Evaluation of Oculus Keratograph 5M Tear Film Scans on Eyes Wearing Contact Lenses

Thesis

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Abstract

The Oculus Keratograph 5M is currently used in clinical practice to analyze various dry eye measurements on the bare eye. Our study aimed to determine the ability of the Keratograph to obtain certain measurements when a contact lens was on eye. A new variable was developed to attempt to quantify the tear film quality.

The Keratograph recorded an analysis video beginning immediately after 2 complete blinks and continued until the participant blinked or for 25 seconds. The Total Measurement Time (TMT) was the time from the start of the video until a blink or 25 seconds, whichever occurred first. The Non-Invasive Keratographic Break Up Time (NIKBUT) was the time from the beginning of the video to the first detectable breakup in any region. The cornea was divided into 192 regions by the Keratograph, which we reduced to 120 regions that had more than 90% reliable measurements over all collected videos. Of those 120 regions, the proportion that exhibited break up before the video ended was calculated and named the Break Up Proportion (BUP). To account for the NIKBUT diagnostic criterion, the Reduced Break Up Proportion (RBUP) only analyzed the first nine seconds. A two-minute rest was given after each of the three videos, and the results from the three videos were averaged. After the last rest period, three photographs were recorded and Tear Meniscus Height (TMH) was measured manually using instrument software and averaged. The measurements were first collected with the bare

eye, then repeated at least 15 minutes after inserting the habitual contact lenses. Only data from the right eyes are included in these analyses.

We enrolled 26 participants, with 22 completing the study. The average ± SD age of participants completing the study was 43.3 ±11.8 years; 77.3% of participants were female; 50% were Caucasian and 31.9% were Black; and the average spherical equivalent of the habitual contact lens prescription was -2.97 ± 2.45D. The median (IQR) for BUP was 11.4 (14.4) percent for the bare eye and 38.7 (25.3) percent for the lens on eye (Wilcoxon signed rank, $p < 0.001$). The median (IQR) for TMT was 14.9 (10.2) seconds for the bare eye and 24.9 (2.2) seconds for the lens on eye (Wilcoxon signed rank, $p < 0.001$). The median (IQR) for NIKBUT was 8.3 (6.1) seconds for the bare eye and 5.5 (5.4) seconds for the lens on eye (Wilcoxon signed rank, $p < 0.03$). The correlation between the NIKBUT and TMT for the bare eye was 0.77 (Spearman correlation, $p < 0.001$). The correlation of the RBUP and TMT for the bare eye was -0.67 (Spearman correlation, $p = 0.001$). The correlation of the BUP and NIKBUT for the bare eye was -0.50 (Spearman correlation, $p = 0.02$). The correlation of the RBUP and NIKBUT for the bare eye was -0.90 (Spearman correlation, $p < 0.001$) and for the lens on eye was -0.69 (Spearman correlation, $p < 0.001$). The median (IQR) for TMH was 0.32 (0.16) millimeters for the bare eye and 0.24 (0.11) millimeters for the lens on eye (Wilcoxon sign rank, $p = 0.002$). The correlation between RBUP and CLDEQ-8 with bare eyes was 0.38 (Spearman correlation, $p = 0.09$). The correlation between TMH and CLDEQ-8 with bare eyes was -0.46 (Spearman correlation, $p = 0.031$).

The Oculus Keratograph 5M was able to obtain dry eye measurements with contact lenses on eye. The reduced break up proportion variable successfully quantified tear film quality of the bare eye, and could be used to help diagnose the severity of dry eye in the future.

Dedication

This thesis is dedicated to my wonderful parents, Terry and Laurie Norris. Because of their constant, unwavering support, I am able to chase even my wildest dreams.

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There are many people who deserve more than just this thank you. First, I would like to thank Dr. Walline for never giving up on me. Through all the ups and downs of my time at Ohio State, you were always there to provide the support I needed to complete this degree.

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Chapter 1. Introduction

1.1 Dry eye description

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."[1] Tears play an important role in ocular surface health, including maintaining a protective barrier, delivering oxygen to the corneal epithelium, providing immunological resources, and creating a smooth refractive surface for vision. Tear film insufficiency can create problems with a patient's ability to wear contact lenses, participate in hobbies like sewing and reading, ability to see clearly throughout the day, and affect their overall quality of life.

The tear film has three indistinct layers. The layer closest to the cornea is the mucin layer. Goblet cells secret mucins, a hydrophilic glycoprotein, onto the ocular surface to help adhere the tear film to the cornea. The liquid portion of the tears is referred to as the aqueous layer. It contains nutrients, like oxygen, for the ocular surface and proteins, like lysozyme, to act as an antimicrobial agent. The external layer is composed of lipids. This helps to form the smooth outer surface, and prevent evaporation of the tears.

There are two classifications of dry eye: aqueous-deficient and evaporative. Aqueous-deficient is then broken down into Sjogren syndrome-related and non-Sjogren

syndrome-related. Sjogren syndrome is an autoimmune disease that attacks the lacrimal gland and the salivary glands, causing both dry eye and dry mouth. Non-Sjogren dry eye is caused by lacrimal gland deficiency or obstruction, a side effect of a systemic medication like an antihistamine or a beta blocker, and issues with the corneal reflexive system due to an ocular surface surgery.[2]

Evaporative dry eye is caused by a deficiency in the meibum or oil component of the tear film. These components are responsible for keeping the tears on the ocular surface. Intrinsic factors that can affect oil production include a low blink rate, lid aperture disorders and Meibomian Gland Deficiency (MGD). Extrinsic factors can also cause a decrease in meibum, including Vitamin A deficiency, preservatives, various ocular surface diseases and contact lenses.[2]

1.2 Prevalence

Dry eye disease is an extremely common eye condition that is mainly managed by optometrists. Symptoms of dry eye are reported in 25% of patients seeking eye care.[3] The prevalence is difficult to determine, due to diagnosis method and population differences, with studies estimating a range from 5 to 50%.[4] An examination of the Beaver Dam study database reported a dry eye prevalence rate of 14% in adults aged 48 to 91 years, based on participant self-reporting frequency and intensity of symptoms. It was determined that women (16.7%) are more likely to develop dry eye than men (11.4%).[5] In the United States alone, more than 20-30 million people have been diagnosed with dry eye. As society increases dependence on screen usage, the number of

presenting dry eye patients will continue to increase. It has been found that there is a significant positive correlation between average computer exposure time and development of dry eye.[6]

1.3 Symptoms

Symptoms of dry eye include blurred or variable vision, dry or burning sensation, grittiness or itching, excessive tearing, redness and many possible others. When the tear film is not smooth and clear, it is unable to provide a proper refractive surface to transmit light, creating blurry vision that is not stable. If there are problems with the aqueous component not being sufficient, the eyes will feel dry due to incomplete tear film coverage. This can lead to a burning sensation from corneal drying and stimulation of the nerve endings. When the tears are not properly flushed off the ocular surface, debris can accumulate, causing itchiness or a foreign body sensation. If the lipid component of the tears is inadequate, evaporation of the tear film increases, leading to greater production of the aqueous component. This leads to excessive tearing, which is, ironically, a very common side effect of dry eye. Redness can occur after excessive ocular surface irritation initiates the inflammatory cascade, causing conjunctival vessels dilation. The type of dry eye determines the type of symptoms with which a patient will present. Aqueous deficient patients are more likely to present with corneal staining, which causes redness, irritation and blurriness symptoms. Evaporative dry eye patients most commonly present with excessive tearing and foreign body sensation. The two types of dry eye can be present concurrently, so diagnosis cannot be determined by symptoms alone.

1.4 Diagnosis

The diagnosis of dry eye is a very complex process. One of the key features of diagnosis and treatment is the completion of symptom surveys. These allow a practitioner to have a subjective measure of the patient's dry eye symptoms. Some examples of commonly used surveys include the Ocular Surface Disease Index (OSDI), the Dry Eye Questionnaire (DEQ-5) and the Contact Lens Dry Eye Questionnaire (CLDEQ-8), and Impact of Dry Eye on Everyday Life (IDEEL). The OSDI consists of 12 questions that are able to discriminate mild from moderate from severe dry eye.[7] The DEQ-5 and the CLDEQ-8 are questionnaires that evolved from the original Dry Eye Questionnaire. The DEQ-5 is only five questions, and is used to quantify the subjective severity of the patient's perceived dry eye.[8] The questions focus on the frequency and intensity of discomfort, the frequency and intensity of dryness, and how often watery eyes occur. The CLDEQ-8 is a survey of 8 questions that ask patients about the comfort and vision of their contact lens-related dry eye.[9] The IDEEL survey consists of 57 questions. It is more disease specific, and is able to discriminate between the different levels of severity of dry eye.[10]

The tear film quantity and quality are important factors in dry eye diagnosis. A few of the various ways to evaluate tear film quantity are Schirmer strip testing, Phenol red thread, and tear meniscus height. The Schirmer strip measures both reflexive and basal tearing levels by placing the strip on the inferior lid and collecting tears for five minutes. With the abnormal value set at less than five millimeters, the sensitivity for dry eye was 80% and the specificity was 53%.[11] The Phenol red thread uses the pH of the

tears to indicate how much has been absorbed in the thread by changing colors. The patient keeps their eyes open for 15 seconds while the test occurs. A normal rate of color change is one millimeter for one second, or 15mm total. The sensitivity and specificity for dry eye when the abnormal value was less than 10mm were 86% and 83% respectively.[12, 13] Tear meniscus height is measured at the location of the change in curvature of the tear film where the inferior cornea and lower eyelid meet. It was used as an estimate of tear thickness, with a critical value of less than 0.25mm.[14] This provides crucial information about the quantity of the tear film.

Some of the numerous ways to evaluate the quality of the tear film are tear break up time (TBUT), osmolarity, detection of matrix metalloprotease-9 (MMP-9), and meibography. TBUT is a measurement of how long it takes for the tears to become disrupted and no longer a smooth, complete surface. This value is decreased in dry eye disease, mucin deficiency, and MGD.[15] The critical value is ten seconds with a sensitivity of 82% and a specificity of 86% as a diagnostic test for dry eye.[15, 16] Another way to measure TBUT is a noninvasive method referred to as non-invasive keratographic tear break up time (NIKBUT). This technique uses the Placido disc reflections to detect break up as opposed to using fluorescein stain, which cannot be used with contact lenses. Osmolarity can be tested with an instrument (TearLab) that requires a 50 nanoliter sample. It gives an estimate of the number of solutes in the tears. The manufacturer determined the cutoff to be 308, and if higher than that it is indicative of dry eye. The InflammaDry is an instrument that can detect MMP-9. With an 85% sensitivity and a 94% specificity for dry eye, this quick test is useful in determining if the tear film

contains signs of inflammation.[17] Meibography is the imaging of the Meibomian glands. This new technology allows practitioners to keep track of the progression of Meibomian gland dysfunction by seeing changes in the glands over time. With fewer functioning Meibomian glands, there is less of the oil component in the tear film, causing evaporation.

Tear function and ocular surface integrity factor in to dry eye syndrome. Various dyes and stains are able to assist the optometrist in evaluating these factors, including fluorescein staining, Rose Bengal, and Lissamine Green. Fluorescein staining is used to detect problems with the epithelium. Positive staining, bright green with cobalt blue light, indicates epithelial loss or debris in the tear film. Negative staining, dark with cobalt blue light, indicates corneal elevation or a disruption of the tear film. Both Rose Bengal and Lissamine Green stain dead or devitalized cells, but Lissamine Green is better tolerated by patients, so it is used more often.[18] When using Lissamine Green, there are 3 staining patterns that represent the various stages of progression of dry eye. From mild to severe the patterns progress from nasal conjunctival staining, nasal and temporal conjunctival staining and then corneal and conjunctival staining.[19] Lissamine Green is also used in assessing the lid wiper to detect lid wiper epitheliopathy. The lid wiper is defined as the region of the superior palpebral conjunctiva that contacts and wipes the front surface of the eye with each blink. There are two possible explanations for why epitheliopathy occurs. First, an inadequate amount of tears causes friction with the ocular surface, leading to inflammation. The other proposed mechanism is that low grade chronic

inflammation of the lid wiper region leads to an increase in friction.[20] It has been found that approximately 88% of symptomatic dry eye patients exhibit lid wiper staining.[21]

1.5 Treatments

A variety of treatments are available, but each require patient compliance. The general strategy is to use regimens that target the patient's symptoms. For minor symptoms, artificial tears are beneficial and can be used as needed. Artificial tears vary in viscosity, from high to low, and are either water-based or oil-based. A preservative may or may not be present. Results are patient dependent. If instillation of artificial tears proves unable to manage the condition, topical medications can be prescribed.

A steroid can reduce ocular surface inflammation by preventing cytokines from stimulating corneal nerve endings. This provides the patient relief from many of their symptoms. Cyclosporine is an immunomodulator that inhibits T-cell proliferation, inhibiting the cell mediated inflammatory response[22]. This allows for an increase in aqueous production. Lifitegrast works in a similar fashion, preventing the activation of T-cells by blocking the receptor, helping to treat aqueous deficient dry eye.[23] For evaporative dry eye, doxycycline is an antibiotic that is able to reduce the melting point of the meibum.[24] This helps to increase the release of oil, helping to treat MGD.

There are multiple dry eye treatments that do not involve eye drops. Punctal occlusion is a technique used, especially for aqueous deficient dry eye. The implantation of a punctal plug helps to maintain the tears on the ocular surface by preventing drainage of tears into the lacrimal system.[25] Warm compresses are often recommended for MGD,

but are only effective if the proper warm compress is used. Based on meibum quality and expressibility, MGDRx EyeBag® and OPTASE™ Moist Heat Mask were able to improve MGD, but a warm wash cloth provided no improvement.[26] The compress needs to maintain its heat long enough to increase the temperature of the oil to be effective, and a warm wash cloth is unable to maintain the warm temperature for a sufficient time.

Maintaining good lid hygiene is commonly recommended for dry eye patients. There is no clear link to improved signs with lid scrubs, but patient symptoms improve with moderate compliance.[27] Newer treatments have been recently developed for treating MGD directly in office. The iLUX MGD Treatment System and LipiFlow Thermal Pulsation System apply pressure and heat directly to the Meibomian glands. It has been shown that these devices equally improve the Meibomian gland scores, ocular disease index scores, and TBUT.[28]

Specialty contact lenses have been shown to be an effective treatment for dry eye. Scleral lenses create a liquid reservoir that bathes the cornea throughout the day, relieving the patient's symptoms. This is typically used for aqueous deficient dry eye after other methods have previously failed. This is not a treatment option for MGD, as the lens can agitate the glands, creating friction and a ropy mucus discharge. This option is prioritized in patients with corneal ectasias and certain corneal conditions to improve both the comfort and vision.

1.6 Contact lens-associated dry eye

Contact lens wear can cause evaporative dry eye. About 50% of contact lens wearers experience dryness symptoms.[29] Contact lens wearers are the most likely to report dry eye, compared to spectacle wearers (24%) and clinical emmetropes (7%).[30] These symptoms often lead to reduced vision, decreased wear time, and ultimately discontinuation of lens wear. It has been shown that after an extended time without blinking, patients wearing hydrogel soft lenses lose about 4 lines of low contrast acuity, compared to less than a line with rigid lens wearers and the bare eye.[31] Contact lenses have been shown to disrupt the basic structure of the tear film. The healthy, bare eye tear film thickness is approximately seven microns. When contact lenses are in place, the tear film splits into pre-lens and post-lens layers, each about one to three microns.[32] The pre-lens layer has a reduced quantity of lipid layer, resulting in an increase in rate of evaporation.[33, 34] This leads to an unstable refractive surface and possible dry eye symptoms. Lens wear can also lead to permanent damage to the Meibomian glands overtime. When compared to a normal population, young contact lens wearers' Meibomian gland appearance was similar to the group of healthy 60 to 69 year olds.[35] The longer duration of lens wear, the more dropout and distortion of the glands was present. The involvement of contact lenses with dry eye is multifactorial, but undeniable.

1.7 NIKBUT vs. TBUT

There are benefits to measuring tear quality non-invasively. It has been found that in dry eye patients, NIKBUT values were longer than TBUT, and more easily

distinguished from healthy participants.[36] For diagnostic criteria, the cutoff time for NIKBUT was 9 seconds with a sensitivity of 68% and a specificity of 70%, whereas the TBUT cutoff time was 5 seconds with 54% sensitivity and 68% specificity.[36] These criteria show that more accurate diagnoses occur when the non-invasive method is used over the invasive method.

1.8 Comparison of tear break up time with and without contact lens wear

Contact lens impacts on the tear film have been studied extensively. In recent years, there has been an increase in the number of studies using objective measurements. One particular study compared tear film surface quality between the bare eye and when the lens was on eye. Using dynamic videokeratoscopy, Placido ring images were analyzed to determine the tear film surface quality. An image-processing technique determined the values for each measurement by focusing on the quality of the reflected ring patterns. It was found that there was a significant difference between the bare eye and lens on eye, with worsened tear film quality with lenses in place.[37]

A more recent study looked at the NIKBUT of the pre-lens and post-lens eye using the Oculus Keratograph. This study used cosmetic soft contact lenses with pigment either on the front or back surface to assess the ability of the Keratograph to focus on the tear film instead of the lens. The NIKBUT measurement was taken before lens insertion, with the lens on eye, and after lens removal. It was found that if the pigment was on the back of the lens surface a successful measurement could be taken. If the pigment was on the front of the lens the device could not properly focus the mire images. It was

concluded that the Oculus Keratograph NIKBUT programing did not properly reflect the mires on the tear film.[38]

A study was conducted comparing the bare eye to the lens on eye after four hours of lens wear to determine if using NIKBUT values could aid in deciding what material of lens should be prescribed to provide optimum comfort. NIKBUT was conducted before contact lens evaluation, after wearing a silicone hydrogel contact lens for four hours, and after wearing a hydrogel contact lens for four hours. Three video measurements were taken per eye at each time point, but only the right eye was analyzed. Visual acuities, slit lamp examination and subjective comfort were analyzed to select between silicone hydrogels and hydrogel contact lenses. The NIKBUT values were then analyzed, and the lens type that demonstrated the longer time was selected. It was found that in 39% of participants, the two types of prescribing methods resulted in the same selection of lens type when using the first NIKBUT for each lens type, and a 35% match in lens selection when analyzing the mean NIKBUT. The researchers concluded that NIKBUT could be an additional resource for prescribing, but not a sole method.[39]

Two other studies investigated the repeatability and the reproducibility of NIKBUT and tear meniscus height data on participants wearing contact lenses. The first study looked at healthy participants and the other focused on participants diagnosed with dry eye. The studies were not comparative, but focused only on whether NIKBUT and tear meniscus height measurements were reliable in each participant population. Both used the Oculus Keratograph 5M to collect measurements. In healthy participants, all measurements exhibited excellent repeatability except the average NIKBUT, which was

not reproducible when the lenses were on eye.[40] The average was determined by the Keratograph for each measurement, based off of each region's NIKBUT value per video. When participants with dry eye were analyzed, NIKBUT measurements were found to be more reliable than the tear meniscus height measurements.[41]

Numerous studies have used the Oculus Keratograph 5M to analyze the impacts of contact lenses on the tear film, but each focused on a different outcome. Very little data have directly compared the bare eye and lens on eye values, especially when looking at the tear meniscus height. For NIKBUT, only the times were analyzed, and not the percentage of breakup that occurred. The Oculus has been shown to have potential to be used for various types of tear film measurements with contact lenses on the ocular surface.

1.9 Study Purpose

This aim of this project was to compare tear film scan measurements using the Oculus Keratograph 5M instrument with and without contact lenses on the eye. Objective testing was used to further understand the effects of contact lens wear on the tear film. Both tear quality and quantity were analyzed. These data may be influential for contact lens fittings in dry eye patients.

Chapter 2. Methods

This study assessed the feasibility of collecting tear film scan data using the Oculus Keratograph 5M instrument on participants wearing contact lenses, and compared the NIKBUT and TMH data on eyes with and without contact lenses. The 22 healthy habitual contact lens wearers participated in a single visit. The measurements were first collected when the participants were not wearing their contact lenses then, after settling for at least 15 minutes, the same measurements were collected on the eyes with lenses in place.

2.1 IRB Approval

This study was performed in compliance with ISO 14155, the International Conference on Harmonization Good Clinical Practice E6, and the Declaration of Helsinki, and was approved by the Sterling Institutional Review Board in Atlanta, GA. All participating participants signed an informed consent form prior to the start of their examination.

2.2 Participants and Entry Criteria

Participants were recruited from the Vision Research Clinic in the Johnson & Johnson Research and Development Center in Jacksonville, FL. A total of 26 participants were screened, and 22 participants (17 females, 5 males) met the eligibility requirements.

The sample size was not calculated because the experiment was not hypothesis-driven. A minimum of 20 participants (40 eyes) was determined to be sufficient to establish the functionality of the instrument and provide preliminary comparison data.

The entry criteria included the ability to read and understand English for informed consent and protocol compliance, at least 18 years of age, habitual soft contact lens wear, and an entrance visual acuity of 20/25 in each eye. A habitual soft contact lens wearer was defined as someone who wore their lenses for a minimum of 6 hours per day, 2 days per week over the last month. Visual acuity was measured using a Snellen acuity chart, and the letter size was recorded as the smallest line the participant could read at least 50% of the letters correctly for OD, OS and OU.

Exclusion criteria were incorporated to eliminate conditions that interfere with contact lens wear, including any known ocular or systemic allergies, systemic diseases, autoimmune disease, use of certain medications (ex. chronic use of steroids), and any ocular infection. Previous ocular or intraocular surgeries or any other eye conditions, including entropion, ectropion, extrusions, chalazia, recurrent styes, glaucoma, history of recurrent corneal erosions, aphakia, moderate to severe corneal distortion, and a history of amblyopia or strabismus. If a female participant self-reported being pregnant or lactating, she was disqualified. Each participant underwent a slit lamp examination, and if any FDA Slit Lamp Classification Scale Grade 3 or greater findings were determined, including edema, corneal neovascularization, corneal staining, tarsal abnormalities, or conjunctival injection, that participant was eliminated from evaluation.

2.3 Oculus Keratograph 5M

The instrument, the Oculus Keratograph 5M, was selected specifically for this project. The settings of the tests were chosen through trial-and-error before the experiment was conducted. For the NIKBUT tests, the illumination setting was set to infrared due to the recommendations of the instruction manual. Infrared light provided less reflexive tearing and allowed the participants to keep their eyes open for longer, allowing for better quality videos in comparison to the white light illumination setting. For the TMH measurements, the white illumination setting was chosen due to the higher quality, colored images. The participant was not required to hold their eyes open for longer than a couple of seconds, so the bright light was not considered a factor.

The Oculus Keratograph 5M analyzed the ocular surface by mapping it out into 192 discrete regions. When the tear film was disrupted, the break up time was reported for each square. The times provided were analyzed to eliminate machine error created from the interference of the contact lens. Only regions that recorded data in 90% of the measurements for both bare eye and lens on eye were included in analysis. The reduced map was then used for data analysis.

2.4 Data Collection Methods

The data collection began with the participants not wearing their contact lenses. After the first set of measurements, the participants inserted their habitual contact lenses that they brought to the appointment from home. After at least a 15-minute period of settling, the protocol was repeated while wearing contact lenses. The NIKBUT videos

were recorded first, with three recordings per eye. After each video, there was a two-minute recovery period. Once the final video was recorded and the recovery period occurred, three TMH images were taken per eye. The photos were taken consecutively, without a rest period.

To complete a NIKBUT measurement, the participants focused on a red cross target while the examiner properly adjusted the focus of the instrument. Once aligned, the participant was prompted to blink two times and then hold their eyes open for as long as they could. Once this was completed the recording automatically began. The measurement stopped automatically when the participant blinked, the device detected extreme tear break up, or after 25 seconds. After the NIKBUT test was completed, the participant rested for two minutes to allow the tear film to recover. During the measurement, if the participant accidently blinked too early, or moved causing an incomplete scan, the examiner waited approximately two minutes before repeating the test.

The TMH still images were captured two seconds after the participant completed a blink. There was no recovery period, with the only rest time in between images being the amount of time to reset the instrument. The images were automatically saved, and analyzed at a later point.

There were 260 NIKBUT videos recorded (three of the right eye without contact lenses, three of the left eye without contact lenses, three of the right eye with contact lenses, and three of the left eye with contact lenses = 12 videos per participant). Four videos did not properly record, and were not available for analysis. We analyzed 263

TMH images (three of the right eye without contact lenses, three of the left eye without contact lenses, three of the right eye with contact lenses, and three of the left eye with contact lenses = 12 images per participant). Only two images of the left eye of one participant were recorded for TMH due to technician error.

2.5 Evaluation Methods

The NIKBUT video was recorded for 24.95 seconds or when the participant first blinked. For analysis, a NIKBUT was set at nine seconds or less, the diagnostic cutoff time for dry eye using the NIKBUT method.[36]

The TMH measurements were recorded manually, by the same experimenter, for each image. The software automatically calculated the measurement from where the experimenter selected as the top of the tear prism and the margin of the lower lid (Figure 2.1). The image was zoomed in to the pixel level then evaluated from the area directly beneath the center of the Placido disc rings. The TMH was calculated as the distance between the upper most part of the tear meniscus and the location where the eyelid margin met the tear film, as shown in Figure 2.1. Only one measurement was recorded per image due to time constraints.

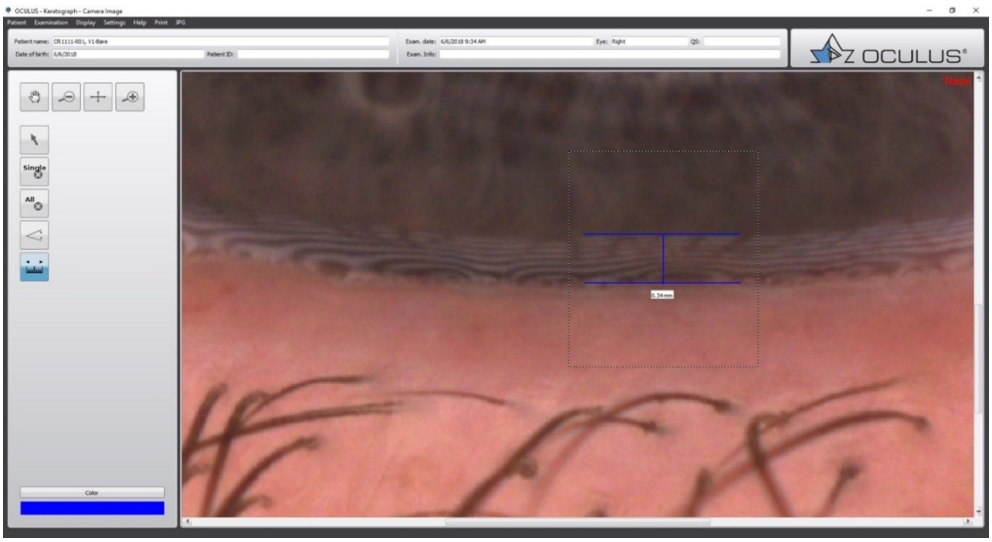

Figure 2.1 Example of TMH measurement

2.6 Variables

Specific variables were created to analyze the data collected for this study. Each variable was used for the bare eye measurements and the lens on eye measurements. For descriptions of each, refer to Table 2.1.

Variable Name	Description
Total Measurement Time (TMT)	The start of the video until a blink or 25 seconds
Non-Invasive Keratographic Break-Up Time (NIKBUT)	Beginning of video to first detectable break up in any region
Break-Up Proportion (BUP)	Proportion of 120 regions that exhibited break up before the end of the measurement period
Reduced Break-Up Proportion (RBUP)	BUP analyzing only the first 9 seconds
Tear Meniscus Height (TMH)	Height of the tear prism from photos measured from the lower lid right below the pupil

Table 2.1 Description of variables

2.7 Statistical Methods

Data for the NIKBUT videos were uploaded from the Keratograph into an excel spreadsheet that was modified by a macro to only contain the data pertinent for analysis. The TMH data were manually measured and entered into a separate excel spreadsheet. The completed data sets were imported into SPSS for further analysis. Only the right eyes were analyzed. Descriptive statistics were performed and Shapiro Wilks test for normality were used to assess the distribution of the variables examined. Many of the variables were not normally distributed, so non-parametric statistics were performed throughout. Comparisons of the medians were conducted using Wilcoxon signed rank tests, and Spearman correlations were performed.

Chapter 3. Results

Of the 26 participants enrolled, 22 qualified for the study. All eligible participants completed the study. A majority of the participants were middle aged, white females. The average ± standard deviation age was 43.3 ±11.8 years. Seventeen of participants were female. Eleven of the participants were Caucasian, seven participants were Black, two participants were Hispanic, and two participants were Asian. The average spherical equivalent of the habitual contact lens prescription was -2.97 ± 2.45D. Twenty-seven percent of the habitual lenses were hydrogels. Seventy-three percent of the habitual contact lenses were from the Acuvue lens brand. A summary of the demographic information is located in Table 3.1.

Demographic	**Mean ± SD**
Age (years)	43.3 ±11.8
Gender (% Female)	77.3
Race (%)	
Caucasian	50
Black	31.9
Hispanic	9.1
Asian	9.1
Refractive Error (D)	
Spherical Equivalent	-2.97 ± 2.45
Contact Lens Material (% Silicone Hydrogel)	73
Contact Lens Brand (% Acuvue)	73

Table 3.1 Demographic and ocular data of participants (n = 22) completing the study

After evaluating each discrete region of the print out map, a total of 120 regions met the criterion of 90% data collection rate. The various regions with more than 10% of the measurements lacking data included the inferior nasal portion, where loss was due to a shadow created by the nose; the central nasal portion, where loss was due to contact lens optic zone interference; the superior portion, where loss was due to eyelash interference; and the outermost and inner most ring, where losses were due to instrument inconsistencies. A detailed version of this map is represented in Figure 3.1.

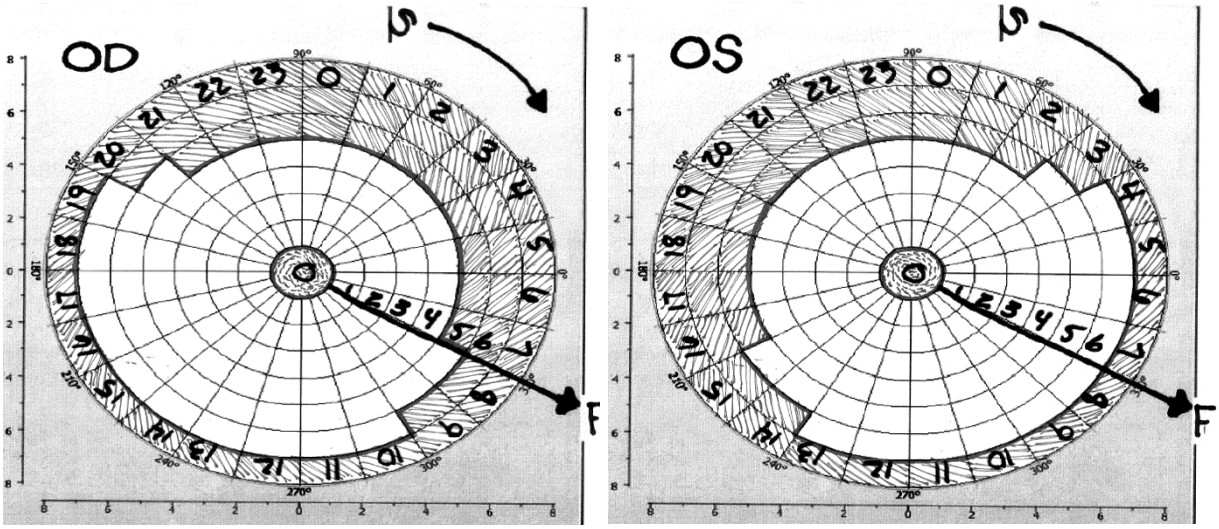

Figure 3.1 Map of analysis regions. White regions were included in analysis, gray areas were eliminated

When analyzing the median break up proportion, contact lens wear resulted in a larger proportion of break up, 38.7 (25.3) percent, than the bare eye median, 11.4 (14.4) percent, (Wilcoxon signed rank, $p < 0.001$). Table 3.2 and Figure 3.2 provide the median (IQR) for the bare eye and contact lens on eye situations.

Break Up Proportion	Bare Eye	CL on Eye
Median	11.4	38.7
Interquartile Range	14.4	25.3

Table 3.2 Median and IQR of break up proportion (BUP) for bare eye and contact lens on eye

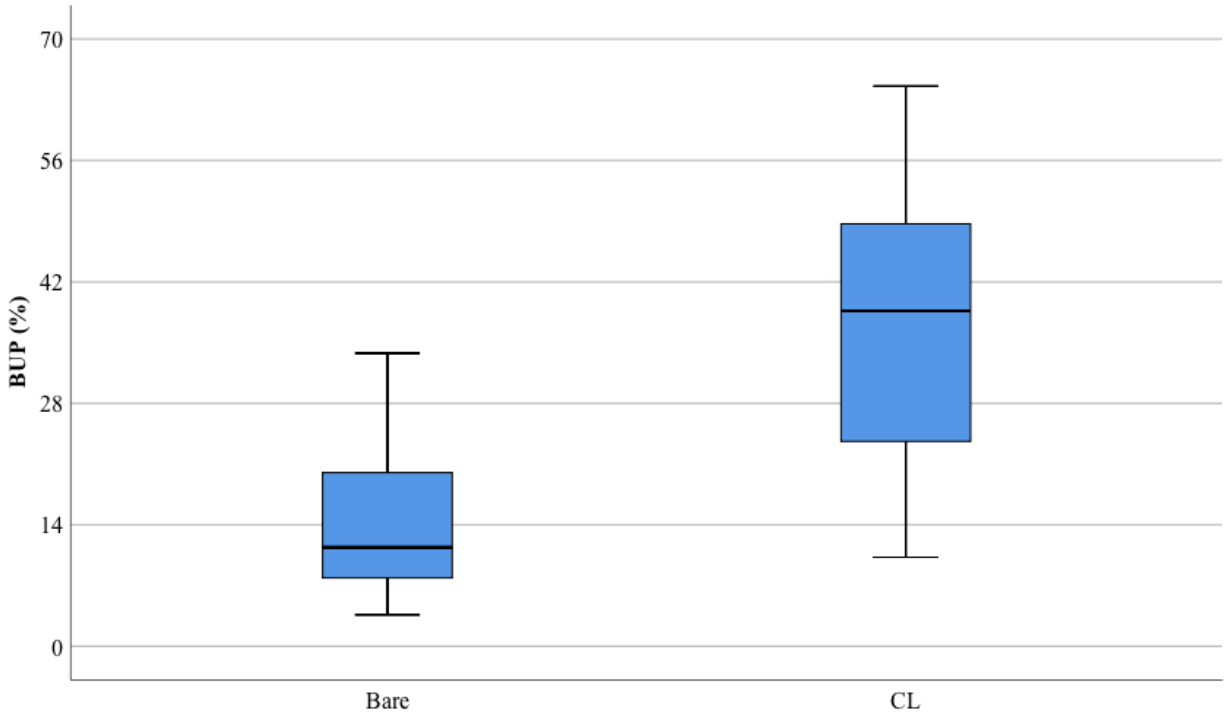

Figure 3.2 Comparison of the break up proportion (BUP) for the bare eye and contact lens on eye. The thick line represents the median, the top of the box represents the 75th percentile, the bottom of the box represents the 25th percentile, and the whiskers represent the 5th and 95th percentiles

When only the first nine seconds of the measurement was analyzed, there was no difference in RBUP between lens presences or absence (Wilcoxon signed rank, p = 0.17). Table 3.3 and Figure 3.3 provide the median (IQR) for the bare eye and contact lens on eye situations.

Reduced Break Up Proportion	Bare Eye	CL on Eye
Median	1.9	5.9
Interquartile Range	7.3	8.5

Table 3.3 Median and IQR of reduced break up proportion (RBUP) for bare eye and contact lens on eye

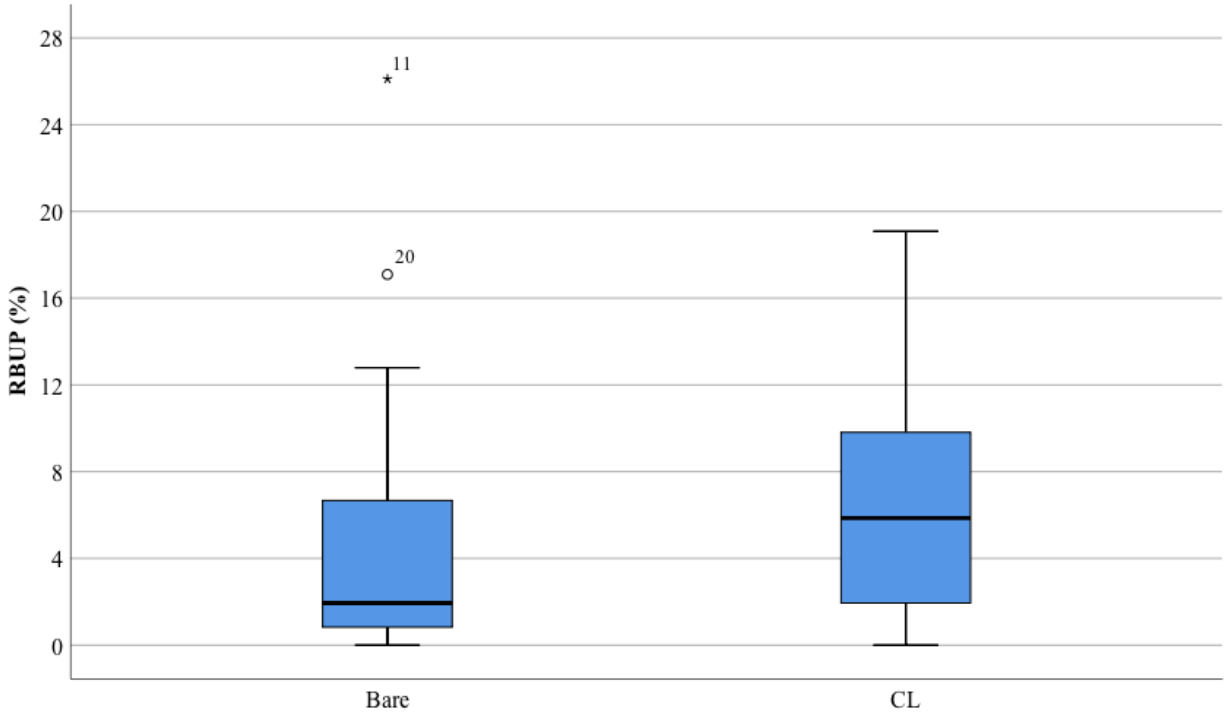

Figure 3.3 Comparison of the reduced break up proportion (RBUP) for the bare eye and contact lens on eye. The thick line represents the median, the top of the box represents the 75th percentile, the bottom of the box represents the 25th percentile, and the whiskers represent the 5th and 95th percentiles

The median measurement time in the videos for the bare eye was 14.9 (10.2) seconds and for the lens on eye was 24.9 (2.2) seconds (Wilcoxon signed rank, $p < 0.001$). With the bare eye, the median NIKBUT was 8.3 (6.1) seconds and with the lens

on eye, the median NIKBUT was 5.5 (5.4) seconds (Wilcoxon signed rank, p = 0.03).

Tables 3.4 and 3.5 and Figures 3.4 and 3.5 include the median (IQR) for each condition.

Total Measurement Time	Bare Eye	CL on Eye
Median	14.9	24.9
Interquartile Range	10.2	2.2

Table 3.4 Median and IQR of total measurement time (TMT) for bare eye and contact lens on eye

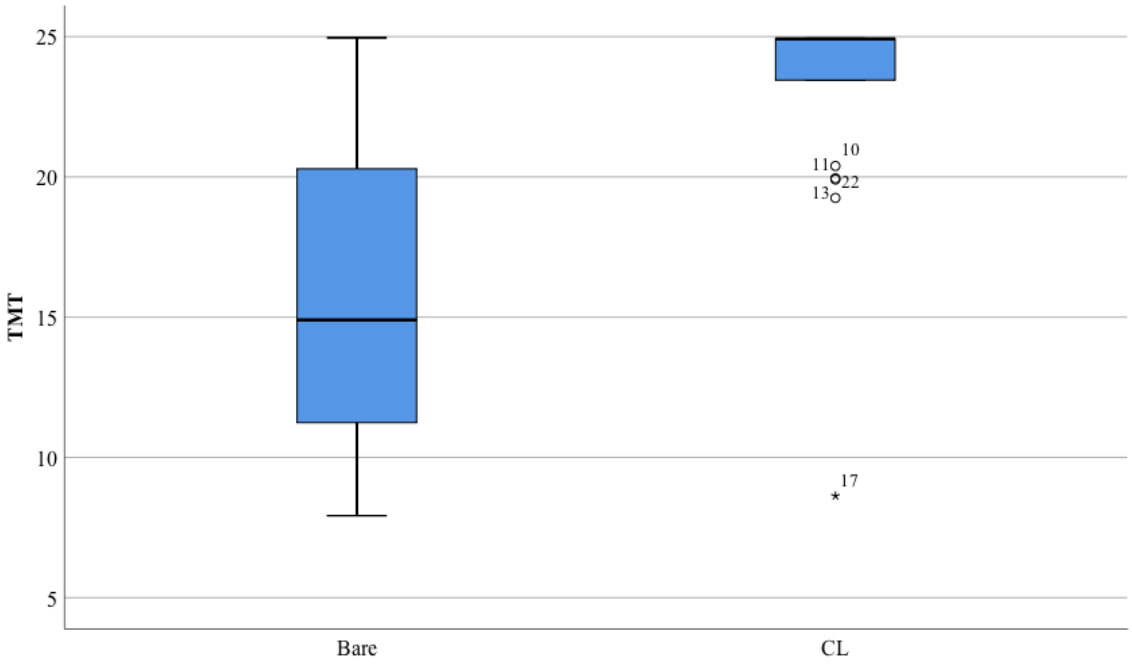

Figure 3.4 Comparison of the total measurement time (TMT) for the bare eye and contact lens on eye. The thick line represents the median, the top of the box represents the 75th percentile, the bottom of the box represents the 25th percentile, and the whiskers represent the 5th and 95th percentiles

NIKBUT	Bare Eye	CL on Eye
Median	8.3	5.5
Interquartile Range	6.1	5.4

Table 3.5 Median and IQR of non-invasive keratographic break up time (NIKBUT) for bare eye and contact lens on eye

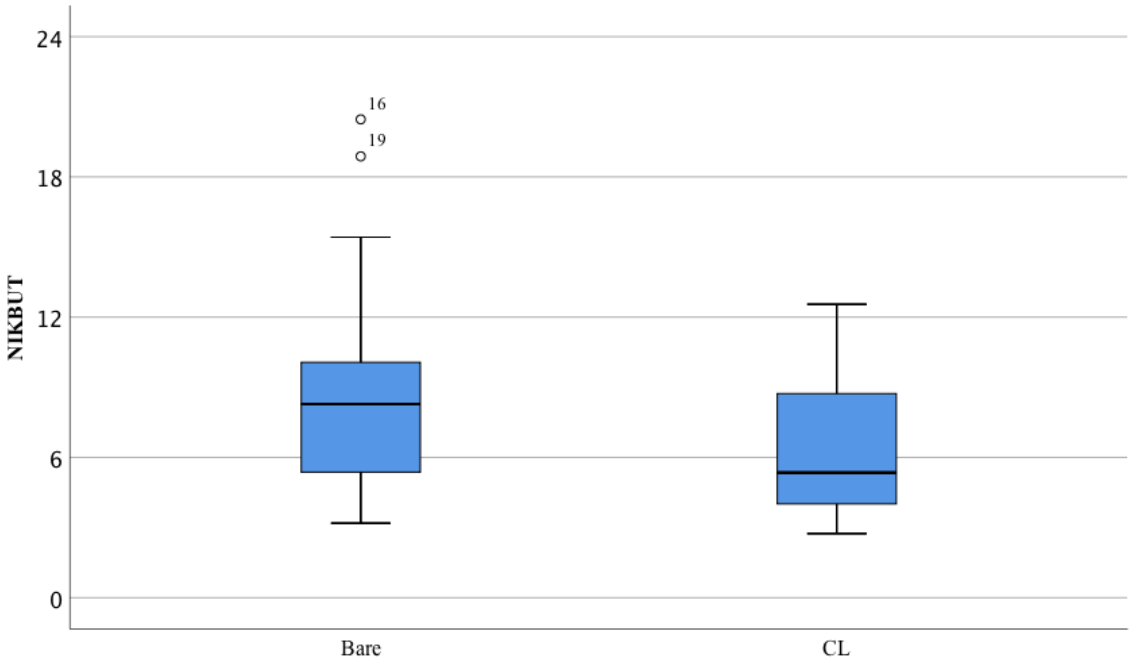

Figure 3.5 Comparison of the non-invasive keratographic break up time (NIKBUT) for the bare eye and contact lens on eye. The thick line represents the median, the top of the box represents the 75th percentile, the bottom of the box represents the 25th percentile, and the whiskers represent the 5th and 95th percentiles

The correlation between the NIKBUT and TMT for the bare eye was 0.77 (Spearman correlation, $p < 0.001$) and for the lens on eye was 0.16 (Spearman correlation, $p = 0.49$). The difference between NIKBUT and TMT were significantly different for the bare eye (Wilcoxon sign rank, $p < 0.001$) and the lens on eye (Wilcoxon sign rank, $p < 0.001$). A graphical representation is depicted in Figure 3.6.

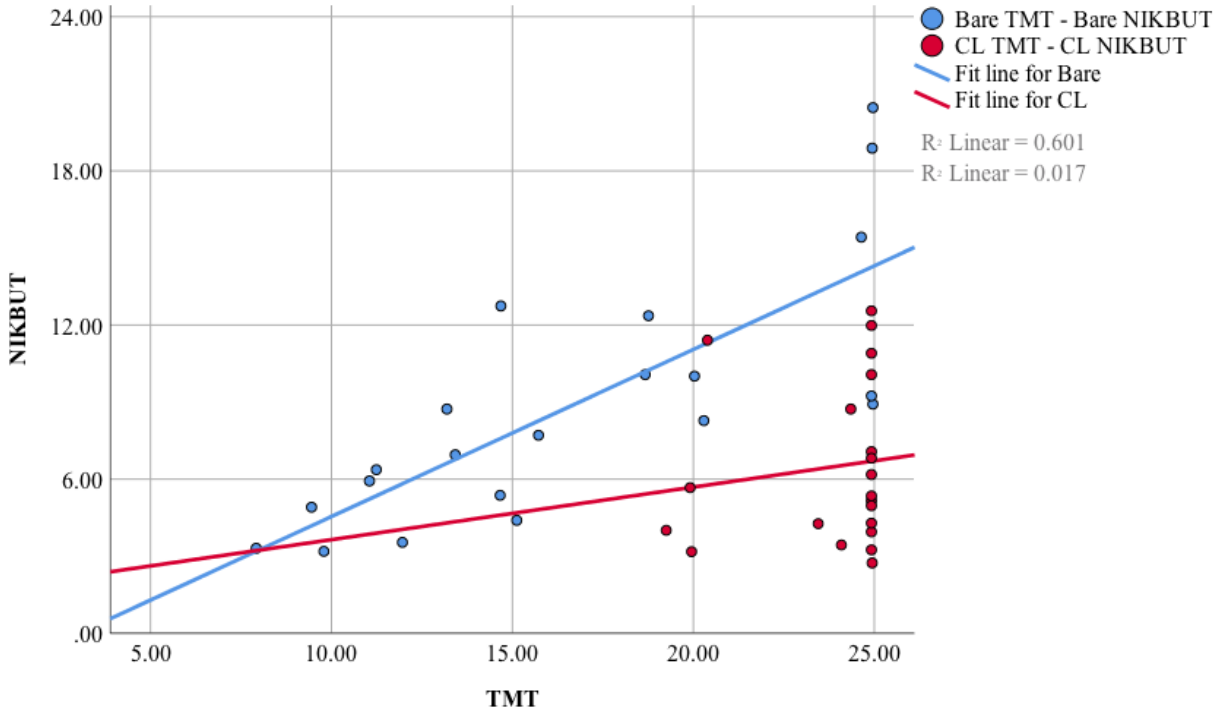

Figure 3.6 Correlation comparison between total measurement time (TMT) and NIKBUT for each condition with a best fit line

The correlation of the BUP and TMT for the bare eye was -0.18 (Spearman correlation, $p = 0.43$) and for the lens on eye was 0.27 (Spearman correlation, $p = 0.22$), which is shown in Figure 3.7.

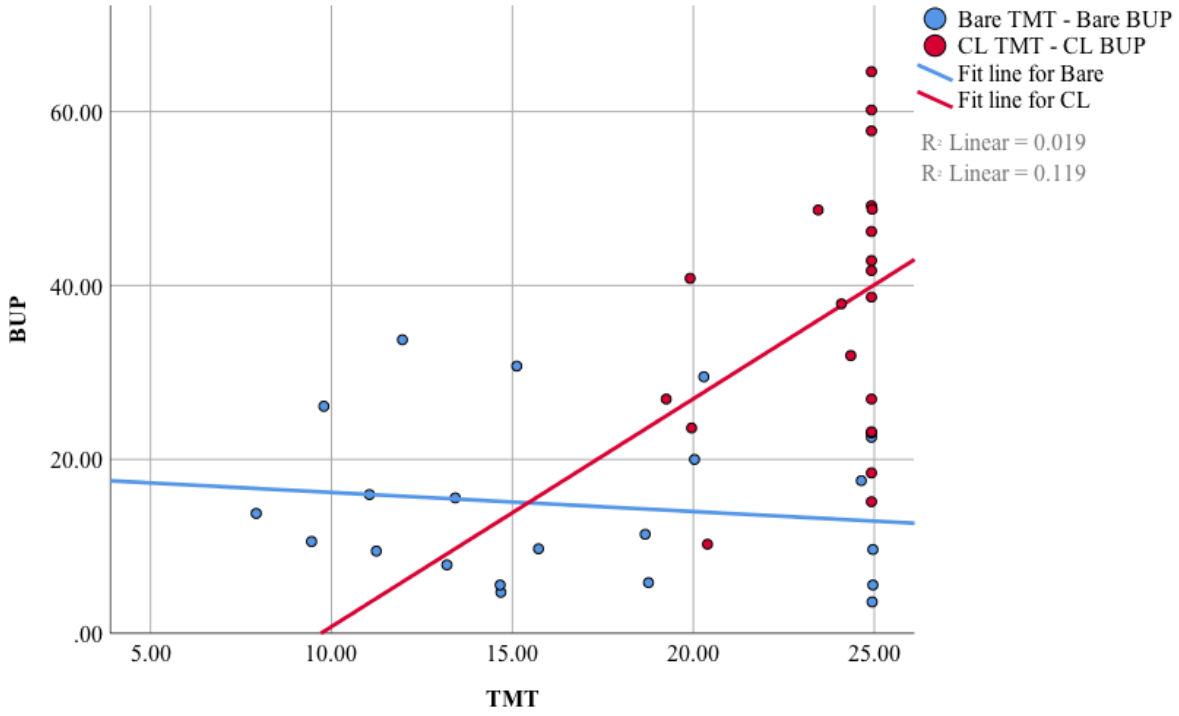

Figure 3.7 Correlation comparison between total measurement time (TMT) and break up proportion (BUP) for each condition with a best fit line

The correlation of the RBUP and TMT for the bare eye was -0.67 (Spearman correlation, $p = 0.001$) and for the lens on eye was -0.18 (Spearman correlation, $p = 0.44$), which is shown in Figure 3.8.

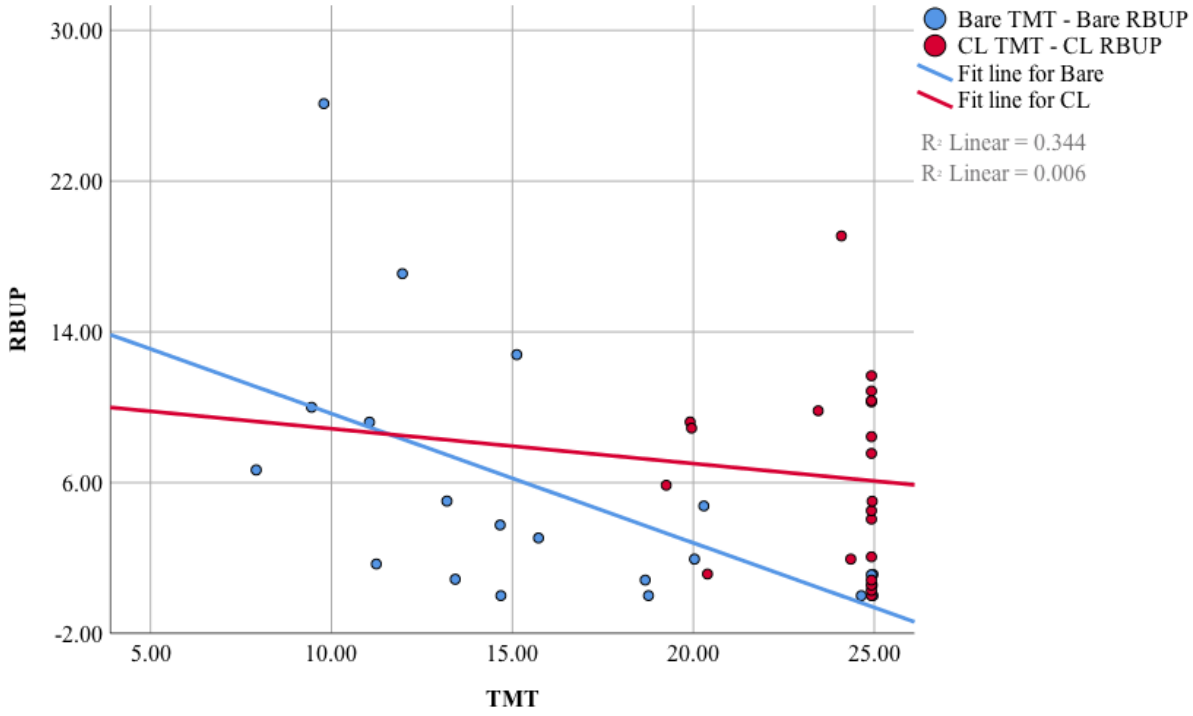

Figure 3.8 Correlation comparison between total measurement time (TMT) and reduced break up proportion (RBUP) for each condition with a best fit line

The correlation of the BUP and NIKBUT for the bare eye was -0.50 (Spearman correlation, $p = 0.02$) and for the lens on eye was -0.20 (Spearman correlation, $p = 0.36$), which is shown in Figure 3.9.

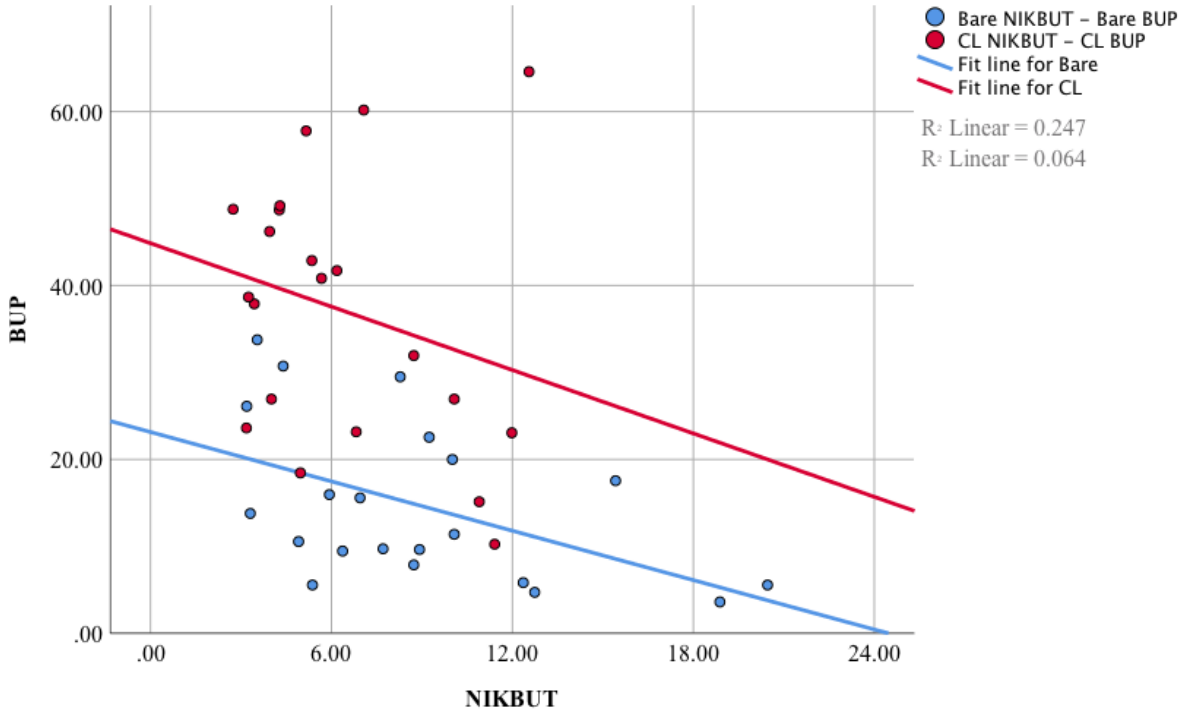

Figure 3.9 Correlation comparison between NIKBUT and break up proportion (BUP) for each condition with a best fit line

The correlation of the RBUP and NIKBUT for the bare eye was -0.90 (Spearman correlation, $p < 0.001$) and for the lens on eye was -0.69 (Spearman correlation, $p < 0.001$), which is shown in Figure 3.10.

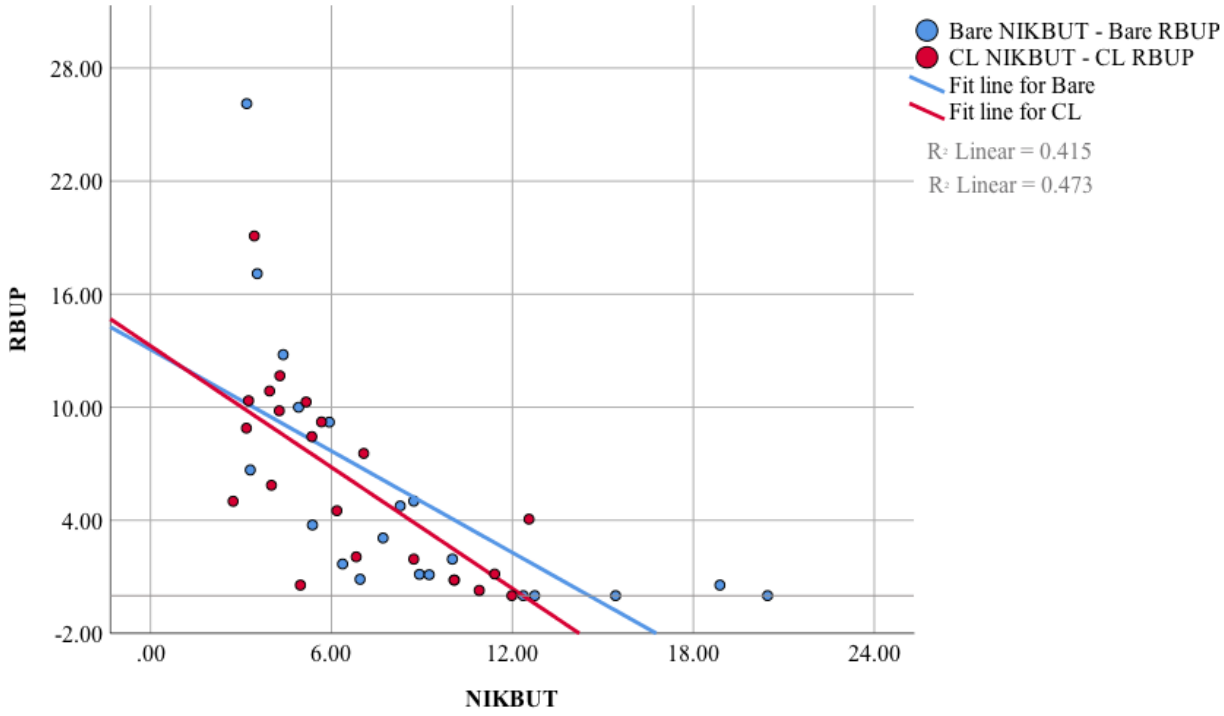

Figure 3.10 Correlation comparison between NIKBUT and reduced break up proportion (RBUP) for each condition with a best fit line

TMH was determined on each participant with and without lenses. The median TMH was 0.32 (0.16) millimeters when the eye was bare and 0.24 (0.11) millimeters with a lens in place. This difference was found to be significant and shown in Table 3.6 and Figure 3.11 (Wilcoxon sign rank, p = 0.002).

Tear Meniscus Height	Bare Eye	CL on Eye
Median	0.32	0.24
Interquartile Range	0.16	0.11

Table 3.6 Median and IQR of tear meniscus height (TMH) for bare eye and contact lens on eye

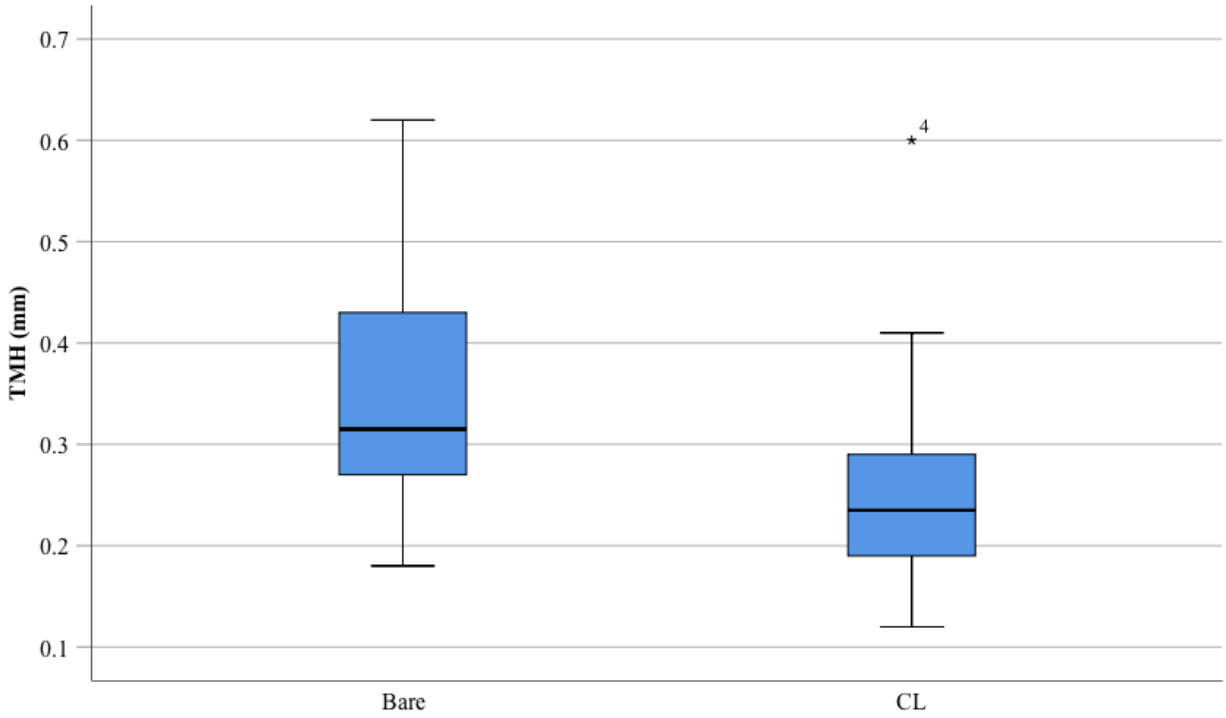

Figure 3.11 Comparison of the tear meniscus height (TMH) for the bare eye and contact lens on eye. The thick line represents the median, the top of the box represents the 75th percentile, the bottom of the box represents the 25th percentile, and the whiskers represent the 5th and 95th percentiles

Each participant completed the CLDEQ-8 survey about their contact lens related dry eye symptoms. The median (IQR) score was 10 (8). The diagnostic cutoff value for dry eye is 12 ± 3. A total of 12 participants scored 12 or less, and 10 participants scored 13 or more, as shown in Table 3.7.

CLDEQ-8 Survey Scores	
< 9	10 participants
9 - 12	2 participants
13 - 15	5 participants
> 16	5 participants

Table 3.7 Summary of CLDEQ-8 survey scores

When the CLDEQ-8 scores were compared to the BUP, the correlation with bare eyes was 0.06 (Spearman correlation, p = 0.80) and the correlation with lenses on eyes was -0.27 (Spearman correlation, p = 0.23), which is shown in Figure 3.12.

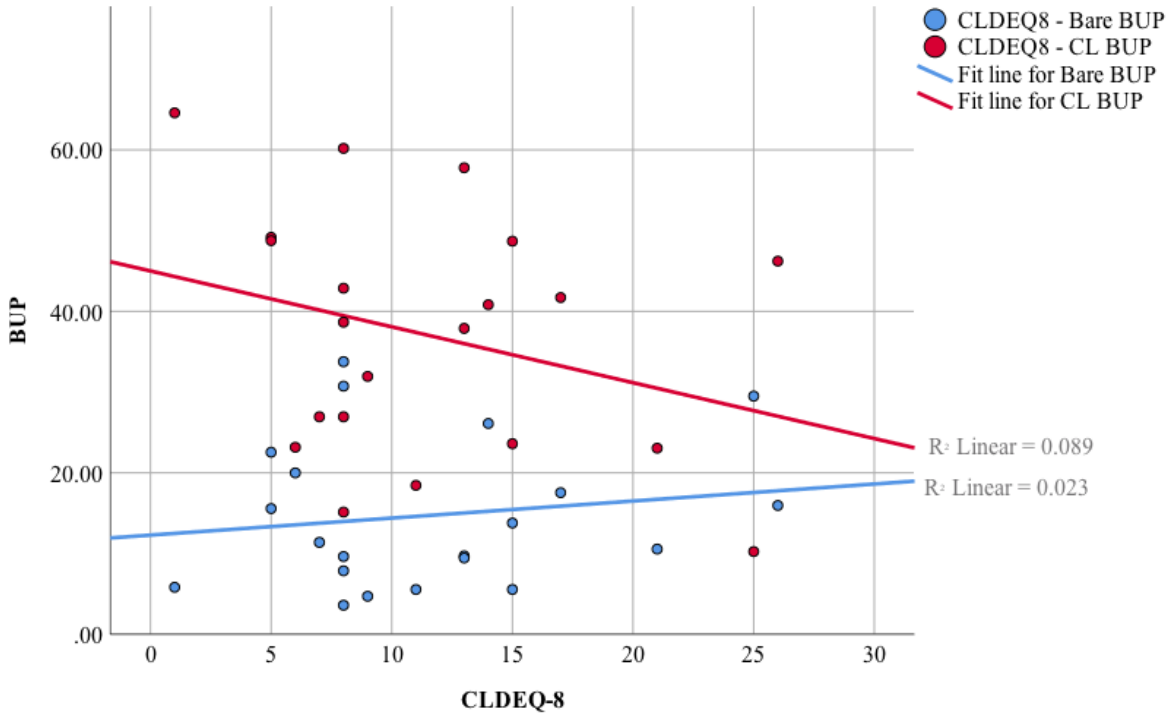

Figure 3.12 Correlation comparison between CLDEQ-8 and break up proportion (BUP) for each condition with a best fit line

When CLDEQ-8 scores were compared to the RBUP, the correlation with bare eyes was 0.38 (Spearman correlation, p = 0.09) and with lenses on eyes was 0.04 (Spearman correlation, p = 0.86). The differences between CLDEQ-8 and both conditions

were found to be significant (bare eye, Wilcoxon signed rank, p = 0.006; lens on eye, Wilcoxon signed rank, p = 0.008), which is shown in Figure 3.13.

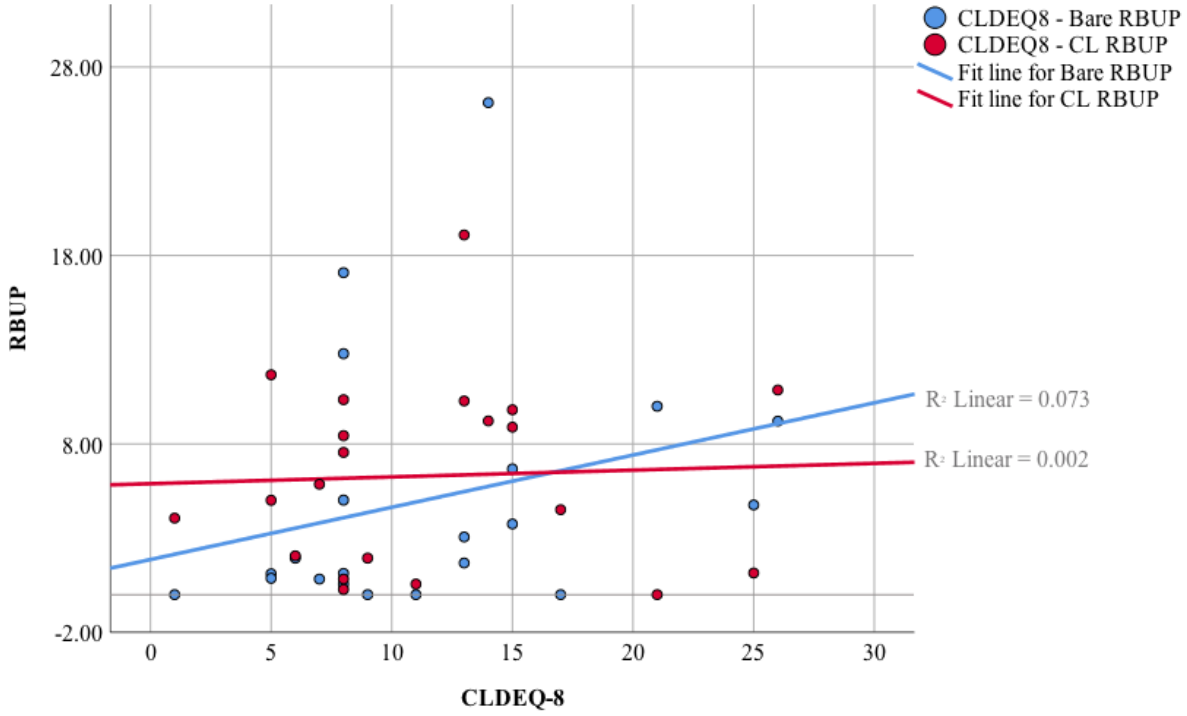

Figure 3.13 Correlation comparison between CLDEQ-8 and reduced break up proportion (RBUP) for each condition with a best fit line

The survey scores were also compared to the TMH. With bare eyes the correlation was -0.46 (Spearman correlation, p = 0.03), and with lenses on the correlation was -0.18 (p=0.42), which is found in Figure 3.14.

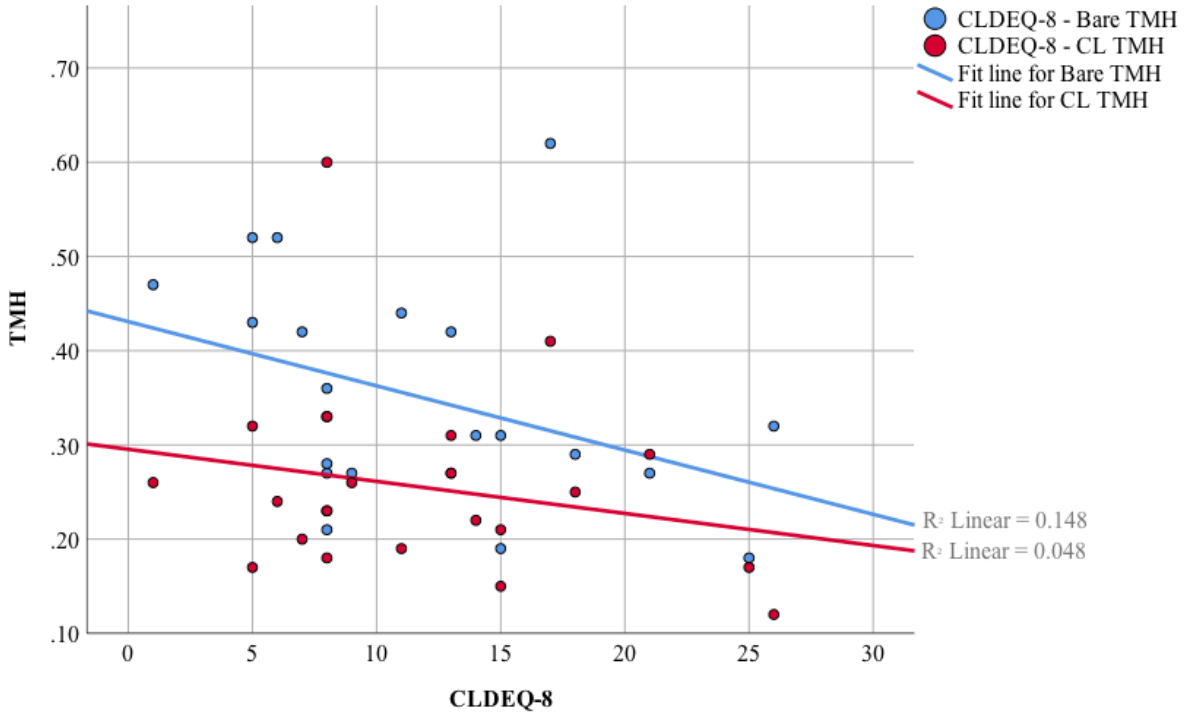

Figure 3.14 Correlation comparison between CLDEQ-8 and tear meniscus height (TMH) for each condition with a best fit line

Chapter 4. Discussion

A novel method for providing a quantified measurement of tear film quality was developed during this study. Using the Oculus Keratograph 5M NIKBUT video scans, the proportion of the tear film that exhibited break up was determined. Previous work has defined a bare eye NIKBUT of nine seconds or less the diagnostic criterion for dry eye disease.[36] Both the total proportion of break up (BUP) and the proportion that occurred in the first nine seconds (RBUP) were analyzed to determine which method would be the best at quantifying tear film quality. The RBUP was not significantly different between the bare eye and the contact lens on eye conditions, but had a significant correlation with TMT and NIKBUT under bare eye conditions and NIKBUT with the contact lens in place. Although the BUP had a significant difference between bare eye and the contact lens on eye, a significant correlation was only found with NIKBUT in the bare eye condition. The RBUP successfully correlated to dry eye diagnostic measurements with the bare eye, but did not when the contact lens was present.

The results indicate that a new diagnostic criterion for NIKBUT with a contact lens-specific time to determine the proportion of break up may be useful for future contact lens studies. A possible reason that there was a significant difference between the contact lens on eye conditions between BUP but not RBUP is that the TMT for the contact lens videos were significantly longer than the bare eye videos. Almost all

participants were able to reach the end of the measurement time without a blink when the lens was in place, but were not able to with the bare eye. This allowed for more break up to occur during the contact lens measurements for the BUP variable. By reducing the evaluation period to nine seconds with RBUP, measurement time was not a factor for the proportion of breakup.

Tear meniscus height and first NIKBUT were used to help aid in determining the validity of tear film measurements over contact lenses using the Oculus Keratograph 5M. There was a significant difference between the two contact lens conditions for both variables. When the contact lenses were on eye, the resulting TMH was smaller than when the eye was bare. This finding supports previous knowledge that contact lenses cause a reduction in the pre-lens tear film thickness.[32] The Keratograph is only able to observe the pre-lens layer, so the reduced TMH was expected. The first NIKBUT occurred sooner when contact lenses were present. Again, this was the expected finding. The pre-lens tear film layer experiences a higher rate of evaporation, leading to an earlier NIKBUT.[34]

When the eye was bare, there was a significant correlation between TMT and NIKBUT, NIKBUT and BUP, NIKBUT and RBUP, TMT and RBUP, and CLDEQ-8 and TMH. This differs from when the contact lens was on eye, with the only significant correlation being between NIKBUT and RBUP. The reason for this may be due to the contact lens providing protection to the ocular surface, reducing the eye's natural dry eye defense mechanisms. Earlier break up correlated with an earlier blink without the contact lens in place, which can be explained by the blink reflex being triggered when stimulated

by tear film disruption. The main layer of the tear film affected during the measurements was the pre-lens layer. Changes to this layer would not be detected by the ocular surface nerve endings, resulting in a lack of blink reflex stimulation. This would lead to a longer measurement period regardless of the quality of the tear film. An earlier break up correlating to a larger break up proportion demonstrates the reduced quality of the lipid layer of the tear film. It has been previously shown that contact lens wear disrupts the lipid layer, so this result is not surprising.[34] The lack of correlation between CLDEQ-8 scores and the contact lens measurements was also not surprising. It was expected that when the contact lens was in place that the TMH would be reduced and that the ocular surface is unable to detect changes in the pre-lens layer, so there would not have been any significant connection between these measurements and dry eye symptoms.

This study was not free from limitations. One major limitation was using the participants' habitual contact lenses instead of standardizing the material and design. The water content differences between silicone hydrogel contact lenses and hydrogel contact lenses have been shown to impact dryness symptoms.[42] This water difference may have impacted the Keratograph measurements. Since silicone is a hydrophobic material, silicone hydrogel contact lenses have a reduced overall surface wettability and an increase in surface deposits. This study included 73 percent silicone hydrogel contact lenses, but did not compare measurements between the two lens material types. Future studies could analyze Keratograph videos of participants in both silicone hydrogel lenses and hydrogel lenses to see if there is a statistically significant difference between surface wettability using the RBUP variable.

An additional contact lens variable that was not analyzed was contact lens design. Different contact lens companies use different wetting agents, which may have impacted the contact lens NIKBUT video measurements as well. This study had 73 percent of contact lenses in the Acuvue family, but even that had variability with seven different Acuvue lens types represented. Future studies could regulate and compare specific contact lens types to determine the impact of lens material and design on tear film measurements.

Another limitation was the errors made in data collection. Although most measurements were obtained by the same examiner, a few participants' measurements were taken by various examiners. Mistakes with data collection resulted in four NIKBUT videos without data and one participant with only two TMH photos taken instead of three. There are minimal opportunities for inter-examiner error, but variations in verbal instructions and TMH image capturing could have led to data variability. A strength of this study was having only one examiner measure the TMH for each image. This eliminated any inter-examiner variability in determining the beginning and end of the TMH during the final measurement.

The TMH section of this study had various limitations. The main constraint was only taking one measurement per image. In future studies, multiple measurements should be obtained per image to ensure the most precise height is determined. Only one location was used to determine TMH as well. Central and peripheral TMH measurements should have been determined to examine if there was variability throughout the length of the lid

margin. Tear meniscus height was only a subsection of this particular study, but could be more thoroughly examined in future research.

Aspects of the CLDEQ-8 comparisons were prone to limitations. Our study took measurements after a 15-minute settlement period. Some questions within the survey asked about end of wear comfort. It is possible that the questions led to participants bias their responses based on end of the day wear, not total wear. To allow for comparisons to better represent the conditions the survey refers to, measurements should be taken at the end of the day in future studies.

Since this study was intended to be a pilot study, the small n value of 22 was not a significant hindrance to the data analyzed, especially since statistically significant findings were produced. Future work with the Oculus Keratograph 5M with contact lenses on eye will need to be done to further validate the device as a staple in contact lens tear film measurements. More detailed analyses of lens properties are warranted to determine the accuracy of the tear film scans.

Chapter 5. Conclusion

This study was conducted to help determine the capabilities of the Oculus Keratograph 5M of obtaining dry eye measurements with contact lenses on eye and the impacts of contact lens wear on the tear film. The break up proportion variable was created to place a quantitative value on tear film quality.

Both the NIKBUT and TMH were significantly different between the bare eye and lens on eye. Contact lens wear resulted in a lower TMH and an earlier NIKBUT, which were the expected findings from previous studies.[32-34] This difference shows that the Keratograph can be used to make basic observations of how the tear film changes when the contact lens is in place.

Using these tests to diagnose dry eye was not appropriate due to the lack of correlation between the CLDEQ-8 scores and the contact lens measurements. The reduced break up proportion variable successfully quantified tear film quality of the bare eye, and could be used to help diagnose the severity of dry eye in the future. Analyzing the reduced break up proportion with contact lenses on eye did not provide significantly useful information about tear film quality, and more research needs to be conducted before this variable can be used for dry eye diagnosis.

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