Ocular Effects of Scleral Lens Wear on Dry Eye Patients

by

Heinz Otchere

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Examining Committee Membership

The following served on the Examining Committee for this thesis. The decision of the Examining Committee is by majority vote

External Examiner	Prof. Jan Bergmanson
	University of Houston College of Optometry
Supervisors	Prof. Lyndon Jones
	Prof. Maud Gorbet
Committee Members	Prof. William Ngo
	Dr. Denise Hileeto
Internal/External Examiner	Prof. Brian Dixon

Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Abstract

Purpose: Dry eye disease (DED) is among the most complex ocular surface diseases to treat. Complaints of ocular discomfort and dryness are common in DED patients and in contact lens wearers. The use of SL to restore the integrity of the ocular surface in a more severe DED has become increasingly accepted among eye care practitioners. However, little is known about this treatment regimen and its impact on ocular surface in mild to moderate DED. Also, the potential impact of coated SL designs incorporating Hydra-PEG (polyethylene glycol) technology on ocular surface health has not yet been fully investigated. This thesis aimed to address this gap in knowledge and determine whether SL (uncoated or Hydra-PEG) could be used as a viable option for patients who are experiencing milder forms of DED. Over the course of the study, participants were asked to complete DE questionnaires; lens settling and vision, corneal thickness, osmolarity and matrix metalloproteinase 9 (MMP-9) in the pre-corneal tear film were investigated. The study also examined the relationship between the respective parameters and compared the two lens pairs.

Methods and Materials: The study was a prospective, double-masked, randomized, dispensing, crossover clinical trial involving five visits, where 20 subjects with mild to moderate dry eye disease (DED) were enrolled. Eligibility of the participants was confirmed following the Tear Film and Ocular Society (TFOS) Diagnostic Report in the first visit: presence of symptoms using the Ocular Surface Disease Index (OSDI) and Standardized Patient Evaluation of Eye Dryness (SPEED) questionnaires (OSDI $\geq$ 13, SPEED $\geq$ 4), plus osmolarity values (> 308 mOsmol/L in either eye or interocular difference of > 8 mOsmol/L) and or a positive MMP-9 result (using InflammaDry® test kit) or both. The second visit involved randomization and dispensing of customized hydra-PEG coated or uncoated SL, where each pair of lenses were worn on a daily wear basis for four weeks. Prior to dispensing the lenses, high contrast (HCVA) and low contrast acuities (LCVA) were recorded. The central corneal clearance (CCC) was measured with Visante^{TM} OCT to determine lens settling over

time. Two standard clinical questionnaires (contact lens impact on quality of life (CLIQ) and contact lens dry eye questionnaire 8 (CLDEQ-8)) and an internally developed wearing habit and subjective rating questionnaire were provided to subjects and completed. The third visit (after 4 weeks) involved follow-up of the first randomized SL, where the lenses were evaluated, and clinical measurements repeated. A wash-out period of at least 48 hours was allowed before dispensing (visit 4) and follow-up (visit 5) of the other pair of SL, using the same procedures, measurement protocols and visit schedule. The SL used in the study were Zen™ RC (Alden Optical, Bausch & Lomb, Lancaster, NY, USA) available in only two diameters (14.80 and 15.40 mm), with a central thickness of 250 μm.

Results: Eighteen females and two males, mean age 29.10 ± 7.48 years, participated in the study. The overall OSDI and SPEED scores were 36.45 ± 17.08 and 12.50 ± 4.03 respectively. There was no significant difference in the CLIQ and CLDEQ-8 scores between uncoated and coated SL. In terms of wearing habit and subjective ratings, no statistically significant differences were observed in any of the parameters (wear time, dryness, burning, vision, and comfort). This suggests that the use of hydra-PEG coated SL did not show greater performance compared to the uncoated SL.

The central corneal clearance (CCC) at the dispensing visit was 260 ± 40 (range: 200 - 300 μm) for both lens pairs. This significantly reduced to 190 ± 40 μm (lens settling: 70 ± 42 μm) for the uncoated SL and 200 ± 30 μm (lens settling: 70 ± 43 μm) for the coated SL at the follow-up visits, (all, $p < 0.001$). Comparing the CCC for the two lens pairs at the follow-up visits, no significant difference was observed, thus, the lens pairs settled at similar rates. In terms of HCVA and LCVA between the two lens pairs at both the dispensing and follow-up visits, there were no significant differences between them. Also, no significant correlations were found comparing the CCC with HCVA and LCVA of each lens pair at both visits.

The CCT at the baseline and follow-up visits were: baseline: 560.55 ± 32.28 μm, post wear of uncoated SL: 557.65 ± 32.10 μm, and post wear of coated SL: 560.50 ± 34.02 μm. There were no significant differences for either lens type for central corneal thickness (CCT) at the baseline and follow-up visits (all, $p > 0.05$). Also, no significant correlations between CCC and CCT were observed at baseline or follow-up visits. These results demonstrated there were minimal corneal hypoxic effects when these SL were worn on a daily wear basis.

For osmolarity measures, there was a statistically significant difference between the baseline and follow-up visit for the coated lenses (311.00 ± 14.86 vs 302.85 ± 7.96 mOsmol/L; $p = 0.04$). While this is statistically significant, the clinical relevance of this small difference remains questionable. Comparing the two lens pairs, no significant difference was found at all visits. The inflammaDry® test results indicated that 80 % of the participants tested positive for elevated MMP-9 at the baseline visit. There was a reduction in MMP-9 positive test results following the SL wear, however, there were no significant differences between the baseline and follow-up visits for each lens pair. Comparing the two lens pairs, no significant difference was observed. For either lens, no correlation was observed between osmolarity and MMP-9 test results.

Conclusion: There is a potential for using SL to manage symptoms in subjects suffering from mild to moderate DED, as the overall wearing habit and subjective ratings showed > 70 % of lens tolerance among the study cohort. SL wear over the month of wear in this cohort induced little change to the cornea or conjunctival tissue. Furthermore, SL may appear to marginally reduce tear film osmolarity, however, further studies are needed to confirm this result and its impact on subjective dryness. The clinical phenomenon of lens settling needs further investigation, especially on its impact on conjunctival morphology. In this cohort of subjects of mild to moderate DED, the hydra-PEG coating technology did not show superior performance over the uncoated lens for any of the factors assessed.

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Dedication

This thesis is dedicated to the life and memory of **Prof. Luigina Sorbara** whose sad event occurred on 10th February 2021. Gina, thanks so much for all the opportunities and you will continue to remain in our hearts. Continue to Rest in Power!

Also, I would like to dedicate this work to my lovely kids: Kenny-Kesty JoHeinz Otchere, Kendrick-Ghartson JoHeinz Otchere, and Kenista-Luigina JoHeinz Otchere. I trust that my academic journey will serve as a source of inspiration for you all, encouraging you to wholeheartedly pursue your own areas of interest.

Love you guys!

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List of Abbreviations

ADDE	Aqueous Deficiency Dry Eye
ADDED	Aqueous Deficiency Dry Eye Disease
ADED	Aqueous Dry Eye Disease
ADES	Asian Dry Eye Society
Anti-VEGF	Antivascular Endothelial Growth Factor
AOID	Anterior Ocular Inflammatory Diseases
APS	Advanced Peripheral System
AP_4A	Diadenosine tetraphosphate
BCR	Base Curve Radius
BCVA	Best Corrected Visual Acuity
BDI	Beck Depression Inventory
BUPs	Breakup Patterns
CCC	Central Corneal Clearance
CCT	Central Corneal Thickness
CCTn	Central Corneal Thinness
CD 11a	Cluster of Differentiation 11a
CD 3,4,8	Cluster of Differentiation 3, 4, 8
CI	Confidence Interval
CLDEQ-8	Contact Lens Dry Eye Question 8
CLIQ	Contact Lens Impact on Quality of Life
CORE	Center for Ocular Research and Education

COVID-19	Coronavirus Disease 19
CSA	Corneoscleral Angle
CSD	Corneal Sagittal Depth
D	Diopter
DE	Dry Eye
DED	Dry Eye Disease
DEQ-5	Dry Eye Questionnaire 5
Dk	Oxygen Permeability
Dk/t	Oxygen Transmissibility
DTS	Dysfunctional Tear Syndrome
e	Eccentricity
EDE	Evaporative Dry Eye
EDED	Evaporative Dry Eye Disease
ELISA	Enzyme-linked Immunosorbent Assay
ELISpot	Enzyme-linked Immunosorbent Spot
GP	Gas Permeable
GVHD	Graft-Versus-Host Disease
HCVA	High Contrast Visual Acuity
HFIM	Hexafluoroisopropyl Methacrylate
HLA-DR	Human Leukocyte Antigen-DR Isotype
HR	High Resolution
HVID	Horizontal Visible Iris Diameter

ICL	Informed Consent Letter
ICRS	Intrastromal Corneal Ring Segment
IL-1α	Interleukin 1 Alpha
IL-1β	Interleukin 1 Beta
IL-4, 8	Interleukin 4, 8
IPL	Intense Pulsed Light
K-Reading	Radius of curvature
K5M	Keratograph 5M
KC	Keratoconus
KCS	Keratoconjunctivitis Sicca
LCVA	Low Contrast Visual Acuity
LFA-1	Lymphocyte Function-Associated Antigen 1
LFU	Lacrimal Functional Unit
LogMAR	Logarithm of Minimum Angle of Resolution
MAM	Membrane Associated Mucins
MAP-K	Mitogen Activated Protein Kinase
MCQ	McMonnies Questionnaire
MDF	Mid-day Fogging
MG	Meibomian Gland
MGD	Meibomian Gland Disease
MMA	methyl Methacrylate
MMP-7,9,10	Matrix Metalloproteinase 7,9,10

MMPs	Matrix Metalloproteinases
MUC-16	Membrane-associated Mucins 16
MUC5 AC	Mucin 5AC, Oligomeric Mucus/Gel-Forming
NA	Non-applicable
NaCl	Sodium Chloride
NaFl	Sodium Fluorescein
NEI	National Eye Institute
NEI VFQ-25	National Eye Institute Visual Functioning Questionnaire 25
NITBUT	Non-invasive Tear Break Up Time
NSS	Non Sjögren Syndrome
OCI	Ocular Comfort Index
OCT	Optical Coherence Tomography
OD	Ocular Dexter (Right Eye)
OR	Odds Ratio
OS	Ocular Sinister (Left Eye)
OSDI	Ocular Surface Disease Index
PED	Persistent Epithelial Defect
PEG	Polyethylene Glycol
PK	Penetrating Keratoplasty
PMMA	Poly Methyl Methacrylate
PSQ	Pain Sensitivity Questionnaire
QoL	Quality of Life

RGP	Rigid Gas Permeable
Sag	Sagittal Height
SANDE	Symptom Assessment Questionnaire in Dry Eye
SCOPE	Scleral Lenses in Current Ophthalmic Practice: an Evaluation
SD	Standard Deviation
SF-12	Short Form 12 Questionnaire
SJS	Stevens-Johnson Syndrome
SL	Scleral Contact Lenses
SPEED	Standardized Patient Evaluation of Eye Dryness
SS	Sjögren Syndrome
TBUT	Tear Break-up Time
TFOD	Tear Film Oriented Diagnosis
TFOS DEWS	Tear Film Ocular Society Dry Eye Workshop
TFOT	Tear Film Oriented Therapy
TMH	Tear Meniscus Height
TRIS	Trimethyl Siloxy Silane
UV	Ultraviolet
VA	Visual Acuity
Zen RC	Spherical Zen Lens Design
Zen RCT	Toric Zen Lens Design

List of Symbols

%	Percentage
º	Degree
g	Gram
hrs	Hours
L	Liter
mg	Milligram
mg/d	Milligram Per Day
min	Minutes
mL	Milliliters
mm	Millimeter
mOsmol/L	Milliosmole per liter
ng/ml	Nanogram per milliliters
nm	Nanometer
pH	Potential Hydrogen
p	Level of statistically significant difference
µm	Micrometer/micron

CHAPTER 1

1.1 Introduction and Literature Review

1.2 Dry Eye

Dry Eye (DE), as it is commonly known, had previously been referred to as "Keratoconjunctivitis Sicca" (KCS). (1, 2) This term was first coined and introduced into the ophthalmic literature by Henrik S.C. Sjögren in 1933. (3, 4) Subsequently, the name Sjögren became associated with the term Sjögren's Syndrome (SS), which was characterized by DE, dry mouth, and multiple extra glandular manifestations. (5) Sex was identified as a significant factor, with 90 % of patients being women. (5) The early definition and understanding of KCS was based on qualitative deficiency resulting from insufficient lipid and mucous secretion or quantitative deficiency from the lacrimal gland. (6, 7) The term "dry eye" was later formulated by a dacryologist, Andrew de Roetth, in 1950 and for many years, this clinical condition was characterized by significant reduction in the aqueous layer of the pre-corneal tear film (dryness of the eye). (8, 9) Other clinical terms which have also been used to designate DE are DE syndrome, (10-13) ocular dryness, (14-16) ocular surface and tear disorder, (17) and dysfunctional tear syndrome (DTS). (18, 19)

The DE condition was classified as one of the ocular surface syndromes which may occur as an independent condition or in combination with other local diseases such as blepharitis or meibomianitis among others. Also, systemic conditions such as diabetes, rheumatoid arthritis and lupus are known to eventually affect aqueous production. (2) In most cases, it was seen as a mild to moderate condition, which could in some patients progress to an advanced state, with severe clinical signs and symptoms. Interestingly, the diagnostic tools to define the presence of DE were fairly limited, consisting of an external examination of the tear film and ocular surface, including tests such as Schirmer's test, vital dye staining of the cornea and conjunctiva and examination of the lid margin. (20, 21) More recent advances in clinical testing, diagnostic protocols, proteomics technology and instrumentation, in addition to novel therapeutic interventions, have expanded our understanding of DE.

1.3 Physiology and Functions of the Precorneal Tear Film

One of the most complex structures of the anterior segment is the pre-corneal tear film, which acts as a barrier between the corneal epithelium and the external environment. (9, 22) The exact thickness of the pre-corneal tear film remains debatable and varies between individuals; however, it is broadly estimated to be around 3 μm and is highly dependent on other factors such as age, sex, integrity of the lacrimal and the accessory glands and the instruments used for its assessment. (23)

Traditionally, the tear film was believed to consist of three distinct layers: lipid, aqueous, and mucin layers. However, recent studies have shown that the tear film has an intricate structure with a complex composition, containing water, electrolytes, mucins, lipids, and over 1500 proteins. (22, 24) Currently, the most accepted theory is that the tear film can best be described as a broadly two-layered structure, consisting of an inner mucus-aqueous layer covered by a complex lipid layer. (9, 25-27) The tear film structure is illustrated in Figure 1-1.

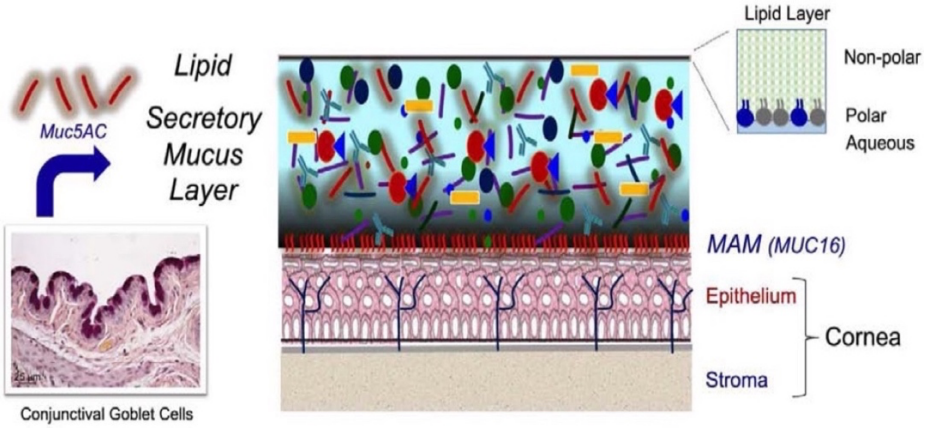


Figure 1-1: Tear film structure.

The tear film consists of membrane associated mucins (MAM) such as MUC16 that form the glycocalyx on the corneal epithelium, a secretory mucus layer containing soluble MUC5AC mucin secreted by the conjunctival goblet cells, aqueous fluid and electrolytes, and proteins secreted by the lacrimal glands. Proteins such as lysozyme, lactoferrin and lipocalin are secreted by acini of the lacrimal gland and primarily act as anti-infective agents. Additionally, inflammatory molecules such as interleukins, transforming growth factor- β2 (TGF-β2) and vitamin A and its metabolites act to reduce inflammation in the tear film. The surface of the tears is covered with a lipid layer with polar lipids adjacent to the aqueous layer and nonpolar lipids interfacing with the air. *Reproduced with permission from*

Functionally, the tear film acts as the optical surface of the eye, providing quality vision when remaining in a stable conformation over the corneal surface. (26, 28) Studies have shown that the tear film and the anterior surface of the eye account for about 80 % of the total refractive power of the human eye. (29-32) Therefore, disruption of the smooth tear film on the corneal surface impacts optical quality and contrast sensitivity and increases optical aberrations that degrade retinal image quality, ultimately leading to blurred vision. The tear film also acts as a lubricant, reducing the shear stress across the ocular surface from the under surface of the eyelids during blinking. According to Korb et al, (33) any condition that distorts the perfectly formed tear film structure in terms of quantity and quality increases this shear stress, which ultimately leads to epitheliopathy of the lid marginal conjunctiva (currently called lid wiper epitheliopathy) that wipes across the ocular surface during blinking. Figures 1-2 and 1-3 show the normal lid wiper and different patterns of lid wiper epitheliopathy.

The increased shear stress can also result in corneal epithelial disease, nociceptor stimulation and pain. The tear film also protects corneal and conjunctival epithelia from environmental stress such as microbes, pollutants, allergens, and adverse environmental conditions (e.g., low humidity, high temperature, windy conditions etc.). This is achieved through secretion of biochemical compounds such as glycoproteins, immunoglobulins, and enzymes that act to protect and repair any damage to the epithelial cells. (34) Also, the ocular surface is known to have a complex network of free nerve endings beneath the epithelial layer of the ocular surface. These nerves act as a protective mechanism for the ocular surface.

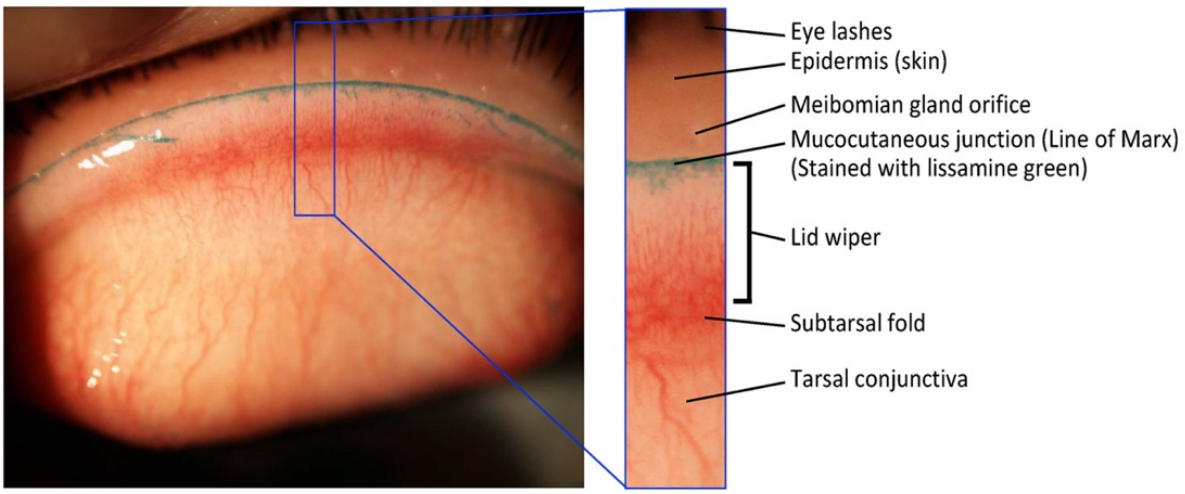


Figure 1-2: Normal everted eyelid, showing normal lid wiper and adjacent anatomical structures.

Lissamine green stain shows mucocutaneous junction (line of Marx). (35) *Reproduced with permission from Elsevier Copyright Clearance Center's RightsLink® Service. Efron N, Brennan NA, Morgan PB, Wilson T. Lid wiper epitheliopathy. Prog Retin Eye Res. 2016; 53:140-174.*

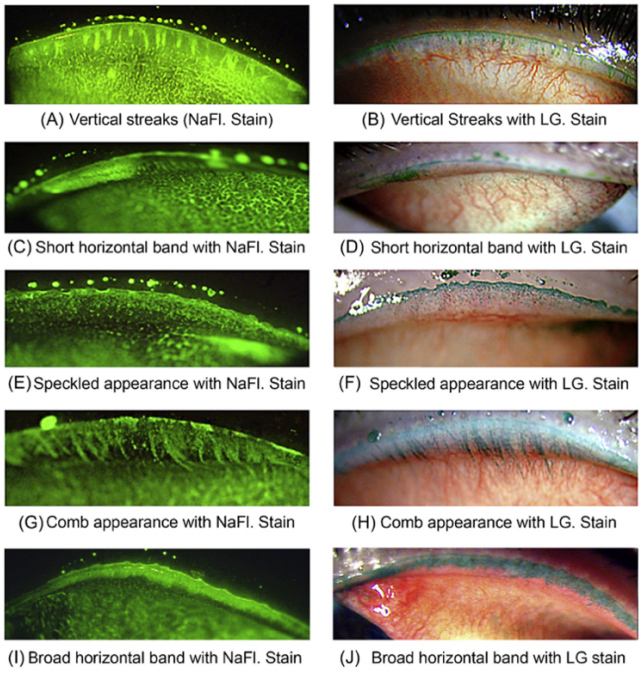


Figure 1-3: Different patterns of lip wiper epitheliopathy.

Reproduced with permission from Elsevier Copyright Clearance Center's RightsLink® Service. Varikooty J, Srinivasan S, Subbaraman L, et al. Variations in observable lid wiper epitheliopathy (LWE) staining patterns in wearers of silicone hydrogel lenses. Cont Lens Ant Eye. 2015;38(6):471-476. (36)

The secretion, delivery, and clearance of the tear film to maintain ocular surface homeostasis is regulated by the lacrimal functional unit (LFU). This unit consists of the tear secretory glands, primarily the lacrimal gland, and accessory glands (Krause and Wolfring), producing the watery serous secretion. (37-39) It is believed that the lacrimal gland is responsible for producing reflex tears, while the accessory glands (which produce about 10 % of the total volume) produce basal or resting tears. (38) The other major glands that are secretory in nature are the Meibomian glands. These glands are modified, holocrine, sebaceous glands embedded in the tarsal plate of both the upper and lower eyelids and are responsible for excreting lipids into the tear film. (40, 41) This film acts as the outer layer between the external environment and the aqueous layer and functions largely to reduce evaporation. Dysfunction of these glands will eventually lead to Meibomian Gland Dysfunction (MGD), which is the major cause of evaporative dry eye disease (EDED), which is described in greater detail in section 1.9. (42)

The other components of the LFU are the surface epithelium, eye lids, lacrimal drainage system, the glandular and mucosal immune system, and the lacrimal nerve plexus. (38, 43) The lacrimal gland is innervated by both the sympathetic and parasympathetic neural systems. The lacrimal nerve (main nerve) from the ophthalmic branch of the trigeminal nerve provides sensory innervation to the gland, and its nerve endings are close to acinar, ductal, and myoepithelial cells, as well as blood vessels, allowing it to control a wide range of lacrimal gland functions. Stimulation of lacrimal gland secretion (parasympathetic innervation) is mediated in part by a neural reflex arc that originates on the ocular surface, with additional trigeminal input from the nasal mucosa. Acetylcholine and norepinephrine are some of the neurotransmitters and neuropeptides released by innervating nerves. Each of these neuromediators interacts with distinct receptors on the surface of lacrimal gland cells, eliciting a specific response in which serous secretion is released to the ocular surface. In contrast, sympathetic innervation is derived from the superior cervical ganglia and transported by the internal carotid plexus and deep petrosal nerve. These nerves connect with the parasympathetic fibers in the pterygoid canal nerve and travel the same route to supply the gland, inhibiting fluid secretion from the lacrimal gland. (44)

Rosenthal et al (45) reported that damage to any of the structure and functions in LFU results in significant reduction in tear secretion and ocular surface epithelial disease, which then leads to a condition now classified as dry eye diseases (DED).

1.4 Definition of Dry Eye

The past thirty years have seen significant improvement in terms of adopting a standardized definition for DED, which acts as a guide for clinicians and researchers in the ophthalmic field. The early challenge in establishing a universally accepted definition of DE was partly due to the complexity of the condition, varied clinical signs and symptoms, lack of a complete understanding of the pathogenesis and other significant systemic conditions which ultimately become associated with DE. (46, 47) To address this challenge, the National Eye Institute (NEI) Industry working group on Clinical Trials in Dry Eye in 1995 defined DE as:

‘‘*Dry eye is a* ***disorder*** *of the tear film due to tear deficiency or excessive tear evaporation which causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort*.” (48)

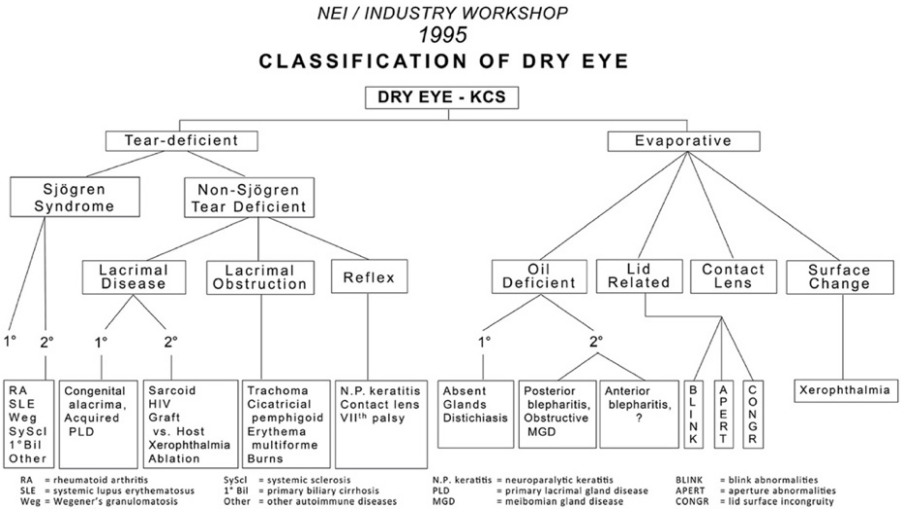


Figure 1-4: The 1995 NEI Classification of dry eye.

Reproduced with permission from Wolters Kluwer Health, Inc. and Copyright Clearance Center. Lemp MA. Report of the national eye institute/industry workshop on clinical trials in dry eyes. CLAO J 1995;21(4):221e32. (48)

This report classified DE into two broad categories: Tear-deficient and Evaporative (see Figure 1-3). Tear-deficient was subclassified into SS and Non- Sjögren's syndrome (NSS), with a range of intrinsic and extrinsic causative factors. In comparison, the evaporative DE condition was subdivided into other factors which could potentially result in DE. A typical example is "oil deficiency" found primarily in individuals with gland distichiasis. (49) Other secondary conditions were lid related conditions such as MGD, (50) contact lenses wear that disturbs the tear film break-up time, (51) and changes in the ocular surface due to dietary deficiencies. (52)

Emboldened in the above definition was that DE was heavily considered as a *"disorder" (with myriads of symptoms causing tear film disruption with unknown or multiple etiologies)*, with much emphasis on tear film tear deficiency or excessive tear evaporation as the main cause of DE. Practically, this definition provided the template on which the diagnosis of DE condition could be assessed in both clinical and research settings.

Further to the above definition, in 2006, a Delphi Consensus Group proposed dysfunctional tear syndrome (DTS) to clinically define DE. (53) According to the Delphi Consensus Group, (53) the recommended guidelines for clinical evaluation of the tear syndrome should be based on the presence or absence of lid margin disease and quality of the tear film. Thus, without lid margin disease, clinical symptoms and signs should be used to determine the presence of DED rather than a variety of clinical tests. Again, the committee's report highlighted that the treatment and clinical decision should focus on the degree or severity of the condition. In view of the proposed definition, four management algorithms (level 1 to 4) were proposed for clinical treatment of DE patients. Level 1 usually ranges from no treatment and psychological support (early stages) to the use of anti-allergic eye drops and avoidance of medications contributing to DE. Level 2 involves the use of unpreserved tears, gels, ointments to secretagogues and short course topical steroids. In level 3, the committee recommended the use of tetracyclines and punctal plugs while for the most severe forms (level 4), the use of oral cyclosporine, acetylcysteine, systemic anti-inflammatory therapy, surgery, moisture goggles and therapeutic contact lenses were recommended.

Given the various anomalies or shortfalls in the NEI (1995) and Delphi (2006) definitions compared to clinical findings such as the impact of DED on visual function, changes in osmolarity and the presence of ocular surface inflammation, and to standardize clinical procedures in terms of diagnostic and therapeutic pathways, a new definition was proposed by the Tear Film and Ocular Society Dry Eye Workshop (TFOS DEWS) in 2007, which defined DE as:

‘‘*Dry eye is a* ***multifactorial disease*** *of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface*.” (17)

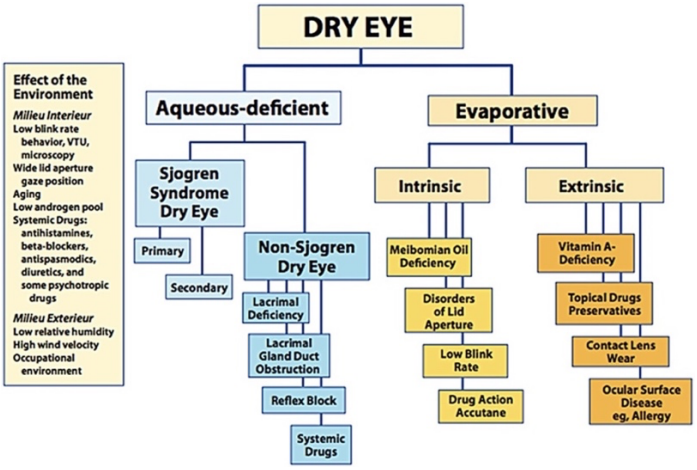


Figure 1-5: Dry Eye classification: 2007 DEWS Report.

The *left box* illustrates the influence of the environment on developing DED. Aqueous-deficient subtypes: Sjögren and non-Sjögren Syndrome. Evaporative subtypes: intrinsic and extrinsic. (17) *Reproduced with permission from Elsevier Copyright Clearance Center’s RightsLink® Service. Craig et al. TFOS DEWS II Definition and classification Report. Ocul Surf. 2017; 15:276–283.*

In the TFOS DEWS 2007 report, *“tear-deficient”* which was clearly defined and established in the NEI, was redefined and termed *“aqueous deficient”* DE and further subdivided into SS and NSS. Evaporative DE was simply re-classified to specify intrinsic and extrinsic categories, based

on the etiological factors. Figure 1-5 presents the Dry Eye classification as defined by the 2007 DEWS report.

The above TFOS DEWS re-definition heralded a new frontier, presenting DE as a complex and multifactorial condition and most importantly for the first time as a *"disease" (with specific symptoms and measurable signs of known etiology or pathogenesis)* state of the ocular surface. Also, it highlighted the symptoms of discomfort, which aligned with the definition by NEI, and the impacts of an unstable tear film on the visual system, which ultimately affects corneal integrity. (48) The clinical effects of osmolarity following evaporation and the consequence of inflammation on the ocular surface which were not seen to play a significant role in the disease process (cause of DE) in the earlier definition were therefore highlighted in the 2007 TFOS DEWS definition and given the needed attention. The concept of homeostasis of the tear film, blink abnormalities and tear component deficiencies were thus considered. It was observed that changes in the tear film stability and osmolarity due to excessive tear evaporation of the ocular surface can serve as the entry point to the pathogenesis of the condition, which then initiate the cascade of the so-called "*Vicious Cycle"* seen in DED. This cycle is explained in more detail in section 1.6.2. (54)

Finally, a new definition of DE was adopted by TFOS DEWS II in 2017 which states that (17) :

"*Dry eye is a* ***multifactorial disease*** *of the ocular surface characterized by a* ***loss of homeostasis*** *of the tear film, and accompanied by ocular symptoms, in which tear* ***film instability*** *and* ***hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities*** *play etiological roles*."

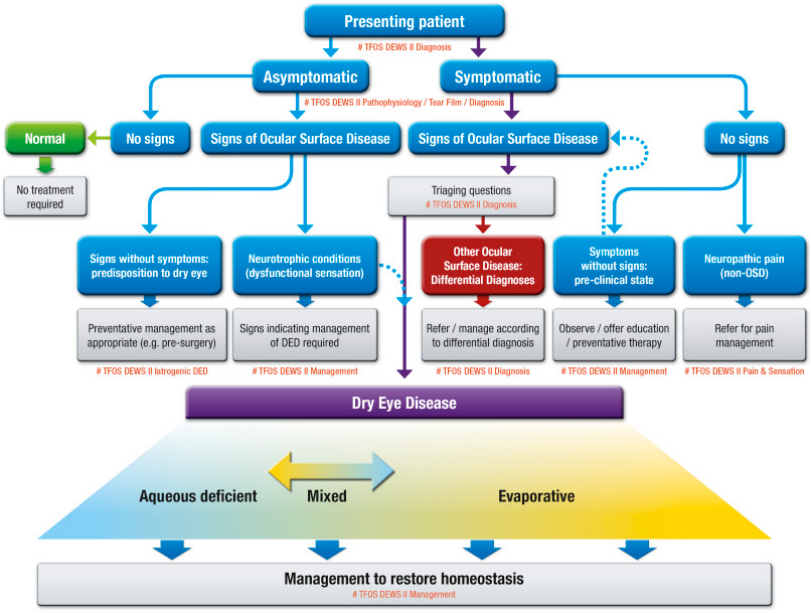


Figure 1-6: Classification of DED.

The upper portion of the figure represents a clinical decision algorithm, beginning with the assessment of symptoms, and followed by review for signs of ocular surface disease. DED exhibits both symptoms and signs and can be differentiated from other ocular surface disease with the use of triaging questions and ancillary test. (17) *Reproduced with permission from Elsevier Copyright Clearance Center's RightsLink® Service. Craig et al. TFOS DEWS II Definition and Classification Report. Ocul Surf. 2017 Jul;15(3):276-283.*

The clinical implication was that the new DED classification would help simplify the assessment, evaluation and diagnosis of the condition. Also, it reaffirms the use of standardized clinical questionnaires and a slit lamp examination with fluorescein dye for the diagnosis of DED. Moreover, the newly proposed classification was designed to consider one of the most challenging factors of DED diagnosis such as the mismatch between presenting DED symptoms with or without clinical signs. (55) Therefore, DED can be classified whether the patient presents with no symptoms (asymptomatic - in which case the definition precludes the patient as having DED) or with presenting symptoms (symptomatic).

Irrespective of the widely accepted definition of DED by TFOS DEWS II, the Asia Dry Eye Society (ADES) recently presented a different opinion on what constitutes DED and how the disease should be assessed, diagnosed, and managed in a clinical situation. Most importantly, the ADES does not recognize ocular surface inflammation and hyperosmolarity as part of the etiology.

The current adopted definition of DED by ADES states:

"Dry eye is a multifactorial disease characterized by unstable tear film causing a variety of symptoms and/or visual impairment, potentially accompanied by ocular surface damage. (56)

Figure 1-7 illustrates the classification and subtypes based on the ADES definition of DED.

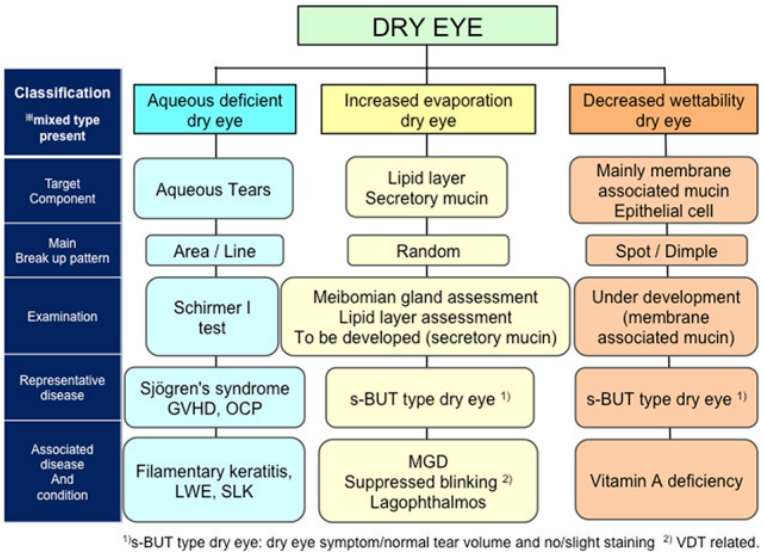


Figure 1-7: DED classification by the ADES.

Reproduced with permission from Elsevier Copyright Clearance Center's RightsLink® Service. Tsubota et al. A New Perspective on Dry Eye Classification: Proposal by the Asia Dry Eye Society. Eye Contact Lens. 2020;46 Suppl 1(1):S2-s13.

1.5 Prevalence of Dry Eye Disease

Determining the prevalence rates of DED has been a daunting task to undertake. (57) The challenge stems from variations in studies which are largely influenced by age, gender, race, patient selection, systemic condition, or geographic location. (9, 58-60) Adding to the complexity inherent in prevalence studies are the lack of standardized clinical diagnostic tools, diagnostic criteria and/or accepted definition on which DED is assessed and diagnosed. (13, 17)

A comprehensive report by TFOS DEWS II Epidemiology Subcommittee estimated the global prevalence rates of DED including symptoms with or without signs range from approximately 5 to 50 %. (61) Prevalence rates where DED was diagnosed primarily on signs have been reported to be higher, with a wide variation and estimated to be up to 75 % among the adult population 40 years and above, mostly affecting women. (57)

According to Ferrand et al. (62), DED was estimated at 6.80 % among the US adult population, which accounted for ~ 16.4 million individuals. It was determined that prevalence increased with increasing age, with rates in younger adults between 18-34 years estimated at 2.70 %, 18.60 % for adults 75 years and older, with higher rates among women (8.80 %, ~ 11.1 million) compared to men (4.50 %, ~ 5.3 million). Interestingly, they reported that demographic characteristics such as race, level of education, and geographic location had no significant influence on the prevalence rate of the condition. Instead, age was determined to have a major impact on the risk of developing DED as individuals aged over 75 years had higher risk (odds ratio (OR): 4.95; 95 % confidence interval (CI): 4.26 - 5.74) compared to those aged 45 - 54 years (OR: 1.95; 95 % CI: 1.74 - 2.20). Also, women were reported to have a higher risk (OR: 2.00; 95 % CI: 1.88 - 2.13) compared to men.

The most recent prevalence study by Papas (58) using a Bayesian model to analyze DED studies published between 1997 and 2021 shows the global estimate at 11.59 ± 0.04 %. For symptomatic disease, the estimate was 9.12 ± 0.04 % (women: 9.50 ± 0.05 %, men: 6.80 ± 0.06 %). The study reported the prevalence rate was lowest in North America (4.60 ± 0.03 %) and highest in Africa (47.90 ± 1.80 %). For signs, prevalence was 35.20 ± 0.30 % (women: 34.70 ± 0.70 %, men: 37.60 ± 0.7 %). North America again showed the lowest regional prevalence of 3.50 ± 0.40 % with

highest recorded prevalence of 42.80 ± 0.40 % in Eastern Asia. Using the TFOS DEWS II diagnostic criteria, the global prevalence rate almost tripled at 29.50 ± 0.80 % (women: 28.10 ± 1.20 %, men: 24.90 ± 1.40).

Using the sub-classification of EDED and Aqueous Deficiency Dry Eye Disease (ADDED), Hom et al (63) estimated that EDED accounted for 67.50 % of the studied population, ADDED was 24.60 % and mixed accounted for 7.80 %. Within ADDED, 76 % were exclusive ADDED while 24 % were mixed. For EDED, 89.60 % were exclusive EDED and 10.30 % were mixed. Other studies have also confirmed that the majority of patients experiencing DED are EDED. (17, 64, 65)

1.6 Dry Eye as a "Disease" Condition

The concept of DE as a *"disease"* entity was first acknowledged in the TFOS DEWS 2007 comprehensive report. (17) Prior, it had largely been referred to as a *"disorder"* (48) of the tear film by the NEI and further re-named by the Delphi consensus group as "*dysfunctional tear syndrome".* (53) The concept of disease entity for DE reflects its association to a pathological process and related to the structure or function of the tear film, with symptoms and clinical signs affecting a specific location on the ocular surface, typically the cornea, conjunctiva or eyelids (66, 67) The following subtopics discuss DED under disruption of the precorneal tear film, inflammatory proteins, symptoms, and clinical signs.

1.6.1 Dry Eye Disease and Disruption of the Tear Film

As a disease condition, studies have shown that the DE causes disruption of the tightly organized tear film layer. (53, 68, 69) Disruption to any of the specific layers is likely to affect the quality, quantity, and the surface integrity of the corneal and conjunctival epithelia. (70) As a result of this disruption, the Japanese and Asian model of DED has focused on "*layer-by-layer"* assessment, diagnosis and treatment which is currently termed *tear-film-oriented diagnosis* (TFOD) and *tear-*

film-oriented therapy (TFOT). (68, 71) The standardized diagnostic criteria based on the tear film assessment according to the ADES is tear film break up of ≤ 5 seconds with other presenting symptoms. Figure 1-8 shows the model of the various tear break up patterns used by the ADES in DED assessment and diagnosis.

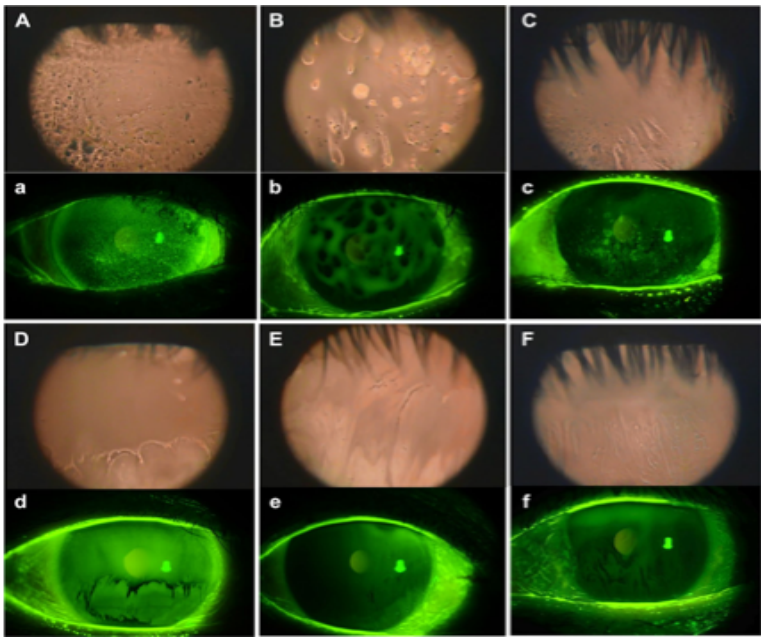


Figure 1-8: Tear breakup patterns (BUPs) observed by video-interferometer.

(DR-1; Kowa Company, Ltd) (**A–F**) and fluorescein patterns (**a**– **f**). Each set of images (e.g., **A** and **a**) was obtained from the same eye. **A** and **a**: Area break; **B** and **b**: Spot break; **C** and **c**: Line break; **D** and **d**: Dimple break; **E** and **e**: Random break; **F** and **f**: Line break with rapid expansion of the breakup regions. Area and line break patterns appear in severe and less-severe ADDE, respectively. Spot break and dimple break indicate decreased-wettability seen in DE. The random break pattern typically appears in EDE. (71) *Reproduced with permission from Japanese Journal of Ophthalmology. Tear-film-oriented diagnosis for dry eye. Yokoi, N, Georgiev GA. Jpn J Ophthalmology, 63, p 127–136 (2019)* (68)

1.6.2 Dry Eye Disease, inflammation and Inflammatory Proteins

Another characteristic feature of DE as a disease condition is the role of inflammation in its pathogenesis. (72) The concept of inflammation playing a pivotal role was first described in detail by Baudouin et al. (73) and the term *"vicious cycle of inflammation"* was proposed to highlight

inflammatory proteins as a main driver in DED. Inflammation generally refers to the process by which the immune system recognizes and eliminates damaging and foreign stimuli. (74) Two forms of inflammation exist: acute and chronic. The inflammation encountered in DED is typically chronic in nature, which results in tear film instability and disruption of the normal function and homeostasis of the tear film of the ocular surface. The precise mechanisms that lead to ocular surface inflammation in DE have yet to be established. However, environmental stressors such as digital devices, wind currents and high temperatures have been shown to cause increased ocular surface evaporation. This results in hyperosmolarity in the tear film, which leads to ocular surface inflammation. Also, these "proinflammatory stimuli" may be exacerbated in individuals with systemic autoimmune diseases (e.g., Sjogren Syndrome) because of malfunction in their intrinsic immunoregulatory pathways. Aging and disease-related androgen hormone deficiency are also known to promote local autoimmune reactions. (76)

In view of this, breaking the inflammatory cycle was proposed as the first step towards the treatment of DED. The vicious cycle includes pre-corneal tear film instability, hyperosmolarity, apoptosis of corneal and conjunctival epithelial cells, and inflammation on the ocular surface. Intrinsic and extrinsic factors are also known to cause oxidative stress, which fuels the vicious cycle, leading to the debilitating symptoms and clinical signs. (75-77)

Available evidence suggests that ocular surface inflammation in DED is mediated by lymphocytes, as identified by lymphocyte activation markers such as cluster of differentiation 11a (CD11a) and Human Leukocyte Antigen-DR isotype (HLA-DR). (78) The CD11a is involved with activation and migration of T-cells to the ocular surface, while the HLA-DR present antigens to the T-helper cells, which then stimulate other immune cells leading to sustained inflammatory response. Immuno-histopathological study on SS and NSS by Stern et al (79) showed that subjects had T-cell infiltrates with upregulation of CD3, CD4, and CD8 and HLA-DR on conjunctival cells.

Inflammatory proteins observed in DED studies include cytokines and matrix metalloproteinases (MMPs). (80-82) According to Solomon et al, (80) individuals diagnosed with DED have increased interleukin (IL) -1 (IL-1α and mature IL-1β) with a corresponding decrease in inactive

precursor IL-1β in the tear film. Also, matrix metalloproteinase-9 (MMP-9) has been found to be highly upregulated in DED patients compared to controls. (83-86)

Intracellular signaling proteins such as mitogen-activated protein kinase (MAP-K) are also known to be integral part of the vicious cycle in DED. MAP-K acts as a key signaling molecule that stimulates the production and release of proinflammatory proteins and cytokines by the ocular surface epithelia, among them being the synthesis of MMP-9. (87) The presence of these inflammatory proteins disrupts the surface membranes and the tight junctions of the epithelial cells typically the glycocalyx mucin and goblet cells. Through osmotic imbalance, mechanical stress, inflammatory stress, and damage to goblet cells and ocular surface defense systems, a series of events culminate in further degradation of the tear film, complete the circle and setting off a self-stimulating vicious cycle. A summary of the signaling molecules and inflammatory proteins identified in the vicious cycle in DED is presented in Figure 1-9.

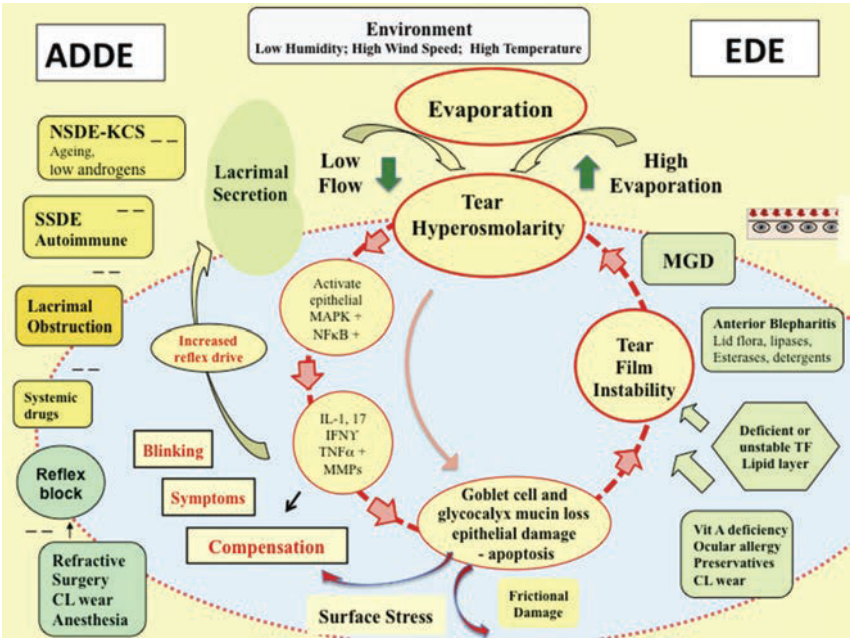


Figure 1-9: The Vicious cycle of DED.

The core mechanism is tear hyperosmolarity. It damages the ocular surface both directly and by initiating inflammation. The cycle of events is shown at the center of the figure. (88) *Reproduced with permission from Elsevier*

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1.6.3 Dry Eye Disease Symptoms and Signs

Like many clinical conditions, DED also produces specific symptoms and signs that can be assessed and measured in clinical situations. (4, 89) The first characteristic symptom and perhaps the most common complaint central to the disease is ocular discomfort. (17) The most common presenting ocular symptoms of discomfort are dryness, redness, foreign body sensation, heavy eye lids, pain, light sensitivity (photophobia), discharge, itching, irritation, blurry vision, and eye fatigue. (90, 91)

Clinically, the first sign to be noticed under slit lamp biomicroscopy with fluorescein is short tear film break-up time (TBUT). (68, 71) According to Yokoi et al, (71) individuals with DED usually have their TBUT observed within 5 seconds or less. These appear as dark spots (due to evaporation), with underlying corneal epithelial damage (See figure 1-9). They postulated that shorter TBUT of the precorneal tear is associated with epithelial damage, and this concept has been the basis for DE diagnosis in Japan and Asian countries. Another clinical sign is the tear meniscus height, volume and area which are significantly reduced in DED compared to healthy eyes. (92) The TFOS DEWS II Diagnostic Methodology report (93) proposed that a tear meniscus height of 0.2 mm is an indication of ADDED, and that this criterion can also be used to determine the severity of the condition. Other clinical signs of DED are corneal epithelial damage, reduced Schirmer's test, positive rose bengal staining, lid wiper epitheliopathy, reduced lipid layer, and reduced meibomian gland score. (94)

1.7 Dry Eye Disease and Its Importance

The effects of DED can significantly affect the health status of an individual, as well as visual outcome and quality of life (QoL). (91) The presenting symptoms also interfere with daily routines

ultimately affecting productivity. (95, 96) The following subtopics describe the effect of DED specifically on QoL, depression and anxiety, and economic burden.

1.7.1 Dry Eye Disease and Quality of Life

Available data suggests that the impact on the physical health of individuals experiencing DED often results from continuous pain and discomfort. (97-99) These symptoms are vast and varied depending on age, sex, environment, immunological response, and severity of the disease. (100-103) The most common complaints are sharp pain, stinging, eye strain, heavy eyelids, stringy mucous discharge, watery eyes, photophobia, and contact lens intolerance. (104) Additionally, low tear production in DED leads to blurred vision and glare or halos around light, which significantly impacts driving. (105)

The psychological effect of DED has been documented by numerous authors. (106-110) A recent meta-analysis study by Wang et al (106) investigated the relationship between DED, self-perceived health status, and self-reported psychological stress burden. Using the TFOS DEWS II diagnostic criteria, it was reported that there was a statistically significant difference between increased self-reported psychological stress and DED, aqueous tear deficiency and MGD (all $p \leq 0.01$). DED is also known to affect individual's cognitive processes, mood and most importantly mental health, partly due to chronic discomfort and pain. (111) Finally, numerous publications have provided evidence of DED negative effects on individual's concentration and performance, which ultimately leads to decreased productivity. (96, 112-114)

Another factor which is known to affect the QoL is the level of independence and the need to be able to undertake daily activities. (115) The chronic nature of DED presents significant impediment as the treatment can be extensively long. (113) Combining daily treatment regimen with routine activities can be burdensome for patients, especially the elderly population, leading to reduced compliance. (116-118) Additionally, individuals experiencing diseases such dementia, Parkinson's, multiple sclerosis, or rheumatoid arthritis may find DED treatment challenging, with

the need for multiple doses of eye drops or use of devices (such as eyelash cleansers, moisture goggles, etc.). (119-121)

1.7.2 Dry Eye Disease, Depression and Anxiety

Available studies showing the possible link between DED, depression and anxiety have received attention in the ophthalmic literature. (108, 122, 123) It has been reported that individuals with DED are at increased risk from psychological stress, severe anxiety, and depression, which are related to symptoms, particularly chronic pain and blurred vision. (117, 122, 123) Using the Pain Sensitivity Questionnaire (PSQ) to determine the relationship between pain sensitivity and ocular discomfort and dryness, Li et al. (124) reported that PSQ scores were found to significantly correlate with higher OSDI scores, lower end-of-day comfort, and increased dryness in patients with ocular discomfort. They concluded that complexity of the pain neural network undoubtedly increases the risk of depression and anxiety in most patients experiencing DED.

Comparing depressive symptoms using the Beck Depression Inventory (BDI) to determine the association between measured parameters, Hallak et al (125) reported significant differences between DED patients and controls on symptoms and depression scores. The established chance ratio of developing depression was 2.79 (95 % CI, 0.96 - 8.12) among DED patients. This effect has also been reported by other authors. (123, 126)

1.7.3 Dry Eye Disease and Economic Burden

The chronicity and burden of long-term treatment including but not limited to costs of medication, medical visits, surgical cost, dietary or palliative supplements as well as direct and indirect costs are well documented. (127-129) Irrespective of the advances in pharmacotherapy and other devices used in the management of DED, these options come with cost, and result in enormous economic burden for most DED patients. Bielory et al (127) reported that of all the ocular pharmacologic agents prescribed in 2011, DED medication accounted for 12.40 % of the total cost of medications prescribed. Figure 1-10 shows the global percentage estimates of the ophthalmic prescriptions sold

in 2011. Also, table 1-1 presents the direct and indirect cost of treating DED in USA and Canada per person per year. Similar patterns have also been reported by other authors. (128, 130)

Table 1-1: Direct and indirect cost of DED treatment in USA and Canada.

Severity of DED	**DED cost in USA, data from Bielory et al** (127)		**DED cost in Canada, data from Chan et al** (131)	
	Direct Cost (US$)	Indirect Cost (US$)	Direct Cost (CAD$)	Indirect Cost (CAD$)
Mild	678	12686	958 ± 1216	5961 ± 6275
Moderate	771	12569	1303 ± 1574	16525 ± 11607
Severe	1267	18168	2766 ± 7161	25485 ± 22879

Direct Costs are expenses related to the treatment of DED and typically covers prescription drugs, out of pocket and insurance coverage, eye care products, medical visits and procedures and nutritional supplements, while indirect costs are not related to disease treatment but refer to effects on the individual such as unpaid time off, loss of wages due to diminished productivity, etc.

A similar study in Europe, where DED prevalence was less than 0.10 %, reported annual costs of prescription for patients with severe DED visiting ophthalmologists at US$1833 in France and US$1092 in UK. These estimates did not include cost of diagnostic tests, specialist referrals and surgical procedures. (132) In Asia, particularly in China, the annual direct economic burden caused by moderate to severe DED ranged from US$265 to $465 per annum. The lower costs may be attributed to the lower standard cost of living compared to the above cited countries. (133)

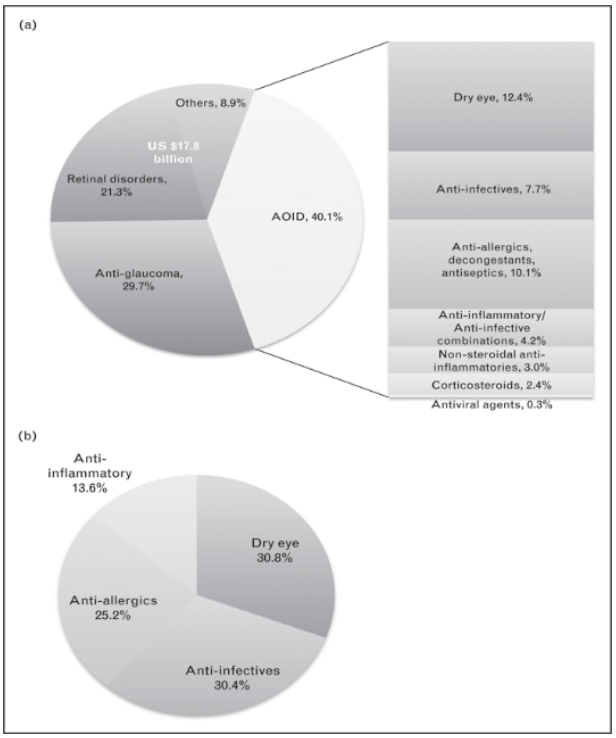


Figure 1-10: Worldwide ophthalmic prescription drugs market, 2011.

Anterior ocular inflammatory disease (AOID) drug sales accounted for 40 % of the ophthalmic market. (b) The AOID market had predominantly 'anti-infectives' in the late 1990s but has since grown to include anti-allergy (25 %), DE (31 %), and anti-inflammatory agents (14 %) as well as the anti-infectives (30 %) almost equally in 2011. *Reproduced with permission from Wolters Kluwer Health, Inc. and Copyright Clearance Center. Bielory, L. Syed, B. A. Pharmacoeconomics of anterior ocular inflammatory disease, Curr Opin Allergy Clin Immunol. 2013, 13 (5), 537-42*

1.6.1 Dry Eye Disease and Sex

According to Vehof et al (134), sex has a significant impact on DED symptoms, with increased symptom scores. Also, women are diagnosed with DED at a much younger age with lower correlation comparing the symptoms and signs in women to men. (135, 136) Additionally, other distinguishing factors are age, (136) autoimmune diseases, (135) and sex hormones. The exact relationship between sex hormones and DED in women still remains unclear, however, it has been

linked to low levels of serum androgen. The decrease levels of androgen may be amplified in sex-specific physiological and pathological situations that disrupt the endocrine system. (137)

In a recent population-based cross-sectional prevalence survey in Ontario, Caffery et al (138) reported that age was a significant factor associated with DED, and this was significant for women but not for men. Studies in Netherlands and Germany also show that women have higher prevalence of mood swings, anxiety disorders and experience more somatic complaints than men. (139, 140) These complex and other unrelated symptoms underscore the disparity in the mismatch between symptoms and clinical signs and the need for proper diagnostic test, understanding the history of patients and most importantly offering treatment for DED.

1.8 Diagnosis of Dry Eye Disease

1.8.1 TFOS DEWS II Diagnostic Criteria for Dry Eye Disease

The recommendation put forth by the TFOS DEWS II Diagnostic Methodology subcommittee provides a clear pathway for clinical diagnosis of DED. (93) To diagnose DED, the subcommittee proposed identifying the presence of *symptoms* and accounting for *at least one positive result of homeostatic markers*. (Figure 1-11) The presence of symptoms should be validated using standardized questionnaires and the recommended cut-off points. Self-administered questionnaires such as Dry Eye Questionnaire 5 (DEQ-5) score ≥ 6 or OSDI score ≥ 13, were proposed. (141) See Appendices 1-1 and 1-2 for the questionnaires. Further to the questionnaires, the subcommittee also recommended to consider positive results of a homeostatic marker of the tear film, such as TBUT or osmolarity. The non-invasive TBUT (using fluorescein) of < 10 seconds was set to determine the quality of the tear film. The optimal diagnostic cut-off for osmolarity was ≥ 308 mOsm/L. However, it was determined that if the interocular difference in osmolarity was > 8 mOsm/L, the individual should also be diagnosed with DED. These diagnostic criteria had been identified based on available data from peer reviewed publications for routine practice and also for effective diagnosis and management plan.

Following the information gathered from the risk factors, questionnaires, and homeostatic markers, clinicians should be able to determine whether the condition is EDED or ADDED. Figure 1-11 illustrates the TFOS DEW II diagnostic criteria for DED.

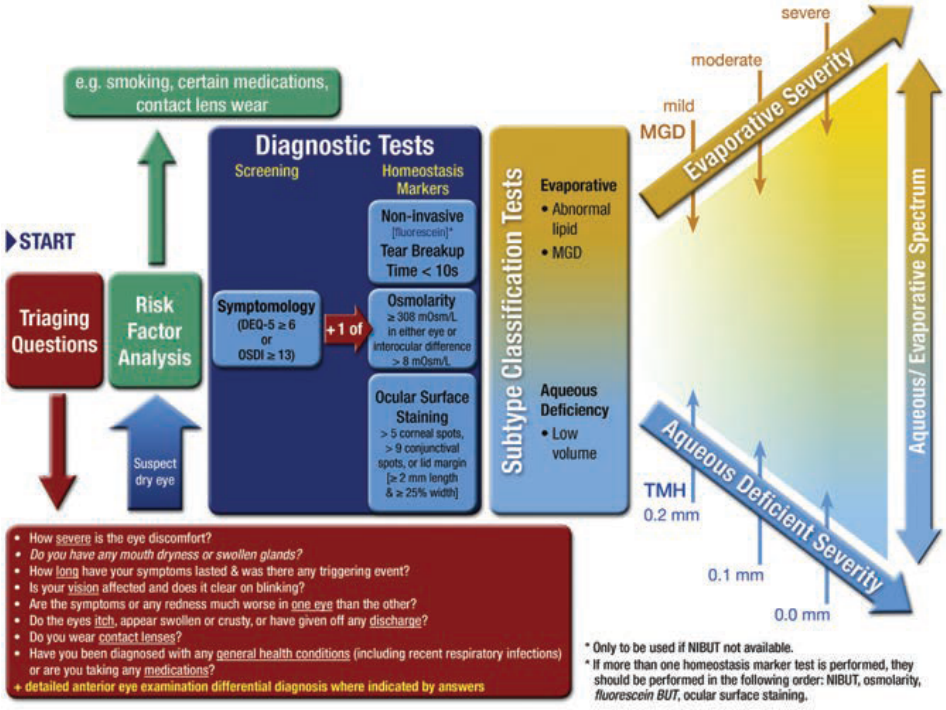


Figure 1-11: TFOS DEWS II Diagnostic Criteria for DED.

Reproduced with permission from Elsevier Copyright Clearance Center's RightsLink® Service. Wolffsohn JS, Arita R, Chalmers R, et al. TFOS DEWS II Diagnostic Methodology report. Ocul Surf. 2017; 15:539–574. (93)

1.8.2 Presence or Absence of Symptoms and Signs of Dry Eye Disease

According to the TFOS DEWS II Diagnostic Methodology Report, (93) if the presenting patient is asymptomatic without any clinical signs, the patient will be deemed normal, and no treatment will be warranted. In comparison, if the patient is asymptomatic with clinical signs, then pre-disposition of DED is diagnosed and should be treated; otherwise, neurotrophic conditions should be suspected if there is dysfunctional sensation. In situations when the presenting patient shows

significant symptoms based on the standardized questionnaire (e.g. DEQ-5 or OSDI), then the clinician needs to look for specific signs related to DED such as corneal or conjunctival staining, reduced TBUT, tear volume, lid margin abnormalities etc. In cases where there are symptoms without signs, neuropathic pain should be suspected, and the patient should be referred for potential pain management. In a situation where both symptoms and signs are present, a final differential diagnosis (e.g., allergic conjunctivitis, atopic conjunctivitis, anterior blepharitis etc.) should be ruled out before initiating treatment for DED.

1.9 Subtypes of Dry Eye Disease

1.9.1 ADDED versus EDED

According to TFOS DEWS II Diagnostic Methodology Report, (93) DED can be categorized into two forms, ADDED and EDED. (See above figures 1-6 & 1-9) The current understanding of DED shows the disease can present itself as ADDED or EDED, or a combination of both, (Figure 1-11). (64, 65) Some tests available to the clinician may point to diagnosing ADDED (e.g., Schirmer test, tear meniscus height, and phenol red etc.) or more so towards EDED (e.g., lid margin examination, meibomian gland assessment etc.). Irrespective of the availability of clinical tests and tendency to lean towards diagnosing a particular subtype over the other (misdiagnosis or mixed diagnosis), it is important to conduct a thorough examination to establish an accurate diagnosis and initiate the appropriate treatment regimen. (142)

Clinically, both ADDED and EDED can result in similar signs, leading to increased tear evaporation and tear instability. According to Rouen and White, (91) more than 80 % of diagnosed cases are EDED, while the remaining 20 % account for ADDED or a combination of both. EDED is typically caused by Meibomian gland dysfunction (MGD), whereby the lipid secretion required to act as a barrier to control evaporation and maintain homeostasis is impaired, mostly due to blockage of the meibomian gland orifices in the presence of a normally functioning lacrimal gland. (143) According to Segev et al, (144) a clinical condition such as pterygium can significantly

affect the tear film lipid thickness, ultimately causing tear instability and eventually leading to EDED. Some authors have also suggested that even though MGD is an underlying factor for EDED, it should be distinguished from other eye lid conditions, such as anterior or posterior blepharitis, which cause reduction in the lipid layer and also excessive evaporation. (145, 146)

In comparison, ADDED is caused by minimal tear secretion by the lacrimal gland, resulting in a hyperosmolar tear film. (147) It has been noted that minimal tear secretion reduces cell volume and increased concentration of solutes which then increases the osmolarity of the tear film. Also, aqueous reduction and changes in cell shape alter the structure of the cell membrane and therefore induces mechanical stress between cells. This then activates the mechanosensitive ion channels such as transient receptor potential vanilloid 1 and Piezo channels by allowing the influx of ions like calcium and sodium into the cells. The increased intracellular ionic concentration stimulates the production of pro-inflammatory cytokines and chemokines. These inflammatory mediators are then released into the tear film, contributing to the inflammatory environment characteristic of DED. (148, 149) Moreover, in autoimmune diseases such as SS, rheumatoid arthritis, lupus erythematosus, and graft versus host disease (GVHD), can affect the secretory glands to cause ADDED and EDED. (147)

Another distinguishing factor between EDED and ADDED is tear hyperosmolarity. In ADDED, hyperosmolarity results from significant decreased tear production from the lacrimal gland with a normal evaporation rate, while EDED occurs with increased evaporation due to lipid insufficiency or thickness. (88) Excessive tear evaporation triggers a cascade of inflammatory events leading to the synthesis of pro-inflammatory tear cytokines and apoptotic cell death ultimately causing damage to the ocular surface. Conventional screening techniques such as Schirmer test, TBUT, ocular surface staining, evaluating the quality and quantity of the tear film and meibomian gland assessment can help with subtype diagnosis.

In terms of treatment, the aim of ADDED treatment is to supplement the limited tears produced by the lacrimal gland with artificial tears or by placing punctal plugs to reduce tear drainage. In moderate to severe cases, anti-inflammatory or immune-modulating drugs can be used to stabilize

the tear film. (150) In comparison to EDED, lid scrubs and warm compresses are primarily used to treat this subtype. LipiFlow® Thermal Pulsation System (TearScience Inc., Morrisville, NC, USA) is also being approved as a treatment option for EDED. (151) This device increases gland function by safely delivering controlled heat and pressure to the meibomian glands so that the blocked meibum is liquefied and pushed up and out of the gland orifices into the tear film.

1.10 Questionnaires for Dry Eye Symptoms

1.10.1 Ocular Surface Disease Index

The OSDI is currently the most commonly used and acceptable questionnaire for DED assessment. (93) This instrument was developed by the Outcomes Research Group at Allergan Inc (Allergan Inc., Irvine, California, USA). (152) This 12-item questionnaire covers three broad areas, of which the first category relates to ocular symptoms of DE, while the second category ask questions on the relationship between symptoms and daily activities. The third category looks at the symptoms induced by environmental conditions such as wind and humidity. The questionnaire is graded on a scale from 0 to 4, where 0 indicates none of the time; 1, some of the time; 2, half of the time; 3, most of the time; 4, all of the time and in some cases NA (non-applicable) (Appendix 1-2). The OSDI is scored using the formula:

OSDI = [(sum of scores for all questions answered) × 100]/ [(total number of questions answered) × 4]

Thus, OSDI is scored on a scale of 0 to 100, with lower scores indicating lower disability while higher scores represent greater severity. (Figure 1-12)

According to the TFOS DEWS II Definition and Classification Report, (17) severity can be determined using the established range scores as a “gold standard” to define DED, and to initiate clinical assessment and treatment. Scores less than 13 (< 13 points) are considered normal, a mild condition ranges from 13 - 22, moderate ranges from 23 - 32 and severe is greater than 33. (17) Figure 1-12 presents the OSDI grading score and severity scale.

Schiffman et al (141) reported that the OSDI can be used as an effective tool in discriminating between normal, mild to moderate, and severe DED. Also, they reported that OSDI scores correlated significantly with other standardized clinical questionnaires such as McMonnies Questionnaire, National Eye Institute Visual Functioning Questionnaire 25 (NEI VFQ-25), and the Short Form 12 (SF-12) questionnaire. Additionally, Johnson et al (153) and Akowuah et al (154) have reported good correlations with Ocular Comfort Index (OCI) scores and DEQ-5. Other studies have also reported on the validity and reliability of the OSDI. (155-158).

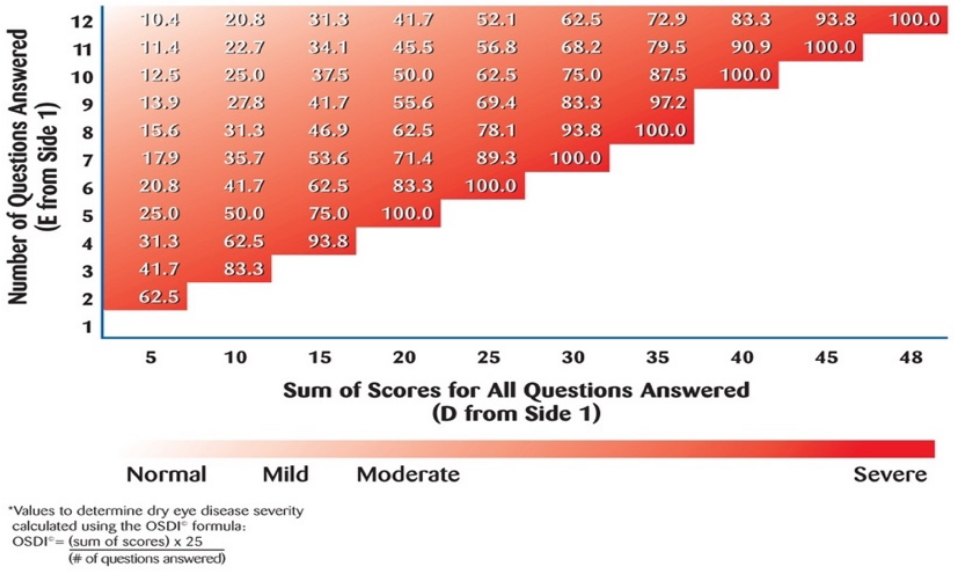


Figure 1-12: OSDI grading score and severity scale.

Reproduced with permission from Elsevier Copyright Clearance Center's RightsLink® Service. Schiffman et al. Reliability and validity of the Ocular Surface Disease Index. Arch Ophthalmol. 2000; 118:615-62.

1.10.2 Standard Patient Evaluation of Eye Disease

The SPEED™ questionnaire developed by TearScience, (Johnson & Johnson Vision, New Brunswick, NJ, USA) is one of the validated and fastest DE questionnaires used in clinical and research setting. (159) SPEED™ provides the ability to differentiate symptomatic from asymptomatic DE patients. The questionnaire is divided into four main sections centered on

symptom timing, frequency, severity, and use of an ocular lubricant. The SPEED™ test on symptoms such as dryness, grittiness, scratchiness, irritation, burning, watering, soreness, and eye fatigue all of which are numbered score (scale of zero to 4). The reference scale ranges between zero and 28, with zero indicating a lack of symptoms and 28 indicating the highest form of symptoms. (160, 161) The SPEED™ questionnaire can be found in Appendix 1-3

Several studies on the SPEED™ questionnaire have been undertaken. (161, 162) Following the assessment of dimensionality, repeatability, validity, and comparisons with four existing DE questionnaires, Ngo et al (162) concluded that the SPEED™ questionnaire was a valid and repeatable tool to assess DE symptoms. Also, they reported that the results correlated with meibomian gland function, suggesting its clinical use for the diagnosis of MGD. Pucker et al (163) also concluded that the SPEED™ questionnaire was effective at grading ocular symptoms in a clinical setting.

1.11 Diagnostic Clinical Tools

1.11.1 Non-invasive Tear Break-up Time

Non-invasive Tear Break-up Time (NITBUT) is one of the most popular and highly recommended tests for measuring tear stability. It involves the use of specular reflection in the form of an illuminated grid projected onto the corneal surface. The observer can manually count the time for the projected grid to break/distort using a stopwatch. Automated devices currently exist where they combined imaging the grid projection with a software algorithm that will detect distortion in the grid to determine the first break-up time. (164)

The Keratograph 5M (K5M, Oculus, Wetzlar, Germany), is currently used in many clinical practices. (165-167) This Placido-based instrument uses infrared light and an integrated software algorithm to detect changes in the rings based on location and records the break-up time. Due to the variability in the tear film, it is recommended that at least three tests be performed and

averaged. According to Kim et al, (166) the K5M was able to detect differences in location and pattern between normal and DED subtypes, playing a critical role in diagnosing DED. Other available devices such as the Medmont E300 corneal topographer (Medmont International Pty Ltd., Victoria, Australia), (168, 169) also uses the Placido-based technology. The sensitivity of the above devices ranges from 82 - 84 %, while the specificity ranges from 76 - 94 % and are therefore recommended for use in most clinical settings. (170-172)

According to TFOS DEWS II Diagnostic Methodology Committee, (93) the NIBUT cut-off for positive finding for DED is as low as 2.7 seconds with automated devices and 10 seconds for subjective techniques.

1.11.2 Osmolarity

Studies have shown that changes in the quality of the pre-corneal tear film results in changes in osmolarity levels. (173-175) For individuals with a normal tear film, such changes are minimal and consistently lower over time while there is a greater variability in the osmolarity levels in DED. Also, it has been noted that the inter-eye differences are larger in DED compared to patients with a normal tear film. (176)

The TearLab Osmolarity System (TearLab Corp, San Diego, CA, USA), a device using a micro-electrode to measure the electrical impedance of the charged particles in a tear sample. (177) Clinically, a cut-off value of 308 mOsmol/L in either eye is used as the threshold to differentiate normal and early stages of DED. (178) However, according to Wolffsohn et al, (93) there are variabilities in tear osmolarity measurements. In mild DED, the reported interocular mean difference was 6.90 ± 5.90 mOsmol/L with wide variabilities in moderate (11.70 ± 10.90 mOsmol/L) and severe (26.50 ± 22.70 mOsmol/L) DED. Therefore, based on multiple studies, an interocular difference of 8 mOsmol/L is recommended to diagnose DED. (93) Regardless of these clinical findings, Thulasi et al (89) pointed out that a normal osmolarity value does not necessarily

preclude the presence of DED, while an increased tear osmolarity should not be considered a benchmark for diagnosis of DED due to variability in measurements.

1.11.3 Ocular Surface Staining

Clinically, sodium fluorescein (2 %), rose bengal (1 %), and lissamine green (1 %) dyes are used in assessing ocular surface stains for grading. (179) Fluorescein staining occurs when there are corneal defects that allow for dye diffusion in intercellular spaces and penetration into the underlying stroma. (180-182) Additionally, according to Bandamwar et al, (182) epithelial cells undergoing apoptosis uptake sodium fluorescein due to increased membrane permeability. Interestingly, it was also reported that healthy cells can uptake sodium fluorescein but at a much lower concentration compared to apoptotic cells, however, these are not likely to be perceived as staining during clinical grading due to the low fluorescence and magnification. Fluorescein staining is increased by rapid diffusion into the stroma and therefore can manifest whenever there is a disruption in cell-cell junctions in the corneal epithelium (as junctions between cells are damaged, fluorescein can then diffuse between the cells and into the stroma). Stromal diffusion explains why fluorescein is best suited to measure corneal epithelial barrier integrity as well as to evaluate the epithelial toxicity caused by agents known to disrupt epithelial tight junctions. Begley et al (183) also pointed out that the time needed for maximum grading of corneal staining varies between a normal and a compromised corneal surface.

According to the TFOS DEWS II Definition and Classification Report, (17) corneal (> 5 spots) or conjunctival staining (> 9 spots) can be combined with symptom scores to determine the severity of DED. Also, the ODISSEY European Consensus Group (184) recommended that symptoms assessment using standardized questionnaire and corneal fluorescein staining are clinically adequate to determine the degree and severity of DED in patients. It further recommended that in cases of discrepancies in symptoms and sign (staining), additional clinical testing may be necessary to define the diagnosis.

Geographic location on the cornea where staining occurs is crucial to the diagnosis of the condition. For example, fluorescein staining can be scored globally over the entire cornea (global scoring), or quadrant specific (central, superior, inferior, nasal, temporal). Central corneal staining is rarely seen in DED, (185) while numerous publications have confirmed the presence of staining in the inferior location in symptomatic DE subjects. (186, 187) According to Chalmers et al, (188) the presence of greater than grade one score plus inferior corneal staining was a useful indicator to differentiate "normals" from participants with DE. The most recent and comprehensive study on geographic distribution of corneal staining and scoring has been undertaken by Woods et al. (179) They concluded that for DE subjects, the inferior quadrant presented the most severe grade of corneal staining. Figure 1-13 shows the inferior staining, and the grading compared to other parts of the cornea.

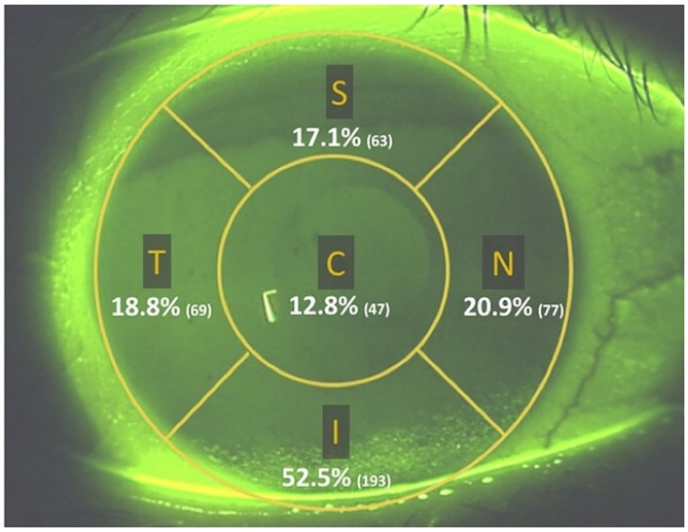


Figure 1-13: Distribution of subjects exhibiting Rank-1 (worst staining) grades in each zone, as a percentage of the total number subjects.

Reproduced with permission from Elsevier Copyright Clearance Center's RightsLink® Service. Woods et al. Geographic distribution of corneal staining in symptomatic dry eye. Ocul Surf. 2020;18(2):258-66. (179)

1.11.4 Other Clinical Testing: Matrix Metalloproteinase-9

One of the inflammatory biomarkers known to play a significant role in DED is matrix metalloproteinase-9 (MMP-9). (83) According to Acera et al, (189) individuals experiencing various degrees of DED have significantly higher MMP-9 in their tear film compared to controls. Laboratory methods such as the enzyme-linked immunosorbent assay (ELISA) and ELISpot were used for analysis of single inflammatory proteins. Novel techniques have also augmented tear analysis, such as Luminex® (Luminex Corp. Texas, USA) and Mesoscale (MesoScale Discovery, Maryland, USA); these can quantify multiple inflammatory proteins using small tear samples. (190) However, while able to determine MMP-9 levels, these technologies are expensive and time-consuming for clinical practice.

The most recent in-office clinical test kit which is gaining popularity among clinicians is the InflammaDry® test kit (Quidel InflammaDry, Sarasota, Florida, USA). (83, 191) This device uses a small tear sample collected from the ocular surface to detect elevated levels of MMP-9. Acera et al (86) pointed out that a positive MMP-9 test (≥ 40 ng/ml) can certainly help guide a treatment plan and support the use of anti-inflammatory therapy. (86) Messmer et al, (192) also reported that the Inflammadry test kit was able to confirm the diagnosis of DED in about 40 % (19 out of 47) study cohort and correlated with other parameters such as OSDI and Schirmer test results

1.12 Dry Eye Disease and Management Options

1.12.1 TFOS DEWS II Dry Eye Disease Management System

TFOS DEWS II Management System recommended a staged management algorithm that can be used in most clinical and research situations (Figure 1-14). (193) The four-stage management plan is described below.

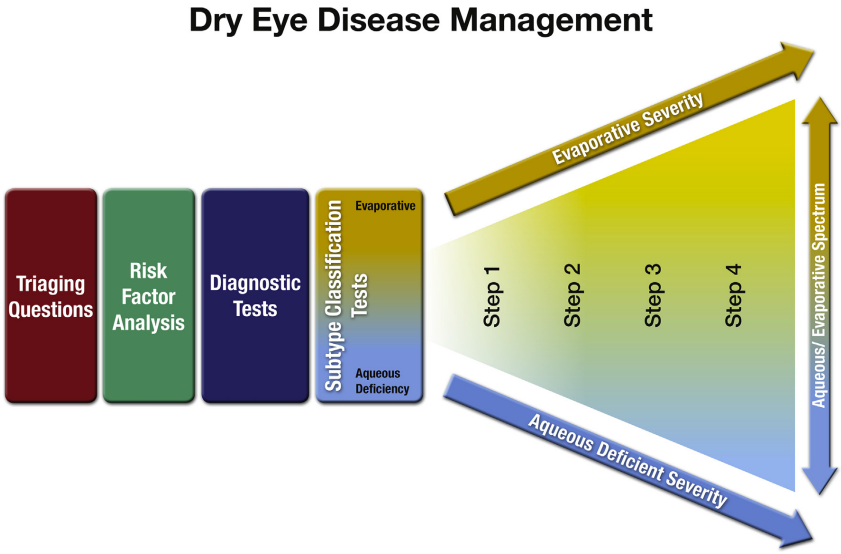


Figure 1-14: TFOS DEWS II management of DED.

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Step 1 therapy for mild DED typically starts with low-risk therapies such as warm compresses and over-the-counter lubricants. (194, 195) The management strategy in ***Step 2*** for moderate to severe forms of DED is more aggressive in its approach. It ranges from non-preserved ocular lubricants including limited-duration of topical corticosteroids, (196-198). Barabino et al (199) reported that tapered doses of loteprednol etabonate 0.50 % suspension controlled ocular surface inflammation and improved ocular symptoms in the study cohort. Also, approved medical devices such as punctal occlusion, (200, 201) moisture goggles, (202, 203) and intranasal tear stimulation device (TrueTear®, Allergan, Pleasanton, CA, USA) among others are also recommended. (15, 204-206) ***Step 3*** emphasizes the use of oral and topical secretagogues, autologous eye drops and contact lenses. (193, 207) The use of contact lenses particularly scleral contact lenses (SL) are highlighted in Section 3.2 to 3.3. Finally, ***Step 4*** of the treatment algorithm includes tapered topical corticosteroids, amniotic membrane grafts, surgical punctal occlusion, and more complex surgical approaches. (208-212) Appendix 1-4 presents the staged management and treatment recommendations for DED from the TFOS DEWS II Management and Therapy Report.

1.12.2 Scleral Contact Lenses and Their Application to the Management of Dry Eye Disease

1.12.2.1 Scleral Contact Lens Growth

The past 20 years have seen a gradual increase in the use of scleral contact lenses (SL), with data suggesting a continuous growth in recent years. (213, 214) For example, figure 1-15b shows the steady growth in SL prescribing patterns from ~1 % in 2014 to more than 5 % in 2017. (215) Additionally, the most recent data from the Contact Lens Spectrum annual market survey showed that SL prescribing increased from 5 % in 2022 to 7 % in 2023. (216) This increase over the past 10 years (as illustrated in Figure 1.15 and combined with recent survey study) can largely be attributed to the materials being used having increased oxygen permeability, the increased availability of SL designs and improved manufacturing methods. (217, 218)

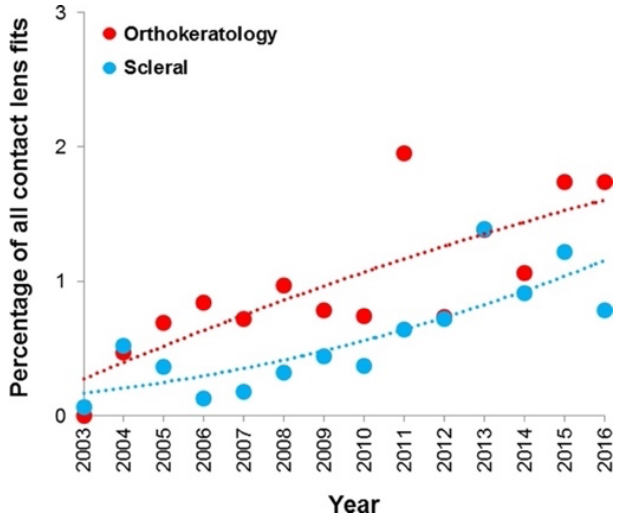


Figure 1-15a: Orthokeratology and SL overall global prescribing patterns as a percentage of all contact lens fits (soft and GP) between 2003 and 2016.

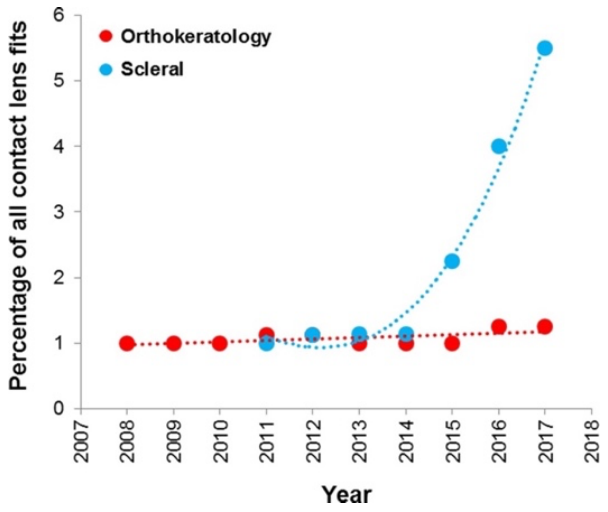


Figure 1-15b: Orthokeratology and SL overall prescribing patterns as a percentage of all contact lens fits (soft and GP) between 2008 and 2016.

Figure 1-15a-b: Orthokeratology and SL overall global prescribing patterns.

Figure 1-15a-b: a. Orthokeratology and SL overall global prescribing patterns as a percentage of all contact lens fits (soft and GP) between 2003 and 2016 (219). 15b Orthokeratology and SL overall prescribing patterns as a percentage of all contact lens fits (soft and GP) obtained from Contact Lens Spectrum annual market research surveys of practitioners between 2008 and 2016. (213) *Reproduced with permission from Elsevier Copyright Clearance Center's RightsLink® Service. Vincent SJ. The rigid lens renaissance: A surge in scleral. Cont Lens Anterior Eye. 2018 Apr;41(2):139-143.*

1.13 Scleral Contact Lenses in Contemporary Clinical Practice

1.13.1 Vision Correction

Vision correction is the primary goal of fitting a SL when managing patients with irregular corneas and high refractive errors. (214, 220) Pullum et al, (221) reported that > 50 % of the patients diagnosed with primary corneal ectasia in his cohort were fitted with SL and constituted the majority of patients wearing such lenses. In a retrospective study, Lo et al (222) reported that SL significantly improved the visual outcome of keratoconus (KC) and irregular astigmatic subjects after refractive surgery. In another retrospective, longitudinal study, Severinsky et al (223)

reported best corrected visual acuity (BCVA) of 0.78 ± 0.25 (range: 0.30 - 1.20) after penetrating keratoplasty and 82 % of the subjects achieved a functional vision of 0.5 or more on the VA chart. Visser et al (224) also reported that SL significantly increased visual outcomes, with a median increase of 0.45 on logarithm of minimum angle of resolution (LogMAR). Other authors such as Scanzera et al (225) and Sah et al (226) have also reported on the significant improvement in visual outcomes following SL wear in diseased eyes.

1.13.2 Ocular Surface Protection

SL are fitted to completely vault over the cornea to rest on the sclera, which ultimately protects the cornea from environmental conditions and the abrasive effect of the eyelids. (227, 228) To achieve this effect and to maximize the impact of the lenses in terms of improving visual outcome and comfort, non-preserved saline solution is used to fill the SL before lens insertion to create a fluid reservoir. (227, 229) The post lens tear film between the back surface of the SL and front surface of the cornea provides ocular surface protection. This characteristic feature has been reported to provide comfort for individuals experiencing complicated conditions such as Stevens-Johnson Syndrome (SJS), GVHD, exposure keratopathy, ocular cicatricial pemphigoid, neurotrophic corneal disease and atopic keratoconjunctivitis. (230) Also, in extremely painful corneal conditions such as bullous keratopathy and epithelial abrasions, SL provide symptomatic relief and comfort for such patients. (231)

Another interesting characteristic feature of the post lens tear film is the impact on healing of epithelial defects. (232, 233) Rosenthal et al (233) reported that the combination of oxygenation and moisture from the post lens tears promote healing of persistent corneal epithelial defects. Paul et al (234) and Sharma et al (232) also noted that high Dk materials, which allow more oxygen directly through the lens material, enhanced re-epithelization and protection of the fragile epithelium. Additionally, in eyelid conditions such as trichiasis, distichiasis, ptosis, and tarsal scarring, SL are effective in forming a mechanical barrier to protect the cornea. (232, 235) Figure 1-16 shows corneal re-epithelization with the wearing of SL.

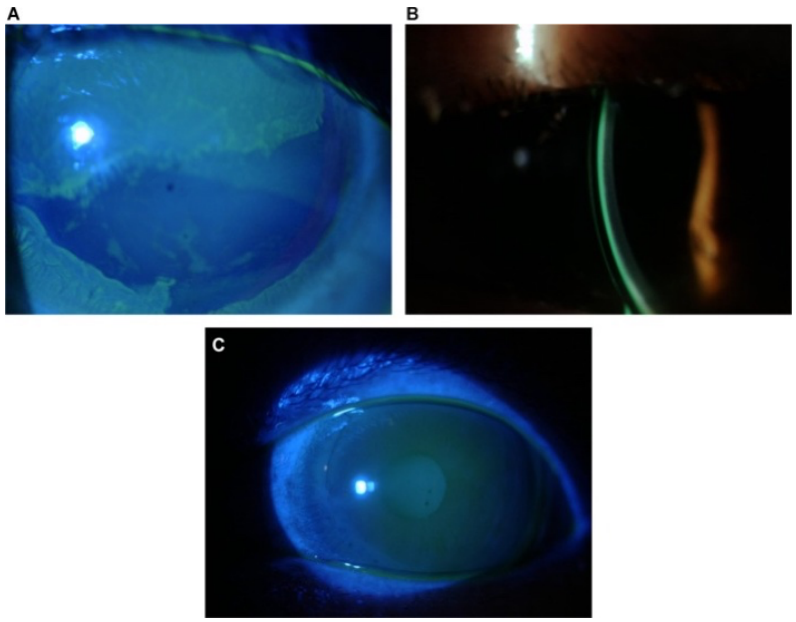


Figure 1-16: Epithelial erosion management with SL.

(**A**) Limbal stem cell disease (**B**) SL on eye (**C**) Re-epithelization after 3 months. (218) *Originally published by and used with permission from Dove Medical Press Ltd. Harthan JS, Shorter E. Therapeutic uses of scleral contact lenses for ocular surface disease: patient selection and special considerations. Clin Optom. 2018; 10:65-74.*

1.13.3 Scleral Lens as a Drug Delivery System (Fluid Reservoir)

Using topical formulations as a fluid reservoir, SL have been used to deliver antibiotics, (236, 237) anti-vascular endothelial growth factor (anti-VEGF) agents, (238, 239) and stem cell therapy. (240) In a recently published prospective consecutive study, Polania-Baron et al (241) reported that, subjects diagnosed with infectious keratitis benefited from 0.50 % moxifloxacin as a solution in the fluid reservoir. This antibiotic solution was replaced every 24 hours until epithelization was complete, and all infections resolved favorably following 1-month of lens wear.

1.13.4 Management of Dry Eye Disease with Scleral Contact Lenses

The use of SL as a management system/therapy for DED is stated in Step 3 of the TFOS DEWS II Management and Therapy Report (193). (Appendix 1-4). Until recently, the use of SL as a therapeutic device for improving corneal healing and enhancing comfort for severe or complicated cases were limited to conditions associated with DE such as primary and secondary SS, (242-245) SJS, (246, 247) GVHD, (248-251) exposure keratitis (252-255) neurotrophic keratopathy, (256, 257) and ocular cicatricial pemphigoid. (258)

In a prospective interventional case series, La Porta Weber et al (259) evaluated the efficacy of the Esclera lens (Esclera; Mediphacos Inc, Belo Horizonte, Brazil) and observed that the lenses significantly improved both symptoms and signs in patients with DED. For example, tear osmolarity decreased significantly from 338.10 ± 27.10 to 314.25 ± 38.80 mOsm/L, p <.001. Also, the OSDI and Short Form 36 version 2 (SF-36v2) surveys showed significant improvements in DE symptoms and QoL (p <.001).

For severe DED, some authors have suggested that SL can be used in combination with other therapies such as punctal occlusion or topical autologous serum, among others, to provide continuous ocular surface hydration while providing optimal visual correction and comfort. (260-262) Alipour et al (263) reported that about 50 % of patients with moderate to severe DE (grades III and IV) were satisfied with their lenses in terms of comfort and that the use of SL delayed the need for artificial tears. Table 1-2 details the various conditions under which SL option is warranted for comfort, corneal healing, mechanical protection and for cosmetic purposes. (264)

Table 1-2: Broad spectrum indications for SL on ocular surface diseases.

Reproduced with permission from Wolters Kluwer Health, Inc. and Copyright Clearance Center. Pullum, K., Whiting, M. A., Buckley, R. J. Scleral Contact Lenses: expanding the role. Cornea. 2005, 24 (3), 269-277. (264)

Mucosal Disorder	**Corneal Disorder**	**Corneal Protection**	**Cosmetic**
Dry eye	Exposure keratitis	Ocular surface disease	Aniridia
Stevens–Johnson syndrome	Epithelial defects	Pain relief	Iris coloboma
Sjogren's syndrome	Epithelial dysplasia	Nerve palsy	Irregular iris
Ocular cicatricial pemphigoid	Neurotrophic keratitis	Keratoconjunctivitis	Microphthalmos
Chemical burn	Filamentary keratitis	Trichiasis	Lagophthalmos
Pterygium	Drug delivery	Entropion	
		Ptosis	
		Persistent epithelial corneal defects	
		Graft vs. Host Disease	

1.14 Scleral Contact Lens Material and Design Characteristics

1.14.1 Scleral Contact Lenses Materials and Properties (Oxygen Transmissibility-Dk/t)

Modern SL are manufactured from significantly different materials from those used 15-20 years ago, with much greater oxygen permeability and enhanced wettability. (265) Polymethyl methacrylate (PMMA) was one of the early contact lens materials, with excellent optical properties, was lightweight and produced acceptable surface wettability and durability. (266) However, they were impermeable to oxygen and their extremely low oxygen permeability (Dk/t) limited their use due to corneal hypoxia. (267, 268) The addition of siloxane components to PMMA resulted in early generation GP materials which then became known as silicone-acrylates. (266) This led to an increase in the Dk values ((Dk = 10 - 30 Barrers, in early materials) as the silicone component allowed direct oxygen transmission through the lens material rather than around the lenses. (251, 266)

While silicone moieties increased oxygen transmission, it produced issues with reduced wettability and increased lipid deposition. (269) This was overcome to some extent with the addition of fluorine as part of the base component. (266, 270) This was achieved through co-polymerization

of fluoromethacrylates such as hexafluoroisopropyl methacrylate (HFIM) with TRIS, MMA, crosslinkers and wetting agents. This resulted in improved mechanical properties and oxygen permeabilities ranging from Dk of 30 - 180 Barrers. (251) Table 1-3 presents the current SL materials, Dk, wettability, and refractive indices.

Table 1-3: Different lens materials, generic names, Dk value, contact angle, and refractive index (SL and GP Materials).

Reproduced with permission from Wolters Kluwer Health, Inc. and Copyright Clearance Center. Chaudhary S, Ghimire D, Basu S, Agrawal V, Jacobs DS, Shanbhag SS. Contact lenses in dry eye disease and associated ocular surface disorders. Indian J Ophthalmol. 2023;71(4):1142-53. (251)

Material name	Generic name	Dk value	Contact angle (in degree)	Refractive index
Boston II	Itafocon A	12	20	1.47
Boston ES	Enflufocon A	18	52	1.44
Boston IV	Itafocon B	19	17	1.47
Boston Equalens	Itaflourofocon A	47	30	1.44
Boston EO	Enflufocon B	58	49	1.43
Boston Equalens II	Oprifocon A	85	30	1.42
Boston XO	Hexafocon A	100	49	1.42
Boston XO2	Hexafocon B	141	38	1.42
Optimum Classic	Roflufocon A	26	12	1.45
Optimum Comfort	Roflufocon C	65	6	1.44
Optimum Extra	Roflufocon D	100	3	1.43
Optimum Extreme	Roflufocon E	125	6	1.43
Optimum Infinite	Tisilfocon A	180	6	1.44

1.14.2 Scleral Contact Lens Wettability and Surface Modification

It has been proposed that higher Dk materials should be selected when prescribing SL for patients typically experiencing DED. (266, 270) Another equally important component is the contact angle or wettability (ability for tear film to spread easily on the surface). The Dk of a material can indirectly impact its surface wettability, as higher Dk materials typically have a higher silicone

content, and thus a more hydrophobic surface. This often results in reduced wettability, increased surface deposits (proteins and lipids, etc.), increased scratches (due to the surface being softer) and thus a shorter replacement frequency. (271, 272) Currently, two methods are employed to modify or coat the surface of SL materials to make them more wettable, thereby reducing friction and discomfort. These are plasma treatment (273, 274) and the use of a hydra-PEG® (polyethylene glycol) coating. (275)

In plasma treatment, the process involves bombarding the lens material with ionized oxygen using a low-temperature plasma in air to create a hydrophilic surface to reduce the wetting angle. (276) Also, the treatment resulted in a smoother lens surface, with surface roughness reduced from 7 nm to 4 nm, contributing to the decrease in wetting angle. A recent publication by Tsai et al (277) suggested that a combination of ultraviolet (UV) laser and oxygen plasma-treated surface could be the future for SL surface treatment, owning to the improved hydrophilic properties compared with the basic plasma technology.

In the case of hydra-PEG® coating technology (Tangible Science LLC, Menlo Park, CA, USA) which is the newest technology to attempt to modify the surface of the SL, a polyethylene glycol (PEG) polymer is used. (278) The PEG is a hydrophilic ("water-loving") polymer produced by combining ethylene oxide with ethylene glycol, ethylene glycol oligomers (molecules having repeating units), and water. The characteristics of the generated PEG can be adjusted by adjusting the reaction parameters such as temperature, pressure, and catalyst type. (279) This polymer based compound has many applications, particularly in drug and biomaterial applications. (280) Also, PEG-based gels, also known as hydrogels, are widely employed for therapeutic biomolecule administration. (281) For example, a PEG coating on lens surfaces has been shown to repel protein molecules on its surfaces due to the flexibility and water soluble properties. (280, 282) Also, it has been postulated that PEG density on the surface of a material is an important factor for resisting protein adsorption. Interestingly, it has been noted that surfaces forming a large number of hydrogen bonds with water molecules produce large repulsive forces on the protein, leading to lower protein adsorption. (278, 281, 283, 284)

In SL, a hydra-PEG® coating on its surfaces has been reported to improve lens wettability, lubricity, protein deposit resistance and tear film break-up time. (285) The hydrogel coating is

bound to the surface of the contact lens, effectively creating a wetting surface on the underlying lens material. This optically clear coating encloses the surface of the lens material, creating a hydrophilic “shell” of approximately 30 - 40 nm thickness.

SL are manufactured using two methods (lathe cutting or molding) and the application of the Tangible hydra-PEG post manufacture is slightly different for each of these. The initial step in the process is to activate the lens surface so that it can covalently link to the hydra-PEG polymers. For cast molded lenses, this is accomplished by adding a functional chemical activator to the lens monomer mix prior to molding. For lathe-cut lenses, this is achieved by subjecting them to a brief plasma cycle post lathing that cleans and activates the lens surface. Once activated, the lenses are soaked in Tangible hydra-PEG polymers during the extraction/hydration step, or the polymers are introduced into the blister pack during the autoclaving process. In either case, once the active lens is immersed in the Tangible hydra-PEG polymers, it forms a bond with the lens surface. (286) (Figure 1-17)

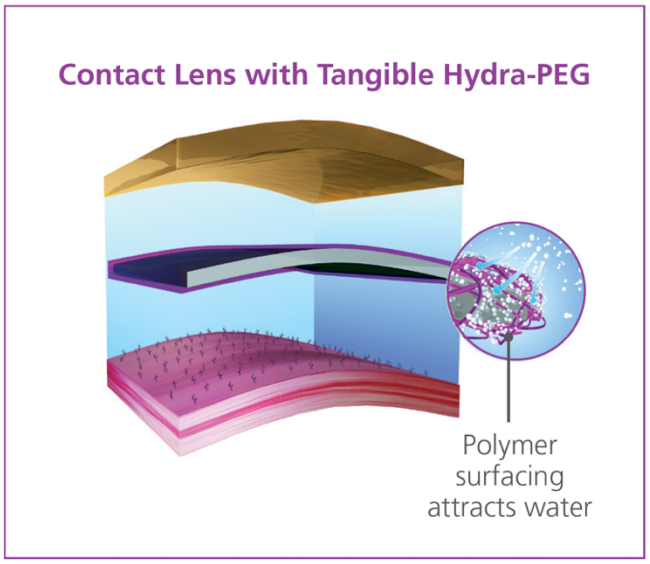


Figure 1-17: Hydra-PEG® coating on lens surface.

The top brown layer represents the tear film while the pink layer represents the corneal thickness with mucins on its surface. The tangible hydra-PEG on the contact lens surfaces (middle layer) creates a mucin-like wetting surface on the underlying material. *Reproduced with permission from Tangible Science LLC, Menlo* Park CA, USA. *https://www.eye-iq.com/uploads/Hydra-PEG-White-Paper.pdf* (286)

The only currently available peer-reviewed study on hydra-PEG on SL reported that the coating significantly reduces the wetting angle as well as visible lipid and protein deposition on its surfaces. (285) According to Mickles et al, (285), in established SL subjects who previously reported SL discomfort, hydra-PEG coated SL significantly improved lens comfort, DE symptoms and frequency of foggy vision among others (all, $p < 0.01$) compared to untreated SL.

1.14.3 Efficacy of Scleral Lenses (Vision, Comfort, Corneal Thickness, and Quality of Life)

To assess the efficacy of SL wear, standardized and validated DE symptom questionnaires, and independent questionnaires can be used. (141, 163, 287) Visual performance can also be assessed with standard VA charts for both low and high contrast visual acuities. (247) Clinical signs such as corneal and conjunctival staining, (288) TBUT, (289) conjunctival redness, (290) tear quality and quantity can also be measured before and after SL wear. (291) Other parameters which can be used to determine the efficacy of the SL are the impact on corneal thickness, (292) hours of lens wear, and complications resulting from the lens wear. (293, 294)

A comprehensive review by Bavinger et al (295) showed that SL consistently had a beneficial effect on patients' comfort, visual function and overall QoL in patients with severe DE. In a retrospective study by Rossi et al (296) on DED associated with GVHD, participants fitted with SL reported significant improvements in BCVA (0.21 ± 0.26 to 0.1 ± 0.14 logMAR, $p = 0.002$), OSDI (92.10 ± 11.30 to 23.50 ± 11.20, $p = 0.002$) and NEI-VFQ 25 scores (41.30 ± 7.00 to 83.10 ± 15.90, $p = 0.003$) In another multicenter related study on efficacy and tolerability of SL, Magro et al (297) reported improvement in QoL in severe DED. All the measured parameters (OSDI; 86 vs 30), VA, (0.33 vs 0.10 logMAR) and Oxford score (3.20 vs 1.30), all: $p < 0.001$) significantly improved within the study period. The treatment continued with mean follow-up of 20.50 months and only 5 patients (8 %) discontinued SL wear. Currently, there are only few published studies on the use of SL on individuals with moderate to severe DED with normal cornea. (263, 298)

Physiologically, the impact of SL on corneal thickness is minimal and mostly stromal in nature. (299) In both short-term closed and open eye studies, no significant difference in mean corneal

thickness before and after wearing SL (lens thickness ranging from 150 to 500 microns) were observed. The reported values were less than the physiological swelling that occurs daily upon waking. (299) In fact, Fisher et al (299) pointed out that the theoretical modelling suggesting overnight closed eye lens edema overestimated the effect of increasing corneal thickness. Table 1-4 summarizes the percentage of corneal swelling with different SL vaults.

Table 1-4: Summary of Studies and Effect of Corneal Clearance, and Corneal Thickness.

Adapted and *reprinted by permission of Informa UK Limited, trading as Taylor & Taylor & Francis Group. Vincent et al. Optical coherence tomography and scleral contact lenses: clinical and research applications. Clin Exp Optom. 2019 May;102(3):224-241.* (300)

Author	Corneal Clearance (μm)	Corneal Edema (%)	Lens Diameter (mm)	Dk	Thickness (μm)	Time (hours)
Arlt et al (295)	Low (209 ± 30) High (630 ± 25)	1.59 ± 0.35 1.76 ± 0.48	16 - 17	125	350	8
Esen et al (296)	Low (100 - 200) Medium (200 - 300) High (> 300)	2.30 1.48 1.42	16.5 - 17.5	140	300	8
Vincent et al (297)	Low (225 ± 21) High (431 ± 26) Low (156 ± 14) High (350 ± 29)	0.95 ± 0.33 1.37 ± 0.25 0.34 ± 0.25 0.65 ± 0.48	16.5	100	300	~ 2 8
Tan et al (298)	Low (< 150, 103 ± 5) Medium (150 - 300, 216 ± 7) High (> 350, 367 ± 9)	1.43 ± 0.23 1.46 ± 0.21 1.54 ± 0.24	15.6	97	438	5

Complications from SL are considered rare and mostly minor. (265, 305, 306) Pullum et al (305) reported that the most common complications of SL were corneal neovascularization (13.30 %), corneal edema (7.40 %), corneal abrasion (3.10 %), and giant papillary conjunctivitis (1.70 %). The higher percentages of complications were attributed to the SL material available at that time.

A recent survey by Schornack et al (307) reported 0.45 %, 0.28 %, 0.17 %, and 0.10 % of corneal edema, corneal neovascularization, toxic keratopathy, and bullae respectively. Similarly, conjunctival complications were also relatively low (conjunctivochalasis: 0.02 %, hyperemia: 0.01 %). A few clinical case reports on conjunctival prolapse, (295) acanthamoeba keratitis, (308) polymicrobial and micro sporidial infections (244) have been published.

Another common complication with the use of SL is mid-day fogging (MDF). (271, 306, 309) It can easily be visualized with a slit-lamp biomicroscope and anterior segment optical coherence tomography (OCT). MDF presents as particulate matter ("*coagulated protein and lipid particles"*) beneath the lens as illustrated in Figure 1-18. It is estimated to be present in approximately 20 - 33 % of SL wearers. (310) Blurred or poor vision has been the commonest complaint; however, this can easily be resolved by removing the lenses, cleaning, and refilling them with new non-preserved saline before reapplying to the eye. (311, 312) This can be a challenging task for most patients and has to be explained thoroughly during the dispensing visit before the patient can be asked to wear the lenses.

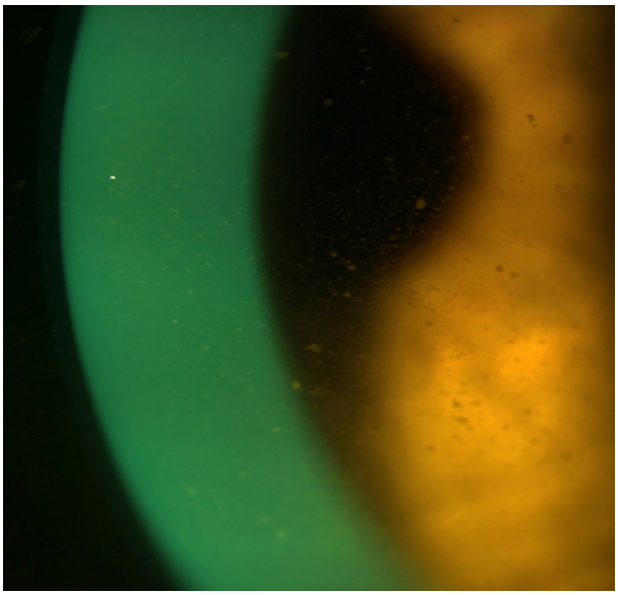


Figure 1-18: Midday fogging caused by larger, coalesced particulates with Slit Lamp Biomicroscope.

Reprinted by permission of Informa UK Limited, trading as Taylor & Taylor & Francis Group. Vincent et al. Optical coherence tomography and scleral contact lenses: clinical and research applications. Clin Exp Optom. 2019 May;102(3):224-241. (300)

1.15 Challenges of Fitting Scleral Contact Lenses

Fitting SL can be considered a complicated and challenging process for most clinicians. (300, 313) This can be attributed to the variabilities, complex lens designs, and chair time, which demand specialist clinical skills to successfully fit these lenses. (217, 314) Also, achieving optimal SL necessitates trial-fitting many lenses, reordering new lenses, and multiple visits, all of which present major challenges for both the practitioner and the patient. (315) According to Macedo-de-Araújo et al, (315) it took an average of 2.35 ± 0.18 hours trial-fitted lenses to obtain optimal fits in the study cohorts. They pointed out that the number of trial lenses decreased considerably to 1.56 ± 0.13 hours at the end of the study period highlighting the need for clinical experience when fitting SL. Furthermore, the scleral asymmetry and rigidity of the lenses make fitting SL more difficult. (316) Numerous studies have reported that the sclera does not exhibit regular astigmatism but a more complicated surface structure, which in some situations requires toric or quadrant specific design to significantly improve the landing zone of the lenses and prevent impingement or blanching in both short- and- long term wear. (306, 317) Other challenging factors that compound SL fitting are the complications such as conjunctival prolapse, midday fogging (MDF) and epithelial bogging. (294, 306)

1.16 Proteases in Dry Eye Disease and Scleral Contact Lenses

It has been established that inflammation plays a significant role in DED, and this is related to the severity of the condition. (17, 86, 318, 319) Regular GP lenses (small diameter lenses) and soft contact lenses are known to cause mechanical trauma to the ocular surface which eventually stimulates the release of inflammatory proteins into the tear film. (319-321) Currently, there are only a few studies on the effect of SL on inflammatory proteins in the tear film and typical

examples are matrix metalloproteinase 9 (MMP-9) and diadenosine tetraphosphate (Ap_4A). (312, 322, 323) MMP-9 is secreted by the stressed ocular surface and basal corneal epithelial cells. An increased presence of MMP-9 in the corneal epithelium and tear film results in tight junction protein breakdown and speeds up apical corneal epithelial cell separation. This in turn exposes less-mature subapical epithelial cells that lack a developed glycocalyx, therefore destruction of these cells. (324) The Ap_4A is a dinucleotide protein synthesized through the conjugation of ubiquitin-like proteins which involves the enzymatic activities of adenosine triphosphate. This protein is known to activate purinergic receptors localized on different ocular structures typically the cornea and conjunctiva. (325) The presence of this unique protein in the tear film is known as a consequence of shear stress induced on the corneal epithelial cells through blinking over the stressed corneal epithelial cell. (325) Physiologically, it has been proposed that Ap_4A on the ocular surface include the induction of tear fluid secretion, lysozyme production or acceleration of corneal wound healing. (326)

Currently, there are only a few studies on inflammatory proteins following SL wear. (322, 323) Carracedo et al (322) studied two inflammatory proteins in the post lens tear film: MMP-9 and Ap_4A concentration before and after wearing SL for 8 hours in KC patients with and without intracorneal rings segment (ICRS). They reported a significant increase in MMP-9 concentrations in the tear film for both groups after SL wear ($p < 0.05$) which were attributed to the stagnation of the post lens fluid and chronic nature of KC. Lower concentrations of Ap_4A were found in non ICRS group ($p < 0.05$) which was attributed to the less shear stress from the epithelial cells due to the presence of the SL over the ocular surface.

In another related study, Walker et al (323) studied the matrix MMP-7, MMP-9 and MMP-10 in the basal tears and tears from the SL lens bowl after the subjects had worn the SL for 8 hours, followed by 4 days of continuous wear. The MMP-9 concentrations were significantly greater in tears collected from the SL bowl than basal tears after 8 hours of lens wear with median and interquartile values as SL bowl tears: 62.70 (13.70, 300.70) vs basal tears: 15.20 (0; 85.10) ng/mL, $p = 0.047$. Interestingly, no significant change in MMP-9 was reported after 4 days of lens wear between the two tear samples. Also, they reported a significant difference in MMP-10 for 8 hours

and 4 days continuous SL wear, (all, $p < 0.001$) however, the MMP-7 concentration was not affected.

The mechanism involved in the significant increase in some of the inflammatory proteins are not fully understood. Some authors have suggested that since MMP-9 is released by corneal and conjunctival cells, the mechanical friction between the SL and the conjunctival epithelium could be responsible for the significant increase in MMP-9 after lens wear. (324, 327) They noted with caution that although SL are fitted with minimal movement, friction between the SL and the conjunctival epithelium could have an effect on the synthesis of inflammatory mediators.

The current studies indicate that there is a need for further research to gain a better understanding of the inflammatory proteins before and after wearing of SL, the short- and long-term effect of SL on DE patients and how to effectively reduce these inflammatory proteins while increasing ocular health for patients.

1.17 Summary Of Literature Review and The Need for Clinical Study

As highlighted in the literature review above, DED is a complex and multifactorial ocular surface condition. (17) The complex etiology and varied geographical prevalence of the disease pose a diagnostic challenge for clinicians, exacerbated by the presence of several causal elements and variations in clinical testing techniques. (61, 100) While there is currently no *"gold standard"* clinical testing for diagnosing and managing of the condition, TFOS DEWS II has proposed a clinical diagnostic pathway and treatment algorithm that may be utilized in routine clinical practice to diagnose and manage DED. (17, 193) Furthermore, clinical research and therapy choices have increased significantly over the last three decades, ranging from low-risk management measures to more complex treatment options for moderate to severe forms of the disorder. (96) With its fluid reservoir, greater diameter, and, most importantly, the innovative technology (hydra-PEG technology) used to coat the surface to promote comfort, SL may provide an alternative treatment approach for mild to moderate forms of DED without associated conditions that has yet to be explored.

There is thus a need to assess the effects of SL wear on QoL, contact lens-related dryness and daily wearing behavior as well as its effects on physiological corneal parameters and ocular health. It is also imperative to characterize the difference in response between hydra-PEG coated SL and non-coated SL. The quest to answer all of these questions and to determine the clinical potential of SL for mild to moderate DED served as the basis for this thesis.

CHAPTER 2

2.1 Clinical Protocol Outline and Methodology

2.2 Introduction

Dry eye disease (DED) affects millions of people globally, with an estimated prevalence between 5 to 50 % (averaging 11.60 %) of the general population. (1-3) The economic impact on countries where a significant number of people experience this debilitating condition costs them billions of dollars. (4, 5) For example, the overall economic burden of DED on the health care system in the United States alone was calculated at US$ 3.84 billion in a survey of 2171 respondents. Extrapolation to the general population estimated that the average cost of managing DED in the US would be US$ 11,302 per patient, with an overall cost of US$ 55.4 billion. (6) The impact on the individual's quality of life (QoL), cost of medication, medical visits, and the effect on the sufferer's mental health leave much to be desired. (7-10) For years, industrial partners have spent billions of dollars and have rallied behind scientists to find lasting solutions to this growing issue, through the development of over-the-counter agents, pharmacological interventions, and medical devices. (11, 12)

The TFOS DEWS II 2017 subcommittees published comprehensive reports on the topic of DED, covering its definition, epidemiology, pathophysiology, and diagnostic methods to a management algorithm, all based on available peer-reviewed publications. (1, 3, 13-18) The subcommittee's report on the management of DED provided streamlined strategies that can be used for treatment of the condition in a clinical setting. (14) The first point of call for treatment typically begins with the low-risk use of over-the-counter artificial tears, in addition to lid hygiene measures. (14) Unfortunately, studies have demonstrated that only 5 % of topically applied medication are absorbed by the ocular surface to resolve the symptoms and signs of DED. (14, 19-22) According to a web-based survey, Uchino et al (22) reported that only 10.20 % of the studied population complied with the instillation frequency specified by their eye care practitioner or followed the advice written on the package insert. They also reported that 61.30 % of the participants applied the topical drops only when they felt it was "necessary", due to the presence of symptoms. These

points demonstrate that patient compliance with traditional methods of DED management through topical medications poses a challenge in alleviating DED signs and symptoms. This may lead to the development of chronic and worsening DED, eventually requiring more extensive management options, at greater cost and potentially increased side effects. (12, 23)

The use of scleral contact lenses (SL) to manage DED is currently a **Step 3** (out of 4) management option in the management algorithm proposed by TFOS DEWS II, being reserved for moderate to severe cases when other interventions have failed. (14) This is not entirely surprising, since the fitting of SL has typically been considered a niche area of clinical practice, due to their relatively complicated fitting process. Additionally, complaints of dryness and discomfort were some of the initial challenges regarding the use of SL. (24-27)

Typically, the fitting of SL has been reserved for the visual rehabilitation of patients with complex and severe corneal irregularities such as keratoconus, (28) pellucid marginal degeneration, (29, 30) high myopia, post laser assisted in-situ keratomileusis, cases of graft-versus-host disease, Sjogren's Syndrome, and Steven Johnson's Syndrome. (31, 32) There are also reports of SL being fit for corneal complications such as persistent corneal erosion, and others. (33-35) Thus, these lenses have become a standard, non-surgical management approach to restore the integrity of the ocular surface and improve visual acuity (VA) in more severe ecstatic (corneal thinning conditions) by practitioners dealing with such complicated cases. (34-36) However, to-date, there have been relatively few reports of the use of SL in the management of DED.

Recent publications demonstrate that there has been a surge in the use of SL globally, and have provided evidence of the impact of SL wear on a variety of factors, especially improved QoL for wearers of the lenses. (37) This significant growth in the prescribing of SL is due to significant improvements in methods to measure corneal shape, standardized fitting philosophies, improvements in lens materials and designs, in addition to the introduction of the hydra-PEG (polyethylene glycol) coating technology (Tangible Science LLC, Menlo Park, CA, USA), which is added to the lens surface to increase wettability, thereby enhancing comfort. (38) Although

studies have shown that this hydra-PEG surface coating can improve contact lens comfort in soft and gas-permeable contact lens wearers, (39, 40) little is known about this surface coating concept on SL and its impact on tear film structure and corneal physiology, particularly in less severe DED cases. (41, 42) These factors, that could potentially influence tear film composition, may aid in better understanding of the impact of SL on the health of the cornea. (41)

While scleral lenses are considered within step 3 of the management options proposed by TFOS DEWS II (a step typically taken with moderate to severe cases when other interventions have failed), no prospective, double-masked, randomized, dispensing, cross over clinical trial has been undertaken to determine the effectiveness of SL wear in subjects experiencing mild to moderate DED who do not have corneal disease or injury and would need SL for vision rehabilitation. This study reports on how a coating on SL (surface modification) impacts QoL, symptoms when wearing SL, physiological impact on corneal thickness, osmolarity and protease levels of the precorneal tear film. The results of this study provides novel insights on whether SL can be used as a viable option for patients who are experiencing milder forms of DED.

2.3 Purpose and Hypothesis

The purpose of the study was to investigate the effects of SL wear on a DE population using coated (hydra-PEG) and uncoated (control) lenses. Osmolarity of the tear film, QoL, corneal thickness, vision, and comfort were assessed before and after dispensing and wearing of the SL for four weeks.

The hypothesis examined was that “SL wear of either uncoated or hydra-PEG coated SL in mild to moderate DED is associated with improved ocular surface health”.

2.3.1 Research Questions

1. Does the wear of SL improve ocular surface health and QoL in subjects with mild to moderate DE?

2. Does the surface treatment of SL with a hydra-PEG coating increase comfort compare to uncoated lenses?

2.3.2 Objectives of the Study

The specific objectives were:

1. To evaluate the impact of coated and non-coated SL on DE symptoms.
2. To determine the amount and change in lens settling of each lens type comparing uncoated and coated SL.
3. To determine the physiological impact of SL and change in corneal thickness comparing uncoated and coated SL.
4. To determine the impact of SL on osmolarity and inflammatory markers in the tear film.
5. To determine the relationship between the measured parameters.

Although objectives two and three might not be directly related to DED, the proposition was that given the hydra-PEG coating on the lens surface, the lenses would be well tolerated and worn for longer period of time. Assessing lens settling and impact of SL on corneal thickness were thus part of the study design.

The primary outcome variables were:

1. DE symptoms
2. Lens settling
3. Corneal thickness
4. Osmolarity and matrix metalloproteinase 9 (MMP-9) evaluations of the tear film
5. QoL and SL dryness scores
6. Wearing habit and subjective ratings
7. Vision

2.4 Materials and Methods

2.4.1 Recruitment of Participants

This section and sections 1.4.3, 1.4.4, and 1.5.5 contain excerpts including images which were adopted and reproduced from my thesis submitted to the University of Waterloo, School of Optometry and Vision Science titled : *"Use of OCT and Oculus Pentacam HR® as Aids in Semi-Scleral Contact Lens Fitting, 2013".* (43) This current study used the same clinical instruments/devices and techniques as described below to clinically measure the lens parameters and take anterior segment scans and corneal maps.

Approval from the Office of Research Ethics, University of Waterloo, Waterloo, ON, Canada was obtained before the study began. All the participants were treated in accordance with the tenets of Declaration of Helsinki and were provided with a written Informed Consent Letter (ICL) to sign before participating in the study.

Participants were recruited from the University of Waterloo Contact Lens Clinic, Ocular Health Clinic, and the University Community. Patients who were registered at the Optometry Clinic and those who had previously participated in DE studies through the Center for Ocular Research and Education (CORE) were invited to participate. With the patient's permission, investigators-initiated recruitment according to the in-person script approved by the Office of Research Ethics (Appendices 2-1a-c). The investigator discussed the project with potential participants, where any questions regarding the study procedures and risks associated with the study were answered. Eligibility was determined using the inclusion and exclusion criteria. Previous contact lens wear was not necessary for participation. Informed consent was obtained from all participants prior to their enrolment in the study (Appendix 2-2).

2.4.2 Inclusion and Exclusion Criteria

A person was eligible for inclusion in the study if he/she:

1. Was at least 18 years old and had full legal capacity to volunteer.
2. Had read, understood, and signed the ICL.
3. Had reduced tear break up time (TBUT) and/or reduced tear meniscus height (TMH), a clinical sign of DED, contact lens discomfort or was symptomatic of DED.
4. Was willing and able to follow instructions and maintain the appointment schedule.
5. Scored ≥ 13 points on the Ocular Surface Disease Index (OSDI) questionnaire.
6. Had greater than 4 points on the Standardized Patient Evaluation of Eye Dryness (SPEED) questionnaire.

A person was excluded from the study if he/she:

1. Was using any topical medications that could likely affect the study outcome.
2. Had undergone any form of corneal surgery.
3. Had any known allergies or sensitivities to the clinical diagnostic products, such as fluorescein dye used in this study.
4. Had clinically significant corneal or conjunctival staining not related to the signs of DE.
5. Had any clinically significant lid or conjunctival abnormalities and active neovascularization on the cornea.
6. Had any anatomic variations of the conjunctiva that could impair proper SL wear/fitting.
7. Had ocular pathology other than DE (e.g., glaucoma, macular degeneration etc.) which could significantly impact visual function and assessment.
8. Was participating in any other type of eye related clinical or research study.
9. Had any active ocular infection and may require topical medications.

10. Was currently taking any systemic medication that could affect the study outcome.

11. Was pregnant.

12. Had been diagnosed, recovered, or tested positive but was asymptomatic with COVID-19.

For the purposes of the study, active ocular disease was defined as infection or inflammation which required therapeutic treatment. Mild (i.e., not considered clinically relevant) lid abnormalities (blepharitis, MGD, papillae), corneal and conjunctival staining and DE were not considered active ocular disease. Neovascularization (non-active) and corneal scars are the result of previous hypoxia, infection or inflammation and were therefore not considered as active ocular disease.

2.4.3 Study Population and Sample Size Calculation

Sample size for this clinical trial was determined based on data currently available in peer-reviewed literature. A study by Mickles et al (41) comparing uncoated and the hydra-PEG coated in 21 DED subjects with complicated corneal diseases and systemic condition reported significant change in CLDEQ-8 score with the hydra-PEG coated lenses compared to uncoated SL after four weeks of lens wear. We determined that similar results would be obtained, therefore, a sample size of 20 was chosen for this clinical trial study. Also, budget constraint was a limiting factor in increasing sample size.

To account for participants dropping out of the study or being unable to adapt to SL wear. 30 DE participants were recruited.

P values of less than 0.05 were considered statistically significant for measured parameters before and after wearing the lenses and also when comparing the two types of lenses .

2.4.4 Study Design

The study was a prospective, double-masked, randomized, dispensing, cross over clinical trial involving five visits. Figure 2-1 shows the diagrammatic representation of the study.

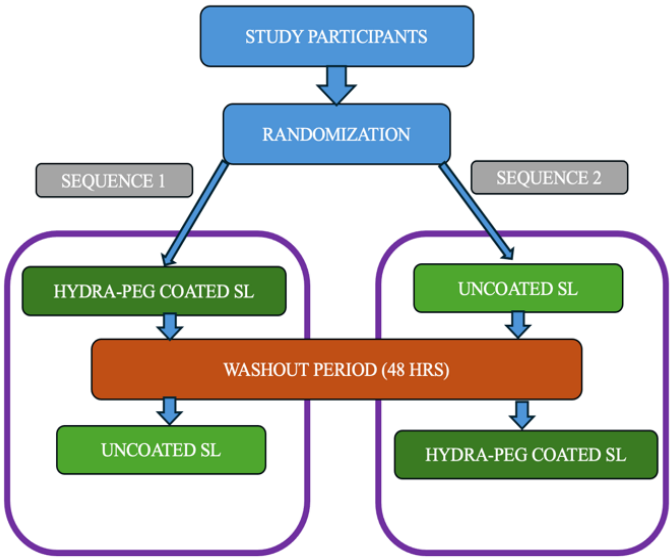


Figure 2-1: Overall Study Design.

The scleral contact lenses (SL) were randomized into sequence 1 and 2. Each lens was worn for four weeks followed by a washout period of at least 48hrs.

2.5 Study Lenses

2.5.1 Zen™ RC Scleral Lenses

The SL used in the study were Zen™ RC (Alden Optical, Bausch & Lomb, Lancaster, NY, USA). The investigators chose these lenses because they are recommended for individuals experiencing DE and also employs a new technology (hydra-PEG) on its surfaces to enhance comfort. Additionally, the design of the lenses allows all the parameters to be adjusted independently to enhance optimum fitting characteristics, something not available with other lenses due to their limited adjustable parameters. The lenses have diameters (14.80 mm or 15.40 mm) for easy insertion and removal especially for new wearers. These lenses are indicated for the normal cornea

with varied designs (e.g., multifocal, and toric designs etc.) and ectatic conditions such as keratoconus, and post-refractive conditions. Also, they are indicated for ocular surface diseases such Sjögren's syndrome, dry eye syndrome and Stevens- Johnson syndrome. In terms of size, with their diameter of 14.80 or 15.40 mm, they can be classified as mini-scleral lenses. The lenses have a central thickness of 250 µm. The SL are manufactured using the Boston XO® (hexafocon A) material, composed of a siloxanyl fluoromethacrylate copolymer and they contain an ultraviolet absorber. The material's refractive index is 1.415 with a Dk of 100. The stated wetting angle without and with Hydra-PEG is 49 ° and 10 ° respectively. It has a specific gravity of 1.27 and < 1 % water content. (44)

The Zen™ RC with Tangible Hydra-PEG® are treated to incorporate the coating on the front and back surfaces of the lens during the manufacturing process. This coating is a thin polyethylene glycol (PEG)-based polymer with 90 % water that is permanently bonded to the surface of the contact lens. The process creates a hydrophilic surface of approximately 30 - 40 nm which is known to significantly increase the wettability of the lens surface. It is interesting to note that the coating enhances the surface properties without altering the chemical and mechanical properties of the lens. Current clinical studies show that this technology significantly improve wettability of the contact lenses compared to uncoated lenses. (41)

In terms of design, the Zen™ RC lenses have four distinct zones, which are all adjustable: central vault, mid-peripheral clearance, limbal clearance and scleral (haptic) alignment (see Figure 2-2).

a) The central vault (also known as the total sagittal height) of the SL can be increased or decreased to ensure total corneal clearance. According to the manufacturer, when the lens is fitted on the eye, the recommended amount of clearance between the front surface of the cornea and the back surface of the SL is expected to be 250 to 350 µm. This amount of clearance can be achieved by using the central lens thickness (250 µm) as a guide when viewed through the slit lamp biomicroscope via an optic section viewing technique. In this study, the Visante™ OCT was used to scan the lenses on the eye to make sure that the amount of central clearance was within the recommended range.

b) The mid-peripheral clearance can be adjusted by changing other parameters to optimize the fitting characteristics. For example, flakes or cloudiness (fogging) under the lens can be resolved by adjusting the lens with a steeper or toric periphery.

c) The limbal clearance is designed to vault over the limbal zone, with an estimated limbal clearance of 50 µm. Irrespective of the standardized design profile, the limbal clearance can be designed as quadrant specific to make sure that the limbal area has enough clearance in a specific quadrant without changing other parameters. According to the manufacturer, a well-adjusted limbal clearance helps to achieve better centration. The junction between the mid-periphery and the limbal clearance is designated as the SmartCurve™ region, which allows customization of the lenses for optimal fitting characteristics and comfort.

d) The edge of the SL (scleral alignment) forms the advanced peripheral system (APS). The APS allows the edge of the lens to be steepened or flattened for the lens to contour optimally on the conjunctival sclera (designed as Steep-10 through Steep-1, Standard, and Flat-1 through Flat-10) in 30 µm increments.

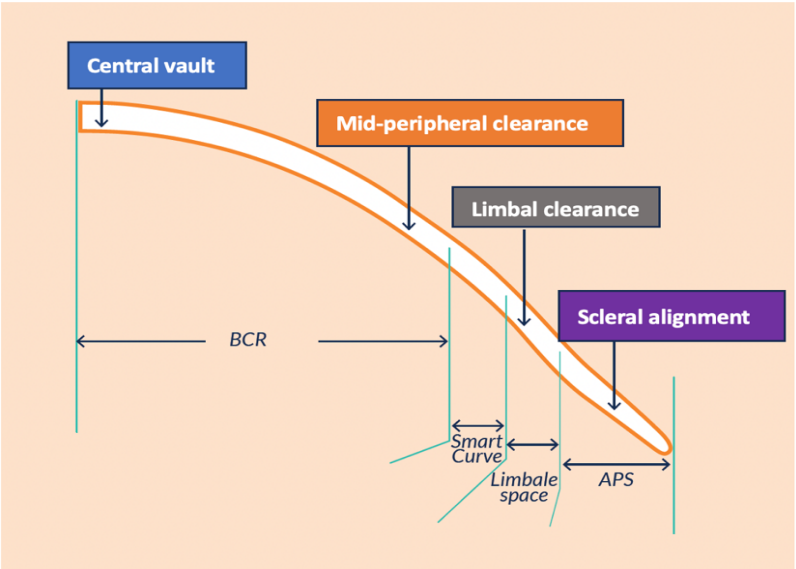


Figure 2-2: Schematic Zen™ RC SL showing four distinct adjustable profile.

Central vault, Mid-peripheral clearance, Limbal clearance and Scleral alignment. BCR: Base Curve Radius, APS: Advanced Peripheral System. (Courtesy Alden Optical, Lancaster, NY, USA)

2.5.2 Zen™ RC Diagnostic Trial Lenses

A twenty predesigned Zen™ RC SL diagnostic trial set (all in -3.00 D; 250 µm thickness) in vials was used in this study. These lenses are grouped into two categories, based on the total diameters of 14.80 or 15.40 mm. Each group has ten lenses, with two each with toric designs (see Figure 2-3). Eight lenses for each group are designated as ZRC (spherical designs) while ZRCT are represented as toric designs. The lenses are labelled with the sagittal height, base curve radius (BCR) in both diopters (D) and in millimeters (mm). The details of the lens parameters are listed in Table 2-1.

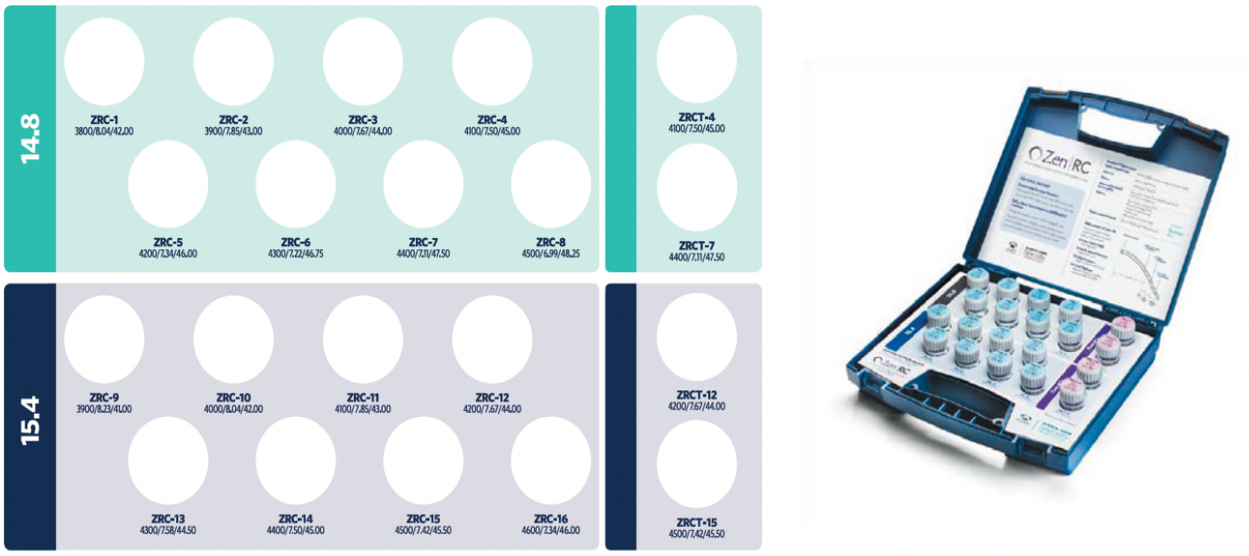


Figure 2-3: Zen™ RC SL diagnostic trial set.

The green area represents 14.80 mm while the blue area represents 15.40 mm. ZRC: Spherical Zen lens design, ZRCT: Toric Zen lens design. (Courtesy Alden Optical, Lancaster, NY, USA).

Table 2-1: Zen™ RC SL diagnostic trial set.

14.80 mm Lens Design				**15.40 mm Lens Design**		
Lens ID	**BCR (mm/D)**	**Sag (µm)**	**Power (D)**	**Lens ID**	**BCR (mm/D)**	**Sag (µm)**
ZRC-1	8.04/42.00	3800	-3.00	ZRC-9	8.23/41.00	3900
ZRC -2	7.85/43.00	3900	-3.00	ZRC -10	8.04/42.00	4000
ZRC -3	7.67/44.00	4000	-3.00	ZRC -11	7.85/43.00	4100
ZRC -4	7.50/45.00	4100	-3.00	ZRC -12	7.67/44.00	4200
ZRC -5	7.34/46.00	4200	-3.00	ZRC -13	7.58/44.50	4300
ZRC -6	7.22/46.75	4300	-3.00	ZRC -14	7.50/45.00	4400
ZRC -7	7.11/47.75	4400	-3.00	ZRC -15	7.42/45.50	4500
ZRC -8	6.99/48.25	4500	-3.00	ZRC -16	7.34/46.00	4600
ZRCT-4	**7.50/45.00**	**4100**	-3.00	**ZRCT-12**	**7.67/44.00**	**4200**
ZRCT-7	**7.11/47.50**	**4400**	-3.00	**ZRCT-15**	**7.42/45.50**	**4500**

BCR: Base curve radius, D: Diopter, Sag: Sagittal height of SL, mm: millimeters, ZRC: Spherical Zen lens design, ZRCT: Toric Zen lens design. µm*:* micron. *Note:* The highlighted lens IDs (***bold***) are toric designs and all SL had predetermined -3.00 D.

2.5.3 Verification of Zen™ RC Diagnostic Trial Lenses

Prior to being used in the study, the Zen™ RC diagnostic trial lenses underwent a clinical examination and verification. After being taken out of the vials, the lenses were cleaned with saline and dried with lens blotting paper. The lenses were thoroughly inspected to make sure there were no chips or cracks and that there was no surface damage. A digital auto lensmeter SLM-5000 (Ryusyo Industrial Co. Ltd., Gun, Japan) was used to measure the power and a radiuscope (American Optical L1200, Scientific Instrument Division, Buffalo, NY, USA) to measure the sagittal height (see section 1.4.4 for method). A profile projector (Mitutoyo Corp., Tokyo, Japan) was used to measure the diameter of the lenses, while a contact lens thickness gauge (Western Ophthalmics, Lynnwood, WA, USA) was used to measure the lenses' central thickness.

2.5.4 Measurement of Sagittal Depth/Height of Lenses

The sagittal heights ("sag") of the lenses were measured with a radiuscope (American Optical L1200, Scientific Instrument Division, Buffalo, NY, USA) using a technique described by Dr. Stephen Byrnes (Optometrist, Londonderry, NH, USA). (43)

A silvered mirror was positioned on the radiuscope stage right beneath the objective piece (Figure 2-4a). When the image was reflected off this surface and focused (first image), the examiner adjusted the wide aperture and turned the coarse dial of the device clockwise (Figure 2-4b). The integrated measurement gauge's initial setting was zero. Subsequently, the SL to be measured was positioned on the silvered mirror, concave side down (Figure 2-4c). The examiner used the device's eyepiece to see through to the mirror, adjusting the lens position until a dim, blurry image of the light bulb filament reflecting off the SL's apex was clearly visible. The objective lens of the microscope was moved anticlockwise until the filament image came into focus, (Figure 2-4d). Next, a gradual move in continuous anticlockwise direction saw a faint reflection (third image) of the inner SL surface, (Figure 2-4e). The fourth image, which reflected off the SL's exterior, was located quite near to the third image (Figure 2-4f). The measurement was now taken off the scale and recorded as the sagittal height of the SL's front surface, which was determined by measuring perpendicularly from the silvered mirror to the SL's front surface. To determine the true sagittal height of the interior of the SL, the center thickness of the SL was deducted from the sagittal height.



Figure 2-4a

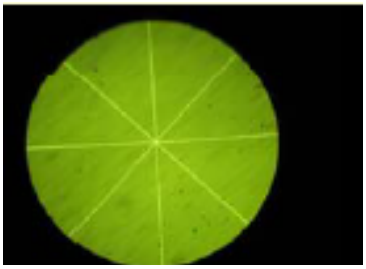


Figure 2-4b

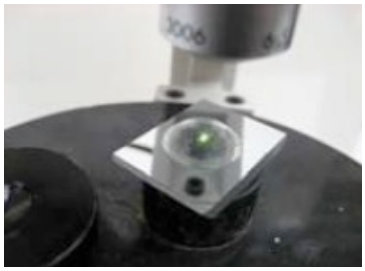


Figure 2-4c

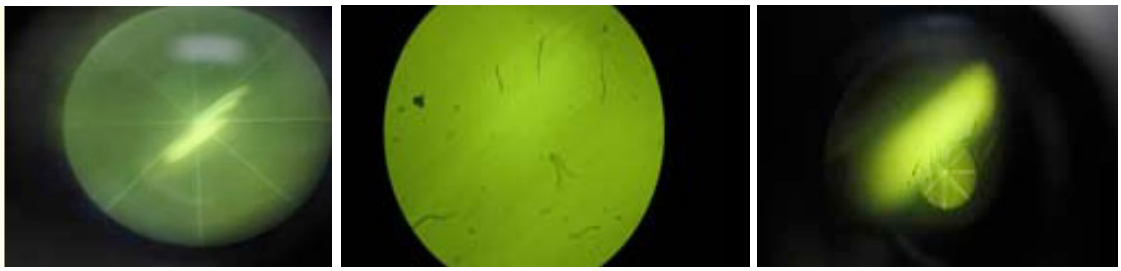


Figure 2-4d Figure 2-4e Figure 2-4f

Figure 2-4a-f: Stages of measurement of the sagittal height of the SL with a radiuscope.

(All photos reproduced with original permission from Dr. Stephen Byrnes-Optometrist, Londonderry, NH, USA. This technique was first presented at Global Speciality Lens Symposium, Las Vegas, USA, 2012 and further reported in a thesis submission titled: Use of OCT and Oculus Pentacam HR® as Aids in Semi-Scleral Contact Lens Fitting. School of Optometry and Vision Science, University of Waterloo, ON, Canada, 2013). (43)

Following the lens verification, all lenses were disinfected with the recommended guidelines from the manufacturer and stored in Boston Simplus in the lens vials until the lenses were ready to use.

2.6 Study Visits and Procedures

The clinical trial study involved five clinical visits. Table 2-2 shows the summary of the clinical visits and time spent on each visit. A washout period of a minimum of 48 hours was applied between lens types and the participants repeated the same wearing schedule with the second pair.

Table 2-2: Summary of clinical study visits.

Visit code	Visits	Time
0-0	Screening, baseline measurements and trial lens fitting	2.5 hrs
1-1	First scleral lens delivery visit (with or without Hydra-PEG) - Lens 1	2.0 hrs
1-2	Follow-up visit (with or without Hydra-PEG)- Lens 1	1.5 hrs
Wash-out Period (48hours minimum)		
2-1	Second scleral lens delivery visit (with or without Hydra-PEG)- Lens 2	1.5 hrs
2-2	Follow-up visit (with or without Hydra-PEG)- Lens 2	1.5 hrs

2.7 Visit 1: Screening and Baseline Measurements

2.7.1 Review of Informed Consent Letter, Ocular History and Screening Questionnaires

All participants read and signed the ICL and were given an opportunity to ask questions (electronically through email) prior to visiting the study center. Participants were also asked to complete two DE screening questionnaires (OSDI and SPEED), which were submitted online ahead of the 1st clinical visit. If any of the participants exhibited symptoms above the cut-off points (OSDI $\geq$ 13, SPEED $\geq$ 4), the participant was then invited to the study center. At the center, participants were once again given an opportunity to ask any other questions relating to their participation in the study. The investigator used the opportunity to explain the study in detail and the need to follow the instructions. The screening form (Appendix 2-3) was used to gather demographic characteristics and information relating to history of contact lens use (if any) as well as current medication (both topical and systemic). Other information relating to allergies and any medical condition that could impact on the parameters to be measured were noted. The inclusion

and exclusion criteria were used to determine if any of the participants were eligible to continue with the other procedures.

High contrast visual acuity (HCVA) and low contrast visual acuity (LCVA) were measured with the logarithm of minimum angle of resolution (LogMAR) VA chart with their habitual contact lenses (if any) or spectacles. The degree of refractive error was not part of the inclusion and exclusion criteria as this was corrected during the SL fitting procedure. Figure 2-5 shows the step-by-step procedure carried out during the screening visit.

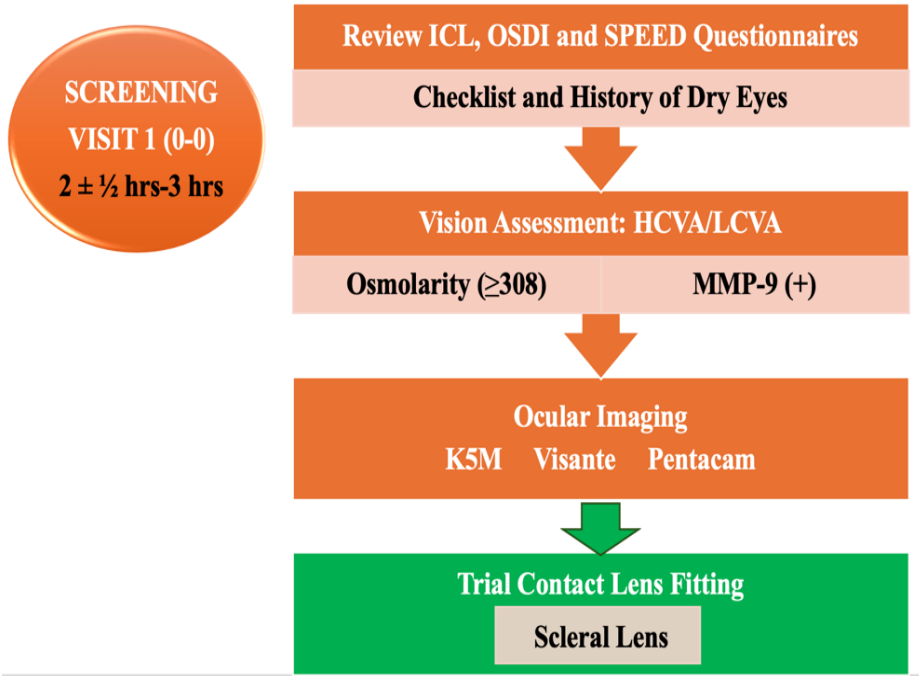


Figure 2-5: Screening and baseline measurement procedures.

2.7.2 Tear Osmolarity Measurement

The TearLab Osmolarity System (TearLab Corp. Escondido, CA, USA, now Trukera Medical, San Diego, CA, USA) was used to detect and indirectly measure tear osmolarity. This device provides an indirect measurement of osmolarity by means of an integrated collecting and analysis device and a temperature-corrected impedance measurement. The process of calculating and

displaying osmolarity involves the application of a calibration curve and the numerical value is shown on the device panel (45).

To measure the osmolarity, the instrument was calibrated each time with the test card to make sure the device was measuring within the acceptable range (between 333 - 334 mOsmol/L). The chip code (e.g., 8 or 10 etc.) was selected to correspond with the test cards to be used (usually same code for a brand-new box).

The participant was seated in the examination chair and the investigator inserted a brand-new test card at the tip of the osmolarity test pen (the colour at the tip of the pen turns green). The participant was asked to slightly raise their head and moved their eye to the nasal direction (depending on which eye for measurement) while the investigator gently pulled down the lower eyelid. The tip of the test card was used to make contact at the temporal side of the lower eyelid. Once the tear film was collected at the tip of the test card, the test pen sensor made a beep sound (the colour turns to purple) to alert the investigator that the tear collection was successful. The test pen was then mounted on the TearLab Osmolarity System Unit to display the osmolarity value. This measurement was done once, starting with the right eye followed by the left eye. This order was used for all the participants throughout the study. Figure 2-6a-b shows the TearLab Osmolarity System and the reading scale.



Figure 2-6a: Tear Osmolarity System

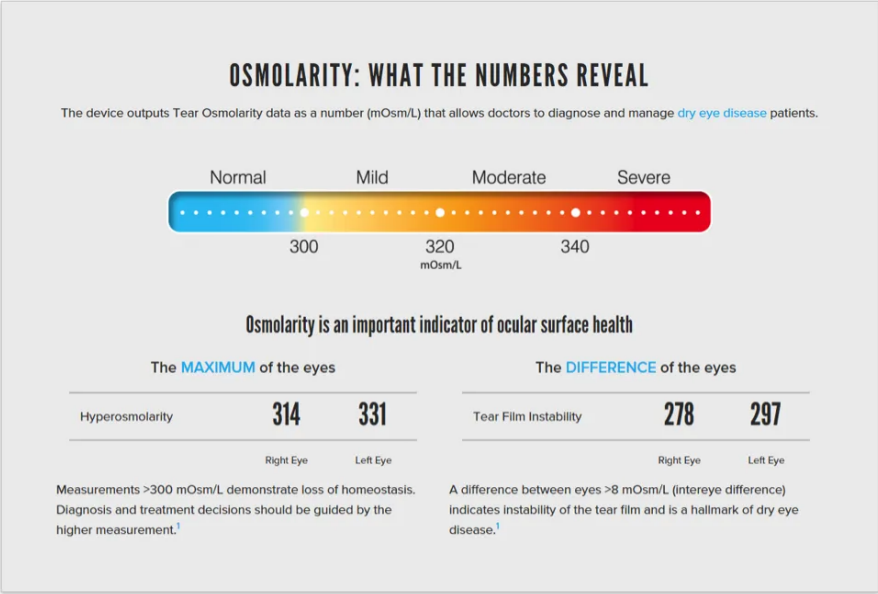


Figure 2-6b: Grading scale

Figure 2-6a-b: TearLab Osmolarity System and reading scale.

(Courtesy Trukera Medical, San Diego, CA, USA)

2.7.3 Levels of Protease with Inflammadry® Test Kits

Following the osmolarity test, the Matrix Metalloproteinase-9 test (MMP-9) was performed using the InflammaDry® test kit (Quidel InflammaDry, Sarasota, Florida, USA). The InflammaDry® test kit is a Clinical Laboratory Improvement Amendments waived (CLIA-waived) test for human tears. (46, 47) This diagnostic device is an immunoassay test for detection of increased levels of MMP-9 in the tear film. It is intended to offer a quick and easy-to-use in office method of assessing DE in both clinical and research settings. It makes use of lateral flow immunoassay technique-based direct sampling micro-filtration technology. The MMP-9, if present in the tear sample, is captured between MMP-9 specific mouse monoclonal at concentrations greater than 40 ng/ml. NeutrAvidin is used “in” the test line to capture the antigen-antibody complex, and a colored line appear with concentration greater than 40ng/ml.

Two foil pouches are included with the test kit; one has the buffer vial, the other has a cassette body with a cover, and a sample collector. The buffer solution contains 200 mM Tris, 10 % Fish 81 (sea block), 0.80 % Tergitol, 100 mM NaCl, 0.10 % Sodium Azide, 0.0126 % Gentamycin, and has a pH of 9.50 ± 0.05. To collect the tear sample for assessment, the participant was seated in the examination chair with their head in the primary position. The investigator pulled down the lower eyelid to expose the palpebral conjunctiva. The sampling fleece was used to dab multiple areas on the palpebral conjunctiva to make sure that enough tears had been collected. To ensure consistency, the investigator made sure the sampling fleece was visibly soaked and glistened. The examiner assembled the test device by gently placing the sampling fleece into the sample transfer window to the test cassette body. The absorbent tip was dipped in a buffer vial for minimum of 20 - 30 seconds, which allowed the buffer to travel across the control zone of the device. After this, the protector cap was used to cover the absorbent tip, and the device was labeled and gently placed on a flat surface. The test kit was graded as either positive or negative after 10 minutes, according to the manufacturer's recommendation. (Figure 2-7)



Figure 2-7: Positive MMP-9 results in both eyes with the InflammaDry® test kit.

OD: right eye, OS: left eye

The investigator determined the eligibility of the participants after the above-described tests had been carried out. The TFOS Diagnostic Report recommendation was used, thus, the presence of symptoms (OSDI ≥ 13, SPEED ≥ 4), plus any of the homeostatic measurements (e.g. high osmolarity) as described above. (18)

Ineligible participants were discontinued from the study, while the eligible participants proceeded with the other steps of the study.

2.7.4 Slit-Lamp Biomicroscopy Examination

The anterior part of the eye was examined using a slit lamp biomicroscope. The participant was positioned in the examination chair such that the forehead touched the forehead strap. To rule out any disorders affecting the eyelashes as well as any abnormal development (e.g., pterygium, blepharitis, etc.) other than lid notching or closed meibomian gland orifices, suggestive of meibomian gland disease (MGD), a comprehensive examination of the ocular adnexa, upper and lower eyelids was conducted. The bulbar conjunctiva was next examined, and its redness was assessed and graded. The study excluded participants who had ptosis, pterygium, or any ocular inflammation that would affect their ability to wear the SL successfully. To rule out corneal erosions, infiltrates, or aberrant anterior chamber reactions, the corneal epithelium, endothelium, and anterior chamber were all evaluated. The cornea was evaluated using cobalt blue light and a Wratten #12 yellow filter after staining with sodium fluorescein (NaFl) (Fluorets; Laboratoire Chauvin, Aubenas, France). This was to ensure that there were no problems from previous contact lens wear or severe corneal staining. Lastly, the upper eyelids were everted, and the palpebral conjunctiva graded (Appendix 2-4).

2.7.5 Photo-documentation of NaFl Patterns with the Keratograph® K5M

Following the slit-lamp examination, the investigator proceeded to use the Keratograph® 5M (Oculus, Wetzlar, Germany) to photo document the corneal surface. The participant was seated at the K5M like the Pentacam instrument. The participant was asked to blink 2 - 3 times and hold

their eyes open for a few seconds until the instrument software took a picture of the eye. This image acquisition was repeated twice. This procedure was used to photograph the cornea and conjunctival staining. This instrument was also used during the SL fitting to ensure proper lens assessment. Figure 2-8 shows corneal staining on the eye imaged with the K5M.

After the fluorescein examination, the participant's eye was washed with non-preserved Sensitive Eyes Saline Plus Solution (Bausch & Lomb, Rochester, NY, USA) and let to sit for about five minutes to make sure the saline had completely dissipated from the eye.

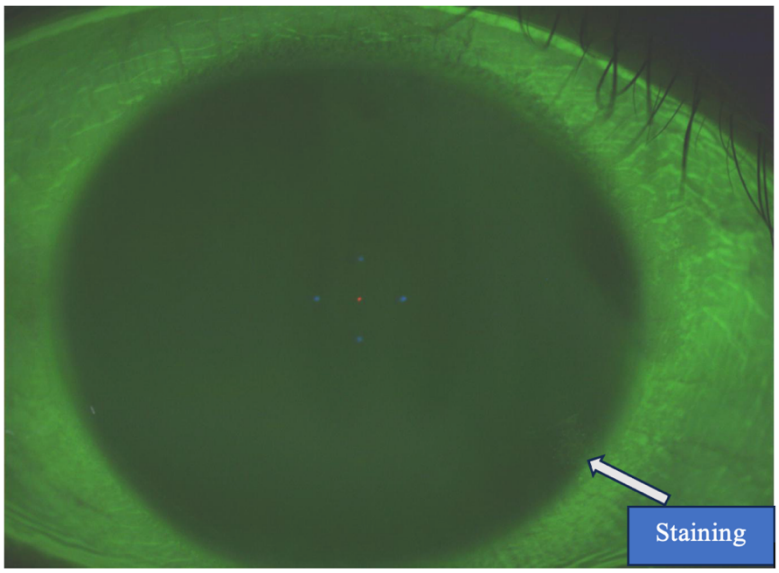


Figure 2-8: Visible corneal staining and with NaFl on the eye using K5M.

2.7.6 Corneal Topography Measurement with the Oculus Pentacam HR®

The Oculus Pentacam HR® (Oculus, Wetzlar, Germany) was used to scan the anterior segment of the eye. See Figure 2-9. No direct contact on the eye was made with the instrument. The subject was instructed to focus on a red fixation point while seated. For every scan, the room light was turned off to obtain a picture free of reflexes. The mires indicated the pupil's center and the corneal apex, and the device was focused and adjusted using the joystick until the real-time image of the corneal surface appeared on the computer monitor. The investigator aligned the horizontal

and vertical crosshairs at the pupil's center, with the assistance of the mires that were displayed on the screen. The instrument was set to capture 25 Scheimpflug images using the automatic release mode settings. For every scan, this process was repeated every two minutes and for each measurement, the subject was instructed to step away from the device so that it could be moved backward and realigned for the subsequent scan using the joystick. The "Quality Specifications" were applied to scans that registered as "**OK**" and any scan that was not registered as **"OK**" by the instrument was repeated.

The radius of curvature measurement (K-reading) was used in conjunction with corneal sagittal depth (CSD) measurements to select the initial SL to fit on the eye. The horizontal visible iris diameter (HVID) was used to determine the diameter of the lenses to be fitted (either 14.80 or 15.40 mm), see section 1.6.1. The corneal thickness was also recorded to determine the impact of the SL on the cornea following the lens wear over the study period.

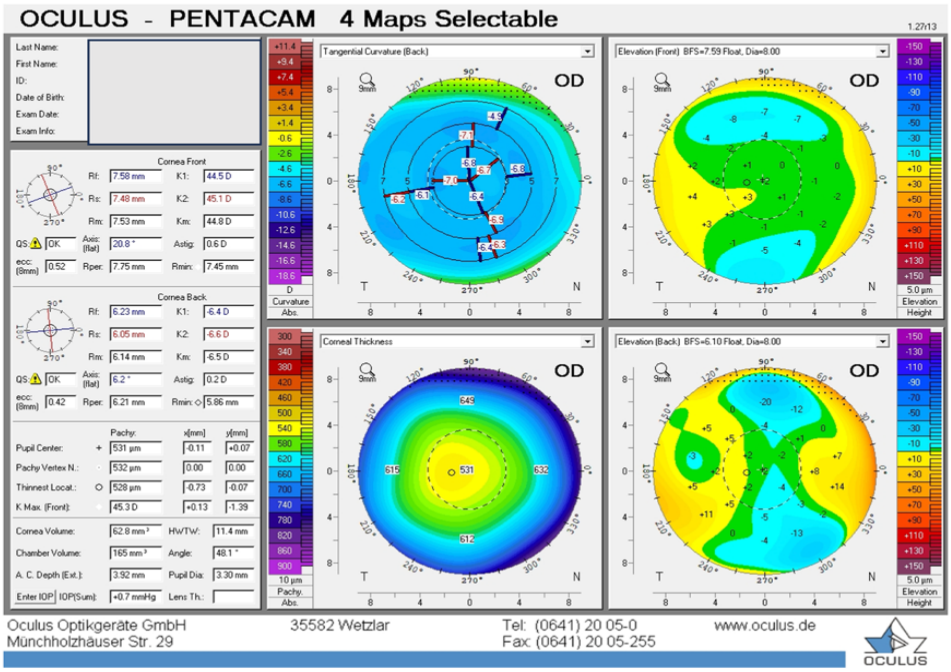


Figure 2-9: Pentacam HR® quad map from a normal corneal scan.

2.7.7 Anterior Segment Imaging with the Visante™ OCT

The CSD was measured using the Visante™ ™ OCT (Carl Zeiss, Meditec, Dublin, CA, USA). The participant's setup was the same as that of the Pentacam HR® device. For every measurement, the device was in "Enhanced Anterior Segment Single" mode. During the scanning process, the participant was told to keep their eyes wide open. After achieving this, the anterior segment was scanned by pressing the capture release button once. The examiner verified that every scan complied with the required standards, which included clear separation of the cornea's anterior and posterior borders, horizontal alignment, and the lack of artifacts.

The integrated, built-in callipers were used to measure the CSD at 14.80 - or 15.40-mm chord, depending on the HVID from the topography map. Two scans were taken at approximately 2-minute intervals and the average CSD was used in conjunction with the K-reading for initial SL selection. Figure 2-10 shows the CSD for 15.40 mm chord (for a lens diameter of 15.40 mm) to be fitted on the eye.

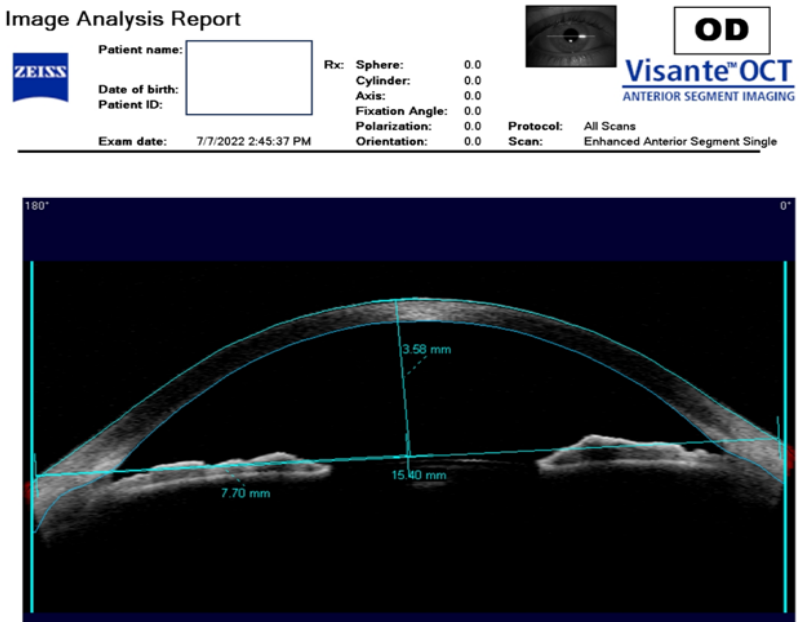


Figure 2-10: CSD measurement with Visante™ ™ OCT for fitting a lens diameter of 15.40 mm.

2.8 Trial Contact Lens Fitting

2.8.1 Lens Selection

All the SL were fitted using the manufacturer's recommendation, combined with CSD data from the Visante™ OCT (Figure 2-10).

The manufacturer provides **two steps** in selecting the initial trial lens to be fitted on the eye. These steps are:

1. Determining the lens diameter:
    a. If the corneal HVID is 11.70 mm or less, use the 14.80 mm diameter.
    b. If the corneal HVID is 11.80 mm or more, use the 15.40 mm diameter.
2. Choose the lens that is closest to the ***average K-reading*** and apply on the eye.

In situations where the K-reading did not correspond to the sagittal height of the SL, the investigator used the measured CSD and added a nominal 350 µm to determine the initial lens. For example, if CSD plus 350 µm (hypothetical value) corresponded with the lens sag and the base curve as indicated on the lens vial, the investigator chose that lens as the initial diagnostic lens to fit on the eye. If the parameters did not correspond, the investigator relied on CSD and an additional 350 µm to select the initial lens. This was based on the fact that some of the participants had normal K-readings, but the CSD were lower compared to the average CSD. In such instances, the K-readings were insufficient to select the initial lens to apply on the eye. This was done to avoid fitting many SL on the eye before achieving the optimal fitting characteristics. Interestingly, the use of CSD as a single parameter from the anterior segment scan has proven to be effective in selecting initial lenses to fit. (48, 49)

2.8.2 Lens Preparation, Cleaning and Application

The lens care system employed in this study included Sensitive Eyes Saline Plus Solution (Alcon Laboratories, Inc., TX, USA), Clear Care Cleaning and Disinfectant Solution with Hydraglyde

(Alcon Laboratories, Inc., TX, USA) and Boston Simplus Comfort Formula Conditioning Solution (Bausch & Lomb Inc., Rochester, NY, USA). In order to ensure that the chosen lens was clear of debris and protein deposits, it was taken out of the lens vial and cleaned with Boston Simplus (physical rub). After that, a thorough saline rinse was performed.

To apply the SL on the eye, a drop of Simplus conditioning solution was applied to the front surface to enhance their initial comfort during insertion. The SL was filled with Addipak saline solution (Teleflex Medical Canada Inc., Markham, Ontario, CA) prior to being inserted into the eye. The SL was mounted on a plunger and dipped in NaFl dye prior to insertion. (Figure 2-11a)

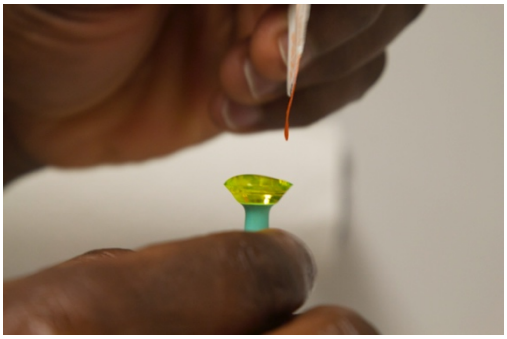


Figure 2-11a: SL on the suction cup and NaFl.



Figure 2-11b: Application of SL on the eye.

Figure 2-11a-b: Shows the preparation of the SL and application.

Using cobalt blue light and a Wratten #12 yellow filter, a slit lamp biomicroscope (Figure 2-11b) was utilized to evaluate the SL as soon as the lens was placed in the eye. This was done to make sure the SL was free of any trapped bubbles. If any discomfort was caused by bubbles larger than 3 mm, the investigator immediately removed the SL and reapplied on the eye for assessment.

All participants who were not able to be trial fitted with any of the diagnostic trial lenses (due to low CSD) were rescheduled after the investigator ordered a “predetermined” trial lens design based

on CSD and added an estimated 350 µm. Assessment was then performed with this trial lenses before the final lens ordering.

2.8.3 Scleral Lens Imaging with the K5M and Visante™ OCT

Immediately after lens examination with the slit lamp, the lens was allowed to settle for 20 - 30 minutes. This was to make sure there was no bearing or contact between the back surface of the lens and the front of the cornea and that the lens was fitting optimally on the patient's eye. Following the lens settling time, the Visante™ OCT was used to obtain a scan to make sure the central corneal clearance (CCC) was within the acceptable range of 250 to 350 µm. If the CCC was less that 250 µm and there were signs of potential touch, the investigator removed the lenses and inserted the next lens with a higher vault and repeated the above process (Figure 2-12c). When an acceptable CCC had been achieved, the investigator assessed and recorded the NaFl pattern at the central, mid-periphery and periphery using an internally generated grading scale. Refer to Appendix 2-5. Figures 2-12a-c and 2-13a-b show the Visante™ OCT scans with toric lens design (in the nasal, temporal, and central areas) and NaFl of spherical and toric designs respectively.

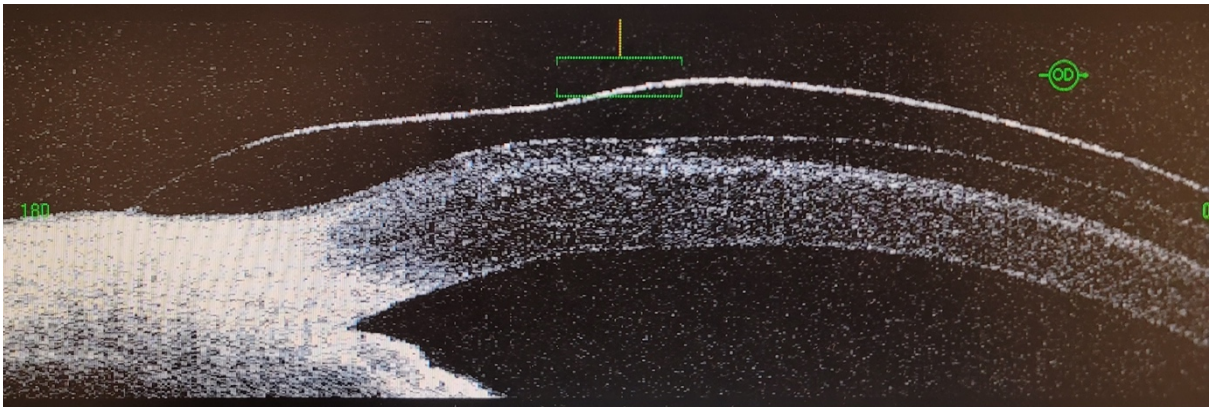


Figure 2-12a: Visante™ OCT scan shows the toric edge design of the SL in the nasal direction. *Note:* the lens vaults over the limbus with characteristic edge design (*"clubbed edge design"*) and contours over the scleral area

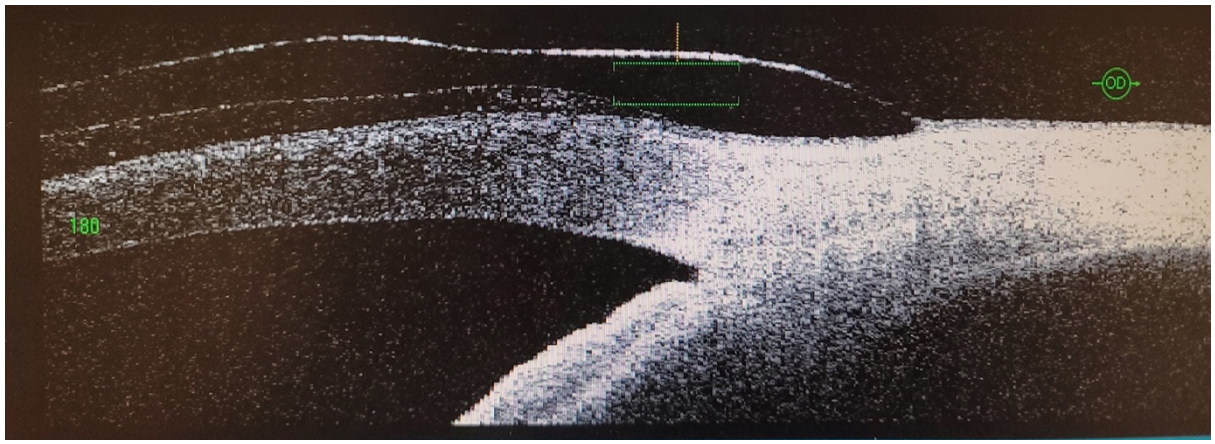


Figure 2-12b: Visante™ OCT scan shows the toric edge design of SL in the temporal direction.

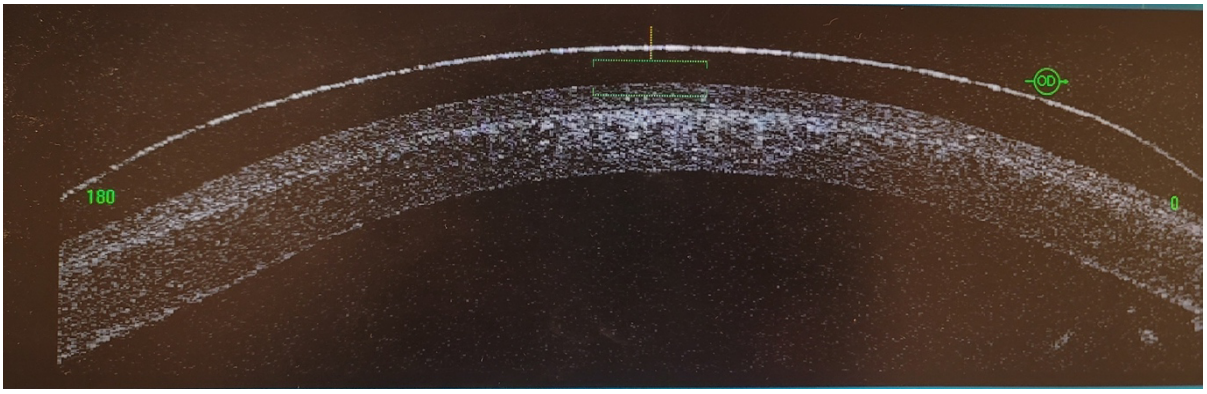


Figure 2-12c: Visante™ OCT scan showing toric profile design. Note the gradual increase in lens thickness from the mid-periphery towards the periphery.

Figure 2-12a-c: Visante™ OCT scans showing the nasal, temporal, and toric profile design of the lens on the eye.

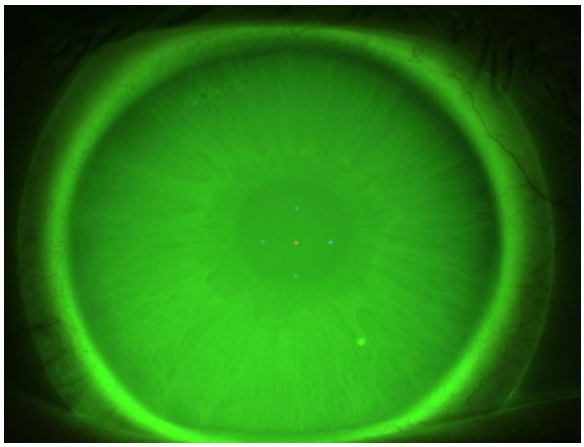


Figure 2-13a: Spherical SL with NaFl on the right eye

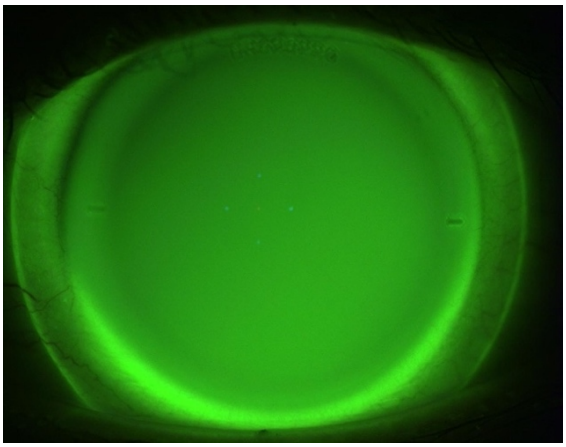


Figure 2-13b: Toric SL with NaFl on the right eye

Figure 2-13a-b: NaFl patterns of spherical and toric (scribe mark on the 3-9 o'clock direction) designs using keratograph, K5M.

The above procedure was also used to measure the CCC before the lens was dispensed and also at the follow-up visit.

2.8.4 Over-refraction, Visual Assessment and Lens Ordering

After photo-documentation and SL scans, an auto-refractor (Nidek Co., Ltd., Gamagori, Aichi, Japan) was used to determine the residual power. Subjective over-refraction was performed over the SL with the phoropter to determine the overall refractive power needed to customize the lens for visual performance. Astigmatic over-refraction of cylinder (-0.50D) or less that did not improve the vision on the LogMAR chart was not included in the final prescription ordered.

Distance high and low contrast visual acuities (HCVA and LCVA) were performed to make sure each participant was able to read at least 0.00 LogMAR and N6 at near.

All the lenses were customized for each participant based on an acceptable CCC, fitting characteristics, and visual performance. Also, all the lenses had a standard central thickness of 250 μm to avoid the lens thickness from influencing corneal physiology (corneal thickness). All the lenses were ordered online using approved Alden Optical Lens Ordering Form (Appendix

2.9 Visit 2: Dispensing Visit

At the dispensing visit, the investigator assessed the cornea with the slit lamp biomicroscope and NaFl to make sure the cornea was free from any staining or any underlying pathological condition. All the Zen™ RC SL delivered by Alden Optical were verified and inspected to make sure they were within the acceptable optical tolerances.

The lenses to be dispensed were randomized by an Optometric Assistant. Neither the investigator nor the participant was aware of the lens type as the lenses were delivered in masked vials. Figure 2-14 shows the step-by-step procedures during the dispensing visit.

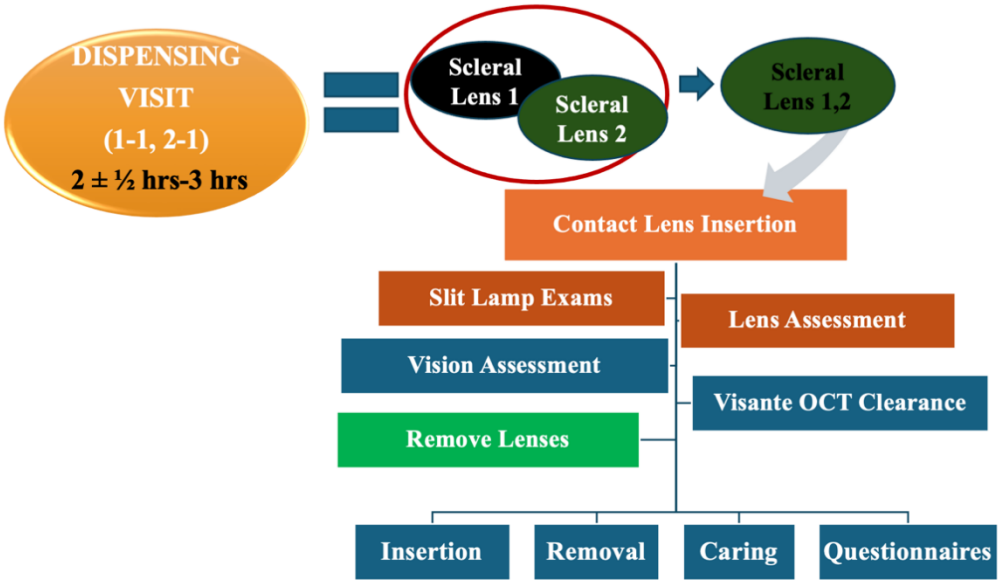


Figure 2-14: Step-by-step procedures at the dispensing visit.

2.9.1 Zen™ RC Lens Insertion and Assessment

The participant was seated in the examination chair and the investigator prepared and applied the SL to make sure the lenses had similar fitting characteristics compared to the trial lens. The slit lamp biomicroscope was used to assess the lens to make sure there were micro bubbles.

The HCVA and LCVA were assessed to make sure the vision was optimum with the lenses. After all the clinical assessment, the investigator removed the lenses and re-cleaned them for training and other measurements.

2.9.2 Zen™ RC Lens Insertion, Removal, and Training

The investigator demonstrated the process of cleaning, disinfection and how the lenses should be handled each day during the study period. The plunger-method of insertion and removal was demonstrated and how the lens should be mounted, filled with the addipak solution, and inserted safely without creating unwarranted bubbles. The tripod-method (using the fingers) was also demonstrated; however, the investigator recommended the plunger-method as the easiest option for insertion and removal of the lenses. (Appendix 2-7)

The participant was allowed to demonstrate/practice all the procedures under supervision. After lens insertion, the investigator re-assessed the lenses, measured the VA and CCC as described above.

Before dispensing the lenses, the investigator made sure all the participants were confident with inserting/applying, removing, and caring for the lenses. The appropriate care systems were dispensed along with the lenses. Participants who were not confident or comfortable with the procedures were rescheduled for another round of training.

2.9.3 Study Questionnaires and Training

As part of the dispensing visit, three questionnaires: Contact Lens Dry Eyes Questionnaire-8 (CLDEQ-8), (Appendix 2-8) Contact Lens Impact on Quality of life (CLIQ) questionnaire (Appendix 2-9) and Wearing Habit and Subjective Ratings (Appendix 2-10) were thoroughly explained to the participant. The questionnaires were completed: CLDEQ-8 (biweekly), CLIQ (monthly) and Wearing Habit and Subjective Ratings questionnaires (daily). These questionnaires

were dispensed to the participant to understand the ocular symptoms, contact lens related dryness, QoL and wearing experience of each pair of lenses. These questionnaires were collected and reviewed for completeness during the follow-up visit.

2.9.4 Wearing Schedule

During the training, the investigator instructed the participants to follow the wearing schedule as stipulated by the manufacturer. The first day of lens wear started with maximum of 4 hours. The second day was increased by 1 - 2 hours until the participants achieved a wearing time of 8 hours within the first week of lens wear. This was followed by 8 to 10 hours (maximum) of each day for the remaining three weeks period. After the washout period (minimum 48 hours), the participants were also instructed to follow the same wearing schedule, starting with 4 hours until they achieved 8 to 10 hours with the other pair of the SL.

2.9.5 Visit 3: Follow-up Visit

Following the four weeks of SL wear, the participant presented at the follow-up visit after wearing the lenses for between 4 to 7 hours. Both HCVA and LCVA were assessed for each eye. This was followed by examining the SL under the slit lamp biomicroscope. The Visante™ OCT was used to scan the SL on the eye to measure the CCC.

The Pentacam HR was used obtain scans of the cornea. NaFl was inserted onto the ocular surface and the K5M was used to photo-document any staining observed, which was graded on the biomicroscopy forms.

The three questionnaires were collected and reviewed for completeness. Figure 2-15 shows the step-by-step procedure conducted at the follow-up visit.

The above procedures were used for both pairs of lenses. The participant exited the study after wearing the two pairs of lenses. Table 2-3 details step-by-step procedures conducted at each scheduled visit.

This clinical trial was registered with the clinical trials registry: www.ClinicalTrials.gov (Clinical Trial Identifier: NCT05079321).

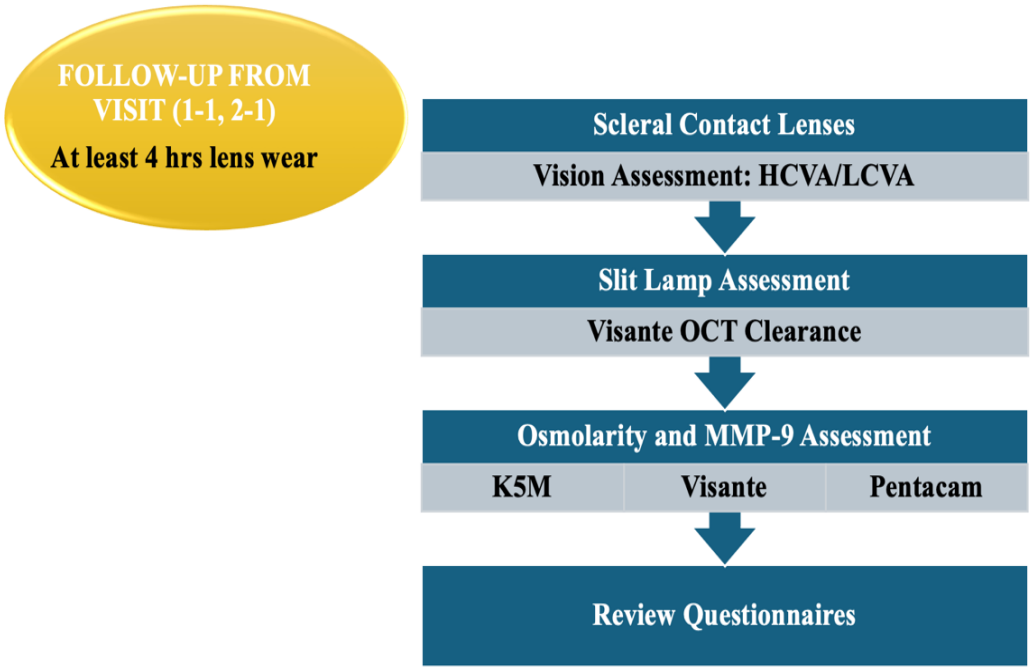


Figure 2-15: Step-by-step procedures at the follow-up visit.

Table 2-3: Summary of procedures at scheduled visits.

Visit	Procedure	Instrument/ Application	Form
Screening, Baseline Visit and Trial Lens Fitting (Visit 0-0)	Informed Consent	-	ICL
	Demographics & Med. History	-	Screening Form
	Ocular Surface Disease and Dryness	Self-Administered Questionnaire	OSDI and SPEED Questionnaires
	Vision Assessment	LogMAR Chart	Study Visit Form for Scleral Lenses
	Osmolarity	Tearlab Osmolarity System	Study Visit Form for Scleral Lenses
	Level Of Protease (MMP-9)	Inflammadry Test Kit	Study Visit Form for Scleral Lenses
	Ocular Surface Imaging	Keratograph 5M (K5M)	Study Visit Form for Scleral Lenses
	Sagittal Depth/Corneal Topography	Visante™ and Pentacam	Study Visit Form for Scleral Lenses
	Biomicroscopy	Slit-Lamp with Camera	Biomicroscopy Form
	Auto-Refraction	Auto-Refractor	Study Visit Form for Scleral Lenses
	TRIAL LENS FITTING		
	Lens Fitting and Examination	Slit Lamp with Camera	Study Visit Form for Scleral Lenses
	Vision Assessment	LogMAR Chart	Study Visit Form for Scleral Lenses
	Lens Fit Evaluation (Clearance)	Visante™	Study Visit Form for Scleral Lenses
Lens Delivery (Visits 1-1, 2-1)	Biomicroscopy/VA	Slit-Lamp with Camera/LogMAR	Biomicroscopy Form
	LENS INSERTION, ASSESSMENT, DISPENSING AND QUESTIONNAIRE		
	Lens Examination	Slit Lamp with Camera	Study Visit Form for Scleral Lenses
	Vision Assessment	LogMAR Chart	Study Visit Form for Scleral Lenses
	Lens Fit Evaluation (Clearance, Etc)	Visante™	Study Visit Form for Scleral Lenses
	Quality of Life Questionnaire	Self-Administered Questionnaire	CLIQ Questionnaire
	Contact Lens Dryness (2x)	Self-Administered Questionnaire	Contact Lens Dry Eye Questionnaire 8
	Wearing Habit and Subjective Ratings (4x)	Analogue Scales	Wearing Habit and Subjective Log Form
Follow-Up Visit (Visits 1-2, 2-2)	Vision Assessment	LogMAR Chart	Study Visit Form for Scleral Lenses
	Lens Examination	Slit Lamp with Camera and K5M	Study Visit Form for Scleral Lenses
	Lens Fit Evaluation (Clearance)	Visante™	Study Visit Form for Scleral Lenses
	CONTACT LENS REMOVAL, ASSESSMENT, QUESTIONNAIRE REVIEW		
	Biomicroscopy	Slit-Lamp with Camera and K5M	Biomicroscopy Form
	Corneal Topography	Visante™ and Pentacam	Study Visit Form for Scleral Lenses
	Osmolarity	Tearlab Osmolarity System	Study Visit Form for Scleral Lenses
	MMP-9	Inflammadry Test Kit	Study Visit Form for Scleral Lenses
	Questionnaire Review	CLDEQ-8, CLIQ, Wearing Habit & Subjective Ratings	N/A
	Participant Exists Study	-	Remuneration Form

CHAPTER 3

3.1 Evaluation of Scleral Contact Lens Wear and Dry Eye Questionnaires

3.2 Introduction

Dry Eye Disease (DED), like most clinical conditions, produces specific symptoms and signs which can directly or indirectly be measured in clinical settings. (1, 2) Interestingly, the symptoms are known to precede the clinical signs and may be the driver which causes patients to seek medical attention. (3) Numerous studies have reported the mismatch between the symptoms and ocular signs of DED, except in severe situations. (4-9) Also, it has been established that self-reported symptoms do not always correlate with improved clinical measurements post treatment, which often include, and typical examples are reduced tear break-up time, ocular surface inflammation and osmolarity levels in the precorneal tear film. (10) Thus, it may be evident that clinical treatment that is initiated may improve clinical signs, without necessarily improving symptoms that affect an individual's daily activities. (10, 11) According to Begley et al, (11) ocular discomfort and dryness are the most frequently reported symptoms in patients with dry eye (DE), and these tend to worsen over the course of the day. Also, they noted that patient symptoms influence DE diagnosis and grading score and correlate significantly compared to other clinical signs or test results. Other commonly reported DE symptoms are grittiness, itching, irritation, burning, redness, photophobia, tearing, puffy eyelids and crusty eyes. (12-14)

Clinically, to quantify these presenting symptoms, many clinical questionnaires/surveys have been developed. (7) Some of these questionnaires focus primarily on symptom assessment, which determines the frequency, severity, and environmental impact of the condition (e.g.: OSDI, SPEED, MCQ etc.). Others also focus on monitoring the impact of treatment on symptoms over time, treatment satisfaction, and quality of life (QoL). (12, 15, 16)

Today’s DED treatment includes over-the-counter-lubricants (17, 18) warm compresses, (19-22) antibiotics, (23) non-steroidal and steroidal anti-inflammatory medications (24, 25) and more advanced treatments such as autologous serum treatment. (26-29) Medical devices such

as intranasal electrostimulation (30) have been employed to boost tear production in order to alleviate symptoms. Available studies show that treated patients reported high satisfaction rate with improved symptoms. (10, 31)

One of the treatment options which has not been explored in detail as a ***first line*** of treatment option for individuals experiencing mild to moderate forms of DED is the wearing of scleral contact lenses (SL). The advantages offered by SL in the management of ocular surface diseases cannot be underestimated in current clinical practice, (32, 33) with available studies suggesting that SL could provide valuable options in the treatment of DED. (34, 35) Firstly, the fluid reservoir offered by the SL may provide relief to the burning sensation often experienced in dry-eye as well as promote re-epithelialization, through a combination of oxygenation, moisture, and protection of the compromised corneal epithelium from the external environment. (36) Added to the above benefits is the advancement in technology, particularly the introduction of Hydra-PEG (polyethylene glycol) coatings on the SL surface. This technology is touted as an innovative way of significantly improving SL comfort levels and the wearing time of lenses for DED patients. (37) Also, the smooth nature of the coating technology is known to reduce the mechanical friction between the front surface of the lens and the tarsal plates of the eyelids. (38) According to Mickles et al, (38) Hydra-PEG coated lenses significantly improved lens comfort, DE symptoms and the presence of conjunctival papillae compared to uncoated SL among DED patients. Regardless of the empirical evidence, SL are typically relegated to complicated corneal cases and not fully utilized for DED until the condition has progressed to an advanced or more severe stage. (32, 39, 40)

Perhaps one of the key factors to limit the clinical use of SL relates to the relatively complicated fitting process, which requires specialized clinical skills and chair time. Another reason is the lack of standardized clinical procedures for assessing the impact on DE symptoms and evaluation of SL-related dryness and how to resolve the symptoms.

Traditionally, clinical outcome measures in SL wearers have been characterized by visual acuity (VA), contrast sensitivity, and/or subjective comfort ratings. (41-43) More recently, an assessment of QoL and other standardized questionnaires have been employed to determine the impact and efficacy of various factors on SL wearers. However, as mentioned earlier in chapter 1, the majority of studies have been carried out on individuals with complicated corneal problems. (44-47) Although these outcome measures provide important information about SL wear, it is very difficult to generalize these measures on complex cases to those patients with mild to moderate DED. Additionally, these give little information about the impact on DE symptoms and daily assessment of SL wear.

While the potential value of SL wear on DED has been reported on moderate to severe dry eye, no study has investigated their potential on patients experiencing mild to moderate DED. The difference in severity in symptoms may result in SL wear having no significant impacts in mild to moderate patients. It is thus important to investigate SL wear in this population to collect clinical data that can help inform future decisions on DED treatment options in mild/moderate dry eye.

The purpose of this study was to:

a) Evaluate the impact of coated and non-coated SL wear on DE questionnaire, specifically on QoL, contact lens related dryness, wearing habit and subjective ratings in patients with mild-moderate DED;
b) To compare the clinical performance of uncoated and coated SL in this patient cohort.

3.3 Objectives

The main objectives of this study were to:

1. Evaluate the QoL and contact lens related dryness scores using standardized clinical questionnaires comparing uncoated and coated SL;
2. Examine the wearing habits and subjective ratings comparing the two lens types;
3. Determine the relationship between the DE questionnaires.

3.4 Methodology

This study was a prospective, double-masked, randomized, dispensing cross-over clinical trial which was carried out at the School of Optometry and Vision Science, University of Waterloo, ON, Canada. The study protocol was approved by the University Research Ethics Board and adhered to the tenets of the Declaration of Helsinki. The details of the study protocol outline, clinical visits including screening and baseline line, dispensing and follow-up have been described in detail in Chapter 2.

The study used three main questionnaires to evaluate the impact of SL on DED symptoms. These were Contact Lens Impact on Quality of Life (CLIQ), Contact Lens Dry Eye Questionnaire 8 (CLDEQ-8) and Wearing Habit and Subjective Ratings questionnaires. These questionnaires were thoroughly explained and given to each participant during the dispensing visits and collected at the follow-up visits, where they were reviewed for their completeness. Table 3-1

3.4.1 Quality of Life Questionnaire

To understand the QoL of SL wear on the subjects, the CLIQ questionnaire was used. (11, 48, 49) This self-administered questionnaire uses 28-item questions which are categorized into five main parameters: ***daily activities, eye symptoms, functional vision, psychometric properties, and refractive correction.*** Each question has a five-step response scale (*1, 2, 3, 4, 5*) of which the participant chooses one to grade their response. The questionnaire is designed in such a way that questions 1 to 20 (*lower score is better*) have divergent responses to questions 21 to 28 (*higher score is better*). (48, 50) This reversed concept is intended to give an overall higher score for better QoL. (Refer to Chapter 2 appendix 2-9) The average of these 28 questions gives the CLIQ raw score, which is then converted to CLIQ person measure using the formula:

$$\mathbf{CLIQ_{person\ measure} = 34.41 \times \log (CLIQ_{raw\ score}/5 - CLIQ_{raw\ score}) + 26.69}$$

This is then analyzed on a scale from 0 to 100, where higher scores indicate better QoL.

3.4.2 Contact Lens Dry Eye Questionnaire 8

To understand the impact of SL on the ocular surface and record the participants' response to discomfort and dryness, the Contact Lens Dry Questionnaire 8 (CLDEQ-8) was used. (51-53) This self-administered 8-item questionnaire is completed biweekly to determine the degree/intensity of ocular surface symptoms while wearing contact lenses. The graded score is used as a management tool to resolve the symptoms in a clinical situation. It comprises five sections: ***discomfort, dryness, changeable/blurry vision, closing the eyes and removing lenses.*** The response scale ranges from 0 to 4/5 depending on the question and the overall score is determined by adding all the responses. (Refer to Chapter 2 appendix 2-8) The score range is 0 to 37, with a higher score indicating greater symptoms.

3.4.3 Wearing Habit and Subjective Rating

This questionnaire was developed internally at the University of Waterloo to understand participants' wearing habits, such as hours of lens wear, number of days lenses are worn and subjective symptoms for each pair of the SL used in the study. This self-administered, 5-item daily questionnaire comprises ***hours of lens wear, dryness, burning, vision, and overall comfort ratings***. (Refer to Chapter 2 appendix 2-10) The response scale ranged from 0-100 (zero-worse possible, 50-average, 100-absence of symptoms) and each question is answered daily after lens wear for each eye. The questionnaire also provided a "comment" section for supplementary data such as experience with "midday fogging, headache, severe redness, itching, lens application or handling challenges" or any other symptom or experience not captured in the questionnaire while wearing the lenses. The responses were aggregated at the end of each week to determine the overall wearing habit and subjective ratings.

Table 3-1:Study Visits and Questionnaires Dispensed and Collected for Completeness.

Visits	Contact Lens Questionnaires		
	CLIQ (monthly/1x)	CLDEQ-8 (bi-weekly/2x)	Wearing Habit and Subjective Ratings (daily/4x)
Screening and baseline	-	-	-
Dispensing for Lens 1 & 2	Yes	Yes	Yes
Follow-up for Lens 1 & 2	Yes	Yes	Yes

CLDEQ-8: Contact lens dry eye questionnaire-8, CLIQ: Contact lens impact on quality-of-life questionnaire, x: number of questionnaires dispensed at the dispensing visits.

3.5 Data Management and Statistical Analysis

Data analysis was conducted using Statistica 13.5 (TIBCO Statistica™. Inc., Tulsa, OK, USA). The means and SD were used to analyze the demographic characteristics, screening and baseline measurements, overall scores of CLIQ, CLDEQ-8 and wearing habit and subjective ratings. An independent t-test was used to determine the statistical significance between the lens types along with the questionnaires used in the study. P values of ≤ 0.05 were considered statistically significant. Pearson and Spearman correlations were also performed to determine the relationship between the measured parameters of the CLIQ, CLDEQ-8 and wearing habit and subjective ratings.

3.6 Results

3.6.1 General Results and Baseline Demographics of the Study

3.6.2 Results from Screening and Baseline Visit

There were 18 females and two males enrolled in the study. Their mean age and standard deviation (SD) were 29.10 ± 7.48 (range: 21- 47) years. The overall OSDI and SPEED scores were 36.45 ± 17.08 and 12.50 ± 4.03 respectively. The habitual VA presented at the screening visit was 0.12 ±

0.24 for high contrast visual acuity (HCVA) and 0.52 ± 0.32 low contrast visual acuity (LCVA). Table 3-2 shows the demographic characteristics at the screening and baseline visit.

Table 3-2: Demographic Characteristics at the Screening and Baseline Visit.

Demographics	Scores
Age	29.10 ± 7.48 years
Sex	Female (n=18, 90%), Male (n=2, 10%)
OSDI	36.45 ± 17.08
SPEED	12.50 ± 4.03
Contact Lens Wearers	(n=10, 50%)
Frequency + Lens type	Daily disposable CL (n=8, 80%), Monthly replacement CL (n=2, 20%)
Comfortable wearing time	2.40 ± 3.20 hours
Years of Lens wear	3.20 ± 4.00 years
Spectacle wearers	(n=7, 35%)
Non-spectacle wearers	(n=3, 15%)
Allergies (pollen/dust)	(n=6, 30%)
Concretions	(n=3, 15%)
Suspected MGD (with lid notching)	(n=3, 15%)
NaFl Staining	(n=10, 50%)
Cornea	(n=4, 20)
Conjunctiva	(n=6, 30%)
Habitual VA	
HCVA	0.12 ± 0.24
LCVA	0.52 ± 0.32

CL: Contact lenses, HCVA: High contrast visual acuity, LCVA: Low contrast visual acuity, MGD: Meibomian Gland Disease, NaFl: sodium fluorescein, OSDI: Ocular Surface Disease Index, SPEED: Standardized Patient Evaluation of Eye Dryness, VA: visual acuity, N: Number of subjects, n=20.

3.6.3 Results on Ocular Characteristics with Scanning Instruments

As part of the screening and baseline measurements, Pentacam HR and Visante™ OCT were used to take a scan of the anterior segment of the eye. Two measurements of corneal topography were taken with the Pentacam. The mean and SD of radius of curvatures (K-reading) were 43.91 ± 1.44 and 43.84 ± 1.40 for right eye (OD) and left eye (OS) respectively. The corneal characteristics measured with the Pentacam are reported in Table 3-3.

Table 3-3: Summary of the ocular characteristics measured with Pentacam and Visante™ OCT at the screening and baseline visits.

Eye	K-reading (D)			HIVD (mm)	Cylinder (-) D	Axis (degrees)	Eccentricity (e)
	Flat	Steep	Average				
OD	42.12 ± 1.31	43.91± 1.44	43.1 ± 1.26	11.75 ± 0.46	1.63 ± 0.88	74.83 ± 80.15	0.54 ± 0.14
OS	42.25 ± 1.25	43.84 ± 1.40	43.03 ± 1.25	11.79 ± 0.49	1.58 ± 0.82	106.43 ± 83.68	0.51 ± 0.16

D= Diopter, HVID= Horizontal visible iris diameter, K: Radius of curvature, mm= Millimeters, OD: Right eye, OS: Left eye; n=20.

Two scans of the anterior segment with the Visante™ OCT were also taken to measure the corneal sagittal depth (CSD). Table 3-4 shows the means and SD of CSD for OD and OS respectively. These parameters were used as supplementary data for selecting a diagnostic SL for fitting the participants.

Table 3-4: Summary of CSD with the Visante™ OCT at the screening and baseline visit.

Eye	Chord measurement for lens diameter on the eye	
	14.80 mm (n=11)	15.40 mm (n=9)
OD	3.43 ± 0.28	3.81 ± 0.18
OS	3.41 ± 0.25	3.78 ± 0.19

CSD: Corneal sagittal depth, mm: Millimeter, OD: Right Eye, OS: Left Eye, n=20

3.6.4 Results of the Scleral Lens and Dry Eye Questionnaires

The mean CLIQ score (person measure) for uncoated and coated SL across all follow-up visits were 38.66 ± 11.45 (range: 24.53 - 64.89) and 40.62 ± 10.16 (25.01 - 64.89) respectively. There was no statistically significant difference ($p = 0.57$) between the two lenses, although coated lenses had a slightly higher overall CLIQ score compared to uncoated lenses. Figure 3-1 shows the box and whisker plot comparing the overall mean scores of each lens type.

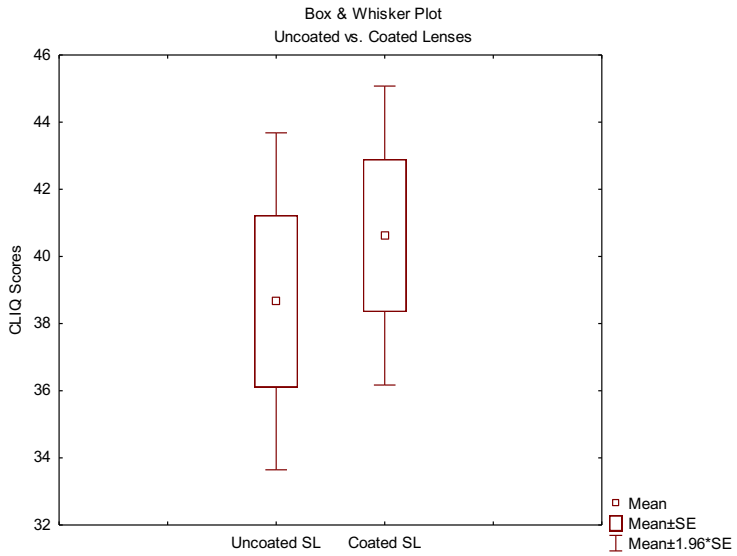


Figure 3-1: Box plots of mean CLIQ score comparing uncoated and coated SL after four weeks of lens wear using the CLIQ questionnaire.

CLIQ: contact lens impact on quality of life, SL: scleral contact lenses. CLIQ scores comparing uncoated and coated SL. Data were collected and calculated after four weeks of SL wear, n=20.

The overall mean CLDEQ-8 score after four weeks of SL for uncoated and coated SL were 17.58 ± 7.20 and 16.85 ± 7.19 respectively. Table 3-5 shows biweekly assessment of each lens type and the *p*-values. There was a significant difference within the uncoated lens ($p = 0.05$), however, no significant difference was observed in the coated lenses ($p = 0.33$) for the bi-weekly assessment. It can be inferred, therefore, that participants had a slightly more difficult time adapting to the uncoated lenses, with slightly higher symptoms within the first two weeks before the symptoms reduced. This was not the case with the coated lenses, as the symptoms appeared to be well tolerated over time. Comparing the two lens types during the four weeks of lens wear, no significant difference was found ($p > 0.05$). Thus, coated lenses did exhibit marginally reduced symptoms (lower scores) compared to uncoated lenses during the four weeks of SL wear, but these differences were not statistically significant.

Table 3-5: Mean and SD of CLDEQ-8 bi-weekly scores comparing uncoated and coated SL after four weeks of lens wear using CLDEQ-8 questionnaire.

CLDEQ-8	**Uncoated Lens** *p= 0.05*	**Coated Lens** *p= 0.33*	**P- values**
Weeks 1-2	18.30 ± 6.86	17.20 ± 7.38	0.63
Weeks 3-4	16.85 ± 7.83	16.50 ± 7.35	0.88

CLDEQ-8: Contact lens dry eye questionnaire 8. CLDEQ-8 scores determine participants' response to discomfort and dryness and are completed bi-weekly after lens wear. The means and standard deviations were calculated bi-weekly as per the design of the questionnaire after four weeks of SL wear, n= 20.

The wearing habit and subjective ratings were assessed for each eye and preliminary results showed no significant differences ($p > 0.05$) for all the symptoms comparing right and left eyes. Therefore, data analysis was performed on the OD data only.

The wearing habit and subjective ratings of each pair of the SL were evaluated and Pearson and Spearman correlation performed to determine the relationship between each of the symptoms measured. The means and SD of the number of days the SL were worn per month were 26.00 ± 3.42 and 26.10 ± 3.65 for uncoated and coated lenses respectively. Table 3-6 shows the overall means of hours of lens wear, dryness, burning, vision, and comfort ratings after the four weeks of lens wear. There were no statistically significant differences between all the measured parameters ($p > 0.60$) comparing uncoated to coated SL. Pearson and Spearman correlation showed a significant negative correlation between CLIQ and CLDEQ-8 questionnaires for all the lens types ($r > -0.50$, $p < 0.05$). This shows that as the CLIQ value increases in QoL, the CLDEQ-8 score decreases (symptoms reduces). Figures 3-2 and 3-3 illustrates the correlations between CLIQ and CLDEQ-8 questionnaires for uncoated and coated lenses respectively. Additionally, a significant correlation within and between uncoated and coated lenses was identified for most parameters, except dryness and vision for the coated lenses ($p < 0.05$, $r > 0.60$). For example, Figure 3-4 shows

the significant correlation between burning and dryness of uncoated lenses, which implies that as symptoms of burning improve overtime (mean 81.53 ± 22.39), so does dryness (mean 73.47 ± 12.23); they also appear to act similarly. A similar pattern was also reported for the coated SL (burning: 83.70 ± 21.57 versus 76.51 ± 21.15), with no correlation found between vision and dryness, Figure 3-5. The details of the weekly wearing habit and subjective ratings for all the lens types are reported in the appendices. (Appendix 3-1)

Table 3-6: Mean and SD of wearing habit and subjective rating comparing uncoated and coated SL.

Measured Parameters	**Uncoated SL**	**Coated SL**	**P-Values**
Hours of lens wear (hours)	7.18 ± 1.75	7.16 ± 1.61	0.97
Dryness	73.43 ± 19.55	76.02 ± 21.78	0.69
Burning	82.18 ± 21.69	83.60 ± 22.16	0.84
Vision	71.71 ± 22.69	71.01 ± 22.61	0.92
Comfort	74.52 ± 17.83	73.01 ± 20.81	0.81

SL: Scleral contact lenses, SD: Standard deviation, The means and standard deviations of the parameters were calculated from all the daily scores after four weeks of lens wear using wearing habit and subjective ratings questionnaire, n=20. For weekly estimates refer to Appendix 3-1.

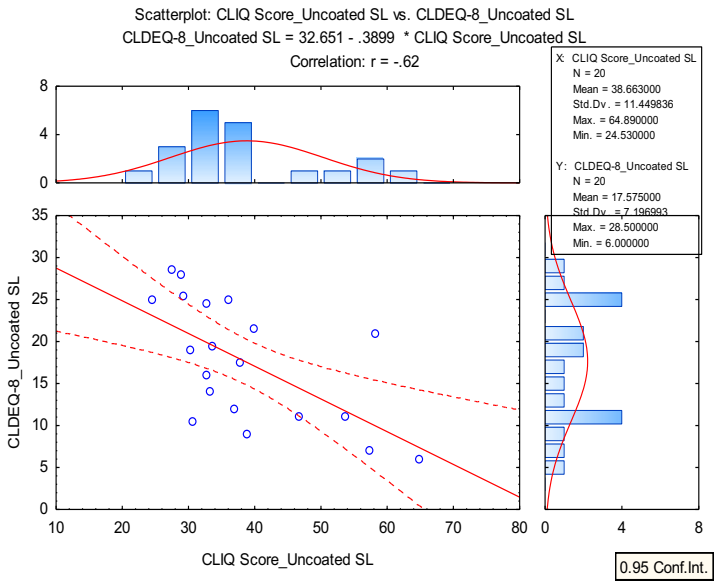


Figure 3-2: Significant inverse correlations between CLIQ and CLDEQ-8 for uncoated SL.

CLDEQ-8: contact lens dry eye questionnaire 8, CLIQ: contact lens impact on quality-of-life questionnaire, n=20. CLDEQ-8 scores determine participants' response to discomfort and dryness and are completed bi-weekly after lens wear. CLIQ scores determines the quality of life and are completed after four weeks of lens wear.

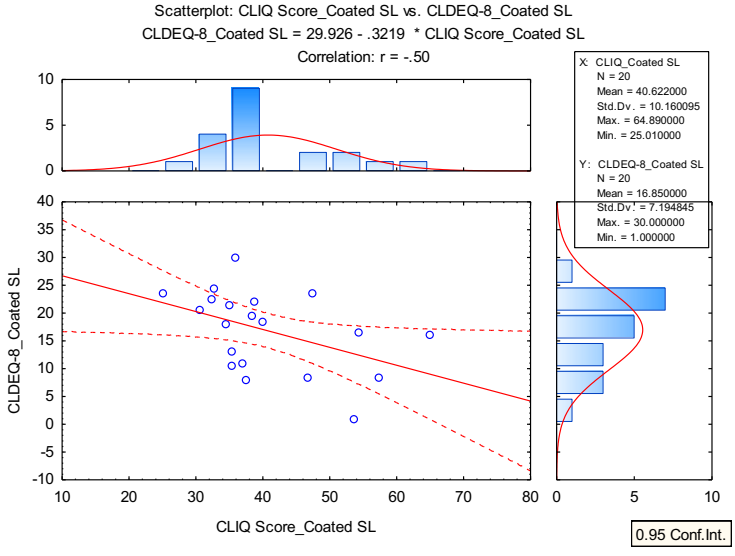


Figure 3-3: Significant inverse correlations between CLIQ and CLDEQ-8 for coated SL.

CLDEQ-8: contact lens dry eye questionnaire 8, CLIQ: contact lens impact on quality-of-life questionnaire, n=20. CLDEQ-8 scores determine participants' response to discomfort and dryness and are completed bi-weekly after lens wear. CLIQ scores determine the quality of life and are completed after four weeks of lens wear.

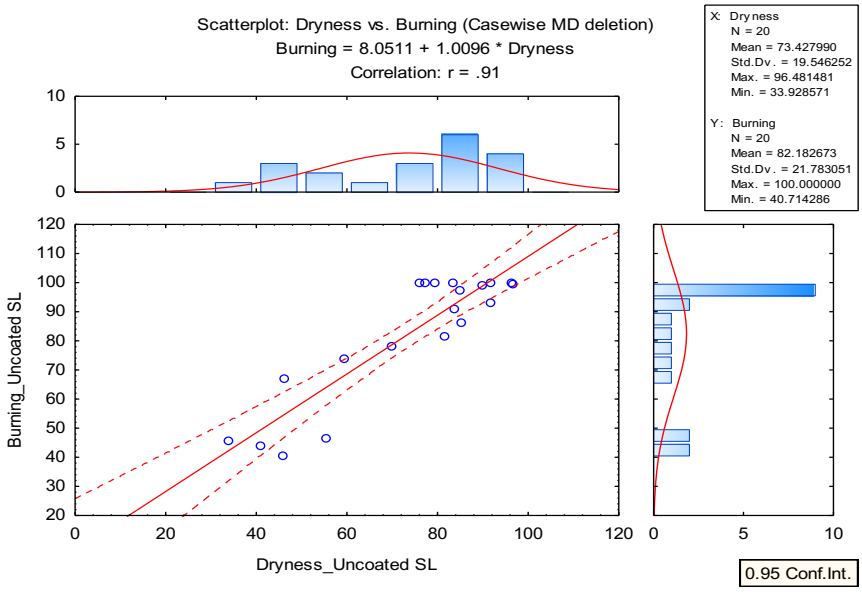


Figure 3-4: Significant correlation between burning and dryness for uncoated SL.

Dryness and burning after four weeks of lens wear was determined using the wearing habit and subjective rating questionnaire, n=20.

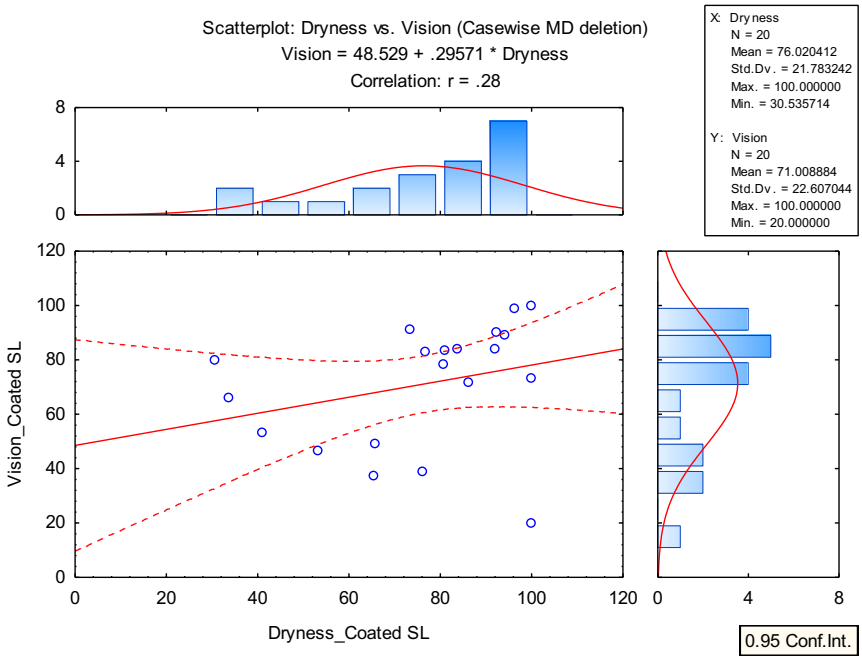


Figure 3-5: Lack of correlation between vision and dryness for coated SL.

The only no correlation graph among the measured parameters was plotted by graphing vision against dryness to determine the relationship between these two parameters after four weeks of lens wear, n=20.

3.7 Discussion

The fitting of SL has increased over the past few years and its impact within the contact lens industry cannot be underestimated. (54-56) Reports suggest that a growing number of clinicians are fitting SL lenses, and SL currently account for 13 % of all rigid contact lenses (RGP) fitted and dispensed in clinical settings.(55, 57). The utility of SL has also expanded and Schornack et al (58), in a survey of 259 patients, reported that SL were dispensed to 87 % of the patients with various corneal ectasia, while 9 % were dispensed for ocular surface disease management. In another related study (SCOPE Study) of 673 subjects, 74 % of the subjects wore SL for corneal irregularities while 16 % accounted for ocular surface diseases. (55) The successful use of SL have been attributed to wider availability, improvement in lens designs, enhanced fitting philosophies and increased oxygen transmissibility of the materials available for SL. According to Harthan et al, (54) more than 50 SL designs were reported to have been dispensed to patients. Furthermore, SL success can be attributed to the fact that SL do not touch the area of greatest sensory nerve

terminal density on the ocular surface, which are located in the cornea, and this may thus contribute to improved comfort for patients. (59, 60)

Despite the growing use of SL over the past 10 years, there is a paucity of studies conducted on QoL, assessment of SL dryness and most importantly daily wearing habit and subjective ratings on "normal" subjects experiencing mild to moderate DED. The purpose of the study was to determine the impact of SL on QoL, CLDEQ-8 scores and wearing habit and subjective ratings while wearing uncoated and coated SL in a randomized clinical trial.

It is evident from the lack of statistical significance in our results that the hydra-PEG coating on the lens surface did not improve the QoL of subjects in this cohort with mild to moderate DED. Using the same 28-item questionnaire on KC subjects, Ermurdus et al (49) reported a mean CLIQ person measure as 45.50 ± 8.20 in a group of subjects wearing gas permeable lenses, 45.40 ± 7.50 in a group of subjects wearing hybrid lenses and 48.40 ± 10.50 in a soft toric-wearing group. There was no significant difference between the lens types ($p = 0.80$). They concluded that contact lenses significantly improved the visual outcome in KC subjects, hence the influence on overall QoL. Pesudovs et al. (41) reported a mean CLIQ person measure on healthy soft contact wearers with at least 1 year of lens experience as 51.20 ± 6.20. The reported QoL with SL in this current study are lower than those reported in the above cited studies. It is worth noting that only 50 % (n=10) of the participants in this current study had any prior contact lens experience and all of these were with soft lenses. The remaining participants had no experience and presented at the study wearing spectacles or without any vision correction. Wearing contact lenses with such large diameters (14.80 or 15.40 mm) that are fairly thick (250 μm) presents significant handling and adaptation challenges, coupled with daunting tasks of daily disinfection, insertion, and midday fogging and these issues may explain the lower recorded scores in this study.

Generally, the CLDEQ-8 questionnaire is used clinically to quantify symptoms associated with contact lens dryness, which is important for assessing lens performance. (51) This 8-item questionnaire, which is completed biweekly, reports on the overall subjects' perceived symptoms

and coping strategies while wearing the contact lenses and how these symptoms can be eliminated overtime. To the best of our knowledge, no previous study has investigated CLDEQ-8 scores for SL wearers who do not have ocular disease and are relatively normal participants experiencing mild to moderate DED. It is therefore difficult to determine whether the overall reported scores of 17.58 ± 7.20 for uncoated SL and 16.85 ± 7.19 for coated SL could be used to inform if modification of the lens design or further management may be required to reduce the effect of SL dryness. However, this study determined these values from a small population (20 subjects) and therefore their clinical significance must be interpreted with care. In the case of soft contact lenses, Chalmers et al (51) reported a diagnostic cutoff ≥ 12 points, with clinical difference of ± 3 points on CLDEQ-8 scale. They suggested that in situations where there is reported higher contact lens dryness, modification or replacement of the lenses would be required. To determine SL related dryness, Mickles et al (38) used the criterion ≥ 12 points in soft contact lenses in their study and reported 24.70 ± 6.70 for SL as their baseline score. Following SL wear in their study cohort, the reported mean CLDEQ-8 was 17.30 ± 6.50 for uncoated SL and 11.90 ± 5.30 for hydra-PEG coated lenses which was significantly different from the baseline scores. These relatively lower and significant scores are not surprising as the study focused on established SL wearers with complicated corneal diseases and severe DED. Also, subjects were selected based on their ability to comfortably wear SL for 8 hours in a day and 5 days in a week. In the case of our study, only 50 % of the subjects had prior contact lens experience (only soft lenses) and all subjects had mild to moderate DED with no associated ocular or medical condition.

According to the TFOS International Workshop on Contact Lens Discomfort, the clinical management often employed in subjects reporting poor CLDEQ-8 scores typically starts with refitting the subject with a different contact lens material, increasing their replacement frequency, prescribing lubricants, or changing the care solution if there is evidence of solution toxicity. (51, 61) To overcome this challenge and avoid refitting visits in our study, all the lenses were carefully examined under the slit lamp biomicroscope to make sure the lenses vaulted adequately over the cornea and limbal area and that lens fit was optimized. Also, scans with the Visante™ OCT were performed to ensure the scleral haptic aligned with the scleral area to avoid impingement and blanching, which could contribute to SL discomfort. Participants who were initially uncomfortable

with a toric lens edge design during the trial fitting process were refitted with spherical lenses and vision optimized before dispensing. Thus, any reported response was based on the participant's own experience with the SL.

One of the parameters which have been used to determine the success of SL wear is the number of hours, days, and or months that lenses are worn. Unfortunately, there is no established number of hours of lens wear in a day that can ultimately determine "the success" of SL wear. This stems from the fact that different authors have cited different wearing times in hours to be considered "successful" lens wear. (62-66) The underlying factors are study design, diagnosis, fitting methods, lens diameter, lens material and the number of hours stipulated by the manufacturer for optimum wear. The general consensus is that 8 - 10 hours/per day may be considered optimum for most subjects wearing SL, (62, 63) which is clearly lower than that which would be expected for typical soft lens wear. Overall number of hours and days of SL in our study were 7 hours per day (range: 3.60 - 11.10 hours) and 26 days (range:15 - 28) in a month, which agrees with previous reports. (62, 67) Macedo-de-Araújo et al, (67) reporting on a one-year prospective study to determine SL wear success in both regular and irregular corneal groups, reported a daily wearing time between 9.80 - 11.10 hours and 5.10 - 5.60 days/per week. Interestingly, these were new SL wearers, and the success rate was estimated at 77 % in subjects with corneal irregularities of different etiologies, and 58 % in participants with healthy corneas. The reasons cited for the low success rate in healthy subjects were handling issues and discomfort. Pullum et al. (66) reported a mean wearing time of 10 hours in 59 % of the patients (n = 538) and Ortenberg (62) also reported 10.50 hours/day (range, 2 - 18 hours). Our wearing time data is similar to that of these previous reports, and it is evident from our study that the hydra-PEG coating did not contribute to longer wearing times in our subjects.

Considering the parameters from the wearing habit and subjective ratings scores, (Table 3-6) burning was reported at the highest percentage (around 82 %), indicating that participants experienced least burning sensation while wearing the lenses compared to all other parameters collected. Subjects' perceived vision with the lenses recorded the lowest percentages (around 71

%) and thus higher dissatisfaction, which can likely be attributed to midday fogging affecting the overall perception of vision. Comfort and dryness ratings were estimated at approximately 75 % while wearing each lens type. These subjective ratings are the first of their kind reported on normal participants experiencing mild to moderate forms of DED. Since there are no established cut-off points to compare our results, it is very difficult to suggest that these scores can be used to make any clinical decision, however, they do provide some valuable information on subjective assessments while wearing the SL.

The strength of this study is based on the randomization of the SL and the use of multiple questionnaires to understand the pattern on QoL, SL-related dryness and wearing habits and subjective ratings. These questionnaires provided valuable information amongst healthy participants wearing SL to determine its impact on their DED. Regardless of the low scores in QoL, and "high" CLDEQ-8 scores, they provide a template upon which other studies can be built. One of the limitations of the study is sample size. The study faced significant challenge in recruiting participants as it was initiated and conducted during the COVID-19 pandemic, therefore, generalizing the results beyond this sample size would be erroneous. The internally generated wearing habit and subjective questionnaire, while not validated, assessed subjects' daily wearing symptoms which were graded in percentages, therefore, there may be subject to some form of bias and other confounding factors. Regardless, they provided valuable information on subjects perceived wearing behavior. Another limitation is that the study did not measure the baseline scores before dispensing and wearing of the lenses for four weeks to assess the change in treatment scores, and thus it is difficult to determine the full impact of scleral lens wear on DED symptoms. Additionally, a significantly higher numbers of female participated in the study, and as such the study is not balanced for sex differences in the population. However, it is recognized that women are disproportionally affected by DED; for example, a large DED study by Vehof et al (68) reported 80.40 % of the study population being female. In the case of our study, women represented 90 % of our study population, and thus while a little higher, the sex composition of our study population aligns with the higher prevalence of DED in women.

In conclusion, this study represents the first attempt to characterize SL-related QoL in healthy participants with mild to moderate DED but no corneal ectasia or frank ocular surface disease using the CLIQ questionnaire, CLDEQ-8 and overall perceived wearing habit and subjective ratings questionnaires. There were no statistically significant differences observed among the parameters comparing uncoated and coated SL. Based on the CLDEQ-8 and CLIQ results, the hydra-PEG coating on the SL did not improve performance over uncoated SL in this study cohort.

CHAPTER 4

4.0 Scleral Contact Lens Settling and Its Effect on Vision

4.1 Introduction

The concept of "lens settling" post placement on the eye is an important part of the lens fitting process for both small diameter rigid lenses and SL. (1, 2) This phenomenon when fitting traditional rigid lenses is somewhat different than when fitting SL as it relates to determining the fluorescein pattern and the fitting characteristics after lens insertion. (3) Upon insertion, RGP lenses induce reflex tearing, and this may be compounded if the lens has a drop of conditioning solution applied to the lens to improve initial comfort for the patient. This makes it extremely difficult to initially assess the fit of the lens and clinicians will typically have to wait for 10 to 20 minutes for the tears to dissipate and for the lens to be stabilized ("settled") on the cornea before lens assessment with fluorescein. (4)

For SL, this concept is even more complicated owing to the fact that the lenses are fitted to completely vault over the corneal and limbal areas to rest on the sclera and the lenses will "settle" down against the eye with the passage of time. Therefore, a better understanding of this clinical feature is important to optimize lens fitting characteristics as it relates to vision, comfort, and overall health status of the eye. There is no accepted definition for lens settling, however, Cerenzie (5) describes it as a "process in which the SL haptic/landing zone sinks into the compressible underlying scleral conjunctiva, which results in a flatter and tighter-fitting lens." This process reduces the distance between the front surface of the cornea and the back surface of the SL and is quantified as the *clearance loss* or more clinically *lens settling*. (1, 6-8) Clinically, the practitioner can estimate the amount of clearance and change in vault by obtaining an optic section with the slit lamp biomicroscope (usually at an angle between 30 to 60 degrees) and comparing this thickness with a known thickness, typically the thickness of the SL or the thickness of the cornea. (9, 10) However, according to Yeung and Sorbara, estimating the amount of corneal clearance using this technique, and most importantly determining the clearance loss, is extremely difficult as there is a tendency for clinicians to subjectively overestimate the amount of clearance loss by

approximately 103.30 μm. (11) Interestingly, this overestimation can occur even for experienced practitioners. (11) Fuller et al (12) also reported that inexperienced SL practitioners significantly overestimate the amount of corneal clearance in normal subjects with declining accuracy as the lens settles overtime. To overcome these issues of inaccurate clinical assessment of lens clearance between the cornea and the lens and the degree to which the lens settles back against the eye, imaging using optical coherence tomography (OCT) allows this critical parameter to be accurately measured. (8)

It is recognized that a poorly fitted SL in which the haptic is not appropriately aligned with the scleral conjunctiva can significantly affect the fitting characteristics and induce complications such as compression and blanching, which may ultimately affect vision, comfort, and conjunctival vasculature. (13) Likewise, a well aligned scleral landing zone on the conjunctiva with optimal corneal vault can change drastically to a less-than-ideal fit overtime. (13) The cause of this SL "sinkage" into the conjunctiva is not fully understood, however, one of the factors which has been hypothesized to influence lens settling is "*suction force*". (14) According to Caroline et al, (15) once the SL is fitted on the eye, this suction force gradually pulls or draws the back surface of the contact lens towards the cornea during the wearing period. This eventually seals off the lens with the surrounding conjunctival tissue. They also pointed out that SL diameter plays a critical role, as a bigger SL creates a greater suction force and could contribute to a greater lens settling time compared to smaller diameter lenses. (13) However, it has been argued by Aldridge (14) that if lens settling is predominantly caused by this suction force, then, it should occur immediately after lens application as this force does not increase over time. Moreover, this force, if fully responsible, should decrease tear exchange during lens wear, but studies have shown that tear exchange occurs and lens settling continues up to 8 hours post lens insertion. (2, 16-19)

The conjunctiva upon which the SL lands is also known to be important in the degree to which the lens "settles" back onto the eye. (20) The compressible and elastic nature of the conjunctiva allows the SL to *"sink in"* to compress the tissues causing lens settling, and the degree of compression is known to vary among individuals. (1, 14) It has been demonstrated by Kaufmann et al (2) that the

SL design may also play a role, as some lenses have a larger landing zone, while others are narrower. Scleral contact lenses with broader landing zones have a bigger surface area against the conjunctiva, resulting in less deep compression. In comparison, a small landing zone will cause increased conjunctival compression, eventually causing significant lens sinkage. This concept has also been demonstrated with study by Nau et al, (21) as different lens designs compressed the conjunctiva by different amounts. Therefore, a careful consideration of lens settling patterns of different SL designs should be taken into consideration during SL assessment.

Another factor known to cause lens settling is the lid force. A recent study by Alonso-Caneiro et al (20) shows that the lid force contributes significantly to morphological changes of the conjunctiva (causing compression), which ultimately affect lens settling. Interestingly, the lid force has a specific and varied effect on each quadrant of the eye. They reported the lid force exerts a greater compression effect of - 49.9 ± 8.5 μm in the superior quadrant compared to the other quadrants. Also, they concluded that 70 % of compression occurs at the conjunctiva/episclera area relative to the underlying scleral tissue.

Regardless of the significant evidence that lens settling occurs over time and in part is related to lens design, elasticity of the conjunctival tissue, eyelid force, and suction force, little is known about the impact of a lens coating such as hydraPEG on lens settling and its effect on vision. Therefore, the purpose of this study was to determine the effect of uncoated and coated SL on lens settling and its effect on vision.

4.2 Objectives

The main objectives of this section of the study were to:

1. Determine the amount and change in lens settling of each lens type comparing uncoated and coated SL.
2. Determine the effect of lens settling on high and low contrast visual acuities and the relationship between these parameters.

4.3 Methodology

4.3.1 Study Design

The research design, participants, recruitment and inclusion and exclusion criteria have been described in detail in chapters 2 and 3. This section and sections 4.2.2 and 4.2.2.1 contain excerpts which were adopted and reproduced from my thesis submitted to the University of Waterloo, School of Optometry and Vision Science titled : *"Use of OCT and Oculus Pentacam HR® as Aids in Semi-Scleral Contact Lens Fitting, 2013".* (22) This current study used the same clinical instruments/devices and techniques as described below to clinically to take anterior segment scans with the Visante™ OCT.

4.3.2 Central Corneal Clearance Measurement with Visante™ OCT

The Visante™ OCT was used to scan the SL on the cornea. The participants were comfortably seated and properly adjusted on the chin rest making sure that their forehead contacted the forehead rest. The examiner set the instrument to "Enhanced High Resolution Corneal Scan Mode" for all measurements. The examiner focused and adjusted settings until the real-time image of the SL on the cornea was shown on the computer monitor. The SL thickness was adjusted to align within the two green horizontal mires displayed on the screen. Following the alignment, the participants were asked to keep their eyes wide open during scanning. Once this was achieved, the examiner pressed the capture release button on the computer to scan the SL and cornea. The integrated software automatically processed the OCT images and simultaneously displayed the SL and its outline at a total diameter of approximately 9.20 mm (figures 4-1and 4-2).

For every scan, the examiner reviewed the image quality making sure both the front and back surfaces of the SL and cornea were clearly visible without any artefacts. After every scan, the participants were asked to pull away from the forehead rest and repositioned themselves for the next scan. Any scan that resulted from misalignment/poor alignment was immediately re-adjusted and the measurement was repeated. All the measurements took place in normal lighting conditions

and these conditions were maintained for all the participants. Two scans were taken for each eye during the dispensing and follow-up visits. (22)

4.3.3 Visante™ OCT Image Processing and Analysis

The Visante™ OCT image was displayed on the computer screen after the scan. The investigator used the integrated ruler to draw a chord (approximately 9.20 mm) as indicated by two vertical green lines by the software. Another ruler was picked to draw a vertical line dividing the 9.20 mm (4.60 mm) to the front surface of the SL. Finally, the distance between the front surface of the cornea and the back surface of SL was measured along the vertical line as central corneal clearance (CCC) as displayed in figures 4-1 and 4-2.

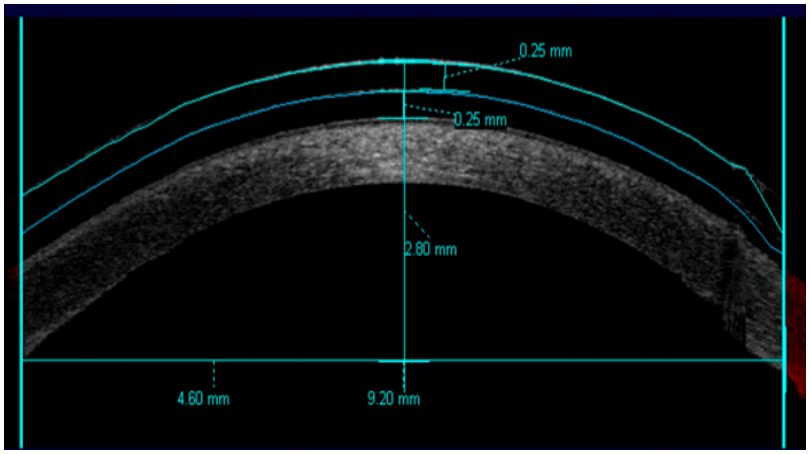


Figure 4-1: Central corneal clearance with Visante OCT was estimated at 250 µm at dispensing visit.

Visante™ OCT scan using "Enhanced High Resolution Corneal Scan Mode". The thickness of the SL is indicated by two curved blue lines at a total diameter of approximately 9.20 mm indicated by two vertical lines. The distance between the front surface of the cornea and the back surface of SL was measured as central corneal clearance, 250 µm (0.25 mm).

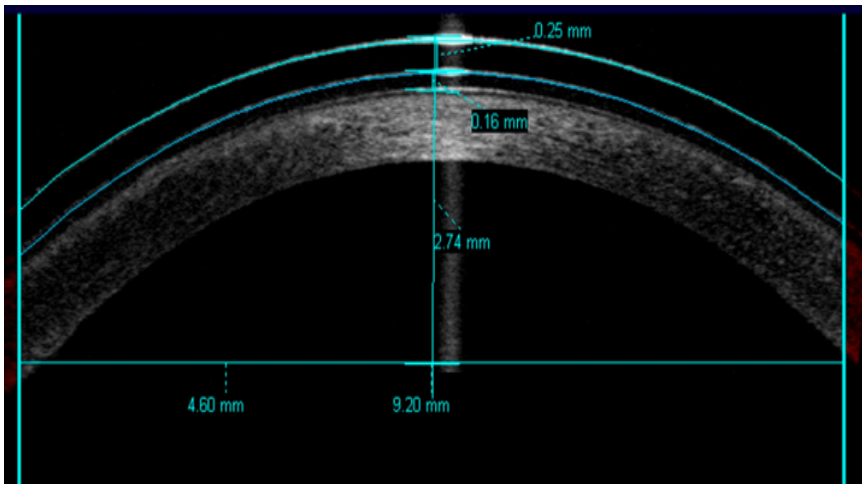


Figure 4-2: Central corneal clearance with Visante OCT was estimated at 160 µm at follow-up visit.

Visante™ OCT scan of the same subject at the follow-up visit after four weeks of SL wear. The scan shows decreased central corneal clearance measured as 160 µm (0.16 mm). The difference between the central corneal clearance at the dispensing and follow-up visits is clinically termed *lens settling*.

Sodium fluorescein (NaFl) staining characteristics of the same lens at the dispensing and follow-up visits are presented in Figure 4-3 and 4-4.

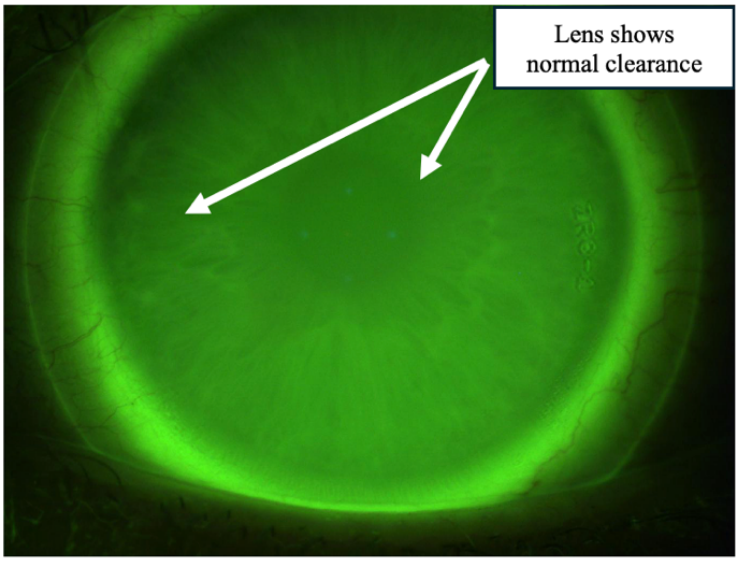


Figure 4-3: Example of NaFl pattern taken with K5M instrument at the dispensing visit.

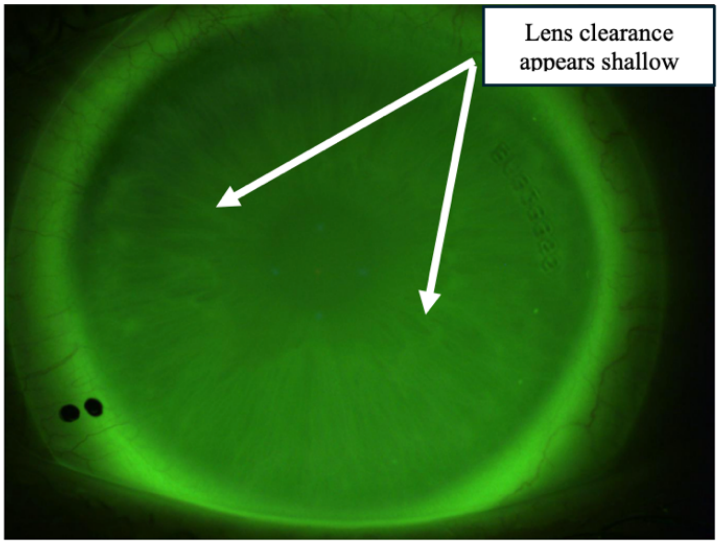


Figure 4-4: Example of NaFl pattern taken with K5M instrument at the follow up visit, after four weeks of scleral lens wear.

4.3.4 Visual Acuity Measurements

The logarithm of the minimum angle of resolution (LogMAR) visual acuity (VA) chart was used to measure HCVA and LCVA. The participants were seated in the examination chair and asked to cover their left eye, and the VA in the right eye (OD) was taken. The LogMAR chart was displayed on the computer monitor and the participants asked to read until they could not read further. At this point, the VA was recorded in decimal values. The investigator then switched to low contrast for the LCVA to be taken in a similar manner. The participants were asked to switch hands and cover the OD while the VA in the left eye (OS) were taken. These measurements were recorded at the dispensing and follow-up visits. This procedure was maintained for all participants throughout the study period.

4.4 Data Management and Statistical Analysis

Data analysis was conducted using Statistica 13.5 (TIBCO Statistica™. Inc., Tulsa, OK, USA). Demographic characteristics, screening and baseline measurements have been reported in Chapter 3. Mean and standard deviation (SD) were used to determine the overall corneal sagittal depth

(CSD), sagittal height of dispensed lenses, number of hours of lens wear before the follow-up visits. Descriptive statistics was used to report on the different types of lens designs dispensed. Independent t-test was used to determine the statistical significance of lens settling between the lens type and VA at dispensing and follow-up visits. The change in lens settling was determined as a percentage of the difference between the CCC at the dispensing and follow-up visits divided by the CCC at the dispensing visit. *P* values of less than 0.05 were considered statistically significant. Pearson and Spearman correlations were also performed to determine the relationship between the amount of lens settling and vision (HCVA and LCVA).

4.5 Results

The measurements described above were taken for each eye and preliminary data analysis showed no significant differences comparing OD and OS, ($p > 0.05$). Therefore, comprehensive data analysis was performed on the OD data only.

The overall mean and SD of the CSD was 3.60 ± 0.30 mm (range: 3.10 - 4.05). The mean and SD of the sagittal height of all the lenses dispensed was 4.07 ± 0.27 mm (3.48 - 4.50). Table 4-1 shows different types of lens designs dispensed during the study period. Details of lens designs and prescriptions for all the participants are available in appendix 4-1.

Table 4-1:Scleral contact lens designs dispensed during the study period.

Lens Design	**Frequency (n/%)**
Spherical	n = 11 (55%)
Front Toric	n = 7 (35%)
Bi-elevation	n = 2 (10%)

n=20.

The mean time and SD of lens wear at the follow-up visit were 3.90 ± 1.88 hours and 3.95 ± 2.05 hours for uncoated and coated lenses respectively, $p > 0.05$. Table 4-2 shows the CCC and lens settling at both the dispensing and follow-up visits for each of the lens type. There were statistically significant differences between the CCC at the dispensing and follow-up visits for each of the SL (all $p < 0.001$). However, there was no significant difference in CCC between the uncoated and coated SL at both visits, table 4-2. Similarly, there was no significant difference between lens settling comparing each lens type. The results indicated that the uncoated and coated SL settled at similar rates at the follow-up visit.

Table 4-2: Central corneal clearance and lens settling for each lens type after four weeks of lens wear using Visante OCT.

SL Type	**CCC and Range (µm)**		**Lens Settling (µm)/ Change in settling (%)**
	Dispensing Visit	**Follow-up Visit**	
Uncoated	260 ± 40 (200 - 300)	190 ± 40 (100 - 290)	70 ± 42 (25 - 125) /26.92
Coated	260 ± 40 (200 - 300)	200 ± 30 (130 - 295)	70 ± 43 (10 - 175) /23.08
P-values	1.00	0.63	0.65

CCC: central corneal clearance, SL: scleral contact lenses, µm: micron. Lens settling was calculated as the difference between the CCC at the dispensing and follow-up visits, change in lens settling is expressed as a percentage of the difference between the CCC at the dispensing and follow-up visits divided by the CCC at the dispensing visit. n=20.

In terms of vision, there were no significant differences comparing the baseline and follow-up visits for each lens pair (all, $p > 0.05$). Table 4-3 illustrates the measures of the VA at both the dispensing and at the follow-up visits which shows no significant differences between the lenses at all visits.

Pearson and Spearman correlation showed no significant correlations ($p > 0.05$, $r < 0.50$) between uncoated and coated lens settling and vision. For example, figures 4-5, 4-6, 4-7 and 4-8 show the relationship between the HCVA and LCVA at the follow-up visit and CCC for each lens type.

Table 4-3:Visual acuity measurements using LogMAR visual acuity chart.

SL Type	Vision			
	Dispensing visit		Follow-up visit	
	HCVA	LCVA	HCVA	LCVA
Uncoated	- 0.05 ± 1.17	0.41 ± 0.30	- 0.05 ± 0.16	0.49 ± 0.28
Coated	- 0.08 ± 0.07	0.43 ± 0.27	- 0.07 ± 0.06	0.35 ± 0.34
P- values	0.46	0.82	0.60	0.15

HCVA: high contrast visual acuity, LCVA: low contrast visual acuity, SL: scleral contact lenses, n=20. The visual acuities were measured at the dispensing visits and also at the follow-up visits after four weeks of lens wear.

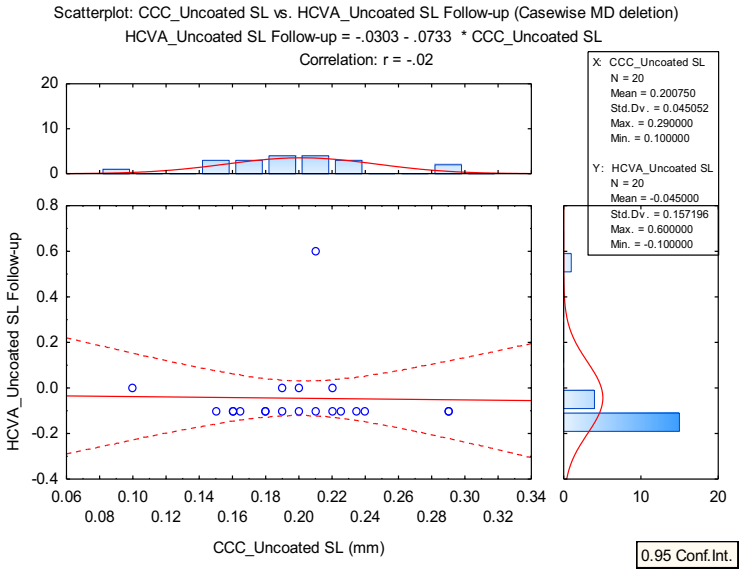


Figure 4-5: Correlation between HCVA and CCC for uncoated SL after four weeks of lens wear.

HCVA: high contrast visual acuity, CCC: central corneal clearance, SL: scleral contact lenses., n=20. The CCC was measured with Visante OCT and the HCVA was measured with LogMAR visual acuity chart.

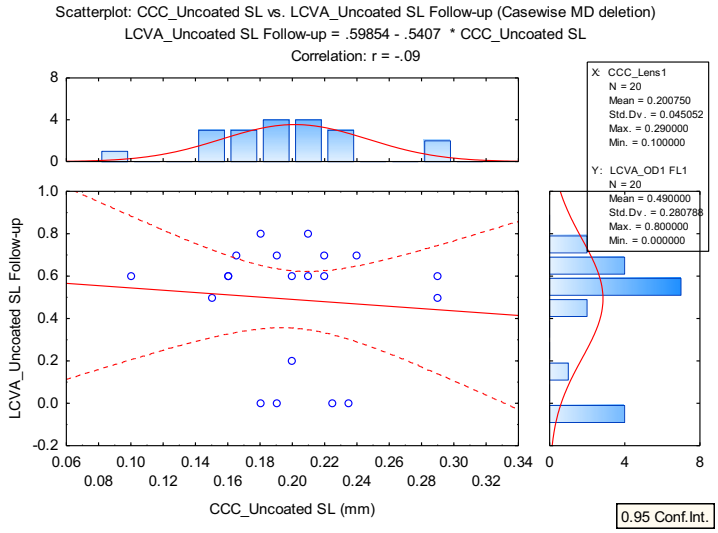


Figure 4-6: Correlation between LCVA and CCC for uncoated SL after four weeks of lens wear.

LCVA: low contrast visual acuity, CCC: central corneal clearance, SL: scleral contact lenses, n=20. The CCC was measured with Visante OCT and the LCVA was measured with LogMAR visual acuity chart.

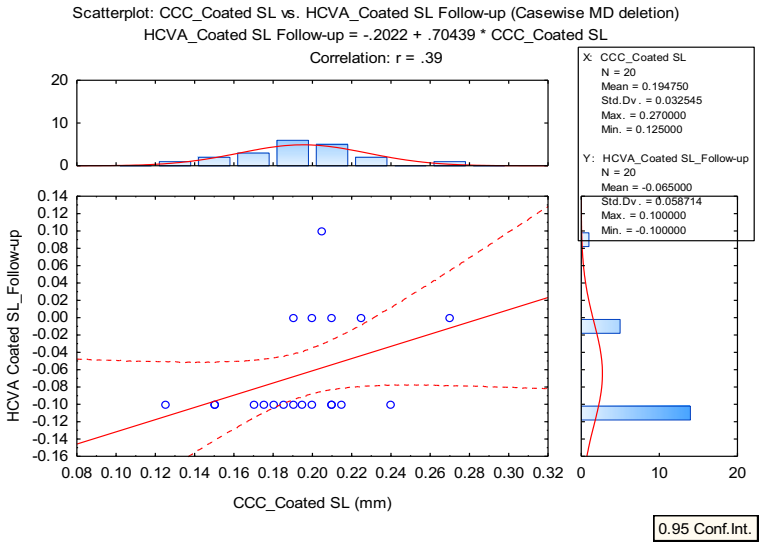


Figure 4-7: No significant correlation between HCVA and CCC for coated SL after four weeks of lens wear.

HCVA: high contrast visual acuity, CCC: central corneal clearance, SL: scleral contact lenses n=20. The CCC was measured with Visante OCT and the HCVA was measured with LogMAR visual acuity chart.

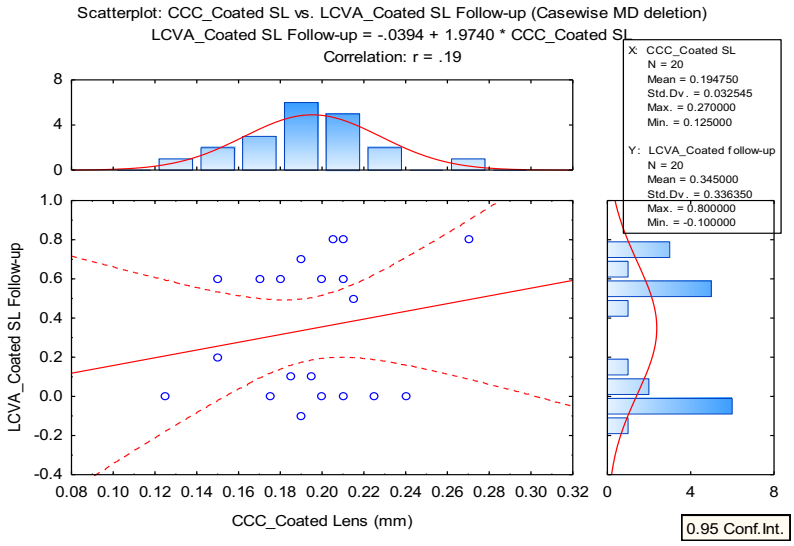


Figure 4-8: No significant correlation between LCVA and CCC for coated SL after four weeks of lens wear.

LCVA: low contrast visual acuity, CCC: central corneal clearance, SL: scleral contact lenses., n=20. The CCC was measured with Visante OCT and the HCVA was measured with LogMAR visual acuity chart.

4.6 Discussion

The concept of lens settling continues to be an important consideration in our understanding of fitting and evaluating SL in clinical settings. What was previously considered as initial lens adaptation in order to assess the SL has developed into a more complex clinical phenomenon, which has attracted lots of clinical research over the past few years. Today's research interest in SL settling has focused on understanding the impact of time, (1) lens designs, (23) interacting forces, (13, 14) the impact of lens settling on the trabecular meshwork and the optic nerve. (24) Additionally, inflammatory protein analysis (25) and, most importantly, a variety of clinical applications have been reported. (11, 23)

One of the challenges in fitting SL still lingers on the estimation of the CCC, as numerous authors have suggested different amounts of optimal clearance, ranging from 250 - 350 µm or 100 - 400 µm. (2, 26, 27) The factors which are known to significantly influence the CCC are lens diameter (as small diameters are fitted with a small amount of clearance and vice versa), lens design and fitting characteristics. (6, 28) Otchere et al (6) demonstrated that the amount of CCC is not a fixed

parameter but a continuum (with critical endpoints), within which clinicians have to balance the fitting characteristics with the resultant VA and comfort. They suggested that fitting SL in the range of 200 µm or less has the tendency to eventually result in touch post settling in some part of the cornea, and that this can affect comfort levels. Also, a CCC of 400 µm or more can eventually affect the fitting characteristics and VA, although comfort may be unaffected (at least in keratoconus patients). Clinically, to subjectively quantify the amount of clearance, Schornack et al. (29) suggested ¼ or ½ of the tear film thickness in comparison to the corneal thickness through the optic section with slit lamp biomicroscope. However, this technique has been reported to cause a potential over or under-estimation and it is also difficult to determine the amount of lens settling over time. (11)

In this study, we used the radius of curvature measurement (K-reading) combined with the CSD to select the initial SL (sag) to apply on the participants. To achieve the recommended CCC as determined by the manufacturer (250 - 350 µm for 14.80 or 15.40 mm), the Visante™ OCT was used to take scans after 30 mins of lens application to make sure all the lenses had initially "settled" and obtained a CCC within the recommended clearance. The mean CCC for both the uncoated and coated SL at the dispensing visit were significantly different from the CCC at the follow-up visits. Our findings are similar to that reported by Bray et al, (30) with a mean CCC of 260 ± 110 µm (range 140 - 470 µm) with a total lens diameter of 15.80 mm fitted on only one eye. Our mean CCC were also within the CCC of 250 - 350 µm suggested by the manufacturer, except in a few cases where the CCC was approximately 200 µm for participants with flatter K-reading and shallow anterior depth. The variation in the K-reading, CSD, lens design and other fitting characteristics (e.g. high myopic cornea had high vault to reduce decentration or bearing/touching) were all factored into designing the lenses for the participants. Since all the lenses were customized (see appendix 4-1), the investigator combined the above cited parameters to determine the optimal fitting characteristics. Additionally, all the lenses were fitted by one investigator who ensured lenses vaulted completely over the limbus and balanced the fitting characteristics with VA, comfort and acceptable CCC for each participant. (21)

There was no statistically significant difference between the uncoated and coated SL as the lenses settled at similar rates. Other studies have also reported similar lens settling in healthy eyes. (19, 21, 31, 32) According to Vincent et al, (31) the CCC reduced significantly overtime and they recorded a lens settling of 76 ± 8 μm after 8 hours of lens wear in normal corneas. They also observed that 45 % of lens settling occurred in about 45 mins and increased to 75 % within 2 hours, after which lens settling achieved relative stability after 4 hours of lens wear. In another related study on regional lens settling in normal cornea, Nau et al (19) pointed out that SL settle by nearly 50 % after 2 hours in all the quadrants (superior, inferior, nasal and temporal regions). The reported amount of lens settling at the central location was 104 ± 43 μm. Bray et al (31) also reported lens settling of 83 ± 22 μm after 6 - 8 hours of lens wear on normal corneas. As illustrated in Figure 4-1a-b, our results are in line with studies reporting on SL lens settling over time.

One of the factors which is known to influence lens settling is the lens design and overall diameter. (2, 21) According to Nau et al, (21) different lens designs settle at different rates. Using 15.00 mm and 18.20 mm Jupiter lenses (Visionary Optics, Front Royal, VA, USA), and 18.00 mm Digiform lenses (TruForm Optics, Bedford, TX, USA) for an initial CCC in the range of 200-300 μm, they reported the change in lens settling as 40 % (121 ± 70 μm) for 15.00 mm, 39 % (149 ± 78 μm) for 18.00 mm and 29 % (143 ± 89 μm) for 18.20 mm lenses, all $p < 0.0001$. This suggests that larger diameter lenses settle more slowly over time. Kauffman et al (2) previously reported similar findings and noted that larger lenses settle slowly and it can take up to 8 hours. Even though this study used two distinct lens diameters (14.80 or 15.40 mm) and also dispensed three different lens designs (*spherical, front toric and bi-elevation*), the study did not investigate the effect of lens diameter or design on lens settling due to the small sample size.

The clinical implication and effect of lens settling on vision is not fully understood. Regardless of the significant differences in CCC at the dispensing and follow-up visits, there were no statistically significant differences between HCVA and LCVA comparing both uncoated and coated lenses. Additionally, there were no significant correlations between these parameters. According to Bray et al, (30) lens settling has minimal effect on refractive components (sphere: + 0.06 ± 0.17 D,

cylinder: + 0.04 ± 0.19 D, axis: 1.06 ° ± 12.12, all $p > 0.05$), with overall best sphere over-refraction of + 0.13 ± 0.30 D ($p = 0.12$). In a related study, Vincent et al (31) reported that lens settling results in negligible power change in the post-lens tear film (- 0.12 ± 0.01 D) and induced prismatic effect of 0.01 ± 0.16 Δ base out and 0.50 ± 0.19 Δ base down relative to the pupil center. They reported that such a small refractive changes did not affect the overall subjective vision. Moreover, a recent publication by Michaud et al (33) reported small changes in residual astigmatism in SL wear (range: - 0.50 to - 0.75D). However, the change in astigmatism did not significantly affect the vision. In this study, the investigator measured the over-refraction after achieving acceptable CCC using a digital autorefractor (Nidek Co., Ltd, Gamagori, Aichi, Japan) and subjective over-refraction performed with the phoropter over the lenses to optimize the VA before dispensing the lenses. Therefore, if lens settling had any impact on visual performance, this should have been seen in the overall subjective VA at the follow-up visits, however, this was not the case. Schornack et al (34) hypothesize that one of the factors which influence the refractive changes in lens settling is the relationship between the K-reading of the cornea and the final radius of curvature of the SL. They suggested that as the K-reading increases (as in keratoconus), the refractive changes increase, therefore, a significant difference should be observed with overall vision. This was not the case in this current study, as the study investigated healthy corneas and observed no significant differences with VA over time.

Limitations of the study included the small sample size (n = 20). The study faced significant challenges in recruiting normal participants with mild to moderate DED for the study, therefore, care should be taken interpreting the results beyond this population. Also, the study participants had normal prolate corneal profiles, therefore, it is not surprising to see no significant differences at the dispensing and follow-up visits for most of the measured parameters.

In conclusion, this study confirms lens settling occurs overtime. The novel hydraPEG coating technology on the lens surface did not influence wearing time and lens settling. A significant change in post-lens tear was observed, however, this phenomenon did not affect the visual performance, as there were no significant differences in HCVA and LCVA and CCC. Additionally,

in this study, no correlation between lens settling and vision was identified. More research is needed to explore lens settling and other clinical factors and mostly importantly the effect on the conjunctival morphology.

CHAPTER 5

5.1 Scleral Contact Lens Wear and Its Effect on the Cornea

5.2 Introduction

Historically, one of the major challenges in the early years of the development of scleral contact lenses (SL) was the hypoxic effect of the lens material on the cornea. (1, 2) These lenses were produced with low oxygen transmissibility (Dk/t) and therefore heavily relied on the surrounding tissues for oxygenation. (3, 4) Since the oxygen delivery through the lens material and the surrounding tissues did not meet the physiological demand of the cornea, it resulted in corneal edema. In a five-year longitudinal study, Tan et al (5) reported that the most common complications of patients wearing SL made from polymethylmethacrylate (PMMA) were neovascularization (13.30 %) and corneal edema (7.40 %) secondary to corneal hypoxia. Other less common complications reported were corneal abrasion (3.10 %) and giant papillary conjunctivitis (1.70 %). Further to the above complications were ulcerative keratitis (0.80 %) and limbal occlusion (0.60 %). (5) To overcome corneal vascularization and edema induced by the SL material, about 23 % of the study cohort were re-fitted with newer SL materials (Optacryl 160, Dk=115), which allowed more oxygen through the lens material. They observed significant corneal vessel regression and in a few cases the vessels remained static. Corneal edema was also significantly reduced. (5, 6)

New materials, primarily through the addition of siloxane groups to the base material, has resulted in materials with higher Dk that pose reduced hypoxic risk to the cornea. (7, 8) More recent publications on SL materials with higher Dk values suggest that the eyes experience less risk of hypoxia and other ocular health issues. (9) The reported Dk available in modern SL materials range from 65 to 200 Dk. (9, 10) This advance has also been linked to the significant growth in SL prescribing patterns, from ~1 % in 2014 to more than 5 % in 2017 and this growth is expected to increase in the coming years. (11) Availability of new laboratory diagnostic techniques for producing the SL offer diverse lens designs and according to Harthan et al (12) there are about 50 SL designs available for clinicians to choose from, depending on the presenting condition requiring fitting with SL. In addition, particularly over the past 10 years, there has been a shift in the

realization of the therapeutic value in using SL to manage irregular corneas (particularly keratoconus and pellucid marginal degeneration) and in their use in the management of ocular surface disease such as that seen in patients with persistent corneal erosion and their use for drug delivery. (4, 13-18) However, despite their known value for therapeutic and cosmetic effects, little is known about the effect of SL (and the impact of the hydraPEG coating technology) on corneal physiology.

To understand the physiological impact of modern day SL with higher Dk values on the cornea, Dhallu et al (10) in a randomized, masked, crossover clinical study of five different SL with varying Dk values (65, 100, 125, 163, and 180+) demonstrated that a SL with the lowest Dk (65) resulted in a greater corneal hypoxic effect of 1.37 ± 1.25 % after 8 hours of open-eye lens wear. In comparison, the mean of the other lenses with ≥ 100 Dk had a reduced hypoxic impact, with typically 0.58 ± 0.99 % corneal swelling, which was significantly different from the Dk = 65 group ($p < 0.001$). They concluded that a SL with a Dk ≥ 125 was deemed safe for SL daily wear with respect to corneal swelling. However, they cautioned that care must be taken in interpreting these results, as daily SL wear (regardless of the lens Dk) could potentially impact corneal physiology depending upon the fluid reservoir depth created between the cornea and the lens.

The tear film reservoir thickness created between the front surface of the cornea and the back surface of the SL is known to influence the physiology of the cornea. (10) The debate on appropriate central corneal clearance (CCC) and how to fit these lenses continues, with widely varying opinions. (19-21) To critically examine the effect of CCC and its influence on physiological increase in corneal thickness, Fisher et al (22) conducted a study on ten healthy participants with normal corneas, using a SL with a Dk of 141, over 90 minutes of lens wear on separate days. The CCC were categorized as either low CCC (mean:144; 95 % confidence interval [CI], 127 - 160 μm), medium CCC (mean: 487; CI, 443 - 532 μm), or high CCC (mean: 726; CI, 687 - 766 μm). The corneal hypoxic responses were 0.69 %, 1.81 % and 2.11 % corneal swelling for the low, medium, and high CCC respectively. No significant difference was found between medium and high CCC; however, a significant difference was observed between the low and high corneal clearances. They concluded that a SL with a reasonably high Dk and low CCC had minimal effect on corneal thickness. Irrespective of the minimal effect of edema observed with a low CCC,

they cautioned that a SL could potentially induce central corneal edema with increasing reservoir thickness, which tended to plateau at a thickness of around 600 μm of clearance.

It has been hypothesized that SL thickness also plays a significant role in the hypoxic effect on the cornea. Pullum et al (23) demonstrated that a SL with a center thickness of 600 μm made from a material with a Dk of 115 evoked corneal edema of approximately 3 %. Kim et al (24) reported that a SL of < 400 μm central thickness and Dk/t > 25 Barrer/cm induced corneal swelling of < 2 % in healthy individuals during short term open eye wear. These studies show the variation in corneal response to SL. It is important to note that these studies were short-term SL wear, thus, long-term SL could possibly induce hypoxic effect on the cornea than those earlier reported.

Using mathematical and theoretical models to predict the effect of SL on the cornea, Michaud et al (25) demonstrated that a SL with a center thickness of > 350 μm, material of Dk 150 and a tear film thickness of > 250 μm can induce corneal edema under open eye conditions. Therefore, considering the factors that influence cornea swelling based on the mathematical model, the suggested SL central thickness should range from 250 - 495 μm, combined with a final post-lens tear layer thickness of 100 - 250 μm. They concluded that, to significantly reduce corneal swelling, clinicians should use the highest Dk lens available (such as > 150 Dk), with a maximal central thickness of 250 μm, fitted with a CCC that does not exceed 200 μm. This suggestion is close to that of Compañ et al, (26) who suggested that to avoid a clinically significant hypoxic effect, the SL selected must be made from a material with a Dk of at least 125, lens thickness of 200 μm and tear reservoir of 150 μm. Tan et al (27) reported that lenses with Dk ranging from 21 to 47 Barrer/cm or lower did not induce a clinically significant hypoxic impact on the cornea in short-term daily SL wear.

To date, no randomized clinical trial has been conducted to determine the effect of surface modification of SL on the cornea of normal subjects experiencing mild to moderate forms of DED. While the surface modification does not impact DK, the coated lenses may be better tolerated and worn for longer period of time, leading to potential changes in cornea physiology. Interestingly, no current study has evaluated the CCC and corneal thickness comparing these two lenses. The purpose of the study was to evaluate the impact of surface treatment on a SL material and its

physiological effect on corneal thickness. In addition, the study determined the change in corneal swelling before and after the wearing of the two pairs of SL and the correlation between CCC and corneal thickness.

5.3 Objectives

The main objectives of this study were to:

1. Determine the physiological impact of SL and change in corneal thickness comparing uncoated and coated SL.
2. Determine the correlation between CCC and corneal thickness comparing the two lenses.

5.4 Methodology

5.4.1 Study Design

The research design, participants, and recruitment for the study, as well as the inclusion and exclusion criteria, have been described in detail in Chapters 2 and 3.

5.4.2 Corneal Thickness Measurement with Pentacam HR®

The Pentacam HR® was used to scan the cornea at the baseline and screening visit as well as the follow-up visits for the two pairs of SL. Two scans were taken at each visit for each eye and for each pair of the SL types worn. The right eye (OD) was taken first, followed by the left eye (OS) and this pattern was maintained for each participant throughout the study period. The instrument displayed the scanned cornea where the corneal thickness locations shown on the left part of the displayed image were recorded for each eye. (Figure 5-2)

The details of how the Pentacam HR® was set up to scan the eye has been described in detail in Chapter 2 section 1.5.8



Figure 5-1: Pentacam HR was used for corneal thickness measurements at both dispensing and follow-up visits.

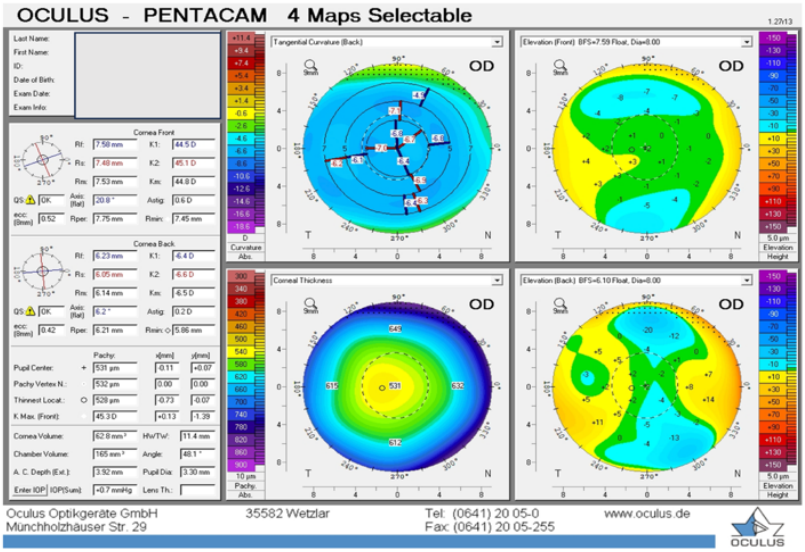


Figure 5-2: Pentacam quad map with data on left-hand side.

The central corneal thickness (CCT) and thinness (CCTn) locations were displayed on the map after the scan as displayed on the left side of the topographic map.

5.5 Data Management and Statistical Analysis

Data analysis was conducted using Statistica 13.5 (TIBCO Statistica™. Inc., Tulsa, OK, USA). Demographic characteristics, screening, and baseline measurements, CCC and lens settling have been reported in Chapters 3 and 4. The mean and standard deviation (SD) were used to determine the central corneal thickness (CCT) and location of the thinnest area on the cornea (CCTn) before lens wear at the screening and baseline and at the follow-up visits. An independent t-test was used to determine any statistically significant difference in corneal thickness between baseline and follow-up visits and also between the two lens pairs. The change in corneal thickness was expressed as a percentage of the differences between the measurements at the baseline and the follow-up visits of each pair of lens type. Pearson and Spearman correlation were used to determine the relationship between CCT and CCC. *P* values of less than 0.05 were considered statistically significant.

5.6 Results

The results of the demographic characteristics, CCC at both the dispensing and follow-up visits, the number of days and hours for each lens type have been described in detail in Chapters 3 and 4. Preliminary statistics showed that there were no significant differences between the right and left eyes, therefore, statistics were exclusively performed on right eyes only. The mean and SD of CCT at the screening and baseline and follow-up visits were; baseline: 560.55 +32.28 μm, uncoated SL: 557.65 ± 32.10 μm, coated SL: 560.50 ± 34.02 μm respectively. There were no significant differences between baseline and follow-up visits for each SL (uncoated SL: $p = 0.78$, coated SL: $p = 1.00$). Comparing the two lens types, no significant difference was found ($p = 0.79$). Similar results were found for CCTn, as no statistically significant differences were found between the baseline and follow-up visits (uncoated SL: $p = 0.84$, coated SL: $p = 0.98$) and lens types ($p = 0.82$). Table 5-1 shows the CCT and CCTn for each visit and lens type.

Table 5-1: Corneal thickness measurements at baseline and follow-up visits Pentacam HR.

Parameter	Baseline Visit (µm)	Follow-up Visit – Uncoated SL (µm)	Follow-up Visit – Coated SL (µm)	P-value **
CCT	560.55 ± 32.28	557.65 ± 32.10 (*p = 0.78)	560.50 ± 34.02 (*p = 1.00)	0.79
CCTn	556.20 ± 31.17	554.78 ± 31.04 (*p = 0.84)	556.21 ± 31.76 (*p = 0.98)	0.82

CCT: central corneal thickness, CCTn: central corneal thinness, SL: scleral contact lenses, µm: micron. *: indicates the p-values between the baseline measurements and each of the lens type, **: indicates the p-values between the uncoated and coated lens SL. The measurements were obtained at baseline and follow-up visits using Pentacam HR device, n=20.

Pearson and Spearman correlation showed no significant correlations between the baseline CCC and CCT for both the uncoated and coated SL ($p > 0.05$, $r < 0.50$). This pattern was also observed at the follow-up visits. Figures 5-3,4,5 and 6 shows the correlations between the CCC and CCT comparing the two lens types at different visits. The change in corneal thickness was observed only in CCTn comparing the baseline to the coated SL (0.06 ± 0.40 %).

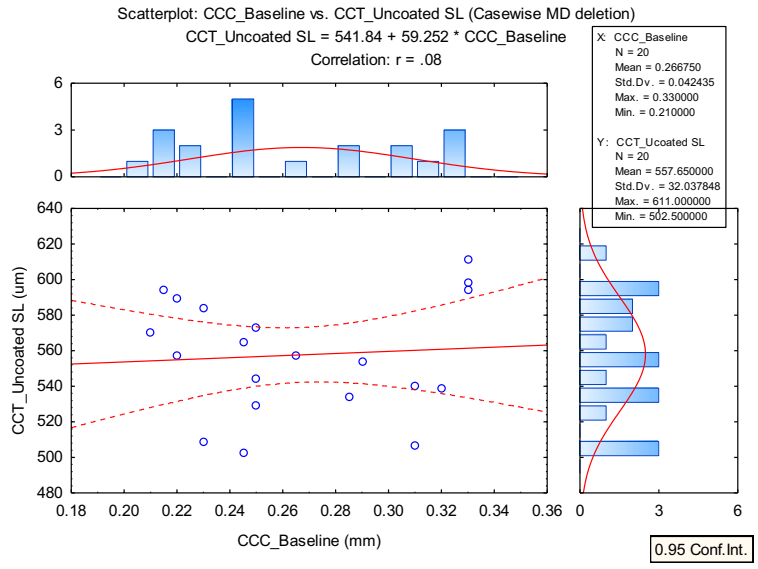


Figure 5-3: Correlation between CCC and CCT at baseline visit for uncoated SL.

CCC: central corneal thickness, CCT: central corneal thickness, SL: scleral contact lenses. These measurements were taken with Pentacam HR and Visante OCT at the baseline visit, n=20.

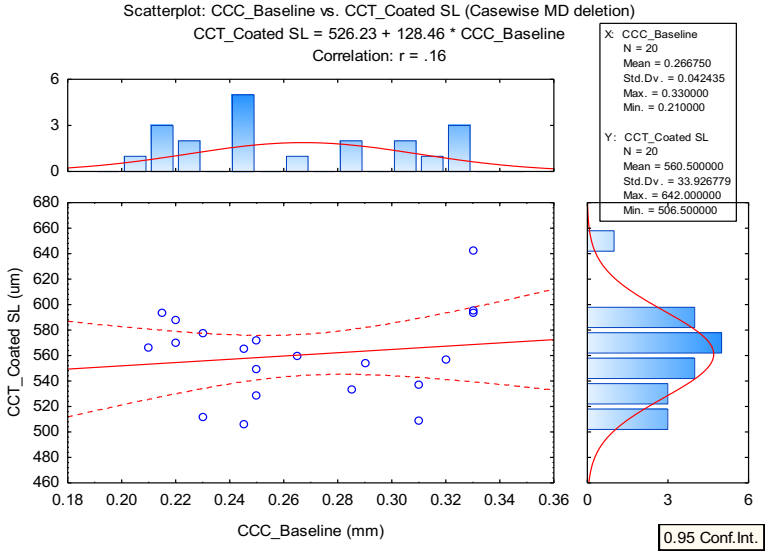


Figure 5-4: Correlation between CCC and CCT at baseline visit for coated SL.

CCC: central corneal thickness, CCT: central corneal thickness, SL: scleral contact lenses. C These measurements were taken with Pentacam HR and Visante OCT at the baseline visit, n=20.

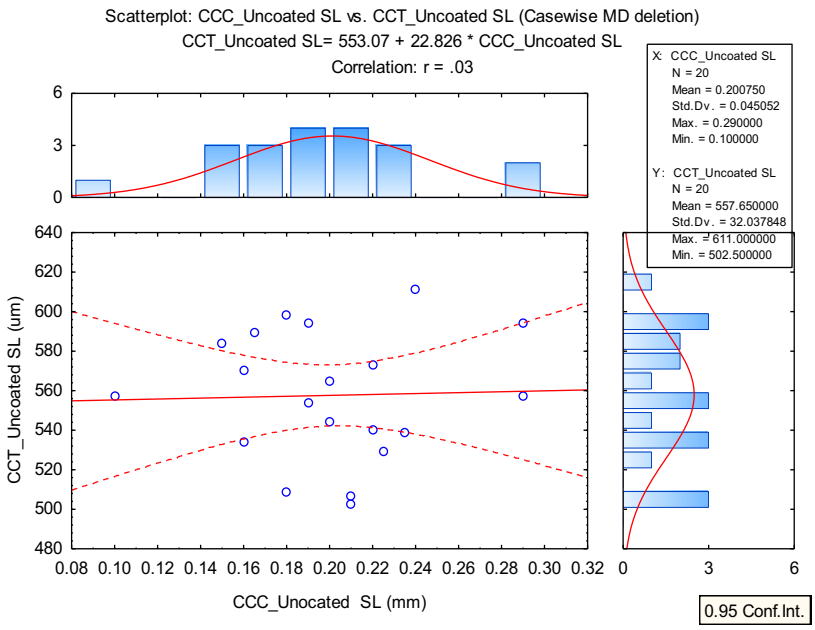


Figure 5-5: Correlation between CCC and CCT at the follow-up visit for uncoated SL.

CCC: central corneal thickness, CCT: central corneal thickness, SL: scleral contact lenses. These measurements were taken with the Pentacam HR and Visante OCT at the follow-up visit following four weeks of lens wear, n=20.

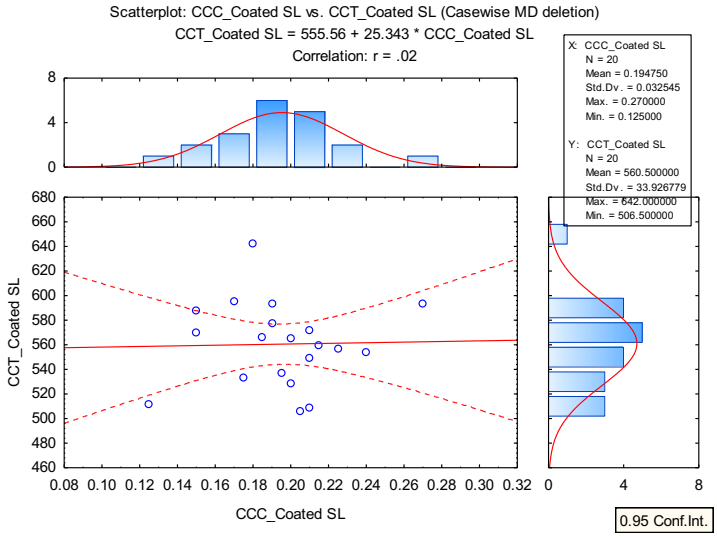


Figure 5-6: Correlation between CCC and CCT at follow-up visit for coated SL.

CCC: central corneal thickness, CCT: central corneal thickness, SL: scleral contact lenses. These measurements were taken with Pentacam HR and Visante OCT at the follow-up visit, following four weeks of lens wear, n=20.

5.7 Discussion

Modern SL are significantly different to previous SL materials, which were originally manufactured from glass and then oxygen impermeable PMMA materials. These SL are manufactured from highly oxygen permeable materials that reduce many clinical complications compared to earlier materials. (7, 28) However, the wide availability of lens designs also present significant challenges, such as complex fitting philosophies, potentially increased chair time and how to properly assess the lenses and resolve clinical complications following lens wear. Coupled with these challenges are the ability to select an appropriate SL based on the material composition, Dk, lens thickness, and design that will evoke less physiological response from the cornea and the surrounding tissues. (7, 25) It is therefore imperative to understand the role of Dk in lens selection, lens thickness and post-lens tear film when assessing the degree of hypoxia induced by a SL.

Currently, there is no accepted model or algorithm which clinicians must follow to determine the Dk, central thickness, and the appropriate vault under which a SL can be fitted, as different manufacturers have different proprietary materials, lens designs, and fitting philosophies. (12, 17, 29, 30) However, recent mathematical models by Michaud et al (25) predicted that to safely and effectively wear a SL on a daily wear basis to invoke a negligible hypoxic effect, the lens selected must have Dk ≥ 125. This model has also been demonstrated by Jaynes et al, (31) using a different mathematical approach.

In this current study, the Zen™ RC lenses were manufactured using the Boston XO® (hexafocon A) material, composed of a siloxanyl fluoromethacrylate copolymer with a Dk of 100. (32) The overall mean and SD for CCT for uncoated and coated lenses were 557.65 ± 32.10 and 560.50 ± 34.02 respectively at the follow-up visits, which were slightly lower than the baseline measurements. There were no significant differences comparing the corneal thickness at the baseline and the follow-up visits and also between the two lens types, all $p > 0.05$.

As previously described, corneal oxygen delivery and lens performance is also related to the tear film thickness between the lens and cornea (19, 33) The general consensus is that if the distance

between the back surface of the lens and the front surface of the cornea is too small, then, this will compromise the cornea due to the possibility of the lens touching the cornea, while the distance being too large could limit the oxygen delivery to the cornea. (24, 34, 35) The predicted acceptable CCC according to Michaud et al was 200 μm, (25) while Compañ et al (26) quoted 150 μm as the required value to minimize any hypoxia. In this study, it was clinically impossible to dispense the SL with a CCC of 150 μm, given the limited diameter of 14.80 or 15.40 mm, variability in the anatomical features of the participants as well as the effect of lens settling. The mean CCC at the dispensing visit was estimated at 0.26 ± 0.04 mm (260 ± 40 μm, range: 200 - 300 μm) for both the uncoated and coated SL, which was slightly higher than the recommended central clearance. The mean and SD of the CCC at the follow-up visits were 0.19 ± 0.04 (190 ± 40 μm, range: 100 - 290 μm) and 0.20 ± 0.03 (200 ± 30 μm, range: 130 - 295 μm) for uncoated and coated SL respectively. There were statistically significant differences between the CCC at the dispensing and follow-up visits for each of the SL ($p < 0.001$). The average time at which the CCC were recorded at the follow-up visits was 3.90 ± 1.88 and 3.95 ± 2.05 hours for uncoated and coated lenses respectively, $p > 0.05$. Given the CCC at the follow-up visits (with lens settling of 70 μm) it was highly unlikely to see significant corneal swelling.

Lens thickness has also been demonstrated to potentially cause corneal edema. (23) However, a recent study by Iqbal et al (36) showed that SL thickness in the range of 200 - 400 μm does not significantly impact corneal edema in a short-term study. This current study used a SL with a thickness of 250 μm, which is similar to the proposed recommendation set forth by Michaud et al (25). This central thickness was maintained for all the participants irrespective of the lens design, to ensure that lens thickness did not adversely influence oxygen transmissibility. Given the lens thickness used in the study, it is not surprising that there were no clinically observable changes in corneal thickness.

It was very difficult to compare our results to some of the already published studies on SL and corneal hypoxia due to a number of factors. First, most of the studies had been carried out on individuals with compromised and complicated corneal ectasias. (22, 36-38) It may therefore be

likely to observe a greater degree of corneal response to SL wear in these wearers, compared to the healthy corneas of the wearers in our study. Also, most of the scanning devices employed in prior studies were optical coherence tomography instruments, which have the tendency to overestimate the cornea thickness centrally. (7, 10, 36, 39) This study used the most sophisticated scanning device which employs a Scheimpflug camera with high sensitivity to detect subtle changes in corneal thickness. (40-42) The other complicating factors are study design, lens profile and parameters, fitting philosophies, wearing time and number of participants enrolled in the study.

One noticeable limitation of this current study is that it did not explore the change in peripheral corneal thickness, even though 35 % of the study participants were fitted with toric lens designs with a characteristic gradual change in lens thickness from the center towards the periphery. This means that there could be limited oxygen delivery in the peripheral region of the cornea which could cause corneal edema.

In conclusion, oxygen delivery to the cornea is critical in order to keep the tissue healthy. Irrespective of the slightly lower Dk of the lens material (Dk 100) used in this study to that theoretically suggested to eliminate corneal hypoxia, no statistically significant differences were found in CCT and CCTn comparing the baseline and the follow-up visits and also between the lens types. The hydraPEG coating on the lens surface did not influence corneal edema, as all the lenses exhibited a similar response. Also, it appears from the study that given the sample size, lens diameter of 14.80 or 15.40 mm, corneal clearance of 260 ± 40 μm, and lens thickness of 250 μm, these may be clinically recommended parameters to invoke minimal corneal hypoxia in normal corneas. More research may be needed to explore different lens designs, and long-term effect and complications of SL as well as topographic changes in corneal thickness.

CHAPTER 6

6.1 The Impact of Scleral Contact Lens Wear on Osmolarity and Inflammatory Markers in the Tear Film

6.2 Introduction

The tear film is a complex, multi-layered structure that covers the ocular surface, providing vital protection, lubrication, and nourishment to the cornea and conjunctiva. (1) The older, "traditional" model of the tear film suggests that it consists of three main layers: lipid, aqueous, and mucin, with each contributing significantly to the stability and functionality of the tear film. (1, 2) However, the current model of the tear film suggests that it consists of an inner interactive hydrated mucus layer against the corneal glycocalyx, covered by an outer lipid layer. (1, 3) The composition and stability are governed by various factors, including but not limited to tear film osmolarity and pro- and anti-inflammatory proteins. Disruptions in tear film homeostasis can lead to ocular surface diseases such as dry eye disease (DED), characterized by symptoms of discomfort, irritation, redness, foreign body sensation, photophobia, and visual disturbances, among others. (4-9) The clinical signs typically observed with the slit lamp biomicroscope include reduced tear break up time (TBUT), reduced tear meniscus height, corneal and conjunctival staining. (5, 10-12) Therefore, maintaining the delicate balance of the tear film is crucial for ocular health and comfort.

Tear film osmolarity refers to the concentration of solutes within the tears, which serves as a fundamental parameter reflecting the osmotic balance and overall health of the ocular surface. (13) Normal tear film osmolarity is also essential for preserving the integrity of the corneal epithelial cells and ensuring ocular comfort. However, environmental conditions, systemic diseases such as diabetes, and other ocular surface disorders are known to cause fluctuations in tear film osmolarity (13) Also, it has been theorized that increased tear film osmolarity is associated with ocular surface inflammation, epithelial cell damage, and symptoms of DED. (14, 15)

Tear film osmolarity is one of the crucial clinical criteria used to distinguish the severity or degree of DED. (16, 17) According to Versura et al, (18) tear osmolarity predicted dry eye (DE) severity

more accurately than Schirmer's test, meibomian gland grading, the Ocular Surface Disease Index (OSDI) questionnaire, TBUT, and corneal and conjunctival staining. Increased tear osmolarity was related to the severity of the DE and showed a linear increase. Lemp et al (17) also found that tear film osmolarity was more sensitive than other clinical tests (such as corneal and conjunctival staining), and more specific than TBUT and Schirmer's test results.

Advancements in diagnostic technology have led to the development of tear film osmolarity testing kits. The most well studied commercially available device for measuring tear film osmolarity is the TearLab Osmolarity System (TearLab Corp. Escondido, CA, USA, now Trukera Medical, San Diego, CA, USA). (17, 19, 20) This available point-of-care test device uses a device using a micro-electrode to measure the electrical impedance of the charged particles in a tear sample. It enables clinicians to accurately measure tear film osmolarity in a clinical setting, providing valuable insights into the underlying pathophysiology of ocular surface diseases, particularly DED. By assessing tear film osmolarity, clinicians can tailor treatment strategies more effectively, monitoring disease progression and response to therapy over time. (20-22)

According to the TFOS DEWS II Diagnostic Methodology Report, (14) a value of 308 mOsm/L in either eye is often regarded as the threshold value in differentiating normal and early stages of DED, with 316 mOsm/L as a cut-off for more advanced DED. A variability of 6.90 ± 5.90, 11.70 ± 10.90, and 26.50 ± 22.70 mOsm/L have been reported in mild, moderate and severe DED respectively. Thus, a difference of 8 mOsm/L between the two eyes is considered to be significant and compatible with an unstable tear film. These thresholds have also been demonstrated by Lemp et al, (17) in which the most sensitive threshold osmolarity between normal and mild or moderate subjects was found to be 308 mOsms/L. While the study has not specifically reported on the sensitivity and specificity of the device at 308 mOsmo/L, it has been reported that at 312 mOsms/L, sensitivity and specificity levels were 72.80 % and 92.00 %, respectively.

In addition to tear film osmolarity testing, another innovative clinical diagnostic tool for ocular surface assessment of the tear film is the InflammaDry® test kit (Quidel InflammaDry, Sarasota, Florida, USA). (23, 24) This point-of-care diagnostic assay detects elevated levels of matrix

metalloproteinase-9 (MMP-9), a pro-inflammatory biomarker commonly associated with ocular surface inflammation. (25) MMP-9 is a proteolytic enzyme produced by stressed ocular surface and glandular epithelial cells. (26) As an inflammatory marker, its concentration is known to be highly elevated in the tears of patients with DED compared to non-DED patients. (26, 27) The InflammaDry® test offers a rapid and non-invasive method for identifying patients with underlying inflammation, aiding in the diagnosis and management of various ocular surface disorders.

Recent studies have shown that MMP-9 is a potentially valuable marker for diagnosing DE. (28-30) According to Acera et al, (31) individuals experiencing varied degrees of DED have significantly higher MMP-9 proteins in their tear films compared to controls. In another study, Messmer et al, (32) reported that the Inflammadry® test was able to confirm the diagnosis of DED in about 40 % of subjects. Therefore, it is evident from the above cited studies that the test kit is an invaluable tool in both clinical and research settings. Recent publications have also highlighted the accuracy, sensitivity, and repeatability of the Inflammadry® test. (29, 32, 33)

It is therefore important to understand the clinical effect of tear film osmolarity and MMP-9 levels, as these diagnostic parameters provide clinicians with objective measures to assess ocular surface health. By understanding the impact of SL wear on tear film osmolarity and MMP-9 levels in the tear film, clinicians can make informed decisions on the ability of the SL options chosen to impact the DED state, ultimately improving the DED condition while wearing the lenses.

To date, no randomized clinical trial has been conducted to determine the effect of SL surface modification on tear osmolarity and MMP-9 levels in normal subjects experiencing mild to moderate forms of DED. Therefore, the purpose of the study was to evaluate the impact of SL surface treatment on osmolarity and MMP-9 levels, as determined by the TearLab Osmolarity System and InflammaDry® test. Also, the study determined the percentage of change in osmolarity levels and the correlation between these measures.

6.3 Objectives

The main objectives of this study were to:

1. Determine the impact of SL on osmolarity and inflammatory markers in the tear film.
2. Assess the percentage change in osmolarity levels and correlation between osmolarity and MMP-9 test results.

6.4 Methodology

6.4.1 Study Design

The research design, participants, and recruitment for the study as well as the inclusion and exclusion criteria have been described in detail in Chapters 2 and 3.

6.4.2 Osmolarity Measurement with Tear Lab Osmolarity System

The TearLab Osmolarity System® was used to detect and indirectly measure the levels of osmolarity of the pre-corneal tear film. By employing an integrated collection and analysis device, the TearLab Osmolarity System® provides an indirect measurement of osmolarity through the use of a temperature-corrected impedance measurement. Osmolarity is computed and shown as a numerical value following the application of a lot-specific calibration curve. (Figure 6-1 and 6-2)

The TearLab Osmolarity System was calibrated each time with the test card to make sure the device was measuring within the acceptable range of 333 - 334 mOsmol/L, as directed by the manufacturer. The right eye (OD) measurement was taken first, followed by the left eye (OS), and this was maintained for all participants throughout the study period. The details of how to use the device to measure the osmolarity of the pre-corneal tear film has been described in detail in Chapter 2 section, 1.5.3



Figure 6-1: TearLab Osmolarity System

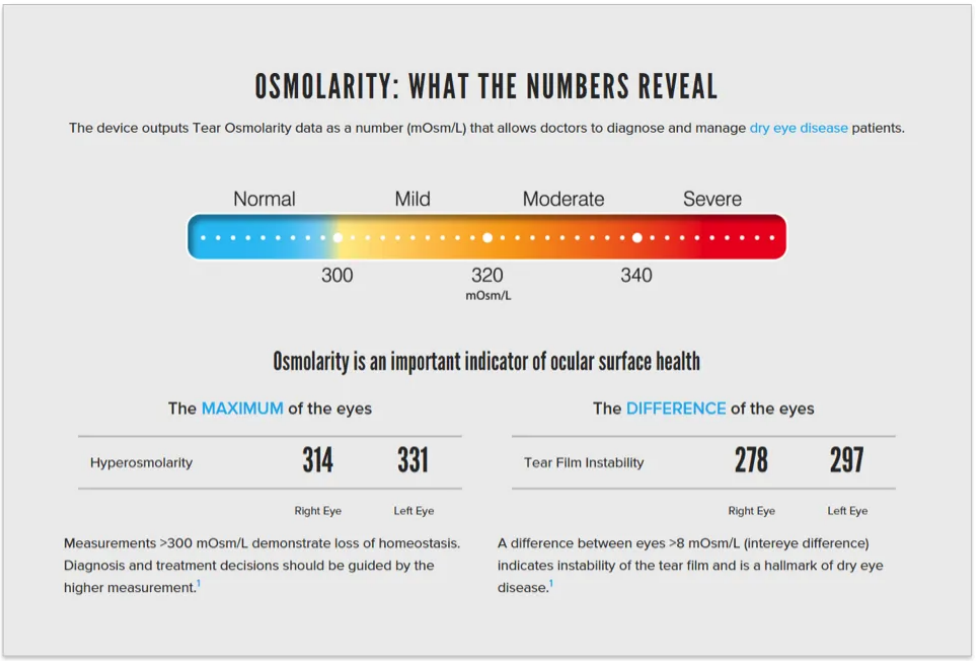


Figure 6-2: TearLab Osmolarity System Grading Scale

Courtesy Trukera Medical, San Diego, CA, USA

6.4.3 Levels of Protease with Inflammadry® Test Kits

Following osmolarity testing, the InflammaDry® test kit was used to qualitatively determine high levels of MMP-9 in the pre-corneal tear film. The InflammaDry® test kit is a Clinical Laboratory

Improvement Amendments waived (CLIA-waived) test for human tears. (33, 34) This diagnostic device is an immunoassay test for visual, qualitative, in vitro detection of increased levels of MMP-9 in the tear film. It is intended to offer quick and easy-to-use in-office ways of assessing DE in both clinical and research settings. It utilizes direct sampling micro-filtration technology which is based on the principle of lateral flow immunoassay technique. MMP-9 concentrations greater than 40ng/ml result in the appearance of a red line, indicative of a positive result. A blue line acts as the quality control line. Thus, clinically, red, and blue stripes at the device window indicate elevated levels of MMP-9. Negative test results will show only the blue line being visible. (Figure 6-3)

The OD measurement was taken first, followed by the OS, and this was maintained for all participants throughout the study period. The details of how to use the device to detect elevated levels of MMP-9 in the pre-corneal tear film have been described in detail in Chapter 2, section 1.5.4



Figure 6-3: InflammaDry® test kits showing positive MMP-9 results.

OD: right eye, OS: left eye. The test kits indicate positive MMP-9 in tears with red and blue stripes in the result window in both the OD and OS.

6.5 Data Management and Statistical Analysis

Data analysis was conducted using Statistica 13.5 (TIBCO Statistica™. Inc., Tulsa, OK, USA). Demographic characteristics, screening and baseline measurements, central corneal clearance, hours of lens wear, lens settling, corneal thickness have been reported in Chapters 3 to 5.

The mean and standard deviation (SD) were used to determine the osmolarity in each eye before lens wear at the screening and baseline and at the follow-up visits. An independent t-test was used to determine the statistically significant difference in osmolarity between baseline and follow-up visits and also between the two lens pairs. The change in osmolarity was expressed as a percentage of the differences between the measurements at the baseline and the follow-up visits of each pair of lens types. Descriptive statistics were used to analyze the InflammaDry® test and these were expressed in percentages. Also, Fisher exact two-tailed test was used to analyze the results from the InflammaDry® test, comparing the results between the lenses at the follow-up visits. Point-Biserial Correlations were performed to determine the relationship between osmolarity and MMP-9 levels of each lens type due to the small sample size and dichotomy of the MMMP-9 results.

6.6 Results

The mean and SD of the osmolarity at the baseline and screening visit for OD and OS were 311 ± 14.86 (range: 287 - 348) and 313.45 ± 29.39 (range: 284 - 397) mOsmol/L respectively, $p > 0.05$. Table 6-1 reports the osmolarity values at the baseline and follow-up visits for each SL pair. Preliminary statistics indicated that there were no significant differences between the eyes at each visit for tear osmolarity and MMP-9 test results, therefore, statistics were performed exclusively on OD only.

Table 6-1: Osmolarity values at the baseline and follow-up visits for the lens pairs using the TearLab Osmolarity System.

Eye	Osmolarity (mOsmol/L)		
	Baseline Visit ($p = 0.74$)	Follow-up Visit – Uncoated SL ($p = 0.68$)	Follow-up Visit – Coated SL ($p = 0.26$)
OD	311.00 ± 14.86	306.40 ± 15.81	302.85 ± 7.96*
OS	313.45 ± 29.39	308.65 ± 17.93	306.85 ± 13.59*

OD: right eye, OS: left eye, SL: scleral contact lenses, n=20. * indicates statistically significant difference comparing the baseline and the follow-up visit, $p < 0.05$.

The mean interocular difference in this study cohort was 2.45 ± 14.53 mOsmol/L. There was a slight reduction in osmolarity levels after SL wear, however, there was no statistically significant difference in tear film osmolarity between the baseline measurements and follow-up measurements for uncoated lenses ($p = 0.35$). In comparison, a statistically significant difference in osmolarity was observed between the baseline and follow-up visits for the coated lenses ($p = 0.04$), table 6-1 and figure 6-4. Comparing the two lens pairs, no significant difference was found at follow-up visits, although the hydra-PEG coated lenses recorded lower osmolarity levels at the follow-up visit ($p = 0.38$). The percentage change in tear osmolarity levels for uncoated and coated SL were 1.48 ± 0.95 % and 2.62 ± 6.91 % respectively.



Figure 6-4: Osmolarity values at baseline and follow-up visits for uncoated and coated SL.

SL: scleral contact lens. The inner small boxes represent mean, bigger boxes represent standard error and whiskers represent standard deviation of osmolarity comparing uncoated and coated SL. The tear osmolarity was measured with Tearlab Osmolarity System and samples were collected at the baseline and follow-up visits at four weeks interval of SL wear, n=20.

As reported in Table 6-2, the InflammaDry® test results indicated that 80 % of the participants tested positive for elevated MMP-9 at the baseline visit. While there was some changes in the number of MMP-9 positive test results following the SL wear, there were no significant differences between the baseline and follow-up visits for either lenses after four weeks of lens wear ($p > 0.05$). Also, the Fisher exact test showed no significant difference in MMP-9 test results comparing the uncoated and coated SL at the follow-up visits, ($p > 0.32$).

Table 6-2: InflammaDry® test results at the baseline and follow-up visits during the study period.

Eye	MMP-9 results (≥ 40 ng/ml)/ %		
	Baseline Visit (p = 1.00)	Follow-up Visit – Uncoated SL (p = 1.00)	Follow-up Visit – Coated SL (p = 0.73)
OD	P: (n=16)/ 80 % N: (n=4)/ 20 %	P: (n=11)/ 55 % N: (n=9)/ 45 %	P: (n=15)/ 75 % N: (n=5)/ 25 %
OS	P: (n=15)/ 75 % N: (n=5)/ 25 %	P: (n=12)/ 60 % N: (n=8)/ 40 %	P: (n=13)/ 65 % N: (n=7)/ 35 %

MMP-9: matrix metalloproteinase 9, N: negative MMP-9 test results, OD: right eye, OS: left eye, P: positive MMP-9 test results, SL: scleral contact lens. n=20.

Using Point-Biserial Correlations for tear osmolarity and MMP-9 test results, there were no correlations between osmolarity, and MMP-9 test results both at baseline (r_{pb} = - 0.22) and follow-up visits (uncoated: r_{pb} = - 0.22 and coated r_{pb} = - 0.12). Figure 6-5, 6-6 and 6-7 illustrate the lack of correlation between these two parameters, as shown by similar median and overlap between the two groups.

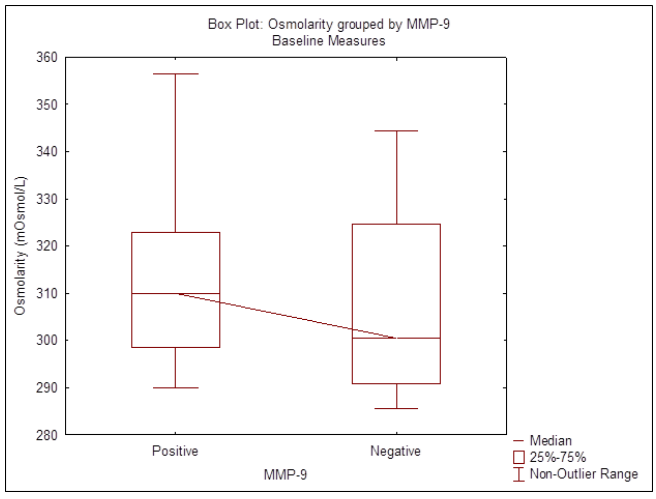


Figure 6-5: Point-Biserial correlations between tear osmolarity and MMP-9 at baseline visit.

MMP-9: matrix metalloproteinase 9. At the baseline visit, osmolarity measurements were obtained using the Tearlab Osmolarity System and MMP-9 test results with InflammaDry® test kit, n=20. Positive means MMP-9 concentration (> 40 ng/ml) and negative means MMP-9 concentration (< 40 ng/ml) in the tear film.

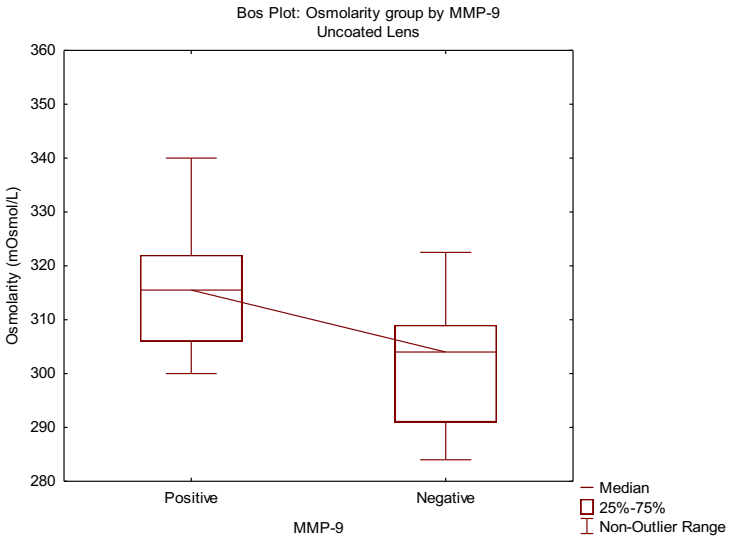


Figure 6-6: Point-biserial correlation between osmolarity and MMP-9 for uncoated SL at follow-up visit.

MMP-9: matrix metalloproteinase 9. Osmolarity measurements were obtained using Tearlab Osmolarity System and MMP-9 test results with InflammaDry® test kit after wearing the uncoated SL for four weeks, n=20. Positive means MMP-9 concentration (> 40 ng/ml) and negative means MMP-9 concentration (< 40 ng/ml) in the tear film.

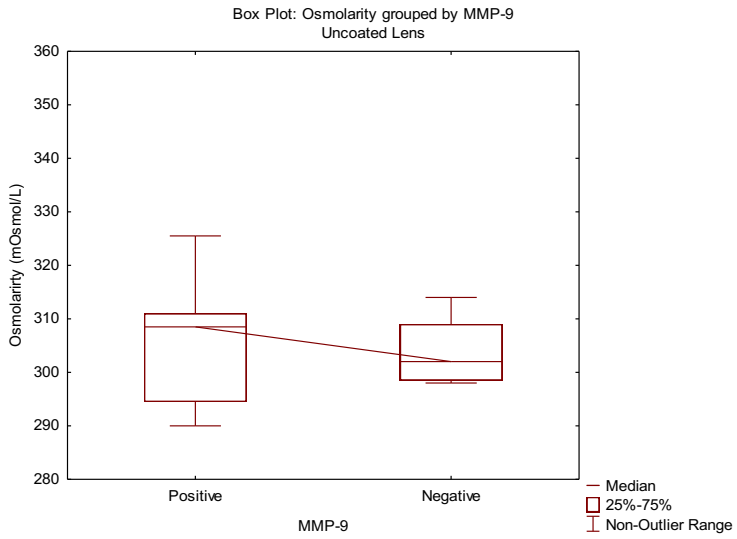


Figure 6-7: Point-biserial correlation between osmolarity and MMP-9 for coated SL at follow-up visit.

MMP-9: matrix metalloproteinase 9. Osmolarity measures were obtained using Tearlab Osmolarity System and MMP-9 test results with InflammaDry® test kit after wearing the coated SL for four weeks, n=20. Positive means MMP-9 concentration (> 40 ng/ml) and negative means MMP-9 concentration (< 40 ng/ml) in the tear film.

6.7 Discussion

Since the introduction of the TearLab Osmolarity System and InflammaDry® test kit into the ophthalmic market, they have been used by eye care practitioners as they offer safe, quick, and easy-to-use in-office ways of measuring, quantifying, diagnosing, and monitoring the progression of DED. (35-41) These novel test kits are highly valuable because of their ability to measure osmolarity levels and detect MMP-9, which have long been found to be significantly higher in the tear film of DED patients compared to controls. (42, 43) The relationship between osmolarity and MMP-9 in the tear film is still debatable, (44-47) however, it has been proposed that the dynamic or fluidic nature of the tear film through evaporation can induce tear hyperosmolarity, which acts as a trigger for the vicious cycle observed in DED. (7) This hyperosmolarity subsequently induces an inflammatory response in the corneal epithelium, eventually leading to the synthesis and release of pro-inflammatory proteins, notably MMP-9. (9, 48, 49) Thus, an increase in osmolarity could induce a significant increase in MMP-9 proteins in the tear film. (29, 47, 50, 51)

The purpose of the study was to evaluate the impacts of SL and surface modification on tear osmolarity and MMP-9 after lens wear. The baseline osmolarity and MMP-9 tests results were combined with OSDI and SPEED scores to determine the participant's eligibility. Therefore, either a higher osmolarity value of > 308 mOsmol/L in each eye or mean difference of > 8 mOsmol/L between eyes and/or a positive MMP-9 result in either eye was needed for the participant to be enrolled in the study according to the eligibility criteria.

The debate on the impact of contact lens wear and change in osmolarity has been ongoing for some time, with varied opinions, as some authors have reported a significant reduction in osmolarity levels after lens removal (52, 53) while others have reported no change in osmolarity. (54-56) Most reports were based on studies on soft contact lenses with different lens materials, study designs, and varied subjects' population, making it difficult to compare our results with many published studies. In comparison, according to Carracedo et al, (56) SL significantly reduced tear osmolarity in keratoconic patients after wearing lenses for 8 hours daily, with a reported median osmolarity value prior to SL removal of 291 mOsmol/L compared to the baseline measures of 301 mOsmol/L. In this study, while statistically significant, only a small reduction in tear osmolarity was found with the hydra-PEG coated lenses.

Environmental factors such as temperature and humidity have been reported to affect tear osmolarity. (57, 58) For example, according to Tomlinson et al, (58) exposure to humidity of 20 % for 10 minutes led to significant changes in tear osmolarity in normal subjects. Other factors such as sex, (59) surgery, (60) and systemic conditions (15) are known to significantly affect tear osmolarity. Also, artificial tears have been reported to reduce tear film osmolarity. (61) In this clinical trial, although it was difficult to control the environmental and other external factors on lens wear, all other clinical factors deemed to have potential effect on tear osmolarity were eliminated through the use of the screening questionnaires. No systemic medication or artificial tears were used throughout the study period, therefore, any observed reduction in osmolarity can be attributed to the SL itself. Our results suggest that the hydra-PEG coating on the SL had a statistically significant effect on reducing tear osmolarity after lens wear. However, the clinical significance of the very small difference measured remains questionable.

To-date, the impacts of SL wear on MMP-9 levels have not been fully explored, making any comparison of our data with other studies very difficult. In this clinical trial, at the baseline visit, 80 % of the participants tested positive for elevated MMP-9 levels in the tear film, while 20 % tested negative. It would be reasonable to suggest that a positive correlation would have been found between MMP-9 and osmolarity, however, this was not the case. This effect can be attributed to the variability in the osmolarity measurements and lack of "sensitivity" of the MMP-9 results, as the test kit shows only positive or negative results and cannot provide information on changes in MMP-9 concentrations. For example, the mean osmolarity for the right eye at the baseline was 311 ± 14.86, with a range of 287 - 348 mOsmol/L. Interestingly, no other correlations were found between the MMP-9 InflammaDry® results and osmolarity for any of the SL pairs at the follow-up visits.

The sensitivity, specificity, and reliability of the InflammaDry® test kit has been documented. (24, 33) Sambursky et al (33) found that the test device showed a sensitivity of 81 % and a 98 % specificity when used to determine DE, which was defined as the presence of subjective symptoms and at least one clinical sign, including reduced Schirmer test, TBUT, and the presence of corneal staining. However, Lanza et al (24) raised questions on the sensitivity of the device. They observed that only 39 % of subjects tested positive for elevated MMP-9 when compared to a standardized DE questionnaire and no significant differences were found between the clinical signs, symptoms, and elevated MMP-9. It was however suggested that not all patients with DE have MMP-9 levels > 40 ng/mL and therefore InflammaDry® test kit could not be used as a confirmatory test for DE patients. This clinical trial did not attempt to make a clinical diagnosis of DE; thus, the sensitivity and specificity of the test kit cannot be extrapolated from this study. Our correlation results also highlight the disparity between the levels of osmolarity and MMP-9, which will need further investigation.

The tear film volume, meniscus height and area at the lower eye lid have been shown to significantly impact the outcome of MMP-9 results with InflammaDry® test kit. (62) To the best of our knowledge, there are only two published papers on the effect of tear film quantity on positivity or negativity of the test results. (62, 63) According to Jun et al, (62) individuals who

tested positive for MMP-9 had significant increased tear meniscus height, area and depth and were significantly different compared to negative MMP-9 test for individuals with decreased tear film profile. In this current study, the tear film volume, meniscus height and other tear film measurements were not explored, therefore, it is difficult to determine the interplay of tear quantity and positivity of our test results.

One of the limitations of our study is that although the study was designed to collect basal tear film and from the SL bowls at the follow-up visits, these were not analyzed to quantify changes in MMP-9 concentration before and after wearing of the lenses due to budget constraints. This would have shed more light on the impact of SL on MMP-9 concentrations in mild to moderate DED. Currently, only a few studies have reported changes in MMP-9 concentrations following SL wear in subjects with normal corneas. (64-66) According to Walker et al, (64) MMP-9 concentrations in the SL bowl significantly increased after 8 hours, however, the concentrations tend to decrease after 3 days of continuous wear. The mechanism is not fully known; however, it has been suggested that accumulation of the fluid reservoir and lack of tear exchange following lens application may be responsible for the increased concentrations of MMP-9 in the tear film. Also, the downward trend in MMP-9 concentration following days of SL wear remains unknown.

In conclusion, the use of SL in this cohort appears to possibly reduce the tear film osmolarity by a small amount. Comparing the two lens pairs, no statistically significant differences in osmolarity levels were observed at the follow-up visit. The hydra-PEG coating did not show superior performance over the conventional SL. Further research is needed to explore tear osmolarity and MMP-9 levels and relations with SL fluid reservoir tear analysis before and after wearing of the lenses.

CHAPTER 7

7.1 Summary of the Study and Future Directions

7.2 Summary of the Study

The thrust of this thesis has focused on investigating the ocular effects of scleral contact lens (SL) wear on individuals experiencing mild to moderate forms of dry eye diseases (DED) using hydra-PEG coated and uncoated lenses. The overall aim was to determine whether these lenses can be used as one of the ***first line*** options for mild to moderate DED in a clinical setting. The study design was a prospective, double-masked, randomized, dispensing, cross over clinical trial involving five visits. The study was formulated around the hypothesis that "*SL wear of uncoated SL or hydra-PEG coated SL in mild to moderate DED is associated with improved ocular surface health"*.

The principal research questions were:

1. Does the wear of SL improve ocular surface health and quality of life (QoL) in subjects with mild to moderate DE?
2. Does the surface treatment of SL with a hydra-PEG coating increase comfort compare to uncoated lenses?

There were 18 females and two males enrolled in the study. Their mean age and standard deviation (SD) were 29.10 ± 7.48 (range: 21- 47) years. The overall OSDI and SPEED scores were 36.45 ± 17.08 and 12.50 ± 4.03 respectively. The habitual visual acuity (VA) presented at the screening visit was 0.12 ± 0.24 for high contrast visual acuity (HCVA) and 0.52 ± 0.32 low contrast visual acuity (LCVA). Tables 7-1 and 7-2 show the inclusion and exclusion criteria as well as the demographic characteristics for the study.

Table 7-1: Inclusion and Exclusion Criteria for the Study.

Inclusion	**Exclusion**
A person was included if he/she: 1. Was at least 18 years old and had full legal capacity to volunteer. 2. Had read, understood, and signed the information consent letter. 3. Had been diagnosed with DED by an Optometrist or Ophthalmologist. 4. Had reduced tear break up time (TBUT) and/or reduced tear meniscus height (TMH), a clinical sign of DED, contact lens discomfort or was symptomatic of DED. 5. Was willing and able to follow instructions and maintain the appointment schedule. 6. Scored ≥ 13 points on the Ocular Surface Disease Index (OSDI) questionnaire. 7. Had greater than 4 points on the Standardized Patient Evaluation of Eye Dryness (SPEED) questionnaire.	A person was excluded if he/she: 1. Was using any topical medications that could likely affect the study outcome. 2. Had undergone any form of corneal surgery. 3. Had any known allergies or sensitivities to the clinical diagnostic products, such as fluorescein dye used in this study. 4. Had clinically significant corneal or conjunctival staining not related to the signs of DE. 5. Had any clinically significant lid or conjunctival abnormalities and active neovascularization on the cornea. 6. Had any anatomic variations of the conjunctiva that could impair proper SL wear/fitting. 7. Had ocular pathology other than DE (e.g., glaucoma, macular degeneration etc.) which could significantly impact visual function and assessment. 8. Was participating in any other type of eye related clinical or research study. 9. Had any active ocular infection and may require topical medications. 10. Was currently taking any systemic medication that could affect the study outcome. 11. Was pregnant. 12. Had been diagnosed, recovered, or tested positive but was asymptomatic with COVID-19.

Table 7-2: Demographic characteristics at the screening and baseline visit.

Demographics	Scores
Age	29.10 ± 7.48 years
Sex	Female (n=18, 90%), Male (n=2, 10%)
OSDI	36.45 ± 17.08
SPEED	12.50 ± 4.03
Contact Lens Wearers	(n=10, 50%)
Frequency + Lens type	Daily disposable CL (n=8, 80%), Monthly replacement CL (n=2, 20%)
Comfortable wearing time	2.40 ± 3.20 hours
Years of Lens wear	3.20 ± 4.00 years
Spectacle wearers	(n=7, 35%)
Non-spectacle wearers	(n=3, 15%)
Allergies (pollen/dust)	(n=6, 30%)
Concretions	(n=3, 15%)
Suspected MGD (with lid notching)	(n=3, 15%)
NaFl Staining	(n=10, 50%)
Cornea	(n=4, 20)
Conjunctiva	(n=6, 30%)

CL: contact lenses, HCVA: high contrast visual acuity, LCVA: low contrast visual acuity, MGD: meibomian gland disease, NaFl: sodium fluorescein, OSDI: ocular surface disease index, SPEED: standardized patient evaluation of eye dryness, VA: visual acuity, n: number of subjects, n=20.

Given the complexity and nature of DED, and the variability in clinical results, the study chose to center on four key objectives, which formed the basis of Chapters 3 to 6.

Chapter 3 focused on evaluating the impact of SL wear on DE questionnaire responses, specifically on QoL, contact lens related dryness, and daily wearing habit and subjective ratings. To understand the influence of SL on DED, three clinical symptoms questionnaires were used.

These were the Contact Lens Impact on Quality-of-Life Questionnaire (CLIQ), Contact Lens Dry Eye Questionnaire 8 (CLDEQ-8) and Wearing Habit and Subjective Ratings. The CLIQ questionnaire showed no statistically significant difference between the two lens pairs ($p = 0.57$). A similar pattern was also reported with the CLDEQ-8 scores (overall score, $p > 0.05$). A significant inverse correlation was reported between CLIQ and CLDEQ-8 questionnaires for both lens types ($r > - 0.5$), which means that as the CLIQ measure increased, the CLDEQ-8 score decreased. It can be inferred from the results that subjects had a better wearing experience, as the SL wear did not induce significant dryness. In terms of the wearing habit and subjective ratings, the average wearing time was identical between the uncoated and coated SL (uncoated: 7.18 ± 1.75 versus coated: 7.16 ± 1.61 hours). All the other symptoms assessed scored more than 70 %, demonstrating that the SL were well tolerated by the participants, with no significant differences between the two lens types. However, our current study was unable to demonstrate that SL wear was associated with an improvement in DED symptoms.

Very few publications have explored the impact of CLIQ on SL wear; these studies compared reports from keratoconic subjects, which were grouped into rigid gas permeable lenses, hybrid, and soft toric contact lens wearers. (1, 2) The results from this current study showed slightly lower CLIQ scores compared to the above cited publications. Possible reasons include differences in study design, experience with the contact lenses and the study cohort.

The wearing habit and subjective ratings questionnaire is the first of its kind to be used to determine the daily wearing pattern or behavior of subjects wearing SL. The results indicate that the SL were well tolerated by the study cohort. Although it might be too early to use this results for any clinical decision making, they do provide valuable information regarding the use of SL among mild to moderate DE patients.

Chapter 4 looked at the degree to which the SL "settled" onto the eye post fitting and its clinical implications as it relates to vision, comfort, and overall health status of the eye. This phenomenon reduces the distance between the front surface of the cornea and the back surface of the SL and is

quantified as the clearance loss, which is commonly termed "lens settling". The mean and standard deviation (SD) of the central corneal clearance (CCC) at the dispensing visit was 260 ± 40 (range: 200 - 300 μm) for both lens pairs. This significantly reduced to 190 ± 40, range: 100 - 290 μm for the uncoated SL and 200 ± 30, range: 130 - 295 μm for the coated SL at the follow-up visits, ($p <$ 0.001). Comparing the two lenses, no significant difference was observed as the lenses settled at similar rates ($p = 0.63$). The actual amount of settling was 70 ± 42 μm (range: 25 - 125; 26.90 %) for uncoated SL and 70 ± 43 μm (range: 10 - 175; 23.10 %) for coated SL, ($p = 0.65$). These results are similar to those previously reported by Nau et al (3), Vincent et al, (4) and Bray et al (5) Also, no significant correlations between CCC and lens settling were observed for uncoated and coated lenses ($p > 0.05$, $r < 0.50$). We concluded that the novel hydra-PEG coating technology on the lens surface does not influence lens settling and that lens settling does not affect visual performance.

Chapter 5 focused on understanding the clinical impact of SL on central corneal thickness (CCT) and change of corneal swelling. Also, central 'thinness' locations (CCTn) of the cornea and correlations with central corneal clearance (CCC) was undertaken to determine the effect of clearance on corneal thickness. The mean and SD at the baseline and follow-up visits were; baseline: 560.55 ± 32.28 μm, post wear of uncoated SL: 557.65 ± 32.10 μm, and post wear of coated SL: 560.50 ± 34.02 μm. There were no significant differences for either lens type for central CCT at the baseline and follow-up visits (all $p > 0.05$). Similar results were found for the thinness locations. No significant correlations between CCC and CCT were observed at the baseline or follow-up visits for either lens type ($p > 0.05$, $r < 0.50$). The change in corneal thickness was observed only in CCTn comparing the baseline to the coated SL (0.06 ± 0.40 %). These results demonstrated there were minimal corneal hypoxic effects when these SL were worn on a daily wear basis.

Chapter 6 examined the impact of SL on osmolarity and matrix metalloproteinase 9 (MMP-9) levels and the relationship between these parameters. There was no statistically significant difference in osmolarity between the baseline levels obtained and those measured post-wear for

the uncoated lenses (311.00 ± 14.86 vs 306.40 ± 15.81 mOsmol/L; $p = 0.35$). However, there was a statistically significant difference in osmolarity measures between the baseline and follow-up visit for the coated lenses (311.00 ± 14.86 vs 302.85 ± 7.96 mOsmol/L; $p = 0.04$). While this is statistically significant, the clinical relevance of this small difference remains questionable. Comparing the two lens pairs, no significant difference was found ($p = 0.38$). The change in osmolarity levels for uncoated and coated lenses were 1.48 % and 2.62 % respectively. There were no correlations between osmolarity and MMP-9 at all visits. More research may be needed to explore the osmolarity levels prior to and after removal of SL and also, relationship between tear analysis and InflammaDry test kit.

7.3 Significance of the Study Results and Clinical Applications

1. There is a potential for using SL to manage symptoms in subjects suffering from mild to moderate DED, as the overall wearing habit and subjective ratings showed > 70 % of lens tolerance among the study cohort.
2. SL wear over the month of wear in this cohort induced little change to the cornea or conjunctival tissue.
3. SL may appear to marginally reduce tear film osmolarity, however, short- and long-term measurements may be needed to determine the sustainability of the lower tear osmolarity and its impact on subjective dryness.
4. The clinical phenomenon of lens settling needs further investigation, especially on its impact on conjunctival morphology.
5. When fitting SL, these results would suggest that a material Dk of 100, corneal clearance of 260 ± 40 μm, lens thickness of 250 μm and lens diameter ranging from 14.80 to 15.40 mm may be required to invoke minimal corneal hypoxia in normal corneas.
6. In this study with this cohort of subjects, the hydra-PEG coating technology did not show superior performance over the uncoated lens for any of the factors assessed. The decision to use the coating is equivocal as it may provide minimal benefit, however it should be remembered that the lenses worn in this study were only used for one month and longer use prior to replacement may provide a benefit.

7.4 Future Directions

This present study has identified four key areas of future research which would contribute knowledge on the use of SL in the management of subjects with mild to moderate DED.

7.4.1 Development and Validation of Standardized Clinical Questionnaires for Evaluating the Performance of Scleral Contact Lenses.

The majority of questionnaires used to assess contact lens performance have focused primarily on soft and rigid gas permeable contact lenses, (6-8) with little work to date on the use of questionnaires to understand the clinical performance of SL. (9, 10) For example, CLIQ used in this study is normally used to quantify the QoL among soft contact lens wearers, even though the developers recommended the 28-item questionnaires can also be used to elicit responses from SL wearers. (2) Similarly, the CLDEQ-8 was purposely developed for soft contact lens wearers to determine their overall wearing experience. (11)

I believe that subjects/patients wearing SL have distinct and varied responses from those wearing soft contact lenses. Therefore, using such questionnaires for SL subjects may not be suitable to determine their true wearing experience or symptom scores. Hence, developing and validating standardized clinical questionnaires which targets parameters more specific and relevant to wearing SL would be beneficial for clinicians.

The wearing habit and subjective rating questionnaire developed for this study could be considered a step in the right direction for understanding the clinical performance of SL. I would therefore suggest critical evaluation and improvement of the questionnaire so that it can be used clinically to elicit the responses of subjects wearing SL.

7.4.2 Scleral Contact Lenses and Midday Fogging

One of the major challenges to successful wearing of SL is midday fogging (MDF), which is the accumulation of particulate matter beneath the lenses. (12-17) McKinney et al (18) estimated that 33 % of SL wearers experience MDF, after an average wearing time of approximately 4.50 hours. Schornack et al (15) also reported 25.80 % among SL wearers. It has been reported that demographic characteristics, lens design and care solutions are not contributing factors of MDF. A recent study by Walker et al (19) has demonstrated that both nonpolar and polar lipids were major contributors to MDF. They determined that protein analysis of the tear reservoir showed no significant difference comparing turbid and non-turbid samples, however, lipid analysis showed significant increase in lipid concentration in the turbid reservoir samples. Although our study did not directly investigate the effect of time and hydra-PEG coating on MDF, some participants reported MDF at least once or twice in a week and this was typically associated with longer wearing time.

It is very difficult to determine whether the hydra-PEG coating had any significant effect on MDF as the wearing habit and subjective ratings did not show any significant difference in terms of vision, which is normally affected by MDF. I therefore propose more research should be conducted on tear reservoir proteomics/lipidomics and its effect on MDF.

7.4.3 Scleral Contact Lens Settling and Clinical Factors

Lens settling is a complex phenomenon which has been investigated by numerous researchers. (5, 20-23) Studies have established that there is no link between lens settling and vision. (4, 5, 24) We found similar results in this study, as there were no correlation between lens settling on high and low contrast visual acuities. Given the number of participants enrolled in the study, I believe there is a need for more studies to understand the impact of lens settling on conjunctival morphology.

7.4.4 Effect of Scleral Lens on Meibomian Glands and the Role of Surface Coating

Available studies have shown that the use of contact lenses affect the anatomical structure of the meibomian glands (MG) compared to non-contact lens wearers. (25-31) The changes in the MG are expressed in terms of atrophy or tortuosity, which are related in part to the duration of lens wear, material composition and modulus. All these studies have been carried out in soft contact lenses. Currently, there is only one study which has attempted to analyze the effect of SL on MG changes. (32) The authors did not find statistically significant difference in meibum expression after 1 year of SL wear in moderate to severe DED subjects. More research may be needed to assess the short-and long-term effects of SL on MG. I believe that perhaps the benefits of hydra-PEG coating will be evident in this type of study, as the smooth coating will potentially reduce the mechanical friction between the front surface of the lens and the tarsal plates.

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Chapter 1

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Chapter 3

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APPENDICES

Appendix 1-1: Dry Eye Questionnaire 5

DRY EYE QUESTIONAIRE (DEQ-5)

Name:

1. Questions about **EYE DISCOMFORT:**

   a. During a typical day in the past month, **how often** did your eyes feel discomfort?

NEVER	RARELY	SOMETIMES	FREQUENTLY	CONSTANTLY
0	1	2	3	4

   b. When your eyes feel discomfort, **how intense was this feeling of discomfort** at the end of the day, within two hours of going to bed?

NEVER HAVE IT	NOT INTENSE AT ALL				VERY INTENSE
0	1	2	3	4	5

2. Questions about **EYE DRYNESS:**

   a. During a typical day in the past month, **how often** did your eyes feel dry?

NEVER	RARELY	SOMETIMES	FREQUENTLY	CONSTANTLY
0	1	2	3	4

   b. When your eyes felt dry, **how intense was this feeling of dryness** at the end of the day, within two hours of going to bed?

NEVER HAVE IT	NOT INTENSE AT ALL				VERY INTENSE
0	1	2	3	4	5

3. Questions about **WATERY EYES:**

   a. During a typical day in the past month, **how often** did your eyes look or feel exessively watery?

NEVER	RARELY	SOMETIMES	FREQUENTLY	CONSTANTLY
0	1	2	3	4

Score:

1a	⊕	1b	⊕	2a	⊕	2b	⊕	3	⊖	TOTAL

Appendix 1-2: Ocular Surface Disease Index Questionnaire

Ocular Surface Disease Index© (OSDI©)[2]

Ask your patient the following 12 questions, and circle the number in the box that best represents each answer. Then, fill in boxes A, B, C, D, and E according to the instructions beside each.

HAVE YOU EXPERIENCED ANY OF THE FOLLOWING *DURING THE LAST WEEK*:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1. Eyes that are sensitive to light?	4	3	2	1	0
2. Eyes that feel gritty?	4	3	2	1	0
3. Painful or sore eyes?	4	3	2	1	0
4. Blurred vision?	4	3	2	1	0
5. Poor vision?	4	3	2	1	0

Subtotal score for answers 1 to 5 (A)

HAVE PROBLEMS WITH YOUR EYES LIMITED YOU IN PERFORMING ANY OF THE FOLLOWING *DURING THE LAST WEEK*:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	
6. Reading?	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine (ATM)?	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A

Subtotal score for answers 6 to 9 (B)

HAVE YOUR EYES FELT UNCOMFORTABLE IN ANY OF THE FOLLOWING SITUATIONS *DURING THE LAST WEEK*:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	
10. Windy conditions?	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A
12. Areas that are air conditioned?	4	3	2	1	0	N/A

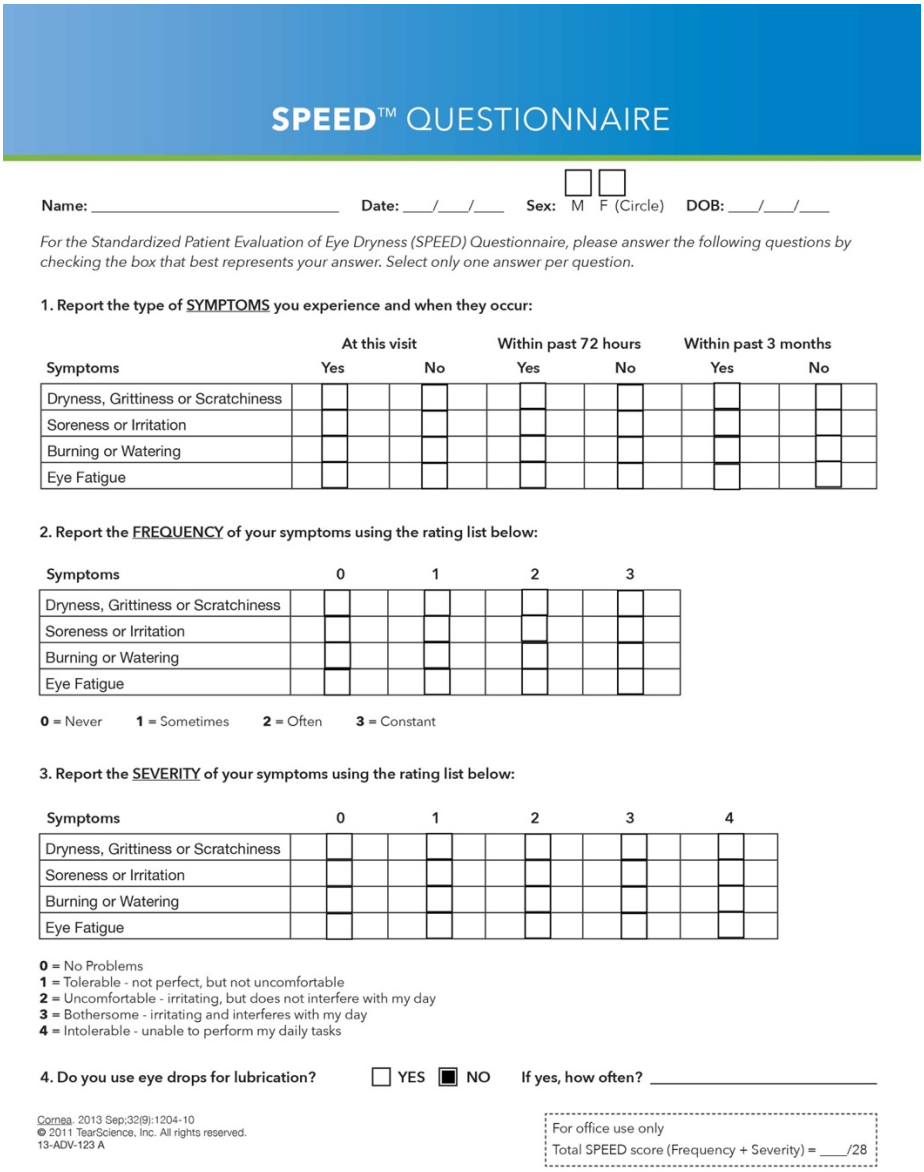
Subtotal score for answers 10 to 12 (C)

ADD SUBTOTALS A, B, AND C TO OBTAIN D (D = SUM OF SCORES FOR ALL QUESTIONS ANSWERED) (D)

TOTAL NUMBER OF QUESTIONS ANSWERED (DO NOT INCLUDE QUESTIONS ANSWERED N/A) (E)

Please turn over the questionnaire to calculate the patient's final OSDI© score.

Appendix 1-3: Standardized Patient Evaluation of Eye Dryness Questionnaire



SPEED™ QUESTIONNAIRE

Name: _____ Date: ____/____/____ Sex: ☐ M ☐ F (Circle) DOB: ____/____/____

For the Standardized Patient Evaluation of Eye Dryness (SPEED) Questionnaire, please answer the following questions by checking the box that best represents your answer. Select only one answer per question.

1. Report the type of SYMPTOMS you experience and when they occur:

	At this visit		Within past 72 hours		Within past 3 months	
Symptoms	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
Dryness, Grittiness or Scratchiness	☐	☐	☐	☐	☐	☐
Soreness or Irritation	☐	☐	☐	☐	☐	☐
Burning or Watering	☐	☐	☐	☐	☐	☐
Eye Fatigue	☐	☐	☐	☐	☐	☐

2. Report the FREQUENCY of your symptoms using the rating list below:

Symptoms	**0**	**1**	**2**	**3**
Dryness, Grittiness or Scratchiness	☐	☐	☐	☐
Soreness or Irritation	☐	☐	☐	☐
Burning or Watering	☐	☐	☐	☐
Eye Fatigue	☐	☐	☐	☐

0 = Never **1** = Sometimes **2** = Often **3** = Constant

3. Report the SEVERITY of your symptoms using the rating list below:

Symptoms	**0**	**1**	**2**	**3**	**4**
Dryness, Grittiness or Scratchiness	☐	☐	☐	☐	☐
Soreness or Irritation	☐	☐	☐	☐	☐
Burning or Watering	☐	☐	☐	☐	☐
Eye Fatigue	☐	☐	☐	☐	☐

0 = No Problems
1 = Tolerable - not perfect, but not uncomfortable
2 = Uncomfortable - irritating, but does not interfere with my day
3 = Bothersome - irritating and interferes with my day
4 = Intolerable - unable to perform my daily tasks

4. Do you use eye drops for lubrication? ☐ YES ■ NO **If yes, how often?** _____

Cornea. 2013 Sep;32(9):1204-10
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13-ADV-123 A

For office use only
Total SPEED score (Frequency + Severity) = ____/28

Appendix 1-4: TFOS DEWS II Management and Therapy Report

Staged management & treatment recommendations for dry eye disease[a,b,c].

Step 1:

- Education regarding the condition, its management, treatment and prognosis
- Modification of local environment
- Education regarding potential dietary modifications (including oral essential fatty acid supplementation)
- Identification and potential modification/elimination of offending systemic and topical medications
- Ocular lubricants of various types (if MGD is present, then consider lipid-containing supplements)
- Lid hygiene and warm compresses of various types

Step 2:

If above options are inadequate consider:

- Non-preserved ocular lubricants to minimize preservative-induced toxicity
- Tea tree oil treatment for Demodex (if present)
- Tear conservation
  - Punctal occlusion
  - Moisture chamber spectacles/goggles
- Overnight treatments (such as ointment or moisture chamber devices)
- In-office, physical heating and expression of the meibomian glands (including device-assisted therapies, such as LipiFlow)
- In-office intense pulsed light therapy for MGD
- Prescription drugs to manage DED[d]
  - Topical antibiotic or antibiotic/steroid combination applied to the lid margins for anterior blepharitis (if present)
  - Topical corticosteroid (limited-duration)
  - Topical secretagogues
  - Topical non-glucocorticoid immunomodulatory drugs (such as cyclosporine)
  - Topical LFA-1 antagonist drugs (such as lifitegrast)
  - Oral macrolide or tetracycline antibiotics

Step 3:

If above options are inadequate consider:

- Oral secretagogues
- Autologous/allogeneic serum eye drops
- Therapeutic contact lens options
  - Soft bandage lenses
  - Rigid scleral lenses

Step 4:

If above options are inadequate consider:

- Topical corticosteroid for longer duration
- Amniotic membrane grafts
- Surgical punctal occlusion
- Other surgical approaches (eg tarsorrhaphy, salivary gland transplantation)

MGD — meibomian gland dysfunction; DED — dry eye disease.

[a] Potential variations within the disease spectrum are acknowledged to exist between patients and the management options listed above are not intended to be exclusive. The severity and etiology of the DED state will dictate the range and number of management options selected from one or more steps.

[b] One or more options concurrently within each category can be considered within that step of the dry eye disease state. Options within a category are not ranked according to importance and may be equally valid.

[c] It should be noted that the evidence available to support the various management options differs and will inevitably be lower for newer management options. Thus, each treatment option should be considered in accordance with the level of evidence available at the time management is instigated.

[d] The use of prescription drugs needs to be considered in the context of the individual patient presentation, and the relative level of evidence supporting their use for that specific indication, as this group of agents differs widely in mechanism of action.

Appendices for Chapter 2
Appendix 1-1a: Email Recruitment Script

- **HEINZ STUDY**

RECRUITING PARTICIPANTS WITH DRY EYE FOR SPECIALTY CONTACT LENS STUDY

Hello,

My name is Heinz Otchere and I am a research associate working on a specialty contact lens study called "HEINZ" at the University of Waterloo, under the supervision of Prof. Lyndon Jones at CORE, School of Optometry and Vision Science.

[optional intro – use when applicable ie. If we have information to review] After reviewing your information against the study criteria, we have determined you may be eligible to participate in a specialty contact lens study.

We are hoping that you may consider participating in this study and have included more details below.

The objective of this study is to evaluate (compare) the ocular effects of two types of specialty (scleral) contact lenses and determine if they improve symptoms of dry eye. Two pairs of scleral lenses (one pair with a specialized coating on the surface, one pair without) will be worn during the study period.

We are looking for symptomatic lens wearers AND non-lens wearers who experience dry eye symptoms, aged 18 or older, to participate in this study. We will custom-fit these specialty scleral lenses, which rest on the white part of the eye (sclera). Due to their custom design and larger fit, these lenses are commonly used for dry eye management and can help relieve ocular discomfort in dry eye patients, including those who may have discontinued using soft contact lenses due to discomfort.

• ABOUT THE STUDY

This study has 5 in-clinic visits spread across approximately a 2-month study duration:

- Visit 1 (0-0) - Screening and baseline measurement and custom lenses ordered – 2.5hrs
- Visit 2 (1-1) - Lens 1 delivery, training & assessments– 2 hrs
- Visit 3 (1-2) - Lens 1 follow-up visit after 4 weeks – 1.5 hrs
  Wash-out period
- Visit 4 (2-1) – Lens 2 delivery & assessments – 1.5hrs
- Visit 5 (2-2) - Lens2 follow-up visit after 4 weeks – 1.5hrs

Total in-visit time commitment – 9 hours

You will also be asked to complete 3 short questionnaires in between study visits (<1 hour total across the study).
The visits will include standard clinical procedures that you might encounter when you attend a routine eye exam. On each visit, both eyes will be assessed with and without contact lenses on the eye. Images

will be taken with a series of instruments, and tear film samples will be collected using small strips designed for tear film analysis.

• PARTICIPANT REQUIREMENTS

- Adults, aged 18 years or older
- Experiences symptoms of dry eye (symptomatic)
- In good ocular and general health and has had a full eye exam in the last 2 years
- Has a prescription of sphere between +20.00 and -20.00DS AND astigmatism up to-3.00DC in each eye
- Anticipates being able to wear the study lenses for at least 8 hours per day, 7 days per week, for the duration of the study

REIMBURSEMENT

In appreciation of your time, you will receive $180 upon study completion. All study contact lenses and solutions will be provided. Parking passes will be provided as required.

• HOW TO PARTICIPATE

If you are interested in participating, please complete and return the attached pre-screening questionnaires by email to hotchere@uwaterloo.ca.

For more information on the HEINZ study, visit http://COREstudies.ca/HEINZ

If you have questions or would like more details, please contact me at hotchere@uwaterloo.ca. You will be provided with all relevant study information prior to study enrollment, and you are under no obligation to participate.

This study has been reviewed and received ethics clearance through a University of Waterloo Research Ethics Board.

• SAFETY DURING COVID-19

We want to let you know that we have revised several of our protocols to keep participants and researchers safe during the pandemic, including enhanced cleaning and mandatory wearing of masks by everyone who is in the Clinic area.

Please note that you will be within 2m (6 feet) of the researcher during some or most of the study visit time. At all times, the furthest possible distance will be maintained.

Sincerely,

Heinz Otchere, OD, MSc
Primary Investigator, PhD candidate
School of Optometry and Vision Science
University of Waterloo

Appendix 1-1b: Email Recruitment Script Modified to Send to Groups

• HEINZ STUDY
RECRUITING PARTICIPANTS WITH DRY EYE FOR SPECIALTY CONTACT LENS STUDY

Hello,

My name is Heinz Otchere and I am a research associate working on a specialty contact lens study called "HEINZ" at the University of Waterloo, under the supervision of Prof. Lyndon Jones at CORE, School of Optometry and Vision Science.

We are hoping that you may consider participating in this study and have included more details below.

The objective of this study is to evaluate (compare) the ocular effects of two types of specialty (scleral) contact lenses and determine if they improve symptoms of dry eye. Two pairs of scleral lenses (one pair with a specialized coating on the surface, one pair without) will be worn during the study period.

We are looking for symptomatic lens wearers AND non-lens wearers who experience dry eye symptoms, aged 18 or older, to participate in this study. We will custom-fit these specialty scleral lenses, which rest on the white part of the eye (sclera). Due to their custom design and larger fit, these lenses are commonly used for dry eye management and can help relieve ocular discomfort in dry eye patients, including those who may have discontinued using soft contact lenses due to discomfort.

• ABOUT THE STUDY

This study has 5 in-clinic visits spread across approximately a 2-month study duration:

- Visit 1 (0-0) - Screening and baseline measurement and custom lenses ordered – 2.5hrs
- Visit 2 (1-1) - Lens 1 delivery, training & assessments– 2 hrs
- Visit 3 (1-2) - Lens 1 follow-up visit after 4 weeks – 1.5 hrs

  Wash-out period
- Visit 4 (2-1) – Lens 2 delivery & assessments – 1.5hrs
- Visit 5 (2-2) - Lens2 follow-up visit after 4 weeks – 1.5hrs

Total in-visit time commitment – 9 hours

You will also be asked to complete 3 short questionnaires in between study visits (<1 hour total across the study).

The visits will include standard clinical procedures that you might encounter when you attend a routine eye exam. On each visit, both eyes will be assessed with and without contact lenses on the eye. Images will be taken with a series of instruments, and tear film samples will be collected using small strips designed for tear film analysis.

• PARTICIPANT REQUIREMENTS

- Adults, aged 18 years or older
- Experiences symptoms of dry eye (symptomatic)
- In good ocular and general health and has had a full eye exam in the last 2 years
- Has a prescription of sphere between +20.00 and -20.00DS AND astigmatism up to-3.00DC in each eye
- Anticipates being able to wear the study lenses for at least 8 hours per day, 7 days per week, for the duration of the study

REIMBURSEMENT

In appreciation of your time, you will receive $180 upon study completion. All study contact lenses and solutions will be provided. Parking passes will be provided as required.

• HOW TO PARTICIPATE

For more information on the HEINZ study, visit http://COREstudies.ca/HEINZ

If you have questions or would like more details, please contact me at hotchere@uwaterloo.ca. You will be provided with all relevant study information prior to study enrollment, and you are under no obligation to participate.

This study has been reviewed and received ethics clearance through a University of Waterloo Research Ethics Board.

• SAFETY DURING COVID-19

We want to let you know that we have revised several of our protocols to keep participants and researchers safe during the pandemic, including enhanced cleaning and mandatory wearing of masks by everyone who is in the Clinic area.

Please note that you will be within 2m (6 feet) of the researcher during some or most of the study visit time. At all times, the furthest possible distance will be maintained.

Sincerely,

Heinz Otchere, OD, MSc
Primary Investigator, PhD candidate
School of Optometry and Vision Science
University of Waterloo

Appendix 1-1c: Social Media Adverts

- **HEINZ STUDY**

RECRUITING PARTICIPANTS WITH DRY EYE FOR SPECIALTY CONTACT LENS STUDY

Social Media, Adverts + Print: copy and images

Possible Hashtags + more as applicable

#ResearchStudy #CORE #COREstudies #UWaterloo #COREuWaterloo #VisionHealth #EyeHealth #HealthyEyes #optometry #ResearchStudies #CurrentStudies #research #study #ocular #EyeResearch #optometrists #HEINZstudy #SpecialtyContactLenses #ContactLenses #ContactLens #scleral #ScleralContactLenses #SuperiorOptics #VisualClarity #breathable #sustainable #EnvironmentallyFriendly #NoPackagingWaste #reusable #DryEyeManagement #CustomizedContactLenses #sphere #CL #dispensing #DryEyeDisease #DED #OcularDiscomfort #sclera #QualityOfLife #QoL #innovation #technology #GetBackIntoContacts #ClinicalResearch #research #GradStudent #OptometryPhD #UWaterlooOptometry #UwOptometry

#WaterlooRegion #KitchenerWaterloo #Kitchener #Waterloo #kwawesome #ontario

Call to Action:

- **Button (paid ads):** Only certain labels are available (eg. 'Learn more'); will link to landing page

- ***In caption text:**
  - Learn more: COREstudies.ca/HEINZ
  - More info: COREstudies.ca/HEINZ
  - More info and registration at COREstudies.ca/HEINZ
  - More info + registration: COREstudies.ca/ HEINZ
  - Link in bio for more information on how to register
  - Link in bio -> 'Current Studies'
  - Click our bio link -> 'Current Studies -> HEINZ
  - Via bio link -> 'Current Studies -> HEINZ
  - Via bio link, or visit COREstudies.ca/HEINZ

Primary Text – On Facebook & Twitter, one of the following copy options will display above one image. (Possible images are included at the end of this document). On Instagram, this copy will display underneath the image.

- **SOCIAL MEDIA CAPTIONS:**

1. Recruiting symptomatic lens wearers AND non-lens wearers who experience dry eye symptoms, aged 18 or older, to participate in a specialty contact lens study. Due to their custom design and larger fit, these lenses are commonly used for dry eye management and can help relieve ocular

discomfort in dry eye patients, including those who may have discontinued using soft contact lenses due to discomfort. *

2. Recruiting participants aged 18+ to be fitted with specialty contact lenses for a study to evaluate if the customized design and larger fit of the lenses will improve dry eye symptoms. Current contact lens wearers AND non-lens wearers may be eligible. Participants will receive $180 upon study completion of 5 study visits, approx. 9 hours. *

3. Seeking contact lens wearers AND non-lens wearers aged 18+ who suffer from dry eye discomfort for a new study to test and determine whether a specialty contact lens made of a breathable material can restore comfort and improve dry eye symptoms. *

Insert one (1) Call to Action, from above. EG. Learn more: COREstudies.ca/HEINZ; Visit http://COREstudies.ca/HEINZ for more info.

• PRINT ADS (DAILY BULLETIN, IN PRINT, THE RECORD, STAFF ASSOCIATION NEWSLETTER) (EXAMPLE)

We are currently recruiting contact lens wearers and non-lens wearers with dry eye symptoms who are at least 18 years of age for a specialty contact lens study. Due to their design and fitting, these scleral lenses can help relieve ocular discomfort and dryness. Contact lenses and care solutions are provided to you at no cost. Eligible participants will attend 5 in-office visits and complete at-home questionnaires. They will receive $180 upon study completion. Total time commitment for HEINZ study visits is approximately 9 hours over 2 months.

All studies conducted at CORE have been reviewed and received ethics clearance through a University of Waterloo Research Ethics Board.

Imagery: Social Media/Adverts/Poster



OTHER images/options:

1.



2.



Appendix 2-2: Informed Consent Letter

School of University of Waterloo 519-888-4567, ext. 33085

Optometry and Vision 200 University Avenue West Fax 519-746-5977

Science Waterloo, Ontario, Canada N2L 3G1
optometry@uwaterloo.ca

Faculty of Science www.optometry.uwaterloo.ca

Ocular effects of scleral lens wear on dry eye patients

Information and Consent Letter

INFORMATION RELATED TO YOUR PARTICIPATION

Please note that your participation in this study does not replace the need for regular eye examinations.

Attending regular eye examinations as recommended by your eye care professional (at least every two years) is essential to ensure that your eyes are healthy. Eye conditions such as glaucoma, diabetes, cataracts and macular disease can only be detected during a full eye examination. Only the front portion of the eye – and, more specifically, only conditions associated with contact lens wear – are assessed during the initial screening visit and all subsequent visits needed for participation in this study. Visits as part of this study do not replace any scheduled visits due with your eye care practitioner. After completion of this study you should resume your eye care with your usual eye care practitioner.

1. What is this study about?

The purpose of the study is to investigate the ocular effects of scleral contact lens wear on a Dry Eye (DE) population using one pair with Hydra-PEG (surface coated) and one pair without (non-coated surface), randomly worn. The other objectives of the study are to evaluate the symptoms of DE, changes to the eye, quality of life, vision and comfort before and after dispensing and wearing each pair of scleral contact lenses for four weeks intervals.

2. Who may participate in this study?

This study will involve a minimum of twenty participants for those having DE. Previous contact lens wear of any lens type is not necessary. To be eligible for this study, you must be at least 18 years old and have been diagnosed with dry eyes by your ophthalmologist/optometrist. Dry eye is a condition in which a person doesn't have enough quality tears to lubricate and nourish front part of the eye. Your vision and ocular health eligibility will be determined at a screening visit.

You may be eligible for inclusion in the study if you:

- Are at least 18 years of age and has full legal capacity to volunteer.
- Have read and understood the information consent letter.
- Have been diagnosed with dry eyes.
- Have reduced non-invasive tear break up time (NITBUT) and/or reduced tear meniscus height (TMH), clinical sign of dry eye disease and contact lens discomfort or are symptomatic of dry eye.
- Are willing and able to follow instructions and maintain the appointment schedule.
- Have greater than 13 points on the OSDI questionnaire.
- Have greater than 4 points on the Standardized Patient Evaluation of Eye Dryness (SPEED).

You may be excluded from the study if you:

- Are using any topical medications that will likely affect the study outcome.
- Have undergone any form of corneal surgery.
- Have any known allergies or sensitivity to the diagnostic pharmaceuticals or products, such as fluorescein, used in this study.
- Have persistent, clinically significant corneal or conjunctival staining using sodium fluorescein dye not related to the signs of dry eye.
- Have any clinically significant lid or conjunctival abnormalities and active neovascularization on the cornea.
- Have anatomic variations of the conjunctiva that can impair proper scleral contact lens wear/fitting.
- Have ocular disease other than dry eye (e.g.: glaucoma, macular degeneration) which may significantly impact visual function and assessment.
- Are participating in any other type of eye related clinical or research study.
- Have any active ocular infection and may require topical medications.
- Are currently taking any systemic medication that may affect the study outcome.
- Are pregnant

- Has been diagnosed, recovered, or tested positive but asymptomatic with COVID-19.

3. What products will be used in this study?

The study will use scleral contact lenses (one pair with Hydra-PEG surface coated and one pair non-coated surface, randomly worn), and contact lens cleaning solutions.

You will be asked to wear each of these lenses between 8-10 hours (not more than 10 hours) daily (7 days in a week) for 1 month. After 1 month of your first pair of lenses, there will be 48 hours of wash out period where you will not be wearing any lenses and the second pair of the lenses will continue following that time.

The type of lenses you will receive will be determined randomly (by chance)- similar to the chance of throwing heads or tails with the toss of a coin. Neither you nor the investigator will get to choose the type of lenses you will receive.

You will not be informed which type of lenses you will be wearing; however, a member of the research team will have this information on file at all times and can provide you with this information at the end of the study if you would like to know.

Depending on which type of lenses you are randomized to, it may be coated or uncoated.

You will be provided with verbal and written instructions explaining how to insert, remove and care for your lenses correctly and safely, including important precautions and warnings. You are expected to follow the instructions given to you. Also, you will be given verbal instructions on how to correctly fill the questionnaires.

Regardless of the study schedule, should you have any difficulty wearing the lenses you should email the investigator immediately or contact *CORE receptionist or on-call optometrist at one of the numbers listed in section 9 if you are concerned about any symptoms you experience.*

If you are unable to maintain the study schedule (for example, due to illness or any problems with the study products) you should inform the investigator immediately. Doing so may or may not affect your participation in the study.

4. What is the time commitment for this study?

This study has a total of five (5) visits (spread over 2 months). The total time commitment for the study visits is approximately 9 hours in total (spread over 2 months duration).

Study visit 1 (2.5 hours) – *Screening, baseline measurement and trial lens fitting:* Your eligibility for this study will be determined using questionnaires and baseline measurements. Other tear tests will also be performed to confirm your DE. You will be trial fitted with scleral contact lenses to make sure the lenses are fitting well and comfortable for you to wear.

Study visit 2 (2 hours) – *Delivery of scleral lens #1:* Your eyes will be examined with slit lamp biomicroscope. Tears will then be collected from your eyes. The investigator will assist you to wear your scleral contact lenses and examine them to make sure the lenses are fitting well on your eyes. Your vision with the lenses will be tested and tears will be collected from the lens bowl when the lenses are removed from your eyes. You will be given three (3) questionnaires to fill out at home for the four weeks of wearing each pair of the scleral contact lenses.

Study visit 3 (1.5 hours) – *Follow-up visit of lens #1*: You will be return after 1 months of contact lens wear. Your contact lenses will be examined, and your vision tested. The investigator will remove the contact lenses from your eyes and collect the tears in the lens bowl. After the lenses are removed, your eyes will be examined once again with slit lamp biomicroscope eye and scans/imaging will be performed.

Study visit 4: (1.5 hours) – *Delivery of scleral lens #2:* The same measurements that were taken in Visit 2 will be repeated at this visit.

Study visit 5 (1.5 hours) – *Follow-up visit of lens #2*: *You will return after 1 month of wearing the second lens pair* The same measurements that were taken in Visit 3 will be repeated at this visit. The study completion forms will be signed to facilitate your remuneration and you will exit the study.

In addition to attending the study visits, you will be asked to complete some home questionnaires. This will take no more than 5 minutes per week.

5. What is expected of me as a participant?

The following procedures will be performed at your study visits.

Please note that most procedures require interaction at less than 6 feet/ 2 metres.

Vision test: You will be asked to read a letter chart.

Osmolarity measurement: You will be asked to sit and lean your head slightly back and gaze toward the ceiling. A handheld device that measures the salt concentration of your tears will gently touch the tear pool at the outer corner of your eye. This measurement can take between approximately 1 to 10 seconds depending on the amount of tears that are present.

Level of protease (MMP-9): You will be asked to sit and lean your head slightly back and gaze toward the ceiling. A handheld device that measures the inflammatory proteins will be used to gently dab multiple times to collect the tears at the inner and outer corners of your eye. This measurement can take between approximately 1 to 20 seconds depending on the amount of tears that are present.

Tear film collection: A small sample of your tears will be collected by holding a small, disposable, sterile glass tube near your lower lid without touching the surface of your eye. This procedure is standard in the study of tears and will be carried out by well-trained, experienced clinical personnel. The sample will be labeled with a code only. All tear samples will be individually frozen and examined at a later date. They will be combined with a series of laboratory chemicals in order to investigate their composition. No genetic material will be analyzed. The resulting chemical combinations will be disposed of using standard laboratory procedures as outlined by the UW Safety Office.

Ocular surface imaging: Your eyes will be scanned/imaged using the Keratograph 5M. You will be asked to be seated at the Keratograph® 5M instrument and you will be asked to blink 2-3 times and hold your eye open for a few seconds until the instrument software takes a picture of the eye. This image acquisition will be repeated two times. This procedure will be used to assess the quality of the tears and abrasion on your cornea.

Sagittal height/Corneal topography: You will be asked to sit at an instrument that take scans (map) of your eyes. The investigator will take two scans of each eye.

Slit-lamp examination (slit lamp biomicroscope): You will be asked to sit at an instrument that uses a bright light beam and microscope to examine both eyes and the contact lenses. The investigator may instill a drop of fluorescein in your eyes; fluorescein is a yellow dye that will reveal any abrasions on the front of your eye (cornea). This dye will dissipate within 10 minutes, though the investigator will rinse your eyes with sterile saline if contact lenses are to be inserted. Digital photographs/ videos of your eyes may be taken. Any photographs/ videos will be labeled with an identification number and will not show any identifying features.

Automated refraction: You will be asked to focus on a target while seated at an instrument that measures your approximate spectacle prescription.

Lens fitting: Contact lenses will be placed on both of your eyes in order to select lenses that provide optimum vision and comfort to be worn during the study.

Lens examination (slit lamp biomicroscope): The investigator will examine the study contact lenses for lens fit, deposits and proper wetting while they are on the eye. In order to assess the lens stability, the investigator will gently rotate the lens on your eye and will ask you to blink to allow it to return to its original position. Digital photographs/ videos of your eyes may be taken. Any photographs/ videos will be labeled with an identification number and will not show any identifying features.

Subjective questionnaires: You will be given three different questionnaires to fill them at home within the period of you wearing your contact lenses. These questionnaires will be returned during the follow-up visits to ensure completeness.

6. Are any risks associated with this study?

Contact lenses can be worn on a daily or extended wear basis. In this study the lenses will be worn on a daily wear basis (NOT extended wear). Adverse events and/or complications in scleral contact lenses are

extremely rare. When contact lenses are worn on a daily wear basis there is a small risk of an adverse event compared to not wearing contact lenses. When contact lenses are worn on an extended wear basis, there is a significantly increased risk of an adverse reaction compared with wearing contact lenses on a daily wear basis. Because this study is a dispensing study, your contact lens wear will be monitored closely by the investigators. You can contact the investigator by phone and email at any time throughout the study.
Complications that may occur during the wearing of contact lenses include discomfort, dryness, aching or itching eyes, excessive tearing, discharge, hyperemia (redness) and variable or blurred vision. More serious risks may include photophobia, iritis, corneal edema or eye infection. It is important to note that you cannot sleep or swim while wearing your contact lenses. Although contact lens-related infections are very infrequent with gas permeable contact lenses, the possibility does exist.

A dye (fluorescein) normally used for eye examinations is being used in this study. Although rare, it is possible that you may have an allergic reaction to the dye. If you have a known allergy to fluorescein, please advise the investigator.
You may feel some eye irritation during and after the osmolarity and levels of protease tests. This irritation may be due to contact between the eye surface and the fleece of the test kit or due to a temporary decrease in the volume of tears in your eye. In most cases, repeated blinking can alleviate this irritation in a very short period of time.

Parts or all of this study will be conducted during the COVID-19 pandemic. Therefore, risks of infection with COVID-19 exist through participation. These risks arise due to possible exposure during commute to and from the study visit as well as during the study visit, particularly due to the closeness of the investigator and you (within 2m for some assessments). The potential effects of COVID-19 are not yet fully known and may include long-term health consequences. In a small percentage, infection with COVID-19 can lead to serious illness, hospitalization, and in rare cases to complications leading to death. Individuals aged 60 and above and those with underlying medical conditions are considered at a greater risk for severe illness from the COVID-19 virus.

In consideration of risks associated with COVID-19, CORE has implemented a series of on-site safety procedures which have been reviewed and approved by the University of Waterloo. These include, but are not limited to, self-screening of all investigators and all participants prior to entering the building, maintaining physical distancing as much as possible, frequent handwashing, wearing of face masks by all investigator and participants, and frequent room and equipment hygiene and decontamination.

In addition to the safety procedures described above, the air is filtered and changed at a level recommended for medical examination rooms and walk-in clinics.

7. How can I minimize the risk of an adverse event?

To decrease the risk of complications, carefully follow the wearing schedule, and cleaning procedures for your lenses and cases as recommended by the study team and outlined in an information package.

8. How will I know if I have had an adverse event?

The following symptoms could indicate that you may have had or are having an adverse response to the study products: excessive tearing, redness, sensitivity to light, pain, discomfort, blurred vision, unusual eye secretions, stinging or burning.

9. What should I do if I experience an adverse event?

If at any time you experience any of the symptoms listed in section 8, you must stop using the study products and contact CORE immediately at either of the following number.

Weekdays	CORE reception desk	519 888- 4742
Evenings/weekends	On-call CORE research optometrist	226 972- 2479

You will also receive this information on a wallet-sized card on your study day which you will be advised to keep on you. In the case of an ocular emergency, please contact CORE at the numbers above. If you are unable to reach anyone from CORE, please consult an eye care practitioner of your choice. If you are unable to source care from an eye care practitioner of your choice and are concerned, please visit the nearest hospital emergency department as soon as possible. In Kitchener-Waterloo, St. Mary's Hospital, Kitchener is the local hospital designated to provide eye care services. If you experience a non-ocular adverse response or illness, please contact CORE at the numbers above and ask to speak with an investigator on this study; we are required to record all health changes while you are participating in our research. If your condition is an emergency, please visit your nearest hospital emergency department, and update CORE when you are able to. The wallet card indicates that you are participating in a CORE study and lists the above contact people and information. If you go to an emergency room, please present this card.

If you experience an adverse event associated with your participation in this study and/or go to the emergency room for treatment, please notify CORE at 519 888-4742 or the investigator at (519) 888-4567 extension 36210. Any costs associated with emergency treatment related to the study will be reimbursed by CORE: upon submission of receipts.

If you become ill or are physically injured as a result of participating in this study, necessary medical treatment will be available, and any additional cost will be sponsor's responsibility. If at any time during the study the investigator feels that it is in your best interest to cease use of study products due to an adverse response you will be discontinued from the study. If this is the case medical care may be arranged to provide treatment and/or follow up visits to ensure that the adverse response has resolved.

10. What are the benefits of participation?

There may or may not be a direct benefit to you. You may find that one of the two (2) lens designs will improve your dry eyes, which may benefit you if you continue to wear the lenses after the study. You may also keep the study lenses (scleral contact lenses) at the end of the study as long you continue care with UW-CLC or your own contact lens specialist. You would have had the opportunity to use one of the newest contact lens designs (surface coated Hydra-PEG) currently being used in many ophthalmic settings which has the potential of reducing the symptoms of dry eyes.

This study may benefit optometric practitioners by expanding their knowledge of contact lens wear and the products available, allowing them to counsel their patients more effectively. This study may help the study sponsor to better understand the performance of the products being used in this study.

11. What are my alternative treatments?

You do not have to be in this study to get help for your eyesight. Some alternatives that are available to you are:

- Eyeglasses
- Commercially available soft or hard contact lenses
- Laser or other refractive surgery
- Usage of no vision correction

12. Will I receive anything in return for my time?

All study products and visits associated with the study will be provided to you at no charge for the duration of the study. You will be reimbursed for the parking costs in our adjacent lot associated with attending study visits. Upon completion of the last study visit you are asked to return all study products (solutions and lenses) before you will be provided with remuneration.

You will receive $20 per scheduled protocol visit hour (including the initial screening visit), up to $180 upon study completion. You will be provided with a cheque or Amazon gift card at your last session. The amount received is taxable. It is your responsibility to report the amount received for income tax purposes. See Section 14 for information about remuneration in the event that your participation in the study ends prematurely (i.e. you decide to withdraw or in the case of an adverse event).

13. What funding do the researchers receive?

The study is funded by Bausch and Lomb. Researchers at CORE may also have received funding from the manufacturers of other products used in this study. This funding is primarily directed towards supporting research and may also occasionally be used to fund professional development activities, for example attending conferences.

14. Can I withdraw from the study? Can my involvement be discontinued?

You are free to decide whether or not to participate in this study. Your decision will not influence the eye care available to you either at the School of Optometry& Vision Science or with your own optometrist. You have the right to withdraw from the study at any time without penalty, by contacting the study

investigator or CORE's receptionist at 519 -888 – 4742. If you choose to discontinue your data will only be included in future statistical analysis if you give your permission for this.

You may be removed from the study if you do not comply with the study instructions, or the investigator believes it to be in your best interest. Your participation may be discontinued and/or the study could be terminated by sponsor or the University of Waterloo's Office of Research Ethics at any time. In the event that you withdraw or are discontinued from the study, you will receive $20 per hour for the time that you were involved in the study.

15. Confidentiality and security of data

All information you provide as a participant, and the link between your identity and any data we collect as result of your participation, including your private health information, plus records of your participation in this study, will be held confidential except as disclosure is required by local, state/provincial and federal laws, and any other regulations, or as described in this informed consent document. You will be assigned an identification number, which will appear on all study records in place of your name. Any data collected in this investigation may be released to the study sponsor, submitted for publication or used in meetings/ presentations. Neither your name nor information disclosing your identity will be released or published.

For the purpose of conducting and monitoring the research, your study records will temporarily contain your name while the study is ongoing, and the records may be inspected at CORE by the study sponsor (Bausch and Lomb), the sponsor's designate, the Office of Research Ethics at the University of Waterloo, and by regulatory authorities in Canada, namely Health Canada; however, no records containing identifiable/personal information will be permitted to leave the custody of CORE. These reviews are done to check on the quality of the study, to check the information collected in this study, to check how the study is conducted, to monitor participants' safety, or for other uses allowed by law.

Worn study lenses and/ or tears without any identifying characteristics, may be retained at CORE for one to two years in case CORE needs them for further research. They will be stored in a way to prevent spoilage of components. No genetic material from your contact lenses or your tears will be analyzed, and no personal identifiers will be on the lens/ tear label. Any left-over samples will be destroyed using the University of Waterloo biowaste disposal procedures.

Digital photographs and/or video recording of your eyes taken for documenting and explaining the information collected in the study will not show any identifying facial features and will be labeled with an identification number rather than your name. These photographs and/or video recordings may be shown to other researchers within CORE or the School of Optometry, to the sponsor and others within their company to explain the data, and may be shown publicly (e.g. presentations or publications).

Paper and electronic records from this study will be kept at CORE/ School of Optometry for a minimum of 25 years. Paper copies of study data are safely held in a secure storage area only available to authorized study personnel and later moved to an approved offsite storage contracted by the University of Waterloo. All electronic study data will be encrypted and stored on secured servers located at the University of Waterloo. Electronic records are protected and strong passwords are required to gain access. In addition, access to the electronic database is limited to a core group of data management personnel and is not

accessible to unauthorized personnel. Records will be confidentially disposed of in accordance with the guidelines laid out by the University of Waterloo. For more information regarding the University of Waterloo's policies on information security you can visit the following website: https://uwaterloo.ca/secretariat/policies-procedures-guidelines/policy-46-information-management.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

16. Other important issues

If you have to undergo any medical treatment or begin to take any medication during the study, or if there is a change in your existing treatment or medication during the study, you must immediately notify the researcher. Additionally, you will be informed of any new findings related to the study that could influence your decision about continuing to participate in the study. If you have any questions regarding the study procedures, please contact us at 519-888-4742 or 519-888-4567 ext 36210.

17. Questions or concerns about participation in the study

This study has been reviewed by and received ethics clearance through a University of Waterloo Research Ethics Board (ORE#40887). If you have questions for the Committee, contact the Office of Research Ethics, at 1-519-888-4567 ext. 36005 or reb@uwaterloo.ca. For all other questions contact Heinz Otchere 1-519-888-4567 ext. 36210 or CORE at 519-888-4742

Declaration of Informed Consent

I have read the above description prior to deciding to participate in this study. I have had an opportunity to ask questions and have received acceptable answers. I agree to adhere to the lens care and wearing instructions provided to me. If I am unable to do so, I shall report this to the investigator as soon as possible.

I am aware that my participation in this study does not replace the need for regular eye examinations, and that attending regular eye examinations is essential to ensure that my eyes are healthy.

I am aware that I may withdraw from the study at any time without affecting my relationship with CORE or the School of Optometry & Vision Science. I am aware that the investigator reserves the right to discontinue my participation from the study at any time, either in regard to the research or the health of my eyes. I agree to return all study materials to the Centre upon discontinuation from, or completion of, the study.

I am aware that my participation in this study is voluntary, but that following study procedures and attending scheduled sessions is important to the success of the research. I am aware that the researcher would appreciate notification if I am unable to attend a scheduled session, so that it can be rescheduled promptly.

I am aware that I need to report any adverse events, changes to my health or medication throughout the study to the study investigators.

I am aware that videos or photographs of my eyes may be taken for educational purposes which may be used in medical or scientific books, magazines, or journals.

I am aware that this study has been reviewed and received ethics clearance through a University of Waterloo Research Ethics Board (ORE file# 40887). I was informed that if I have questions for the Committee, I can contact the Office of Research Ethics, at 1-519-888-4567 ext. 36005 or reb@uwaterloo.ca.

I am aware that any data collected during the course of the study will be secured in accordance with University of Waterloo policies.

With full knowledge of all foregoing, I agree, of my own free will, to participate in this study. I also consent to the collection, use and disclosure of my personal health information and study data from this study.

I am aware that I will receive a copy of this information and consent letter. I am aware that by signing this form I do not waive my legal rights or release the investigator(s), sponsor and/or involved institution(s) from their legal and professional responsibilities.

_____ _____

Signature of participant Date

_____

Printed name of participant

_____ _____

Signature of person explaining consent Date

Appendix 2-3: Screening Forms

SCREENING FORM

Date _____ **Study** _____ **Participant** _____ **Participant ID** _____

ICL Checklist for Prospective Participant (PP)

- ☐ ICL given to PP
- ☐ PP given ample time to read ICL
- ☐ PP given opportunity to ask questions
- ☐ PP initialed all pages
- ☐ PP, investigator, and witness correctly signed and dated ICL
- ☐ PP given copy of ICL
- ☐ PP forgot copy of ICL – copy has been mailed to address listed in pre-screening database
- ☐ PP took ICL home to discuss with family member(s) or friend(s)

History:

Year of birth _____ (YYYY) Age_____ ☐ Female ☐ Male ☐ Other ☐ Prefer not to say Occupation_____

Current Lens Wear:

Current lens type: _____ Average wearing time: hours/day _____ days/week _____total # years wear _____

Replacement frequency: _____ Current care system: _____

Comfortable/tolerable wearing time: _____ hours/day Comfortable wearing time less than average wearing time: ☐ Yes ☐ No

Presence of symptoms of dryness & discomfort: ☐ Yes ☐ No Use of rewetting /lubricant drops: ☐ Yes ☐ No

If "Yes": Current rewetting drops: _____ How often do you insert drops: ____ / day

____ / week

Other relevant history:

General Health _____Medications (current medications or taken within the past 3 months) _____

Allergies _____ Smoker? _____

OD

INCLUSION / EXCLUSION CRITERIA (Dry Eyes) Please tick one

INCLUSION			**EXCLUSION**		
Y	**N**		**Y**	**N**	
☐	☐	Is at least 18 years of age and has full legal capacity to volunteer	☐	☐	Is using topical medications that will likely affect the study outcome
☐	☐	Has read, understood and signed the information consent letter	☐	☐	Has undergone any form of corneal surgery
☐	☐	Has been diagnosed with dry eyes.	☐	☐	Has any known allergies or sensitivity to the diagnostic pharmaceuticals or products, such as fluorescein, used in this study
☐	☐	Has reduced tear break up time (NITBUT) and/or reduced tear meniscus height (TMH), clinical sign of dry eye disease and contact lens discomfort or is symptomatic of dry eyes	☐	☐	Has persistent, clinically significant corneal or conjunctival staining using sodium fluorescein dye not related to the signs of dry eye
☐	☐	Is willing and able to follow instructions and maintain the appointment schedule.	☐	☐	Has any clinically significant lid or conjunctival abnormalities and active neovascularization on the cornea
☐	☐	Has greater than 13 points on the OSDI	☐	☐	Anatomic variations of the conjunctiva that can impair proper scleral or soft contact lens wear
☐	☐	Has greater than 4 points on the Standardized Patient Evaluation of Eye Dryness (SPEED).	☐	☐	Ocular pathology other than dry eye (e.g. glaucoma, etc.) which may significantly impact visual function and assessment
			☐	☐	Has any active ocular infection and may require topical medications
			☐	☐	Has been diagnosed, recovered, or tested positive but asymptomatic with COVID-
			☐	☐	Currently taking any systemic medication that may affect the study outcome
			☐	☐	Is pregnant

Based on the study inclusion/exclusion criteria, is the participant suitable for the study? ☐ **Yes** ☐ **No**

Participant to continue in study? ☐ **Yes** ☐ **No**

Investigator signature:

_____ **Date:** _____

Appendix 2-4: Biomicroscopy Form

OS

INCLUSION / EXCLUSION CRITERIA (Dry Eyes) Please tick one

INCLUSION			EXCLUSION		
Y	**N**		**Y**	**N**	
☐	☐	Is at least 18 years of age and has full legal capacity to volunteer	☐	☐	Is using topical medications that will likely affect the study outcome
☐	☐	Has read, understood and signed the information consent letter	☐	☐	Has undergone any form of corneal surgery
☐	☐	Has been diagnosed with dry eyes.	☐	☐	Has any known allergies or sensitivity to the diagnostic pharmaceuticals or products, such as fluorescein, used in this study
☐	☐	Has reduced tear break up time (NITBUT) and/or reduced tear meniscus height (TMH), clinical sign of dry eye disease and contact lens discomfort or is symptomatic of dry eyes	☐	☐	Has persistent, clinically significant corneal or conjunctival staining using sodium fluorescein dye not related to the signs of dry eye
☐	☐	Is willing and able to follow instructions and maintain the appointment schedule.	☐	☐	Has any clinically significant lid or conjunctival abnormalities and active neovascularization on the cornea
☐	☐	Has greater than 13 points on the OSDI	☐	☐	Anatomic variations of the conjunctiva that can impair proper scleral or soft contact lens wear
☐	☐	Has greater than 4 points on the Standardized Patient Evaluation of Eye Dryness (SPEED).	☐	☐	Ocular pathology other than dry eye (e.g. glaucoma, etc.) which may significantly impact visual function and assessment
			☐	☐	Has any active ocular infection and may require topical medications
			☐	☐	Has been diagnosed, recovered, or tested positive but asymptomatic with COVID-
			☐	☐	Currently taking any systemic medication that may affect the study outcome
			☐	☐	Is pregnant

Based on the study inclusion/exclusion criteria, is the participant suitable for the study? ☐ **Yes** ☐ **No**

Participant to continue in study? ☐ **Yes** ☐ **No**

Investigator signature:

_____ **Date:** _____

Biomicroscopy

Section A: Slit Lamp Examination

Right Eye		Left Eye
☐ All Negative		☐ All Negative
Present / absent	Lids - flakes	Present / absent
Present / absent	Lid Margin Notching	Present / absent
Present / absent	Lashes matted	Present / absent
Present / absent	Conjunctival redness diagram	Present / absent
Present / absent	Conjunctival chemosis	Present / absent
Present / absent	Conjunctival discharge	Present / absent
Present / absent _____ - sectoral Y / N circumlimbal	Limbal hyperemia location	Present / absent sectoral - _____ circumlimbal – Y / N
Present / absent	Corneal Edema	Present / absent
Present / absent _____ - sectoral Y / N circumlimbal	Corneal Vascularization location	Present / absent sectoral - _____ circumlimbal – Y / N
_____Number	Corneal scar diagram	Number _____
Watery Mucous Ropy Muco-purulent	Discharge	Watery Mucous Ropy Muco-purulent
Clear Cells Flare	Anterior Chamber	Clear Cells Flare
0 1 2 3		0 1 2 3

Section B Corneal Infiltrates

☐ All Absent		☐ All Absent
number	Corneal Infiltrates	number
#_____Size_____Depth_____Stain____Location	Central	#_____Size_____Depth_____Stain____
#_____Size_____Depth_____Stain____Location	Mid-peripheral	#_____Size_____Depth_____Stain____
#_____Size_____Depth_____Stain____Location	Peripheral	#_____Size_____Depth_____Stain____

Size (diameter of largest infiltrate)
0 = none
1 = <0.5 mm
2 = 0.5 to 1mm
3 = >1 to 1.5mm
4 = >1.5mm

Depth of large infiltrate
0 = none
1 = epithelial
2 = sub-epithelial
3 = mid stromal
4 = deep stromal

Staining
0 = none
1 = epithelial
2 = stromal glow
3 = pooling with thinning of epithelium
4.= absent epithelium

Section C Corneal Fluorescein Staining

_____Type_____Stain____Location	Central	Location_____Stain_____Type_____
_____Type_____Stain____Location	Mid-peripheral	Location_____Stain_____Type_____
_____Type_____Stain____Location	Peripheral	Location_____Stain_____Type_____

Staining
D = Diffuse
L = Localized
O = Overlying

Type
Sup = Superficial
Coal = Coalesced
Micro = Micropunctate

Signature: _____ Date: _____

Appendix 7

Appendix 2-5: Study Visit Forms

Date_____(ddmmyy) Study: _____Participant _____ID_____

A. SCREENING VISIT: SCREENING AND BASELINE MEASUREMENTS (VISIT 0-0)

1. PARTICIPANT SIGNS ICL

YES	NO	PLEASE TICK ONE

2. INVESTIGATOR RETRIEVES OSDI AND SPEED QUESTIONNAIRES FROM PARTICIPANT

3. VISUAL ACUITY

VA (□Contact Lens/□Spectacle/ □ None) Tick one	**OD**		**OS**	
	HCVA	LCVA	HCVA	LCVA
LogMAR (normal Illumination)				

4. OSMOLARITY MEASUREMENTS WITH TEARLAB OSMOLAIRTY SYSTEM® (>308 mOsm/L)

Osmolarity (mOsm/L)	**OD (1)**	**OS (1)**	**OD (2)**	**OS (2)**
With CL (Tick)				
Without CL (Tick)				

5. LEVELS OF PROTEASE (MMP-9) WITH INFLAMMADRY® TEST KITS

Protease Levels: Positive/Negative/Invalid (≥40ng/ml/<40ng/ml)	**OD**	**OS**
With CL (Tick □)		
Without CL (Tick □)		

DETERMINE ELIGIBILITY	**YES**	**NO**

6. <u>TEARS FROM THE OCULAR SURFACE (BASELINE)</u>

YES	NO	PLEASE TICK

7. SLIT LAMP BIOMICROSCOPY (PLEASE FILL OUT BIOMICROSCOPY FORMS FOR EACH EYE)

8. OCULAR SURFACE IMAGING: K5, CORNEAL TOPOGRAPHY, SAGITTAL HEIGHT AND AUTOREFRACTION

OD1 OD2 OS1 OS2

Parameters	**Pentacam HR**			**Pentacam HR**			**Pentacam HR**			**Pentacam HR**		
Simulated K: Flat D/Steep D	_____D/_____ D			_____D/_____ D			_____D/_____ D			_____D/_____ D		
Average K (D)												
Corneal cyl and axis	_____X_____			_____X_____			_____X_____			_____X_____		
Pachymetry (cen & thin pts) µm	_____/_____			_____/_____			_____/_____			_____/_____		
HVID (mm) (<11.7=14.8: >11.8=15.4)												
Pupil diameter (mm)												
e-value												
Sagittal Height with Visante @15mm Hori & Vert (mm)	H_____/V_____			H_____/V_____			H_____/V_____			H_____/V_____		
Topographic Corneal Thickness with Spectralis OCT @10mm (@090 and @180 µm)	**Eye**	**+5S**	**+4**	**+3**	**+2**	**+1**	**0**	**-1**	**-2**	**-3**	**-4**	**-5I**
	ODV											
	OSV											
		+5N	**+4**	**+3**	**+2**	**+1**	**0**	**-1**	**-2**	**-3**	**-4**	**-5T**
	ODH											
	OSH											
Autorefraction (sph/cyl/axis)	__/_____/___			__/_____/__			__/_____/___			_/_____/_		

Keys: K=radius of curvature, D=diopter, V=vertical, H=horizontal, HVID=horizontal visible diameter, S=superior, I=inferior, N=nasal, T=tempor

TRIAL LENS FITTING

9. TRIAL LENS FITTING AND EXAMINATION WITH ZEN™RC DIAGNOSTIC LENSES

9a. SCLERAL CONTACT LENS FITTING

	OD			OS		
Lens Parameters	**Trial # 1**	**Trial # 2**	**Trial # 3**	**Trial # 1**	**Trial # 2**	**Trial # 3**
Lens Type						
BC/ D/ PWR/CT/Sag	/ / /	/ / /	/ / /	/ / /	/ / /	/ / /
Auto OR	/ /	/ /	/ /	/ /	/ /	/ /
VA (HCVA/LCVA)	/	/	/	/	/	/
CC (um) with Spectralis OCT						

FINAL SCLERAL LENS TO ORDER: BC: DIAM: P: CT: SAG: TINT:

COMMENT(S):

Keys: BC= base curve, OR=over refraction, VA=visual acuity, HCVA=high contrast visual acuity, LCVA=low contrast visual acuity, CC=central clearance, D=diameter, CT=central thickness, PWR= power

9b. SCLERAL LENS ASSESSMENT WITH SLIT LAMP CAMERA (FLUORESCEIN PATTERN)

	OD			OS		
Fluorescein Rating with Slit Lamp Camera	**Trial # 1**	**Trial # 2**	**Trial # 3**	**Trial # 1**	**Trial # 2**	**Trial # 3**
Central -2 = flat, moderate dark touch area -1 = slightly flat, small dark noticeable touch at centre 0 (250-350) = alignment across optic zone +1 = slightly steep, noticeably brighter at centre +2 = steep, clearly noticeable central pooling	-2 -1 0 +1 +2	-2 -1 0 +1 +2	-2 -1 0 +1 +2	-2 -1 0 +1 +2	-2 -1 0 +1 +2	-2 -1 0 +1 +2
Limbal Zone -2 = flat, fluorescein under MP merging into edge -1 = slightly flat, slight fluorescein under MP 0 (50-100) = alignment, smooth transition into edge +1 = slightly tight, narrow or slight dark band before edge +2 = tight, moderate pressure just before the edge lift	-2 -1 0 +1 +2	-2 -1 0 +1 +2	-2 -1 0 +1 +2	-2 -1 0 +1 +2	-2 -1 0 +1 +2	-2 -1 0 +1 +2
Scleral Zone -2 = excessive -1 = slightly excessive 0 (no toric needed) = optimal +1 = slightly insufficient +2 = insufficient	-2 -1 0 +1 +2	-2 -1 0 +1 +2	-2 -1 0 +1 +2	-2 -1 0 +1 +2	-2 -1 0 +1 +2	-2 -1 0 +1 +2

NOTE: 1. PLEASE REMEMBER TO TAKE PICTURES OF THE FLUORESCEIN PATTERNS DURING LENS ASSESSMENT

2. IF THE LENS REQUIRES MODIFICATION DURING DISPENSING VISIT, PLEASE RECORD AND MAKE THE NECESSARY ADJUSTMENT AND REORDER THE LENSES.

3. RESCHEDULE APPOINTMENT, WHEN NECESSARY, FOR REFITTING AND DISPENSING

B. <u>DISPENSING VISIT: LENS INSERTION, ASSESSMENT AND QUESTIONNAIRE (VISITS 1-1, 2-1)</u>
<u>10a. SLIT LAMP BIOMICROSCOPY (PLEASE FILL OUT THE BIOMICROSCOPY FORMS)</u>

Indicate whether it is the Right Eye (OD) or Left Eye (OS) and examine appropriately.

<u>10b. VISUAL ACUITY</u>

VA (with Contact Lens)	**OD**		**OS**	
LogMAR (Normal Illumination)	HCVA	LCVA	HCVA	LCVA

11a. SCLERAL LENS ASSESSMENT WITH SLIT LAMP (FLUORESCEIN PATTERN)

	OD	OS
Fluorescein Rating with Slit Lamp Camera	**Lens #**	**Lens #**
Central -2 = flat, moderate dark touch area -1 = slightly flat, small dark noticeable touch at centre 0 (250-350) = alignment across optic zone +1 = slightly steep, noticeably brighter at centre +2 = steep, clearly noticeable central pooling	-2 -1 0 +1 +2	-2 -1 0 +1 +2
Limbal Zone -2 = flat, fluorescein under MP merging into edge -1 = slightly flat, slight fluorescein under MP 0 (50-100) = alignment, smooth transition into edge +1 = slightly tight, narrow or slight dark band before edge +2 = tight, moderate pressure just before the edge lift	-2 -1 0 +1 +2	-2 -1 0 +1 +2
Scleral Zone -2 = excessive -1 = slightly excessive 0 (no toric needed) = optimal +1 = slightly insufficient +2 = insufficient	-2 -1 0 +1 +2	-2 -1 0 +1 +2

11b. VISUAL ACUITY

Visual Acuity (with scleral lens**)**	**OD**		**OS**	
LogMAR (normal illumination)	HCVA	LCVA	HCVA	LCVA

12. TOPOGRAPHIC CORNEAL CLEARANCE WITH SPECTRALIS OCT @10MM

Parameter	**Spectralis OCT @10mm**			
	ODV @090 μm	**OSV @090 μm**	**ODH @180 μm**	**OSH @180 μm**
+5 Sup				
+4 Sup				
+3 Sup				
+2 Sup				
+1 Sup				
centre (0)				
-1 Inf				
-2 Inf				
-3 Inf				
-4 Inf				
-5 Inf				

13. SCLERAL LENS REMOVAL AND TEAR COLLECTION

*Investigator carefully removes scleral contact lenses and collects tears from the bowl (**baseline tears**)*

14. TRAINING ON LENS INSERTION, CARE AND STUDY MATERIALS (1-1, 2-1)

Investigator trains participants on lens insertion, care and dispensing of study materials

15a. STUDY LENSES AND CARE SYSTEM

I. Zen™ RC scleral lenses (non-coated surface or Hydra-PEG coated, randomly selected)
II. Clear Care and Disinfecting Solution
III. Boston Simplus Comfort Formula Conditioning Solution
IV. Sensitive Eyes Saline
V. Minims Saline

15b. QUESTIONNAIRES TO BE FILLED BEFORE FOLLOW-UP VISIT

1. Contact Lens Dry Eye Questionnaire 8 (CLDEQ-8) - 2x

2. Contact Lens Quality of Life Questionnaire (CLIQ) - 4x

3. Wearing habit/experience log along with subjective grading scales - 4x

4. Black/blue pen

C. <u>FOLLOW-UP VISIT: PARTICIPANT WEARING SCLERAL CONTACT LENSES (1-2, 2-2)</u>
Note: Participant arrives at least 4hours of lens wear on appointment day

16. <u>VISUAL ACUITY</u>

Visual Acuity (with scleral lens)	**OD**		**OS**	
LogMAR (normal Illumination)	HCVA	LCVA	HCVA	LCVA

<u>17a. TOPOGRAPHIC CORNEAL CLEARANCE WITH SPECTRALIS OCT</u>

Parameter	**Spectralis OCT @10mm**			
	ODV @090 μm	**OSV @090 μm**	**ODH @180 μm**	**OSH @180 μm**
+5 Sup				
+4 Sup				
+3 Sup				
+2 Sup				
+1 Sup				
centre (0)				
-1 Inf				
-2 Inf				
-3 Inf				
-4 Inf				
-5 Inf				

17b. SCLERAL LENS ASSESSMENT WITH SLIT LAMP (FLUORESCEIN PATTERN) WITH LENS ON THE EYE

	OD	OS
Fluorescein Rating with Slit Lamp Camera	**Lens # 1**	**Lens # 2**
Central -2 = flat, moderate dark touch area -1 = slightly flat, small dark noticeable touch at centre 0 (250-350) = alignment across optic zone +1 = slightly steep, noticeably brighter at centre +2 = steep, clearly noticeable central pooling	-2 -1 0 +1 +2	-2 -1 0 +1 +2
Limbal Zone -2 = flat, fluorescein under MP merging into edge -1 = slightly flat, slight fluorescein under MP 0 (50-100) = alignment, smooth transition into edge +1 = slightly tight, narrow or slight dark band before edge +2 = tight, moderate pressure just before the edge lift	-2 -1 0 +1 +2	-2 -1 0 +1 +2
Scleral Zone -2 = excessive -1 = slightly excessive 0 (no toric needed) = optimal +1 = slightly insufficient +2 = insufficient	-2 -1 0 +1 +2	-2 -1 0 +1 +2

18. CONTACT LENS REMOVAL, ASSESSMENT AND QUESTIONNAIRE REVIEW

Note: Participant arrives after 4hours of lens wear on appointment day

19. TEAR COLLECTION FROM THE LENS BOWL

*Note: Investigator removes contact lens and collect tears from lens bowl (**standard tears**)*

20. OSMOLARITY MEASUREMENTS WITH TEARLAB OSMOLARITY SYSTEM

Osmolarity (mOsm/L)	**OD (1)**	**OS (1)**	**OD (2)**	**OS (2)**
Without CL				

21. LEVELS OF PROTEASE (MMP-9) WITH INFLAMMADRY®

Protease Levels: Positive/Negative/Invalid (≥40ng/ml/<40ng/ml)	**OD**	**OS**
Without CL		

22. SLIT LAMP BIOMICROSCOPY (PLEASE FILL OUT THE BIOMICROSCOPY FORMS)

Indicate whether it is the Right Eye (OD) or Left Eye (OS) and examine appropriately.

23. TOPOGRAPHIC CORNEAL THICKNESS WITH SPECTRALIS OCT @10MM

Parameter	Spectralis OCT @10mm			
	ODV @090 μm	**OSV @090 μm**	**ODH @180 μm**	**OSH @180 μm**
+5 Sup				
+4 Sup				
+3 Sup				
+2 Sup				
+1 Sup				
centre (0)				
-1 Inf				
-2 Inf				
-3 Inf				
-4 Inf				
-5 Inf				

24. CORNEAL TOPOGRAPHY WITH PENTACAM WITHOUT LENS ON THE EYE

OD1 OD2 OS1 OS2

Parameters	**Pentacam HR**	**Pentacam HR**	**Pentacam HR**	**Pentacam HR**
Simulated K Readings Flat D/Steep D	**_____D/_____ D**	**_____D/_____ D**	**_____D/_____ D**	**_____D/_____ D**
Average K (D)				
Corneal cyl and axis	**_____X_____**	**_____X_____**	**_____X_____**	**_____X_____**
Pachymetry (cen & thin pts) µm	**_____/_____**	**_____/_____**	**_____/_____**	**_____/_____**
HVID (mm)				
Pupil diameter (mm)				
e-value				

25. QUESTIONNAIRE REVIEW

Investigator collects and reviews all questionnaires for completeness.

General comment(s)/Discovery:

PARTICIPANT EXITS THE STUDY

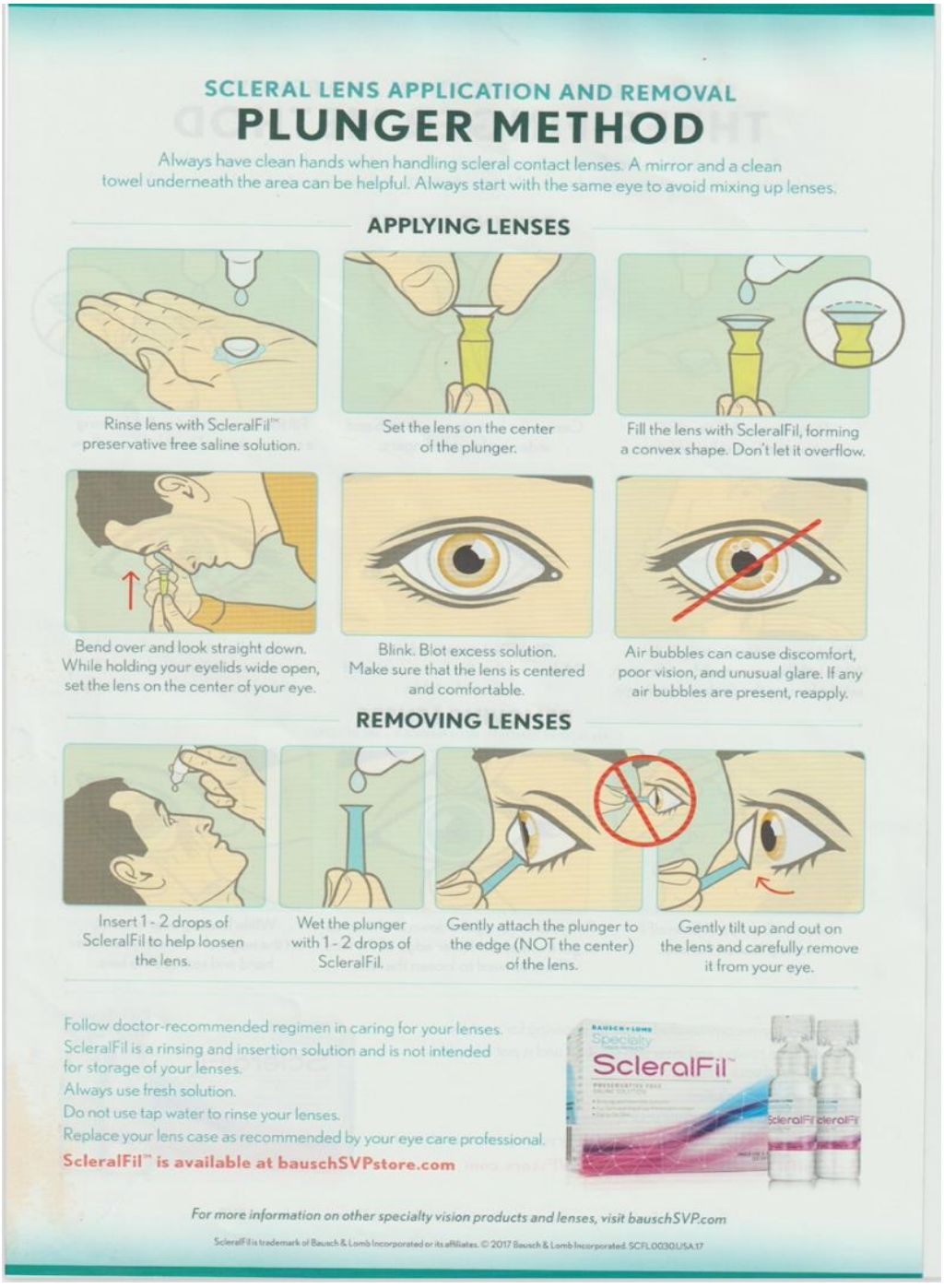
Appendix 2-6: Alden Optical Lens Ordering Form

ORDER FORM: Alden Optical from Heinz Otchere, University of Waterloo, Contact Lens Clinic

Fax Number 1-800-899-5612

Final Lens Design	**Right eye-Lens 1**	**Left eye-Lens 1**
Laboratory	Alden Optical	Alden Optical
Lens Name	(TPC or NONE)	(TPC or NONE)
Material	BXO (Z) Clear Hydra-PEG Yes or No	BXO (Z) Clear Hydra-PEG Yes or No
Base Curve		
Power		
Diameter: 14.8 or 15.4mm		
Profile (Mid-peripheral) Curve 1=Prolate, 2=Oblate		
Sagittal depth: (3500 to 5000µm)		
Scleral Alignment Periphery APS-Horizontal APS-Vertical Micro-vault		
Limbal Clearance (µm)		
CT (mm)		
Lens ID	BLACK dot drilled @base, Laser Engrave Lens ID# EZ Exchange Warranty expiry date	2 BLACK dots drilled @base, Laser Engrave Lens ID# EZ Exchange Warranty expiry date
Reference Number		
Lot #		
Invoice #		

Appendix 2-7: Scleral Lens Application and Removal



SCLERAL LENS APPLICATION AND REMOVAL

PLUNGER METHOD

Always have clean hands when handling scleral contact lenses. A mirror and a clean towel underneath the area can be helpful. Always start with the same eye to avoid mixing up lenses.

APPLYING LENSES

Rinse lens with ScleralFil™ preservative free saline solution.

Set the lens on the center of the plunger.

Fill the lens with ScleralFil, forming a convex shape. Don't let it overflow.

Bend over and look straight down. While holding your eyelids wide open, set the lens on the center of your eye.

Blink. Blot excess solution. Make sure that the lens is centered and comfortable.

Air bubbles can cause discomfort, poor vision, and unusual glare. If any air bubbles are present, reapply.

REMOVING LENSES

Insert 1 - 2 drops of ScleralFil to help loosen the lens.

Wet the plunger with 1 - 2 drops of ScleralFil.

Gently attach the plunger to the edge (NOT the center) of the lens.

Gently tilt up and out on the lens and carefully remove it from your eye.

Follow doctor-recommended regimen in caring for your lenses.
ScleralFil is a rinsing and insertion solution and is not intended for storage of your lenses.
Always use fresh solution.
Do not use tap water to rinse your lenses.
Replace your lens case as recommended by your eye care professional.

ScleralFil™ is available at bauschSVPstore.com

For more information on other specialty vision products and lenses, visit bauschSVP.com

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Appendix 2-8: Contact Lens Dry Eye Questionnaire 8

Patient/Subject #:_____
Date:__/___/____Time:_____

CONTACT LENS QUESTIONNAIRE-8 (CLDEQ-8)

1. Questions about **EYE DISCOMFORT**:

   a. During a typical day in the past 2 weeks, **how often** did your eyes feel discomfort while wearing your contact lenses?

      0 Never
      1 Rarely
      2 Sometimes
      3 Frequently
      4 Constantly

   When your eyes felt discomfort with your contact lenses, **how intense was this feeling of discomfort…**

   b. At the end of your wearing time?

Never have it	Not at All Intense				Very Intense
0	**1**	**2**	**3**	**4**	**5**

2. Questions about **EYE DRYNESS**:

   a. During a typical day in the past 2 weeks, **how often** did your eyes feel dry?

      0 Never
      1 Rarely
      2 Sometimes
      3 Frequently
      4 Constantly

   When your eyes felt dry, **how intense was this feeling of dryness**…

   b. At the end of your wearing time?

Never have it	Not at All Intense				Very Intense
0	**1**	**2**	**3**	**4**	**5**

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3. Questions about **CHANGEABLE, BLURRY VISION:**
   a. During a typical day in the past 2 weeks, **how often** did your vision change between clear and blurry or foggy while wearing your contact lenses?

      0 Never
      1 Rarely
      2 Sometimes
      3 Frequently
      4 Constantly

   When your vision was blurry, **how noticeable was the changeable, blurry, or foggy vision** …

   b. At the end of your wearing time?

Never have it	Not at All Intense				Very Intense
0	**1**	**2**	**3**	**4**	**5**

4. Question about **CLOSING YOUR EYES:** During a typical day in the past 2 weeks, **how often** did your **eyes bother you so much that you wanted to close them**?

   0 Never
   1 Rarely
   2 Sometimes
   3 Frequently
   4 Constantly

5. Question about **REMOVING YOUR LENSES:** How often during the past 2 weeks, did your eyes *bother you so much* while wearing your contact lenses that you felt as if you needed to stop whatever you were doing and **take out your contact lenses**?

   1 Never
   2 Less than once a week
   3 Weekly
   4 Several times a week
   5 Daily
   6 Several times a day

Appendix 2-9: Contact Lens Impact on Quality of Life Questionnaire

The Contact Lens Impact on Quality of Life (CLIQ)

Welcome to CLIQ, a questionnaire designed to measure the quality of life of people who wear contact lenses.

If you have any questions on any part of the questionnaire, please contact:

Konrad Pesudovs PhD; Research Fellow, Flinders University, South Australia. Email:
Konrad.Pesudovs@flinders.edu.au

• INSTRUCTIONS

This is a simple questionnaire with 28 questions formatted as in example 1 below. Please complete pages 1-4 using a tick (9) as shown:

Example: How much difficulty do you have reading very small print?

Not applicable	None at all	A little bit 9	A moderate amount	A lot	So much that I can't do this activity

Thank you for agreeing to participate.

• QUESTIONS

1. *How much difficulty do you have driving in glare conditions with your contact lenses?*

Don't drive for reasons other than my vision	None at all	A little bit	A moderate amount	A lot	So much that I can't do this activity

2. How much difficulty do you have performing any activity due to dim lighting with your contact lenses?

Don't drive for reasons other than my vision	None at all	A little bit	A moderate amount	A lot	So much that I can't do this activity

---

3. During the past month, how often have you experienced your vision changing / fluctuating throughout the day, either improving or deteriorating with your contact lenses?

Don't know / Not applicable	Never	Occasionally	Fairly often	Very often	Always

4. During the past month, how often have you experienced focusing difficulties with your contact lenses?

Don't know / Not applicable	Never	Occasionally	Fairly often	Very often	Always

5. During the past month, how often have you experienced your eyes feeling tired or strained with your contact lenses?

Don't know / Not applicable	Never	Occasionally	Fairly often	Very often	Always

6. During the past month, how often have you experienced red / painful / itchy / burning / sore / uncomfortable / gritty or dry eyes with your contact lenses?

Don't know / Not applicable	Never	Occasionally	Fairly often	Very often	Always

7. How much trouble is the routine care of your contact lenses; e.g. cleaning, using eye drops?

Don't know / Not applicable	None	A little bit	A moderate amount	Quite a lot	Extreme

8. How much trouble is having to think about your contact lenses before doing things; e.g. travelling, sport, going swimming?

Don't know / Not applicable	None	A little bit	A moderate amount	Quite a lot	Extreme

9. How much trouble is having to carry additional cleaning supplies for contact lenses when travelling?

Don't know /	None	A little bit	A moderate amount	Quite a lot	Extreme

Not applicable					

10. How much trouble is having to insert things into your eyes: e.g. contact lens, eye drops?

Don't know / Not applicable	None	A little bit	A moderate amount	Quite a lot	Extreme

11. How much trouble is being unable to have good, comfortable vision all day with your contact lenses? *(If you have good, comfortable vision all day, please answer "None")*

Don't know / Not applicable	None	A little bit	A moderate amount	Quite a lot	Extreme

12. How concerned are you about the initial and ongoing cost to buy your current contact lenses?

Don't know / Not applicable	Not at all	A little bit	A moderate amount	Quite a lot	Extremely

13. How concerned are you about the cost of your next contact lenses?

Don't know / Not applicable	Not at all	A little bit	A moderate amount	Quite a lot	Extremely

14. How concerned are you about the cost of unscheduled maintenance of your contact lenses; breakage, loss, running out of supplies?

Don't know / Not applicable	Not at all	A little bit	A moderate amount	Quite a lot	Extremely

15. How concerned are you about having to increasingly rely on your contact lenses since you started to wear them?

Don't know / Not applicable	Not at all	A little bit	A moderate amount	Quite a lot	Extremely

16. How concerned are you about your vision being not as good as it could be with your contact lenses?

Don't know / Not applicable	Not at all	A little bit	A moderate amount	Quite a lot	Extremely

17. How concerned are you about medical complications from your contact lenses?

Don't know / Not applicable	Not at all	A little bit	A moderate amount	Quite a lot	Extremely

18. How concerned are you about eye allergies/ eye infections from your contact lenses?

Don't know /	Not at all	A little bit	A moderate amount	Quite a lot	Extremely

Not applicable					

19. How concerned are you about falling asleep in your contact lenses?

Don't know / Not applicable	Not at all	A little bit	A moderate amount	Quite a lot	Extremely

20. How concerned are you about eye protection from ultraviolet (UV) radiation?

Don't know / Not applicable	Not at all	A little bit	A moderate amount	Quite a lot	Extremely

---

We are now interested in the effect that your contact lenses have had on the way you have been feeling. The effect on your feelings may be obvious (e.g., you may feel that you look better in your contact lenses) or it may be indirect (e.g., you may feel more confident since wearing contact lenses because you feel that you look better).

21. During the past month, how much of the time have you felt that you have looked your best when wearing contact lenses?

Don't know / Not applicable	Never	Occasionally	Fairly often	Very often	Always

22. During the past month, how much of the time have you felt happy with your facial appearance when wearing contact lenses?

Don't know / Not applicable	Never	Occasionally	Fairly often	Very often	Always

23. During the past month, how much of the time have you felt that you think others see you the way you would like them to when wearing contact lenses (e.g. intelligent, sophisticated, successful, cool, etc)?

Don't know / Not applicable	Never	Occasionally	Fairly often	Very often	Always

24. During the past month, how much of the time have you felt complimented / flattered when wearing contact lenses?

Don't know / Not applicable	Never	Occasionally	Fairly often	Very often	Always

25. During the past month, how much of the time have you felt confident when wearing contact lenses?

Don't know / Not applicable	Never	Occasionally	Fairly often	Very often	Always

26. During the past month, how much of the time have you felt happy when wearing contact lenses?

Don't know / Not applicable	Never	Occasionally	Fairly often	Very often	Always

27. During the past month, how much of the time have you felt able to do the things you want to do when wearing contact lenses?

Don't know / Not applicable	Never	Occasionally	Fairly often	Very often	Always

28. During the past month, how much of the time have you felt eager to try new things when wearing contact lenses?

Don't know / Not applicable	Never	Occasionally	Fairly often	Very often	Always

Date _____ Study _____Investigator _____ ID _____ Lenses 1, 2 (Please circle one)

The following questions relate to your wearing habit, symptoms and comfort ratings which you may or may not be experiencing with the contact lenses you are wearing in this study. Please select a value from 0 (worse possible) up to 50 (average) up to 100 (absence of symptom) which most adequately describes how you feel about your study lenses and enter this in the box next to each question's scale, R=right eye; L=left eye

WEEK 1 (Date: ……..ddmmyyyy)

Parameters (Right Eye)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Comment(s)
How many hours did you wear your study lenses?								
How would you rate your dryness with your study lenses?								
How would you rate burning with your study lenses?								
How would you rate your vision with respect to cloudy/filminess (blinking to clear) with your study lenses?								
How would you rate overall comfort with the study lenses?								
Parameters (Left Eye)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Comment(s)
How many hours did you wear your study lenses?								
How would you rate your dryness with your study lenses?								
How would you rate burning with your study lenses?								
How would you rate your vision with respect to cloudy/filminess (blinking to clear) with your study lenses?								
How would you rate overall comfort with the study lenses?								

Other general comment(s):

Date _____ Study _____Investigator _____ ID _____ Lenses 1, 2 (Please circle one)

The following questions relate to your wearing habit, symptoms and comfort ratings which you may or may not be experiencing with the contact lenses you are wearing in the study. Please select a value from 0 (worse possible) up to 50 (average) up to 100 (absence of symptom) which most adequately describes how you feel about your study lenses and enter this in the box next to each question's scale, R=right eye; L=left eye

WEEK 2 (Date: ……..mmddyyyy)

Parameters (Right Eye)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Comment(s)
How many hours did you wear your study lenses?								
How would you rate your dryness with your study lenses?								
How would you rate burning with your study lenses?								
How would you rate your vision with respect to cloudy/filminess (blinking to clear) with your study lenses?								
How would you rate overall comfort with the study lenses?								
Parameters (Left Eye)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Comment(s)
How many hours did you wear your study lenses?								
How would you rate your dryness with your study lenses?								
How would you rate burning with your study lenses?								
How would you rate your vision with respect to cloudy/filminess (blinking to clear) with your study lenses?								
How would you rate overall comfort with the study lenses?								

Other general comment(s):

Date _____ Study _____Investigator _____ ID _____ Lenses 1, 2 (Please circle one)

The following questions relate to your wearing habit, symptoms and comfort ratings which you may or may not be experiencing with the contact lenses you are wearing in the study. Please select a value from 0 (worse possible) up to 50 (average) up to 100 (absence of symptom) which most adequately describes how you feel about your study lenses and enter this in the box next to each question's scale, R=right eye; L=left eye

WEEK 3 (Date: ……..mmddyyyy)

Parameters (Right Eye)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Comment(s)
How many hours did you wear your study lenses?								
How would you rate your dryness with your study lenses?								
How would you rate burning with your study lenses?								
How would you rate your vision with respect to cloudy/filminess (blinking to clear) with your study lenses?								
How would you rate overall comfort with the study lenses?								
Parameters (Left Eye)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Comment(s)
How many hours did you wear your study lenses?								
How would you rate your dryness with your study lenses?								
How would you rate burning with your study lenses?								
How would you rate your vision with respect to cloudy/filminess (blinking to clear) with your study lenses?								
How would you rate overall comfort with the study lenses?								

Other general comment(s):

Date _____ Study _____Investigator _____ ID _____ Lenses 1, 2 (Please circle one)

The following questions relate to your wearing habit, symptoms and comfort ratings which you may or may not be experiencing with the contact lenses you are wearing in the study. Please select a value from 0 (worse possible) up to 50 (average) up to 100 (absence of symptom) which most adequately describes how you feel about your study lenses and enter this in the box next to each question's scale, R=right eye; L=left eye

WEEK 4 (Date: ……..mmddyyyy)

Parameters (Right Eye)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Comment(s)
How many hours did you wear your study lenses?								
How would you rate your dryness with your study lenses?								
How would you rate burning with your study lenses?								
How would you rate your vision with respect to cloudy/filminess (blinking to clear) with your study lenses?								
How would you rate overall comfort with the study lenses?								
Parameters (Left Eye)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Comment(s)
How many hours did you wear your study lenses?								
How would you rate your dryness with your study lenses?								
How would you rate burning with your study lenses?								
How would you rate your vision with respect to cloudy/filminess (blinking to clear) with your study lenses?								
How would you rate overall comfort with the study lenses?								

Other general comment(s):

Appendix 3-1: Mean and Standard Deviation of Weekly Wearing Habit and Subjective Ratings and Lens Type

Measured Parameter	Uncoated SL				Coated SL			
	Week 1	**Week 2**	**Week 3**	**Week 4**	**Week 1**	**Week 2**	**Week 3**	**Week 4**
Hours of Lens Wear	6.47 ± 1.72	7.31 ± 1.72	7.36 ± 1.91	7.57 ± 1.82	6.78 ± 1.67	6.60 ± 1.80	7.57 ± 1.63	7.56 ± 1.82
Dryness (%)	69.06 ± 21.41	75.49 ± 22.56	75.16 ± 20.72S	74.67 ± 20.40	73.41 ± 25.55	74.92 ± 21.66	76.82 ± 20.19	78.91 ± 21.47
Burning (%)	83.00 ± 21.82	80.50 ± 25.02	82.30 ± 24.19	83.08 ± 20.71	85.12 ± 21.20	81.60 ± 22.71	84.02 ± 21.84	83.40 ± 25.10
Vision (%)	68.20 ± 22.97	71.47 ± 22.07	76.22 ± 38.11	70.15 ± 22.36	70.31 ± 23.81	71.23 ± 24.95	70.27 ± 24.05	72.20 ± 21.09
Comfort (%)	69.98 ± 19.83	75.95 ± 21.91	75.21 ± 20.59	76.66 ± 17.22	72.51 ± 21.34	72.99 ± 24.35	72.66 ± 21.84	73.98 ± 22.17

SD: Standard deviation, SL: Scleral contact lens

Appendix 4-1: Details of Lens Design, Prescription for all the Participants at the Dispensing Visit

Participant ID	Lens Design	Prescription at Dispensing Visit	
		Right Eye	Left Eye
LS03	Spherical/Prolate	BC: 8.04 PWR: -3.00 D:14.80 SAG: 3750 CT: 250 LC: 200 F0	BC: 8.04 PWR: -2.75 D:14.80 SAG: 3750 CT: 250 LC: 200 F0
LS05	Front Toric/Prolate	BC: 7.50 PWR: -2.7.5/-0.25X90 D:14.80 SAG: 4100 CT: 250 LC: 200 F0	BC: 7.50 PWR: -2.7.5/-0.25X90 D:14.80 SAG: 4100 CT: 250 LC: 200 F0
LS06	Spherical/Prolate	BC: 7.85 PWR: -3.50 D:14.80 SAG: 3900 CT: 250 LC: 150 F0	BC: 7.85 PWR: -3.50 D:14.80 SAG: 3900 CT: 250 LC: 150 F0
LS07	Front Toric/Prolate	BC: 7.67 PWR: -4.7.5/-0.75X74 D:14.80 SAG: 4400 CT: 250 LC: 125 F4 (360)	BC: 7.67 PWR: -5.00 D:14.80 SAG: 4400 CT: 250 LC: 125 F2 (360)
LS10	Spherical/Prolate	BC: 7.42 PWR: -6.00 D:15.40 SAG: 4500 CT: 250 LC: 175 F0	BC: 7.42 PWR: -5.50 D:15.40 SAG: 4500 CT: 250 LC: 175 F0
LS12	Spherical/Prolate	BC: 7.58 PWR: -3.50 D:15.40 SAG: 4300 CT: 250 LC: 175 F3 (360)	BC: 7.58 PWR: -3.50 D:15.40 SAG: 4300 CT: 250 LC: 175 F3 (360)
LS13	Spherical/Prolate	BC: 8.24 PWR: -1.25 D:14.80 SAG: 3480 CT: 250 LC: 100 F1 (360) FLEX: -1.0	BC: 8.24 PWR: -1.25 D:14.80 SAG: 3480 CT: 250 LC: 100 F1 (360) FLEX: -1.0
LS14	Front Toric/Prolate	BC: 7.67 PWR: -6.50/-0.75X45 D:15.40 SAG: 4250 CT: 250 LC: 125 F1 (360)	BC: 7.67 PWR: -6.00/-0.75X135 D:15.40 SAG: 4250 CT: 250 LC: 125 F1 (360)
LS15	Spherical/Prolate	BC: 8.04 PWR: -3.00 D:14.80 SAG: 3800 CT: 250 LC: 125 F2 (360)	BC: 8.04 PWR: -3.25 D:14.80 SAG: 3800 CT: 250 LC: 125 F2 (360)
LS16	Spherical/Prolate	BC: 7.94 PWR: -3.50 D:15.40 SAG: 4060 CT: 250 LC: 125 F3 (360)	BC: 7.94 PWR: -3.50 D:15.40 SAG: 4060 CT: 250 LC: 125 F3 (360)
LS17	Bi-elevation/Prolate	BC: 7.85 PWR: -0.75 D:14.80 SAG: H3700/V3820 CT: 250 LC: 50 F:H/V 3 (360)	BC: 7.85 PWR: -0.75 D:14.80 SAG: H3700/V3820 CT: 250 LC: 50 F:H/V 3 (360)
LS18	Bi-elevation/Prolate	BC: 7.80 PWR: -5.75 D:14.80 SAG: H3700/V4000 CT: 250 LC: 50 F:H/V 3 (360)	BC: 8.04 PWR: -2.25 D:14.80 SAG: H3700/V4000 CT: 250 LC: 50 F:H/V 2 (360)
LS20	Spherical/Prolate	BC: 7.67 PWR: -7.75 D:14.80 SAG: 4100 CT: 250 LC: 50 F2 (360)	BC: 7.67 PWR: -8.25 D:14.80 SAG: 4100 CT: 250 LC: 50 F2 (360)
LS22	Front Toric/Prolate	BC: 7.58 PWR: -10.00/-0.75X75 D:15.40 SAG: 4300 CT: 250 LC: 100 F2 (360)	BC: 7.58 PWR: -9.00/-0.75X75 D:15.40 SAG: 4300 CT: 250 LC: 100 F2 (360)
LS23	Front Toric/Prolate	BC: 7.85 PWR: -8.25/-3.75X140 D:15.40 SAG: 4200 CT: 250 LC: 100 F1 (360)	BC: 7.85 PWR: -8.75/-4.75X180 D:15.40 SAG: 4200 CT: 250 LC: 100 F1 (360)
LS24	Front Toric/Prolate	BC: 7.50 PWR: -8.00 D:15.40 SAG: 4400 CT: 250 LC: 125 F2 (360)	BC: 7.50 PWR: -4.50 D:15.40 SAG: 4400 CT: 250 LC: 125 F2 (360)
LS25	Front Toric/Prolate	BC: 7.67 PWR: -1.25/-0.50X45 D:14.80 SAG: 4200 CT: 250 LC: 125 F: H2/V3 (360)	BC: 7.67 PWR: -1.25/-0.50X155 D:14.80 SAG: 4200 CT: 250 LC: 125 F: H2/V3 (360)
LS27	Spherical/Prolate	BC: 7.67 PWR: -5.25 D:15.40 SAG: 4300 CT: 250 LC: 100 F1	BC: 7.67 PWR: -5.25 D:15.40 SAG: 4300 CT: 250 LC: 100 F1
LS28	Spherical/Prolate	BC: 8.04 PWR: -2.00 D:14.80 SAG: 3900 CT: 250 LC: 100 F1	BC: 8.04 PWR: -2.00 D:14.80 SAG: 3900 CT: 250 LC: 100 F1
LS29	Spherical/Prolate	BC: 8.34 PWR: -3.00 D:14.80 SAG: 3825 CT: 250 LC: 100 F1	BC: 8.34 PWR: -3.00 D:14.80 SAG: 3825 CT: 250 LC: 100 F1

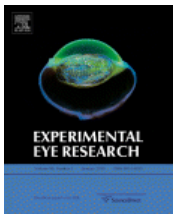
BC: base curve, CT: central thickness, D: diameter, F: scleral alignment (increases by 30 μm), Flex: flexure, H: horizontal meridian, LC: limbal clearance, PWR: power, Sag: sagittal height of lens, V: vertical meridian

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The 1995 NEI Classification of Dry Eye

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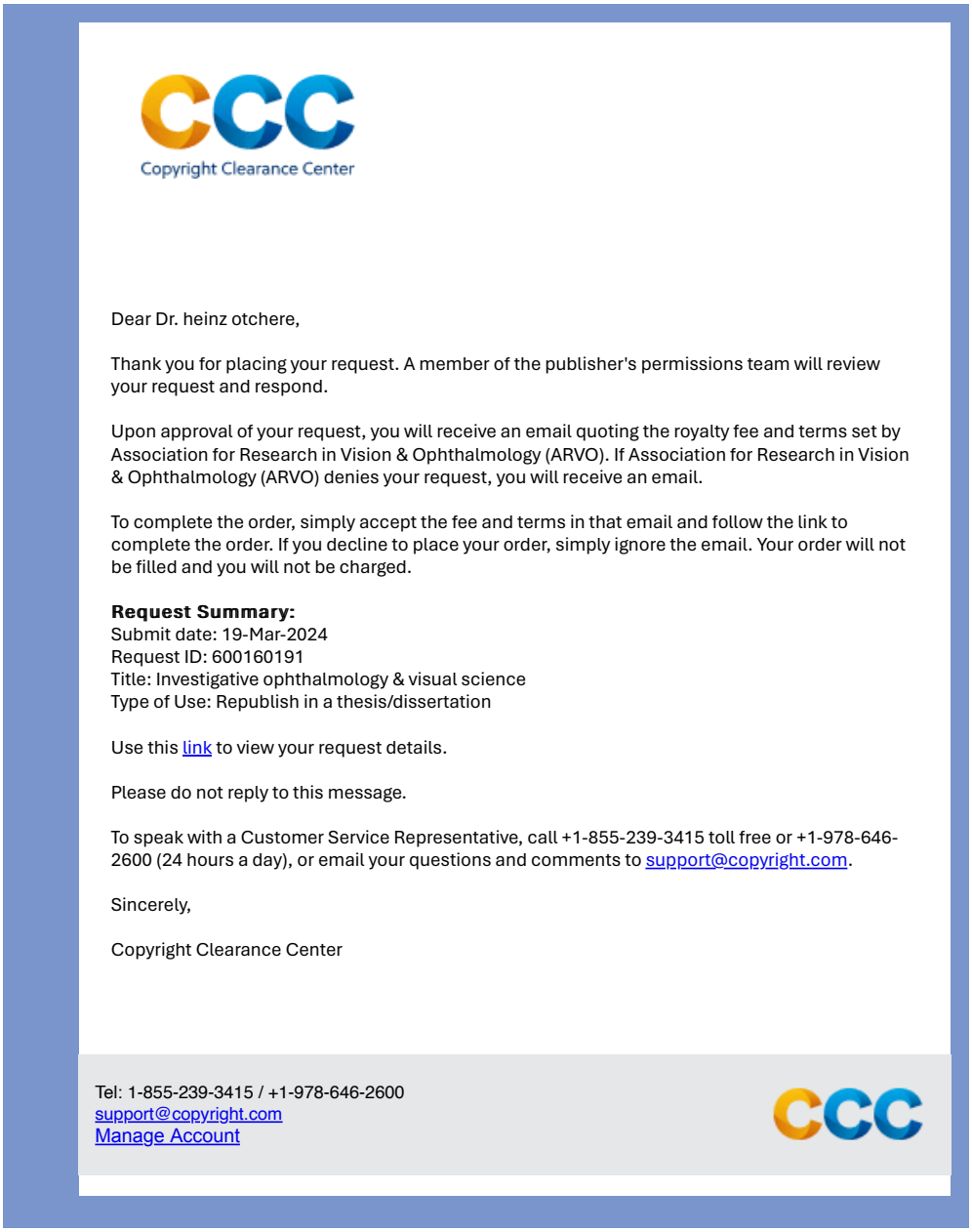
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Tear Breakup Patterns (BUPs) Observed by Video-Interferometer

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Date: Thursday, March 28, 2024 at 10:44:02 AM Eastern Daylight Saving Time
From: Kylie Maden
To: heinz Otchere
Attachments: Screenshot 2024-03-28 at 10.33.38 AM.png

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Kylie

Kylie Maden
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From: heinz Otchere <hotchere@uwaterloo.ca>
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Midday Fogging Caused by Larger, Coalesced Particulates with Slit Lamp Biomicroscope

Tuesday, March 26, 2024 at 09:48:57 Eastern Daylight Time

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Type of use: Academic
Article title: Optical coherence tomography and scleral contact lenses: clinical and research applications
Article DOI: 10.1111/cxo.12814
Author name: Stephen J Vincent PhDa*, David Alonso?caneiro PhDa & Michael J Collins PhDaa Contact Lens and Visual Optics Laboratory, School of Optometry and Vision Science, Queensland University of Technology, Brisbane, Queensland, Australia,
Journal title: Clinical and Experimental Optometry
Volume number: 102
Issue number: 3
Page numbers: 224–241

Visante OCT Image Analysis Showing Scleral Sagittal Height and Corneoscleral Angle Measurements in one Cross Section

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Different Lens Materials, Generic Names, Dk Value, Contact Angle, and Refractive Index (SL and GP Materials)

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Order Number:	501894118
Publication:	Indian Journal of Ophthalmology
Title:	Contact lenses in dry eye disease and associated ocular surface disorders
Type of Use:	Thesis/Dissertation
Order Ref:	Table 1-3
Order Total:	Not Available

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