that was recently published, Glasson and coworkers (2003) compared 20 “successful” contact lens wearers to 18 previous contact lens wearers who became intolerant and no longer wore lenses on various “clinical” and tear protein outcomes (Glasson, Stapleton et al., 2003). No difference in tear proteins was found, although differences in non-invasive tear breakup time (NITBUT), tear meniscus height, and the numbers of symptoms reported by the patients were observed. While this study provides some initial insight into contact lens-related intolerance, there were significant methodological limitations which limit its applicability. Particularly, the clinical measures are subjectively graded by clinicians, who were not masked to “disease” status, and there was no consideration of power or sample size relative to clinically relevant differences in outcomes.

Related to the stability of the PLTF is the hydration of a hydrogel contact lens. It is thought that if the PLTF is unstable, particularly as the lipid layer is altered, this may lead to surface dehydration of a lens and patient symptoms of dryness. Thus, measures of lipid layer appearance, stability, and thickness could be important particularly as they may relate to dehydration of lenses. This may be true not only for hydrogel lenses in
general but also for specific classifications of hydrogel lenses relative to nominal water content.

**Contact Lens Utilization and Public Health Significance**

The need for refractive correction is significant world-wide. It is estimated that there are about 35 million contact lens wearers in the United States and about 100 million contact lens wearers world-wide (Barr, 2004). A recent international survey of 13,787 contact lens fits (new and existing fits) showed that the average contact lens wearer is 30.6 years old and that about two-thirds of contact lens wearers are female (Morgan, Efron et al., 2004). In 86% of new fits and 79% of refits, hydrogel lenses were used, compared to rigid gas permeable materials (Morgan, Efron et al., 2004). Of hydrogel lenses, 14% were low water (< 50%) and 84% were high water (> 50%); the other 2% were silicone hydrogel materials (Morgan, Efron et al., 2004).

Consideration of these factors is important in terms of their relation to contact lens-related dry eye for several reasons. First, numerous contact lens wearers suffer from dry-eye related symptoms. Depending on the criteria for the frequency and/or severity of symptoms, somewhere between 25% and 75% of lens wearers (perhaps up to about 17 million in the US) suffer from dry eye symptoms during lens wear. Based on a restrictive definition of dry eye syndrome including both signs and symptoms, one study found that 25% of contact lens wearers had dry eye syndrome, which was significantly higher than among non-contact lens wearers (Hikichi, Yoshida et al., 1995). Extrapolating this
frequency to the number of contact lens wearers in the United States means that almost nine million contact lens wearers may suffer from contact lens-related dry eye syndrome. The number of contact lens wearers continues to grow, and it is likely that the prevalence of contact lens-related dry eye syndrome will increase, as there have been no significant advances made to reduce the dry eye problem in lens wearers.

These symptoms are directly related to the continuation of lens wear in both the short- and long-term. Dry eye symptoms during contact lens wear could lead to a reduction in wearing time or possibly a discontinuation of contact lens wear for many patients, although these outcomes are not well understood. One study found that within five years of lens wear, 12% of contact lens patients discontinued contact lens wear permanently (Pritchard, Fonn et al., 1999). The primary reasons for contact lens discontinuation were discomfort (49%) and dryness (9%) symptoms. Forty-nine percent of patients who discontinued lens wear were refitted at least once due to the discomfort, and all had reduced their lens wearing times prior to discontinuation. In another survey of 199 patients who had discontinued contact lens wear the most common reason for lens discontinuation was discomfort (72% of patients) (Schlanger, 1993). Although larger-scale studies of eye care utilization are needed to further our understanding of these outcomes, these studies provide insight into the prognosis of contact lens-related dry eye patients. A second reason for understanding the frequency of use of various materials, in
particular for hydrogel lens wearers, is that certain material characteristics may be directly related to symptoms during lens wear.

**An Evaporative Model of Contact Lens-Related Dry Eye**

Although common, the mechanism of contact lens-related dry eye symptoms is not understood. Alterations in the lipid layer of the tear film, whether short-term lipid instability produced by the mere presence of a contact lens or long-term changes in the lipid-producing meibomian glands, may lead to contact lens dehydration and dry eye symptoms. It is hypothesized that lipid layer instability, induced simply by the presence of a lens or by meibomian gland atrophy associated with long-term lens wear, leads to contact lens dehydration and patient symptoms. This dehydration is potentially more likely to occur in hydrogel lenses that are higher in nominal water content (> 50%), as previous studies have shown that these are the most susceptible to dehydration (Helton and Watson, 1991; McConville, Pope et al., 1997; and Efron and Morgan, 1999).

In the short term, when a contact lens is placed on the ocular surface, disruption of the superficial lipid layer occurs. Following the initial disturbance, the aqueous tears evaporate from the pre-lens tear film (PLTF), and the contact lens may dehydrate. Over the longer term, a contact lens may lead to structural alterations of the meibomian glands, which are the lipid-producing, holocrine glands embedded in the tarsal plates of the eyelids. If the meibomian glands are altered by the long-term wear of a contact lens, this could lead to pre-lens tear film instability, followed by contact lens dehydration. The
post-lens tear film (POLTF) is likely then absorbed through the contact lens and is evaporated into the atmosphere. It is at some point during this process that dry eye symptoms occur; however, we do not understand the relation between the symptoms, contact lens dehydration, and the tear film. This depletion may lead to the dryness and discomfort symptoms and mechanical desiccation of the ocular surface.

Clinicians have therefore relied on the theoretical argument that lenses (especially of high water content) tend to maintain their hydration when placed on the eye, and for that reason, absorb the PLTF and POLTF, drying the eye. This may be associated with dry eye symptoms. However, no studies have confirmed this. One study conducted by Efron and Brennan (1988) evaluated the dehydration of low water content hydrogel lenses in relation to contact lens-related dry eye symptoms. They found that “the lenses of patients who reported that their eyes never felt dry during lens wear had a higher water content that those who often experienced ‘dryness’ (p < 0.05).” This is counterintuitive to what has been proposed and needs further study.

It is important to note that regardless of the mechanism of contact lens dehydration, the process is likely a cyclical one involving lens drying and rehydration. Once the lens surface has begun to dehydrate (through any or all of the previously mentioned mechanisms), a swelling pressure is created, drawing water from deep within the lens to the surface. The depth of this dehydration has been predicted theoretically by Fatt (1989) and may range from 0.03 mm for low water content lenses to 0.07 mm for
higher water content lenses (Fatt, 1989). This may expose the cornea to the dehydration cycle associated with the lens, leading to corneal staining. With each blink the lens might be rehydrated to some extent; however, the rehydration does not replace the water lost in the first 60 to 120 minutes of lens wear. The contact lens loses and then reimbibes water, but the process must eventually come to a steady-state; if it did not, the lens would continually lose or gain water. As the lens begins to dehydrate, water conductivity should increase. High water content materials lose more water before this equilibrium is met than low water content lenses. Again, for lenses of mid-to-low water content, water conductivity within the lens quickly increases with lens dehydration; this is based on predictions from laboratory measurements from Fatt (1989). However, clinical data also support this finding showing that high water content lenses lose more water than low water content lenses (Brennan and Efron, 1987; and Efron, Brennan et al., 1987). The steady-state equilibrium is presumably reached in 3 to 5 minutes, which has been determined theoretically and in vivo (Efron, Brennan et al., 1987; and Fatt, 1989). As Fatt (1989) proposes, after the steady-state equilibrium is established, the posterior surface boundary may close, alleviating any chance of post-lens tear film absorption. This may be particularly true in successful, asymptomatic contact lens wearers; however, this is probably not true in patients with dry eye symptoms or those who wear their lenses on an overnight basis.
Specific Aims

The specific aims of the research related to this dissertation are to test the hypotheses that evaporative tear film and contact lens factors associated with contact lens-related dry eye symptoms include:

a) Meibomian gland disease,
b) Decreased pre-lens tear film lipid layer thickness,
c) Short pre-lens tear film noninvasive tear breakup times,
d) A reduction in hydrogel water content,
e) An increase in hydrogel refractive index, and
f) High water content hydrogel lens wear.
CHAPTER 2

METHODS

Study Design Overview

A cross-sectional survey with nested case-control study design was used to test factors associated with contact lens-related dry eye symptoms. An overview of the Contact Lens and Dry Eye Study design is seen in Figure 1. A cross-sectional survey study (Phase I) will be conducted in approximately 800 to 1,000 contact lens-wearing patients using the Contact Lens Dry Eye Questionnaire (CLDEQ) (Nichols, Mitchell et al., 2002). This survey has been shown to be an efficient and accurate method of screening contact lens wearers. For Phase II (i.e., the nested case-control phase), contact lens-related dry eye cases and controls were identified within the cross-sectional cohort of surveyed patients, making it possible to then identify additional factors or exposures potentially related to contact lens-related dry eye symptoms. The examination and statistical analyses presented here are intended to address which “evaporative” factors are associated with contact lens-related dry eye and the relative strength of the associations (i.e., adjusted odds ratios and 95% confidence intervals for the odds ratios).
Phase I—Entry Criteria, Recruitment, and Subject Selection

Patients must have been wearing contact lenses (hydrogel or rigid gas permeable) during the last thirty days prior to enrollment in either phase of the study ($\geq 1$ day per week), and patients must be at least 14 years old. Patients for Phase I were recruited from The Ohio State University College of Optometry clinics and non-clinic sources (to protect from a clinic-based sample bias). Prior to enrolling in Phase I, patients were asked to complete HIPAA documents (Human Subjects Informed Consent documents were waived for this phase of the study), and they were informed that they might be contacted to return for a comprehensive interview and dry eye examination. Patients were asked about their interest in being contacted for Phase II of the study. They were then asked to complete the CLDEQ. The instrument has better screening performance compared McMonnies’s questionnaire with a sensitivity of 83%, specificity of 67%, and an area under the ROC curve of 0.82 (McMonnies, 1986; and Nichols, Mitchell et al., 2002). All individuals that indicated they were interested in Phase II were asked to participate, although they could decline participation after learning more about the examination phase of the study.

Phase II—Examination Phase Primary Outcomes

Subjects first completed Human Subjects Informed Consent documents that were approved by the Biomedical Institutional Review Board of the Ohio State University according to the tenets of the Declaration of Helsinki. In this phase of the study, a dry eye
examination was performed. Data collection for cases and controls was performed in an identical manner without examiner knowledge of survey screening (disease) status. Safeguards were used to protect against the clinician becoming unmasked relative to disease status (i.e., study coordinator performed scheduling, ophthalmic survey was self-administered at the completion of the examination). All clinical tests were performed on the right eye of the subject, with appropriate rest intervals associated with the more ‘invasive’ tests that might induce tearing.

Data collection for cases and controls was performed in an identical manner without examiner knowledge of survey screening (disease) status. All outcome procedures performed in the Phase II examination are found in Table 3. From preliminary analyses related to this study, it was determined that the Contact Lens Dry Eye Questionnaire used for recruitment and screening of patients required a second administration. This survey was re-administered at the completion of the Phase II examination in order to ensure appropriate disease classification {Nichols, 2004 #6942}. Although these data have been presented previously, they are presented within this dissertation in order to illustrate the importance of these findings relative their relation to dry eye outcomes. The primary outcomes measures related to the hypothesis testing in this report are detailed in the following text.
Pre-Lens Lipid Layer Thickness

The TearScope Plus instrument was used in this study to assess pre-lens tear film lipid layer thickness. This system uses the method of “thickness dependent fringes” (TDF), whereby the wavelength and angle are the same but the thickness is variable. Thus, TDFs are oscillations in the reflectance spectra as a function of thickness for any wavenumber (inverse of wavelength). Using this method, a series of light and dark fringes are observed with maxima and minima corresponding with constructive and destructive interference, respectively. A broadband light source is used (rather than a monochromatic light source) for viewing of the lipid layer. Black and white responses are associated with thin films (< 120nm), whereas orange, brown, blue, and yellow colors are associated with medium thicknesses (120-300nm), which is related to the blue-yellow response of the visual system. As the lipid layer, which is a high-index, thin film, is generally less than 100nm, and the order (m) is less than 0.5, lighter regions from TDFs correspond to thicker regions of lipid. We have found good reliability within- and between-graders in preliminary studies using this technique (Nichols, Nichols et al., 2002). The TearScope Plus is mounted on a slit-lamp biomicroscope (Haag-Streit BQ 900, Bern, Switzerland). All lipid layer interference measures are taken on the right eye of each subject. The patient is asked to blink normally while the examiner assigns a real-time tear (lipid layer) interference pattern classification (using the Guillon/TearScope scheme).
Pre-Lens Tear Film Noninvasive Breakup Time (PLTF-NITBUT)

The TearScope Plus instrument was used to examine PLTF-NITBUT. Again, in pilot studies, we have found that the TearScope Plus instrument is reliable when examining this outcome measure within- and between-examiners (Nichols, Nichols et al., 2002). This method reduces any alteration of the tear film by the instillation of fluorescein and minimizes the potential for reflex tearing. When obtaining NITBUT, patients are asked to hold both eyes open and the examiner times the interval from the last blink to the first break, dry spot, or distortion occurring in the tear pattern (Cho, 1991; Cho, Brown et al., 1992; and Cho and Brown, 1993). Patients are encouraged to blink if they feel discomfort to avoid reflex tearing. If a patient blinked during the test sequence prior to tear film break-up, he or she was instructed to rest briefly to allow the tear film to stabilize, and the measure was repeated with reinforcement of the instructions. Three measures of PLTF-NITBUT were taken, and an average of these three is used in statistical analyses.

Water Content and Refractive Index

There are several methods of measuring hydrogel lens water content including gravimetric methods, nuclear magnetic resonance imaging, and refractometry. The recommended techniques of the International Organization for Standardization (ISO) for measuring hydrogel water content are via refractometry and gravimetric methods (1997). These methods, especially gravimetric, are somewhat costly and time-consuming (Galas
and Enns, 1993). Refractometry is the most feasible method in clinical research studies for measuring the water content of a soft lens. This method is possible due to the fact that the refractive index of a soft lens is dependent on its water content (Fatt and Chaston, 1980; and Mousa, Callander et al., 1983). In refractometry, the water content is determined by measuring the refractive index of the contact lens relative to the refractive index of the prism used in the refractometer (Brennan, 1983). The difference determines the angle of refraction of the limiting ray and the extent of illumination of the internal scale of the refractometer (percent water or solid content depending on the refractometer) (Brennan, 1983; and Efron and Brennan, 1987).

Hand-held versions of refractometers are often used in the food and wine industry for the measurement of sugar concentration (i.e., the Brix scale = the number of sucrose grams in 100gm of sucrose solution). These instruments were originally described for use with contact lenses by Brennan (Brennan, 1983). The Atago CL-1 (Atago Company Ltd, Tokyo, Japan) can be used to measure the water content of contact lenses clinically, although the instrument is no longer manufactured (Efron and Brennan, 1987). The Atago N2, which is currently manufactured, is another hand-held refractometer that can be used to measure the water content of hydrogel lenses. This instrument is moderately priced and is easy to use relative to other instruments. Another alternative is the Index Instruments’ CLR 12-70 (Cambridge, UK), which is the only available automated refractometer designed to measure not only the water content, but also the refractive index of hydrogel
lenses. Although the instrument is expensive, it is easy to use in a clinical research setting. The fact that it is automated should, in theory, reduce errors between operators when making measures. In preliminary studies, we have shown that the CLR12-70 is indeed more reliable and valid than the Atago hand-held refractometer (Nichols and Berntsen, 2003; and Nichols, Mitchell et al., 2003). Thus, this instrument is used in this study.

Following a contact lens fit assessment, the patient was instructed to remove his or her right contact lens and to immediately place it on the refractometer. Refractive index and water content were then determined by the instrument. These values are eventually compared to the nominally reported refractive index and water content for the specific lens type in order to determine dehydration of the lens. Refractive index increases as water content decreases; thus, as a lens dehydrates, its refractive index increases. Because silicone hydrogel lenses do not maintain a linear relation between water content and refractive index, water content measures are not feasible using a refractometer. Thus, only refractive index values are obtained when a patient is wearing a silicone hydrogel lens. For both refractive index and water content, change is determined as follows: nominal value – measured value.

**Material Type**

Hydrogel lens dehydration, especially of higher water content materials, may be a factor associated with contact lens-related dry eye symptoms. One of the fundamental
determinants of the tear film-contact lens interaction is the water content of the contact lens. All hydrogel lenses lose water when taken from a vial or blister pack and placed on the ocular surface. In general, low water content lenses may lose about 1% of water content, high water content lenses may lose up to about 5%, and no lenses have ever been shown to completely dehydrate during lens wear (dehydration levels are at most 15%). Clinicians rely on a theoretical argument that lenses of high water content attempt to maintain their hydration when placed on the eye and for that reason absorb the pre- and post-lens tear film, drying the eye. The tear film is absorbed by the contact lens, evaporated into the atmosphere dehydrating the contact lens, which then produces symptoms. Accordingly, if the eye already exhibits an inadequate tear quantity or quality, a high water content lens will exacerbate symptoms. For these reasons, it is important to consider the influence of water content/dehydration of lenses in patients with contact lens-related dry eye. We will determine both the utilization of high/low water content and ionic/non-ionic contact lenses in our analyses to see if they are associated with contact lens-related dry eye symptoms (by FDA hydrogel lens grouping).

In addition, specific analyses will be conducted of the most commonly worn materials in terms of their relation to contact lens-related dry eye. For these specific subgroup analyses, the two most commonly worn lens materials will be identified, and the percent of dry eye and non-dry eye subjects wearing that material will be reported, in addition to a chi-square statistic. Additionally, material-specific analyses will be
conducted for measured dehydration (through water content or refractive index), and t-tests of the average dehydration for the DE and NDE groups will be reported for these outcomes.

**Meibography**

Patients underwent digital video meibography imaging, and transillumination of the right lower eyelid was conducted using a Dolan-Jenner transilluminator and fiber-optic light guide using near-infrared (IR) light (650 to 700 nm). Central images from the right lower eyelid were recorded using a Hitachi KP-M2R near-IR one-chip CCD camera. The camera is mounted on a slit-lamp and hooked directly to a computer for video capture and each sequence was 1200 frames in length. All images were captured from the central eyelid at 10X slit-lamp magnification. We are able to capture up to 15 individual glands in our central image sequences, while there are reported to be approximately 20 or so whole glands in the lower eyelid of humans (Tiffany, 1995). A single frame from each video sequence representing the best quality image (i.e., illumination and focus) was selected for grading.

In general, ‘normal’ meibomian glands appear as grape-like clusters with acini that are hypoilluminescent (Jester, Rife et al., 1982). Ducts and orifices transmit light and appear as hyperilluminescent regions surrounded by the gland acini. Complete or “whole” meibomian glands are those which traverse the lid linearly roughly 3 to 4 mm; those which do not traverse the lid fully or are found in small, irregular clumps are
termed “partial” meibomian glands. The first grading scale (termed the gestalt scale) was one in which the reader assessed the images using the following grades: Grade 1 (no partial glands), Grade 2 (less than 25% of the image contains partial meibomian glands), Grade 3 (between 25% and 75% of the image contains partial meibomian glands), and Grade 4 (more than 75% of the image contains partial meibomian glands). Sample images associated with each of these grades can be found in Figure 2. The second grading scale was one in which the reader counted the number of complete meibomian glands in the image, with no credit given for partial glands. The reader always graded the image first using the gestalt scale and then proceeded with individual complete gland counting in order to prevent bias associated with the more quantitative gland counting approach. All images were graded by one masked reader, who graded each image on two occasions separated by at least 7 days. When there were discrepancies associated with the two readings for the gestalt scale made by the first masked reader, a second masked reader adjudicated the grade by performing an independent assessment of the image. The grade determined by the second masked reader was used for analyses in this regard. For gland counting, an average of the two readings performed by the first examiner was used in statistical analyses.

Patient-Related Factors

Patient-related factors including age, gender, educational status, total household income, and smoking status were evaluated in terms of their relation to dry eye status.
Several of these outcomes have been implicated in previous epidemiological studies of dry eye disease. All of these outcomes were obtained through self-report.

Phase II—Examination Phase Secondary Outcomes

Osmolarity

A 200-nanoliter tear sample was taken for analysis of osmolarity using the Advanced Instruments osmometer. This system is preferred over older edition osmometers due to the small tear film sample size necessary (200 nanoliters compared to 2-20 microliters). The sample was taken from the meniscus of the right eye using a capillary tube. Caution was taken such that the ocular surface was not irritated to reduce the potential for reflex tearing.

Phenol Red Thread Test

Tear production rates and/or tear volume were determined using the Zone Quick phenol red thread test (Menicon, USA). Measurements were taken on the right eye. The thread was inserted over the inferior lid margin toward the temporal canthus. The patient was instructed to look straight ahead for 15 seconds blinking normally. After this time, the thread was removed and measured to the nearest millimeter.

Corneal and Conjunctival Staining

Staining of the ocular surface was recorded for five areas of the cornea as proposed in the Report of the NEI Dry Eye Workshop (Lemp, 1995). A 5µl sample of 2% liquid fluorescein was applied to the bulbar conjunctiva using a Finnpipette adjustable (5-
40 uL) micropipette. Following instillation, a Wratten #12 blocking filter was used to enhance contrast in examining for staining of the cornea. Each of the five corneal locations was graded in terms of the surface area corneal staining. Corneal staining surface area will be graded for each of the five locations, and a total “surface area” staining score will be generated (our of 20 possible points). A modified version of the Cornea and Contact Lens Research Unit (CCLRU) Grading Scales will be used for surface area grading as follows:

Grade 0: None
Grade 1: 1-15% Surface Area
Grade 2: 16-30% Surface Area
Grade 3: 31-45% Surface Area
Grade 4: > 45% Surface Area

Lissamine green staining of the conjunctiva was evaluated as it has been found to induce significantly less ocular irritation than rose bengal and shows an identical staining pattern (Manning, Wehrly et al., 1995; and Kim and Foulks, 1999). Staining was assessed by using a 10 µL of a 1% liquid solution applied to the bulbar conjunctiva using a Finnpipette adjustable (5-40 uL) micropipette. Following instillation, conjunctival staining was graded in each of the six areas diagrammed schematically in the aforementioned Report of the NEI Dry Eye Workshop using the surface area grading scheme as seen above (Lemp, 1995).
Sample Size

Sample size is an important consideration for any study, as it determines the power for testing of hypotheses. Sample size calculations for these analyses are driven by the evaporative factors proposed to be associated with contact lens-related dry eye symptoms. Sometimes in studies, the interest is not in changes between proportions or means, but rather, the odds of an outcome occurring. This is true in part for these proposed analyses, as our interest is in predicting patient with contact lens-related dry eye symptoms. Sample size estimations are driven by the statistical method that might be utilized to analyze the data collected, which in this case is through comparison of means and proportions (traditional parametric and nonparametric hypothesis testing), and through logistic regression where the outcome is the presence or absence of symptoms.

Table 4 shows sample sizes estimates for Phase II of the study. All sample size estimates in this table have been inflated by 10% for margin of error correction (i.e., sampling errors, missing data, etc.). These sample size calculations also assume a one-to-one ratio of dry eye cases to controls. The largest sample size required is associated with high water content contact lens wear, which shows that at least 330 cases and controls are needed to detect a clinically significant increase in the odds (OR = 2.25) of contact lens-related dry eye given high water content lens wear. Thus, the total sample size needed for the case-control phase (Phase II) of the study is driven by high water content lens wear—approximately 330 patients. This sample size will allow for the detection of clinically
relevant differences in the other evaporative factors proposed as being associated with contact lens-related dry eye symptoms. One assumption associated with this sample size calculation was that all patients would be appropriately classified using the screening survey. No adjustments were made for inappropriate classification of disease status.

**Statistical Analyses**

All statistical analyses described below were performed with SAS, Version 8.02 (SAS Institute, North Carolina) or SPSS, Version 12 (SPSS, Chicago, IL).

*Assessment of Reliability of CLDEQ Disease Classification*

**95% Limits of Agreement.** This method was used to examine the test-retest reliability of the CLDEQ short-form scoring index (Nichols, Mitchell et al., 2002). The mean difference of the test-retest values relative to zero represents bias (tested with a one-sample t-test), and the width of the 95 percent limits of agreement represents the reliability of the outcome. When appropriately using this analysis, the differences between measures should be normally distributed. Correlations between the difference in scores and the average of the scores, age, and days between survey administrations were determined using Pearson’s correlation coefficients. Given our large sample size (n = 274), the study had 80 percent power to find a correlation coefficient as small as 0.17 to be statistically significant (α = 0.05). Therefore, evaluation of the magnitude of the reported correlation coefficient is suggested using the following guidelines: a correlation of 0.1 to 0.3 is small, 0.3 to 0.5 is moderate, and greater than 0.5 is large (Cohen, 1992).
A subgroup analysis was also conducted using a two-sample t-test to determine the impact of patient gender on test-retest reliability of the CLDEQ short-form scoring index. **Intraclass Correlation Coefficient.** The intraclass correlation coefficient (ICC) was also used to examine the test-retest reliability the CLDEQ scoring index, and the 95 percent confidence interval associated with the ICC is also reported. It has been recommended that an ICC should exceed 0.90 if a technique is to be used for individual assessments in clinical practice and 0.70 for discriminating among groups in research (Shrout and Fleiss, 1979). We also determined the number of administrations (m) required to obtain a desired ICC (p∗) using the lower limit of the 95 percent confidence interval according to the method of Shrout and Fleiss (Shrout and Fleiss, 1979).

**Kappa Statistic.** The simple kappa statistic (K) was used to examine the test-retest reliability of dry eye disease status based on the scoring algorithm, which provides a true measure of agreement. Kappa values are classified for reference as follows: < 0.00 (poor reliability), 0.00 to 0.20 (slight reliability), 0.21 to 0.40 (fair reliability), 0.41 to 0.60 (moderate reliability), and 0.61 to 0.80 (substantial reliability), greater than 0.8 (close to perfect reliability) (Fleiss and Cohen, 1973; and Landis and Koch, 1977). A subgroup analysis was also conducted to determine the effect of days between survey administrations, age, and gender on the test-retest reliability of individual CLDEQ items. The days between survey administrations and age subgroups were determined using the median values for each of these outcomes.
Logistic Regression. Logistic regression was used to examine patient-related predictors of misclassification of disease status. Predictors examined included variables such as gender, marital status, income, age, race, educational status, and time between survey administrations. All predictors were considered for inclusion in multivariate modeling; however, in the final multivariate model, variables were significant only if \( p < 0.05 \). Odds ratios (OR), 95% confidence intervals (95% CI), and \( p \)-values are reported. Multivariate models were determined using a backward selection technique, and all variables in these models were examined for interactions. Significant predictors from the multivariate models are reported.

Assessment of Evaporative Factors with Self-Reported Dry Eye

Descriptive Statistics. Continuous variables were described using measures of central tendency including averages and medians (when appropriate). Standard deviations and minimum and maximum values were used to provide an indication of dispersion of these data. Frequencies (or percents) were used for variables that were categorical in nature.

Hypothesis Testing. Logistic regression was used to determine the relation between self-reported dry eye disease (a dichotomous outcome) and independent variables (predictors). Logistic regression analyses require independence of observations. This is certainly the case in this dataset, as these data were obtained from individual subjects and each subject’s data occurs only once. Another assumption underlying logistic regressions is linearity of the logit for continuous variables. To examine this assumption, logit values
for each continuous predictor variable were plotted versus the actual value of the predictor variable. If linearity was questionable, additional modeling of the variable was performed after categorization. Initial univariate logistic regression models were produced to describe the relationship between each individual predictor variable and the outcome (y = dry eye (DE) or not dry eye (NDE)).

Upon completion of the univariate analyses, a multivariate analysis was performed. In the initial step of this procedure, a logistic model including all independent variables associated with dry eye disease in the univariate models at $\alpha = 0.10$ level (i.e. the p-value was less than 0.10) was performed. Stepwise variable selection was used to determine those predictors significantly associated with dry eye disease in a multivariate model. Using this model, a forward selection procedure was performed allowing each excluded predictor, regardless of significance level in the univariate model, the opportunity to enter the multivariate model. At each step, the predictor with the smallest p-value was included. Model building was stopped when no other predictors added significantly ($\alpha = 0.05$) to the model. Once the multivariate model was established, the variables in the model were examined for two-way interactions. An interaction between two variables implies that the relationship between one of the variables and dry eye disease status is not constant across the other. These interaction terms in the model were examined by first creating the appropriate product of the two terms and then examining the Wald statistic and p-value for their significance. Significant interactions were
included in the model (p < 0.05). This concluded the model building steps and led to a final model that best predicted self-reported dry eye status.

The Hosmer-Lemeshow goodness-of-fit test was used to examine the calibration of the model (Hosmer and Lemeshow, 2000). When the chi-square value for this test is small (large p-value), the model is considered well calibrated (i.e., the model provides accurate estimates of the probability of predicting dry eye status based on the independent variables). The discriminative ability of the models was evaluated using the area under the Receiver Operating Characteristic (ROC) curve (i.e., can the model accurately discriminate between those who self-report dry eye disease and those who do not?). Discrimination was assessed using the following guidelines for area under the ROC curves: 0.5 indicates no discrimination, between 0.7 and 0.8 indicates acceptable discrimination, between 0.8 and 0.9 indicates excellent discrimination, and greater than 0.9 indicates outstanding discrimination (Hosmer and Lemeshow, 2000).
CHAPTER 3

RESULTS

A total of 763 patients completed the CLDEQ on one occasion (Figure 3). Overall, 339 patients (44.4%) were classified in the DE group and 424 (55.6%) were classified in the NDE group. Of those completing the CLDEQ, 316 (41.4%) stated they were not interested in participating in the Phase II examination. Of the 316 not interested in Phase II, 95 (30.1%) were classified in the DE group and 221 were classified in the NDE group (69.9%). Of the 763 patients, 447 stated they would be interested in participating in the Phase II examination. Of these patients, 244 (54.6%) were classified as in the DE group and 203 (45.4%) were classified in the NDE group. Of the 447 interested in participating in Phase II, 325 patients (75% of those interested in participating) completed the study at the date of these analyses (3/25/04). Of these patients, 172 (52.3%) were classified as having contact lens-related dry eye disease, and 153 (47.7%) were classified as not having contact lens-related dry eye disease.

CLDEQ Disease Classification Schemes

Two hundred seventy-four patients completed the CLDEQ on two occasions. The first was to recruit and screen patients, and the second was at the completion of the Phase II examination visit. The average age of this sample was 30.9 ± 10.8 years, and 67.5%
were women. All were current contact lens wearers. The mean ± standard deviation CLDEQ index score from the first visit was 1.02 ± 0.80 (range = –0.74 to 4.50); the mean ± standard deviation CLDEQ index score from the second visit was 0.98 ± 0.88 (range = –1.83 to 4.50). The mean difference between administrations was –0.05 ± 0.75, and the distribution of differences displayed normality (Figure 4) and did not significantly differ from zero (t = –1.02, p = 0.30). The 95 percent limits of agreement associated with test-retest reliability were –1.51 to 1.42 units (Figure 5). There was no correlation between the difference in CLDEQ score and the average index score (r = 0.13, p = 0.04), age (r = –0.02, p = 0.79) or the number of days between survey administrations (r = –0.04, p = 0.51). The mean difference between CLDEQ index scores was –0.08 ± 0.55 for males and –0.03 ± 0.83 for females; these mean differences did not differ statistically (t = 0.57, p = 0.57). The ICC for test-retest reliability of patient responses to the CLDEQ index score was 0.61 (95% CI: 0.53, 0.68). In order to obtain an ICC of 0.70, three administrations of the CLDEQ would be required in future studies.

Table 5 presents the overall test-retest reliability of dry eye classification for the sample. A significant percent of individuals misclassified their dry eye status, with more patients going from a positive dry eye status to a negative dry eye status (13.9%) than the converse (7.3%). In total, 21.2% of the sample misclassified disease status upon re-administration of the CLDEQ. The simple kappa statistic associated with the test-retest reliability for these data was 0.58 (95% CI: 0.48, 0.67). The simple kappa statistic for
females was 0.50 (95 % CI: 0.37, 0.62), and for males it was 0.69 (95 % CI: 0.53, 0.84). The group was stratified based on the median age (26 years) and the kappa statistic for the younger subgroup was 0.56 (95 % CI: 0.42, 0.69) and for the older group was 0.59 (95 % CI: 0.45, 0.73).

Univariate analyses from logistic regression models shown in Table 6 indicate that no patient-related variables were significantly related to dry eye misclassification. There was an indication of gender-related differences in misclassification, with females showing a slight predominance in this regard (OR = 1.88, 95% CI: 0.95, 3.70). In multivariate modeling, there was a significant interaction between gender and age ($p = 0.02$), although no other socio-demographic factors were related to misclassification. For females less than 45 years of age, the odds of misclassifying dry eye status were 2.50 (95% CI: 1.20, 5.20).

**Evaporative Factors Associated with Self-Reported Dry Eye**

Relative to the aforementioned analyses, two datasets are reported here for statistical hypothesis tests. The first data set is one including all patients who had a Phase II examination ($n = 325$)—the “full dataset”. Patients in the full dataset have been classified according to their dry eye status using the CLDEQ score from the first administration (at the screening). Of these patients, 172 (52.3%) were classified as having contact lens-related dry eye disease, and 153 (47.7%) were classified as not having contact lens-related dry eye disease.
The second dataset is referred to as the “clean dataset”. It includes all patients who had a Phase II examination; however, only patients who completed the CLDEQ on two occasions are included in this dataset. Further, patients who misclassified themselves upon re-administration of the CLDEQ are not included in this dataset. There were 274 patients who completed the CLDEQ on two administrations and also had a Phase II examination (this is the data set reported on in the previous section). However, as previously reported, 58 (21.2%) of these patients misclassified their dry eye status upon re-administration of the CLDEQ. Thus, the clean dataset is composed of 216 individuals with 116 (53.7%) were classified as having contact lens-related dry eye disease and 100 (46.3%) were classified as not having contact lens-related dry eye disease.

Univariate Analyses of the Datasets

Tear Film Factors. Tables 7-9 display univariate logistic regression analyses address various tear film associated with self-reported dry eye disease. As can be seen in many of the analyses, variables that show significance in terms of their relation to dry eye status for the full dataset generally show even greater significance in the clean dataset in terms of their relation to self-reported dry eye, regardless of the modest reduction in sample size. This underscores the importance of the previous analyses relating to misclassification bias related to self-reported dry eye.

Table 7 shows that PLTF NITBUT differed by dry eye status for both the full and clean datasets. In the full dataset, the difference in the means between groups was 1.85
seconds (p = 0.03); in the clean dataset, the difference in the means between groups was 3.81 seconds (p = 0.001). Table 9 shows that the distribution of lipid layer thickness for dry eye groups was different for both the full and clean datasets (p = 0.04 and p = 0.0006, respectively). For both datasets, thinner lipid layers were associated with self-reported dry eye. Neither method of meibography grading showed a significant relation to self-reported dry eye in univariate analyses (e.g., gland counting or gestalt analyses).

Contact Lens-Related Factors. No measurable contact lens-related factors were related to self-reported dry eye status in either the full or clean datasets (Table 7). In the clean dataset, the average percent dehydration in the DE group was $-4.23 \pm 3.41\%$, while it was $-3.73 \pm 3.14\%$ for the NDE group (p = 0.39). Similarly, dehydration as measured through change in refractive index was $0.0195 \pm 0.0094$ for the DE group, while it was $0.0176 \pm 0.0074$ for the NDE group (p = 0.17).

We conducted a post-hoc analysis to determine hydrogel dehydration relative to nominal water content (Table 14), rather than relative to the dry eye status outcome as reported above. In both the full and clean datasets, the average dehydration for nominally-reported low water materials was significantly less than the nominally-reported high water content materials. In the clean dataset, the average dehydration was $-0.73 \pm 1.77\%$ for low water content materials and $-4.24 \pm 3.20\%$ for high water content materials ($t = 6.74, p < 0.0001$). Table 15 shows that dehydration was also greater for higher water content materials when measured through refractive index in both datasets.
(p = < 0.0001 and 0.0001, respectively). Thus, although higher water content lenses do indeed dehydrate significantly more than low water content lenses, these data suggest that dehydration may not play a role in dry eye symptom reporting.

A few nominal contact lens material characteristics were associated with self-reported dry eye. For both datasets, there was no difference in the utilization of RGP compared to hydrogel materials in relation to dry eye (Table 10). Table 11 shows, however, that for the clean dataset, FDA classification of hydrogel material was associated with self-reported dry eye (p = 0.04); for this analysis, the data revealed that patients wearing Group 1 materials had a decreased risk of self-reported dry eye compared with patients wearing Group 4 materials (9.5% vs. 26.3%). In the clean dataset, both nominal water content and ionicity were related to self-reported dry eye. Table 12 shows in the clean dataset that the percent of self-reported dry eye subjects using an ionic lens (31.3%) was significantly higher than the percent of non-dry eye patients using an ionic lens (20.3%) (p = 0.04). Table 13 shows in the clean dataset that the percent of patients with self-reported dry eye using a high water content lens (41.2%) was significantly higher than the percent of subjects without self-reported dry eye using a high water content lens (17.6%) (p = 0.03). However, Table 7 shows that the average percent dehydration did not differ between groups in either the full or clean datasets (p = 0.48 and 0.39, respectively). For instance, in the clean dataset, the average percent dehydration for those with DE was about 0.5% more than those without DE. However,
measurement of hydrogel water content is difficult, variable, and not possible in with some hydrogel materials (e.g., Focus Night and Day and Durasoft); thus, missing data is an issue in this regard. Similar to water content, differences in average refractive indices between DE and NDE groups were not significant but in the expected direction (p = 0.80 and 0.17, respectively).

The two most commonly worn materials across the sample were the etafilcon A and lotrafilcon A materials. Table 16 shows that about 34% of hydrogel lens wearing patients in the full dataset wear etafilcon A (32% of the patients in the clean dataset wear the etafilcon A material). There is no difference, in either the full or clean datasets, in the percent of DE vs. NDE subjects wearing lenses of etafilcon A material (about 50% of DE subjects and 50% of NDE subjects wear etafilcon A lenses in both datasets). As can be seen in this table, there is no difference in dehydration for the etafilcon A material when comparing DE and NDE groups in either the full or clean datasets. Lotrafilcon A was the second most commonly worn material lens across the sample; about 16.5% of patients in the full dataset and 11.6% of patients in the clean dataset worn lenses of this material. As seen in Table 17, no difference existed in dehydration profiles of the lotrafilcon A material when comparing the DE and NDE groups in either the full or clean datasets (in both datasets, both the DE and NDE groups showed lens dehydration of about 0.5%).

**Patient-Related Factors.** Very few patient-related socio-demographic factors were related to self-reported dry eye status including educational status, household income, and
cigarette smoking (Tables 18-21). However, gender was related to self-reported dry eye status in both the full and clean datasets (Table 18). For the full dataset, the percent of contact lens-wearing women who reported dry eye was 40.6, while the percent of contact lens-wearing men who reported dry eye was 12.3 (p < 0.0001). In the clean dataset, the percent of contact lens-wearing women who reported dry eye was 41.2, while the percent of contact lens-wearing men who reported dry eye was 12.5 (p < 0.0001). This is noteworthy in that the clean dataset ‘controls’ for the previously reported finding that younger women tend to be those who misclassify their dry eye status in that all patients who misclassify were excluded from analysis in the clean dataset.

Secondary Outcomes

Univariate analyses of the full dataset showed that the difference in osmolarity means between groups 6.97 mOsm (p = 0.07); for the clean dataset, the difference in means between groups was 13.96 mOsm (p = 0.004). For both the full and clean datasets, the average phenol red thread test for the DE and NDE groups did not statistically differ in univariate analyses (Table 7). Similarly, for both the full and clean datasets, the average corneal and conjunctival staining scores did not differ between DE and NDE groups (Table 7).

Multivariate Analyses of the Datasets

Table 22 details multivariate logistic regression analyses of the factors associated with self-reported dry eye status in hydrogel lens wearers. RGP lens wearers were not
included in this analysis as univariate analyses showed no difference between hydrogel and RGP lens wearers in terms of self-reported dry eye. As can be seen for both the full and clean datasets, osmolarity, gender, and meibography gland count were related to dry eye status. For the clean dataset, age dropped from significance in the model, as it is likely the exclusion of young women (i.e., misclassifiers) affected the analysis in this regard. Significant factors in the clean dataset associated with dry eye status included osmolarity (OR = 1.10, p = 0.02), gender (OR = 2.87, p = 0.006), meibography gland count (OR = 1.13, p = 0.03), nominal water content (OR = 1.03, p = 0.03), and PLTF NITBUT (OR = 0.94, p = 0.03). In the clean multivariate model, pre-lens lipid layer thickness and NITBUT were highly correlated (e.g., co-linear) in the model (Spearman’s r = 0.68, p < 0.0001). Given their co-linear relation, lipid layer thickness dropped from the model in the selection procedure, while NITBUT was retained.
Contact Lens-Related Dry Eye Symptom Reporting

Clearly, patients have significant dry eye symptoms associated with contact lens use. Using the scoring algorithm that we developed for the Contact Lens Dry Eye Questionnaire (CLDEQ), we showed in both the full and clean datasets that about 50% of contact lens patients report symptoms that are significant enough that a doctor would suggest that patient has contact lens-related dry eye. Again, our algorithm previously developed for use with the CLDEQ was designed based on the prediction on the examination of over 350 contact lens wearers where doctors were asked to state whether or not the each patient had contact lens-related dry eye after their non-directed examination (Nichols, Mitchell et al., 2002). The patient also completed a survey with 10 dry eye-related symptoms (which the doctor was masked to), and the symptoms were modeled in terms of their predictive status of the doctor’s diagnosis.

The findings of this study regarding dry eye status of contact lens wearers is in good agreement with aforementioned studies’ previous estimates of the frequency of dry eye symptoms in contact lens wearers. Table 1 shows that between about 25 and 75% of patients report dry eye symptoms; the frequency estimates reported depend heavily on the
definition of significant symptoms. Thus, the CLDEQ scoring algorithm predicts a
doctor’s diagnosis of contact lens-related dry eye, and over 50% of the current study’s sample indicated by self-report this status.

Interestingly, there have been no groups who have studied either the reliability of dry eye symptom reporting of contact lens wearers or its effect on classification of disease status through self-report. Most recent, major epidemiological studies of dry eye disease use self-report of dry eye as the outcome (Bandeen-Roche, Munoz et al., 1997; Doughty, Fonn et al., 1997; Shimmura, Shimazaki et al., 1999; Moss, Klein et al., 2000; and Schaumberg, Buring et al., 2001; Schaumberg, Sullivan et al., 2003; and Moss, Klein et al., 2004); however, the issue of appropriate classification of disease status through this method has not been previously addressed. As shown in these data, about 21% of contact lens-wearing patients will change the classification of their dry eye status if asked on two separate occasions. Additionally, misclassification of disease status appears, from these data, to be directional rather than nondirectional as patients tended to go from a dry eye positive to dry eye negative status upon second administration of the survey. Although the effect of misclassification on tear film and other outcomes can be observed in the analysis of the full and clean datasets, it is unclear how this directional misclassification impacts the validity of the sample. In order to examine the effect of directional misclassification, one might conduct an analysis of two other subgroups of this dataset.
This would include comparisons of the two groups of patients who misclassify their dry eye status (those who go from dry eye positive to dry eye negative vs. the converse).

It is also unclear how these data relative to dry eye disease, taken from contact lens wearers, would relate to general dry eye disease in this regard. From the few other studies of the reliability of symptom reporting in patients with general dry eye disease, it seems very likely that the problem of misclassification bias would exist regardless of contact lens wear. For instance, in a recent study, Nichols and coworkers (2004) showed the reliability of individual symptom reporting in patients with dry eye disease to be at best, moderate (weighted kappa values were about 0.60) (Nichols, Mitchell et al., 2004). Thus, it seems very likely that misclassification of disease status through self-report is a likely potential culprit associated with some of the controversies of the results associated with other epidemiological studies of this disease.

**Tear Film Factors Associated with Contact Lens-Related Dry Eye**

The analysis of both the full and clean datasets provides insight not only relative to the relation of tear film and ocular surface factors to self-reported dry eye disease but also relative to the impact of misclassification of disease status. The univariate analyses provide a good example of this, as most of the factors associated with dry eye in the full dataset become even more significant in the clean dataset, even though there is quite a modest reduction in sample size (due to the elimination of patients who misclassify their
disease status). This is true for NITBUT, osmolarity, and pre-lens tear film lipid layer thickness.

Clinical intuition suggests that it is extremely important for the contact lens to remain “wetted” with a coherent tear film over its surface in order to provide good comfort, vision, lubrication, prevent surface drying, remove debris and particulate, and counter contamination and infection during lens wear. A lens that is non-wettable is one that will show quick pre-lens tear film breakup, as a wettable film will spread uniformly without breakup. In the clean dataset, NITBUT for patients with DE was about 3.5 seconds shorter on average than for patients without DE. Tear film break-up followed by evaporation of the pre-lens tear film and dehydration of the lens may be the primary mechanism of contact lens-related dry eye. Fatt (1990) theorized a cycle that reaches equilibrium water content through evaporative water loss at the anterior lens surface during tear film break-up, with rehydration occurring during the blink and stable tear film interval (Fatt, 1990). As Fatt (1990) states, “If the loss were greater than the gain, the lens will be eventually totally dehydrated—a phenomenon not clinically observed.”

Young and Efron (1991) measured pre-lens lipid layer thickness and NITBUT over lenses of various water contents but did not study the relation of these outcomes to dry eye status. They found no significant differences in lipid layer thickness by lens type (the average thickness across lens types was 0.09 μm); however, they did find a significant difference in aqueous layer thickness between lens types where thicker layers
were associated with the higher water content materials. This was also true of NITBUT, where longer break-up times were associated with higher water content materials. No association was found between lens dehydration (measured with a refractometer) and PLTF thickness or stability. They conclude that higher water content lenses support a thicker and more stable pre-lens tear film, but the mechanism of this is unclear, as other studies have not shown that wettability is related to nominal water content. The study does not necessarily provide insight into the mechanism of contact lens-related dry eye.

Bruce and coworkers (1995) hypothesized that tear break-up time and lens deposits were the mechanisms for the dryness symptom associated with contact lens wear (Bruce, Golding et al., 1995). In their study, two groups were classified based on the symptoms (24 cases and 26 controls), and pre-lens thinning times (a.k.a., pre-lens NITBUT) were measured and compared between the groups. The median pre-lens NITBUT for the symptomatic group was 3 seconds and it was 3.5 seconds for the asymptomatic group (p = 0.93). The authors conclude that pre-lens tear stability was not associated with patient comfort. This is contrary to the finding of the current analyses and may reflect a lack of masking in the Bruce study, in addition to the small sample sizes in each (as NITBUT measures are notoriously unreliable).

Analysis of the clean dataset has also shown that osmolarity is also significantly related to dry eye status, both in univariate and multivariate models. Gilbard and coworkers (1986) suggested that increased osmolarity is the hallmark characteristic of
contact lens-related dry eye, which in part, has created some dogma relative to this topic through the years. This is true as osmolarity can only be measured by a handful of research groups worldwide and thus, it has not been confirmed by more than one investigator. Gilbard and coworkers suggest that “Decreased corneal sensitivity, with a resultant decrease in tear secretory rates, is the most likely cause for increased tear-film osmolarity…” A more recent study showed that in normal patients, contact lens wear alone might lead to an increase in tear film osmolarity (Iskeleli, Karakoc et al., 2002). Although the mechanism of increased osmolarity cannot necessarily be directly derived from these data, a viable alternative might be related to tear film evaporation. As patients with DE in this sample have a reduction in the superficial lipid layer thickness, they may be more susceptible to evaporation of the pre-lens tear film than those patients without DE. An increase in tear film evaporation might lead to a more concentrated tear film and a resultant increased osmolarity.

The final tear film factor that showed a significant relation to self-reported dry eye in both the full and clean dataset’s multivariate analyses was meibography (gland count). However, the result was in the opposite direction of what was expected—in other words, a count of more glands was associated with self-reported dry eye. This result is entirely unclear, as previous information has suggested that contact lens wear may be associated with meibomian gland disease. One study attempted to examine the prevalence of meibomian gland dysfunction, suggesting 49% of lens wearers and 39% of the normal
population have some form of meibomian gland dysfunction, although these numbers did not differ statistically (Ong, 1996). Henriquez and Korb (1982) examined 38 contact lens wearers with “contact lens intolerance” and 12 age and gender-matched controls in terms of meibomian gland function. In this study, the meibomian glands of the lower lid margin were expressed, and these contents were studied microscopically. They found that meibomian gland obstruction was principally the result of desquamated epithelial cells that aggregate in keratotic clusters obstructing the meibomian glands. This result applied to wearers of rigid (or hard lenses) but not to hydrogel lens wearers.

Another study examine 50 optometry students for meibomian gland dysfunction (Marren, 1994). In this study, both meibomian gland orifices and expression were examined, but gland structure was not. Contact lens wear, the use of eye cosmetics, lack of eye rubbing, and atopy were proposed as being related to meibomian gland dysfunction. The author stated that there was no correlation between meibomian gland dysfunction and any of these factors. Unfortunately, there were issues with this study’s poor design, small sample size, and outcomes assessment, which are likely factors contributing to this negative result.

In a clinical trial examining the efficacy of meibomian gland therapy during contact lens wear, Paugh and coworkers (1990) treated 21 contact lens patients with meibomian gland dysfunction. Patients were assigned to lids scrubs and massage in one eye for a period of two weeks. Masked examiners then evaluated the change in gland
expression, staining, comfort, and fluorescein TBUT. The authors suggested that there was a statistically significant increase in TBUT in the treatment eye but not in the control eye. No statistical analyses were conducted for the other outcomes. Thus, the issue of altered meibomian gland function relative to contact lens use remains in question. The initial data presented in this work does not support the notion of altered meibomian gland structure with contact lens wear.

**Contact Lens Factors Associated with Contact Lens-Related Dry Eye**

Univariate analyses of these data show several interesting suggestions regarding contact lens factors that might be associated with contact lens-related dry eye. First, it does not appear that rigid lens wear is protective against contact lens-related dry eye in any way. Clinicians often suggest that rigid lenses might be preferred for patients with dry eye, although there is a lack of study on this topic. There has been much information and speculation regarding various hydrogel factors that might be related to dry eye during contact lens wear. One of the biggest issues is the use of high water content lenses. The prominent thought relating to the use of high water content lenses is that they dehydrate to a greater extent than lower water content materials. These data show that the use of higher water content lenses do indeed dehydrate to a greater extent than low water content lenses and that the use of high water content lenses may be associated with contact lens-related dry eye. However, these data do not show that lens dehydration is related to contact lens-related dry eye.
Several small-scale studies have evaluated contact lens dehydration and patients’ symptoms, with varied results (Efron and Brennan, 1988; Lowther, 1993; Pritchard and Fonn, 1995; and Fonn, Situ et al., 1999). Efron and Brennan (1988) found that patients wearing low water content lenses that maintained their hydration (as compared to low water content lenses that dehydrated) generally reported that their eyes never felt dry during lens wear (p < 0.05). Pritchard and coworkers (1995) examined the dehydration of three different water content hydrogel lenses and the relation of this dehydration of lens movement, diameter changes, and dryness symptoms. Similar to these data, they found that the high water content lens dehydrated the most, followed by the mid-water and low-water content lenses, respectively. Each lens continued to dehydrate over the seven-hour wear period. Although dryness symptoms increased during the seven hour wear period, there was no relation of these symptoms to lens type. There were no correlations found between dehydration, movement, diameter and dryness symptoms. Finally, Fonn and coworkers performed a similar study, but used two groups of patients—one with symptoms of dryness and the other without such symptoms. This was a contralateral eye study in which patients were asked to wear the Acuvue and Proclear lenses for a period of seven hours. Lens water content was measured with an Atago CL-1, and patients recorded their dryness and comfort over several periods throughout the day. The study showed significantly more dryness, decreased comfort, and reduced pre-lens NITBUT in the “symptomatic” group. However, no relation was found between lens dehydration and
dryness, comfort, or NITBUT for either lens type. Not surprisingly, changes in comfort were significantly associated with dryness over the wear period for both lens types. Thus, the evidence to date seems to suggest that although high water content lens use may be associated with contact lens-related dry eye symptoms, dehydration of these lenses does not seem to be the mechanism associated with the symptoms.

**Patient-Related Factors Associated with Contact Lens-Related Dry Eye**

There is a gap in scientific information regarding patient-related factors associated with contact lens-related dry eye. Although this may be true, there was no indication that many socio-demographic outcomes were related to dry eye status in contact lens wearers. Gender was significantly related to dry eye status, however, as females were much more likely to report dry eye disease. This was true even after controlling for female-related misclassification of disease status. In fact, gender was the most significant outcome related to dry eye disease in contact lens wearers across all analyses. There are two potential explanations for this finding. First, females obviously have various endogenous hormonal issues that may impact dry eye status relative to males. Examples of these issues include monthly menstrual cycling, oral contraceptive use, menopause, and hormone replacement therapy usage. The relation of these things to dry eye disease, in general, is only starting to be understood.

A second potential explanation associated with this finding may be related to the finding of previous studies that women seem to be more likely to report symptoms of
disease than men (Bishop, 1984; and Page, 1997; Almeida, Trone et al., 1999; and Ladwig, Marten-Mittag et al., 2000). This has been shown to be true after controlling for
disease status differences through objective measures of disease, similar to our
multivariate analysis (Rahman and Liu, 2000). The relation of gender to dry eye disease
status remains unclear as the effect of hormonal status relative to tear function must be
determined prior to conclusions being made about this topic.
CHAPTER 5

CONCLUSIONS

The Contact Lens and Dry Eye Study (CLADES) is a cross-sectional survey with nested case-control study designed to aid in understanding the symptoms and factors associated with those symptoms that contact lens wearers experience. As the study is still ongoing, the data and analyses presented here are and should remain confidential. A cross-sectional survey of 763 individuals showed that about 45% of contact lens wearers experience significant dry eye symptoms (significant enough to warrant a doctor to suggest that the patient has contact lens-related dry eye disease). This estimate of the magnitude of contact lens-related dry eye is in good agreement with that of the other studies that have been conducted.

Patients who completed the Phase II examination were also asked to complete the CLDEQ a second time in order to determine issues relating to the reliability of classification of dry eye status through self-report. These data were used to determine the scope of misclassification through this self-reported disease status, predictors of misclassification, and the impact of misclassification on hypothesis testing of the data. Assessment of reliability of self-reported disease status showed that slightly more than 20% of patients misclassify their disease status through self-report. Further, patients who
tended to misclassify their disease status were young women. This result is unique in that it is the first to evaluate misclassification bias associated with self-report of dry eye status and the first to show predictors of misclassification. Numerous recent, large-scale epidemiological studies of dry eye disease use self-reported methods to determine disease status. These data suggest that at least two assessments of disease status are required for this type of study, in addition to the need to control for a socio-demographic variable related to the sample. Related to these specific results, other studies have shown that women tend to report symptoms more than men, but there is no indication from the literature regarding why gender would play a role in self-reported misclassification. It could be that monthly menstrual/hormonal cycles may play a role in the variability of dry eye reporting in women, although these data have not been used to test this notion.

Another aim of this work was to assess the impact of misclassification on hypothesis testing using the dataset. The results from these analyses showed that factors that were close to significance or mildly significant in a full dataset (including all patients examined) showed a strong significance in a clean dataset (excluding patients who misclassified their disease status). This is true even though the sample size was reduced by about 20 to 30%, which would generally lead to a reduction in the ability to show significance due to a reduction in power.

Numerous hypothesis tests were conducted in this work, the aim of which was to examine evaporative tear film, contact lens, and other factors that might predict self-
reported dry eye status in contact lens wearers. These results can be best summarized as follows:

1) Meibomian gland structure changes were not associated with dry eye. In fact, the analyses showed a trend whereby patients with dry eye disease had more whole meibomian glands than those without dry eye disease (this was true in both the full and clean datasets). This result is entirely unclear at this point, as the opposite was expected. Although these images go through a rigorous protocol in terms of reading and grading, it could be that there are still problems with human assessments of the images. Our previous analyses showed fair between-reader reliability of grading these images. Newer, computer-based processing and analysis of the images may be valuable in this regard. It could be that there are no structural changes that occur with contact lens wear, although functional changes could still exist. In other words, glands might not necessarily show observable damage, although a stimulus like contact lens wear could induce a change in the way they function. A contact lens could lead to a reduction in neural feedback that regulates lipid secretion from the glands. Further work is needed to understand these issues.

2) The pre-lens lipid layer thickness of patients with dry eye tended to be thinner than in patients without dry eye. This outcome was highly correlated with pre-lens tear film thinning, so it did not remain significant in multivariate modeling. From the previous analysis, it does not appear as though there are structural changes to the meibomian
glands that would induce this thinning (which was a primary hypothesis of this work). There must be another explanation for this finding, although the outcomes associated with CLADES will not provide evidence for this alternative explanation. One preliminary hypothesis is quick thinning times (described below) associated with the pre-lens tear film leads to a thin lipid layer. In other words, because the pre-lens tear film thins so quickly over a contact lens, the lipid layer does not have time to establish itself in a uniform manner and thus, the layer appears thin.

3) Pre-lens thinning rates for contact lens-related dry eye subjects is significantly faster than for contact lens wearers without dry eye. Although this result may not be surprising per se, this study is one of the first to show this result. Although thinning rates are not well understood, thinning of the precorneal or pre-lens tear film is likely related to wettability of the surface. The cornea is very wettable, as the glycocalyx and mucin help the aqueous tears spread over its surface. Further, the polar lipids of the precorneal tear film also aid in reducing the surface tension of the tears. However, a hydrogel lens has no such glycocalyx and thus, its surface is not wettable like the precorneal tear film. The lack of a glycocalyx in addition to an alteration in the polar lipids of the lipid layer during contact lens wear could be the mechanism of contact lens-related dry eye.

4) These analyses do not provide conclusive evidence that dehydration of a hydrogel lens is associated with contact lens-related dry eye symptoms. Dehydration, measured directly through water content or refractive index, was not related to patient symptoms in
univariate or multivariate analyses. However, nominal water content was associated with dry eye status in both univariate and multivariate analyses of the clean dataset. This is perplexing in that one of the few measurable characteristics associated with water content (i.e., dehydration) did not show a relation to dry eye status, although the nominal indication of water content did. Ionicity did not show a relation to dry eye status in the final multivariate models. Clearly, these data and analyses do show that high water content lenses dehydrate more than low water content lenses, although this dehydration does not seem to be related to dry eye status.

5) Gender was related to dry eye status in contact lens wearers, whereby females were more likely than males to self-report dry eye. The explanation of this result is unclear, although research in other disciplines has shown that women tend to report more symptoms of disease even after controlling for disease status through an objective measure. This is a likely explanation for this result, although these data cannot rule out alternative hypotheses relating to hormonal status in relation to self-reported dry eye disease.

In summary, these preliminary analyses have shown the importance of appropriately classifying disease status through self-reported measures and have also provided some initial insight into potential factors associated with dry eye status in contact lens wearers. Future studies will address significant findings from the analysis of
the entire CLADES dataset in relation to developing a more thorough knowledge of the mechanism of dry eye in contact lens wearers.
BIBLIOGRAPHY


Bishop GD. Gender, role, and illness behavior in a military population. *Health Psychol* 1984;3: 519-34.


82


Efron N and Brennan NA. The soft contact lens refractometer. The Optician 1987;194: 29-41.


Fatt I. Changes in dimensions of soft contact lenses while one the eye. The Optician 1983;185: 11-14.


Landis JR and Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33: 159-74.


Lowther GE. Comparison of hydrogel contact lens patients with and without the symptoms of dryness. *ICLC* 1993;20: 191-94.


Appendix A
Tables and Figures
<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Symptoms Evaluated</th>
<th>Response</th>
<th>Results</th>
</tr>
</thead>
</table>
| Brennan, et al., 1989    | 104| 1) Scratchy  
2) Dry  
3) Watery | Frequency  
1) Often  
2) Seldom  
3) Never | 1) Dryness = 75%*  
2) Scratchy = 52%  
3) Watery = 30%  
*Significantly higher |
| Guillon, et al., 1997    | 184| ?                                     | ?                                 | Dryness = 44%                                |
| Doughty, et al., 1997    | 3285| “Symptoms of dry eyes”                | Y/N                               | 50% of lens wearers                           |
| Vajdic, et al., 1999     | 171| 1) Redness  
2) Dryness  
3) Grittiness  
4) Ocular Pain  
5) Excessive Blinking | Frequency  
1) Never  
2) Sometimes  
3) Often  
4) Constantly | ≥ Often, SCLs wearers  
1) Redness: 14%  
2) Dryness: 16%  
3) Grittiness: 3%  
4) Ocular Pain: 3%  
5) Excessive Blinking: 3% |
| Begley, et al., 2000     | 83 | 1) Dryness  
2) Scratchiness  
3) Soreness  
4) Light Sensitivity  
5) Blurry/Changeable Vision | Frequency & Intensity  
(analogue) | Freq: Dryness > Blurry Vision > Scratchiness > Light Sensitivity > Soreness |
| Begley, et al., 2001     | 367| CLDEQ  
1) Discomfort  
2) Dryness  
3) Visual Changes  
4) Soreness & Irritation  
5) FB Sensation  
6) Burning and Stinging  
7) Light Sensitivity  
8) Itching | Frequency  
1) Never  
2) Infrequently  
3) Frequently  
4) Constantly  
5) Not Sure  
Intensity  
1 (Not Intense)  
5 (Very Intense) | Frequency  
1) Discomfort (79%)  
2) Dryness (77%)  
3) Visual Changes (77%) |

Table 1. Studies of dry eye symptoms during contact lens wear.
Table 2. Meibomian gland lipid components found in the lipid layer of the tear film. Table was adapted from McCulley and Shine, 2003.

<table>
<thead>
<tr>
<th>NonPolar Lipids</th>
<th>Origination</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wax esters</td>
<td>Synthesized (acinus)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>44</td>
</tr>
<tr>
<td>Sterol esters</td>
<td></td>
<td>33</td>
</tr>
<tr>
<td>Triglycerides</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Diglycerides</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Monoglycerides</td>
<td></td>
<td>Trace</td>
</tr>
<tr>
<td>Fatty Alcohols</td>
<td></td>
<td>Trace</td>
</tr>
<tr>
<td>Hydrocarbons</td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Polar Lipids</th>
<th>Origination</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrosides</td>
<td>Acinar and Ductal Cell Derived&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4</td>
</tr>
<tr>
<td>Ceramides</td>
<td>Zwitterionic</td>
<td>Trace</td>
</tr>
<tr>
<td>Phospholipids</td>
<td>Polar&lt;sup&gt;d&lt;/sup&gt;</td>
<td>6</td>
</tr>
<tr>
<td>Free Fatty Acids</td>
<td>Degradation Products&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2</td>
</tr>
</tbody>
</table>

<sup>a</sup> Acinus
<sup>b</sup> Plasma membranes
<sup>c</sup> Bacterial, peroxisomal, or lysosomal lipases
<sup>d</sup> Polar phospholipids include sphingomyelin, phosphatidylethanolamine, phosphatidic acid, and phosphatidylserine (which promotes a polar lipid monolayer).
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Lens Lipid Layer Thickness (TearScope)</td>
<td>Clinical</td>
</tr>
<tr>
<td>Tear Film Stability (PLTF NITBUT)—3 measures</td>
<td>Clinical</td>
</tr>
<tr>
<td>Contact Lens Fit Assessment</td>
<td>Clinical</td>
</tr>
<tr>
<td>Contact Lens Refractometry (CLR 12-70)</td>
<td>Clinical</td>
</tr>
<tr>
<td>Socio-demographic Survey</td>
<td>Survey</td>
</tr>
<tr>
<td>Osmolarity Tear Sample</td>
<td>Clinical</td>
</tr>
<tr>
<td>Health Behaviors &amp; Exposures Survey</td>
<td>Survey</td>
</tr>
<tr>
<td>Positive and Negative Affect Scale (PANAS)</td>
<td>Survey</td>
</tr>
<tr>
<td>Slit-Lamp Biomicroscopy</td>
<td>Clinical</td>
</tr>
<tr>
<td>Phenol Red Thread Test</td>
<td>Clinical</td>
</tr>
<tr>
<td>Meibography</td>
<td>Clinical</td>
</tr>
<tr>
<td>Fluorescein Staining</td>
<td>Clinical</td>
</tr>
<tr>
<td>Lissamine Green Staining</td>
<td>Clinical</td>
</tr>
<tr>
<td>Medical History</td>
<td>Survey</td>
</tr>
<tr>
<td>Contact Lens and Ophthalmic History</td>
<td>Survey</td>
</tr>
<tr>
<td>Contact Lens Dry Eye Questionnaire (Short-Form)</td>
<td>Survey</td>
</tr>
</tbody>
</table>

Table 3. Procedures performed in the Phase II Clinical Examination.
<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Criteria</th>
<th>Prevalence or Mean for Control Group</th>
<th>Odds Ratio or Percent Difference</th>
<th>Number Per Group</th>
<th>Total Sample Size‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meibomian Gland Disease</td>
<td>Gestalt Grade ≥ 3</td>
<td>19.6%</td>
<td>2.25</td>
<td>136</td>
<td>300</td>
</tr>
<tr>
<td></td>
<td>Gland Count &lt; 7 Glands</td>
<td>41.7%</td>
<td>2.25</td>
<td>107</td>
<td>236</td>
</tr>
<tr>
<td>NITBUT</td>
<td>20% Reduction</td>
<td>13.0 ± 7.6 sec</td>
<td>20%</td>
<td>137</td>
<td>302</td>
</tr>
<tr>
<td>Contact Lens Dehydration</td>
<td>40% Reduction</td>
<td>-3.4% ± 3.5%</td>
<td>40%</td>
<td>136</td>
<td>313</td>
</tr>
<tr>
<td>High Water, Hydrogel CL Wear</td>
<td>&gt; 50% Nominal Water Content</td>
<td>68.9%</td>
<td>2.25</td>
<td>150</td>
<td>330</td>
</tr>
</tbody>
</table>

†Prevalence estimates for control group based on the first 200 sampled patients in CLADES.
‡Increased by ~10% for a margin of error correction (i.e., missing data).

Table 4. Sample size estimates need for analyses associated with Phase II of CLADES.
<table>
<thead>
<tr>
<th>Dry Eye Status Second Administration</th>
<th>Dry Eye Status—First Administration</th>
<th>Row Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>116 (42.3%)</td>
<td>20 (7.3%)</td>
</tr>
<tr>
<td>No</td>
<td>38 (13.9%)</td>
<td>100 (36.5%)</td>
</tr>
<tr>
<td>Column Totals</td>
<td>154 (56.2%)</td>
<td>120 (43.8%)</td>
</tr>
</tbody>
</table>

Table 5. Test-retest data associated with the CLDEQ classification scheme. Numbers in parentheses represent percentages.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Misclassified*</th>
<th>Not Misclassified*</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>30.1 (9.7)</td>
<td>31.1 (11.1)</td>
<td>0.99</td>
<td>0.52</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.96 - 1.02)</td>
<td></td>
</tr>
<tr>
<td>Time Between Survey Administrations (Days)</td>
<td>46.3 (34.7)</td>
<td>38.3 (33.9)</td>
<td>1.01</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(1.00 - 1.02)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>22.4%</td>
<td>35.3%</td>
<td>REFERENCE</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>77.6%</td>
<td>64.7%</td>
<td>1.88</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.95 - 3.70)</td>
<td></td>
</tr>
<tr>
<td>Marital Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partner</td>
<td>36.2%</td>
<td>37.0%</td>
<td>REFERENCE</td>
<td></td>
</tr>
<tr>
<td>No Partner</td>
<td>63.8%</td>
<td>63.0%</td>
<td>1.04</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.57 - 1.89)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>81.0%</td>
<td>78.7%</td>
<td>REFERENCE</td>
<td></td>
</tr>
<tr>
<td>Non-White</td>
<td>19.0%</td>
<td>21.3%</td>
<td>0.87</td>
<td>0.70</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.41 - 1.80)</td>
<td></td>
</tr>
<tr>
<td>Income</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30K</td>
<td>36.2%</td>
<td>36.6%</td>
<td>REFERENCE</td>
<td></td>
</tr>
<tr>
<td>30-74,999K</td>
<td>39.7%</td>
<td>36.2%</td>
<td>1.11</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.57 - 2.17)</td>
<td></td>
</tr>
<tr>
<td>&gt; 75,000K</td>
<td>24.1%</td>
<td>27.2%</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.42 - 1.91)</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HS Grad</td>
<td>19.0%</td>
<td>22.7%</td>
<td>0.86</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.35 - 2.14)</td>
<td></td>
</tr>
<tr>
<td>AS or BS</td>
<td>60.3%</td>
<td>56.0%</td>
<td>1.11</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.53 - 2.32)</td>
<td></td>
</tr>
<tr>
<td>Masters +</td>
<td>20.7%</td>
<td>21.3%</td>
<td>REFERENCE</td>
<td></td>
</tr>
</tbody>
</table>

* Descriptor presented as a mean (SD) or percentage.

Table 6. Association between univariate patient-related factors and dry eye misclassification.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Status</th>
<th>Full Dataset (n = 325)</th>
<th>Clean Dataset (n = 216)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Gland Count&lt;sup&gt;a&lt;/sup&gt;</td>
<td>DE</td>
<td>162</td>
<td>7.56 ± 3.62</td>
</tr>
<tr>
<td></td>
<td>NDE</td>
<td>149</td>
<td>7.24 ± 3.67</td>
</tr>
<tr>
<td>PLTF-NITBUT (sec)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>DE</td>
<td>172</td>
<td>8.95 ± 6.26</td>
</tr>
<tr>
<td></td>
<td>NDE</td>
<td>153</td>
<td>10.80 ± 8.42</td>
</tr>
<tr>
<td>Dehydration (%)&lt;sup&gt;c, d&lt;/sup&gt;</td>
<td>DE</td>
<td>104</td>
<td>−4.43 ± 3.53</td>
</tr>
<tr>
<td></td>
<td>NDE</td>
<td>94</td>
<td>−4.09 ± 3.27</td>
</tr>
<tr>
<td>Δ Refractive Index&lt;sup&gt;e, f&lt;/sup&gt;</td>
<td>DE</td>
<td>123</td>
<td>0.0185 ± 0.0098</td>
</tr>
<tr>
<td></td>
<td>NDE</td>
<td>121</td>
<td>0.0182 ± 0.0081</td>
</tr>
<tr>
<td>Osmolarity (mOsm)</td>
<td>DE</td>
<td>157</td>
<td>304.29 ± 32.77</td>
</tr>
<tr>
<td></td>
<td>NDE</td>
<td>139</td>
<td>297.32 ± 31.61</td>
</tr>
<tr>
<td>Phenol Red (mm/15 sec)</td>
<td>DE</td>
<td>172</td>
<td>20.55 ± 7.24</td>
</tr>
<tr>
<td></td>
<td>NDE</td>
<td>153</td>
<td>20.82 ± 6.48</td>
</tr>
<tr>
<td>Fluorescein Staining&lt;sup&gt;f&lt;/sup&gt;</td>
<td>DE</td>
<td>171</td>
<td>1.68 ± 2.99</td>
</tr>
<tr>
<td></td>
<td>NDE</td>
<td>153</td>
<td>2.01 ± 3.60</td>
</tr>
<tr>
<td>Lissamine Green Staining&lt;sup&gt;f&lt;/sup&gt;</td>
<td>DE</td>
<td>172</td>
<td>4.78 ± 4.44</td>
</tr>
<tr>
<td></td>
<td>NDE</td>
<td>153</td>
<td>4.89 ± 4.51</td>
</tr>
<tr>
<td>Age (years)</td>
<td>DE</td>
<td>172</td>
<td>31.05 ± 10.37</td>
</tr>
<tr>
<td></td>
<td>NDE</td>
<td>153</td>
<td>29.31 ± 10.38</td>
</tr>
<tr>
<td>Years of CL Wear</td>
<td>DE</td>
<td>172</td>
<td>13.58 ± 8.92</td>
</tr>
<tr>
<td></td>
<td>NDE</td>
<td>153</td>
<td>11.83 ± 8.37</td>
</tr>
</tbody>
</table>

<sup>a</sup> 14 images not gradable in the full dataset and 10 images not gradable for the clean dataset.

<sup>b</sup> Average of three measures.

<sup>c</sup> Measured – nominal

<sup>d</sup> There were 22 RGP lens wearers in full dataset and 17 in the clean dataset. Values were excluded if dehydration (measured – nominal) was either more than 2% or less than −15%.

<sup>e</sup> There were 22 RGP lens wearers in this sample, leaving 303 potential refractive index measures.

<sup>f</sup> Sum of grade 0 to 4 for five corneal areas defined by NEI dry eye report (20 total). Two values were missing.

<sup>g</sup> Sum of grade 0 to 4 for six conjunctival areas defined by NEI dry eye report (24 total).

<sup>h</sup> P-values were obtained through univariate logistic regression analyses.

Table 7. Table of continuous tear film and contact lens descriptive factors by dry eye group.

102
<table>
<thead>
<tr>
<th>Gestalt Grade</th>
<th>Full Dataset(^a)</th>
<th>Clean Dataset(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DE (percent)</td>
<td>NDE (percent)</td>
</tr>
<tr>
<td>1 (no partial glands)</td>
<td>54 (17.8)</td>
<td>49 (16.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>33 (16.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24 (12.0)</td>
</tr>
<tr>
<td>2 (&lt; 25% partial glands)</td>
<td>73 (24.0)</td>
<td>72 (23.7)</td>
</tr>
<tr>
<td></td>
<td>50 (25.0)</td>
<td>54 (27.0)</td>
</tr>
<tr>
<td>3 (25% to 75% partial glands)</td>
<td>22 (7.2)</td>
<td>20 (6.6)</td>
</tr>
<tr>
<td></td>
<td>16 (8.0)</td>
<td>13 (6.5)</td>
</tr>
<tr>
<td>4 (&gt; 75% partial glands)</td>
<td>8 (2.6)</td>
<td>6 (2.0)</td>
</tr>
<tr>
<td></td>
<td>6 (3.0)</td>
<td>4 (2.0)</td>
</tr>
</tbody>
</table>

| Logistic Regression p-value           | 0.96                | 0.61                 |

\(^a\) n = 304, 21 images were not gradable
\(^b\) n = 200, 16 images were not gradable

Table 8. Table of meibography gestalt grading by dry eye group.
<table>
<thead>
<tr>
<th>Lipid Layer Classification</th>
<th>Full Dataset (n = 324, 1 missing)</th>
<th>Clean Dataset&lt;sup&gt;b&lt;/sup&gt; (n = 216)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DE (percent)</td>
<td>NDE (percent)</td>
</tr>
<tr>
<td>Absent (0-13 nm)</td>
<td>15 (4.6)</td>
<td>6 (1.8)</td>
</tr>
<tr>
<td>Open Meshwork (13-50nm)</td>
<td>38 (11.7)</td>
<td>28 (8.9)</td>
</tr>
<tr>
<td>Closed Meshwork (13-50nm)</td>
<td>31 (9.6)</td>
<td>28 (8.6)</td>
</tr>
<tr>
<td>Wave/flow (50-70nm)</td>
<td>58 (17.9)</td>
<td>54 (16.7)</td>
</tr>
<tr>
<td>Amorphous (80-90nm)</td>
<td>15 (4.6)</td>
<td>19 (5.9)</td>
</tr>
<tr>
<td>Colored Fringe Brown (90-140nm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colored Fringe Blue (&gt; 140 nm)</td>
<td>3 (0.9)</td>
<td>2 (0.6)</td>
</tr>
</tbody>
</table>

Univariate Logistic Regression p-value 0.04<sup>a</sup> 0.0006<sup>b</sup>

<sup>a</sup> OR = 0.84, 95% CI = 0.72 to 0.99

<sup>b</sup> OR = 0.70, 95% CI = 0.57 to 0.86

Table 9. Table of pre-lens tear film lipid layer thickness by dry eye group.
<table>
<thead>
<tr>
<th>Material</th>
<th>Full Dataset (n = 325)</th>
<th>Clean Dataset (n = 216)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DE (percent)</td>
<td>NDE (percent)</td>
</tr>
<tr>
<td>RGP</td>
<td>13 (4.0)</td>
<td>9 (2.8)</td>
</tr>
<tr>
<td>Soft</td>
<td>159 (48.9)</td>
<td>144 (44.3)</td>
</tr>
<tr>
<td>Univariate Logistic Regression p-value</td>
<td>0.56</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Table 10. Table of soft vs. RGP lens wear by dry eye group.
<table>
<thead>
<tr>
<th>FDA Classification</th>
<th><strong>Full Dataset</strong></th>
<th></th>
<th><strong>Clean Dataset</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DE (percent)</td>
<td>NDE (percent)</td>
<td>DE (percent)</td>
<td>NDE (percent)</td>
</tr>
<tr>
<td>Group 1 (Low Water, Nonionic)</td>
<td>35 (12.4)</td>
<td>43 (15.2)</td>
<td>19 (9.5)</td>
<td>32 (16.1)</td>
</tr>
<tr>
<td>Group 2 (High Water, Nonionic)</td>
<td>30 (10.6)</td>
<td>21 (7.4)</td>
<td>21 (10.6)</td>
<td>16 (8.0)</td>
</tr>
<tr>
<td>Group 3 (Low Water, Ionic)</td>
<td>5 (1.8)</td>
<td>0 (0.0)</td>
<td>4 (2.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Group 4 (High Water, Ionic)</td>
<td>78 (27.6)</td>
<td>71 (25.1)</td>
<td>53 (26.3)</td>
<td>37 (18.6)</td>
</tr>
<tr>
<td>Univariate Logistic Regression p-value</td>
<td>0.29</td>
<td></td>
<td>0.04</td>
<td></td>
</tr>
</tbody>
</table>

*a* n = 283, 22 RGP wearers, 20 lenses could not be identified  
*b* n = 182, 17 RGP wearers, 17 lenses could not be identified  
*c* Group 1 significantly differs from group 4 (OR = 0.42, 95% CI = 0.21 to 0.84, p = 0.01).

Table 11. Table of hydrogel FDA classification by dry eye group.
<table>
<thead>
<tr>
<th>Nominal Ionicity</th>
<th>Full Dataset(^a)</th>
<th></th>
<th>Clean Dataset(^b)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DE (percent)</td>
<td>NDE (percent)</td>
<td>DE (percent)</td>
<td>NDE (percent)</td>
</tr>
<tr>
<td>Ionic</td>
<td>83 (29.5)</td>
<td>71 (25.1)</td>
<td>57 (31.3)</td>
<td>37 (20.3)</td>
</tr>
<tr>
<td>Nonionic</td>
<td>65 (23.0)</td>
<td>64 (22.6)</td>
<td>40 (22.0)</td>
<td>48 (26.4)</td>
</tr>
<tr>
<td>Univariate Logistic Regression p-value</td>
<td>0.56</td>
<td>0.04(^c)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) n = 283 (22 RGP wearers and 20 lenses could not be identified).
\(^b\) n = 182 (17 RGP wearers and 17 lenses could not be identified).
\(^c\) OR = 1.84, 95% CI = 1.03 to 3.33.

Table 12. Table of hydrogel nominal ionicity by dry eye group.
Table 13. Table of hydrogel nominal water content by dry eye group.

<table>
<thead>
<tr>
<th>Nominal Water Content</th>
<th>Full Dataset&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Clean Dataset&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DE (percent)</td>
<td>NDE (percent)</td>
</tr>
<tr>
<td>&lt; 50%</td>
<td>107 (37.8)</td>
<td>92 (32.5)</td>
</tr>
<tr>
<td>≥ 50%</td>
<td>41 (14.5)</td>
<td>43 (15.2)</td>
</tr>
</tbody>
</table>

Univariate Logistic Regression p-value: 0.45 for Full Dataset and 0.03<sup>c</sup> for Clean Dataset.

<sup>a</sup> n = 283 (22 RGP wearers and 20 lenses could not be identified).
<sup>b</sup> n = 182 (17 RGP wearers and 17 lenses could not be identified).
<sup>c</sup> OR = 2.06, 95% CI = 1.08 to 3.93.
### Table 14. Table of measured hydrogel dehydration by nominal water content (excludes Focus Night and Day and Durasoft wearers and individuals with missing water content measures).

<table>
<thead>
<tr>
<th>Nominal Water Content</th>
<th>Full Dataset Mean ± SD % Dehydration</th>
<th>Clean Dataset Mean ± SD % Dehydration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n)</td>
<td>(n)</td>
</tr>
<tr>
<td>&lt; 50%</td>
<td>−0.60 ± 1.66 (23)</td>
<td>−0.73 ± 1.77 (15)</td>
</tr>
<tr>
<td>&gt; 50%</td>
<td>−4.76 ± 3.28 (175)</td>
<td>−4.24 ± 3.20 (115)</td>
</tr>
<tr>
<td><strong>Unpaired t-test</strong></td>
<td><em>t</em> = 9.78, <em>p</em> &lt; 0.0001</td>
<td><em>t</em> = 6.74, <em>p</em> &lt; 0.0001</td>
</tr>
</tbody>
</table>

Values were excluded if dehydration (measured – nominal) was either more than 2% or less than −15%.
<table>
<thead>
<tr>
<th>Nominal Water Content</th>
<th>Full Dataset</th>
<th>Clean Dataset</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD Δ Refractive Index (n)</td>
<td>Mean ± SD Δ Refractive Index (n)</td>
</tr>
<tr>
<td>&lt; 50%</td>
<td>0.0119 ± 0.0068 (77)</td>
<td>0.0126 ± 0.0052 (50)</td>
</tr>
<tr>
<td>&gt; 50%</td>
<td>0.0213 ± 0.0083 (167)</td>
<td>0.0212 ± 0.0082 (109)</td>
</tr>
<tr>
<td>Unpaired t-test</td>
<td>t = –9.78, p &lt; 0.0001</td>
<td>t = –7.96, p &lt; 0.0001</td>
</tr>
</tbody>
</table>

Table 15. Table of measured hydrogel dehydration (refractive index) by nominal water content (excludes Durasoft wearers and individuals with missing water content measures).
<table>
<thead>
<tr>
<th>Etafilcon A Usage</th>
<th>Material Utilization</th>
<th>Dehydration (water content)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Full Dataset (n = 103)</td>
<td>Clean Dataset (n = 63)</td>
</tr>
<tr>
<td>DE Group</td>
<td>50 (48.5%)</td>
<td>32 (50.8%)</td>
</tr>
<tr>
<td>NDE Group</td>
<td>53 (51.5%)</td>
<td>31 (49.2%)</td>
</tr>
<tr>
<td>Hypothesis Test</td>
<td>$\chi^2 = 0.09$</td>
<td>$\chi^2 = 0.02$</td>
</tr>
<tr>
<td></td>
<td>p = 0.77</td>
<td>p = 0.90</td>
</tr>
</tbody>
</table>

Table 16. Analysis of etafilcon A usage relative to dry eye status and dehydration.
## Table 17. Analysis of lotrafilcon A usage relative to dry eye status and dehydration.

<table>
<thead>
<tr>
<th>Lotrafilcon A Usage</th>
<th>Material Utilization</th>
<th>Dehydration (refractive index)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Full Dataset (n = 50)</td>
<td>Clean Dataset (n = 35)</td>
</tr>
<tr>
<td>DE Group</td>
<td>21 (58.0%)</td>
<td>13 (37.1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NDE Group</td>
<td>29 (42.0%)</td>
<td>22 (62.9%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothesis Test</td>
<td>χ² = 1.28</td>
<td>χ² = 2.31</td>
</tr>
<tr>
<td></td>
<td>p = 0.26</td>
<td>p = 0.13</td>
</tr>
</tbody>
</table>
| Gender | Full Dataset  
| (n = 325) | Clean Dataset  
| (n = 216) |
|---------|-------------------|-------------------|
|         | DE (percent) | NDE (percent) | DE (percent) | NDE (percent) |
| Male    | 40 (12.3)    | 70 (21.5)       | 27 (12.5)    | 49 (22.7)      |
| Female  | 132 (40.6)   | 83 (25.5)       | 89 (41.2)    | 51 (23.6)      |
| Univariate Logistic Regression p-value | < 0.0001<sup>a</sup> | < 0.0001<sup>b</sup> |

<sup>a</sup> OR = 2.78, 95% CI = 1.73 to 4.48
<sup>b</sup> OR = 3.17, 95% CI = 1.77 to 5.67

Table 18. Table of gender by dry eye group.
<table>
<thead>
<tr>
<th>Education</th>
<th>Full Dataset (n = 325)</th>
<th></th>
<th></th>
<th>Clean Dataset (n = 216)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DE (percent)</td>
<td>NDE (percent)</td>
<td>DE (percent)</td>
<td>NDE (percent)</td>
<td></td>
</tr>
<tr>
<td>HS Graduate</td>
<td>36 (11.1)</td>
<td>30 (9.2)</td>
<td>27 (12.5)</td>
<td>22 (10.2)</td>
<td></td>
</tr>
<tr>
<td>Associate or Bachelors</td>
<td>98 (30.2)</td>
<td>91 (28.0)</td>
<td>62 (28.7)</td>
<td>59 (27.3)</td>
<td></td>
</tr>
<tr>
<td>Master’s or Higher</td>
<td>38 (11.7)</td>
<td>32 (9.9)</td>
<td>27 (12.5)</td>
<td>19 (8.8)</td>
<td></td>
</tr>
<tr>
<td>Univariate Logistic Regression p-value</td>
<td>0.90</td>
<td></td>
<td>0.67</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 19. Table of educational status by dry eye group.
<table>
<thead>
<tr>
<th>Household income</th>
<th>Full Dataset (n = 322, 3 missing)</th>
<th>Clean Dataset (n = 213, 3 missing)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DE (percent)</td>
<td>NDE (percent)</td>
</tr>
<tr>
<td>&lt; $30,000</td>
<td>65 (20.2)</td>
<td>51 (15.8)</td>
</tr>
<tr>
<td>30,000-$74,999</td>
<td>63 (19.6)</td>
<td>51 (15.8)</td>
</tr>
<tr>
<td>≥ $75,000</td>
<td>42 (13.0)</td>
<td>50 (15.5)</td>
</tr>
<tr>
<td>Univariate Logistic Regression p-value</td>
<td>0.27</td>
<td>0.80</td>
</tr>
</tbody>
</table>

Table 20. Table of total household income by dry eye group.
| Smoking Status<sup>a</sup> | Full Dataset  
(n = 325) | Clean Dataset  
(n = 216) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DE (percent)</td>
<td>NDE (percent)</td>
</tr>
<tr>
<td>No</td>
<td>151 (46.5)</td>
<td>139 (42.8)</td>
</tr>
<tr>
<td>Yes</td>
<td>21 (6.5)</td>
<td>14 (4.3)</td>
</tr>
<tr>
<td>Univariate Logistic</td>
<td>0.38</td>
<td>0.33</td>
</tr>
<tr>
<td>Regression p-value</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Defined as those who acknowledge “currently smoking cigarettes”.

Table 21. Table of smoking status by dry eye group for the full dataset (n = 325).
<table>
<thead>
<tr>
<th>Predictor</th>
<th>Full Dataset (n = 263)*</th>
<th>Predictor</th>
<th>Clean Dataset (n = 153)b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>p-value</td>
<td>Odds Ratio (95% CI)</td>
</tr>
<tr>
<td>Age</td>
<td>1.03 (1.00 to 1.06)</td>
<td>0.05</td>
<td>Age</td>
</tr>
<tr>
<td>Osmolarity</td>
<td>1.01 (1.00 to 1.02)</td>
<td>0.07</td>
<td>Osmolarity</td>
</tr>
<tr>
<td>Gender (Female)</td>
<td>3.38 (1.92 to 5.95)</td>
<td>&lt; 0.0001</td>
<td>Gender (Female)</td>
</tr>
<tr>
<td>Meibography Gland Count</td>
<td>1.10 (1.02 to 1.18)</td>
<td>0.02</td>
<td>Meibography Gland Count</td>
</tr>
<tr>
<td>Phenol Redc</td>
<td>1 0.49 (0.23 to 1.03)</td>
<td>0.03</td>
<td>Nominal Water Content</td>
</tr>
<tr>
<td></td>
<td>2 1.09 (0.50 to 2.36)</td>
<td></td>
<td>PLTF NITBUT</td>
</tr>
<tr>
<td></td>
<td>3 0.45 (0.22 to 0.91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model Diagnostics</td>
<td>auROC = 0.70</td>
<td></td>
<td>Model Diagnostics</td>
</tr>
</tbody>
</table>

*a 303 total subjects. Forty observations were deleted due to missing values for response or explanatory variables, resulting in an effective sample size of 263 (136 are classified with DE and 127 are NDE).

*b 216 total subjects. Sixty-three observations were deleted due to missing values for response of explanatory variables, resulting in an effective sample size of 153 (81 are classified with DE and 72 are NDE).

c Quartiles for phenol red test are as follows: Q1: ≤ 15 mm/15 seconds, Q2: 15-20 mm/15 seconds, Q3: 21-24 mm/15 seconds, and Reference group: > 25 mm/15 seconds.

Table 22. Multivariate logistic regression analyses of tear film and patient-related factors associated with hydrogel contact lens-related dry eye status for the full and clean datasets. RGP lens wearers were not included. Only significant variables (p ≤ 0.05) from the final models are listed (age was retained in the models regardless of significance).
Figure 1. Contact Lens and Dry Eye Study Design.
Figure 2. Sample images associated with the meibography gestalt grading scale.
Figure 3. Distribution of surveyed CLADES patients.
Figure 4. Distribution of test-retest differences associated with CLDEQ Index.
Figure 5. Bland-Altman plot of difference vs. mean for CLDEQ Index. The dashed line represents the average difference in scores between administrations (i.e., bias), and the solid lines represent the width of the 95% limits of agreement (i.e., test-retest reliability).