Overnight Corneal Swelling and Deswelling with Silicone Hydrogel Lenses

by

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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.

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Abstract

Purpose: To compare central corneal swelling (CS) after eight hours of sleep in eyes wearing 12 different silicone hydrogel (SiHy) contact lenses (CLs) and to model between-subject variability in CS and deswelling. **Methods:** 29 neophytes wore 12 SiHy lenses with a central transmissibility range of 31 to 211 Dk/t units (4 SiHy CLs x 3 different powers) on separate nights, in random order, and in one eye only. Central corneal thickness in both lens-wearing and no-lens contralateral eyes was measured using digital optical pachymetry before lens insertion, immediately after lens removal on waking, then 20, 40 minutes, 1, 2 and 3 hours later. Descriptive analysis and Repeated Measures ANOVA (Re-ANOVA) were conducted to verify the distribution of individual CS and average differences in CS among CL types, respectively. Simultaneous analysis of group and between-subject effects for CS vs. Dk/t as well as for deswelling vs. time was carried out using mixed modeling. The following hypotheses were tested:

- Average CS in lens-wearing or in control eyes is normally distributed.
- There is a correlation in average CS between lens-wearing and control eyes.
- There are statistically significant differences in overall CS between the lens types.
- There are constant between-subject differences in CS over the range of SiHy Dk/ts.
- CS on eye-opening (intercept) can explain most of the between-subject differences in corneal deswelling.
- Individual CS or deswelling response can be predicted by lens Dk/t.
- Individual CS or deswelling response can be predicted by their age, sex or refractive error.

Results: Distribution of corneal swelling in both lens and control eyes, both on average and for each CL, was not significantly different from a normal curve ($p>0.20$ for all). When averaged over CL powers, CS with lotrafilcon A was significantly higher than galyfilcon A (Re-ANOVA, $p<0.001$). Mixed modeling of CS vs. Dk/t showed a significant effect of Dk/t ($p<0.001$) only in lens-wearing eyes (and no significant effect for any other/subject-related predictors in either eyes). However, mixed modeling also showed constant between-subject differences in CS, irrespective of SiHy Dk/t differences. More than 90% of between-subject differences in corneal deswelling vs. time (in both lens-wearing and no-lens eyes) was explained by between-subject variability in CS (intercept) compared to <10% of between-subject variability in the slope of CS over time. Although Dk/t was a significant predictor of the average corneal deswelling response in lens-wearing eyes, the contribution of Dk/t to between-subject differences in corneal deswelling (intercept/slope) was trivial. In lens-wearing eyes only, age was inversely related to the rate of corneal deswelling. **Conclusions:** Although descriptive analysis showed the CS among study subjects was normally distributed this initial analysis was incapable of providing any useful insight into the structure and/or predictors of between-subject variability in CS response. In addition, the average group analysis (ANOVA) showed a difference in the average CS between the highest and lowest O_2 transmissible SiHy materials (averaged over lens power for each CL type). However, due to its averaging nature, this traditional group analysis masked the largest source of variability in CS that is the individual-specific differences in corneal response to hypoxia. In contrast, mixed modeling showed that, despite the strong inverse relation between CS and CL DK/t, between-subject differences in CS is the largest source of CS variability but it is not dependent on CL Dk/t. Therefore, the results of this novel CS analysis suggest that the individual differences in closed-eye CS, and NOT the average

differences in CS response among different SiHy CLs, should be the main consideration in clinical decision-making.

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Dedication

I dedicate this work to my wife Bita, and to my children Lilia and Sam whom without their love, patience, sacrifice and support none of this would be possible

.....…, and to my parents to whom I simply owe everything.

Table of Contents

List of Figures

List of Tables

Chapter 1

Introduction

1.1 Corneal structure

The cornea is the anterior transparent tissue of the eye and it is the window of the eye to the world. Average corneal thickness is about 536 μm.[1] However, wide between-subject differences in corneal thickness has been reported.[1-3] Transparency of the cornea is dependent on its unique structure and physiology.[4, 5] Two different cellular barriers surround the cornea on its inside and outside limits. The anterior barrier is the relatively impermeable corneal epithelium with tight intercellular junctions that protects the cornea from the physical environment and microbial invasions and acts as a passive membrane working on osmotic equilibration of salt. The corneal epithelium is ~50 μm thick with reported between-subject coefficient of variation (CV) of ~8%[6] and it consists of 4-6 layers of cells that are replaced every ~10 days through migration of limbal basal epithelial stem cells from limbus towards the central corneal epithelial basal posterior layer. The anterior part of the corneal epithelium is in direct contact with tear film providing the smooth refractive surface of the eye. The tight junctions between the corneal epithelial cells act as a barrier to stop tears penetrating the cornea.[7] However, an experiment[8] showed the lack of tight junctions in corneal epithelial cultured cells in-vitro suggesting the possibility of some outward pumping of fluids in the cornea.[9] Bowman layer is an acellular layer of ~15-μm thickness of the anterior stroma (between-subject CV = ~25%).[6] Any damage to Bowman layer will cause a scar due to the lack of regeneration capability of this layer.

The corneal stroma is the thickest layer of the cornea making ~85% of corneal thickness (between-subject CV = ~10%)[6] and has an important role in corneal transparency by its uniquely organized lamella structure of collagen fibrils.[10] Collagen fibers and stromal intercellular matrix are secreted from stromal keratocytes cells.[11, 12] Stromal keratocytes are mainly found in the anterior stroma and contain a protein/crystalline to prevent light backscatter from keratocytes which could interfere with corneal transparency.[13] Tightly packed collagen fibrils in the anterior stroma provide strength and rigidity for maintaining the corneal shape and anterior curvature, even under stress of corneal swelling.[11] Descemet Membrane is an acellular layer of ~10 μm thick that separates stroma from the endothelium. Corneal striae and folds occur due to flattening of Descemet Membrane from stromal swelling.[14, 15]

The corneal endothelium is the posterior leaky barrier of single layer mosaic of hexagonal cells with ~4 μm thickness. Corneal endothelial cells do not have the capability to regenerate. The number of endothelial cells decrease by age from an average of ~4000 cell/ mm^2 in childhood to ~3000 cell/mm^2 in 30s and to ~2500 cell/mm^2 in 80s.[16] The loss of cell by age is compensated by enlargement of the existing cells (polymegathism) and changes is the shape of the endothelial cells (polymorphism/pleomorphism).

The posterior corneal endothelium is in direct contact with the aqueous humor to permit passage of water and nutrition into stroma and removal of waste products from the avascular cornea.[17] Corneal endothelial cells act as a biological pump (through active pumping of water into the aqueous humor) to maintain a relative deturgescent state (78% of water/hydration[18]) that is inversely related to endothelial cell size and variance of the cell shape.[19] The leak occurs through intercellular spaces between the endothelial

cells and the pump is mainly through intracellular route that mediated by the properties of the anterior (stromal side) and posterior (aqueous side) of the endothelial cell membranes.[9] Although the steady state of relative corneal dehydration is maintained through balancing of individual leak and pump mechanisms, the extent of intersubject variability in the steady state of either endothelial leak or pump rate is unknown.

1.2 Corneal swelling

In the absence of lens wear, the cornea in open-eye conditions is exposed to the atmospheric partial oxygen pressure (PO_2) of 155 mmHg.[20] Under closed eye conditions the PO_2 is reduced to about one third (55 mmHg), which is largely from the oxygen supplied by the palpebral conjunctival blood vessels.[20] The cornea metabolizes the glucose inefficiently even when a non-lens wearing eye is exposed to atmospheric oxygen. This is because it metabolizes more than 85% of glucose[21, 22] anaerobically leading to 18 times less energy compared to aerobic metabolic pathway of glucose. There are no data available about inter-individual differences in ratio of glycolysis (metabolizing glucose) by anaerobic versus aerobic routes in either corneal steady state of hydration or hypoxic conditions. The reduction of oxygen in anaerobic conditions affects corneal metabolism leading to increased lactic acid production from increased anaerobic metabolism. Elevated levels of lactic acid increase osmotic pressure in the corneal stroma leading to extra water retention by this tissue.[23-25] This mainly occurs by water absorption by stromal hydrophilic ground substance or mucopolysaccharides/glycosaminoglycans (GAGs) from the anterior chamber, across the leaky corneal endothelium.[26] This phenomenon can physiologically occur during sleeping when the eyelids are closed (overnight corneal swelling) and this physiological

corneal swelling found to be about 3-4% in non-contact lens wearers.[27-29] Typically, the cornea is at its maximum thickness on waking in the morning and it gradually recovers to its normal thickness within a few hours after eye opening.[27, 28, 30-34] A contact lens barrier can also induce corneal swelling. Therefore, corneal swelling is often used as a method of determining if the cornea is receiving sufficient oxygen through a contact lens.[35-37] Previous studies did not find any evidence for corneal epithelial swelling due to anoxia[38] or hypoxia.[39] O'Leary et al.[40] did not find any epithelial swelling after 6 hours of corneal anoxia. Using OCT, Wang et al.[41] found that the epithelial thickness across the horizontal corneal meridian did not change after 3 hours closed-eye wear of either a thick hydrogel or a PMMA lens. This was despite finding significant amounts of contact lens induced topographical corneal swelling with each lens type in this study.

There are reports suggesting a minimal change in the anterior cornea because of corneal swelling[42-44] and that the cornea/stroma mainly swells posteriorly.[45] This is also supported by findings from other studies on physical,[46-48] physiological,[49, 50] and structural[11, 51, 52] properties of the cornea. The high resistance of anterior stroma to water absorption was demonstrated by Muller et al.[53] when anterior 120 μm of the stroma remained relatively unswollen after storing human corneal samples in a deionized water solution for 6 months. Also, Edelhauser[45] pointed to the lower water content of the mammalian anterior than posterior stroma[54] in line with higher ratio[55] of a less hydrophilic GAGs[56] (dermatan sulfate) in the anterior stroma compared to higher ratio of a more hydrophilic GAGs (keratan sulfate) content in the posterior stroma. However, between-subject differences in the structure and/or GAG composition of either anterior or posterior corneal stroma have not been investigated and there are no reports of this

source of variation and its possible effect on between-subject differences in corneal swelling in the literature.

1.3 Corneal deswelling

O'Neal and Polse[31] showed that corneal swelling recovery followed a nonlinear time course with the rate of recovery decreased as the cornea thinned. They found that, on average of 2.5 hours after stopping the hypoxic stimulus, the open eyes returned to baseline from 60 microns of hydrogel lens induced corneal swelling. More recently, Fonn et al.[33] showed an average of 6.32% difference in overnight corneal swelling between hydrogel and silicone hydrogel lens-wearing eyes in neophyte participants (average overnight corneal swelling of 8.66 ± 2.84 % with etafilcon A vs. 2.34% ± 1.26% in control eyes, and 2.71% ± 1.91 with lotrafilcon A vs. 1.44% ± 0.91% in control eyes). However, average recovery from corneal swelling with each lens to the baseline occurred at a faster rate in the lens-wearing than the control eyes with no lens wear so that corneal thickness in both eyes returned to the baseline within 3 hours of waking and lens removal.

Corneal recovery from hypoxia induced swelling starts immediately upon exposure to higher atmospheric partial oxygen pressure in open-eye conditions. O'Neal and Polse [31] suggested a significant role (by contributing as much as 80% to corneal recovery from soft lens induced closed eye corneal swelling) for higher tear osmolarity after eye opening (from tear evaporation) to draw water from the cornea. However, a significant role for tear evaporation in corneal deswelling was questioned by others when they did

not find a difference in corneal deswelling rate under low and high humidity conditions.[57] In this latter experiment, corneal swelling was induced by wearing low Dk soft contact lenses only under open-eye conditions thereby minimizing the effect size for finding any differences (compared to the closed-eye conditions in the former experiment). Therefore, further studies are required to determine the average proportional contribution of tear evaporation and the endothelial pump to corneal deswelling after eye opening. Irrespective of its percent contribution to corneal deswelling after removing the hypoxic stress, the endothelial pump acts as an active ion pump that works to move the water from cornea to the anterior chamber. This is achieved by actively pumping of bicarbonate ions (HCO_3^-) from the stromal side of the corneal endothelial cell membranes into the anterior chamber side of these cells thereby increasing the osmotic pressure in the anterior chamber side of the cell membranes.[58] This will move water from the cornea into the anterior chamber by osmosis until the steady state of partial corneal dehydration (deturgescence) is met.[58]

A constant corneal endothelial pump speed under steady state of corneal physiological hydration has been suggested.[31, 59] However, there is a lack of evidence for a clear feedback mechanism like neural pathways to adjust the speed of endothelial pump based on the state of corneal hydration. There is some evidence for possible mechanisms to control the speed of the endothelial pump through water channels in the endothelial cell membrane.[60] In any case, between-subject differences in the speed of the endothelial pump is unknown. Steady state partial corneal dehydration (deturgescence) is maintained through an ongoing perfect balance between continuous active pumping and passive leaking functions of the corneal endothelium to maintain corneal transparency (Maurice pump-leak mechanism[61]). The limbal vasculature is

reported to not play a role in providing required nutrition and oxygen for corneal metabolism.[62] The cornea receives required oxygen for its respiration from the anterior surface through diffusion of atmospheric oxygen that is dissolved in the tear film and the source of nutrition like glucose and amino acids for the avascular cornea is the aqueous humor[17] although the exact reason for leakiness of corneal endothelium is still unclear.[58] Also, the extent of individual variations in endothelial leakiness is unknown. In addition, between-subject differences in stromal water absorption (between-subject differences in leak or stromal imbibition pressure which could be driven by unknown between-subject differences in the composition/density of the stromal ground substance and/or between-subject differences in the ratio of anaerobic/aerobic metabolism or the amount of lactate) is also unknown.

Therefore, in summary, the extent of individual variations in the controlling parameters of pump-leak mechanism is unknown, not only for the steady state of the corneal hydration, but also for hypoxia induced corneal swelling and recovery from it. In addition, understanding between-subject differences in corneal deswelling and its possible predictors was not the main objective of previous studies. Although previous experiments were mainly focused on measuring the average recovery rate (from corneal swelling) significant differences in the corneal recovery rate in normal subjects between younger (average of 24 years) and older (average of 72 years) age groups has been reported in the literature.[63]

1.4 Corneal oxygen supply in contact lens wear

1.4.1 Oxygen transmissibility (Dk/t)

The term “oxygen transmissibility” (Dk/t) describes the oxygen diffusion through a contact lens material by accounting for both oxygen permeability coefficient (Dk) of the lens material and lens thickness (t).

The units of Dk and Dk/t are 10^{-11} (cm2/sec)(mlO_2/ml x mmHg) or “Barrer”[64] (named after a well-known chemist, Richard Barrer [65]) and 10^{-9} (cm/sec)(mlO_2/ml x mmHg) or “Barrer/cm”, respectively. Central Dk/t of a contact lens is calculated by using the central lens thickness of the lens. In hydrogel lenses oxygen dissolves in the water and diffuses from the anterior to the posterior lens surface. There is a direct relationship between the logarithmical Dk in conventional hydrogels with the equilibrium water content of the material.[66, 67] The maximum Dk of a hydrogel material would be around 80 units for a hypothetical 100% water content. [68]

Soft lens transmissibly has been significantly improved by the advent of different silicone hydrogel lens materials in the past 2 decades. In contrast to hydrogel lenses, an inverse relation between lens water contact and Dk was shown[69] in silicone hydrogel lenses where a decrease in Dk was associated with increasing water content of the silicone hydrogel. Therefore, unlike hydrogel lenses, passage of oxygen through silicone hydrogel lenses is not limited by maximum permeability of water. The highest reported value for central oxygen transmissibility in current silicone hydrogel lenses is 211 Dk/t units (lotrafilcon A 24% water content @-3.00 D, Dk = 140 units).

1.4.2 The role of the post lens tear film in contact lens wear

With rigid (PMMA) lenses, tear pumping due to blinking was the main source of oxygen delivery to the cornea, as zero oxygen diffusion occurs through this lens material. However, the tear pump alone is incapable of providing sufficient oxygen to minimize corneal swelling with PMMA lenses in daily wear.[70] This is evident by the reduction in hypoxic corneal complications reported with the advent of rigid gas permeable (RGP) lenses.

A minimum critical central Dk/t of between 8 to 20 units was suggested to avoid open-eye central corneal swelling with RGP lenses.[71] The lower Dk/t suggested critical value for RGP lenses than the Holden and Mertz daily wear Dk/t criterion of 24 units was attributed to additional corneal oxygenation from blink-induced tear pumping in RGP lens wear. A study by Swarbrick et al.[71] did not find any evidence for the presence of osmotic corneal swelling caused by reflex tearing from RGP lens wear in unadapted subjects. This was attributed to a smaller decrease in tear tonicity by rigid lens adaptation[72] than in experiments in which the eye was exposed to a hypotonic solution of low osmolarity,[73] as osmotic corneal swelling did occur with corneal exposure to these solutions. Lower peripheral corneal swelling with RGP lenses than soft lenses of the same Dk/t is expected, due to the smaller diameter and greater tear pumping that occurs with rigid lenses.[74]

Using an interferometric method, King-Smith et al.[75] demonstrated an average pre- and post-lens tear film thickness in a polymethyl methacrylate (PMMA) lens as 3 and 30 μm, respectively. Their measurements for the average pre- and post-lens tear film thickness

in a hydrogel lens were 2.31 and 2.34 μm respectively. There are no reports on between-subject differences in pre- and post-tear film thickness in the literature.

Fatt et al. [76] showed post lens tear oxygen tension in soft lenses is solely dependent on the oxygen diffusion through the lens material, rather than the tear pumping that occurs with PMMA lenses. This was later confirmed by Polse et al[77], who found that the oxygen delivery to the cornea by tear pumping for hydrogel lenses was very small, and they suggested that oxygen delivery to the cornea by a hydrogel lens was mainly by diffusion through the material. Therefore, due to the lack of a notable tear pump after blinking with soft lenses, the effect of tear mixing to equilibrate the oxygen tension under a soft lens is insignificant.[78, 79]

McNamara et al.[80] found that post lens tear exchange rate can only be improved by ~0.6% per blink after switching from a 13.5 mm to a smaller 12 mm diameter soft lens. Paugh et al. [81] concluded that their fluorophotometric protocol appeared to be capable of discriminating post lens tear exchange between a marketed etafilcon A and a prototype lotrafilcon A. However, it is worth noting that like modern RGP lenses any improvement in tear exchange with silicone hydrogel lenses minimally impacts corneal oxygen delivery in these high oxygen permeable lenses. A recent review by Muntz et al.[82] reported that various methods did not lead to any significant improvements in tear exchange under a soft contact lens. They also listed several drawbacks for the commonly used fluorophotometric technique as an indirect measurement of post lens tear flow, such as measurement errors from corneal and conjunctival staining by the fluorescein dye[83], inducing a tear reflex[84] by the method, possible changes in tear osmolarity and tear production by the use of fluorescein, and the inherent limitation of

the technique by measuring the decay of a fluorescein dye instead of the actual tear exchange rate.

A recent study by Maki et al.[85] found that the flow of the post-lens tear film was dependent on the thickness profile and the design of the hydrogel lenses. They developed a mathematical model for the average flow of the post-lens tear fluid in response to the mechanical suction pressure of deformed contact lenses from blinking. Although their results showed that the post-lens flow was sensitive to the hydrogel lens thickness profile, the differences were small. They concluded that the dependence of the post-lens tear replenishment on the hydrogel lens thickness profile was clinically insignificant. In summary, considering the absence of significant post-lens tear exchange in soft lenses, oxygen transmissibility is the main indicator for gauging corneal oxygen delivery by soft lenses. Although intersubject differences in post lens tear film thickness was not the focus of previous study[85], this is expected to have a minimal effect on between-subject variability in corneal swelling.

1.4.3 Oxygen models to determine minimum O_2 requirements

Polse and Mandell [86] suggested that to maintain normal corneal physiology a minimum oxygen tension of 11-19mmHg at the anterior corneal surface is required. Fatt pioneered corneal PO_2 distribution studies[87, 88] and provided an earlier model of corneal oxygen profile underneath a lens by considering the cornea as a single layer[89]. Harvitt et al.[90] mathematically expanded this model to a five layer model of distribution of oxygen tension across the cornea and contact lens and included the effect of increasing acidification from contact lens wear on the corneal oxygen consumption model. To avoid corneal anoxia, they suggested a minimum Dk/t of 35 units in open eye and 125 units in

closed eye conditions. Based on measurements of tear oxygen tension in four subjects, Bonanno et al.[91] estimated that human corneal oxygen consumption rate after 5 minutes of eye closure with soft contact lens wear (4.2 to 99 Dk/t units) ranged from 3.7×10^{-6} to 2.2×10^{-4} $mLO_2/cm^3/$ sec. The wide range of corneal oxygen consumption rate in such a small sample size suggests even greater variability in population consumption rate. Brennan[92] estimated total oxygen consumption of the cornea with contact lens wear based on his 8 layer mathematical model[93] of corneal oxygen diffusion. He estimated that lenses with an oxygen transmissibility of >20 (open eye) and 300 (closed eye) Dk/t units will satisfy 100% of the corneal oxygen demand. Corneal oxygen consumption rate in this model was calculated as 44.8 nL/ cm^3/sec with Dk/t of >20 and >300 units in open and closed eye conditions, respectively. In this model, lenses with 15 and 50 Dk/t units for daily and continuous wear, respectively, will satisfy 96% of the normal long-term total oxygen consumption required, suggesting a minimal oxygen effect from increasing lens Dk/t above the Holden-Mertz criteria of 24 Dk/t for daily wear or 87 Dk/t units for extended wear (EW).[92, 93]

More recently, Chhabra et al.[94] mathematically modeled a cornea-contact-lens system by coupling the glucose metabolism, lactate production and acidosis with oxygenation of the cornea. From this model, they proposed a new physiologic index as “Oxygen Deficiency Factor (ODF)” to assess the extent and severity of hypoxia in the cornea. They calculated an average maximum human corneal oxygen consumption rate of 1.05×10^{-4} $mL/cm^3/$ sec.[95] However, Leung et al.[96] argued that the model by Chhabra et al.[94] may not predict corneal swelling under epithelial hypoxic conditions, as the transport of NaCl or water was not considered in the model. They proposed a new metabolic model for contact lens induced corneal swelling by including the effect of tear film tonicity.

Larrea et al.[97] devised a mathematical model to simulate the previous experimental results from Bonanno et al.[98] for tear oxygen tension after 5 minutes of soft contact lens wear with eye closure. In a recent mathematical analysis, Compan et al[99] calculated an average human corneal oxygen consumption rate of 1.47 x 10^{-4} mL/cm^3/ sec using the Chhabra et al.[94] and Larrea et al.[97] mathematical models in combination with previous experimental results for tear oxygen tension from Bonanno et al.[98, 100]

Alvord et.al[101] constructed a 2-D model of a -3.00 D contact lens on eye. A minimum peripheral lens Dk/t of >125 units was required to fully oxygenate the cornea. Brennan[102] argued that Alvord did not account for posterior corneal partial oxygen pressure from the aqueous. He estimated that by accounting for the posterior corneal partial oxygen pressure the minimum required peripheral Dk/t would be < 30 units and not > 125 units.

More recently Takatori et al.[103] developed a quasi-2-D metabolic model with an emphasis on quantifying the effect of cornea and soft lens thickness variations on corneal oxygen demand, taking into consideration aerobic and anaerobic metabolism and bicarbonate buffering. They suggested an “excess lactate factor” in addition to the “Oxygen Deficiency Factor” (Chhabra et. al.[94]) to assess corneal hypoxia.

Of the mathematical models, perhaps only Harvitt et al.[90] and Brennan[92, 93] provided some clear suggestions for minimum Dk/t requirements in open and closed eye contact lens wear. The proposed mathematical models can only provide a prediction based on their underlying *average* assumptions; they were essentially developed based on some possible average group variables (average model parameters from preceding clinical studies/review papers) to try to predict average corneal swelling in response to a change in lens Dk/t. The individual corneal physiological response to contact lens wear can only

be measured through well-designed clinical experiments. The effect of between-subject variability of underlying variables on between-subject variability in the predicted corneal swelling response (from the respective model) was never modeled, and so obviously cannot be accounted for in these hypothetical models.

1.4.4 Experimental minimum requirements for contact lens transmissibility

The focus in the area of contact lens induced corneal swelling in the past was mainly in the area of closed-eye lens wear, lacking long-term studies for contact lens induced corneal swelling in daily wear. The minimum suggested criterion to avoid any measurable average central corneal swelling in open-eye lens wear is ~20-24 Dk/t units in the lens centre.[104, 105] The results of current short-term studies found that minimal average ocular physiological impact in open-eye soft contact lens wear could be expected with a minimum central Dk/t ~25 units.[106, 107] This level of central lens oxygen transmissibility induced minimal (~0.2%) average central corneal swelling. However, between-subject differences in contact lens induced corneal swelling in daily wear has not been investigated in the past.

Early studies[108, 109] for open-eye contact lens wear showed approximately 2% average central corneal swelling with daily wear of conventional hydrogel lenses with low oxygen transmissibility. Weissman et al.[108] used 3 hydrogel contact lenses: one 38.5% water content lens with estimated Dk/t of 6 unit, and two lenses with 55% nominal water content and DK/t values of 12 and 20 units. After 8 hours of open-eye wear, they reported an average 2.2% central corneal swelling with Dk/t of 6 units, and 1.5% swelling with lenses of either 12 or 20 Dk/t units.

La Hood[109] reported an average 1.7% central corneal swelling after 8 hours open-eye wear of a hydrogel lens with Dk/t of 14 units (74% water content). However, the average central corneal swelling increased to 7.9% when a low water content (43%) with Dk/t of 4 units was used. A more recent study by Morgan et. al.[105] found a maximum average central swelling of 4.8% with open-eye wear of a low oxygen transmissible hydrogel lens.

Holden and Mertz[104] and then Morgan et. al.[105] suggested a criterion of 24 and 19.8 Dk/t units, respectively to avoid average central corneal swelling in daily wear. In a recent study Moezzi et al.[106] found an average of ~0.2% central corneal swelling after 8 hours of daily wear of etafilcon A lenses (Dk/t = 25.5 units @-3.00D, water content 58%) in a range of -1.00 to -6.00 D minus lens powers. In another recent 12-hour study using hydrogel and silicone hydrogel daily disposable contact lenses (central Dk/t range of 24 - 156 units) in open-eye wear, Del Águila-Carrasco et al.[110] found that the maximum average central swelling occurred with the lowest Dk/t (Hilafilcon B). However, after 12 hours of contact lens wear the maximum increase in the average central corneal thickness was ~1 μm. As noted above the focus of all of these previous reports were on average corneal swelling in daily wear. The minimum suggested Dk/t of 20-24 units in daily wear is to achieve this average swelling and do not reflect individual Dk/t requirements.

In a landmark study Holden and Mertz[104] determined that a lens with a transmissibility of 87 Dk/t units limits average overnight corneal swelling to 4% which is the similar level of average physiological corneal swelling without lens wear. This study had a small sample size of 10 subjects. In another study Holden and Mertz et al.[28] found between 10-13% increase in corneal thickness upon awaking using a high water content, a medium water

content and a low water content hydrogel contact lens. Holden and Mertz[28, 104] suggested that up to maximum of 8% overnight swelling with extended wear contact lenses would be desirable as this level of edema allows the cornea to regain normal thickness during the day. Therefore, as no hydrogel contact lenses could meet the 87 Dk/t criterion, Holden and Mertz[104] suggested Dk/t of 34 units as a compromise minimum requirement for extended wear since this compromised lens Dk/t would induce an average of 8% overnight swelling and would allow full recovery on average soon after eye opening. Obviously, this does not mean that corneal swelling in every individual will recover to baseline after eye opening if they wore extended wear soft contact lenses of 34 Dk/t or even 87 Dk/t units but only in an average person, a hypothetical concept that may not match any individuals in the population.

More recently, a value of 125 x 10^{-9} Dk/t units has been proposed as the critical Dk/t of a lens to prevent lens-induced overnight corneal anoxia.[90] Again, all of these Dk/t criteria were determined based on group average corneal swelling and are incapable of enabling the prediction of *actual* individual corneal swelling values from a particular contact lens Dk/t (unless the individual coincidentally is the same as the group average). The availability of the silicone hydrogel lenses that meet or exceed the Holden and Mertz[104] criterion for EW allowed researchers to examine whether they can limit overnight swelling to the level of no lens wear. However, attempts to prove this hypothetical concept appear to have failed, as the silicone hydrogel lens-wearing eyes showed slightly (about 1-2%) greater overnight corneal swelling compared to no lens wear.[111]

In a study by Fonn et al.[33], etafilcon A hydrogel lenses (Dk = 18 units) showed an average of ~6% greater overnight corneal swelling than lotrafilcon A silicone hydrogel

contact lenses (DK = 140 units) in neophyte subjects when the lenses were worn only in one eye (8.66 ± 2.84 % overnight corneal swelling with etafilcon A vs. 2.71±1.91% with lotrafilcon A lenses). The same study showed as much as 6.32% difference in average overnight corneal swelling between the hydrogel lens-wearing and the contralateral control eyes with no lens wear (2.34 ± 1.26 % and 1.44±0.91% with control eyes paired with etafilcon A and lotrafilcon A lenses, respectively). Another study by Fonn et al.[112] in neophyte participants compared overnight swelling induced by lotrafilcon B silicone hydrogel (Dk/t, 138) and etafilcon A (Dk/t, 25.5) lenses in one eye only to the contra-lateral control eyes with no lens. Average central corneal swelling induced by etafilcon A (7.1% ± 1.9%) on eye opening was significantly higher than with lotrafilcon B contact lenses (2.8% ± 1.2%). The average swelling of the non-lens wearing contralateral control eyes were 2.7% ± 0.8% and 1.9% ± 0.9% with etafilcon A and lotrafilcon B lenses, respectively. These studies showed that the average corneal swelling could be lowered by using contact lenses of higher oxygen transmissibility.

In the last 40 years, attempts have been made to determine minimum required contact lens oxygen transmissibility in closed eye (and to lesser extent in open-eye) contact lens wear. However, the main focus in all previous mathematical models/clinical experiments was only on determining a hypothetical average minimum oxygen Dk/t contact lens (presumably to partly assist/guide the contact lens industry) and not necessarily in understanding the safe wear of contact lenses by an actual person (unless, again, this person coincidentally performed exactly the same as the ‘average’). Individual physiological responses to contact lens wear may deviate quite substantially from a hypothetical average. If a contact lens meets this average minimum Dk/t (in either mathematical or experimental models) we might expect that the population average

corneal swelling would be close to the predicted corneal swelling from these models/experiments. Previous models/experiments are incapable of addressing the expected amount of corneal swelling in any actual patient wearing a contact lens.

1.4.5 Average versus central oxygen transmissibility

Under closed-eye conditions maximum corneal swelling occurs at the corneal centre.[44, 113] Therefore, central corneal swelling can be used as the index of corneal physiological response to contact lens wear. There are reports that closed-eye hydrogel contact lens wear induced higher central corneal swelling with higher than with lower minus lens powers despite their similar central oxygen transmissibility.[28, 113, 114] Also, it was shown that using the central lens Dk/t underestimated the closed-eye central corneal swelling with minus and overestimated the swelling with plus powered hydrogel contact lenses.[115] Therefore, central corneal swelling in closed-eye hydrogel contact lens wear was explained by the average lens transmissibility Dk/t instead of the central Dk/t.[28, 115-119] The effect of average versus central oxygen transmissibility with silicone hydrogel lens wear has not been investigated in previous studies. However, a local effect for central lens Dk/t [119] (compared to average Dk/t) in closed-eye silicone hydrogel lens wear can be expected, based on its similarities to the effect of DK/t (greater corneal oxygen availability) in open-eye wear of hydrogel lenses.[105, 106] The second experimental chapter of this thesis will examine whether overnight central corneal swelling with silicone hydrogel lenses can be better explained by using their central or average Dk/t.

1.5 Application of corneal swelling studies

Corneal swelling is an index of the corneal response to hypoxia. Corneal epithelium is a relatively impermeable tissue with about ~2-4x less permeability to water[7, 120, 121] and ~100x lower permeability to passage of ions than the endothelium.[122] Therefore water and required nutrients/glucose mainly enter the cornea from the aqueous humor through the corneal endothelial layer.[17] However, corneal epithelium is permeable to atmospheric air,[123, 124] with its permeability to carbon dioxide is almost 20x that of oxygen.[20, 94] So, the main source of corneal oxygen is from atmospheric air with the corneal epithelial cells exposed to 21% atmospheric oxygen, equivalent to a partial O_2 pressure of 155 mmHg. Even under open eye conditions with no contact lens in place (i.e. under steady state of corneal hydration), the corneal epithelium metabolizes most of the glucose (~85%) through the inefficient anaerobic pathway versus ~15% through the more efficient aerobic pathway.[21, 22] Water and CO_2 are the only products of metabolism of glucose in the aerobic pathway. Lactate that is produced through the anaerobic pathway slowly diffuses to the stroma, thereby drawing water into the stromal ground substance through an osmotic effect and leading to corneal swelling. Under steady state open eye conditions, the endothelial pump actively moves the additional water into the anterior chamber, maintaining the state of partial corneal hydration of 78%, so-called corneal deturgescence (relative dehydration), to maintain corneal transparency. In this process lactate is also moved into the anterior chamber in an exchange with buffering bicarbonate (from the anterior chamber) to balance the corneal pH.[58] However, under hypoxic conditions, the physiological balance of corneal hydration can no longer be maintained as the endothelial pump can no longer overcome the amount of stromal

excess water absorption from the excessive lactate production under anaerobic conditions. The net result of any increase in the percentage of anaerobic metabolism is an increase in corneal thickness that is directly proportional to the increase in corneal hydration, partly because the corneal lateral diameter cannot change. The corneal response to oxygen deprivation is not only a phenomenon of contact lens wear; it has also been found under anoxia with nitrogen filled goggles[125-127]. The direct linear relation between corneal hydration and corneal thickness exists because of the fixed amount of stromal ground substance (components of the stromal proteoglycan gel like substance) in any corneal tissue and that water is only absorbed by the stromal ground substance and not by stromal collagen fibrils. The ratio of corneal hydration to corneal thickness is determined by the ratio of the fixed dry substance of cornea to variable water, leading to a direct linear relationship between corneal hydration and corneal thickness. However, between-subject differences in the ratio of water to components of the dry stromal ground substance - in either corneal steady state or any swollen states - are unknown. Corneal hydration cannot be easily measured in *in vivo* clinical research conditions but corneal thickness can be easily measured by pachometric methods. That is why measurement of corneal swelling/thickness is used as the main index of corneal physiological response to hypoxia, as it reflects the state of relative corneal excessive hydration. This indicates a shift in the balance of corneal metabolic activity toward the anaerobic condition that is not compensated by active endothelial pumping of water (due to a physiological pump deficit) at any dynamic thickness/hydration level in relation to hypoxia.

1.6 Why study corneal deswelling?

Previous studies have shown that cornea starts to return to its steady state hydration/thickness upon removal of hypoxic stimulus. This was true for physiological swelling from overnight eye closure as well as in contact lens induced corneal swelling in daily wear or overnight wear. Corneal deswelling occurs because, after removal of hypoxic stress, epithelial cells stop producing excessive lactate as the ratio of anaerobic and aerobic corneal metabolism returns to its normal. Simultaneously, the endothelial pump begins to gradually overcome its deficit by pumping the residual excessive water from the stroma. In a landmark study, O'Neal and Polse[31] found a non-linear course for the recovery from corneal swelling, with the greatest amount of deswelling occurring within the first hour after removing the hypoxic stress. Thereafter a gradual decrease in average corneal thickness/swelling continues, asymptoting to a level below baseline in the next two hours. In a study[128] with diseased corneal endothelium (Fuchs' endothelial dystrophy), after 2-hour closed-eye wearing of a low DK/t hydrogel lens, there was a slower average deswelling than that of subjects with normal corneas in the same age group. This was despite those subjects with Fuchs' dystrophy exhibiting a significantly lower average amount of contact lens induced corneal swelling. In this study, they also found that some diseased corneas did not return to their original thickness even after ~16 hours (typical number of waking hours) after removing the hypoxic stress.[128] Therefore, the recovery rate of corneal deswelling can reflect the function of a corneal endothelial pump and its physiological status/health. However, between subject differences in the corneal endothelial pump function and intersubject variability of the

recovery rate from corneal swelling (between-subject differences in corneal deswelling) has not been a focus of previous studies.

1.7 Subject characteristics and corneal swelling (CS differences in people)

1.7.1 Age, sex, refractive error

An effect for subject differences in sex and refractive error on corneal swelling or deswelling has not been found in the literature. Also, despite corneal endothelial morphological changes being reported due to normal aging,[129] an effect of age on contact lens induced corneal swelling under closed-eye conditions has not been shown.[63, 130] However, there are reports of an inverse relation between the rates of corneal recovery from contact lens induced corneal swelling and age.[63, 130]

The effect of age on contact lens induced corneal swelling in open-eye lens wear has also not been previously studied. However, based on the results from closed-eye lens wear studies and availability of higher oxygen concentration in open-eye conditions it would be reasonable to assume that there are no clinically significant effects of age on average open-eye corneal swelling. The effect of age on corneal deswelling rate in open-eye lens wear is also unknown. This lack of information about average effects of age leads to the other obvious observation that there is no information about the variability between people at different ages and how this within-person and between person swelling and deswelling changes over the lifespan.

1.7.2 Between-subject variability of corneal swelling

Large intersubject variability for overnight corneal swelling is reported as a result of contact lens induced hypoxia[98, 131, 132] or anoxia with no lens wear.[127] However, the focus

of previous studies was on lens oxygen transmissibility properties as the main variable rather than the subjects as the main source of variability in the corneal swelling response. Therefore, the efforts of the previous studies were focused on pinpointing an average threshold for contact lens DK/t to avoid an average swelling response to contact lens wear and without considering a role for subjects as an important source of variability in this regard. This view is clearly reflected in the published study by Staarmann and Schoessler in 1991[132] when the authors reported observing high levels of intersubject variability in overnight corneal swelling of 12 study subjects (with 5 rigid and 2 soft contact lens types) in the abstract of their article without providing any relevant data on the intersubject differences in the paper. How might a reader possibly know if this was actual between-subject differences in corneal swelling or an intermittent systematic or random measurement error by their method? Was between subject differences constant across the different Dk/t? Was there a pattern in between-subject differences with different lenses? Was there a similar or a different response pattern for between-subject differences in overnight corneal swelling with no lens wear? Was the reported unknown high level of intersubject variability affected by using different contact lenses on different study nights? In other words, what was the contribution or the role of Dk/t to intersubject variability in corneal swelling? Finally, in order to scientifically conclude that there was a high level of intersubject variability in corneal swelling (as reported in the last sentence in their abstract) it would appear that more rigorous mathematical/statistical methods should be employed, something they did not do. The structure/pattern of between-subject differences in corneal swelling (and deswelling) and their possible predictors have not been a focus of the studies in the past, although some attempts have been made to explain the possible predictors that may partly predict individual differences.

Stickel and Bonanno[98] suggested that epithelial and endothelial metabolic rates are more important than stromal thickness in determination of corneal oxygen demand as they found no relation between corneal thickness and tear oxygen tension. In addition, a few previous studies suggested an association in between-subject differences in corneal swelling and between-subject differences in corneal metabolism and endothelial function.[133, 134]

1.8 Introduction to mixed modeling philosophy

We could (if interested) perhaps investigate whether an individual's corneal swelling is systematically different than the average corneal swelling but inferences about individuals should not be made from average results. If ten different people measure a physical variable (for example length of an object) and we average their measurements, the result will probably be a more accurate measure of that variable (using the same measurement protocol). However, the opposite could not be logically correct: If we measure 10 different people for a variable (example their height) the average will not necessarily represent any individual in that group.[135] Therefore, the average may be useful in conditions when the same thing is measured repeatedly but not when different individuals are being measured for the same variable.

In general, previous studies reported the average results of corneal swelling and not the individuals' results. These previous efforts were mainly focused on understanding lens oxygen performance by examining the relation between lens Dk/t and average corneal swelling across subjects. By treating all subjects as a homogenous group, contact lens induced corneal swelling was explained by the group average swelling response for

predictor variables, such as a lens, to gauge its performance experimentally, and to attempt to apply the conclusion to the real world. However, due to inherent problem with "averaging" using 'classical' experimental design and analysis[136, 137] (ANOVA/regression, for example), the experimenters inadvertently ignored the potential of large intersubject variability of corneal swelling; i.e. not all corneas swell to the same. The assumption and implication in doing this, is that all subjects, more or less, behave like an average, similar to the result of average analysis.[151, 152] This approach could be misleading, especially when one attempts to expand to the clinical implications of the results or to use the results to provide clinical guidelines. These methods not only are unable to demonstrate the structure of possible between-subject differences that contribute to the average results in the first place, but also, they are incapable of enabling the proper investigation of possible reasons for individual differences by the analysis.

ANOVA mainly provides two different approaches to dealing with repeated measures (within-subject effects): The first approach is through multivariate analysis. In this approach ANOVA assumes that repeated measurements of the same outcome are different outcome variables at each time-point. However, within-subject measurements (repeated measurements of the outcome variable for any subject over time or any other repeated metrics) are related to each other because these repeated responses are from the same subject. Multivariate analysis has to account for the relation among repeated responses from each subject (for the assumed independent outcomes) by assuming no limits for the existing relation/numerical representation among within-subject repeated measurements (mathematically this is an unstructured residual matrix i.e. different variances across time points and different co-variances between each pair of time points for each subject). The number of estimated/free parameters to mathematically represent

the relation among repeated measurements of outcome for each subject is directly related to the number of repeats and the sample size.[138-140] Therefore, except for a small number of repeats with an adequate sample size, the estimation of these parameters to define within-subject relationships of the repeated measure can be mathematically impossible (too many free parameters from insufficient data).

To provide another solution for this difficulty in parameter estimation, a univariate ANOVA could be a second approach in repeated measures ANOVA. In this instance, as is apparent from its name, the outcome at different times is considered to be the same type of scalar value. However, the problem of accounting for correlations among repeated responses from the same subject still exists. In an attempt to deal with this problem, correlations among variances (sphericity) of within-subject measurements are assumed in the univariate repeated measures of ANOVA leading to limited options for defining the relation in within-subject repeated measurements (residual matrix structure in statistical term) in this model.[141, 142] One of these options, is by assuming only one variance and only one co-variance for the whole residual matrix, independent of the number of repeated measures (compound symmetry).[141, 142] The univariate model parameter estimates are only as good as whether the actual data points comply with the model assumption of sphericity, something which is difficult to demonstrate using existing tests (e.g. Mauchly's test of sphericity[143]).[144]

In summary, repeated measures ANOVAs may still provide valid parameter estimates for simpler average models with smaller number of repeats, or for some more complex models, if the data happen to follow the underlying model assumptions.[144] Repeated measures ANOVAs by themselves are incapable of providing any useful insight into between-subject differences. In addition, another limitation of repeated measures

ANOVAs is its inability to account for missing data meaningfully, so that all subjects must have the same number of repeats. ANOVA is only capable of addressing average nesting effects in multi-level/hierarchical models without providing any insight about the components of the nesting (due to losing information after averaging the nest contents).[137, 145]

Fortunately, in the last few decades new approaches have emerged to solve these problems. One of these new perspectives of data analysis is mixed modeling, which is an extension of linear models.[146, 147] The “mixed” in this modeling is parallel and simultaneous analysis of both average (fixed) and individual/subject (random) effects.[148, 149] The mixed modeling procedure simultaneously estimates the fixed effect parameters for the observed data (i.e. group effects) and the variance of the random effects (i.e. between-subject effects).[148-150] In the model we can continuously compare different iterations until it reaches the peak likelihood (or the minimum of the inverse of the likelihood) of all estimated model parameters simultaneously reflecting the actual data.[151] Models can be compared using likelihood ratio tests to verify whether the added complexity in each model significantly improves the fit of the model.[152, 153] This may be achieved by first comparing the full model (model with all appropriate model parameters/predictors) with an empty model (i.e. a model without any predictors) to see if the full model has significantly improved the fit (i.e. likelihood). This is followed by comparing the full model to the other nested models, and among the nested models to find the best fit. In this process “Deviance” (defined as -2 log likelihood) is used instead of comparing the actual likelihoods.[152] The Deviance statistic in mixed modeling can be considered as an analogue to R^2 test of goodness of fit (the proportion of total variance

explained by the model/regression) in the classical regression models. The best fit mixed models are achieved by the highest probability of the model for the given data. The statistical significance of the difference in Deviance between two nested model in mixed modeling is estimated based on a chi-square distribution with a difference equal to the difference between number of parameters in the two models.[152, 154]

Mixed modeling includes the subject as a random factor in the model thereby accounting for dependency/relation of measurements from the same subject at different time points. The selection of a mathematical representation for explaining the relation among within-subject repeated measurements in mixed modeling is not constrained [155-158] by the theoretical limits[143] in ANOVA. In addition, by including subject as a random factor in the model the relation among between-subject measurements (mathematically this is the *random* variance and covariance matrix of the model) can simultaneously be computed.[149, 150, 159, 160] The beauty of adding the subject as a random factor in a mixed/hierarchical model is that it is more powerful than the possible solution of estimating each individual regression parameters separately. Therefore, mixed modeling has proved to be a powerful tool to analyze both the between-subject and the fixed effects simultaneously.[159-161]

Our goal from mixed model analysis of corneal swelling, is to specifically add an analysis of the between-subject random structure of corneal swelling to the average analysis of the fixed effects, in an attempt to more adequately understand contact lens induced corneal swelling under closed eye conditions, and corneal deswelling over time when eyes were subsequently opened. Average analysis / analysis of fixed effects (ANOVA or regression analysis) is incapable of investigating between-subject differences/random effects.[162] Furthermore, measurement errors from Simpson's

paradox[163-166] can affect the average analysis due to averaging among the study clusters in the conventional analysis such that the other relationships within the data may be masked or even reversed. In addition, the mixed model analysis can concurrently investigate the impact of other factors or covariates that might explain why some individuals behave differently.[152, 159]

In summary, numerous physical and physiological between-subject differences exist that could potentially impact both their swelling response to hypoxia and their recovery from swelling. There is no reason to believe an association among the potential predictive variables of corneal swelling. Therefore, they could all be independent from each other. For x number of independent variables there will be x! (factorial) combinations that might be the number of ways these predictors affect individual responses. Therefore, the effect of the number of independent variables on the swelling and deswelling response is complex, in part simply due to this number of possible permutations/combinations. It is self-evident that narrowing down the expected response from an individual to an average number (rather than studying that particular individual responses) is an oversimplification that is potentially misleading, especially if this assumption leads to suggesting a treatment or intervention (in this case, recommending a specific contact lens to a particular individual). In my journey to study between-subject variations in corneal swelling I started with traditional descriptive analysis of the results in the first experimental chapter (chapter 2), then continued with traditional ANOVA approach to study the average data and whether the results were in line with what would be expected from the previous studies. Lastly, in the 3rd experimental chapter (chapter 4) I used an approach to look at the data from a novel angle to see if mixed modeling could provide a

clearer understanding of between-subject differences in corneal swelling and deswelling responses and, with this method, what were the possible associations of these outcomes to a number of hypothetically important predictor variables.

The following primary hypotheses were tested in the respective chapters:

Chapter2:

- Average CS in lens-wearing or in control eyes is normally distributed.
- There is a correlation in average CS between lens-wearing and control eyes.

Chapter3:

- There are statistically significant differences in overall CS between the lens types.
- There are statistically significant differences in CS between the lens types for each lens power.

Chapter4:

- There are constant between-subject differences in CS over the range of SiHy Dk/ts.
- CS on eye-opening (intercept) can explain most of between-subject differences in corneal deswelling.
- Individual CS or deswelling response can be predicted by lens Dk/t.
- Individual CS or deswelling response can be predicted by their age, sex or refractive error.

Chapter 2

Distribution of overnight corneal swelling across subjects with 4 different silicone hydrogel lenses

The following manuscript titled above was submitted to Eye & Contact Lens[167] and it is the subject of the first experimental (chapter 2) of my thesis with minor proof changes along with my changes in the numbering of Tables, Figures and references for integration into my thesis.

Authors' Contributions to this manuscript (please check relevant boxes for each author):

Author	Concept/Design	Data Collection	Data Analysis	Article Writing	Article Editing
Amir Moezzi	x	x	x	x	x
Desmond Fonn	x				x
Jalaiah Varikooty		x			x
Doris Richter					x

2.1 Overview

Purpose: To determine distribution of central corneal swelling (CCS) across subjects after 8 hours of sleep in eyes wearing silicone hydrogel lenses with various oxygen transmissibility (Dk/t) values and in eyes without lenses. Methods: Twenty nine neophytes wore lotrafilcon A (Dk, 140), balafilcon A (Dk, 91), galyfilcon A (Dk, 60) and senofilcon A (Dk, 103) lenses in powers -3.00, -10.00 and +6.00 D on separate nights, in random order, and on one eye only. The contralateral eye (no lens) served as the control. Central corneal thickness was measured using a digital optical pachometer before lens insertion and immediately after lens removal on waking.

Results: The average difference between the mean (7%) and the median (6.8%) CCS of all lenses was only 0.2% suggesting a normal distribution. There was no correlation between the mean and the range of the CCS ($r=0.058$, $p=0.766$). Normal CCS distributions were also found with each lens as well as the control eyes ($p>0.20$ for all). There was a significant correlation between lens-wearing and control eyes ($r=0.895$, $p<0.001$), and between lotrafilcon A and each of the other three lenses for mean CCS across the study participants ($p<0.001$ for all).

Conclusions: Distribution of corneal swelling in both lens and control eyes followed a normal curve. An individual's corneal swelling response seems to be independent of lens type.

2.2 Key words

Corneal thickness, Corneal swelling, Variability, Optical pachometry, Silicone hydrogel lenses, Oxygen transmissibility.

2.3 Introduction

Hypoxia induced corneal swelling is a well-known phenomenon and one of the primary indices of corneal physiological change.[36] It has been shown that corneal swelling is inversely related to the contact lens oxygen transmissibility.[104, 126, 168, 169] Holden and Mertz hypothesized that in order to avoid overnight corneal swelling, a lens should have a minimum oxygen transmissibility (Dk/t) of 87±3.3 (barrer/cm).[104] More recently, a value of 125 (barrer/cm) has been proposed as the critical Dk/t of a lens to prevent lens-induced overnight corneal anoxia.[90] The goal of industry was to develop high oxygen transmission soft lenses and studies have shown that silicone hydrogel lenses induce less overnight corneal swelling compared to conventional hydrogel lenses[33, 112, 170-173] and very little more than the non-lens wearing eye.[33, 111, 112, 174]

Traditionally, studies such as this have relatively small sample sizes because of the precision of measuring corneal thickness and being able to detect small statistically significant differences between lenses. Typically central tendency, usually means and some form of variance (e.g. standard deviations) are reported, but not the individuals' results. Describing average results is important for comparison between stimuli. However, not all subjects swell within a safe margin that may be represented by the mean, especially if exposed to high powered thick lenses, since high intersubject variability has been reported as a result of contact lens induced hypoxia[98, 131-133] or anoxia.[127]

This study compared central corneal swelling (CCS) after 8 hours of sleep in eyes wearing four different silicone hydrogel lens types in three dioptric powers with various oxygen transmissibilities (Dk/t), 12 lenses in total. Only one lens was worn per night, the other eye of the participant serving as a control. The purpose of this study was to determine average and the distribution of overnight corneal swelling response across study participants. The average results of this study has been submitted for publication as a separate article (Moezzi AM, Fonn D, Varikooty J, et al., unpublished data).

2.4 Materials and methods

2.4.1 Subjects

This was a non-dispensing, randomized and double-masked study. Based on the data from previous corneal swelling studies at the Centre for Contact Lens Research (CCLR), 26 subjects were required to detect a 0.8± 1.2% difference in CCS with a power of 0.90 at $\alpha = 0.05$. In this study 37 neophytes were enrolled and 29 completed the study (14 female, 15 male). Eight participants chose to discontinue from the study for personal reasons (relocation, finding a new job, etc.) before completing all follow-up visits. Only the data from the participants who completed all study visits were included for data analysis. The mean age of the participants was 27.1 ± 7.9 years (median 25 years, ranging from 17 to 50 years). Table 2-1 summarizes the refractive characteristics of the study participants. Ethics approval was provided by the Office of Human Research Ethics, University of Waterloo, and informed consent was obtained from each subject

prior to enrolment in the study. All subjects were treated in accordance with the tenets of the Declaration of Helsinki.

Table 2-1. Participant refractive characteristics (Mean Dioptres ± SD)

		OD	OS
K-readings	Flat K	42.94 ± 1.42	42.84 ± 1.35
	Steep K	43.44 ± 1.63	43.48 ± 1.52
Corneal cylinder		-0.69 ± 0.42	-0.77 ± 0.46
Refractive error	Sphere	-0.29 ± 1.32	-0.14 ± 1.53
	Cylinder	-0.38 ± 0.41	-0.41 ± 0.48

2.4.2 Instrumentation and lenses

Central corneal thickness of each eye was measured using a computerized optical pachometer mounted on a Zeiss 30 SL-M biomicroscope. A standard deviation of about ±5 μm has been estimated for a typical set of 5 repeated measurements by this instrument. To enhance precision, from the seven consecutive measurements, the highest and the lowest readings were trimmed and the average of the remaining 5 measures was the recorded value. The parameters of the lenses used during the study are presented in Table 2-2. Corneal swelling was derived from the percentage difference in corneal thickness compared with the baseline measurements using the following formula

Corneal swelling % = (measured corneal thickness – baseline corneal thickness) x 100 / baseline corneal thickness.

Table 2-2. Lens parameters

Lens	Material	Manufacturer	Dk (Barrer)	Central Dk/t (Barrer/cm) (Nominal for -3.00)	Power (D)
Night & Day®	lotrafilcon A	CIBA Vision	140	175	-3.00 -10.00 +6.00
PureVision®	balafilcon A	Bausch & Lomb	91	101	-3.00 -10.00 +6.00
Acuvue® Advance™	galyfilcon A	Johnson & Johnson Vision Care	60	86	-3.00 -10.00 +6.00
Acuvue® OASYS™	senofilcon A	Johnson & Johnson Vision Care	103	147	-3.00 -10.00 +6.00

2.4.3 Lens metrology

Central lens thickness was measured (masked for lens type and power) using a digital lens thickness gauge (Rehder Development Company, Castro Valley, CA, USA). A random sample (20%) of contact lenses within each power and lens type used in this study was measured. For each lens power the central transmissibility was calculated using the following formula:

Central Dk/t = Dk (barrer) / centre thickness (cm).

Manufacturers' quoted Dk values were used for calculation of central lens transmissibility. The measured thickness and calculated Dk/t values are recorded in table 3.

Table 2-3. Central lens thickness (mean ± SD) and transmissibility by lens and power

lotrafilcon A		**senofilcon A**		**balafilcon A**		**galyfilcon A**	
Lens power: -10.00 D							
Thickness (microns)	Dk/t (Barrer/cm)	Thickness (microns)	Dk/t (Barrer/cm)	Thickness (microns)	Dk/t (Barrer/cm)	Thickness (microns)	Dk/t (Barrer/cm)
66±4.7	211	66±2.5	156	86±3.8	106	62±1.4	96
Lens power: -3.00 D							
Thickness (microns)	Dk/t (Barrer/cm)	Thickness (microns)	Dk/t (Barrer/cm)	Thickness (microns)	Dk/t (Barrer/cm)	Thickness (microns)	Dk/t (Barrer/cm)
67±4.5	208	64±5.5	162	89±2.5	103	66±2.5	91
Lens power: +6.00 D							
Thickness (microns)	Dk/t (Barrer/cm)	Thickness (microns)	Dk/t (Barrer/cm)	Thickness (microns)	Dk/t (Barrer/cm)	Thickness (microns)	Dk/t (Barrer/cm)
199±11.0	70	198±3.4	52	194±5.3	47	196±2.9	31

2.4.4 Procedures

Baseline corneal thickness was measured at 4:00 pm on the same day of each overnight visit. For each overnight period one of the study lenses was placed on one eye (according to a randomization table) in the evening prior to sleep. Participants were then carefully examined to ensure that the lenses were fitting properly, that there were no post lens debris trapped between the lens and the cornea and the lens was comfortable. The following morning participants were woken at 7am to remove the lens. Immediately after removal, corneal thickness of each eye was measured using an optical pachometer interfaced to a PC.

The anterior segment was examined with a slit lamp biomicroscope (with and without the instillation of fluorescein) for safety purposes after the last measurement.

2.4.5 Data analysis

Descriptive statistics were generated for all variables. Repeated measures analysis of variance (Re-ANOVA) was used to examine the effect of lens material and power. Tukey HSD Post-hoc tests were used to determine the significance of all pair-wise differences. Pearson's correlation was used to examine correlations between variables. Kolmogorov Smirnov test (K-S test) was used to test the normality of the distribution. P-values of less than 0.05 were considered to be statistically significant. The data from all the 29 study participants are included in all of the results reported.

2.5 Results

There was a significant difference in central swelling across lens types, lotrafilcon A inducing the least (6.2 ± 2.8 %) and galyfilcon A the most (7.6 ± 3.0 %) (Re-ANOVA, $p<0.001$) with a significant effect of lens power (Re-ANOVA; $p<0.001$). The +6.00 D power induced significantly greater central swelling than the -10.00 and -3.00 D (post-hoc tests; $p<0.05$ for both). Immediately after lens removal, all lenses induced significantly more central corneal swelling than their respective controls (all post-hoc tests; $p<0.05$). These results have been submitted for publication as a separate article as mentioned in the Introduction.

The distribution of mean central corneal swelling of all lenses across the study participants was not significantly different than the expected normal distribution ($p>0.20$) (Figure 2-1). The average difference between the mean (7%) and the median (6.8%) CCS of all lenses was only 0.2% also suggesting a normal distribution. Similar results were also found for the mean CCS of control eyes ($p>0.20$) (Figure 2-2). Normal

distributions of CCS were also found when considering the 12 lenses and controls individually ($p>0.20$ for all).

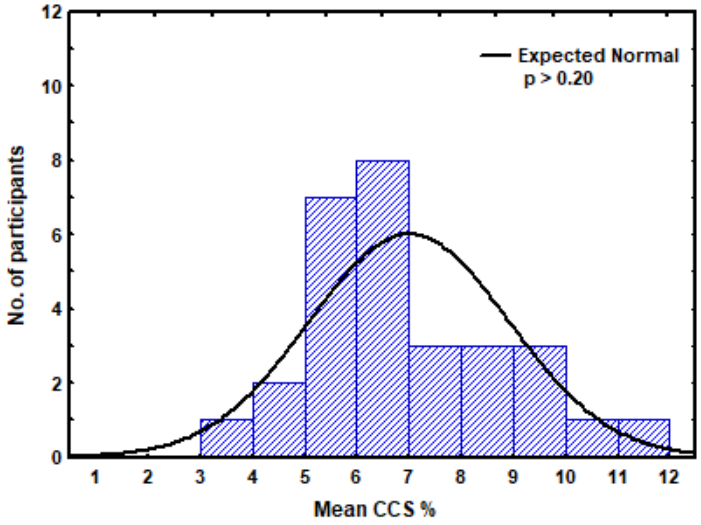

Figure. 2-1. Distribution of the mean CCS across the study participants in lens-wearing eyes.

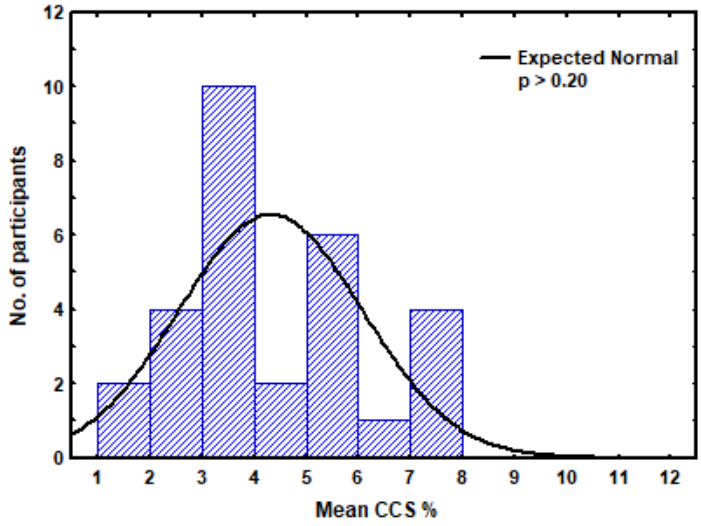

Figure. 2-2. Distribution of the mean CCS across the study participants in control eyes.

Figure 2-3 shows individuals' CCS (average of the three powers) for lotrafilcon A versus the range of CCS for the three other silicone hydrogel lens types. Lotrafilcon A induced less than or equal to the minimum CCS of the other three lenses in about half of the participants. This figure also shows that the range of CCS was independent of individuals' mean CCS. This is statistically demonstrated in Figure 2-4 where there was no correlation between the mean and the range of the CCS (r=0.058, p=0.766).

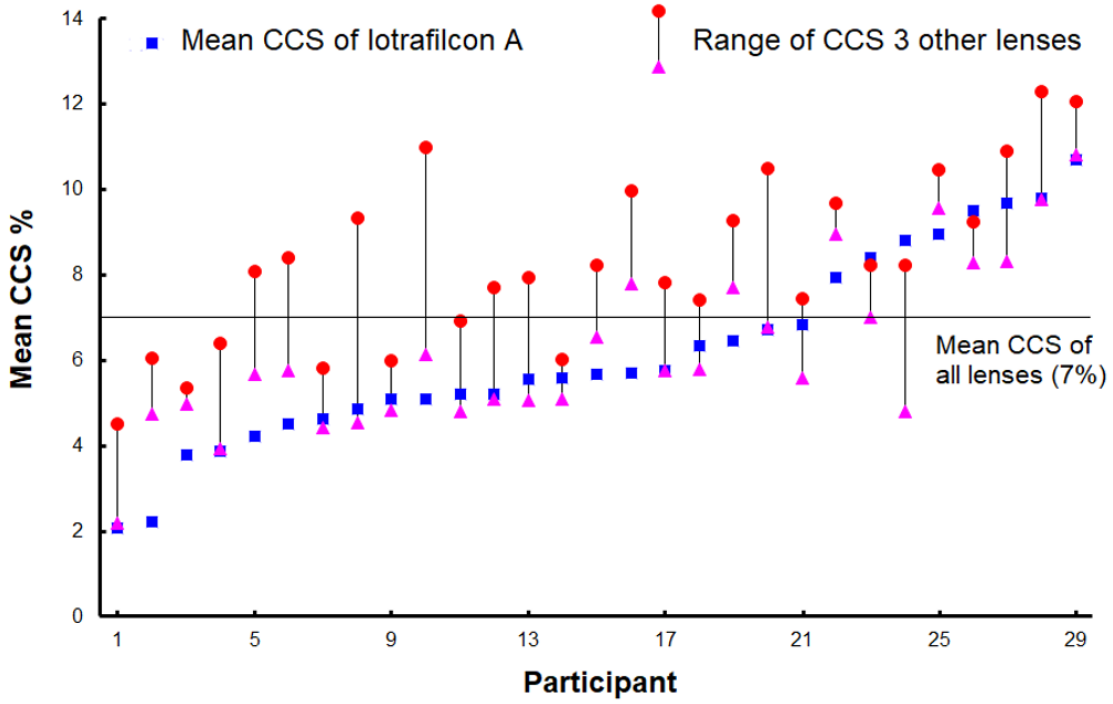

Figure. 2-3. Comparison of individuals' CCS of Ciba lotrafilcon A versus the range of CCS for the 3 other Silicone Hydrogel lenses.

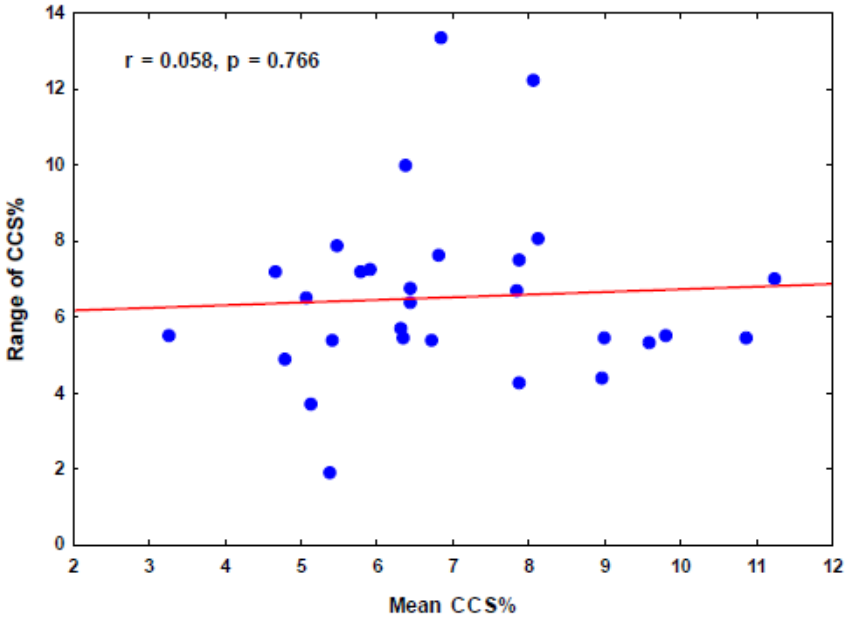

Figure. 2-4. Relation between mean and range of CCS of the study participants.

There was a significant correlation between CCS in lens-wearing and control eyes across the participants (r=0.895, p<0.001) (Figure 2-5), and a significant correlation between lotrafilcon A and each of the other three study lenses for mean CCS (r=0.736, p<0.001 for lotrafilcon A and galyfilcon A, r=0.703, p<0.001 for lotrafilcon A and balafilcon A, r=0.7141, p<0.001 for lotrafilcon A and senofilcon A).

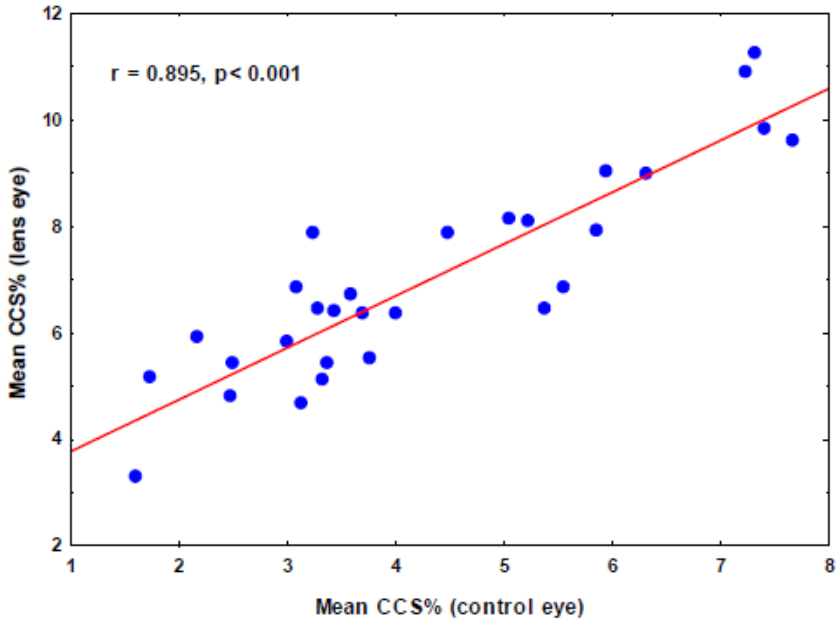

Figure. 2-5. Correlation between lens-wearing and control eyes for mean CCS of the study participants.

2.6 Discussion

In this study we used 12 different silicone hydrogel lenses with central oxygen transmissibility values ranging from $31x10^{-9}$ to $211x10^{-9}$. Iotrafilcon A induced the least and galyfilcon A induced the most corneal swelling. These results are consistent with the difference in the calculated oxygen transmission values between the silicone hydrogel lenses shown in table 3. +6.00 D induced greater central corneal swelling than the -10.00 and -3.00 D when averaged across lens types. This result can be explained by the greater central lens thickness of +6.00 D compared to the other two minus lens powers.

Overnight wear of each lens in this study induced more corneal swelling than that observed in the non-wearing contralateral control eyes. This result is supported by previous studies using a similar design with other silicone hydrogel lenses.[33, 111, 112] There is a dearth of reports containing distributional data beyond central tendency in corneal response studies and a similar observation has also been reported in other science.[175] Parametric statistics assume normal distribution of a data set. In this case the mean values represent the central tendency of the data.[176] Including some information about the data distribution in a scientific paper provides a potential for uncovering individual deviations that may otherwise be hidden in the analysis of means. Analysis of the shape of a frequency distribution reveals whether the mean can adequately represent the central tendency of the data set or the data is skewed and influenced by the extreme values in the data set. The latter case will disqualify the mean as an adequate descriptor of the data.[177-179] For this reason a skewed data set should first be transformed to a distributional shape that is closer to a normal curve before attempting parametric analysis.[177, 178, 180] The other important issue is to determine whether the data set has only one peak since discrete data containing two or more peaks can sometimes resemble a normal distribution which may results in misleading conclusions.[181, 182]

In this study we found a very small difference between mean and median corneal swelling in both lens-wearing and control eyes which indicates an insignificant skewness of the data (Figures 1 and 2). Although mean CCS is essential for between lens comparisons, it is an insufficient predictor of an individual's corneal swelling with a lens. An insignificant correlation between the mean and the range of CCS as illustrated in

Figure 2-4 indicates that the range of corneal swelling for any individual is independent of the mean of corneal swelling of that individual.

Previous studies with conventional hydrogel lenses found greater amounts of corneal swelling in some individuals and suggested a stress test using a thick HEMA lens under closed eyes conditions to identify the so called high swellers.[31] However, a strong correlation between lens-wearing and control eyes for corneal swelling across the study participants in this study (Figure 2-5) suggests that the measurement of overnight corneal swelling without lens wear would be a sufficient test for identifying higher swelling individuals. This view is further supported with findings of strong correlations across study participants for corneal swelling with lotrafilcon A versus each of the three other lenses and indicates a consistent and systematic pattern for the intensity of the individual corneal swelling response. Even with the use of high oxygen transmissible contact lenses in this study some individuals did reach high levels of corneal swelling. This highlights the importance of differential oxygen transmissibility with silicone hydrogel lenses, especially in higher powers.

2.7 Conclusion

Corneal swelling response of individuals is independent of lens type and can be categorized as low, medium and high swellers as illustrated in Figure 2-3. Distribution of corneal swelling in both lens and control eyes followed a normal curve.

Chapter 3

Overnight Corneal Swelling with High and Low Powered Silicone Hydrogel Lenses

The following manuscript titled above was submitted to Journal of Optometry[162] and it is the subject of the second experimental (chapter 3) of my thesis with minor proof changes along with my changes in the numbering of Tables, Figures and references for integration into my thesis.

Authors' Contributions to this manuscript (please check relevant boxes for each author):

Author	Concept/Design	Data Collection	Data Analysis	Article Writing	Article Editing
Amir Moezzi	x	x	x	x	x
Desmond Fonn	x				x
JalaiahVarikooty		x			x
Trefford Simpson	x				x

3.1 Overview

Purpose: To compare central corneal swelling after eight hours of sleep in eyes wearing four different silicone hydrogel lenses with three different powers. **Methods:** Twenty-nine neophyte subjects wore lotrafilcon A (Dk, 140), balafilcon A (Dk, 91), galyfilcon A (Dk, 60) and senofilcon A (Dk, 103) lenses in powers -3.00, -10.00 and +6.00 D on separate nights, in random order, and on one eye only. The contralateral eye (no lens) served as the control. Central corneal thickness was measured using a digital optical pachometer before lens insertion and immediately after lens removal on waking. **Results:** For the +6.00 D and -10.00 D, lotrafilcon A induced the least swelling and galyfilcon A the most. The +6.00 D power, averaged across lens materials, induced significantly greater central swelling than the -10.00 and -3.00 D (Re-ANOVA, $P<0.001$), (7.7 ± 2.9 % vs. 6.8 ± 2.8 % and 6.5 ± 2.5 % respectively) but there was no difference between -10.00 and -3.00 D. Averaged for power, lotrafilcon A induced the least (6.2 ± 2.8 %) and galyfilcon A the most (7.6 ± 3.0 %) swelling at the centre (Re-ANOVA, $p<0.001$). Central corneal swelling with +6.00 D was significantly greater than -10.00 D lens power despite similar levels of average lens transmissibility of these two lens powers. **Conclusions:** The differences in corneal swelling of the lens-wearing eyes are consistent with the differences in oxygen transmission of the silicone hydrogel lenses. In silicone hydrogel lenses central corneal swelling is mainly driven by central lens oxygen transmissibility.

3.2 Key Words

Corneal swelling, Silicone Hydrogel lenses, Oxygen transmissibility, Optical pachometry, Corneal thickness.

3.3 Introduction

Hypoxia induced corneal swelling is a well-known phenomenon and one of the primary indices of corneal physiological change during contact lens wear. Holden and Mertz[104] hypothesized that the minimum oxygen transmissibility (Dk/t) of a lens should be 87 ± 3.3 x 10^{-9} (cm ml O_2)/(ml sec mmHg) in order to prevent overnight lens induced corneal swelling. More recently, a value of 125 x 10^{-9} (cm ml O_2)/(ml sec mmHg) has been proposed as the critical Dk/t of a lens to prevent lens-induced overnight corneal anoxia.[90] Studies have shown that silicone hydrogel lenses induce less corneal swelling compared to conventional hydrogel lenses when worn overnight.[112, 171, 172] Although all -3.00 D silicone hydrogel contact lenses meet the Holden & Mertz criterion of 87 x 10^{-9} (cm ml O_2)/(ml sec mmHg) for the central lens transmissibility, no one has reported the effect of higher powered silicone hydrogel lenses (decreased Dk/t) on central corneal swelling. Previous corneal swelling studies with silicone hydrogel lenses including a previous study by the current authors[111] used low powered silicone hydrogel lenses and compared between the lens types. Although Steffen et al.[173] studied overnight swelling with silicone hydrogel lenses in a range of powers between -1.00 to -6.00 D to correct 25 adapted daily soft contact lens wearers it is unclear how many subjects wore higher powered lenses in this dispensing study and they did not compare corneal swelling across lens powers.

Previous studies with conventional hydrogel lenses showed greater central corneal swelling with higher minus lens powers than lower minus powers with the same material, central thickness and central oxygen transmissibility (Dk/t).[28, 113, 114] Tomlinson and Bibby[115] showed that the central corneal swelling in minus powered hydrogel lenses was underestimated and in plus powered lenses was overestimated based on the central lens transmissibility. These findings led to the conclusion that the central lens transmissibility is a poor predictor of the magnitude of central corneal swelling and the response is influenced by the averaging of the lens oxygen transmission.[28, 115-119] To our knowledge no one appears to have investigated the influence of local central compared to average Dk/t of silicone hydrogel lenses to determine the primary driver of overnight central corneal swelling with these lenses.

The main aims of this study were to compare differences in central corneal swelling between different silicone hydrogel lens materials in high and low powered lenses and to determine if at high levels of oxygen transmissibility central corneal swelling with silicone hydrogel lenses can still be differentiated. In addition, to investigate whether central corneal swelling is primarily driven by central or average lens transmissibility. Therefore, we compared central overnight corneal swelling induced by four different silicone hydrogel lenses with three different powers and tested the following null hypotheses:

1) There are no statistically significant differences in central corneal swelling between the lens types for each lens power.

2) There are no statistically significant differences in overall central corneal swelling between the 4 lens types.

3) There are no statistically significant differences in overall central corneal swelling between the 3 lens powers.

4) Average oxygen lens transmissibility is not the main driver of central corneal swelling in silicone hydrogel lenses.

Distribution of central corneal swelling across subjects from this study has been published[167] showing that both the lens-wearing and control eyes followed a normal curve. This validates the use of parametric statistics for data analysis and the use of mean values to represent the central tendency of the data in this paper.

3.4 Materials and methods

3.4.1 Subjects

This was a non-dispensing, randomized and double-masked study. Based on the data from previous corneal swelling studies at the Centre for Contact Lens Research (CCLR), 26 subjects were required to detect a 0.8 ± 1.2% difference in central corneal swelling with a power of 0.90 at $\alpha = 0.05$. In this study 37 neophytes were enrolled and 29 completed the study (14 female, 15 male). Eight subjects chose to discontinue from the study for personal reasons (relocation, finding a new job, etc.) before completing all follow-up visits. Only the data from the subjects who completed all study visits were included for data analysis. The mean age of the subjects was 27.1 ± 7.9 years (median 25 years, ranging from 17 to 50 years). Every subject wore each of the 12 lenses according to a randomization table. Table 3-1 summarizes the refractive characteristics of the subjects enrolled in the study. Ethics approval was obtained from the Office of Human Research Ethics, University of Waterloo, and informed consent was obtained for each subject prior to enrolment in the study. All subjects were treated in accordance with the tenets of the Declaration of Helsinki.

Table 3-1. Subject refractive characteristics (Mean Dioptres ± SD)

		OD	OS
K-readings	Flat K	42.94 ± 1.42	42.84 ± 1.35
	Steep K	43.44 ± 1.63	43.48 ± 1.52
Corneal cylinder		-0.69 ± 0.42	-0.77 ± 0.46
Refractive error	Sphere	-0.29 ± 1.32	-0.14 ± 1.53
	Cylinder	-0.38 ± 0.41	-0.41 ± 0.48

3.4.2 Instrumentation and lenses

Corneal thickness of each eye was measured using a computerized digital optical pachometer mounted on a Zeiss 30 SL-M biomicroscope. To enhance precision for obtaining the corneal thickness measurement at each time point, seven consecutive measurements were taken and the highest and the lowest readings were excluded by the instrument's custom software. The average of the remaining five measures was the recorded value of the corneal thickness provided that the standard deviation of these five measurements did not exceed 5 μm, otherwise the measurement of that time point was repeated.

Corneal swelling was derived from the percentage difference in corneal thickness compared with the baseline measurements using the following formula

Corneal swelling % = (measured corneal thickness – baseline corneal thickness) x 100 / baseline corneal thickness.

The parameters of the lenses used during the study are presented in Table 3-2.

Table 3-2. Lens parameters

Lens	Material	Manufacturer	Dk (cm^2/sec) (ml O_2/ml mmHg)	Central Dk/t (cm ml O_2)/(ml sec mmHg) (Nominal for -3.00)	Power (D)
Night & Day®	lotrafilcon A	CIBA Vision	140 x 10^{-11}	175 x 10^{-9}	-3.00 -10.00 +6.00
PureVision®	balafilcon A	Bausch & Lomb	91 x 10^{-11}	101 x 10^{-9}	-3.00 -10.00 +6.00
Acuvue® Advance™	galyfilcon A	Johnson & Johnson Vision Care	60 x 10^{-11}	86 x 10^{-9}	-3.00 -10.00 +6.00
Acuvue® OASYS™	senofilcon A	Johnson & Johnson Vision Care	103 x 10^{-11}	147 x 10^{-9}	-3.00 -10.00 +6.00

3.4.3 Lens metrology

Central lens thickness was measured (masked for lens type and power) using a digital lens thickness gauge (Rehder Development Company, Castro Valley, CA, USA). This measurement was conducted on a random sample of the study contact lenses (i.e. 20% of lenses) worn by the subjects after lens removal. For each lens power central transmissibility was calculated using the following formula:

Central Dk/t (cm ml O_2)/(ml sec mmHg) = Dk (cm^2/sec) (ml O_2/ml mmHg) / central t (cm).

The measured central thickness and calculated Dk/t values are recorded in Table 3-3.

Table 3-3. Central thickness (mean ± SD) and transmissibility by lens and power

	Lens centre thickness (microns)			Lens central Dk/t ((cm ml O_2)/(ml sec mmHg))		
Lens	-10.00 D	-3.00 D	+6.00 D	-10.00 D	-3.00 D	+6.00 D
lotrafilcon A	66 ± 4.7	67 ± 4.5	199 ± 11.0	211	208	70
senofilcon A	66 ± 2.5	64 ± 5.5	198 ± 3.4	156	162	52
balafilcon A	86 ± 3.8	89 ± 2.5	194 ± 5.3	106	103	47
galyfilcon A	62 ± 1.4	66 ± 2.5	196 ± 2.9	96	91	31
Mean	70	72	197	142	141	50

Table 3-4. Computed harmonic average thickness and average lens transmissibility by lens and power for 6.8 mm cord diameter

	Average lens thickness (microns)			Lens average Dk/t ((cm ml O_2)/(ml sec mmHg))		
Lens	-10.00 D	-3.00 D	+6.00 D	-10.00 D	-3.00 D	+6.00 D
lotrafilcon A	121	85	145	116	165	97
senofilcon A	123	82	143	84	126	72
balafilcon A	144	107	140	63	85	65
galyfilcon A	121	85	138	50	71	43
Mean	127	90	142	78	111	69

3.4.4 Computing harmonic average lens thickness and harmonic average lens transmissibility

In this study harmonic average lens thickness over a cord diameter of 6.8 mm[115] for each lens was computed using the software by Douthwaite.[183] Harmonic average lens transmissibility values were calculated by applying manufacturers' quoted lens permeability values to these data using the following formula:

Harmonic average Dk/t (cm ml O_2)/(ml sec mmHg) = Dk (cm^2/sec) (ml O_2/ml mmHg) / Harmonic average lens thickness (cm).

The computed harmonic average lens thickness and calculated harmonic average Dk/t values are recorded in Table 3-4.

3.4.5 Procedures

For each overnight period one of the study lenses was placed on one eye (according to a randomization table) in the evening, prior to sleep. Subjects were then carefully examined to ensure that the lenses were fitting properly, that there were no debris trapped between the lens and the cornea and the lens was comfortable. The following morning subjects were woken at 7 am to remove the lens. Immediately after removal, subjects were escorted to the exam room with their eyes closed. Corneal thickness of each eye was measured immediately after eye opening, after the subjects were comfortably seated at the optical pachometer. Each measurement was then repeated on both eyes every 20 minutes over the first hour after eye opening and every hour for the subsequent two hours.

Central corneal thickness in both lens-wearing and control eyes was measured using a modified optical pachometer interfaced to a PC. The anterior segment was examined with a slit lamp biomicroscope (with and without the instillation of fluorescein) for safety purposes after the last measurement.

3.4.6 Data analysis

Descriptive statistics were generated for all variables. The effects of lens type and lens power were examined. P-values of less than 0.05 were considered to be statistically

significant. Repeated measures analysis of variance (Re-ANOVA) was used to examine the effect of lens type (lotrafilcon A, senofilcon A, balafilcon A and galyfilcon A) and lens power (-3.00, -10.00 and +6.00 D). When appropriate the Huynh–Feldt (HF) correction was applied to adjust the p values and the HF corrected p values are reported in this paper. For each lens power, to compare the effect of lens type, a separate Re-ANOVA was conducted. Tukey HSD Post-hoc tests were used to determine the significance of all pair-wise differences.

3.5 Results

The results of the central corneal swelling for all lens types and powers are shown in Table 4-5.

Table 3-5. Mean (± SD) overnight central corneal swelling

Eye	Lens-wearing (swelling %)			No lens (swelling %)		
Lens	-10.00 D	-3.00 D	+6.00 D	-10.00 D	-3.00 D	+6.00 D
lotrafilcon A	6.0 ± 2.8	5.6 ± 2.6	7.0 ± 2.7	3.7 ± 3.1	4.2 ± 2.6	5.0 ± 3.3
senofilcon A	6.9 ± 2.9	6.8 ± 1.7	7.2 ± 2.6	4.4 ± 2.5	4.4 ± 2.1	4.4 ± 2.0
balafilcon A	6.7 ± 2.4	7.1 ± 3.1	7.8 ± 2.9	3.9 ± 1.8	4.4 ± 3.1	4.1 ± 2.5
galyfilcon A	7.7 ± 3.1	6.4 ± 2.2	8.8 ± 3.1	5.1 ± 2.2	3.8 ± 2.1	4.4 ± 3.1

1) Differences in central corneal swelling between the lens types for each lens power

Overnight central corneal swelling for each lens type with each lens power is shown in Figure 3-1. For each lens power in Figure 3-1, there was a statistically significant effect of lens type (Re-ANOVA, $P_{HF}<0.05$ for all). The +6.00 D galyfilcon A lens induced greater corneal swelling than lotrafilcon A and senofilcon A (post-hoc tests; $p<0.05$ for both), but was not different than balafilcon A (post-hoc test; $p>0.05$). The -10.00 D lens

also induced greater swelling with the galyfilcon A than lotrafilcon A (post-hoc test; $p<0.05$), but not than the other two lenses (post-hoc tests; $p>0.05$ for both). With -3.00 D lens, swelling induced by balafilcon A was greater than lotrafilcon A (post-hoc test; $p<0.05$), but was not different than the other two lenses (post-hoc tests; $p>0.05$ for both).

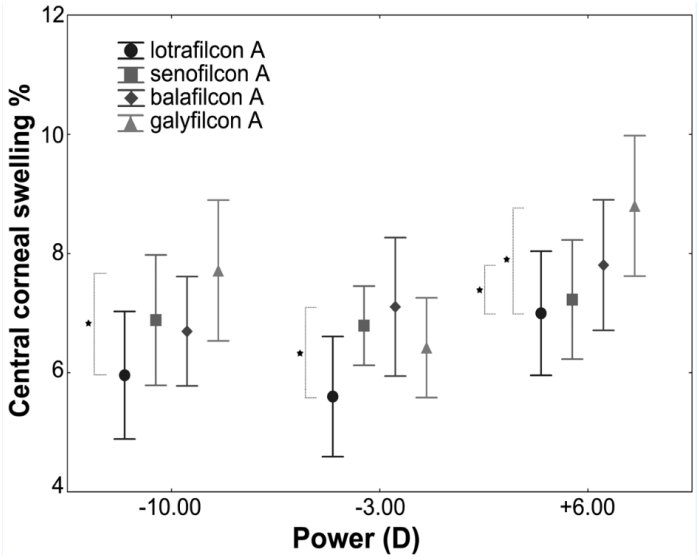

Figure 3-1. Overnight central corneal swelling for each lens power (vertical bars denote 0.95 confidence intervals, the significantly different pairs are indicated by brackets and asterisks).

2) Effect of lens type on central corneal swelling

Averaged for power, there was a significant effect of lens type (Re-ANOVA, $p_{H\text{-}F}<0.001$) lotrafilcon A induced the least (6.2 ± 2.8 %) and galyfilcon A the most central corneal swelling (7.6 ± 3.0 %) (post-hoc tests; $p<0.05$). There was no difference between galyfilcon A, balafilcon A and senofilcon A, and between lotrafilcon A and senofilcon A (post-hoc tests; $p>0.05$). Immediately after lens removal, all lenses induced significantly

more central corneal swelling than their respective controls (all post-hoc tests; $p<0.05$) (Figure 3-2).

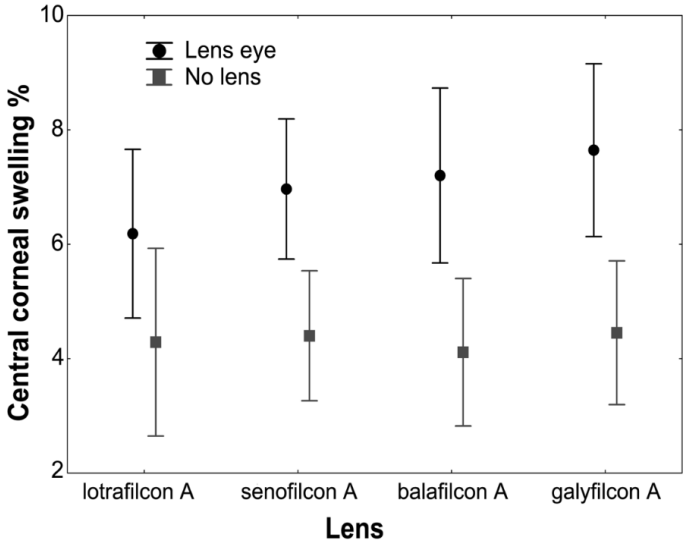

Figure 3-2. Overnight central corneal swelling (lens vs. control) (vertical bars denote 0.95 confidence intervals).

3) Effect of lens power on central corneal swelling

There was a significant effect of lens power on central corneal swelling (Re-ANOVA; $p_{H\text{-}F}<0.001$) as illustrated in Figure 3. The +6.00 D power, averaged across lens materials, induced significantly greater central swelling than the -10.00 and -3.00 D (post-hoc tests; $p<0.05$ for both), (7.7 ± 2.9 vs. 6.8 ± 2.8 and 6.5 ± 2.5% respectively) but there was no difference between -10.00 and -3.00 D (post-hoc test; $p>0.05$) (Figure 3).

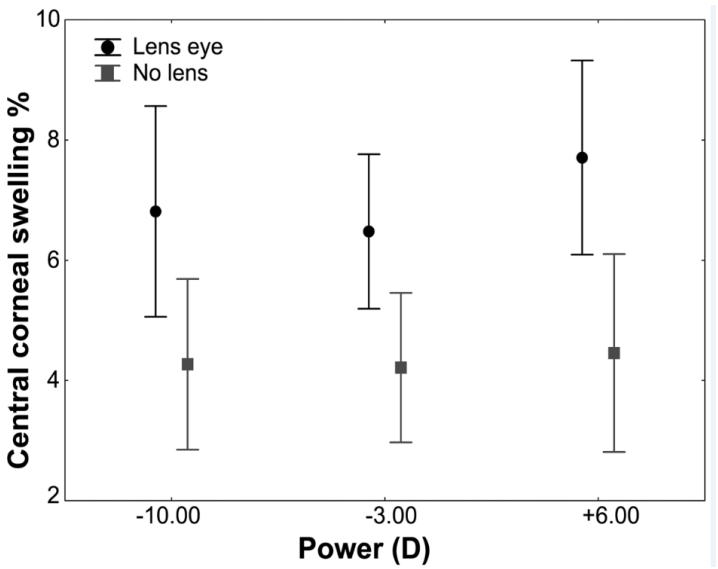

Figure 3-3. Overnight central corneal swelling by lens power (lens vs. control) (vertical bars denote 0.95 confidence intervals).

4) Computed central and harmonic average lens transmissibility

The central lens thickness measurements and respective calculated central oxygen transmissibility values (from the permeability values provided by the lens manufacturers) of each lens type and computed values of harmonic average lens thickness and average lens transmissibility over 6.8 mm cord diameter are shown in Tables 3 and 4 respectively. For each lens type as expected and can be seen from these tables the central lens transmissibility of high and low minus powered lenses were similar and both were markedly different than the central Dk/t in plus lens power (Table 3-3). In contrast, harmonic average lens transmissibility values in high powered plus and minus lenses were similar and notably different than harmonic average Dk/t in -3.00 D lens (Table 3-4).

3.6 Discussion

In this study we used 12 different silicone hydrogel lenses with central oxygen transmissibility values ranging from 31 to 211 x 10^{-9} (cm ml O_2)/(ml sec mmHg). Central corneal swelling differences between the lens types were particularly pronounced in high powered lenses and are clearly seen in both +6.00 D and -10.00 D lens powers in Figure 3-1, suggesting that the corneal swelling response especially in the higher lens powers may be minimized by using silicone hydrogel lenses in the higher transmission end. These results are consistent with the difference in the calculated central oxygen transmission values between the silicone hydrogel lenses shown in Table 3-3 and show that at high levels of Dk/t, central corneal swelling with silicone hydrogel lenses can still be differentiated based on the lens oxygen transmissibility. The exception to this statement was galyfilcon A which did not induce the most swelling among lenses in -3.00 D power (Figure 3-1) as would be predicted from the other lens power results in this study and other published work.[184-186] This can be attributed to sampling or perhaps other possible uncontrolled lens specific or ocular surface related factors which may have influenced the corneal swelling response in addition to lens Dk/t warranting further investigation in future studies. The small but significant differences in central corneal swelling between the study lenses in each high powered group (i.e. -10.00 or +6.00) (Figure 3-1) are probably not clinically relevant. However, some subjects exhibited high levels of corneal swelling as we reported previously[167] and for those it would seem sensible to use the lenses that cause the least amount of swelling.

Figure 3-2 demonstrates an inverse relationship between oxygen transmissibility and mean overnight central corneal swelling induced by the silicone hydrogel study lenses.

Also, this figure illustrates that with all study lenses, the lens-wearing eye showed significantly more swelling than in the contralateral non-lens wearing eye as shown previously,[33, 111, 112] suggesting that even lenses that exceed the Holden and Mertz 87 x 10^{-9} (cm ml O_2)/(ml sec mmHg) [1] will not avoid overnight lens induced edema (Table 3-5). The additional swelling produced by the lens compared to the same closed eye condition without the lens has been partially attributed to lens-related corneal swelling factors other than hypoxia.[35, 125, 187-191]

Despite differences in thickness of the central and peripheral cornea there are similar oxygen demands across the cornea, independent of corneal location.[192] Even after blinking, the effect of tear mixing to equilibrate the oxygen tension under a soft lens is insignificant.[79] To maintain normal corneal physiology and health, it is important that high powered soft contact lenses provide sufficient local oxygen transmissibility through the thickest part of the lens.[90, 193-195] Bruce[194] compared local Dk/t measurements of spherical lotrafilcon A and balafilcon A lenses of various powers and found that lotrafilcon A exceeded the Holden and Mertz criterion of 87 x 10^{-9} (cm ml O_2)/(ml sec mmHg) at all lens locations in the range of +3.00 to -6.00 powers, however only balafilcon A of +1.00 D power met this criterion across the lens. In our study none of the plus powered lenses met the minimum Dk/t of 87 x 10^{-9} (cm ml O_2)/(ml sec mmHg) at the centre as the highest central Dk/t was 70 x 10^{-9} (cm ml O_2)/(ml sec mmHg) with +6.00 D lotrafilcon A (Table 3-3). All minus powered lenses in this study meet or exceed the Holden and Mertz criterion for extended wear at the centre (Table3).

Previous studies with conventional hydrogel lenses under closed eye conditions showed greater central corneal swelling with higher minus lens power but the same centre thickness as the lower power lenses, and similar levels of central corneal swelling with

minus compared to plus hydrogel lenses. This was despite greater central thickness and therefore lower central Dk/t of plus lens powers. These findings were explained by assuming that average of the central area of the lens instead of local central lens transmissibility was responsible.[28, 115-119] However, findings from these previous studies with hydrogel lenses are at odds with results from our study with silicone hydrogel lenses (Figure 3).

For the ease of illustration, the mean values of central and average lens transmissibility for each lens power are shown in the right side of the last rows in Tables 3 and 4 respectively. Central corneal swelling with +6.00 D was significantly greater than -10.00 D lens power (Figure 3) despite similar levels of average lens transmissibility of these two lens powers (Table 3-4, last row). However, central oxygen transmissibility in + 6.00 D was significantly lower than -10.00 D lens power as shown in Table 3-3 and this is in line with the higher central corneal swelling induced by +6.00 D lenses in this study. Therefore, the greater central swelling induced by +6.00 D compared to the -10.00 D and -3.00 D in Figure 3 can be explained by the lower central oxygen transmission of the plus lens power. Also central corneal swelling induced by -10.00 and -3.00 D lens powers in Figure 3 were not significantly different despite obvious differences in average lens transmissibility between high and low minus lens powers (Table 3-4, last row). In contrast, the similar level of central corneal swelling induced by -10.00D and -3.00 D lens powers (Figure 3) can be easily predicted from the similarity in central lens transmissibility between these two lens powers as shown in Table 3-3 (last row). A correlation analysis (that was not statistically significant as only three pairs of data were compared) showed a very strong linear association between central corneal swelling and central lens Dk/t ($r^2 = 0.94$) and a weaker association between the central corneal

swelling and average lens transmissibility (r^2 = 0.68).Therefore, these findings from our study suggest that in silicone hydrogel lenses central corneal swelling is mainly driven by central lens oxygen transmissibility. Average oxygen transmissibility is less likely to primarily affect the outcome here and a likely reason was that these lenses were in the high transmissibility range. These results are in agreement with a suggestion from at least one previous study which predicted a more prominent role for the effect of local oxygen transmissibility, rather than the averaging effect in higher transmissible hydrogel lenses.[119]

Chapter 4

Mixed model analysis of between-subject variability in overnight corneal swelling and deswelling with silicone hydrogel lenses

The following manuscript titled above was submitted to Investigative Ophthalmology & Visual Science[196] and it is the subject of the third and final experimental chapter (chapter 4) of my thesis with minor proof changes along with my changes in the numbering of Tables, Figures and references for integration into my thesis.

Authors' Contributions to this manuscript (please check relevant boxes for each author):

Author	Concept/Design	Data Collection	Data Analysis	Article Writing	Article Editing
Amir Moezzi	x	x	x	x	x
Natalie Hutchings					x
Desmond Fonn					x
Trefford Simpson	x				x

4.1 Overview

Purpose: To model between subject variability of corneal swelling (CS) and deswelling after overnight wear of silicone hydrogel (SiHy) contact lenses.

Methods: Twenty nine neophyte subjects wore twelve SiHy lenses with central transmissibility range of 31 to 211 Dk/t units on separate nights, in random order, and in one eye only. The contralateral eye served as the control. Central corneal thickness was measured using digital optical pachymetry before lens insertion, immediately after lens removal on waking, then 20, 40 minutes, 1, 2 and 3 hours later. Mixed modeling was conducted for simultaneous analysis of group and between-subject effects of CS and deswelling.

Results: The best model for overnight CS vs. Dk/t was linear with a random intercept showing constant between-subject differences in CS for different Dk/ts. The best fit for corneal deswelling vs. time was a curvilinear random intercept and random slope model. About 90% of the total between-subject deswelling variance in either lens or control eyes was due to the intercept variability with much less (~10%) being due to the variability of the individual deswelling rate (slope). Subject age, gender and ametropia were not predictors of individual corneal swelling in the Swelling vs Dk/t analysis. Age, however, was a significant (inverse) predictor of the rate of corneal deswelling, only in lens-wearing eyes.

Conclusions: A large proportion of variability in corneal swelling is because of subject-specific differences in corneal response to hypoxia. This shows that “low swellers” and “high swellers” actually do exist.

4.2 Introduction

Corneal swelling is regarded as one of the main indices of corneal physiological change as a result of corneal oxygen deficiency produced by contact lens (CL) wear.[197, 198] The post-lens tear oxygen tension in soft lenses is dependent on the oxygen diffusion through the lens material [76, 77] and the effect of the tear pump on tear mixing to equilibrate the oxygen tension under a soft lens is insignificant.[78, 79] Therefore, oxygen diffusion through contact lenses plays a vital role in maintaining corneal health and normal physiology in soft lens wear.[199, 200] Corneal oxygen deprivation may lead to corneal swelling (thickening) from water absorption by the corneal stroma. This is believed to primarily be from the increased stromal osmotic gradient resulting from the accumulation of lactic acid from anaerobic metabolism in the cornea.[23] It would appear self-evident, therefore, that the level of lens induced corneal swelling is inversely related to the oxygen transmissibility of the contact lens.[104]

The average overnight corneal swelling of 3-4% occurs in response to eye closure [30] in non-lens wearers [27-29, 34] and sleeping with a contact lens on the eye, further deprives the cornea of the oxygen supply from the palpebral vasculature, maximizing the hypoxic stress and potentially leading to increased corneal edema.[168] Even silicone hydrogel (SiHy) lenses with high oxygen transmissibility do not limit the overnight corneal swelling to the level of no lens wear [33] and so some subjects may reach potentially unsafe levels of overnight corneal swelling while wearing these highly oxygen permeable lenses.[167]

Lens attributes, have been the primary focus of experiments examining the interactions between lens wear and corneal swelling. There is another aspect of the response to lenses, and that is the variability between subjects wearing the lenses. This has, in our opinion, been neglected. Two studies have specifically focused on intersubject/between-subject variability in corneal swelling [127, 131], but it has been mentioned in others.[98, 131, 132] It appears that the between-subject variability in corneal swelling is not dependent on lens oxygen transmissibility (Dk/t) because there is a similarly wide range of swelling response while wearing SiHy lenses,[167] and, interestingly, has been demonstrated with anoxia in the absence of any CL wear.[127] These findings suggest that differences in the amount of corneal swelling between individuals (with similar oxygen supply) can be attributed to individual differences in corneal physiological response to hypoxia (a random effect of subject) rather than the CL wear itself.

Perhaps the absence of a direct examination of the role of subject variability in the many experiments examining corneal swelling during lens wear is a statistical one: Generally, in previous reports of corneal swelling, an averaging approach such as the 'classical' repeated measures Analysis of Variance (Re-ANOVA) or regression analysis has been used.[28, 33, 44, 104, 111, 162] This approach compares group mean outcomes as fixed effects and is mathematically unable to address the structure of the underlying subject variability, i.e. the random effects or the individual specific responses. This random structure of corneal swelling or deswelling has never been reported. In our experiment, we conducted a 'standard' corneal swelling experiment: Corneal thickness was measured with and without, and before and after overnight lens wear to examine swelling response and its recovery. The novel aspect of our report is to NOT be limited in what we are able to

analyze about our predictor variables by only using averages: This is the first report about simultaneously controlling for both fixed (average) and random (subject) effects in SiHy lens induced overnight corneal swelling (CS) and deswelling analyses compared to no lens wear in the contralateral eye. We therefore took a 'traditional' experimental/analytical route to assess overnight corneal swelling when wearing contact lenses.[162] However, the current study was also designed to measure the magnitude of the between-subject variability of CS and the magnitude of between-subject variability in deswelling after lens removal. In addition, we attempted to examine the association of between-subject variability of CS itself (intercept of the deswelling over time regression) and the individual recovery (variability in the slope of the recovery). Analysis of the whole range of CS and deswelling using this statistical approach can provide evidence for the presence of people in the sample who might be clinically referred to as "high-" and "low-swellers", and also whether the course of recovery (within the study 3-hour limit) in high-swellers is the same or different than low-swellers. We also simultaneously examined the influence of the independent variables of age, gender, and the refractive error (auto-refraction spherical equivalent) in addition to the lens related independent variable of Dk/t on corneal swelling and deswelling over the 3-hour period after eye opening and lens removal.

Explicitly, then, the primary purpose of this study was to model the random structure of overnight central corneal swelling while wearing or not wearing SiHy contact lenses as well as deswelling after lens removal. We analysed *central* corneal swelling as an index of corneal swelling response in overnight wear as maximum corneal swelling in closed-eye conditions expected to occur at the corneal centre.[44]

4.3 Materials and methods

This was a double-masked study and all lenses were worn in random order and on a randomly determined eye (each decided with randomization tables established before the experiment was begun). The study was performed in compliance with the ethical principles of the Declaration of Helsinki. The study received ethics clearance through the Office of Research Ethics (ORE) at the University of Waterloo. Informed consent was obtained from all subjects prior to enrolment in the study.

SUBJECTS

Based on previous data [33, 111] 26 subjects were required to detect an 0.8 ± 1.2% difference in central corneal swelling with a power of 0.90 at $\alpha = 0.05$. In this study 37 neophytes were enrolled and 29 completed the study (14 female, 15 male). The mean age of the subjects was 27.1 ± 7.9 years (median 25 years, ranging from 17 to 50 years). Eight subjects chose to discontinue their participation in the study for non-lens related, personal reasons (relocation, finding a new job, etc.) before completing all follow-up visits: There is no reason to suppose that these participants would have added anything different to the data set. Only the data from the subjects who completed all study visits were included for data analysis. Table 4-1 summarizes the refractive characteristics of the study subjects.

Table 4-1.[1] Subject refractive characteristics (Mean Dioptres ± SD)

		OD	OS
K-readings	Flat K	42.94 ± 1.42	42.84 ± 1.35
	Steep K	43.44 ± 1.63	43.48 ± 1.52
Corneal cylinder		-0.69 ± 0.42	-0.77 ± 0.46
Refractive error	Sphere	-0.29 ± 1.32	-0.14 ± 1.53
	Cylinder	-0.38 ± 0.41	-0.41 ± 0.48

4.3.1 Contact lenses

We used 4 SiHy lenses with 3 powers to change the Dk/t within each lens type. These 12 SiHy lenses and their nominal parameters are listed in Table 4-2. Central lens oxygen transmissibility (Dk/t) values were calculated using central lens thickness measurements and the manufacturers' quoted lens permeability (Dk) values in the following formula:

$$Central\ Transmissibility, \frac{Dk}{t} = \frac{Oxygen\ Permeability\ \left(\frac{cm^2}{sec}\right)\left(\frac{ml O_2}{ml\ mmHg}\right)}{Central\ Lens\ Thickness\ (cm)}$$

Giving units for Dk/t of $\frac{cm\ ml O_2}{ml\ sec\ mmHg}$.

The central thickness and calculated Dk/t values that are presented in Table 4-3 were used as the lens transmissibility values in our analysis.

INSTRUMENTS

Corneal thickness of each eye was measured using a digital optical pachometer mounted on a Zeiss 30 SL-M biomicroscope. To enhance precision of the corneal

[1] Not reported in the paper; refractive error range was between +4.00 D to -5.75 D sphere with zero to -1.50 D of cylinder.

thickness measurement at each time point, seven consecutive measurements were taken and the highest and the lowest readings were trimmed by the instrument's custom software. The average of the remaining five measures was the recorded value of the corneal thickness provided that the standard deviation of these five measurements did not exceed 5 μm, otherwise the measurement of that time point was repeated. The pachometer was calibrated at the beginning of the study using a method described elsewhere [201], and its calibration was verified and maintained throughout the study period.

Corneal swelling was defined as the percent of the difference in corneal thickness relative to baseline using the following formula:

$$\%\ corneal\ swelling = 100\ x\ \frac{(measured\ corneal\ thickness - \ baseline\ corneal\ thickness)}{baseline\ corneal\ thickness}$$

This is also how we defined the following terms throughout the paper:

Corneal swelling (CS): increase in corneal thickness that was measured on eye opening in the morning (Time = 0.0 hours)

Corneal deswelling: reduction in corneal thickness over the 3-hour period after lens removal (the function relating corneal swelling to time after eye-opening).

Table 4-2. Lens parameters

Lens	**Material**	**Manufacturer**	**Dk** (cm^2 / sec) x (mlO_2 / ml mmHg)	**Central Dk/t*** (cm mlO_2) / (ml sec mmHg)	**Lens power (D)**
Night & Day®	lotrafilcon A	CIBA Vision	140 x 10^{-11}	175 x 10^{-9}	-10.00, -3.00, +6.00
Acuvue® OASYS™	senofilcon A	Johnson & Johnson Vision Care	103 x 10^{-11}	147 x 10^{-9}	-10.00, -3.00, +6.00
PureVision®	balafilcon A	Bausch & Lomb	91 x 10^{-11}	101 x 10^{-9}	-10.00, -3.00, +6.00
Acuvue® Advance™	galyfilcon A	Johnson & Johnson Vision Care	60 x 10^{-11}	86 x 10^{-9}	-10.00, -3.00, +6.00

* Nominal values for -3.00 D lens power.

Table 4-3. Lens centre thickness (mean ± SD) and transmissibility (Dk/t) by lens and power

	Lens centre thickness (μm)			Lens central Dk/t * x 10^{-9} (cm mlO_2) / (ml sec mmHg)		
Lens	-10.00 D	-3.00 D	+6.00 D	-10.00 D	-3.00 D	+6.00 D
lotrafilcon A	66 ± 4.7	67 ± 4.5	199 ± 11.0	211	208	70
senofilcon A	66 ± 2.5	64 ± 5.5	198 ± 3.4	156	162	52
balafilcon A	86 ± 3.8	89 ± 2.5	194 ± 5.3	106	103	47
galyfilcon A	62 ± 1.4	66 ± 2.5	196 ± 2.9	96	91	31

4.3.2 Procedures

Baseline corneal thickness (both eyes) was measured before lens insertion at each overnight visit. One of the randomly assigned study lenses was placed on the randomly predetermined eye, prior to sleep at 11 pm. Subjects were then carefully examined to ensure that the lenses were fitting properly, that there was no debris trapped between the lens and the cornea and that the lens was comfortable. The following morning subjects were woken at 7am to remove the lens. Immediately after removal, subjects were escorted to the exam room with their eyes closed. After the subjects were comfortably seated at the pachometer corneal thickness of each eye was measured immediately after eye opening. This measurement was then repeated on each eye every 20 minutes over the first hour after eye opening and every hour for the subsequent two hours. The anterior segment was examined with a slit lamp biomicroscope for safety purposes (with and without the instillation of fluorescein) after the last measurement.

4.3.3 Data analysis

Statistical analyses were performed using IBM SPSS software Version 22 or higher (IBM SPSS, New York, USA). The following mixed model analyses were conducted:

1) Analysis of corneal swelling (%) over the range of Dk/t of study lenses controlling for subjects' age, and refractive error (auto-refraction spherical equivalent) as covariates, gender as a fixed factor, and subject (intercept and/or slope) as a random factor(s). The intercept represents the level of CS with eye closure (with or without a lens) and the slope represents the rate of corneal swelling as a function of lens Dk/t.

2) Analysis of corneal deswelling (%) during the 3-hour period after lens removal, controlling for oxygen transmissibility, subjects' age and refractive error as covariates, gender as a fixed factor, and subject (intercept and/or slope) as a random factor(s). The intercept represents the level of CS following eye closure (with or without a lens) and the slope represents the rate of corneal deswelling per hour.

Lens-wearing and contralateral control eyes (with no lens wear) were separately analyzed with mixed modeling of either swelling or deswelling data.

The mixed modeling procedure simultaneously estimates the fixed effect parameters for the observed data (i.e. group effects) and the variance of the random effects (i.e. between-subject effects). A number of mixed models were iteratively constructed, beginning with linear models where only the intercept or the slope were modeled as random between-subject factors, moving to a more complex linear model where both the intercept and the slope were modeled as random between-subject factors, and, lastly, a curvilinear (quadratic) model with the intercept and slope as random between-subject

factors. As part of the process of model selection, each model's deviance (-2x log likelihood) was computed. To compare between the fixed effected among progressively more complex models (nested), the log likelihood ratio test (LLRT) was used, which takes the difference in the deviance value for each model and tests whether the added complexity significantly improves the fit of the model by testing the magnitude of the LLRT to critical values of the X^2 distribution (Accepting the null hypothesis, H_0, indicates that the added complexity does not improve the model fit; Rejecting the null hypothesis indicates the converse). In addition, generally a parsimony criterion was used when model log likelihood ratios did not show a statistical difference; in these instances the simplest model was accepted. The model fit was similarly evaluated for inclusion of 2- or 3-way interactions of the fixed effects. For the selected 'best' models, the models were re-run to generate restricted -2x log likelihood values with Hurvich and Tsai's (AIC_C) criterion (which accounts for bias in log likelihood estimations with small sample sizes) to optimise the estimate of the variance of the random effects for the fitted model.[202] The estimates from this model are those that are reported in the results section.

To serve as a comparison with the more typical approach where between-subjects effects are not considered, a marginal (population average) linear/curvilinear model with only fixed effects was also run to determine if between-subjects effects contributed statistically. Because this analysis in all cases, produced worse fits to the data compared to the mixed models these results (marginal models) are not reported here.

4.4 Results

1) Overnight corneal swelling (CS on eye opening) vs. Dk/t in lens-wearing and control eyes

Central corneal swelling induced by overnight wear of the 12 SiHy lenses in the subjects as a function of central lens oxygen transmissibility is shown in the lens-wearing (left panel) and control eyes (right panel) in Figure 4-1.

The best fit model for overnight corneal swelling vs. Dk/t in both lens and control eyes was a linear model with a random intercept. To verify between-subject variability of the slope of the corneal swelling over Dk/t, we attempted to add a random slope in the model. However, the linear model with a random slope and the curvilinear model failed to converge (and so could not be computed) most likely due to a close-to-zero slope variance.

In the final linear model (with a random intercept), the mean intercept of the corneal swelling response was significantly greater than zero in both lens and control eyes. In this model there was a significant effect of lens Dk/t on corneal swelling in lens-wearing eyes (Table 4-4A); this means that the slope of the swelling vs. Dk/t function was statistically different from zero. However, we did not find any effect of lens Dk/t on corneal swelling in the control eyes with no lens wear (Table 4-4B). Age, gender and spherical equivalent of the refractive error in either lens or control eyes were also not statistically significant predictors of corneal swelling (Table 4-4A and B). As the model converged only for a random intercept, 100% of the between-subject variance in the model was explained by the variance of the intercept (Table 4-5).

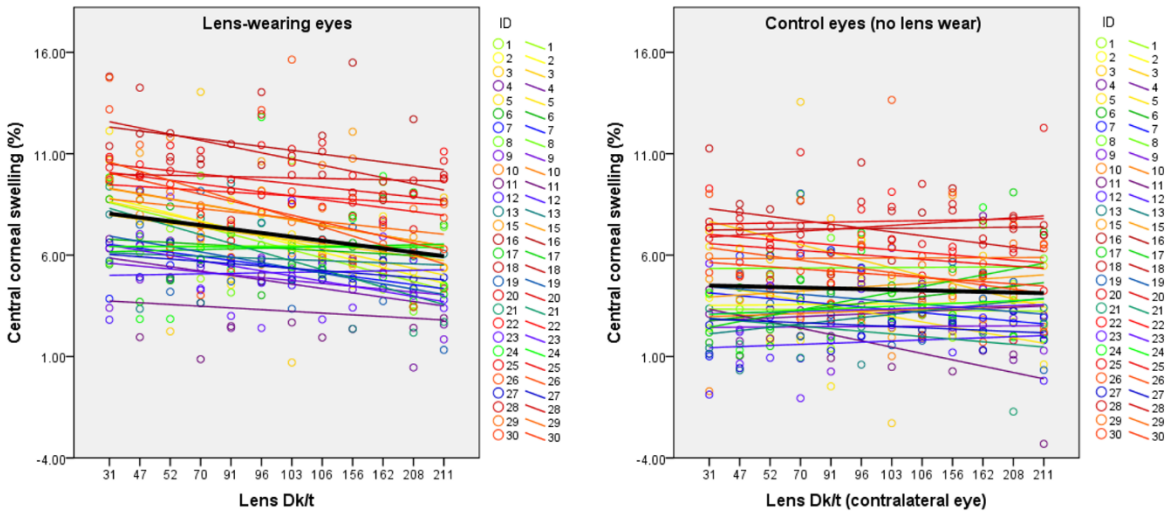

Figure 4-1. Overnight central corneal swelling vs. Dk/t in lens-wearing (left panel) and control (right panel) eyes by subject ID (linear fit, bold lines = average central swelling trajectory of all subjects across Dk/t). In the left panel the fitted lines show that there is more CS with low Dk lenses and generally the slope of the lines is negative. In the right panel (the non-lens wearing eyes) there is no relationship between Dk/t in the other eye and corneal swelling and the slope is generally zero. In each panel individuals' slopes and mean slope are statistically the same. Also apparent is the change in color from red to blue in both panels illustrating that higher swellers (warmer colors) are consistently separated (lens-wearing or non-lens wearing) from lower swellers (cooler colors) regardless of lens wear.

Table 4-4. Group effects: Estimates of fixed effects in the linear model with random between-subjects intercept of overnight corneal swelling in lens (Table 4-4A) and control (Table 4-4B) eyes as a function of lens Dk/t. SE is the standard error of the estimated

parameter, df is the degrees of freedom (rounded to integer), t is estimate of t-statistic and Sig. is the p-value for t for the given df

Table 4-4A Estimates of Fixed Effects* (lens eye)

Parameter	Estimate	SE	df	t	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Intercept	7.156	1.339	25	5.345	**0.000**	4.40	9.912
Dk/t	-0.011	0.002	307	-5.755	**0.000**	-0.015	-0.007
Refractive error	0.293	0.237	24	1.238	0.228	-0.196	0.782
Age	0.026	0.048	24	0.541	0.594	-0.074	0.126
[Gender=Female]	1.021	0.769	24	1.326	0.197	-0.567	2.608
[Gender=Male]	0†	0	.	.	.	.	.

* Dependent Variable: Corneal swelling (%).

† This parameter is set to zero because it is redundant.

Table 4-4B Estimates of Fixed Effects* (control)

Parameter	Estimate	SE	df	t	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Intercept	4.299	1.271	25	3.382	**0.002**	1.683	6.914
Dk/t	-0.002	0.002	307	-1.189	0.235	-0.006	0.002
Refractive error	0.206	0.225	24	0.915	0.369	-0.258	0.669
Age	-0.005	0.046	24	-0.119	0.906	-0.100	0.089
[Gender=Female]	1.088	0.730	24	1.491	0.149	-0.418	2.594
[Gender=Male]	0†	0	.	.	.	.	.

* Dependent Variable: Corneal swelling (%).

† This parameter is set to zero because it is redundant.

Table 4-5. Between-subject effects: Estimates of variances of random intercept in the model for overnight corneal swelling in lens and control eyes. SE is standard error of the estimate of the variance and Sig. is the p-value for variance given its estimate and standard error

Eye	Parameter	Estimate	SE	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Lens-wearing	Intercept Variance	3.040	0.978	**0.002**	1.618	5.712
Control	Intercept Variance	2.712	0.880	**0.002**	1.436	5.123

2) Corneal deswelling (the function relating CS <u>to time</u> after eye-opening) in lens-wearing and control eyes

The recovery from swelling (corneal deswelling) induced by overnight wear of the 12 SiHy lenses in the subjects during the 3-hour period after eye opening (and lens removal) is shown in Figure 4-2 (light lines). These can be compared to the linear fits averaged across individuals for the 12 lenses (bold lines) in the lens-wearing (left panel) and control eyes (right panel).

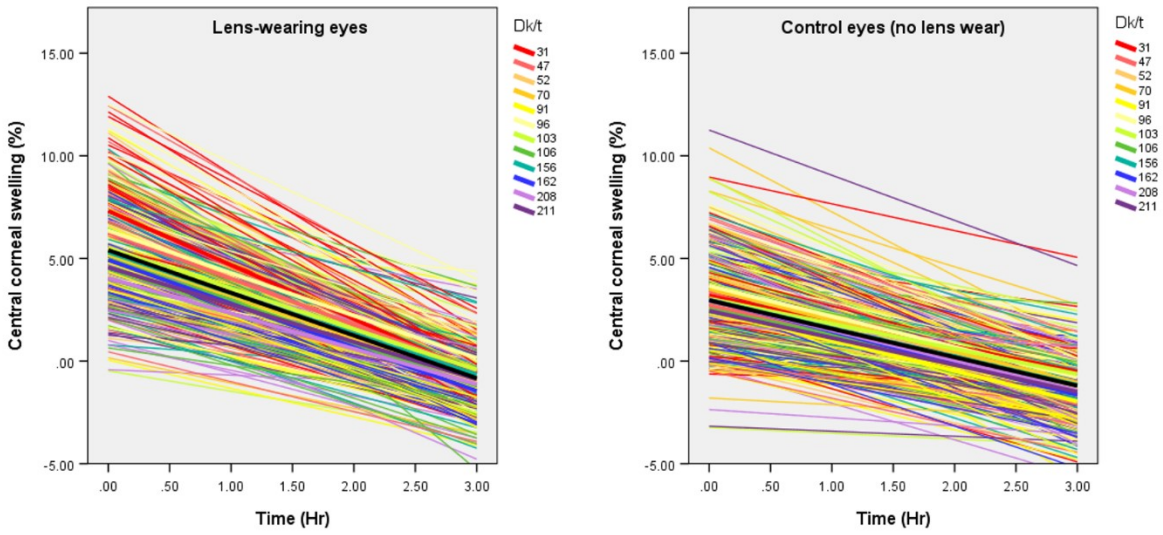

Figure 4-2. Linear regressions for individual corneal swelling vs. time after eye opening (light lines) and averaged across subjects (bold lines) for each lens Dk/t in lens-wearing and control eyes (left and right panels respectively). In each panel, slope of the lines is negative and individuals' slopes and grand mean slope (black bold line) are statistically different. In the left panel, a general gradation of warm to cool colors (low to higher Dk/t respectively) is apparent, whereas that is not the case in the control (non-lens wearing eye).

There was a significant effect of time, Dk/t and age on corneal deswelling in the lens-wearing eyes (Table 4-6A). However, in controls, only the effect of time was statistically significant (Table 4-6B).

Table 4-6. Group effects: Estimates of the fixed effects in the linear model with random intercept and slope for corneal deswelling following overnight lens wear in lens-wearing (Table 4-6A) and control (Table 4-6B) eyes. SE is the standard error of the estimate of the pertinent intercept or slope, df is the degrees of freedom (rounded to integer), t is the estimate of the t-statistic and Sig. is the p-value for t for the given df

Table 4-6 (A). Estimates of Fixed Effects* (lens eye)

Parameter	Estimate	SE	df	t	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Intercept	5.373	0.612	40	8.774	**0.000**	4.135	6.610
Time	-2.105	0.125	27	-16.880	**0.000**	-2.361	-1.849
Dk/t	-0.011	0.003	10	-3.558	**0.005**	-0.018	-0.004
Time * Dk/t	0.003	0.001	10	4.176	**0.002**	0.001	0.005
Age	0.037	0.013	24	2.884	**0.008**	0.011	0.064
Refractive error	-0.002	0.063	24	-0.035	0.973	-0.132	0.128
[Gender=Female]	-0.278	0.204	24	-1.361	0.186	-0.699	0.144
[Gender=Male]	0†	0	.	.	.	.	.

* Dependent Variable: Corneal swelling (%).
† This parameter is set to zero because it is redundant.

Table 4-6 (B). Estimates of Fixed Effects* (control eye)

Parameter	Estimate	SE	df	t	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Intercept	1.611	0.575	43	2.805	**0.008**	0.452	2.770
Time	-1.053	0.103	26	-10.226	**0.000**	-1.265	-0.842
Dk/t	-0.002	0.002	9	-1.064	0.314	-0.006	0.002
Time * Dk/t	-0.000	0.001	9	-0.529	0.609	-0.002	0.001
Age	0.022	0.017	24	1.296	0.207	-0.013	0.058
Refractive error	-0.042	0.084	24	-0.494	0.626	-0.216	0.132
[Gender=Female]	0.200	0.274	24	0.729	0.473	-0.366	0.765
[Gender=Male]	0†	0	.	.	.	.	.

* Dependent Variable: Corneal swelling (%).
† This parameter is set to zero because it is redundant.

Table 4-7. Between-subject effects: Estimates of variances of random effects in the linear random intercept and random slope model for overnight corneal deswelling function in lens-wearing and control eyes

Eye	Source of variability	Intercept variance	Slope variance	Correlation*
Lens-wearing	Between subject (except Dk/t)	3.016	0.218	**-0.99**
	Between subject (Dk/t)	0.290	0.011	**-0.77**
	Between subject (total)	3.305	0.229	
Control	Between subject (except Dk/t)	2.155	0.151	**-0.95**
	Between subject (Dk/t)	0.030	0.005	0.05
	Between subject (total)	2.185	0.156	

*Correlation between random intercept and random slope

Analysis of the partitioned variances of the random effects in Table 4-7 showed that in the linear mixed model of the lens-wearing eye, 93% of the total between-subject variance (variance of intercept + variance of the slope) was due to total between-subject differences in the intercept and 7% of the variance was caused by the variance of the slope. Although the overall between-subject variance was 29% lower in the control eyes, interestingly, the same proportions of the total between-subject variances (93% for intercept, and 7% for slope) were found in the control eyes. The slope was inversely related to the intercept both in the lens or control eyes ($p=0.01$ for both).

In the lens-wearing eyes, 9% of the between-subject variance of the intercept and 5% of the between-subject variance of the slope were because of the differences in Dk/t of the study lenses (Table 4-7). In the controls, the proportion of between-subject variances due to the differences in lens Dk/t consisted of 1% of the between-subject variance in the intercept and 5% of the between-subject variance in the slope, respectively (Table 4-7).

Based on the apparent shape of the individual distributions of corneal deswelling over time (Figure 4-3) we also modeled the data using a curvilinear (quadratic) fit for both fixed and random effects (Figure 4-4).

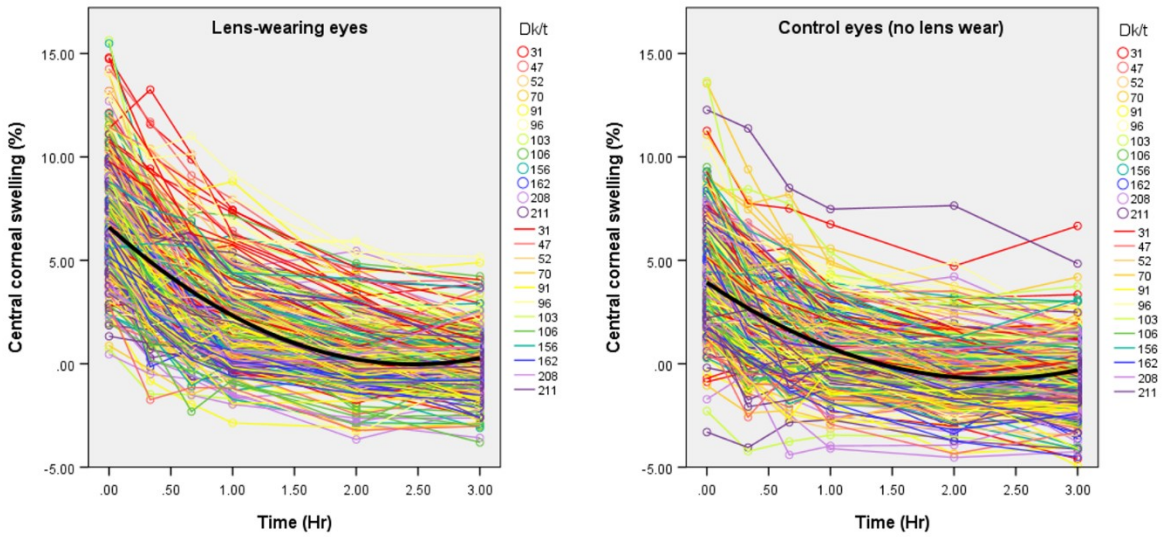

Figure 4-3. Individual data (symbols) for individual corneal deswelling vs. time after eye opening (connected with light lines) for each Dk/t in lens-wearing and control eyes (left and right panels, respectively). Generally, compared to Fig. 4-2, it is apparent that the data are curvilinear (black bold lines = grand mean curvilinear trajectory of corneal deswelling).

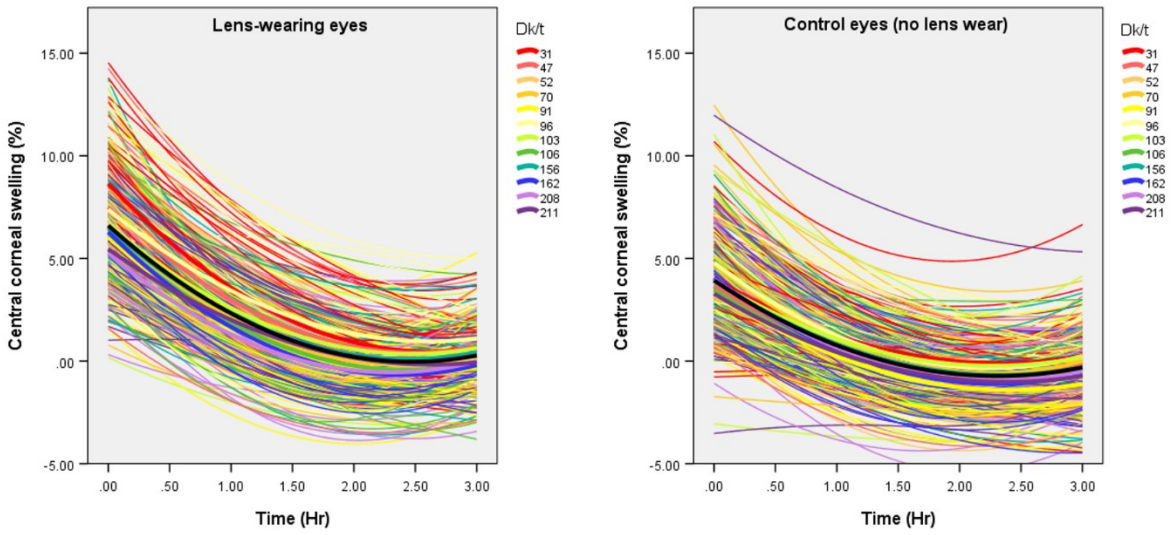

Figure 4-4. Curvilinear (quadratic) regressions for individual corneal deswelling vs. time after eye opening (light lines) and averaged across subjects (bold lines) for each lens Dk/t in lens-wearing and control eyes (left and right panels, respectively, black bold line = grand mean curvilinear trajectory). In comparison to Figure 4-2 with linear fitted functions this graph shows that curvilinear functions also fit the data well, with similar random effects to Figure 4-2. In the left panel, a general gradation of warm to cool colors (low to higher Dk/t respectively) is apparent, whereas that is not the case in the control (non-lens wearing eye).

Similar to the linear mixed model, in the curvilinear mixed model of corneal deswelling, there were significant effects of time, oxygen transmissibility and age on corneal deswelling in the lens-wearing eyes (Table 4-8A). Also similar to the linear fit results, in the curvilinear model, time was the only significant predictor of control deswelling (Table 4-8B).

The comparison between the linear and curvilinear models with random between-subject effects showed that the best fit in both lens-wearing and control eyes was the curvilinear mixed model with random intercept and random slope (Figure 4-4). While the overall model (fixed and random effects) was best fit with a random intercept and random slope, examination of the partitioned between-subject variances (Table 4-9A & 9B) indicates minimal contribution of the curvilinear slope (variance of 0.010 and 0.012 in lens and control eyes, respectively) to the between-subject variances in the curvilinear model.

Table 4-8. Group Effects: Estimates of fixed effects in the curvilinear model of overnight corneal deswelling with random intercept and slope in lens-wearing (Table 4-8A) and control eyes (Table 4-8B): SE is standard error of estimate of pertinent intercept or slope, df is degrees of freedom, t is the estimate of the t-statistic and Sig. is p-value for t for the given df

Table 4-8 (A) Estimates of Fixed Effects* (lens eye)

Parameter	Estimate	SE	df	t	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Intercept	6.874	0.627	43	10.963	**0.000**	5.609	8.138
Time	-5.501	0.248	102	-22.217	**0.000**	-5.992	-5.010
Time^2	1.042	0.060	207	17.338	**0.000**	0.923	1.160
Dk/t	-0.013	0.003	11	-4.002	**0.002**	-0.020	-0.006
Time * Dk/t	0.007	0.002	167	4.081	**0.000**	0.003	0.010
Time^2 * Dk/t	-0.001	0.000	306	-2.523	**0.012**	-0.002	-0.000
Age	0.037	0.013	24	2.873	**0.008**	0.010	0.063
Refractive error	-0.006	0.063	24	-0.088	0.930	-0.135	0.124
[Gender=Female]	-0.284	0.203	24	-1.396	0.176	-0.704	0.136
[Gender=Male]	0†	0	.	.	.	.	.

* Dependent Variable: Corneal swelling (%).
† This parameter is set to zero because it is redundant.

Table 4-8 (B) Estimates of Fixed Effects* (Control)‡

Parameter	Estimate	SE	df	t	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Intercept	3.289	0.580	51	5.674	**0.000**	2.125	4.452
Time	-3.651	0.167	29	-21.818	**0.000**	-3.993	-3.308
Time^2	0.761	0.032	36	23.561	**0.000**	0.696	0.827
Dk/t	-0.002	0.002	10	-1.329	0.214	-0.006	0.001
Age	0.021	0.016	27	1.265	0.216	-0.013	0.055
Refractive error	-0.039	0.081	27	-0.483	0.633	-0.204	0.126
[Gender=Female]	0.172	0.262	27	0.655	0.518	-0.366	0.709
[Gender=male]	0†	0	.	.	.	.	.

* Dependent Variable: Corneal swelling (%).
† This parameter is set to zero because it is redundant.
‡ Insignificant interactions between Dk/t * Time (p=0.969), and between Dk/t * Time^2 (p=0.864) were removed to improve the fit of the model.

Table 4-9. Between-subject Effects: Estimates of variances of random effects in the curvilinear random intercept and random slope model for overnight corneal deswelling in lens-wearing (A) and control (B) eyes

Table 4-9 (A) Estimates of variances (lens eye)

Source of Variance	Intercept variance	Slope variance	Correlation*	Slope^2 variance
Between subject (except Dk/t)	3.368	0.538	-0.94	0.010
Between subject (Dk/t)	0.289	0.011	-0.76	†

*Correlation between random intercept and random slope

† Could not be computed

Table 4-9 (B) Estimates variances (control eye)

Source of variance	Intercept variance	Slope variance	Correlation*	Slope² variance
Between subject (except Dk/t)	2.845	0.567	-0.97	0.012
Between subject (Dk/t)	0.031	0.005	0.07	†

*Correlation between random intercept and random slope

† Could not be computed

4.5 Discussion

RANDOM INDIVIDUAL CONTRIBUTIONS TO CORNEAL SWELLING

We examined the effect of Dk/t on corneal swelling in lens-wearing and contralateral control eyes (no lens) using mixed modeling. Perhaps the most important finding here was that the best statistical description for overnight corneal swelling in both lens and control eyes was a linear random intercept model with no variation in the slope of the overnight corneal swelling across the range of Dk/t between subjects. To our knowledge this is the first time that the structure of the random individual contributions to corneal swelling has been explored and reported, and the results highlight the importance of between-subject differences; some swell a little and others swell more, and the group mean swelling is not the best descriptor.

Our analysis revealed that the differences in CS among different subjects in either lens or control eyes remained constant (did not change) by a change in lens Dk/t. This means that, for the range of lens Dk/t of 31 - 211 units in this study, subjects exhibiting both

lower and higher levels of corneal swelling consistently showed this across the whole Dk/t range. Those who swelled least to one lens, swelled least to the others and those who swelled most swelled most to all lenses. This again reinforces the simple notion that in evaluating the response to lenses of different Dk/t, the lens characteristics are important, but it is critical to consider the *subject* characteristics as well.

In the simultaneous analysis of fixed (overall) effects of CS we did not find a statistically significant effect of age, gender or refractive error on the magnitude of CS in either lens-wearing or control eyes. This is in line with lack of evidence for any of these predictors in the literature and suggests that the between-subject variability in corneal swelling could perhaps be explained by more complex underlying individual differences. Many other uncontrolled individual factors such as differences in the physical size of the globe, differences in palpebral conjunctival area, differences in palpebral conjunctival vessel density, palpebral conjunctival vessel permeability, corneal epithelial/endothelial morphological variabilities etc. could potentially impact the between-subject variability in corneal swelling. It may not be feasible to control for all possible individual differences that could possibly impact the CS in a single study. However, based on the literature [133, 134, 203, 204] we suggest adding individual measures of corneal oxygen demand (corneal metabolic activity) and a measure of individual endothelial morphological variability (endothelial function) in a future mixed model analysis to investigate other biologically plausible predictors of between-subject differences in corneal swelling.

The analysis of the between-subject (random effect) variances in our study showed that the between-subject variability in CS was not dependent on Dk/t despite corneal swelling itself (obviously) being dependent on Dk/t. Put simply, the difference between subjects existed independently of the lens Dk/t inducing the swelling, In addition, individual CS

responses for the entire range of Dk/t could be predicted from a response of an individual to a single Dk/t using the overall slope of CS over Dk/t. This is because of lack of difference among individual slopes of CS over the range of Dk/t in the best fit model (random intercept model of corneal swelling, Figure 4-1, Table 4-5).

RANDOM INDIVIDUAL CONTRIBUTIONS TO CORNEAL DESWELLING

We examined the recovery of corneal swelling in lens-wearing and contralateral control eyes (no lens) over the 3-hour period after eye opening (and lens removal) using mixed modeling. In general our results showed that there was a difference in swelling (model intercept) and deswelling (model slope). In the linear deswelling model in both lens and control eyes (Figure 4-2) our analysis revealed that the between-subject variability in corneal deswelling function was mostly due to between-subject differences in their intercept, with less contribution from the function's slope. Also, the between-subject differences in corneal deswelling function in lens-wearing eyes was minimally affected by wearing 12 different lenses (Dk/ts) in the 12 study nights (Table 4-7A and B).

The between-subject variances of the squared term of the slope ($time^2$) in the curvilinear model were close to zero, contributing to only 0.25% and 0.37% of the total between-subject variance in lens-wearing and control eyes, respectively (Tables 9A and B). This indicates that this random effect (between-subject variability in the rate of deswelling), in either lens-wearing or control eyes, was largely linear. Therefore, the between-subject variability of corneal deswelling can similarly be described by the between-subject variances of the linear function in either linear or curvilinear models of corneal deswelling. This confirms sufficiency of the linear term for explaining the random effects in corneal deswelling, and that it could be considered as a parsimonious substitute for

the more complex curvilinear model of corneal deswelling. The main advantage of using the more complex curvilinear model would be its improved intercept and slope estimates. Subject gender and refractive error were not predictors of individual corneal deswelling functions in lens-wearing or control eyes in our analysis. In lens-wearing eyes only, however, there was a decrease in deswelling rate of ~0.04% per hour by each additional year of age (Table 4-8A, p=0.008). Our finding of slower recovery from corneal swelling in older age is in line with findings from previous studies, [63, 130] with statistically significantly slower recovery of corneal swelling in older compared to younger groups after 2 hours of closed eye CL wear. It is also worth noting that these previous studies [63, 130] did not control for any no-lens wear. The slower corneal deswelling rate in older individuals might be attributed (among other things) to lower endothelial pump function in older individuals [130] by endothelial morphological changes [129] with older age. An association between endothelial morphological changes and endothelial pump function (recovery from swelling) was found in both normal [130] and diseased [128, 205] corneal endothelium in the past.

OVERALL DISCUSSION

Our study was not designed to stratify age and the oldest subject in our study was only 50 years old. Despite this rather truncated age sampling, our data buttress previous reports that age does affect corneal deswelling. We did not find any other results from the fixed effects analyses of either corneal swelling and/or deswelling models that could be deemed unexpected/surprising. This provides some evidences for external/internal validity of the mixed modeling analysis approach in our study.

To our knowledge this is the first report on simultaneous modeling of fixed (average) and random (subject) effects in corneal swelling or deswelling. Our analyses of the random subject effects of CS over the range of Dk/t of study lenses provides support for the random intercept model to best explain the between-subject variability in CS in either lens-wearing or control eyes. The corneal deswelling functions, in either lens or control eyes, could be best explained by random intercept *and* slope models. The between-subject differences in both corneal swelling over Dk/t (Figure 4-1) and corneal deswelling over time (Figures 2 and 4) functions were not dependent on lens Dk/t. This detailed insight could not be revealed through average analysis / analysis of fixed effects (ANOVA or regression analysis).[162] Furthermore, the average analysis is prone to measurement errors from Simpson's paradox[163-166, 206] and that by averaging among the study clusters (in this context, high-swellers and low-swellers and their rate of deswelling) other relationships within the data may be masked or reversed. In addition, the mixed model analysis can concurrently investigate the impact of other factors or covariates that might explain why some individuals behave differently (such as the effect of age on corneal deswelling). This analysis enabling the combination of random and fixed effects provides novel insights into, and therefore examination of testable theories of how, subject variability contributes to the outcome in ways not possible using more 'traditional' methods.

In addition to statistically demonstrating the presence of between-subject variability in overnight CS, the analysis also points to smaller differences between individual corneal deswelling rates after eye opening, irrespective of lens Dk/t. The negative correlation between the random intercept and random slope of corneal deswelling function shows that there is a faster deswelling rate with greater initial swelling.

Following the removal of hypoxic stress, individual deswelling responses in this study were mainly affected by their differences in the intercept of the corneal deswelling function. This was demonstrated by the main proportion ~90% of the total between-subject variance in either lens or control eyes being due to between-subject differences in the intercept with much less (~10%) of the between-subject variance being due to the variability of the slope (or in the individual corneal deswelling rate). As can be seen in Figures 2-4 the small increase in the individual deswelling rate (from the inverse relation between random intercept and random slope in Table 4-7) in higher swellers was not enough to produce the convergence of their individual deswelling functions, so they did not all cross the time axis for zero swelling at the same point as did the lower swellers. Therefore, although higher swelling individuals deswelled slightly faster, it would generally still take them longer than lower swellers to reach the baseline level. The incomplete recovery of higher swellers at 3 hours after lens removal is evident from the same Figures (2-4).

4.6 Conclusions

Our goal from mixed model analysis of corneal swelling, was to specifically add an analysis of the between-subject random structure of CS to more adequately understand CL induced CS in closed eye conditions and corneal deswelling over time when eyes were subsequently opened. Mixed modeling enabled us to analyze both the between-subject and the fixed effects simultaneously. Our analysis confirmed that individual CS responses could not be predicted from the overall results or from any of the subject-related controlled independent variables (age, gender or refractive error). We showed

that there are large statistical components in the model due to between-subject variation: This demonstrates statistically that there is a range of swelling (“low swellers” to “high swellers”) in a group of participants. For a new patient in the chair during a routine clinical visit, it would be impossible to determine whether they are a higher or low sweller using routine clinical tools. Therefore, it is reasonable, where possible, to use the lenses with the highest oxygen transmissibility to minimize the risk of corneal oxygen deficiency in closed-eye lens wear, and examine each individual’s swelling response to the lens.

Chapter 5

Discussion

Perhaps it would not be an exaggeration to say that the main question of this study was whether lens oxygen transmissibility is still an important factor impacting corneal physiology when high oxygen transmissible SiHy lens materials are used. The first impression based on previous closed-eye studies would be that, due to higher Dk/t of SiHy contact lenses compared to hydrogels, the differences in Dk/t of different SiHy lenses should no longer be a concern. This is because the possible differences in average overnight corneal swelling with different SiHy lenses is expected to be small and perhaps clinically unimportant. The main question is whether this superficial conclusion of the average results of closed-eye corneal swelling among different SiHy lens materials is sufficient to allow CL practitioners to follow an evidence-based approach in clinical practice when seeing a likely (non-average) corneal sweller/patient in the chair.

I initially tried to understand the structure of between-subject differences in corneal swelling using traditional descriptive analysis of the results in the first experimental chapter (chapter 2) of my thesis. I chose this traditional path as a routine statistical practice to see if the insight from the descriptive analysis could shed some light on possible differences in the closed-eye response of an individual/non-average sweller to the average/group corneal swelling response results from overnight wear of different high oxygen transmissible SiHy lenses in this study. I was hoping that the results of this analysis could provide some evidence to help readers/contact lens practitioners in their

clinical decisions with recommending SiHy lenses with proper oxygen transmissibility for overnight wear to a new patient. Through this analysis, I found that the average distribution of the mean central corneal swelling (CS) induced by the 12 SiHy study lenses across the study participants was not significantly different than the expected normal distribution (Figure 4-1). I also found similar results for the normal distribution of the mean CS in the control eyes (Figure 2-2). In addition, in either lens-wearing eye or no-lens control eyes, the distributions of overnight CS induced by each of the 12 study lenses was not significantly different than the expected normal distribution. I returned to my initial question to see if this could guide me when approaching a new patient in the chair. Here the best guess for me was to use the standard deviation. However, how do I know where, under the normal curve, a patient (sitting in my patient's chair in front of me) is? Are they in the middle, in the tail, or somewhere in-between? Would there be any way that I could predict the expected corneal swelling for this specific patient? To answer these questions, I tried to explain some of the between-subject differences in corneal swelling by comparing individuals' CS (average of the three powers) for lotrafilcon A (the highest Dk/t) versus the range of CS for the three other silicone hydrogel lens types. This analysis showed that lotrafilcon A induced less than or equal to the minimum CS of the other three lenses in about half of the participants. At the time I thought that perhaps I had found some answers but, now at the end of my journey, I am not sure how I might directly attack the question I asked about my patient from these data and from my analysis. Could evidence-based practice be based on a game/gamble of unknown probabilities for the actual patients? As practitioners would we be willing to take this gamble if it was to be done with our own eyes?

When I look back I see that my learning from all of these descriptive analysis in chapter 2, although necessary to confirm normality before conducting further parametric tests in chapter 3, appears to be ineffective in answering the main question of whether or not I should prescribe a *particular* SiHy Dk/t to *optimize* corneal physiological performance under closed-eye conditions in an *actual* patient. With that in mind, however, there are still important results to be gleaned from chapter 2: There were significant positive correlations between CS in lens-wearing and control eyes across the participants (Figure 2-5), and significant positive correlations between mean CS in the eye with the lotrafilcon A and each of the other three study lenses. This is because the individual responses to SiHy CL and non-lens wear, and across the SiHy lenses in the study was systematic: The results suggesting that high-swellers and low-swellers may exist (i.e., those who swell more under one circumstance, swell more under the others and those who do not, generally do not, with this arrangement in the data producing statistically significant positive correlations). But can we predict who would be a high or low sweller? What are the possible predictable variables to differentiate them before prescribing a particular Dk/t for extended wear? Perhaps, the strong correlation between lens-wearing and control eyes for corneal swelling across the study participants in this study (Figure 2-5) suggests that the measurement of overnight corneal swelling without lens wear could be a sufficient test for identifying higher swelling individuals. This view is further supported with findings of strong correlations across study participants for corneal swelling with lotrafilcon A versus each of the three other lenses and indicates a consistent and systematic pattern for the intensity of the individual corneal swelling response. Differentiating between high and low swellers before suggesting a particular SiHy CL material in clinical practice, especially in higher powers and in extended lens

wear, could perhaps be one of the most important proactive measures for protecting the eye from possible long-term effects of oxygen deficiency[125, 193, 207-219] in an individual. This is because this study showed that even with the use of high oxygen transmissible SiHy contact lenses some individuals did reach high levels of corneal swelling (Figure 2-3). Also, there are no other known clinical predictors, as of yet, to differentiate between a new patient being a high sweller and a low sweller, unless examining the cornea after wearing a particular lens and after sufficient time under closed eye conditions.

In the second experimental chapter (chapter 3), I used the traditional ANOVA approach to compare the average data to see whether the results were in line with what would be expected from the previous studies. In this chapter, I also wanted to see if the differences between corneal physiological responses to SiHy oxygen transmissibility could be still differentiated in the high transmission range of SiHy lenses and, more importantly, whether the new answers from this chapter could shine any light to help me with a new patient in the chair. I compared the average results by averaging clusters (in this context 4 different materials x 3 different lens powers) in 3 different formats. The most important finding from the average analysis was that the differences in corneal swelling between the 3 lens powers could be somehow differentiated based on the lens material especially in high powered CLs as shown in Figure 3-1. However, the average differences in overnight central corneal swelling with the highest and lowest oxygen transmissible SiHy CLs for +6.00 and -10.00 D high powered lenses were 1.8 and 1.7% respectively. Could these relatively low average differences be used as a guideline in clinical practice for risk assessment of compromising corneal physiology in a particular patient? Could we expect every patient to show this average difference in corneal

swelling with different SiHy materials in high-powered lenses? Even if this were the case, would there be a different level of risk by choosing a lower transmissible SiHy material for a low sweller versus a high sweller?

Similarly, comparison of the average results when each lens material averaged over all lens powers showed the expected trend in lowest average corneal swelling with highest average Dk/t to the lowest corneal swelling with the highest average Dk/t as shown in Figure 3-2. Although, the small difference of 1.4% in average corneal swelling (averaged by the 3 lens powers) between the lowest and highest oxygen transmissible SiHy materials may seem clinically irrelevant, it shows the effect of averaging, averaging and more averaging in classical parametric analysis, on distorting the impression of the results and its possible effects on decisions in clinical practice in general. This is done by an unintentional/premature/oversimplified approach by averaging across the study clusters that can lead to drawing attention to a treatment-centered approach (average difference in treatment while averaging its effect across different peoples) rather than comparing actual differences in patient responses (different people) to the treatment.

Perhaps the main novel finding from this average analysis of collapsing different SiHy materials over 3 lens powers in the third chapter (Figure 3-3) was that the average +6.00D induced an average of 0.9% and 1.2% higher corneal swelling than the average -10.00 and the average -3.00 D SiHy CLs, respectively. In addition, the small difference of 0.3% in average central corneal swelling between the average -10.00 and -3.00D SiHy CLs was not statistically significant. These findings were in contrast of findings from previous studies with conventional hydrogel lenses under closed eye conditions that showed greater central corneal swelling with higher minus lens power but the same

centre thickness as the lower power lenses, and similar levels of central corneal swelling with minus compared to plus hydrogel lenses. These findings from previous studies were explained by assuming that the average of the central area of the lens instead of local central lens transmissibility was responsible.[28, 115-119] However, our novel finding that in silicone hydrogel lenses, central corneal swelling is mainly driven by central lens oxygen transmissibility (and average oxygen transmissibility is less likely to primarily affect the outcome) can be easily explained by comparing central Dk/t to average Dk/t of the study lenses in Tables 3-3 (central lens Dk/t) and 3-4 (average lens Dk/t). This part of the analysis in chapter 3 shows that average analysis could still be useful in answering some questions when the focus is on comparing the average results between different *treatments*, but not trying to expand the average results to explain the differences in the effect of treatments in different *subjects.* Clinically, patients may be at added risk because between-subject differences in response to different lenses is different from average between-lens differences. By comparing the average differences between lenses in inducing central corneal swelling in chapter 3 we learned that SiHy CLs with higher Dk/t induced slightly lower average corneal swelling than SiHy CLs of lower Dk/t, and that this differentiation in corneal swelling among SiHy CLs lenses is more pronounced in the high-powered CLs. However, these findings did not add anything to our knowledge about between-subject differences in corneal swelling with closed-eye CL wear and so, returning to the patient in the chair, did little to help in clinical decision making: We have not gained any knowledge from the average analysis about the required oxygen performance of a SiHy for overnight wear, for a new patient in clinical practice. This is why, in general, this old analysis approach is in not only incapable of providing an appropriate insight but also may misguide clinicians in selecting the best

available treatment for a particular patient from an evidence-based perspective. This is because of the fundamental problem that is created by averaging different clusters of the data in the classical parametric (ANOVA/regression) analysis thereby hiding/minimizing/reversing the actual between-subject differences in response to the treatment.[151, 152,176-179, 219] Therefore, in the 4th and final chapter of my thesis, I tried to look at corneal swelling (and deswelling) from a novel perspective to see if I could better differentiate and/or predict between-subject differences in the individual corneal swelling/deswelling in contrast to the between-CL differences in the average corneal response.

The 4th chapter of my thesis is the first report on simultaneous analysis of random (subject) and fixed (average) effects in overnight swelling and deswelling with SiHy CLs compared to no lens wear in the contralateral eye. In this novel approach to analysing corneal swelling I used mixed modeling (i.e. simultaneous analysis of random/individual and average/fixed effects) to not only examine the average differences in corneal swelling/deswelling from different Dk/t SiHy CLs but also to simultaneously estimate the extent of between-subject differences in corneal swelling/deswelling in their individual responses. In addition, using this analysis, I simultaneously examined the impact of possible non-lens related variables of subject's age, gender and refractive error besides the CL dependent variable of Dk/t as possible predictors of corneal swelling/deswelling in lens-wearing eyes or in non-lens wearing contralateral control eyes.

Using this analysis, for the first time, I could clearly see the structure of individual differences in overnight corneal swelling across the whole range of SiHy CL Dk/t in the study in the lens-wearing and control eyes (Figure 4-1). Although, the lens Dk/t had a

significant effect on corneal swelling in the lens-wearing eye, important findings from this analysis included the confirmation of the large variability between subjects to hypoxia and that the individual responses to hypoxia had a clear pattern, showing a final fit to a linear model with random (subject driven) intercept and a statistically fixed slope (across the range of different Dk/t CLs). This was because all between-subject variance in the model was accounted for by the intercept variance (or the variance of corneal swelling or differences in between-subject corneal swelling). Although the CL Dk/t was a predictor for the amount of corneal swelling in the lens-wearing eye (Table 4-4) the between-subject differences in corneal swelling was not dependent on the Dk/t. This is because of the random intercept structure of between-subject differences in corneal swelling: Subjects followed the same pattern across the whole study DK/t range (31-211 Dk/t units). If they were high swellers with a CL Dk/t they were high-sweller across the whole range of the Dk/t and if they were low-swellers with a CL Dk/t they remained low-sweller across the range. Clearly, the average corneal swelling (bold line in Figure 4-1) could not represent between-subject differences in corneal swelling and therefore was an inappropriate predictor for an individual's corneal swelling to a particular lens. In contrast to lens-wearing eyes, there was no significant effect of DK/t on corneal swelling in the non-lens eyes. However, the best fit model for corneal swelling with no lens wear was still a random intercept model (with a fixed slope of ~zero) showing the consistency in corneal swelling response to closed eye with no-lens wear across the 12 nights of the study period. This again highlights the consistency of the structure of between-subject variability in corneal swelling, irrespective of lens wear. Moreover, the consistency between individual responses to corneal hypoxia between lens-wearing and no lens eyes is demonstrated by the consistent apparent change from warmer colors (high

swellers) on the top to cooler colors (low swellers) on the bottom for each subject (Figure 4-1). This is consistent with finding of a strong correlation between average corneal swelling response in CL wearing and non-wearing eyes in chapter 2 (Figure 2-5). In light of findings of no significant effect of age, sex and refractive error as predictors of corneal swelling in our analysis, SiHy CL Dk/t is the strongest predictor of corneal swelling across the study SiHy Cls. However, between-subject differences in corneal swelling is in a different domain (subject related properties) that could not be explained by the differences in CL Dk/t. Therefore, the quest for predictors of individual corneal swelling remains an ongoing pursuit and its answer would be subject to further studies by measuring and adding the other possible relevant predictors (as suggested in chapter 4) to mixed modeling in future studies. In current clinical practice, it would not be justifiable to put a new patient at risk of compromising their eye health by using lower oxygen transmissible SiHy CLs while CLs of higher oxygen transmissibility are available. Given the current knowledge, any guess work on clinical risk assessment in this regard would be close to gambling unless, at least, the normal overnight corneal physiological response (no lens) is first measured to identify whether they are a low-sweller, a high-sweller, or somewhere in between.

For the last analysis in the 4th chapter of my thesis for the first time I used mixed modeling to investigate between-subject differences in corneal deswelling (recovery of corneal swelling) in both lens-wearing and no-lens control eyes over the 3-hour period after eye opening/lens removal. Mixed model analysis showed that the lens Dk/t has a minimal effect on between-subject differences in corneal swelling in the lens-wearing eye and close to no effect in the non-lens wearing eyes. The best fit model for corneal

deswelling in either lens-wearing or control eyes was a curvilinear random intercept and random slope model. This model explained ~90% of between-subject differences (variances) in corneal deswelling by the random intercept (initial amount of individual corneal overnight swelling upon waking) and only ~10% of between-subject differences in corneal deswelling by the random slope (differences between) individual corneal deswelling rate/slope over the 3-hour period in either lens-wearing or control eyes. This clearly highlights the importance of between-subject variability in corneal swelling as the main player in the course of recovery from corneal swelling with a smaller role for between-subject differences in the recovery rate over time. As a comparison, the differences in the Dk/t of the 12 study lenses had a minimal contribution of only ~9% and 1% as the source of between-subject variability of the intercept (overnight swelling) in the lens-wearing and control eyes, respectively. This again clearly highlights the greater impact of between-subject differences in swelling in response to hypoxia (and deswelling) rather than between-lens differences in their Dk/t. Therefore, the former and not the latter should have a greater role in clinical decision making. These novel insights from looking at a modern perspective to the same data that were analyzed in the previous two chapters (chapters 2 and 3) could clearly not be obtained through any general/average analysis. This new insight from mixed modeling can now guide that earlier hypothetical clinical encounter with a new patient rather as an individual who could react differently than another individual to the same treatment, and not be perhaps mislead by the data from an average subject (and so, for example, not considering the response to a specific material/power being that of a high-sweller or a low-sweller).

As shown in chapter 4, mixed modeling, in addition to examining subject driven random effects, also enabled simultaneous estimation of the fixed/average effects of predictor variables (age, sex refractive error) in addition to the lens related predictor variable of SiHy CL Dk/t on corneal swelling and deswelling in lens-wearing and control eyes. The mixed model for corneal swelling across Dk/t showed that corneal swelling (intercept in either corneal swelling or deswelling models) in an individual could not be predicted from any of the subject-related independent variables in this study in either lens-wearing or no-lens eyes. However, age was a predictor of corneal recovery from the overnight swelling in the lens-wearing eyes. These findings were in line with the previous literature[63, 130], perhaps buttressing the validity of this new approach. This is particularly interesting considering the limited age range of the study subjects (mean age 27.1 ± 7.9 years, median 25 years, ranging from 17 to 50 years).

As indicated in the discussion section in chapter 4 numerous other subject-related variables separately or in combination, or even possibly genetics, may potentially affect individual corneal responses to corneal hypoxia. The results of my analysis in chapter 4 suggest a modern and novel perspective to potentially pinpoint the main predictors of corneal swelling between subjects. It is apparent that it is not lens-dependent variable of CL Oxygen transmissibility but some other subject-related variables that still remain unknown. By combining measurements of other plausible subject-related variables (as noted in the discussion section of chapter 4) with mixed modeling, in future studies we may begin to start solving the puzzle of the source of between-subject variability of corneal swelling.

The results of my analysis strongly suggest that clinicians need to recommend the highest available oxygen permeable CL in overnight wear to minimize the eye health risks from hypoxia unless they first determine the extent of their patients' corneal response to hypoxia, before recommending any CLs for overnight wear.

The common accepted guidelines for Optometry practice suggest an evidence-based approach for selecting proper diagnostic tests/treatments/interventions. The main question is probably the meaning of the "evidence". Is that an "average" effectiveness of a treatment for an average individual? A quick random review of the literature in our discipline will confirm that current "evidence" is typically for the average hypothetical patient. This general problem of how little between-subject variability in response to a treatment is assessed and how little the sources of variability are reported in the literature is probably a general statistical oversight.

This highlighting of the problem of evaluating mean clinical evidence can be extended much further: Does the absence of mixed modeling and specifically the absence of direct examination of intersubject variability invalidate all the published (and also, perhaps, about-to-be-published) science in our discipline related to the physiology, pathophysiology, biophysics and clinical aspects of the effect of lens wear and hypoxia on the cornea? Of course, this query could be extended to a much broader view of Optometry and Vision Science, or even healthcare in general. What is required is a novel (or at least modified) experimental approach, involving research design, data analysis and reporting of experimental outcomes, emphasizing the role of average ***and*** variable effects (particularly the role of ***random subject effects***). Overcoming the

current shortcomings is partly statistical, in theory, in practice, in education, and again, in reporting: The current statistical shortcoming may be partly due to the lack of availability of appropriate statistical methods at the time of an experiment, due to the analytical complexity of mixed modeling (or other appropriate tools) and also, perhaps, a lack of enough expertise in the scientists doing the experiments, who are unable to properly communicate the importance of this different approach to the statistical experts on whom they rely. This is in part due to the so-called "Cargo Cult"[220] environment of analytic approaches to scientific results. A solution to these shortcomings of scientific practice requires a modified approach in experimentation in the future, and so dealing with the previous science is problematic: Should it all be discarded, or are there remedies for examining this historical work more completely? First, available data from these past studies could be ***re-examined*** using mixed modeling to reveal the pattern of possible between-subject differences. On the other hand, if it were not possible to re-examine the data from the past studies, the average between-treatment results could be used, but, perhaps, more caution should be applied. In particular, in clinical interpretations of this historical (average) scientific work, the conclusions about ***individual*** patients/clients should be closely monitored when it is based on recommendations about mean effects. The average results of the differences between treatments may be useful particularly when between-subject variability is small compared to the between-treatment differences (i.e., large effect size).

The results from the last experimental chapter of my thesis suggest that, in addition, there might be a need for an experimental ***re-examining*** of past studies in which average between-treatment differences were reported. These might then be examined

with new, appropriate, between-subject differences reported in addition to average treatment differences. This has the potential to produce profound change to current clinical guidelines, with new evidence-based approach that includes between-subject differences. Also, more fully describing experimental variability in our subjects, in turn prompts new, more complete additional scientific experimentation to understand the factors causing this newly described between-subject differences better. As an example related to my topic of experimental corneal swelling and deswelling, individual measures of corneal oxygen demand (corneal metabolic activity) and a measure of individual endothelial morphological variability (endothelial function) can be included in a future clinical trial with mixed model analysis to start our journey to reveal biologically plausible predictors of between-subject differences in corneal swelling and deswelling.

As shown in the final experimental chapter of my thesis, limiting the response from an individual to a treatment to only an average hypothetical response, instead of properly investigating relevant individual responses to that treatment, is an oversimplification that could be misleading. Especially, if this assumption leads to suggesting a treatment or intervention (e.g. overnight SiHy CLs with lower Dk/t) to a real patient with an unknown response. Preventing this is perhaps what is most important, scientifically, when designing an experiment, and when analysing/reporting study results.

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