CHANGES IN TEAR FILM METRICS AND OCULAR SIGNS INDUCED BY DIFFERENT TYPES OF REFRACTIVE CORRECTION IN AN AGING POPULATION

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Changes in Tear Film Metrics and Ocular Signs Induced By Different Types of Refractive Correction in an Aging Population

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DECLARATION

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other University or other institution of Learning

Dr. Santiago García-Lázaro and Dr. Teresa Ferrer-Blasco, from the University of Valencia, and **Prof. James S.W Wolffsohn**, from the Aston University Ophtalmic Research Group, CERTIFY that the present report entitled "Changes in Tear Film Metrics and Ocular Signs Induced By Different Types of Refractive Correction in an Aging Population", summarizes the research work carried out, under their supervision, by **Mr Edouard Lafosse** and constitutes his thesis to apply for the degree of **Doctor of Philosophy in Optometry and Vision Sciences**.

And to make it be on record, and complying with current legislation, they sign the present certificate in Valencia, on the ____ day of _____of the year two thousand and eighteen.

Dr. Santiago García-Lázaro Dr. Teresa Ferrer Blasco Prof. James S.W Wolffsohn

Dr. Santiago García-Lázaro Dr. Teresa Ferrer Blasco Prof. James S.W Wolffsohn

I dedicate this thesis to my parents,

For their support and putting me through the best education possible. I would not have been able to get to this stage without them.

“Tout vient à point à qui sait attendre”

François Rabelais, Pantagruel (Livre IV, chapitre 48), 1535.

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ACRONYMS

ADDE: Aqueous deficient dry eye

Ag: Antigen

APC: Antigen presenting cell

AS-OCT: Anterior segment optical coherence tomography

BAK: Benzalkonium chloride

BUT: Break up time

CCR7: C-C motif chemokine receptor type 7

CCT: Central corneal thickness

CK: Cytokines

CL: Contact lens

CLD: Contact lens discomfort

CLDEQ-8: Eight-item contact lens dry eye questionnaire

CNS: Central nervous system

C-ScL: Corneo-scleral lenses

DC: Dendritic cell

DED: Dry eye disease

DEQ-5: Five-item dry eye questionnaire

DEWS: Dry eye workshop

EDE: Evaporative dry eye

EGF: Epidermal growth factor

FD-OCT: Fourier domain optical coherence tomography

FGF: Fibroblast growth factor

FLACS: Femtosecond laser assisted cataract surgery

ICAM-1: Intracellular adhesion molecule-1

IOL: Intra ocular lens

Ig: Immunoglobulin

IL: Interleukin

IL-1RA: Interleukin 1 receptor antagonist

INF-ɣ: Interferon gamma

IPL: Intense pused light

LASEK: Laser Epithelial Assisted Keratomileusis

LASIK: Laser-assisted in situ keratomileusis

LFA-1: Leucocyte factor antigen 1

LFU: Lacrymal functional unit

LG: Lacrymal gland

LINE: LASIK-Induced neurotrophic epitheliopathy

LN: Lymph node

LT: Lens thickness

MAMs: Membrane associated mucins

MAPK: Mitogen activated protein kinase

MCJ: Muco-cutameous junction

MG: Meibomian gland

MGD: Meibomian gland dysfunction

MHC: Major histocompatibility complex

MMP: Metalloproteinase

NFD: Nerve fiber density

NGF: Nerve growth factor

NF-κB: Nuclear factor kappa B

NK: Natural killer

OCT: Optical coherence tomography

OSDI: Ocular surface disease index

OU: Oculus uterque

PLTF: Pre-lens tear film

PoLTF: Post-lens tear film

PPARγ: Proliferator-activated receptor gamma

PRK: Photorefractive keratectomy

PRO: Patients reported outcomes

RGP: Rigid gas permeable

RMS: Root mean square

SANDE: Symptoms assessment in dry eye

ScLs: Scleral lenses

SL: Slit lamp

SMILE: Small incision lenticule extraction

snRNPs: small nuclear ribonucleoprotein particle

SPEED: Standard deviation of eye dryness

TBUT: Tear break up time

TD-OCT: Time domain optical coherence tomography

TF: Tear film

TFLL: Tear film lipid layer

TFOS: Tear film and ocular surface

TGFβ: transforming growth factor beta

TJ: Tight junctions

TLR: Toll-like receptor

TM: Tear meniscus

TMA: Tear meniscus area

TMD: Tear meniscus depth

TMH: Tear meniscus height

TMH-F: Fluorescein-tear meniscus height

TMR: Tear mensicus radius

TNFα: Tumor necrosis factor

TIMP-1: Tissue inhibitor of metalloproteinase

UV: Ultra violet

VDT: Visual display terminal

WHO: World health organization

Resumen

La integridad de la superficie ocular, en otras palabras, su capacidad para responder adecuadamente a los desafíos ambientales, depende de la integración adecuada de la información desde la superficie ocular, la transmisión de la señal creada hacia el cerebro y la generación de una respuesta, que modulará la función secretora así como la inmunidad local de la superficie ocular. Es fácilmente comprensible que cualquier alteración de uno de los tres pasos de este ciclo cerrado pueda desencadenar una respuesta inapropiada y desequilibrar aún más los mecanismos compensatorios que tienen lugar en la superficie ocular.

La unidad funcional de la lágrima se puede definir como un conjunto de estructuras anatómicas cuyo funcionamiento armonioso mantiene la osmolaridad lagrimal dentro de límites estrechos. Está compuesto por la córnea y la conjuntiva, ambas protegidas por los párpados superior e inferior. Las estructuras mencionadas anteriormente comparten la misma ruta principal de inervación aferente representada por el quinto nervio craneal (es decir, el nervio trigémino) y sus ramas terminales que permiten que la córnea y la conjuntiva tomen información relacionada con los cambios ambientales y la transmitan al tronco cerebral. Los nervios corneales proporcionan un rango de modalidades de entrada aferentes tales como el dolor (nociceptor), estímulos mecánicos (mecanorreceptores) y temperatura (termorreceptor). Las glándulas lagrimales y el parpadeo representan la parte efectora de la unidad funcional de la lágrima. La secreción de las glándulas lagrimales es activada en respuesta a la estimulación de las vías aferentes de la superficie ocular y permiten una secreción adecuada de lágrima ortogando valores adecuados de osmolaridad en condiciones fisiológicas. Este lazo eferente es impulsado por una inervación secretora parasimpática que transmite la señal de respuesta desde el tronco cerebral hacia las glándulas lagrimales

(principales, palpebrales y accesorias), las células caliciformes de la conjunctiva, las glándulas de Meibomio, y adapta la secreción y composición de la lágrima a los desafíos ambientales. El drenaje apropiado de la lágrima también está involucrado en este ciclo reflejo ya que la película lagrimal se evapora en parte en la superficie ocular, pero también necesita ser evacuada dado que la secreción lagrimal es un proceso continuo.

Según la definición incluida en el informe del TFOS DEWS II, "El *síndrome de ojo seco* es una enfermedad multifactorial de la superficie ocular que se caracteriza por una pérdida de homeostasis de la película lagrimal y que va acompañada de síntomas oculares, en la que la inestabilidad e hiperosmolaridad de la película lagrimal, la inflamación y daño de la superficie ocular y las anomalías neurosensoriales desempeñan papeles etiológicos". El término multifactorial es apropiado ya que se han identificado numerosos factores desencadenantes: edad, sexo, hormonas, ambiente, cirugía ocular, particularmente cirugía de cataratas, enfermedades autoinmunes, uso de lentes de contacto, medicamentos sistémicos y conservantes en colirios entre otros. Todos estos factores pueden ser potencial desencadenantes de uno o ambos subtipos de la enfermedad.

La hiperosmolaridad de la lágrima, junto con la pérdida de estabilidad de la película lagrimal, es la piedra angular de la cascada de inflamación. Ambas condiciones conducen al estrés celular y a los procesos inflamatorios (tanto agudos como crónicos), que inducen a la autoalimentación y promueven el círculo vicioso del *síndrome de ojo seco*. A medida que la enfermedad progresa, se aumenta gradualmente el daño a nivel de la superficie ocular que se caracteriza por la pérdida celular. Otro hallazgo clave son las anomalías neurosensoriales. De hecho, las vías aferentes alteradas que involucran mecanismos que se explicarán con más detalles en este trabajo, previenen una recepción adecuada de la información en la superficie

ocular fomentando aún más la autopromoción de la enfermedad. Una amplia gama de patologías y trastornos, cambios relacionados con la edad, condiciones ambientales e intervenciones quirúrgicas pueden desencadenar cascadas inflamatorias que conducen a la sequedad o empeorar los procesos inflamatorios en curso en la superficie ocular. A pesar de esta multitud de puertas de entrada, todas las etiologías del *síndrome de ojo seco* comparten una vía inflamatoria común que conduce al daño de la superficie ocular: muerte celular, aumento de la tasa de descamación y renovación de las células epiteliales y, sobre todo, alteraciones de las vías aferentes que conducen a la autoperpetuación del círculo vicioso de la enfermedad.

La importancia científica de los estudios epidemiológicos se basa en una definición y clasificación precisa de la enfermedad, que hasta hace poco representaba el principal desafío ya que no se había adoptado un consenso sobre los criterios diagnósticos objetivos y subjetivos. Además, la ausencia de pruebas "gold estándar" para diagnosticar la patología, que va de la mano con una heterogeneidad reconocida entre signos y síntomas, hace que la interpretación y comparación de diferentes estudios epidemiológicos sea más difícil de evaluar.

Sin embargo, aún considerando el *síndrome de ojo seco* como una enfermedad cuyo diagnóstico está basado principalmente en la sintomatología, los estudios epidemiológicos que se centran solo en los signos clínicos son fuente de una variación considerable en los valores de prevalencia. La estandarización de los criterios de diagnóstico y las pruebas clínicas son el gran objetivo a alcanzar. La situación actual podría explicar las dificultades a las que se enfrentan los investigadores cuando se trata de criterios de diagnóstico; las pruebas clínicas de ojo seco que evalúan el mismo parámetro no tienen la misma sensibilidad y especificidad

en el diagnóstico de la enfermedad, las pruebas utilizadas a menudo solo evalúan un aspecto de la patología, no se han elegido “gold estándares” o una combinación de pruebas para evaluar las características clínicas. A estos factores, se le deben añadir una gran cantidad de signos de la patología, todos ellos con distinta gravedad, una sensibilidad al dolor específico de cada individuo, la presencia de patologías de la superficie ocular y cambios en la unidad funcional de la lágrima relacionados con la edad y/o condiciones sistémicas con impacto ocular. Con todo ello, hace que un diagnóstico adecuado basado en signos y síntomas sea realmente un desafío.

El primer informe de TFOS estableció que la hiperosmolaridad y la inestabilidad de la película lagrimal son los factores clave de la enfermedad. A partir de esa afirmación, se pueden definir dos subtipos de la enfermedad: el *ojo seco acuo-deficiente*, donde la hiperosmolaridad se debe a una disminución del contenido acuoso disponible en la superficie ocular (secundaria a la secreción lagrimal reducida) en presencia de una tasa de evaporación normal. El *ojo seco evaporativo* es el otro subtipo de la enfermedad, y en este caso, la hiperosmolaridad sigue a una tasa excesiva de evaporación en presencia de una función lagrimal normal.

Según el Informe de Epidemiología de TFOS, la prevalencia de la enfermedad basada en los síntomas y en los signos clínicos muestra un cambio gradual desde los 50 años. Parece muy probable que se produzcan cambios importantes relacionados con la edad en la unidad funcional de la lagrima en este período de la vida (que podrían deberse a una combinación de envejecimiento del ojo y cambios sistémicos), posiblemente desequilibrando los complejos mecanismos de homeostasis de la superficie ocular y desencadenando o excacerbando signos y síntomas de sequedad. De hecho, cuando se trata de factores de riesgo para la enfermedad,

el envejecimiento, de nuevo dependiendo de los criterios de diagnóstico y la variabilidad de la definición del ojo seco, parece ser el factor más consistente asociado con la enfermedad.

Cada parte del cuerpo humano está sujeta al envejecimiento y la unidad funcional de la lágrima no es una excepción: la glándula lagrimal, el borde palpebral, las glándulas de Meibomio y la conjuntiva se ven afectadas en su estructura y función a lo largo de la vida. Varios cambios histopatológicos relacionados con la edad ocurren en la glándula lagrimal. En primer lugar, se produce un grado bajo de dacrioadenitis junto con atrofia acinar. La fibrosis periacinar y la pérdida paraductal de vasos sanguíneos tienden a aparecer en adultos jóvenes, pero su incidencia aumenta con la edad. Curiosamente, los conductos secretores que siguen a los acinos se dilatan a lo largo de la vida y muestran una mayor tortuosidad, lo que sugiere la presencia de una obstrucción de los conductos. La infiltración linfocítica de las glándulas lagrimales está directamente relacionada con el envejecimiento, ya que se encontró que su incidencia era mayor en sujetos de edades superiores a los 40 años. Se concentra principalmente alrededor de los conductos secretores y acinos que conducen a su destrucción gradual. Además, se cree que el envejecimiento de la glándula lagrimal se acompaña de una infiltración de grasa y disminución de la masa de la misma glándula, lo que finalmente conduce a: la disfunción de la glándula lagrimal, a la reducción de la secreción refleja y del tiempo de ruptura de la película lagrimal. Sin embargo, se cree que la disminución reportada en la literatura de los valores reflejos de Schirmer a lo largo de la vida podría deberse a una variedad de factores como: una reducción del número de neurotransmisores secretores, a la pérdida de la funcionalidad de la glándula lagrimal y más importante, a la pérdida de sensibilidad de la vía aferente que se origina en la superficie ocular. De hecho, las vías corneales aferentes terminales que toman información relativa a los estímulos mecánicos y químicos en la

superficie ocular, pierden sensibilidad con la edad, lo que reduce el impulso sensorial hacia la glándula lagrimal.

Además de los cambios mencionados anteriormente que tienen lugar en la unidad funcional de la lágrima, se producen dos procesos adicionales de deterioro visual relacionados con la edad a nivel del cristalino que conducen a la presbicia y cataractogénesis respectivamente, destacando la necesidad de una corrección óptica. El presente manuscrito describirá estos dos cambios relacionados con la edad y el impacto potencial de las soluciones refractivas existentes para corregirlos y su impacto sobre diferentes parámetros de la superficie corneal y la lágrima que podrían desencadenar signos y síntomas relacionados con el *síndrome de ojo seco*.

Desde un punto de vista visual, posiblemente la presbicia (pérdida progresiva de la capacidad de acomodación) sea la característica principal del envejecimiento ocular. La acomodación es el proceso por el cual el ojo, más precisamente el cristalino, cambia su forma para permitir el enfoque sobre objetos cercanos. Este fenómeno óptico se basa en la contracción del músculo ciliar, que a su vez ablanda las fibras ciliares unidas al cristalino y permite que la lente adopte una forma más curva, lo que aumenta su poder de refracción y reduce la distancia focal al objetivo de interés. La presbicia, es uno de los defectos de refracción más comunes ya que toda la población desarrollará eventualmente presbicia, siendo el factor de riesgo mayor la edad avanzada, aunque otros elementos pueden influir en su inicio y progresión (enfermedad, medicamentos, trauma,…).

Según la OMS, la catarata es la principal causa de ceguera y se espera que la pérdida de visión útil afecte a 16 millones de personas en todo el mundo. La cataractogénesis es multifactorial y puede desarrollarse a partir de una amplia variedad de causas; la radiación ultravioleta, en

particular ultravioleta B, (Involucrada en los cambios de cataratas corticales), factores genéticos, fármacos sistémicos, enfermedades infecciosas, pero el envejecimiento es, con mucho, el principal factor de riesgo para su aparición. Induce un amplio espectro de cambios con respecto a los procesos bioquímicos que tienen lugar en el cristalino que conducen a la alteración del equilibrio hídrico, de las proteínas, de las vitaminas y las enzimas, y es responsable de la pérdida progresiva de la transparencia de la lente. La catarata relacionada con la edad parece ser el resultado de un proceso prolongado y gradual de desnaturalización de proteínas que constituyen el cristalino, que puede ocurrir principalmente de tres maneras diferentes: condiciones ambientales mantenidos (principalmente radiación ultravioleta), reducción de la estabilidad intrínseca de las proteínas del cristalino o perdida progressiva de la homeostasis celular del cristallino.

El *síndrome de ojo seco*, se ha convertido en un problema de salud pública en todo el mundo, ya que su impacto en los sistemas de salud está creciendo constantemente. Además del costo económico, el impacto social de la enfermedad se afianzó y se relaciona con una calidad de vida reducida debido al impacto de la enfermedad en la función visual y comfort del paciente. Todo ello deriva en una mayor frecuencia de visitas médicas, aumento en las tasas de depresión y una productividad laboral reducida. Numerosos estudios han analizado la influencia del envejecimiento sobre los signos y síntomas del *síndrome de ojo seco* y, según ellos, la edad es un factor de riesgo significativo para la enfermedad ya que las personas mayores de 50 años presentan una prevalencia del *síndrome de ojo seco* que aumenta significativamente, siendo las mujeres el sexo más afectado.

Existen diversos métodos para corregir la presbicia que se podrían dividir en no quirúrgicos y quirúrgicos. En el primer grupo se incluirían desde gafas (incluyendo simples lentes de lectura,

bifocales, trifocales y multifocales) hasta lentes de contacto con diferentes geometrías (monovisión, bifocales, visión simultánea,…). Es necesario indicar que la primera opción es un método no invasivo mientras que la segunda, al adaptar la lente de contacto, ésta se asienta en la película lagrimal, alterando su estructura normal e interactuando con la superficie ocular, posiblemente empeorando un entorno ya desequilibrado. Por otro lado, la cirugía refractiva es otra opción disponible [cirugía de cataratas con implantación de lentes intraoculares de geometría diferente (monofocal, bifocal, trifocal), cirugía refractiva corneal] pero su caracter invasivo, aún habiendo realizado grandes avances en los últimos tiempos, podría perturbar la superficie ocular y empeorar o inducir signos y síntomas de sequedad ocular.

El objetivo de este proyecto es evaluar los cambios en las métricas de película lagrimal y los signos oculares inducidos por diferentes tipos de corrección refractiva (implantación de lente intraocular y lentes de contacto) centrándose en la población de mayor edad, ya que la prevalencia de la enfermedad de ojo seco aumenta con la edad, y debido a la presbicia, la mayoría de las personas mayores de 40 años necesitan corrección refractiva para distancia lejana, visión intermedia o cercana, o para las tres.

En el **Capítulo 1**, se realiza una introducción general, exponiendo diversos aspectos relacionados con la patofisiologia del síndrome de ojo seco, las manifestaciones clínicas del envejecimiento al nivel ocular describiendo la presbicia y la catarata. Además, se exponen las opciones terapéuticas tanto ópticas como quirúrgicas para ambas condiciones.

En el **Capítulo 2**, se justifica la importancia del estudio del impacto de las ayudas ópticas para corregir la presbicia sobre los signos y síntomas de sequedad ocular y se plantean la hipótesis y los objetivos de la Tesis Doctoral.

En el **Capítulo 3**, se describe la metodología general que se va a seguir en los estudios clínicos que componen esta Tesis Doctoral. Se exponen las características de las muestras de sujeto estudiadas, los criterios de inclusión y además se describen los instrumentos de medida utilizados para obtener los resultados de los estudios presentados en posteriores capítulos. Además, se describen los procedimientos estadísticos utilizados para analizar los resultados y sacar, a partir de ellos, conclusiones.

En el **Capítulo 4**, el objetivo fue evaluar el rendimiento de un nuevo material de lente de contacto desechable diaria en la superficie ocular de una población présbita. Se adaptó un material de lente de contacto diario con gradiente de agua (delefilcon A) en una población présbita y se evaluó durante el primer día de desgaste del material. Para lograr ese objetivo, se investigaron los parámetros de la película lagrimal y superficie ocular a lo largo de un tiempo de porte de 8 horas. Las medidas se realizaron al inicio del estudio, veinte minutos después de la inserción del lente de contacto y a las 8 horas de uso. Se comenzó por las pruebas menos realizando posteriormente las más invasivas: agudeza visual, refracción monocular y binocular, biomicroscopía de lámpara de hendidura del segmento anterior, osmolaridad, área del menisco lagrimal inferior, examen topográfico y evaluación del tiempo de ruptura de la película lagrimal usando fluoresceína. Los participantes fueron reclutados entre los empleados de la Universidad de Valencia y no presentaron ninguna patología de segmento anterior o cirugía corneal previa. La edad promedio de los participantes fue de 50,0 ± 4,4 años, con edades comprendidas entre 41 y 60 años. El error de refracción equivalente esférico medio fue + 1,11 ± 0,35 D y varió de -4,25 a +2,50 D. De los 40 ojos incluidos, 18 fueron miopes (error esférico medio equivalente -2,80 ± 0,72D) y 22 hipermétropes (+ 0,90 ± 0,24D). Se encontraron cambios significativos en los valores de osmolaridad entre los valores basales (306,93 ± 2,32 mOsm / L) y 20 minutos (312,43 ± 2,42 mOsm / L) ($p < 0,05$). Los valores del

área del menisco lagrimal disminuyeron a lo largo del día (de 0,020 ± 0,003 mm^2 a 0,017 ± 0,03 mm^2) (P = 0,061), pero no fueron estadísticamente significativos. El estudio de las aberraciones de la superficie ocular de orden superior mostró un incremento estadísticamente significativo entre el valor inicial (0,38 ± 0,21 µm) y 20 minutos (0,61 ± 0,44 µm) (P≤0,001), y entre el inicio y las 8 horas (0,64 ± 0,41 µm) (P≤0,001). El tiempo de ruptura de la película lagrimal empeoró al final del día de 10,4 ± 0,4 segundos en los valores iniciales a 9.0 ± 0.3 segundos después de 8 horas de desgaste del lente de contacto (P <0,05). No se encontraron diferencias estadísticamente significativas entre las mediciones al inicio del estudio y después de 8 horas de porte de lente de contacto con respecto a la tinción corneal con fluoresceína (P = 0,727) y la tinción conjuntival (P = 0,092). De acuerdo con nuestros resultados, no se encontraron cambios significativos con respecto a la tinción de la córnea o la conjuntiva al final del día, lo que significa que incluso si la osmolaridad estaba por encima de los valores de corte, no fue clínicamente significativa ya que no hubo daño celular. Los valores de osmolaridad no cambiaron durante el tiempo de uso, lo que puede implicar que las propiedades de la superficie de la lente de contacto permanecieron estables durante las 8 horas de porte proporcionando suficiente lubricación y transmisión de oxígeno a la superficie ocular para no inducir ninguna tinción adicional. Sin embargo, si los cambios de osmolaridad se produjeran en un patrón similar durante un tiempo prolongado, la integridad corneal podria verse comprometida. Además, se especuló que los aumentos en la osmolaridad a los 20 minutos también podrían deberse en parte a la respuesta de la superficie ocular a la inserción de la lente de contacto, y a una interacción de la lágrima con el material, pudiendo ser diferente para cada paciente.

También se sabe que el *síndrome de ojo seco*, de acuerdo con su gravedad, induce un aumento significativo de las aberraciones, lo que implica que, en el caso del desgaste de la lente de

contacto, la calidad de la superficie de la película lagrimal previa a la lente se vería afectada. El hecho de que las aberraciones de alto orden de la superficie ocular permanezcan bastante estable durante el período de uso puede implicar que la calidad de superficie de la película lagrimal y la dinámica de la película lagrimal prelente se vieron mínimamente afectados a lo largo del día. Concluimos que la inserción de la lente de contacto desechable diaria induce una disminución inicial de la estabilidad de la película lagrimal observada por valores de osmolaridad que aumentan después de 20 minutos de uso, pero no afectó las mediciones del menisco lagrimal y pareció transitoria, ya que al final se produjo una disminución aunque sin alcanzar valores iniciales del período de uso. Las aberraciones de la superficie ocular permanecieron estables a partir de la inserción del lente de contacto, lo que demuestra una distribución uniforme de la película lagrimal sobre la superficie del lente de contacto.

En el **Capítulo 5**, el objetivo fue evaluar el efecto de la modalidad de uso de lentes de contacto en la fisiología de la superficie ocular durante un mes en una población présbita. Un total de 40 ojos de 40 sujetos, empleados de la Universidad de Valencia, no portadores de lentes de contacto, con edades comprendidas entre 41 y 60 años, se incluyeron en este estudio. Se utilizaron dos materiales con diferentes modalidades de porte: una lente de contacto desechable diaria (Delefilcon A) y una lente de contacto de porte mensual (Lotrafilcon B). Se evaluaron los siguientes parámetros durante el mes de uso para cada material: cuestionario OSDI, cuestionario CLDEQ-8, agudeza visual y refracción, biomicroscopía con lámpara de hendidura, examen topográfico, medida del espesor corneal central usando un tomógrafo de coherencia óptica y un biómetro, medidas de osmolaridad, del tiempo de ruptura de la película lagrimal usando fluoresceína y área del menisco lagrimal inferior. Los parámetros previamente descritos se midieron en: condiciones basales (t0), después de 20 min (t1) y a las 8 horas después de la inserción (t2), por la mañana (t3) y por la tarde (t4) del día 30 excepto

para OSDI / CLDEQ -8, que se evaluaron al final del período de uso para cada material de lente de contacto. El porte de la lente de contacto se interrumpió durante cuatro días entre cada período de un mes como medida de lavado. Las puntuaciones OSDI obtenidas en (t0) y (t4) para las lentes de uso diario y extendido fueron 8,5 (t0), 13,2 8 (t4) y 24,4 (t4) puntos respectivamente, y mostraron diferencias significativas solo con respecto a la lente de contacto de uso mensual (p = 0,042). Los puntajes del CLDEQ-8 obtenidos en (t0) y (t4) para los materiales de uso diario y mensual fueron de 6,2 ± 3,8 (t0) puntos, 10,6 ± 8,5 (t4) puntos y 18,1 ± 9,8 (t4) puntos respectivamente, y mostraron diferencias significativas con el lotrafilcon B dando las puntuaciones más altas (P = 0,012).

Para ambas lentes, el área del mensico lagrimal inferior disminuyó con el tiempo (p <0,001) y (p <0,002) respectivamente. El análisis post-hoc reveló solo diferencias significativas para la lente diaria entre las mediciones tomadas al inicio (t0) / (t2), (t0) / (t3), (t0) / (t4), así como también entre (t1) / (t2) y (t1) / (t4) (p <0.05). Para la lente de contacto mensual, se encontraron diferencias significativas entre (t0) / (t1) (p = 0,016), (t0) / (t3) (p = 0,009), (t0) / (t4) (p = 0,001) y (t1) / (t4) (p = 0,017).

No se encontraron diferencias estadísticamente significativas en la osmolaridad a lo largo del día y al final del mes para cada lente. Al comparar ambas lentes, existen diferencias significativas en (t1) (p = 0,006) y en (t2) (p = 0,002), con valores mayores para Delefilcon A. Para ambas lentes, las aberraciones de orden superior de la superficie ocular mostraron diferencias significativas con el tiempo mientras que la prueba de Wilcoxon encontró diferencias significativas entre (t0) / (t1), (t0) / (t2), (t0) / (t3) y (t0) / (t4) (p <0,001) para cada lente, respectivamente. No se encontraron diferencias entre lentes a lo largo del mes de uso. Con respecto al grosor central total, al comparar ambas lentes, se encontraron diferencias

significativas entre todas las comparaciones pareadas (p <0,001) con valores de espesor más altos para la lente desechable diaria.

La sintomatología evaluada a través de dos cuestionarios puso en evidencia diferencias al nivel de la comodidad de uso entre ambos materiales mostrando un incremento de la sintomatología par el lotrafilcon B mucho mas importante que para el material de uso diario. Delefilcon A presenta un módulo superficial muy bajo de 0.025 MPa (núcleo de 0,76 MPa) mientras que el material Lotrafilcon B tiene un módulo general de 1,2 MPa haciéndolo más rígido. Esto podría inducir una mayor incomodidad durante el período de estudio en comparación con el material de lente de contacto diario (ya que el diseño de la lente afecta la comodidad de la lente) y en parte explicar los puntajes de sintomatología más altos obtenidos para el material de lente de contacto de uso mensual.

Dado que cada participante del estudio no presentó signos y/o síntomas de *síndrome de ojo seco*, parece razonable suponer que la reducción en los valores del área del menisco lagrimal inferior encontrados en el presente estudio podría deberse a la desestabilización de la película lagrimal por el material de la lente de contacto, independientemente del tipo de lente, y también a la gran variabilidad de este parámetro a lo largo del día.

Con respecto a los valores de osmolaridad, el ligero aumento puntual en la osmolaridad encontrado para el material de lente de contacto diario no fue clínicamente significativo ya que volvió a los niveles basales a lo largo del mes de uso y no produjo cambios significativos en las tinciones vitales. El material de lente de contacto de porte mensual también mostró valores constantes de osmolaridad entre cada visita, lo que nos permite plantear la hipótesis de que ambos materiales proporcionan una alta compatibilidad y una mínima perturbación con la superficie ocular de los portadores neófitos presbitas de lente de contacto.

Los materiales de lente de contacto utilizados en este estudio son diferentes ya que aunque ambos son lentes de hidrogel de silicona, su contenido en agua y estructura central difieren. Sobre la base de esta observación, se esperaban diferencias significativas durante un mes de uso con respecto a la calidad de la película lagrimal pre lente y las aberraciones de alto orden de la superficie ocular resultantes. Sin embargo, no se encontraron disparidades al comparar lentes, excepto por los valores al final del día [(t2) / (t4)] que sugieren que la película lagrimal pre lente podría haber mostrado variaciones locales a las 8 horas de porte con el uso de lotrafilcon B. La calidad de la superficie de la película lagrimal y su dinámica fueron mínimamente impactados durante un mes de porte de lentes de contacto. Ambos materiales valorados en este estudio proporcionaron un comportamiento visual satisfactorio y similar en el ojo, y se mantuvieron bastante estables a lo largo del período experimental. Sin embargo, los resultados de la sintomatología valorados en los test subjetivos mostraron un mejor comportamiento para la lente de uso diario.

En el **Capítulo 6**, el objetivo del estudio fue evaluar y comparar el efecto de lentes corneo-esclerales y esclerales en los parámetros de la película lagrimal y el grosor corneal en sujetos présbitas sanos. Treinta ojos de 30 sujetos présbitas (54 ± 4 años; rango: 46-63 años) completaron el estudio. Los sujetos usaron dos lentes de contacto, asignadas aleatoriamente, con potencia neutra y diferentes diámetros [12,7 mm (lente corneo-escleral), 18 mm (lente escleral)]. Como parte de la exploración del estudio, cada uno de los participantes fue valorado en términos de agudeza visual, refracción, biomicroscopía con lámpara de hendidura, examen topográfico, medición del espesor corneal central con tomografía de coherencia óptica. Al inicio del estudio, después de 20 min (t1) y al cabo de 8 horas después de la inserción (t2), se evaluó el área del menisco lagrimal mediante la tomografía de coherencia óptica, el espesor

corneal central así como la osmolaridad lagrimal. Se pautó 4 días de lavado entre los dos portes.

En cuanto al área del menisco lagrimal, los valores medianos con la lente corneo-escleral, para las medidas basales, a los 20 min y a las 8 horas fueron 0,0213, 0,0216 y 0,0152 mm^2, respectivamente, mientras que con la lente escleral se obtuvo 0,0213, 0,0205 y 0,0137 mm^2, respectivamente. Para ambas lentes, las diferencias fueron significativas con el tiempo ($p < 0,001$), mientras que el análisis post-hoc reveló solo diferencias significativas entre las mediciones tomadas a las 8 horas y los otros dos períodos anteriores ($p < 0,001$).

En términos de espesor corneal central, con la lente corneo-escleral se midieron 549, 555 y 563 µm, y con la lente escleral 549, 556, 577 µm, para los diferentes estadios. Para ambas lentes, la prueba de Friedman fue estadísticamente significativa entre visitas ($p < 0,001$), mientras que el análisis post-hoc reveló diferencias estadísticamente significativas para todas las comparaciones pareadas ($p < 0,001$).

La osmolaridad medida fue 296, 298 y 305 mOsm / L y 296, 299 y 306 mOsm / L para la lente corneo-escleral y lentes escleral, respectivamente, en cada estadio. Para ambas lentes, se encontraron diferencias estadísticamente significativas entre las visitas ($p < 0,001$), mientras que el análisis post-hoc reveló diferencias estadísticamente significativas entre todos los períodos comparados ($p \leq 0,002$).

El envejecimiento de la población aumenta la probabilidad de desarrollar *síndrome de ojo seco* ya que el aumento de la edad se asocia con una mayor prevalencia de trastornos sistémicos y oculares que pueden alterar la homeostasis del segmento anterior. Las lentes esclerales presentan una doble ventaja para esta población ya que pueden ser una buena plataforma óptica para corregir la presbicia a través de la multifocalidad y proteger la superficie ocular

mediante la bóveda de la córnea. Se necesitan más estudios para identificar mejor los beneficios que los lentes esclerales podrían aportar a una población de mayor edad con patologías del segmento anterior y para comprender mejor el papel potencial de esas lentes en la restauración / mantenimiento de la homeostasis de la superficie ocular durante períodos más largos.

En el **Capítulo 7**, el objetivo del estudio piloto fue evaluar el impacto de la cirugía de catarata sobre la métrica de la película lagrimal, la superficie ocular y la función de las glándulas de Meibomio. Se incluyeron 11 pacientes diagnósticado de catarata (62,1 ± 10,7 años; rango: 40-75 años). Los pacientes fueron visitados dos veces: 7 días antes de la cirugía de catarata, y 7 días después del procedimiento quirúrgico. En cada visita, se valoró la sintomatología de acuerdo con el informe de metodología diagnóstica TFOS DEWS II utilizando los tests subjetivos OSDI y DEQ-5. El dispositivo I-Pen (I-MED Pharma Inc.) se usó para evaluar la osmolaridad del tejido ocular al nivel de la membrana conjuntival palpebral inferior. Después de medir el tiempo de ruptura de la película lagrimal usando fluoresceína, la tinción de la córnea y la conjuntiva se evaluaron según la escala de clasificación de Efron para la tinción de la superficie ocular. La altura del menisco lagrimal inferior se evaluó usando lámpara de hendidura, la expresividad del meibum se valoró mediante la aplicación de presión digital al tercio central del tarso superior usando la escala Arita et al. El valor de corte del meiboscore como criterio para el diagnóstico de disfunción de las glándulas de Meibomio fue ≥3.

El sistema de meibografía estaba compuesto por una lámpara de hendidura equipada con un filtro transmisor de infrarrojos junto con una cámara digital que permite capturar imágenes fijas de infrarrojos o videos de grabación de la morfología de las glándulas de Meibomio. Las áreas donde no se pudo visualizar el tejido glandular se consideraron áreas de pérdida de las

glándulas de Meibomio. Los puntajes de meibografía, que cuantifican la obstrucción de las glándulas de Meibomio, se obtuvieron utilizando grados de la escala de Arita et al. El puntaje total de meibografía fue la suma de las puntuaciones de los párpados superior e inferior y toma valores entre 0 a 6. La media del puntaje DEQ-5 fue de 9,82 (rango de SD 1,9 de 1 a 18) antes de la cirugía, de los cuales el 63% (n = 7) tuvieron una puntuación basal mayor a 6 (indicativos de síntomas de síndrome de ojo seco leves o mayores). Después de la cirugía, la puntuación media de DEQ-5 fue de 14 (SD 1,9 rango de 3 a 20), de los cuales el 82% (n = 9) tuvieron una puntuación mayor a 6. Se encontró un aumento significativo en la puntuación de DEQ-5 después de la cirugía (prueba de Wilcoxon p = 0.017). La puntuación promedio de OSDI al inicio del estudio fue de 36 (SD 4,8 rango 4 a 62) de los cuales el 91% estaban por encima del puntaje de corte para *síndrome de ojo seco*. La puntuación OSDI media después de la cirugía fue de 42,4 (rango SD 8 a 67), de los cuales 91% estaban por encima del puntaje de corte para *síndrome de ojo seco*. Se encontró un aumento significativo en la puntuación OSDI después de la cirugía (prueba t de muestras pareadas p = 0.03). La correlación entre estos dos cuestionarios fue moderada (Pearson's r= 0.60, Spearman's ρ= 0.57 p= 0.05). Los valores medios del tiempo de ruptura del menisco lagrimal fueron de 8.6 s (SD 0.5 rango de 6 a 11 s) antes de la cirugía y 8.4 s (SD 0.6 rango de 6 a 11 s). No se encontraron diferencias significativas entre los valores previos y posteriores a la cirugía (p = 0,608). Las puntuaciones medias de tinción fueron de 0,3 (SD 0,5 rango o a 1) y 1,3 (SD 0,5 rango 1 a 2) antes y después de la cirugía, respectivamente.

La tinción vital aumentó significativamente a través de la cirugía (p = 0,004). Los valores medios de la altura del menisco lagrimal inferior fueron 0.26 mm (SD 0,03 rango 0,10 a 0,40 mm) y 0,27 mm (SD 0,03 rango 0,15 a 0,40 mm) antes y después de la cirugía respectivamente. No se pudieron evidenciar diferencias entre las citas. La media de los valores de osmolaridad

eran 299,2 mOsm / L (SD 4,6 desde 282 a 333 mOsm / L) y 294 mOsm / L (SD 2,3 desde 275 hasta 303 mOsm / L) antes y después de la cirugía, respectivamente. Los valores de osmolaridad no mostraron cambios significativos durante el estudio (p = 0,66). Las puntuaciones medias de expresividad de las glándulas de Meibomio fueron de 1,0 (SD 0.3 rango 0 a 2) y de 1,7 (intervalo SD 0,3 rango 0 a 3) antes y después de la cirugía, respectivamente. De los 11 pacientes incluidos en este estudio, 6 presentaron un meiboscore antes de la cirugía ≥3 que los clasificó como pacientes con disfunción de las glándulas de Meibomio. La expresión de las glándulas de Meibomio fue significativamente más difícil de realizar después de la cirugía (p = 0,011). En cuanto a las imágenes de infra-rojo de las glándulas de Meibomio, los promedios fueron de 2.5 (SD 0.4 rango de 1 a 4) para pre- y post-cirugía, respectivamente. No se detectaron diferencias estadísticas entre las citas para este parámetro. A partir de los resultados obtenidos en este estudio piloto, planteamos la hipótesis de que la cirugía de cataratas promueve la obstrucción de las glándulas de Meibomio a corto plazo, ya que solo se pudieron evidenciar cambios funcionales (reducción de la expresividad glándulas de Meibomio) y la meibografía infra-roja no mostró ninguna alteración estructural significativa. Tal como ya han propuesto algunos autores, es más probable que los cambios estructurales que afectan las glándulas de Meibomio, que no se encontraron en el presente estudio, sean más el resultado de una disfunción crónica que una parte de los resultados de la cirugía de catarata a corto plazo. El presente estudio no pudo dilucidar los mecanismos exactos por los cuales ocurren cambios funcionales a corto plazo en las glándulas de Meibomio después de la cirugía; sin embargo, es muy probable que incluso sin signos significativos de daño de la estructura de las glándulas de Meibomio, la cirugía de cataratas parece afectar su función. La literatura previa sugiere que la inflamación inducida por la cirugía, la infección bacteriana de la superficie ocular alterada, los medicamentos post-operatorios que contienen

conservantes o la combinación de los anteriores juegan un papel impotrtante en el desarrollo del *síndrome de ojo seco* después de la cirugía de catarata incluso en diferentes extensiones. Sin embargo, sería interesante para el seguimiento de los cambios que tienen lugar en la conjunción muco-cutánea y línea de Marx tanto superiores como inferiores, dado que el ensanchamiento y desplazamiento anterior de la línea de Marx son un buen indicador del estado funcional de las glándulas de Meibomio.

Este estudio tiene algunas limitaciones. En primer lugar, se realizó en un número relativamente pequeño de sujetos y no tenía un grupo control que no se hubiera sometido a cirugía de cataratas. En segundo lugar, no se estudió el estado de higiene del párpado y no se evaluó la línea de Marx y la conjunción muco-cutánea, lo que podría haber proporcionado información valiosa sobre el impacto de la cirugía en estos parámetros; de hecho, un estudio previo mostró cambios significativos en la vasculación del margen del párpado y el desplazamiento de la junción muco-cutanea irreversible a través de la cirugía. En tercer lugar, la expresividad del meibum no se midió objetivamente utilizando un dispositivo que proporcionara presión estandarizada en el margen palpebral. Nuevas terapias están surgiendo con el fin de tratar la disfunción de glándulas de Meibomio, tales como los sistemas de luz pulsada intensa que se usan para tratar la enfermedad. Se encontró información valiosa con respecto a la función de las glándulas de Meibomio, pero se necesita más investigación para evaluar el impacto de esta terapia en pacientes con disfunción de las glándulas de Meibomio en los resultados de la cirugía.

Como conclusión general de esta tesis doctoral, cabe señalar que el ojo, así como todo el cuerpo humano, está sujeto al proceso de envejecimiento, cuyas manifestaciones más notables son la presbicia y opacificación del cristalino, pero también todas las estructuras del

segmento anterior se someten a cambios funcionales y morfológicos relacionados con la edad, desde las glándulas lagrimales (glándula lagrimal principal, glándulas de Meibomio, células caliciformes) hasta los párpados y la conjuntiva. Estos cambios reducen tanto la cantidad como la calidad de la secreción lagrimal, evitan una repartición óptima de la película lagrimal en la superficie ocular que puede potencialmente inducir / empeorar los signos y síntomas de sequedad ocular.

La prevalencia del síndrome de ojo seco aumenta con la edad, debido a los procesos de envejecimiento antes mencionados que van de la mano de una mayor prevalencia de enfermedades sistémicas (y su medicación asociada) con efectos secundarios oculares. En ese sentido, compensar la presbicia requiere una anamnesis exhaustiva previa, así como una evaluación de la unidad funcional de la lagrima en busca de procesos patológicos / inflamatorios en curso.

Se pueden considerar múltiples enfoques al corregir la presbicia y la catarata, el objetivo común es restaurar la visión y brindar un confort sostenible al paciente. La gran mayoría de las opciones de refracción disponibles, a excepción de las lentes oftálmicas, se consideran invasivas y podrían perturbar la homeostasis de la superficie ocular. La corrección de la presbicia mediante lente de contacto (desde lente de contacto corneal hidrofílica o rígida permeable al gas hasta diseños esclerales y semiesclerales con diferentes geometrías) puede alterar la estructura normal de la película lagrimal interactuando con la superficie ocular, posiblemente empeorando un entorno ya desequilibrado. La cirugía refractiva es otra opción disponible [cirugía de cataratas con implantación de lentes intraoculares de geometría diferente (monofocal, bifocal, trifocal), cirugía refractiva corneal] pero su invasividad, incluso si se han realizado grandes pasos hacia adelante, perturba también la superficie ocular y

puede empeorar o inducir signos y síntomas de sequedad. Es obligatorio realizar una evaluación exhaustiva de la sintomatología y del estado general de salud del segmento anterior al corregir la presbicia con opciones refractivas invasivas. Con ello, además de permitir una identificación precisa de las estructuras debilitadas de la unidad funcional de la lágrima, tambien ofrece la posibilidad de elaborar una estrategia adecuada para optimizar los resultados a corto y largo plazo en funión de la opción de refracción elegida.

La identificación adecuada de los cambios que tienen lugar en la unidad funcional de la lágrima es una condición *sine qua non* para introducir medidas de profilaxis en masa en los exámenes optométricos y oftalmológicos de rutina. El diagnóstico precoz de esta condición multifactorial es el mejor medio para prevenir, si no retrasar, su aparición y las complicaciones posiblemente inducidas por diferentes tipos de correcciones refractivas. Se necesita más investigación para identificar mejor los síntomas relacionados con la enfermedad, así como los primeros signos de la enfermedad en la superficie ocular con el fin de dar soluciones a una población que envejece y está dispuesta a ser independiente de la corrección con lentes oftálmicas. El conocimiento global sobre la sensibilidad ocular, el daño y sus vías asociadas se ha incrementado significativamente; sin embargo, los mecanismos exhaustivos a través de los cuales *síndrome de ojo seco* se desarolla y afecta aún más la homeostasis de la superficie ocular no se comprenden completamente debido a su alta complejidad y a los numerosos mecanismos implicados. Se necesitan investigaciones adicionales sobre la neuropatogénesis de la alteración de la sensación ocular en el *síndrome de ojo seco* para profundizar en los conocimientos relacionados con los mecanismos de homeostasis, la respuesta ocular al daño nervioso y su papel en la aparición y perpetuación del *síndrome de ojo seco* en una población que se enfrenta a nuevos desafíos debido al envejecimiento, pero también a la aparición de nuevas técnicas de cirugía refractiva.

Thesis Summary

Ocular surface integrity, in other words, its ability to respond adequately to environmental challenges, depends on a proper information intake at the ocular surface, the transmission of the created signal to the brain and the generation of a response, that will modulate secretory function and local immunity. It is easily understandable that any disturbance of one of the three steps of this closed loop could trigger an inappropriate response and further unbalance the compensatory mechanisms taking place at the ocular surface.

The LFU can be defined as a set of anatomical structures whose harmonious functioning maintains tear osmolarity within narrow limits. It is composed of the cornea and the conjunctiva, both protected by the upper and lower lids. All of the structures named above share the same main afferent innervation path represented by the fifth craneal nerve (i.e. trigeminal nerve) and its terminal branches, which allow the cornea and the conjunctiva to take information related to environmental changes and transmit it to the brainstem. Corneal nerves provide a range of afferent inputs modalities such as pain (nociceptor), mechanoreception and temperature (thermoreceptor). Lacrymal glands and blink response are the effectory part of this LFU. LGs are stimulated in response to ocular surface afferent inputs and allow appropriate tear secretion and proper osmolarity values in physiological conditions. This efferent loop is driven by a parasympathetic, secretory innervation which transmits the response signal to the LGs (main, palpebral and accessory), the conjunctival goblet cells, the MGs and adapts tear secretion and composition to environmental challenges. Proper drainage of tears is also involved in this reflex loop as tear secretion is in part evaporated at the ocular surface but also needs to be evacuated since lacrimal secretion is a continuous process.

According to TFOS DEWS II, “Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles”.

The term multifactorial is appropriate since numerous factors have been identified as triggers: age, gender, hormones, environment, ocular surgery and more particularly cataract surgery, auto immune diseases, CL wear, systemic medications, preservatives in eyedrops between others, all of the former potentially conducting to one or both subtypes of the disease.

Tear hyperosmolarity, next to a loss of tear film stability, are keystone of the inflammation cascade, both leading to cellular stress and the inflammatory processes, as acute as chronic, inducing auto alimentation and promoting the vicious circle of dry eye disease. As the disease progresses, ocular surface is gradually jeopardized and is characterized by cellular loss. Other key findings are the neurosensory abnormalities; indeed, impaired afferent pathways involving mechanisms that will be explain in further details, prevent a normal information intake at the ocular surface further fostering the auto-promotion of the disease.

A wide range of pathologies and disorders, age-related changes, environmental conditions and surgical interventions can trigger inflammatory cascades leading to dryness or worsen ongoing inflammatory processes at the ocular surface. Despite this multitude of entry doors, all of the etiologies of dry eye share a common inflammatory pathway leading to ocular surface damage: cellular death, increased epithelial cells shedding and turnover and above all, impaired afferent pathways leading to self-perpetuation of the vicious circle of the disease.

The scientific significance of epidemiological studies relies on a precise definition and classification of the disease, which, until recently, represented the main challenge for DED as

no consensus was adopted regarding dry eye objective and subjective diagnostic criteria. Furthermore, the absence of gold standard tests to diagnose the pathology, which goes hand to hand with an acknowledged heterogeneity between signs and symptoms, make the interpretation and comparison of different epidemiological studies more difficult to assess.

However, even if DED is considered a symptoms-driven disease, epidemiological studies focusing only on clinical signs are source of a considerable variation in prevalence values. Standardization of diagnostic criteria and clinical tests are the great goal to achieve. The actual situation could explain the difficulties searchers are facing when it comes to diagnosis criteria; dry eye clinical tests evaluating the same parameter don't have the same sensibility and specificity in diagnosing the disease, tests used often only assess one aspect of the pathology, no gold standard or combination of tests have been chosen to evaluate clinical features; adding to the previous statements a great extent of DED signs, all of them with distinct severity, sensitivity to pain specific to each individual, age-related/ongoing ocular surface pathologies and systemic conditions with ocular impact or age-related changes taking place in the LFU, make a proper diagnosis based on both signs and symptoms challenging.

The first TFOS report stated that hyperosmolarity and tear film instability are the key drivers of DED. From that statement, two subtypes of the disease could be defined: ADDE where tear hyperosmolarity is due to a decrease of the aqueous content available on ocular surface (secondary to reduced tear secretion) in presence of a normal tear evaporation rate. EDE is the other subtype of the disease, and in this case, hyperosmolarity follows an excessive tear evaporation rate in the presence of normal lacrimal function.

According to the TFOS Epidemiology Report, prevalence of the disease based on symptoms and on clinical signs both show a gradual shift from aged 50. It seems very likely that important

age-related changes take place in the LFU at this period of life (that could be due to a combination of aging eye and systemic changes), unbalancing the complex homeostasis mechanisms and leading to onset or excacerbation of signs and symptoms of dryness. Indeed, when it comes to risk factors for the disease, increased age, again depending on diagnostic criteria and variability of the definition of DED, appears to be the most consistent factor associated with dry eye.

Every part of the human body is subject to aging and LFU is no exception: LG, the eyelid area, MGs and conjunctiva are affected in their structure and function over the life span. Various histopathologic age-related changes occur in LGs. In the first place, a low grade of dacryoadenitis occurs along with acinar atrophy, periacinar fibrosis and paraductal blood vessel loss tend to appear in young adults but increases with age. Interestingly, the secretory ducts following the acini dilate over the life span and show an increased tortuosity suggesting the presence of an obstruction of the ducts. LG lymphocytic infiltration is directly related to aging as its incidence was found to be higher in subject aged 40 and older. It is mainly concentrated around the secretory ducts and acini leading to their gradual destruction. Besides, it is believed that LG aging comes with fatty infiltration and decrease in LG mass, the former eventually leading to LG dysfunction, reduced reflex tear secretion and breakup time. However, it is thought that the reported decrease in reflex Schirmer values over the life span could be due to a variety of factors such as reduced availability of secretory neurotransmitters, loss of functionality of the gland itself as explained earlier and more important, loss of sensory drive originating from ocular surface. Indeed, terminal afferent corneal pathways taking information relative to mechanical and chemical stimuli at ocular surface, loose sensitivity with age, which is expected to reduce sensory drive to the lacrimal gland.

Over and above to the age-related changes aforementioned taking place in the LFU, two additional, visual impairing processes take place within the eye and more precisely within the crystalline lens leading to presbyopia and cataractogenesis respectively, highlighting the need for an optical correction. The present manuscript will describe these two age-related changes and the potential impact of existing refractive approaches to correct them on the onset/ worsening of dry eye signs and symptoms.

Accommodation is the process by which the eye, more precisely the crystalline lens, changes its shape in order to focus on near objects. This optical phenomenon relies on the contraction of the ciliary muscle, which in turn loosens the ciliary fibers attached to the crystalline lens. It allows the lens to take a more curved shape, which increases its refractive power and reduces the focal length to the target of interest. With age, the lens progressively looses its ability to change shape, it is called presbyopia. Presbyopia refers to the age-related progressive loss of accommodation of the crystalline lens that result in an inability to focus on near objects. It is one of the most common refractive defects as everyone eventually develops presbyopia, increased age being the major risk factor even if other elements may influence its onset and progression (disease, medications, trauma). Presbyopia directly affects quality of life over all in high-income countries where the main near distance activities involve writing and reading.

According to the WHO, cataract is the leading cause of blindness and the loss of useful vision is expected to affect 16 million people worldwide. Cataractogenesis is multifactorial, and can develop from a wide variety of causes ; UV radiation (in particular UV B) are involved in cortical cataract changes, genetic factors systemic drugs, infectious diseases, but aging is by far the major risk factor for its onset. It induces a broad spectrum of changes regarding biochemical processes taking place in the lens leading to alteration in water balance, proteins,

vitamins and enzymes, being responsible for progressive loss of lens transparency. Age-related cataract seems to be the result of a prolonged and gradual process of crystalline proteins denaturation, which can occur principally in three different ways: repeated environmental insults (mainly UV radiation), reduction in intrinsic stability of crystalline proteins, or decline of lens cell homeostasis.

DED has become a public health issue worldwide as its impact on healthcare systems is growing steadily. In addition to the economic cost, the social impact of the disease gained a foothold and showed reduced quality of life due to the major impact of the disease on patient's visual function with more frequent visits to the physician, higher frequency of depression and reduced workplace productivity between other impairments. Numerous studies have looked into the influence of aging on dry eye signs and symptoms and according to them, age is a significant risk factor for the disease as people over 50 years old present a prevalence of dry eye increasing significantly with women being more affected. The burden to become for the society is thus undeniable.

Various refractive means exist to correct presbyopia, from spectacles (including simple reading glasses, bifocal, trifocals and multifocal), to CLs with different geometries (monovision, bifocals, simultaneous vision). However, CLs, once upon eye, sit in the TF, disturbing its normal structure and interact with the ocular surface possibly worsening an already unbalanced environment. Refractive surgery is another option available (cataract surgery with implantation of different geometry IOLs (monofocal, bifocal, trifocal), corneal refractive surgery) but its invasiveness, even if great steps forwards have been made, could as well disturb the ocular surface and worsen or induce signs and symptoms of dryness.

The aim of this project is to evaluate changes in tear film metrics and ocular signs induced by different types of refractive correction (refractive surgery, IOL implantation and CL) focusing on the older population, since the prevalence of DED increases with age and due to presbyopia most people over 40 need refractive correction for distance, intermediate or near vision, or all three.

In **Chapter 1**, a general introduction is made, exposing various aspects related to the pathophysiology of dry eye syndrome, the clinical manifestations of aging on the eye describing anterior segment changes as well as presbyopia and cataract onset, and therapeutic and optical treatment options for these conditions.

In **Chapter 2**, the importance of studying the impact of optical aids to correct presbyopia on the signs and symptoms of ocular dryness is justified describing the actual situation using epidemiological data. The hypothesis and objectives of the Doctoral Thesis are presented.

In **Chapter 3**, the general methodology and designs choosed in the clinical studies that compose this Doctoral Thesis are described. This chapter presents the characteristics of the parameters evaluated as well as the devices used to obtain the results of the studies presented in subsequent chapters.

In **Chapter 4**, the purpose was to assess the performance of a new daily disposable CL material on the ocular surface of a presbyopic population. A water gradient daily CL material (delefilcon A) was fitted in a presbyopic population and evaluated over their first day of CL wear. To achieve that goal, TF and ocular surface parameters were investigated across a 8 hours' time of CL wear. Tear film metrics were evaluated at baseline, twenty minutes after CL insertion and then at 8 hours of CL wear. Measurements were taken from the less to the most invasive test as follow: visual acuity, monocular and binocular refraction, anterior segment slit

lamp biomicroscopy, osmolarity, measurement of the inferior TMA, topographic examination and TBUT assessment using fluorescein. Participants were recluted among the employees of the University of Valencia and did not present any anterior segment pathology or previous corneal surgery. The average age of the participants was 50.0±4.4 years, ranging between 41 and 60 years old. Mean spherical equivalent refractive error was +1.11±0.35 D and ranged from -4.25 to +2.50 D. From the 40 eyes included, 18 were myopic (mean spherical equivalent error -2.80±0.72D) and 22 hypermetropic (+0.90±0.24D). Significant changes in osmolarity values were found between baseline (306.93±2.32 mOsm/L) and 20 minutes (312.43±2.42 mOsm/L) ($p < 0.05$). TMA values diminished across the day (from 0.020±0.003 mm2 to 0.017±0.03 mm^2) (P=0.061), but were not statistically significant. Ocular surface higher order RMS aberrations showed a statistically significant increase between baseline (0.38±0.21 µm) and 20 minutes (0.61±0.44 µm) (P≤0.001) and between baseline and 8 hours (0.64±0.41 µm) (P≤0.001). TBUT worsened by the end of the day from 10.4±0.4 seconds at baseline to 9.0±0.3 seconds after 8 hours of CL wear (P<0.05). No statistically significant differences were found between the measurements at baseline, and after 8 hours of CL wear regarding fluorescein corneal (P=0.727) and conjunctival staining (P=0.092). According to our results, no significant changes were found regarding corneal or conjunctival staining by the end of the day, which means that even if osmolarity was above cut-off values, it was not clinically significant since there was no significant cellular damage. Osmolarity values did not change over the time of wear, which may imply that CL surface properties remain rather stable during the 8 hours of CL wear and provide enough oxygen transmission and lubrication to the ocular surface in order not to induce any additional staining. However, if the osmolarity changes occured in a similar pattern over longer-term wear, corneal integrity could well be compromised. Besides, we

speculated that increases in osmolarity at 20 minutes might also be partly due to both an ocular surface response to CL insertion, and an individual tear interaction with the CL material.

DED, according to its severity, is also known to induce a significant rise in aberrations, which implies that in the case of CL wear, pre-lens tear film surface quality would be impacted. The fact that ocular surface high order RMS remained rather stable during the wearing period may imply that the pre-lens TFSQ and dynamics were minimally impacted over the course of the day. We conclude that CL insertion induces an initial decrease in TF stability observed by osmolarity values rising after 20 minutes of wear, but it did not impact tear meniscus metrics and seemed to be transitory, as a decrease, without reaching baseline values, occurred by the end of the wearing period. Ocular surface aberrations remained largely stable from CL insertion, demonstrating an even repartition of TF over the CL material surface.

In **Chapter 5**, the purpose was to assess the effect of lens wearing modality on the ocular surface physiology across a month in a presbyopic population. A total of forty eyes of 40 subjects, employees of the University of Valencia, no previous CL wearers, aged between 41 and 60 years old, were included in this study. Two different wearing Schedule CL material were used: a daily disposable CL (delefilcon A) and a monthly CL (lotrafilcon B). The following parameters were evaluated across the month of wear for each CL material: OSDI questionnaire, CLDEQ-8 questionnaire, visual acuity and refraction, SL biomicroscopy, topographic examination, CCT measurements using OCT and a swept-source biometer, osmolarity measurements, TBUT and TMA. Previously described parameters were measured at: baseline (t0), 20 min margin (t1) and 8 hours margin after insertion (t2), in morning hours (t3) and in the afternoon (t4) of the 30th day excepted for OSDI/CLDEQ-8 that were assessed at the end of the wearing period for each CL material. CL wear was discontinued for four days

between each period of one month of wear in order for the eyes to fully recover. OSDI scores obtained at (t0) an (t4) for the daily and EW lenses were 8.5, 13.2 and 24.4 points respectively and showed significant differences over time only regarding the EW lens (p=0.042). CLDEQ-8 scores obtained at (t0) and (t4) for the daily and extended wear EW material were 6.2 ± 3.8 points (t0), 10.6 ± 8.5 points (t4) and 18.1 ± 9.8 points (t4) respectively and showed significant differences lotrafilcon B giving the higher scores (P=0.012). For both lenses, TMA decreased with time (p<0.001) and (p<0.002) respectively (Figure 2). The post-hoc analysis revealed only significant differences for the daily lens between the measurements taken at baseline (t0)/(t2), (t0)/(t3), (t0)/(t4), as well as between (t1)/(t2) and (t1)/(t4) (p<0.05). For the EW lens, significant differences were found between (t0)/(t1) (p=0.016), (t0)/(t3) (p=0.009), (t0)/(t4) (p=0.001) and (t1)/(t4) (p=0.017). No statistical significant differences in osmolarity were found across the day and at the end of the month for each lens (Figure 3). When comparing both lenses, significant differences exist at (t1)(p=0.006) and at (t2) (p=0.002) values being greater for Delefilcon A . For both lenses, higher order aberrations showed significant differences with time whereas Wilcoxon test found significant differences between (t0)/(t1), (t0)/(t2), (t0)/(t3) and (t0)/(t4) (p<0.001) for each lens respectively. No differences were found between lenses across the month of lens wear. Regarding overall central thickness, when comparing both lenses, significant differences were found between all paired comparisons (p<0.001) with higher thickness values for the daily CL material. The symptomatology evaluated through two questionnaires revealed differences at the level of comfort of use between both materials, showing an increase in symptomatology for lotrafilcon B much more important than for the daily material. Delefilcon A presents a very low surface modulus of 0.025 MPa (core of 0.76 MPa) whereas Lotrafilcon B material has an overall modulus of 1.2 MPa making it more rigid. This could induce increased discomfort across the period of study

compared to the daily CL material (as lens design affects lens comfort) and partly explain the higher symptomatology scores obtained for the EW CL material.

Since every participant of the study did not present any signs and symptoms of DED, it seems reasonable to surmise that the reduction in TMA values found in the present study might be due to: the destabilization of TF by CL material regardless of lens type as well as to the large day to day variability of this parameter.

Regarding osmolarity values, the slight punctual raise in osmolarity found for the daily CL material was not clinically significant since it came back to baseline levels across the month of wear and did not lead to any significant changes in vital stainings. The EW material showed as well constant values of osmolarity between each visit, which allow us to hypothesize that both materials provide high compatibility and minimum disturbance with the ocular surface of first time presbyopic CL wearers.

CL materials used in this study are different and, even if both are silicone-hydrogel lenses, their water content and core structure do differ. On the basis of this observation, significant differences were expected to be found across a month of wear regarding PLTF quality and the resulting ocular surface high order aberrations. However, no disparity were found when comparing lenses, except for the end of the day values ((t2)/(t4)) which suggests that PLTF might have showed local end of the day variations regarding lotrafilcon B. Pre-lens TFSQ and dynamics were minimally impacted across a month of CL wear. Both CL materials fitted in this study provided satisfactory and similar objective on-eye behavior and remained rather stable along the experiment period. However, subjective symptoms showed a greater increase from baseline regarding the extended wear lens. Comfort seems to be impacted by CL material modulus, parameters of both CLs being otherwise very resembling.

In **Chapter 6**, the aim of the study was to assess and compare the effect of the C-ScL and ScLs on TF parameters and corneal thickness in healthy presbyopic subjects. Thirty eyes from thirty presbyopic subjects (average age from thirty presbyopic subjects (average age 54 ± 4 years, range: 46-63 years) completed the study. The subjects wore two contact lenses, randomly assigned, with neutral power and different diameters [12.7 mm (C-ScL), 18 mm (ScL)]. As part of the study screening, each of the participants underwent a comprehensive ophthalmic examination, which included, in the order as follow: visual acuity, refraction, slit lamp biomicroscopy, topographic examination, CCT measurement using OCT. At baseline, 20 min margin (t1) and 8 hours margin after insertion (t2), the area of the tear meniscus was evaluated with OCT as well as CCT and tear osmolarity. CL wear has been discontinued for four days between each measurement in order for the eyes to fully recover. For the C-ScL, median values for basal, 20 min, and 8 hours were 0.0213, 0.0216, and 0.0152 mm^2, respectively. For the ScL, median values obtained for basal, 20 min, and 8 hours were 0.0213, 0.0205, and 0.0137 mm^2, respectively. For both lenses, significant differences with time ($p<0.001$), while the post-hoc analysis revealed only significant differences between the measurements taken at 8 hours and the other two earlier time periods ($p<0.001$). For the C-ScL, median values for basal, 20 min, and 8 hours were 549, 555, and 563 µm, respectively. For the ScL, median values obtained for basal, 20 min, and 8 hours were 549, 556, 577 µm, respectively. For both lenses, Friedman test was statistically significant between visits ($p<0.001$), while the post-hoc revealed statistically significant differences for all paired comparisons ($p<0.001$). For the C-ScL, mean values for basal, 20 min, and 8 hours were 296, 298, and 305 mOsm/L, respectively. For the ScL, mean values for basal, 20 min, and 8 hours were 296, 299, and 306 mOsm/L, respectively. For both lenses, statistically significant differences between visits ($p<0.001$),

while the post-hoc revealed statistically significant differences between all paired time periods ($p \leq 0.002$). Ageing population is more prone to develop DED as increased aged is associated with higher prevalence of systemic and ocular disorders that may disturb anterior segment homeostasis. ScLs present a double advantage for this population as ScL can be a good optical platform for correcting presbyopia through multifocality as well as protecting the ocular surface by vaulting the cornea. Further studies are needed to better identify the benefits of the ScL could bring to an older population with anterior segment pathologies and to better understand ScL potential role in restoring/maintaining ocular surface homeostasis over longer periods of time.

In **Chapter 7**, the goal of the pilot study was to assess the impact of cataract surgery on tear film metrics, ocular surface and meibomian gland function. Eleven patients with cataract (mean [±SD] age 62.10 [±10.7] years (range 40 – 75 years, median 63.5 years) were included. Patients were seen two times; seven days before cataract surgery, and 7 days after the surgical procedure. At each visit, the following tests were performed:

Symptomatology was evaluated according to the TFOS DEWS II Diagnostic methodology report using the Ocular Surface Disease Index Questionnaire (OSDI) and the 5-Item Dry Eye Questionnaire (DEQ-5). The I-Pen device (I-MED Pharma Inc.) was used to assess the osmolarity of the ocular tissue on the inferior palpebral conjunctival membrane. As non-invasive methods were not available, fluorescein tear film break-up time (TBUT) was evaluated by using blue illumination and a yellow filter (Wratten #12), and placing a single fluorescein strip (previously shaken) at the outer canthus of the inferior eyelid. After measuring TBUT, corneal and conjunctival staining were assessed by evaluating the extent of the staining of conjunctiva and cornea (central, superior, temporal, inferior, and nasal) was

graded from 0 (none) to 4 (severe), according to the Efron's grading scale for ocular surface staining. Lower TMH was evaluated using a SL. Expressibility of the meibum was scored by the application of digital pressure to the central third of the upper tarsus using Arita et al. scale. The cutoff value of the meiboscore as a criterion for the diagnosis of MGD was found to be ≥3.

The meibography system was composed of a SL equipped with infra-red transmitting filter coupled with a digital camera allowing to capture infrared still images or recording videos of the morphology of meibomian glands. Areas where glandular tissue could not be visualized were considered areas of MGs dropout.

Meibography scores, which quantify obstruction of meibomian glands, were obtained using grades from. The total meibography score was the sum of the scores of the upper and lower lids and was recorded as 0 to 6. The mean Five-item DEQ score was 9.82 (SD 1.9 range 1 to 18) before the surgery of which 63% (n=7) had a baseline score greater than 6 (indicative of mild or greater DED symptoms). Post-surgery, mean DEQ score was 14 (SD 1.9 range 3 to 20) of which 82% (n=9) had a score greater than 6. A significant increase in DEQ-5 score was found after surgery (Wilcoxon test p= 0.017). Mean OSDI score at baseline was 36 (SD 4.8 range 4 to 62) of which 91% were above the cut-off score for DED. Post-surgery, mean OSDI score was 42.4 (SD 5 range 8 to 67) of which 91% were above the cut-off score for DED. A significant increase in OSDI score was found after surgery (Paired sample t-test p=0.03). The correlation between these two questionnaires was moderate (Pearson's r= 0.60, Spearman's ρ= 0.57 p=0.05). Mean TBUT values were 8.6 s (SD 0.5 range 6 to 11 s) before surgery and 8.4s (SD 0.6 range 6 to 11 s). No significant differences were found between pre- and post-surgery values (p= 0.608). Mean staining scores were 0.3 (SD 0.5 range o to 1) and 1.3 (SD 0.5 range 1 to 2)

pre- and post-surgery respectively. Vital staining significantly increased through the surgery (p=0.004). Mean TMH values were 0.26 mm (SD 0.03 range 0.10 to 0.40 mm) and 0.27mm (SD 0.03 range 0.15 to 0.40mm) pre- and post-surgery respectively. No differences could be evidenced between the appointments. Mean osmolarity values were 299.2 mOsm/L (SD 4.6 range 282 to 333 mOsm/L) and 294 mOsm/L (SD 2.3 range 275 to 303 mOsm/L) pre- and post-surgery respectively. Osmolarity values did not show significant changes during the study (p= 0.66). Mean MGs expressibility scores were 1.0 (SD 0.3 range 0 to 2) and 1.7 (SD 0.3 range 0 to 3) pre-and post-surgery respectively. From the 11 patients included in this study, 6 presented a pre-surgery meiboscore ≥3 which classified them as having MGD. MG expression was significantly more difficult to perform after the surgery (p= 0.011). Regarding IR imaging of MGs, mean grades were 2.5 (SD 0.4 range 1 to 4) for pre- and post-surgery respectively. No statistical differences were detected between appointments for this parameter. From the results obtained in this study, we hypothesize that cataract surgery further promotes short-term MG obstruction, as only functional changes (reduction in MG expressibility) could be evidenced and IR meibography did not show any significant structural alteration. As proposed by Han et al., it is more likely that structural changes impacting MGs, which were not found in the present study, are more the result of a chronic dysfunction than a part of the short-term cataract surgery outcomes. The present study could not elucidate the exact mechanisms by which functional short-term changes occur in MGs following the surgery; however, it is very likely that even without significant signs of MG structure damage, cataract surgery seems to impact MG function. Previous literature suggests that surgery-induced inflammation, bacterial infection from breached ocular surface, preservative-containing postoperative medications or combination of the former, are thought to play a role, even if in different extents. However, it would be interesting to follow-up changes taking place in both upper and lower MCJ and

Marx's line, as widening and anterior displacement of Marx's line is a good indicator of meibomian glands orífices status. This study has some drawbacks. First, it was conducted in a relatively small number of subjects and did not have a control group that had not undergone cataract surgery. Second, the lid hygiene status was not studied and Marx's line and MCJ not evaluated which could have given valuable information on the impact of the surgery on these parameters; indeed, a previous study showed significant changes in lid margin vasculature and irreversible MCJ displacement through the surgery. Third, meibum expressibility was not objectively measured using a device that delivers standardized pressure on the lid. Promizing therapies are emerging in order to treat MGD, such as IPL systems used to treat the disease, which gave valuable information regarding MG function, further investigation is needed to assess the impact of this therapy in MGD patients on surgery outcomes.

As a general conclusion of this doctoral thesis, it should be noted that the eye, as well as the entire human body, is subject to the process of aging, the most remarkable manifestations of which are the presbyopia and opacification of the lens, in other words, cataract. Almost every anterior segment structure undergoes age-related functionnal and morphological changes, from LGs (main lacrymal gland, MGs, goblet cells) to eyelids and conjunctiva. These changes reduce both quantity and quality of tear secretion, prevent an optimal repartition of the TF on the ocular surface potentially leading to/ worsening signs and symptoms of dryness. DED prevalence increases with age, because of the aforementionned aging processes that go hand to hand with an increased prevalence of systemic diseases with ocular side-effects as well as its associated medications. In that sense, compensating presbyopia or getting rid of a clouded lens require a previous comprehensive anamnesis as well as assessment of the LFU looking for on-going pathological/ inflammatory processes. The great majority of refractive options available, apart from eyeglasses, are considered as invasive and could easily perturb the ocular

surface homeostasis. Multiple approaches can be considered when correcting presbyopia and cataract, the common goal being to restore vision and give sustainable comfort to the patient. Presbyopia correction can be achieved through eyeglasses (monofocal, bifocal, trifocal and multifocal lenses) and the former approaches are not expected to induce or worsen signs and symptoms of dryness. Presbyopia correction through CLs is another option (from corneal RGPs to semi-scleral and scleral designs with different geometries such as monofocal, bifocal, soft CLs). However, CLs, once upon eye, sit in the TF, disturbing its normal structure and interact with the ocular surface possibly worsening an already unbalanced environment. Refractive surgery is another option available (cataract surgery with implantation of different geometry intra ocular lenses (IOL) (monofocal, bifocal, trifocal), corneal refractive surgery) but its invasiveness, even if great steps forwards have been made, disturbs as well the ocular surface and can worsen or induce signs and symptoms of dryness. An exhaustive assessment of symptomatology and anterior segment general state of health is mandatory when correcting presbyopia with invasive refractive options. It allows for a precise identification of the weakened structures of the LFU and the elaboration of an appropriate strategy in order to optimize short and long-term outcomes for the refraction option that has been chosen for the patient. Proper identification of changes taking place in the LFU is is a condition *sine qua none* to introduce mass prophylaxis measures in routine optometric and ophtalmologic exams. Early diagnosis of this multifactorial condition is the best mean to prevent, if not delay, its onset and the complications possibly induced by different types of refractive corrections. Further research is needed in order to better identify disease-related symptoms as well as the early signs of the disease on the ocular surface in order to fulfill the requirement of an aging population willing to be spectacle independent. Global knowledge regarding ocular sensation, damage and its associated pathways have significantly increased; however, the thorough

mechanisms through which DED rises and further affects ocular surface homeostasis are not fully understood due to its high complexity and to the numerous mechanisms involved. Further research regarding the neuropathogenesis of impaired ocular sensation in DED is needed in order to deepen the knowledge regarding homeostasis mechanisms, ocular response to nerve damage and its role in DED onset and perpetuation in a population that faces new challenges due to aging but also to the emergence of new refractive techniques.

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CHAPTER 1

INTRODUCTION

1.1 Tear Film

The TF is a complex structure designed to cover and protect the anterior segment of the eye (anterior portion of the conjunctiva and the cornea) [Willcox et al. 2017]. TF is the first refractive surface of the eye and as such, is essential to keep the visual system healthy and functional [Craig et al. 2017]. Besides, it provides mechanical functions and a defensive environment to the ocular surface structures. TF mainly spreads over three compartments: the fornix (and its associated retrotarsal space), the preocular TF and tear menisci (from the lower and upper lids). Preocular TF presents a thickness around 2-5.5µm over the corneal area [King-Smith et al. 2004, King-Smith et al. 2000, Chen et al. 2010]. It is usually described as a trilaminar structure composed of an outermost lipid layer, an aqueous layer and an innermost mucin layer, each of which has a specific function in its formation and stability [Holly et Lemp 1977 (1), Wolff 1946]. It is widely accepted that the aqueous and mucin layers form a mucoaqueous gel, this layer providing an increased gradient of mucins from the aqueous layer towards the epithelium [Dilly 1994, Cher 2008]. Tears, from their formation to their evacuation, involve three main components: secretory system, distribution system and excretory system [Holly 1980].

The secretory system consists of the lacrimal glands: main lacrimal gland, accessory lacrimal glands of Wolfring and Krause, goblet cells, ciliary glands of Moll and Zeis, and the MGs of the tarsal plate [Holly 1980, Mishima et al. 1966]. The main lacrimal gland and accessory glands of Krause and Wolfring [Ubels et al. 2012] secrete the aqueous phase of TF with a smaller portion secreted by the conjunctiva [Dartt 2002]. LGs secrete continuously the aqueous phase of the TF with the rate of 1.2µL/min [Mishima et al. 1966]. Meibomian, Zeis and Moll glands secrete lipids, which gives the lipid layer of TF [Korb 2002, Kunnen et al. 2016] and globet cells located

in the conjunctival epithelium produce mucins, which form the mucinous phase of TF [Gipson 2007].

The distribution system is composed of the eyelids, whose main function is to distribute the tear and to mix all its components through the blinking and redistribute them on the exposed ocular surface [Stern et al. 1998]. This is a two-step process following the blink as described by Brown and Dervichian [Brown et Dervichian 1969], upper lids pulling tears over the cornea by capillary attraction (negative hydrostatic pressure originating from the forming tear meniscus) and lipid layer secondarily spreading upon the TF, dragging additional tears to thicken and stabilize it. During the blinking interval, TF thinning is mainly due to evaporation [Peng et al. 2014 a, Peng et al. 2014 b, Bron et al. 2004, King-Smith et al. 2009, Nichols et al. 2005, Craig et Tomlinson 1997].

The excretory system is composed of the upper and lower canaliculi, lacrimal points, sacs and ducts; its function is to favor lacrimal drainage towards the lacrimal fossa, since once TF is formed, it is spread by action of eyelids (blinking) and the remaining part of the TF (which is not evaporated) is then drained towards superior and inferior lacrimal canaliculi, the common canaliculus and the lacrimal sac, to the lacrimonasal canal [Doane 1981, Klein et al. 1998]. Tears help to protect the corneal surface while maintaining hydration of the corneal epithelium and reducing friction forces, whereas blinking favors the continuous moisturization of the ocular surface spreading TF all over the exposed area of the anterior segment of the eye [Durán-de-la-Colina et Arntz. 2004].

1.2 Tear film structure

The classical TF model is described as a trilaminar structure [Holly 1977, Wolff et al. 1946] formed by an external lipid layer, an intermediate aqueous layer and an innermost mucin layer

[Durán-de-la-Colina et Arntz 2004, Craig et al. 2017, Pflugfelder et al. 1998, Stern et al. 2004, Stern et al. 1998, Holly 1980, Korb 2002]. It is now widely accepted that TF is a complex system, where the aqueous and mucous layers are mixed, forming an upper gelatinous layer and a high concentration of mucins in its innermost part (in contact with the epithelia) [Durán-de-la-Colina et Arntz 2004, Craig et al. 2017, Pflugfelder et al. 1998, Stern et al. 2004, Stern et al. 1998, Holly 1980, Korb 2002].

1.2.1 Tear Film Lipid Layer

TFLL is produced by MGs located in the upper tarsal conjunctiva (25-31 glands) and inferior tarsal conjunctiva (20-26 glands) [Bron et al. 1998a]. This is the thinnest layer of the tear film ranging from 0.015 to 0.160 µm with a mean thickness of approximately 40 nm [King-Smith et al. 2010]. Its main function is to stabilize TF by reducing surface tensions [Miller 1968)]. It also reduces and retards water evaporation [Pearlman, 2015], but does not prevent it [Millar et Schuett 2015, Georgiev et al. 2014], forming a structure that prevents the collapse of the tear film [Millar et Schuett 2015] and enables TF to form a thin layer. It secondarily avoids mixing (and further contamination) with skin lipids, which could, partly explain its antimicrobial properties [Mudgil 2014]. It is believed that TFLL, due to its complex composition, is organized according to a multi-layered model [Cwiklik 2016]. TFLL composition has been thoroughly analyzed [Millar et Schuett 2015] as various studies suggested that DED associated with a deficient TFLL could be due to changes in meibum composition [Brown et al. 2013, Butovich 2009, Green-Church et al. 2011, Lam et al. 2011, Pucker et Nichols 2012]. Indeed, TFLL is formed by an anterior or external zone, which is in contact with the external environment, and is constituted by non-polar hydrophobic lipids: cholesterol esters, waxes and triglycerides [Bron et al. 2004a] responsible for the delayed evaporation of TF [Bron et Tiffany 2004b, King-

Smith et al. 2010]. The posterior lipid layer is formed by polar lipids, phospholipids and free fatty acids, and is located at the interface with the aqueous layer [Bron et al. 2004a, King-Smith et al. 2010]. Thus, high polarity lipids forming this phase (phospholipids, glycolipids and sphingolipids) ease the extension of the hydrophobic lipid layer, the outermost lipidic layer, on the hydrophilic aqueous layer of the tear [Bron et al. 2004a, King-Smith et al. 2013]. Mechanical effect of blinking induces Riolan's muscle contraction, which allows lipid secretion from MGs, and increases TF thickness [Korb 2002].

1.2.2 Aqueous tear film layer

Aqueous layer is produced by the acini of the lacrimal glands and by the soluble mucins secreted by goblet cells [Sullivan 2012a, Harriet et Kuonen 2004] providing an optically smooth surface [Montes-Micó et al. 2005]. Aqueous secretion originates from the main LG, located in the supero-temporal orbital cavity, and the accessory lacrimal glands of Krause (fornix) and Wolfring (between the peripheral edge of the tarsus and the fornix) [Craig 2002]. Aqueous layer is considered the main layer of TF [Holly 1980] representing more than 98% of its thickness (7µm) [Craig et al. 2017]. This layer is composed of electrolytes, proteins, enzymes and metabolites [Craig et al. 2017]. It contains antibacterial proteins (lysozyme and lactoferrin), albumin, lipocalin, FGF, NGF, Ig, mainly IgA, considered as one of the first line of defense of ocular surface; aqueous phase also contains glucose, glycogen and oxygen, used as nutrients by the avascular cornea [DEWS 2007, Craig 2002, Lemp 1995]. Lipocalin plays a key role in the posterior lipid transition zone (with the aqueous phase), as it binds to the polar lipids forming an interface increasing stability of TF [Korb 2002]. EGF and TGFβ, originating from the aqueous phase, respectively maintain homeostasis by promoting renewal of corneal surface epithelial cells [Tseng et Tsubota 1997] and play an immunomodulatory role. Lacrimal

gland also secretes several CKs such as IL-1 and TNFα, fundamental immunological markers that participate in maintaining the balance and protection of ocular surface [DEWS 2007, Conrady et al. 2016].

1.2.3 Mucins tear film layer

Mucin layer is composed of Igs, salts, urea, glucose, leukocytes and enzymes such as peroxidase and lysozyme [Nichols et al. 1985].

Mucins play a major role in ocular surface homeostasis through its capacities to: lubricate the ocular surface, reduce friction forces (and hence mechanical stress); clear waste and debris, and prevent dessication of corneal and conjunctival epithelial cells providing an efficient barrier function [Stephens et McNamara 2015, Mantelli et Argüeso 2008]. Three main types of mucins have been identified at the ocular surface: gel forming, MAMs and soluble mucins. Each one of the former is expressed by different components of the LFU and participate in different extents to the homeostasis of the ocular surface.

1.2.3.1 Gel-forming mucins

This type of mucins is secreted by goblet cells. Goblet cells lye intercalated in the conjunctival epithelium with a greater density at the nasal side and fewer cells at the superior and inferior bulbar quadrants [Kessing 1968, Moore et al. 1987]. They extend through the entire thickness of the conjunctival epithelia, their basal side in contact with the basal membrane and their apex in contact with ocular surface [Gipson 2016]. They are filled with mucin granules containing a filamentous structure: a large secretory glycoprotein called MU5AC [Inatomi et al. 1996], which, once liberated at the ocular surface, binds to the components of the aqueous layer and forms a gel. The spread of this gel onto ocular surface allows to trap and remove

cellular debris but also acts as a scaffold for CKs and antimicrobial molecules as well as reducing shearing stress during blink [Mantelli et Argüeso 2008].

1.2.3.2 Membrane Associated Mucins

This type of mucins, also called cell-surface associated mucins [Mantelli et Argüeso 2008], is mainly located at the apex of ocular mucosal epithelial cells [Mantelli et Argüeso 2008] [Govindarajan et Gipson 2010]. They markedly differ from the gel-forming mucins as they are composed of two main parts: an extra cellular domain, extending 200-500 nm into the muco-aqueous phase [Mantelli et Argüeso 2008]; which possesses anti-adhesive properties that allow the muco-aqueous phase to move freely across the ocular surface and by that mean clear debris [Sumiyoshi et al. 2008] and prevent the adhesion of foreign bodies [Aristoteli et al. 2003]; and a cytoplasmic tail which is bound to cytoskeletal components and cell-cell junctions. Membrane associated mucins secrete glycocalyx, which prevent the penetration of dyes such as rose bengal used to assess epithelial damage and epithelial barrier integrity [Blalock et al. 2007]. The authors show that MUC16 abrogation (MUC16 is one of the MAMs) [Mantelli et Argüeso 2008, Govindarajan et Gipson 2010] in cultured human corneal epithelial cells results in loss of cell surface protection against dye penetrance and increased Staphylococcus. aureus adherence, suggesting that cell surface-associated mucins contribute to the formation of a protective barrier against injury and pathogens [Argüeso et al. 2006] and as such there are considered to provide a protective cell surface barrier function [Mantelli et Argüeso 2008]. They also play an important role in tear film stabilization [Govindarajan et Gipson 2010]. Among them, we can find MUC 1, MUC 16 and MUC 20 located across the entire corneal and conjunctival epithelia. MUC 4 is another subtype of MAMs, which expression is

mainly restricted to the conjunctiva, but can also be found in the limbus and lacrimal gland [Mantelli et Argüeso 2008, Govindarajan et Gipson 2010].

1.2.3.3 Soluble mucins

Interestingly, soluble mucins are not found in the tears even if they are expressed by conjunctival cells and lacrimal glands [Jumblatt et al. 2003]. Little is known about their function within the ocular surface but they are thought to perform an antibacterial function [Bobek et Situ 2003].

1.3 THE LACRIMAL FUNCTIONAL UNIT

1.3.1 Definition

Ocular surface integrity, in other words, its ability to respond adequately to environmental challenges, depends on a proper information intake at the ocular surface, the transmission of the created signal to the brain and the generation of a response, that will modulate secretory function and local immunity. It is easily understandable that any disturbance of one of the three steps of this closed loop could trigger an inappropriate response and further unbalance the compensatory mechanisms taking place at the ocular surface.

Figure 1.1. The lacrymal functionnal unit as described by Stern et al. 2013.

The LFU can be defined as a set of anatomical structures whose harmonious functioning maintains tear osmolarity within narrow limits [Sullivan et al. 2012]. The ocular surface is composed of the cornea and the conjunctiva, both protected by the upper and lower lids. All of the structures named above share the same main afferent innervation path represented by the fifth craneal nerve (i.e trigeminal nerve) and its terminal branches, which allow the cornea and the conjunctiva to take information related to environmental changes and transmit it to the brainstem. Corneal nerves provide a range of afferent inputs modalities such as pain (nociceptor), mechanoreception and temperature (thermoreceptor) [Bron et al. 2017]. Lacrymal glands and blink response are the effectory part of this LFU. Lacrymal glands are stimulated in response to ocular surface afferent inputs and allow appropriate tear secretion and proper osmolarity values in physiological conditions. This efferent loop is driven by a parasympathetic, secretory innervation which transmits the response signal to the lacrimal glands (main, palpebral and accessory), the conjunctival goblet cells, the MGs [Bron et al. 2017] and adapts tear secretion and composition to environmental challenges.

Proper drainage of tears is also involved in this reflex loop [Paulsen 2003] as tear secretion is in part evaporated at the ocular surface but also needs to be evacuated since lacrimal secretion is a continuous process.

1.4 DRY EYE DISEASE

1.4.1 Definition

According to TFOS DEWS II, “Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles” [Craig et al. 2017].

The term multifactorial is appropriate since numerous factors have been identified as triggers: age gender, hormones, environment, ocular surgery and more particularly cataract surgery, auto immune diseases, contact lens wear, systemic medications, preservatives in eyedrops between others, all of the former potentially conducting to one or both subtypes of the disease [Baudouin et al. 2017].

Tear hyperosmolarity, next to a loss of tear film stability, are keystone of the inflammation cascade, both leading to cellular stress and the inflammatory processes, as acute as chronic, inducing auto alimentation and promoting the vicious circle of dry eye disease. As the disease progresses, ocular surface is gradually jeopardized and is characterized by cellular loss. Other key findings are the neurosensory abnormalities; indeed, impaired afferent pathways involving mechanisms that will be explain in further details through the next paragraph, prevent a normal information intake at ocular surface further fostering the auto-promotion of the disease.

1.5 PATHOPHYSIOLOGY OF DRY EYE DISEASE

In order to properly understand the signs and symptoms of DED and the complex relationships that unite them, it is important to get a precise picture of the mechanisms involved in the pathophysiology of the disease. As defined earlier, a wide range of pathologies and disorders, environmental conditions and surgical interventions can trigger inflammatory cascades leading to dryness or worsen ongoing inflammatory processes at the ocular surface. Despite this multitude of entry doors, all of the etiologies of dry eye share a common inflammatory pathway leading to ocular surface damage: cellular death, increased epithelial cells shedding and turnover and above all, impaired afferent pathways leading to self-perpetuation of the vicious circle that will be described later on.

The first TFOS report stated that hyperosmolarity and tear film instability are the key drivers of DED [DEWS 2007]. From that statement, two subtypes of the disease could be defined: ADDE where tear hyperosmolarity is due to a decrease of the aqueous content available on ocular surface (secondary to reduced tear secretion) in presence of a normal tear evaporation rate. EDE is the other subtype of the disease, and in this case, hyperosmolarity follows an excessive tear evaporation rate in the presence of normal lacrimal function [Bron et al. 2017]. Different etiologies of both subtypes of the diseases are summarized Table 1 and Table 2.

Aqueous Deficient Dry Eye (ADDE)					
Sjögren Syndrome Dry Eye (SSDE) Associated systemic diseases: -Rheumatoid arthritis -Polyarteritis nodosa -Systemic lupus erythematosis -Wegener granulomatosis -Systemic sclerosis -Mixed connective tissue disease	Non-Sjögren Syndrome Dry Eye (NSDE) -Intrinsic Lacrimal Gland Deficiency -Lacrimal gland ablation -Congenital alacrima	Age-related dry eye -Inflammatory and other lacrimal gland infiltration -Sarcoidosis -Lymphoma -Viral infection -Radiation injury	Lacrimal Gland Obstruction -Cicatricial conjunctivitis -Graft Versus Host Disease -Stevens-Johnson Syndrome -Cicatricial pemphigoid -Trachoma -Chemical injury	Hyposecretory States-Failure of the Lacrimal Functional Unit Reflex Afferent Block -Topical anesthesia -Trigeminal nerve injury -Refractive Surgery -Neurotrophic keratitis Secretomotor Block: -Parasympathetic damage -Pharmacological inhibition	Other Disorders -Meige Syndrome -Diabetes Mellitus -Pseudoexfoliation

Table 1. Causes of Aqueous Deficiente Dry Eye.Taken from (Bron et al. 2017)

Evaporative Dry Eye (EDE)	
Meibomian Glands Diseases:	**Secondary to systemic Dermatoses:**
Meibomian Gland Dysfunction (MGD)	-Rosacea
Primary:	-Seborrheic dermatitis
-Meibomian Seborrhea	-Atopic dermatitis
-Obstructive MGD (Cicatricial / non-cicatricial)	-Ichtyosis
Secondary to Local Disease:	-Psoriasis
-Anterior blepharitis	
-Ocular surface inflammation	**Secondary to chemical Exposure**
-**Contact lens wear**	**Disorders of Lid Aperture, Congruity, Dynamics**
	-Blink-Related
	Ocular Surface-Related Evaporative Dry Eye
	-Allergic Eye Disease
	-Vitamin A Deficiency
	-Short Breakup Time Dry Eye
	-Iatrogenic Disease

Table 2. Causes of Evaporative Dry Eye.Taken from (Bron et al. 2017)

Actually, both subtypes of DED could be considered as evaporative forms since, indeed, increased evaporation eventually occurs in both subtypes and is responsible for high osmolarity values at the ocular surface. Furthermore, hybrid forms of DED are not uncommon as explained by Bron et al.:"It was recognised that these subtypes of DED may coexist and this is the case in Sjögren syndrome where lacrimal deficiency frequently coexists with MGD" [Shimazaki et al. 1998, Krenzer et al. 2000, Bron et al. 2017] making the diagnosis sometimes difficult.

When the disease evolves in ADDE, TF thickness reduction affects TFLL spreading and could possibly lead to a functional EDE [Bron et al. 2017]. Conversely, a severe form of EDE could (through the afferent corneal nerve impairment), reduce the information intake at the ocular surface and lead to a secondary ADDE [Bron et al. 2017]. This why it is important to emphasize the recommendations made by Bron et al. that ADDE/EDE are only classifications for the initial states of DED, since, as DED evolves, regardless of its subtype, tear break up eventually occurs within the blink interval adding an extra evaporating component to the disease [Bron et al. 2017].

Ocular surface integrity, in physiological conditions, is ensured by both resident immune cells and the epithelial barrier. It is important to understand that ocular surface is subject to constant solicitation originating from the outside world: mechanical trauma, temperatures variations [Belmonte 2013], wind speed, foreign bodies, allergens and antigen adherence to ocular surface [Baudouin et al. 2017, Baudouin et al. 2013, McDermott et al. 2005, Stern et al. 2013]. Any of the risk factors named above can easily jeopardize ocular surface homeostasis and initiate an acute inflammatory cascade.

The role of the LFU is to respond as far as possible to these threats, controlling actively the local immune system by initiating an inflammatory response only when homeostasis is at stake, maintaining at the same time tolerance to commensal flora and auto-antigens [Schaumburg et al. 2011]. In that sense, corneal tissue can be considered as an immune privileged site which goal is to maintain its transparency and thus preserve vision [Streilein 2003]. Among the main resident immune cells we can find resident T lymphocytes ($CD8^+$ γδ/ Natural Killer (NK) (which response damages target tissue but also facilitate dendritic cells maturation through INF-γ) [Coursey et al. 2014, Zhang et al. 2012, Chen et al. 2011a, Bonaccorsi et al. 2015] and regulatory $CD4^+$ that permanently interact with anti-inflammatory factors such as IL-1, IL-1RA, matrix protease inhibitors such as TIMP-1 [Gupta et al. 1996, Sobrin et al. 2000, Solomon et al. 2001, Barabino et Dana 2007, Stern et al. 2013], and an immunosupressor and anti-inflammatory cytokine : TGF- β2 [Baudouin et al. 2017, Baudouin et al. 2013]. Furthermore, a number of proteins presenting antimicrobial properties are present in the tears: defensins (subtypes α and β), lysozyme, lactoferrin and lipocalin between others [Vinding et al. 1987, Zhou et al. 2004].

The role of physical barrier at the ocular surface is played by a set of structures (derived from the epithelia or the epithelia itself) that work together in order to maintain ocular surface homeostasis. Gels mucins (produced by goblet cells), glycocalyx [Spurr-Michaud et al. 2007], ensure ocular surface lubrication, prevent adherence of foreign bodies and form an interface with ocular surface epithelia providing stability of the tear film. Corneal epithelium microvillosities serve as anchor points on which MAMs can bind and further interact with the mucin gel secreted by goblet cells and mix to the aqueous layer of the tear film [Argüeso et al. 2013]. The most important part of this physical barrier is represented by the epithelia (cornea and conjunctiva) considered as the “gate keepers” of the ocular surface [Ueta 2008, Bron et

al. 2017]. Intercellular junctions of the corneal and conjunctival epithelia contribute in a major way to the integrity of this barrier [Argüeso et al. 2013]. Corneal epithelium provides 4 types of intercellular junctions from the outermost apical layer to the innermost basal layer: TJ being the principal guarantor of an effective sealing [Sugrue et Zieske 1997, Tsukita et al. 2001], adherens junctions (zonula adherens throughout the different layers), desmosomes (macula adherens located in the wing cell layer) and gap junctions (basal cell layer) [Argüeso et al. 2013]. The most superficial epithelial layer contains TJs, located between two adjacent cells in its apical part, which role is to serve as a barrier to the diffusion of molecules (such as vital stainings) in the paracellular space by sealing the intercellular space [Argüeso et al. 2013]. Tight Junctions are composed of several precursors (claudins, occludin, junctional adhesion molecule-A) that are the target of some pro-inflammatory cytokines (MMP-3, MMP-9 [Luo et al. 2004, Huet et al. 2011, Pflugfelder et al. 2005] and TNF-α) [Bron et al. 2017, Tanaka et al. 2013] liberated during the acute and chronic phase of the inflammation and responsible for epithelial cells apoptosis that is clinically observed as an increased uptake of vital staining. The other junctions' types (desmosomes, hemi-desmosomes, and adherens junctions) play a structural and anchoring role [Suzuki et al. 2003] between neighbor cells and corneal layers, whereas gap junctions facilitate cellular communication and differentiation [Argüeso et al. 2013].

Accelerated evaporation increases the solute concentration (mainly glucose, sodium, potassium, and chloride) of the tear at the ocular surface giving rise to hyperosmolarity. Following surface dessication (and subsequent cooling at the ocular surface) trigger thermoreceptors responsible for the initiation of compensatory mechanisms involving: increased lacrimal secretion and blink rate [Nakamori et al. 1997, Wu et al. 2014, Belmonte et al. 2017] the former inducing discomfort. Besides, ocular surface dryness induces mechanical

issues such as increased friction forces between the lid wiper of both upper and lower lid and ocular surface possibly initiating inflammatory events [DEWS 2007, Bron et al. 2017]. Increased osmolarity, through the induced cellular damage, leads to exposure of nerve endings and to an increased stimulation [Dastjerdi et Dana 2009, Stevenson et al. 2012]. Nerve endings exposure initially induces a higher blinking rate and lacrimal secretion liberating neuropeptides (Neuropeptide Y, Substance P, calcitonine) leading to neurogenic inflammation, and NGF liberation (by nerve endings) [Baudouin et al. 2017] that will promote nerve regeneration at the ocular surface. However, too much and prolonged stimulation over time causes reduction in corneal sensitivity and can modify tear composition by inflaming lacrimal glands, creating toxic tears, where pro-inflammatory factors will be released on ocular surface and further promote the innate inflammation process [Rolando et al. 2005, DEWS 2007, Mantelli et al. 2010, Lambiase et al. 2012]. Besides, hyperosmolarity directly affects ocular surface epithelial cells (cornea and conjunctiva) inducing cellular stress to which the cells will respond through innate acute immunity processes and by initiating a programmed death called apoptosis.

Indeed, cellular stress can by-pass the epithelium barrier by the induction of an intra cellular cascade involving MAPK [Li et al. 2004; Luo et al. 2004, 2005, Stevenson et al. 2012, Stern et al. 2013], a protein with enzymatic activity located in the cytoplasm that, once activated, translocates to the nucleus of the cell and regulates the expression of a transcription factor called NF-κB. According to Schulze-Osthoff et al., [Schulze-Osthoffet al. 1997] NF-κB “has an established role in the regulation of numerous genes involved in cellular defense mechanisms in response to immune and inflammatory processes”. Among the targeted genes of this transcription factor, we can find the pro-inflammatory CKs IL-1 and TNF-α and IL-6 [Yoon et al. 2007, Tishler et al. 1998, Lam et al. 2009], whose main activity is “pro- inflammatory”, in other

words, to spread the inflammation signal to neighbour cells and allow recruitment of other immunity cells involved in the transition between the acute, innate response to a chronic, adaptive, antigen-specific, blood-mediated immunity. Other target genes of NFκB are the one coding for chemokines. By the same intra cellular mechanism explained earlier, CKs liberated in the tears by the epithelial cell will bind to its specific receptor located at the surface of another epithelial cell (all corneal and conjunctival cells possess receptors to various types of CKs). The principal consequence of this cascade of activation is the liberation of more pro-inflammatory CKs on ocular surface, but also the up-regulation of MMP-9 by corneal epithelial cells inducing, as explained earlier, the disruption of the epithelial corneal barrier [Li et al. 2006, Chotikavanich et al. 2009]. Besides, these inflammatory mediators also allow the maturation of immature APCs, which are DCs mainly located along the basal membrane of the corneal epithelium and stroma [Brissette-Storkus et al. 2002, Hamrah et al. 2003, Sosnova et al. 2005, Chinnery et al. 2008]. DCs are present in physiological conditions in corneal and conjunctival tissue and their main function is to continuously sample antigen from their environment [Saban et al. 2014]. These DCs are more densely represented in corneal periphery and their number decreases centripetally [Knickelbein et al. 2009]. However, in response to repeated inflammatory insults, their number is known to increase [Schaumburg et al. 2011]. DCs play a key role in the transition of the immune response (from acute to chronic) thanks to their ability to stimulate T cell activation in the lymph node [Khandelwal et al. 2013, Schlereth et al. 2012, Schaumburg et al. 2011, Chen et al. 2013, Stern et al. 2013, Pflugfelder et al. 2009, Saban et al. 2013]. Indeed, DCs located in the affected tissue (i.e the cornea/conjunctiva) present the ability to recognize pathogens (that can be auto-antigens) and detect inflammatory signals. The recognized Ag is then internalized through different mechanisms and disrupted so as it can be presented through MHC at the cell surface [Saban

et al. 2014, Bron et al. 2017]. DCs can also detect inflammatory signals mainly represented by ILs liberated secondary to cellular hyperosmotic stress. Both mechanisms induce the maturation of the DC, which will give the DC the ability to present the Ag at its surface to other immune cells and more importantly, migratory abilities, an essential stage in the transition from acute to chronic inflammation. Naïve T cell stimulation in the LN relies on the migration of the DCs from the cornea/conjunctiva to LN paracortex, and this is made possible by the C-C chemokine receptor type 7 CCR7 [Saban et al. 2013, Forster et al. 1999, Scandella et al. 2002, Saeki et al. 1999, Ohl et al. 2004, Forster et al. 2008, Yanagihara et al. 1998]. Chemokines are chemotactic cytokines, upregulated in inflammation processes that control patterns of migration and the positioning of immune cells and influence every aspect of the immune system [Comerford et Mccoll 2011]. In the case of DED, DCs maturation is induced by recognition of the Ag, but the triggering of the adaptative immune response requires the activation of T cells in the LN. This requires gaining access to the lymphoid vessels at the limbo, then migrate to the LN parenchyma and get access to the naive T cells [Saban 2014]. During its maturation, DCs upregulate the expression of CCR7 [Saban et al. 2013, Saban 2014]. The propagation of the inflammation signal allows an upregulation of CCR7 ligands at the surface of endothelial cells located inside lymphoid vessels and the creation of a chimiotactic gradient that goes from the lymphatic vessel to the LN [Forster et al. 1999, Ohl et al. 2004, Martin-Fontecha et al. 2003]. Once in the LN, DCs locate in the paracortex where they will meet naive helper T cells (T_h) and initiate the differentiation of LT $CD4^+$ in two main lineages; T_h 1 mediated immunity or T_h 17 cell subsets. [El Annan et al. 2009, De Paiva et al. 2009 a, Niederkorn et al. 2006]. In the LN, T_h 1 subset LT acquires the ability to secrete INF-ɣ at the ocular surface whereas T_h17 lineage secretes IL-17. The homing of these activated inflammatory cells is blood mediated and requires the expression of endothelial adhesion molecules to guide them back

to the inflammation site [Comerford et Mccoll 2011]. ICAM-1 is an adhesion molecule expressed by conjunctival, corneal epithelium and by blood vessel endothelium in DED [Bron et al. 2017; Pisella et al. 2000]. ICAM-1 interacts with a type of receptor expressed by activated T cells (T_h1 and T_h17) called leucocyte factor antigen 1 (LFA-1) and induces: rolling, transmigration and activation both in LN and at the site of inflammation [Perez et al. 2016]. In the case the inflammation site is located onto the cornea (knowing that cornea, in physiological conditions, is devoid of blood/lymphatic vessels) [Stevenson et al. 2012], the homing of T_h1 and T_h17 cells is facilitated by the production of prolymphangiogenic molecules such as vascular VEGF D and VEGF C. The arrival of T_h 1 and T_h17 cells on the inflammation site exerts their pathologic effect as T_h1-secreted INF-ɣ and T_h17-secreted IL-17 promote the liberation of proinflammatory CKs, MMPs (MMP-3 and MMP-9), chemokines [De Paiva et al. 2009b, Coursey et al. 2013 , Dohlman et al. 2013] leading to disruption of epithelial barrier corneal and decrease in goblet cells density [Stevenson et al. 2012, De Paiva et al. 2009b, Chauhan et al. 2011; Chauhan et al. 2009]. The liberation of pro-inflammatory factors on ocular surface is expected to reach every structure within the LFU.

1.6 AGING, AGING EYE AND DED

The National Institute on Aging of the National Institutes of Health (USA) gave a comprehensive definition of aging: “Aging is a complex natural process involving every molecule, cell, and organ in the body. In its broadest sense, aging merely refers to changes that occur during the lifespan.” [Dollemore 2008]. As proposed by Rocha et al. [Rocha et al.2008] a set of two main theories could explain the process of aging, from programmed mechanisms inducing senescence to error signals leading to aging, but no consensus on the origin of age-related changes can fully explain the processes undergone by the human body

through the years [Gatza et al. 2008, Jarrard et al. 1999, Makrantonaki et al. 2006, Sarkisian et al. 2007, Abdel-Rahman et Cowen 1994, Ishimaru et al. 1997 ,Ishimaru et al. 2000, Meites 1990, Sander et al. 2006, Tanaka 1990 , Kikuchi et al. 2007, Lim 2006, Schwarze et al. 2005, Sharma et al. 2005, Artandi et al. 2002, Inoue et al. 2003, Alves et al. 2005, Shamanin et Androphy 2004, Wiktor-Brown et al. 2006].

1.6.1 Age-related changes taking place in the LFU

Every part of the human body is subject to aging and LFU is no exception: LG, the eyelid area, MGs and conjunctiva are affected in their structure and function over the life span. Various histopathologic age-related changes occur in LG. In the first place, a low grade of dacryoadenitis occurs along with acinar atrophy, periacinar fibrosis and paraductal blood vessel loss tend to appear in young adults but increases with age [Damato et al. 1984, Nasu et al. 1984, Obata et al. 1995]. Interestingly, the secretory ducts following the acini dilate over the life span and show an increased tortuosity suggesting the presence of an obstruction of the ducts [Rocha et al. 2008]. Obata et al. suggest that since acini and ducts are anatomically closely related, the obstruction of the ducts could influence the atrophic changes taking place in the acini [Obata et al. 1995]. LG lymphocytic infiltration is directly related to aging as its incidence was found to be higher in subject aged 40 and older [Nasu et al. 1984]. It is mainly concentrated around the secretory ducts and acini leading to their gradual destruction; Damato et al and Nasu et al. [Damato et al. 1984, Nasu et al. 1984] proposed that the lymphocytic infiltration generates fibrosis, a secondary response to chronic inflammation. Besides, it is believed that LG aging comes with fatty infiltration and decrease in LG mass, the former eventually leading to LG dysfunction, [Bukhari et al. 2014, El-Fadaly et al. 2014, Nasu et al. 1984] reduced reflex tear secretion and breakup time [Patel et Farrell 1989]. However,

Rocha et al. [Rocha et al. 2008] emphasize the fact that the reported decrease in reflex Schirmer values over the life span [Van Haeringen 1997, Seal 1985] could be due to a variety of factors such as reduced availability of secretory neurotransmitters, loss of functionality of the gland itself as explained earlier and more important, loss of sensory drive originating from ocular surface [Rocha et al. 2008]. Indeed, terminal afferent corneal pathways taking information relative to mechanical and chemical stimuli at ocular surface, loose sensitivity with age, which is expected to reduce sensory drive to the lacrimal gland [Bourcier et al. 2005, Millodot 1977, Acosta et al. 2006]. Another argument in favor of the diminution of LG function with age lies in the analysis of the lacrimal-derived proteins (peroxidase, lyzozyme, lactoferrin) which amount decreases with age [McGill et al. 1984, Seal 1985, Pietsch et Pearlman 1973, Bonavida et Sapse 1968, Mathers et al. 1996].

Alterations of the eyelid include lid laxity [Chhadva et al. 2016] MG atrophy [Alghamdi et al. 2016] and gland loss/dropout [Den et al. 2006, Norn 1987] the former increasing with age as seen using noninvasive meibography [Arita et al. 2008]. Furthermore, Arita et al. and Ban et al. used noncontact infrared meibography to emphasize decreased mean duct length and percent acini area in older when compared to younger, asymptomatics subjects [Arita et al. 2008, Ban et al. 2013]. Decreased hormonal levels, particularier androgen levels, shown to decline in older adult male, are associated with changes occuring in the function of MGs. [Sullivan et al. 2002]. Bron et al. proposed an interesting theory regarding Marx's line, a vital dye staining pattern [Knop et al. 2011a, Knop et al. 2010, Donald et al. 2003, Norn 1985], located behind the MCJ [Knop et al. 2011b], in lifespan keratinization of terminal meibomian ducts possibly leading to MGD. MCJ is a shifting zone of the epithelia properties, changing from keratinized epithelium of the lid margin skin, which is hydrophobic, to a hydrophilic parakeratinized conjunctival epithelium [Knop et al. 2011b]. Marx's line is a staining pattern

that extends from lacrimal puncta to outer canthi of both upper and lower lids, it is very limited in width in younger subjects (few cells wide) [Donald et al. 2003], but tends to broaden and loose regularity with age along with the neighbour MCJ [Bron et al. 2017]. The staining of this particular zone is believed to be the result of permanent increased osmolarity at this site (secondary to a local high evaporation rate), increasing epithelial cell and glycocalyx secreting cells turnover eventually leading to insufficient cell maturation and to the corresponding vital staining [Bron et al. 2011a, Bron et al. 2011b]. Furthermore, local maintained hyperosmolarity leads to an increased epithelium permeability and could be used as a route for pro-inflammatory CKs released in response to osmotic stress (IL-1β, INF-ɣ, MMPs, TNFα) and reach the nearby meibomian gland terminal ducts. As specified by [Li et al.2010], liberation during a lifespan of IL-1 β and INF- ɣ locally, through their ability to favor the expression of cornified precursor proteins, could participate to hyperkeratinisation of meibomian terminal ducts, a prerequisite to MGD onset. Conjunctiva seems to be rather resistant to age-induced damage [Giebel et al. 2005, Zhu et al. 2010, Labbe et al. 2005, Abdel-Khalek et al. 1978].

Over and above to the age-related changes aforementioned taking place in the LFU, two additional, visual impairing processes take place within the eye and more precisely within the crystalline lens leading to presbyopia and cataractogenesis respectively, highlighting the need for an optical correction. The next paragraphes will describe these two age-related changes and the potential impact of existing refractive approaches to correct them on the onset/ worsening of dry eye signs and symptoms.

1.6.2 Age-related changes to the crystalline lens: presbyopia onset

Accommodation is the process by which the eye, more precisely the crystalline lens, changes its shape in order to focus on near objects. This optical phenomenon relies on the contraction

of the ciliary muscle, which in turn loosens the ciliary fibers attached to the crystalline lens. It allows the lens to take a more curved shape, which increases its refractive power and reduces the focal length to the target of interest. With age, the lens progressively looses its ability to change shape, it is called presbyopia. Presbyopia refers to the age-related progressive loss of accommodation of the crystalline lens that result in an inability to focus on near objects. It is one of the most common refractive defects as everyone eventually develops presbyopia, increased age being the major risk factor even if other elements may influence its onset and progression (disease, medications, trauma) [American Optometric Association 2010]. Presbyopia directly affects quality of life over all in high-income countries where the main near distance activities involve writing and reading [McDonnell et al. 2003, Patel et West 2007]. It affected 1.3 billion people worlwide in 2011 [Frick et al. 2015], and up to 2 billion people in 2012 [Charman 2013].

This trend is expected to keep on increasing as fertility rates have fallen to very low levels in most world regions and people tend to live longer [He 2015]. Various theories exist to explain the presbyopia onset process like for instance changes in tissue elasticity and ciliary body [Glasser et al. 2001, Heys et al. 2004, Strenk et al. 2005, McGinty et Truscott 2006], but increased stiffness of the lens with age is the main accepted theory [Weeber et al. 2007]. With advancing age, oxidative processes within the protein constituting crystalline fibers lead to a progressive diminution of lens elasticity/flexibility and hence to a loss of accommodation [Hanson et al. 2000, Lou 2003]. Crystalline lens growth is characterized by an increase in the inelastic mass that is responsible for lens shape changes allowing for lens power variation and thus lead to a diminution in near distance focusing abilities [Goertz et al. 2014]. A great variety of symptoms occurs during presbyopia onset such as eyestrain and headaches as well as blurred vision after or when performing maintained near tasks.

1.6.3 Age-related changes to the crystalline lens: cataract genesis

According to the WHO, cataract is the leading cause of blindness [Thylefors et al. 1995, WHO Global initiative for the eliminitation of avoidable blindness 2000] and the loss of useful vision is expected to affect 16 million people worldwide [Asbell et al. 2005]. Cataractogenesis is multifactorial, and can develop from a wide variety of causes ; ultraviolet (UV) radiation (in particular UV B) are involved in cortical cataract changes [West et Valmadrid 1995, McCarty et Taylor 2002, Hollows et Moran 1981], genetic factors [Hammond et al. 2000, Hammond et al. 2001] systemic drugs, infectious diseases [Shichi 2004] but aging is by far the major risk factor for its onset [Thylefors et al. 1995, WHO Global initiative for the elimination of avoidable blindness 2000, Asbell et al. 2005]. It induces a broad spectrum of changes regarding biochemical processes taking place in the lens leading to alteration in water balance, proteins, vitamins and enzymes, being responsible for progressive loss of lens transparency [Pescosolido et al. 2016]. Age-related cataract seems to be the result of a prolonged and gradual process of crystalline proteins denaturation, which can occur principally in three different ways: repeated environmental insults (mainly UV radiation), reduction in intrinsic stability of crystalline proteins, or decline of lens cell homeostasis [Hejtmancik et Kantorow 2004, Truscott 2005]. According to Halsbeck et al. [Haslbeck et al. 2015], a protein with a chaperone-like activity called α-Crystallins seems to delay this aging-process mainly by its ability to bind, even partially, to denatured proteins (i.e βγ-crystallins) [Horwitz 2003, Datiles 2008]. However, Shiels et Hejtmancik found that the level of this unbound protein decreased sixfold in individuals with a clear lens [Shiels et Hejtmancik 2017]. Binding properties of this protein get saturated as age increases and complexes formed, aggregate to the point that they are large enough to generate opacities, and thus, to scatter light [Shiels et Hejtmancik 2017]. Based on the location of the opacities, three main types of age-related cataract exist: cortical,

nuclear posterior subcapsular; mixed forms are not unusual. Cataract onset is usually bilateral but typically asymmetrical.

1.6.4 Existing refractive means to correct presbyopia and their potential impact on dry eye signs and symptoms

Various refractive means exist to correct presbyopia, from spectacles (including simple reading glasses, bifocal, trifocals and multifocal), to CLs with different geometries (monovision, bifocals, simultaneous vision). However, CLs, once upon eye, sit in the TF, disturbing its normal structure and interact with the ocular surface possibly worsening an already unbalanced environment. Refractive surgery is another option available (cataract surgery with implantation of different geometry IOLs (monofocal, bifocal, trifocal), corneal refractive surgery) but its invasiveness, even if great steps forwards have been made, could as well disturb the ocular surface and worsen or induce signs and symptoms of dryness.

1.6.4.1 Spectacle Correction

Correction of presbyopia using spectacle is achieved with either single vision or multifocal lenses [Jalie 2008]. Single vision spectacles also known as reading spectacles, are monofocal lenses intended only to correct near vision; if patients require correction for distance vision, he will have to use separate glasses depending on the target he wants to look at. Multifocal lenses include bifocal, trifocal and progressive lenses, which require a change of gaze in order to look through the zone of appropriate correction. Bifocal and trifocal lenses present the main advantage of providing a full lateral field of vision which is not the case with progressive

lenses, that despite great improvements made to enhance the periphery of the lens, eye direction when glasses are on are limited because peripheral vision is subject to distortions due to the unwanted astigmatism surrounding the narrow corridor of progression. While progressive lenses provide a smooth transition between far- and near-vision through a narrow corridor of intermediate vision, bifocal and trifocal lenses present a drawback lying in the image jump occurring at the top edge of the transition between lenses responsible for the formation of ghost images possibly disturbing vision. Despite the few drawbacks of different spectacle approaches to correct presbyopia, it is considered as a reliable option opted by a great majority of the presbyopic population. However, spectacle dependence has been proven to impact quality of life for this age-based population [Luo et al. 2008].

Spectacles are not expected to induce dry eye. However, environmental stress (low relative humidity or high air velocity) [Koh et al. 2012] might be responsible for higher and faster evaporation rate leading to dry eye symptoms and to the consequences on the ocular surface already described earlier [Wolkoff et al. 2005, Wyon et Wyon 1987]. The influence of temperature and humidity has already been assessed in a previous study using controlled-environment chambers [Maruyama et al. 2004]. Koh et al. compared normal and dry eye subjects before and after airflow exposure evaluating TMA, TMH using OCT and TBUT [Koh et al 2012]. They found significant decrease in TMH and TMA values for the dry eye group ($P=0.027$) whereas the normal group only presented an increased TMA. It seems that having a preexisting dry eye (evaporative dry eye in this case) influences the response of the ocular surface to adverse environment exposure. Indeed, Koh et al. found a significant increased blinking rate in the dry eye patients (up to 59 % $P=0.039$) whereas no change occured in the normal eyes sample ($P=0.917$) after exposure to airflow [Koh et al. 2012].

Besides, it could be hypothesized that spectacles frames and optical lenses, depending on its shape and on the surface covered, might present some degree of protection regarding airflow exposure. Waduthantri et al. evaluated the impact of a commercially available retention spectacles for evaporative dry eye patients evaluating TBUT and symptoms at baseline and 3 months after treatment [Waduthantri et al. 2015]. A close-fitting wrap around frames seems to play an important role in decreasing signs and symptoms of dry eye by increasing peri-ocular humidity [Tsubota et al 1994, Savar et al 1979]. Waduthantri et al. found a significant amelioration of signs, symptoms, corneal fluorescein staining ($P<0.05$) for all the parameters previously cited with retention spectacles [Waduthantri et al. 2015].

1.6.4.2 CLs

Varieties of options for CL correction are available on the market: single vision (combination CL and reading glasses), monovision, bifocal designs and at last but not least, multifocal designs [Bennett 2008, Llorente-Guillemot et al. 2012]. According to a survey conducted by Morgan et al., only 16% of all CL wearers are patients with presbyopia, which shows that this interesting market remains untapped [Morgan et al. 2011]. Besides, less than a third of those over the age of 45 years (hence presumably presbyopic) were prescribed multifocal (CL): the majority of presbyopes (63 per cent) were fitted with non-presbyopic corrections (distance prescription and additional reading spectacles for near) and only a 29 per cent with multifocal lenses [Morgan et al. 2011]. The low rate of prescribing multifocal CLs designs appears to pertain to several factors: inadequate fitting skills and reluctance of the practitioner that perceives this type of fitting as being technically complex and time-consuming [Morgan et al. 2011].

CL can correct presbyopia through: movement – 'alternating images' which only works with RGPs and needs tight lids and careful fitting; or through 'simultaneous' images in which both distance and near optics are placed in front of the pupil to split the incoming light [Pérez-Prados et al. 2016]. The optic zone of the CL (corresponding to the pupil area) is composed of several powers from near to far vision, which allows both distance and near targets to be imaged on the retina at the same time. The brain suppresses the most blurred image which otherwise may alter the quality of the best image selected for a given task. This optical concept is based on blur interpretation and/or blur tolerance of superimposed multiple images on the retina formed by the miscellaneous powers of the lens [Bennett 2008]. Superimposition of images produces an increase in depth of focus for high-contrast targets, but also can cause glare and loss of contrast sensitivity; the latter is exacerbated when the contrast of the target and the lighting condition are low, especially in near vision conditions [Plakitsi et Charman 1995, Montés-Micó et Alió 2003, Montés-Micó et al. 2004].

Not every CL wearer is able to achieve acceptable comfort during the time they wear the CLs and this can eventually lead to discontinuation and dropout. Despite the fact that many studies have looked into the subject, precise estimates of CL dropout remain unclear [Weed et al. 1993, Pritchard et al. 1999, Harknett et al. 2001, Jutai et al. 2003, Richdale et al. 2007, Rumpakis 2010, Dumbleton et al. 2013b, Sulley et al. 2017]: between 12%-43% of CL wearers drop out the CL permanently; CLD (24%) and dryness (20%) being the primary reasons of discontinuation [Pritchard et al. 1999, Richdale et al. 2007, Dumbleton et al. 2013b, Young et al. 2002, Sulley et al. 2017]. According to Dumbleton et al., "discomfort" is the most frequently cited reason for discontinuing CL wear (up to 51% of lapsed CL wearers) [Dumbleton et al. 2013b], but its precise meaning to individuals is more complex to assess. CLD has been defined as the "condition characterized by episodic or persistent adverse ocular sensations related to

lens wear, either with or without visual disturbance, resulting from reduced compatibility between the contact lens and the ocular environment, which can lead to decreased wearing time and discontinuation of contact lens wear" [Dumbleton et al. 2013b]. Indeed, the terms dry eye and CLD closely interlace, since a patient that presents signs and symptoms of dry eye has more propensity to have CLD [Begley et al. 2001]. Furthermore, CLD can be associated with the following visual signs: conjunctival hyperhemia, corneal staining, meibomian glands dropout, lid wiper epitheliopathy [Dogan et al. 2018] that can be found as well in CL associated dry eye. However, it may not be associated with any of the former signs, which makes the diagnosis more difficult. Little progress has been made regarding solutions to alleviate/eliminate CLD despite great advances in technology [Efron 2017], and the resulting CL discontinuation is a real issue for the industry as recent estimates evaluate the annual loss to reach several hundreds of millions of dollars [Nichols et al. 2013]. When a CL is fitted on a patient's eye, TF is separated in a pre- and postlens TF. In addition to the changes in composition of the two created TFs, prelens TF stability is reduced due to the thinning of the lipid layer; tear volume on the anterior surface of the CL is also diminished, both events leading to increased evaporation rate and dewetting compared to the normal TF [Dumbleton et al. 2013b]. Changes observed in tear lipid composition of prelens TF are associated events but up to now, it is not clear if those changes are induced by CL itself or if they were already present before CL wear [Dumbleton et al. 2013a, Dumbleton et al. 2013b]. It has been hypothesized that CL wear might impact the function of MGs as reduced MGs function has been associated with CL wear [Pritchard et al. 1999, Richdale et al. 2007, Young et al. 2002, Dumbleton et al. 2013a]. DED in CL wearers is associated with reduction in wearing time [Pritchard et al. 1999], increased risk of dessication (and raised osmolarity) and thus higher rates of infection [Bruinsma et al. 2001]. It appears that a uniform prelens TF is considered a key factor in order

to achieve comfort, good vision, lubrication and prevent infections during wearing time [Pritchard et al. 1999, Richdale et al. 2007, Dumbleton et al. 2013b, Young et al. 2002, Dumbleton et al. 2013a, Begley et al. 2001, Dogan et al. 2018, Bruinsma et al. 2001]. Dry eye patients tend to present a thinner prelens TF than the patients without DED, which could lead to a shorter prelens thinning time and increased friction [Nichols et Sinnott 2006]. Besides, lipid layer thinning, evaporation and CL material dewetting are likely to be due to the electrostatic interaction of the polar heads of the TF with CL material leading to an alteration of the lipid layer, increased evaporation and eventually dewetting of CL surface [Nichols et Sinnott 2006]. Osmolarity also is an increased parameter in DED CL wearers since significant differences have been found between healthy and DED CL wearers [Nichols et Sinnott 2006]. This could mainly be explained by the fact that DED CL wearers present a thinner prelens TF and hence are more prone to evaporation, TF instability being one mechanism of increased osmolarity. According to Fonn et al., there is no existing relationship between lens dehydration, dryness and TF thinning time [Fonn et al. 1999]. However, it is thought that high water content CL attract polar heads components of the TF causing disruption of the prelens TF and thus evaporation and/or dewetting [Dumbleton et al. 2013, Fonn et al. 1999].

The physiological changes of an advancing age on the ocular surface and TF might decrease the tolerance for CLs and increase the risks of complications [Dumbleton et al. 2013]. However, recent findings give new insights on the possible reasons for CLD and the mechanisms involved seem to share common pathways with DED: CL is considered as one of the main risk factors for ocular surface and corneal inflammation [Wagner et al. 2011, Thakur et Willcox 2000, Robertson 2013, Sweeney et al. 2003].

Indeed, CL wear, in addition to reduced TF stability and an increased ocular staining [Purslow et al. 2005, Muselier-Mathieu et al. 2013] can potentially lead to: hypoxic stress to the corneal tissue and mechanical friction (shear stress) which in turn can jeopardize ocular surface epithelia and create an entry door for pathogens [Chao et al. 2016]. CL fitting, even if successful, can lead to typical signs of inflammation as previously described by Efron (i.e hyperhemia, pain, swelling, increased temperature and eventually loss of function, in this case CL discontinuation) and be translated by the wearer as discomfort [Efron 2016]. Upgrading the fit, changing CL material and wearing schedule or even prescribing eyedrops are the main solutions available to alleviate those signs, but we have to keep in mind that in some cases these changes are not sufficient as prolonged inflammation can lead to complications that require CL discontinuation. Chao et al. proposed a two steps mechanism [Chao et al. 2016] to explain dryness and discomfort sensations during CL wear as a result of a sub-clinical inflammation in the presence of a functionnal LFU [Belmonte et al. 2004, Rosenthal et Borsook 2012]. When a CL is inserted on a patients's eye, regardless of biocompatibility characteristics of the material or the quality of the fit, the human body will consider CL as a foreign body and as such, an immunological response is expected to occur [Thakur et Willcox 2000, Oppenheim et al. 1991].

Considering the case that CL material is free of pathogen agents (which is expected to occur in the majority of cases), sub-clinical inflammation might be induced by friction of epithelial surfaces with CL material leading to cellular damage and to the classical inflammatory cascade. Redfern et al. described the role of an innate immune response receptor family, the toll-like receptors, (TLRs) that can be activated by endogenous cellular components liberated by apoptotic cells (either due to friction of CL material with ocular surface or to raised osmolarity as found in DED) and which activation has been proven in pathophysiology of DED [Chao et al.

2016, Redfern et Mcdermott 2010]. These endogenous ligands, such as snRNPs, activate the TLRs and the NFκB pathway leading to the production and liberation of CKs and chemokines including: IL-α and β, Il-6, IL-8 and IL-17A, INF ɣ and TNFα [Pearlman et al. 2008]. The liberation of these CKs upregulates inflammation as it allows for the activation of APCs (i.e dendritic cells), the former playing a key role in spreading inflammation by promoting cellular communication as well as setting the vicious circle of DED. [Barabino et al. 2012, Baudouin et al. 2017]. TNFα is responsible for cell apoptosis through epithelial barrier disruption and promotes inflammation [Tanaka et al. 2013, Hu et al. 2013]; IL-1 is a very powerful CK that promotes further inflammation [Dinarello 2011]. IL-6 is a key CK, first due to its pleiotropism, and second because its levels in tears are highly correlated with DED severity [Chao et al. 2016, Gabay 2006], it has been found in CL wearers but not in non-lens wearers [Schultz et Kunert 2000]. IL-17 and INFɣ complete the vicious circle of ocular inflammation, both of them inducing further epithelial cells apoptosis [Chao et al. 2016, de Paiva et al. 2009a].

These pro-inflammatory CKs play a key role in CLD as IL-6, TNFα and MMP-9 are increased in healthy CL wearers [Schultz et Kunert 2000, González-Pérez et al. 2012, González-Pérez et al. 2012, Kallinikos et al. 2006]. CLD and DED seem to share similar inflammatory pathways which allow us to affirm that, even if the response is not always as strong as in DED (i.e sub-clinical inflammation), the same ligands resulting from ocular surface insult (either due to friction of CL material with ocular surface (low lubricity)/inadequate fit/ patient-related interaction with CL material leading to raised osmolarity as found in DED) trigger a common intracellular pathway leading to the liberation of pro-inflammatory CKs eventually initiating the closed loop of inflammation vicious circle as described by [Baudouin et al. 2013].

To sum up, TF factors (stability and efficient turnover), CL parameters, wearing schedule and environmental conditions [Nichols et Sinnott 2006] interact from the moment CL is inserted and can impact in different extents TF structure and ocular surface integrity. Taking into account age-related changes taking place in the LFU, it is understandable that CL fit in an older population is expected to be more challenging and, in this regard, deserves further investigation.

1.6.4.3 Surgical techniques

1.6.4.3.1 Corneal innervation and physiological role

The cornea contains the highest density of sensory nerves of the whole human body with about 44 nerve bundles entering the cornea around the limbus centripetally [Al-Aqaba et al. 2010]. Corneal sensation is made possible by large nerve fibers originating from the long ciliary nerve of the ophthalmic division of the trigeminal nerve (fifth pair of cranial nerve). Large nerve fibers enter the cornea equally in all quadrants and spread to cover the entire corneal surface [Muller et al. 1997]. Nerve fibers enter the cornea in the middle third of the stroma and then climb to the superior layers forming a plexus in the sub-Bowman's layer that densely innervates central cornea [Muller et al. 1996]. Corneal nerves finish their path in the wing cell layer of the epithelium after going through Bowman's layer and losing their myelin's sheath. Corneal nerves are the angular stone of ocular surface homeostasis constantly adapting ocular surface response to environmental challenges. Free nerve endings, more precisely the intra epithelial sensory terminals, are stimulated in response to different stimuli (temperature, mechanical and chemical inputs between others) giving rise to afferent impulses that will travel along the ophthalmic branch of the trigeminal nerve to the central nervous system (CNS) [Marfurt et al. 2010]. It allows for the detection of potentially damaging stimuli and the

induction of defensive reflexes [Chao et al. 2016] provided by the efferent pathways such as lacrimation, blinking and regulation of different lacrimal glands secretions. Furthermore, nerve bundles play an important trophic role for the corneal epithelium, modulate immune response as well as wound healing process [Belmonte et al. 2004]. The different surgical procedures that will be described later on, use the cornea as an entry door to perform the medical gesture. As such, it is expected that corneal integrity is somehow jeopardized leading to alterations of the closed loop of the LFU and to the main anterior segment adverse effect of ocular surgery: DED.

1.6.4.3.2 Cataract surgery and dry eye

It is the most commonly performed elective surgery with an estimated 19 million procedures being performed every year worldwide [Trikha et al. 2013, Donaldson et al. 2013]. The WHO is counting on a significant increase of this surgery by the year 2020 (estimated 32 million procedures a year) as number of people over 65 is expected to increase significantly [Brian et Taylor 2001].

Furthermore, IOL implantation is gaining popularity in presbyopic population mainly due to the necessity to be spectacle independent and to bypass the limitations of corneal surgery to correct high refractive defects [Charman 2014]. Thus, IOLs are used in cataract patients as well as in young presbyopic subjects.

Multifocal IOLs, like for spectacles, present a wide ranges of correction modalities, from bifocal, trifocal to extended depth of focus geometries and within these designs, multifocality can be achieved based on two optical principles: refraction and diffraction.

Before any surgical treatment, biometric measurements are required in order to calculate the power of the IOL to be implanted; the accuracy of these measurements mainly rely on TF quality and stability [Montés-Micó 2007]. In the case tear TF is jeopardized by one of the multifactorial causes of DED, accuracy of measurements is reduced and could lead to unconformity with post-surgical expected refractive outcomes. Pre-operative assessment of the patient is one mandatory requirement in order to obtain reliable measurements.

Surgical treatment for cataract involves the removal of the clouded lens and its replacement with an IOL; the main goal of this surgical procedure being to regain visual acuity getting rid of the opacified and light scattering lens and correct adequally the refractive defect of the patient. However, in the case that a clear lens is replaced for refractive purposes, the term “refractive lens exchange” or “clear lens exchange” is used. The indication for surgery mainly relies on patient’s visual needs, the risks, benefits, as well as patient's expectations.

Following topical anesthetics (eyedrops) instillation, small temporal clear corneal incision, around 2.8 mm in length, is made in order to access the anterior chamber [Lam et al. 2013]. In order to reach the opacified lens, a circular incision is made to open the anterior capsular bag, this is called capsulorrhexis. The lens, now accessible, is then disaggregated using ultrasounds (phacoemulsification) and the pieces that result from its disruption are sucked out of the eye [Lam et al. 2013]. Posterior capsular bag is conserved as it will be used as a support for the prosthesis to be implanted. An IOL is then inserted and placed properly in the capsular bag using the haptics. Newer technique, previously used for the creation of lamellar flaps in laser assisted in situ keratomileusis (LASIK) (described later on in the present work), has been adapted to the cataract surgery [Gogate et al. 2005, Donaldson et al. 2013] from corneal incisions to capsulotomy and previous fragmentation of the lens before

phacoemulsification: FLACS is far more accurate than mechanical devices at the cutting edge of technology and better procedure safety and clinical outcomes are expected, [Nagy et al. 2009] with reports demonstrating higher capsulorrhexis precision and reduced ultrasound power during the phacoemulsification [Donaldson et al. 2013, Palanker et al. 2010]. One drawback of this technique is the pressure to which the peri-limbic conjunctiva is subjected by the suction ring, which has been proven to reduce goblet cells density and be identified as an important risk factor in the pathology of LASIK-induced DED [Friedman et al. 2011, Rodriguez et al. 2007].

Risk factors for dry eye following cataract surgery, regardless of the technique used are well known, but the mechanisms through which they induce dry eye are yet to be established. The following risk factors could be related to disruption of corneal nerves and harm to the epithelia through the surgical procedure : eyedrops containing active agents/preservatives affecting the epithelium pre, peri and post-surgery [Salomão et al. 2009, Walker 2004], forced opening of the eyelid with the blepharostat prevents normal blinking thus an even repartition of the TF on ocular surface [Cho et Kim 2009], long microscopic light exposure times which leads to thermal damage [Salomão et al. 2009, Walker 2004, Cho et Kim 2009], repeated irrigation of the ocular surface may impact the goblet cells density and further impact TF stability [Salomão et al. 2009, Walker 2004, Cho et Kim 2009, Nakamori et al. 1997)] and for sure incision location and accuracy that will be discussed later on.

One of the main difficulties in assessing dry eye is the lack of gold standard test [Chao et al. 2016], which eventually leads to a variable prevalence of the disease. Dry eye after cataract surgery is as such expected to give discordant values from one study to another mainly due to the different diagnostic tests used and their inherent specificity and sensitivity [Li et al. 2007,

Kasetsuwan et al. 2013]. However, the great majority of studies agree that the surgical procedure induces/worsens signs and symptoms of ocular dryness [Salomão et al. 2009, Cho et Kim 2009]. Furthermore, a recent report from TFOS [Chao et al. 2016], shares new insights regarding inflammation processes and dry eye signs onset that could highlight the mechanisms involved at the ocular surface. As said before, transection of corneal nerves interrupts the feedback loop of the LFU, and corneal/conjunctival damage induced by surgical procedure are expected to generate inflammation.

According to Baudouin et al., damage or ongoing disease processes to any component of the LFU are expected to induce signs and symptoms of DED [Baudouin et al. 2013]. DED, as defined earlier, is a multifactorial disease and as such, it is expected that in cataract surgery induced DED, various factors act as triggers in its onset: neurogenic inflammation and epithelial (corneal and conjunctival) damage induced by surgical gesture being the more important [Kasetsuwan et al. 2013]. On one hand, epithelial damage during surgery is the root of the activation of stress-associated intra-cellular transduction cascades involving MAP-kinase and NF- κB [Baudouin et al. 2013, Srinivasan et al. 2017, Li et al. 2004, Li et al. 2006, Luo et al. 2004, Luo et al. 2005], responsible for the liberation of pro-inflammatory CKs: IL-1β, IL-6, TNFα, INFɣ, MMP-1,-3,-9,-13, being the main pro-inflammatory messengers involved in DED pathogenesis/vicious circle [Baudouin et al. 2013, Srinivasan et al. 2017, Li et al. 2004, Li et al. 2006, Luo et al. 2004, Luo et al. 2005, Stevenson et al. 2014, Stern et al. 2013, Brignole-Baudouin et al. 2017, Calonge et al. 2010, Redfern et al. 2015, DEWS 2007]. The spread of inflammation signaling molecules on ocular surface further upregulates expression of their receptors and adhesion factors that facilitate recruitment and migration of inflammatory mediators promoting inflammation process [Stern et al. 2013, Brignole-Baudouin et al. 2017]. Activation signals occurring after the union of the pro-inflammatory CKs on epithelial cells

surface either promotes liberation of other CKs or induces apoptosis responsible for the positive vital staining of cornea and conjunctiva. Dessicating stress induced by surgery and epithelial damage gives rise to an immediate « innate » ocular surface response, which is a broad-spectrum answer to the surgical damage [Baudouin et al. 2013]. On the other hand, surgery-induced corneal nerve damage induces corneal sensitivity impairment [Chao et al. 2016].

This further affects negatively blink rate and reflex-induced lacrimal secretion [Calonge et al. 2010] which eventually leads to TF instability and increase in osmolarity values [Calonge et al. 2010]. According to the TFOS II definition and classification report, the new definition of DED places osmolarity increase (at the same level as ocular damage and TF instability) as key etiologies of DED onset [Craig et al. 2017]. Tear hyperosmolarity induces epithelial cell hyperosmolarity leading to the liberation of pro-inflammatory CKs inducing cellular apoptosis and the corresponding ocular surface staining. Previous studies have investigated the pathophysiology of dry eye after cataract surgery: Kasetsuwan et al. found a significant dry eye signs and symptoms in a healthy population after cataract surgery; the prevalence of dry eye diagnosed with OSDI was 9.8%, the incidence of dry eye diagnosed with different tests was 68.4% with TBUT, 11.9% with Schirmer test and 58.7% with the Oxford Schema Staining respectively 7 days following surgery [Kasetsuwan et al. 2013]. Cho et al evaluated 70 eyes from 35 patients with no signs or symptoms of dry eye before cataract surgery.

All of the parameters evaluated in this study BUT, Schirmer test, TMH and subjective symptoms worsen after cataract surgery until the second month post-operatively [Cho et al. 2009]. Li et al. used the ocular surface disease index questionnaire (OSDI), TBUT, Schirmer test, corneal and conjuntival staining as well as impression cytology before and after cataract

surgery and found DED in all patients after the surgical procedure [Li et al. 2007]. Khanal et al. and Kohlaas et al. found a decrease in central corneal sensitivity which was associated with a reduced tear production [Khanal et al. 2008, Kohlhaas et al. 1997]. Ram et al. [Ram et al. 2002] evidenced a slight decrease in TBUT test and Schirmer's test. Oh et al. found a significant decrease in TBUT and conjunctival cell count at one day from surgery; however, full recovery of corneal sensation at one month was not achieved and dry eye symptoms were worse and did not return to normal levels even after 3 months [Oh et al. 2012].

A former cataract surgery technique, called extracapsular cataract extraction requires a larger incision and thus is expected to induce more corneal sensitivity loss [Hoffman et al. 2005]. This is confirmed by Oh et al. and Khanal et al. as a 2.8 mm and 4.1 mm incisions respectively were performed in each study and lead to significant differences in corneal sensitivity recovery as the more reduced incisions led to complete recovery within 1-3 months and only to a focal diminution of corneal sensation whereas the larger incision lead to a longer time of complete recovery. Incision shape, depth and regularity clearly affect post-surgery healing [Khanal et al. 2008, Oh et al. 2012]. Furthermore, micro incisional procedures such as phaco emulsification are expected to induce less hyopesthesia than more conventional techniques [Ram et al. 2002, Oh et al. 2012, Hoffman et al. 2002, and Kissner et al. 2007]. Corneal sensitivity is significantly reduced just after cataract surgery [Oh et al. 2012]. However, the healing process is already ongoing as new neurites rapidly emerge, and after 25 days NGFs are released to regenerate the subepithelial corneal axons [Marfurt et al. 2010, Park et al. 2016].

Goblet cells are located on the conjunctiva, they are responsible for mucin secretion and play a key role in TF stability [Kashima et al. 2014] and ocular defense against foreign bodies [Hodges et Dartt 2013], so it is easily understandable that any dysfunction in these cells could

lead to evaporative dry eye [Kashima et al. 2014, Hodges et Dartt 2013, Sutu et al. 2016]. Several studies report a decrease in goblet cell density after cataract surgery [Li et al. 2007] which can last up to three months after the surgical procedure [Oh et al. 2012]. However, the reason of this decrease is multifactorial: inflammation, and more precisely MMPs, IL-1 and TNF α induce goblet cell apoptosis [Park et al. 2016, Kashima et al. 2014, Sutu et al. 2016, and Pflugfelder et al. 2013] so it is not surprising that goblet cell loss occurs during the acute phase of inflammation. Besides, potential toxicity of antiseptic agents used during the surgical procedure as well as topical multi-dose eyedrops with preservatives seem to play a role in the onset of dry eye signs and symptoms: BAK, is one of the most commonly used preservatives in ocular topical drugs and is recognized to induce, apart from goblet cells apoptosis, conjunctival squamous metaplasia, disruption of the corneal epithelium barrier and tear film instability between other [Baudouin et al. 2010].

Authors	Sample	Tests performed	Results
[Kasetsuwan et al. 2013]	92	OSDI Oxford Staining Schirmer I TBUT	DED Prevalence 7 days postoperatively OSDI: 9.8% Oxford Staining: 58.7% Schirmer I: 11.9% TBUT: 68.4%
[Li et al.2007]	37 (50 eyes)	NEI-VFQ25 OSDI BUT Schirmer Test I Fluorescein staining (Oxford and van Bijsterveld Impression Cytology TMH with fluorescein	NEI-VFQ25 Improvement in functional indices and ocular pain aggravated before/after surgery OSDI did not show any changes BUT significantly worse (P<0.01) Fluorescein staining (Oxford and van Bijsterveld Increase of staining at one-month post-surgery. OSDI did not show difference before/after surgery Impression Cytology TMH disminshed significantly 70% >0.3mm pre-surgery and 70% post-surgery maintained at 1 month and 3 months after surgery

Authors	Sample	Tests performed	Results
[Ram et al. 2002]	23 (25 eyes)	Schirmer test with anesthesia TFBUT	The mean preoperative Schirmer score was 4.80 mm ± 2.01 (SD) and the mean postoperative score, 3.80 ± 2.40 mm The mean preoperative TFBUT was 4.00 ± 1.87 seconds (range 0 to 9 seconds) and the mean score at the last follow-up, 3.40 ± 1.60 seconds
[Cho et al. 2009]	49 (98 eyes)	Dryness symptoms TMH (SL and graticule) Schirmer test without anesthesia Fluorescein TBUT	Significant aggravation in dryness symptoms/TMH/Schirmer/FBUT at 2 months post-operatively ($p<0.05$)
[Kohlhaas et al. 1997]	26	Corneal sensitivity (Draeger aesthesiometer)	Markedly reduced corneal sensitivity in central corneal and discretely hyposensitive in the 6 o'clock position
[Khanal et al. 2008]	18	Corneal sensitivity (Non-Contact Corneal Aesthesiometer (NCCA) Osmolarity (freezing point depression) Tear Evaporation Turnover rate (TTR) (automated scanning fluorophotometer)	A significant decrease was seen postoperatively in central corneal sensitivity at 3 days ($p < 0.001$), 2 weeks ($p < 0.001$), 1 month ($p = 0.003$) and 3 months ($p = 0.009$) Osmolarity significantly rises 3 days after surgery but decreases across the 3 months post-surgery (no statistical differences with pre-operative values) Significant increase in evaporation at 3 days and 2 weeks post-surgery. Significant reduction in TTR at 3 days until two weeks post-surgery

Authors	Sample	Tests performed	Results
[Oh et al. 2012]	30 (48 eyes)	Own symptoms questionnaire Corneal sensitivity (Cochet–Bonnet esthesiometer) Schirmer Test 1 Fluorescein BUT	Significant differences in overall symptomatology score in comparison with pre surgery ($p<0.01$) Decrease of goblet cells density at 1 day post-surgery ($P<0.01$) but not at 1 month or 3 months Significant decrease in mean corneal sensitivity at one day post-surgery ($p<0.05$) that comes back to normal values at one month Not significative differences for Schirmer test TBUT significantly decreased at day 1 post surgery.
[Kissner et al. 2007]	26 (52 eyes)	Corneal surface aberrations (corneal wavefront instrument): Trefoil and astigmatism	Surgery increased Trefoil and astigmatism ($p<0.05$)
[Park et al. 2016]	34 (8 eyes)	Ocular symptoms FTBUT Schirmer I Test Corneal fluorescein staining (NEI scale) Corneal sensitivity (Cochet-Bonnet aesthesiometer Multiplex immunoassay kits	Significant increase at 1 day, 1 month, 2 months post-surgery ($p<0.05$) for the dry eye group. Significant differences post-surgery between dry eye and non-dry eye groups (TBUT values being lower in the dry eye group $P<0.01$) Significant lower FTBUT in the dry eye group ($p<0.01$) Significant lower Schirmer I in the dry eye group ($p<0.05$) Significant corneal staining differences between groups (dry eye group presenting the higher staining score $p<0.01$) Corneal sensitivity showing a significant higher threshold in the dry eye group ($p<0.05$) Significant increase in CKs levels at 1 month and 2 months after suergery in comparison with day 1 post surgery.

Table 3. Prevalence of Dry Eye after Cataract Surgery

1.6.4.3.3 Corneal refractive surgery

- PRK

PRK procedure requires previous corneal anesthesia because corneal epithelium is removed manually before the application of an excimer laser in order to reshape the stroma and thus, modify corneal power. It is a surface technique anterior to Laser Epithelial Assisted Keratomileusis (LASEK) and LASIK procedures. Indeed, PRK is based on previous corneal epithelium removal using alcohol solution (corneal epithelium is discarded) [Helena et al. 1997, Browning et al. 2003]; the underlying corneal tissue is then reshaped using the excimer laser. No flap is needed for this procedure. Recovery is longer than LASIK technique since it takes more time (around a week) for epithelial cells to grow [Browning et al. 2003]. Eye infection is more frequent with this technique due to corneal exposure [Helena et al. 1997, Browning et al. 2003]. PRK induces temporary decrease in sub basal corneal nerves density for up to a year, and complete recovery might take as long as two years [Erie 2003]. Other studies stand that recovering corneal sensitivity could only take three months [Shikawa et al. 1994, Campos et al. 1992]. However, Ozdamar et al. reported sensibly disminished BUT and Schirmer tests (up to 50%, 6 weeks after after the procedure in comparison with controls [Ozdamar et al. 1999]. Campos et al. [Campos et al. 1992] as well as Pérez Santonja et al. [Pérez-Santonja et al. 1999] found that up to 96% of the PRK patients completely recovered corneal sensitivity after three months post-surgery. On the other hand, Hong et al. [Hong et Kim 1997] found different results revealing that up to 73 % of patients complained of DED and about half of the cohort had significantly reduced BUT. This is in agreement with both Lee and al. [Lee et al. 2000] and Nejima et al. [Nejima et al. 2005] in which studies significantly reduced tear secretion was found post-surgery after three months.

Authors	Sample	Tests performed	Results
[Erie et al. 1997]	14 (24 eyes) eyes from 14 patients	Confocal microscopy (epithelial and central thickness/keratocyte density/corneal nerve density)	Significant increase in epithelial thickness (21%) ($p<0.001$) at 12 months post-PRK and was maintained at 36 months. No change in stromal thickness from 1-36 months after surgery ($p=0.35$) Keratocyte population at the anterior stroma did not reach pre-operative values ($p<0.01$) Decrease up to 60% of subbasal nerve bundle density at 12 months post-surgery ($p<0.001$) before almost reaching pre-operative values ($p=1.0$)
[Ishikawa et al. 1994]	17 eyes from myopic subjects	Corneal sensitivity with two group of patients: Shallow photoablation (0 to 30 µm) Deep photoablation (31 to 70 µm)	Superior corneal sensation loss in the deep ablation group with no recovery within one month of the surgery. Corneal fluctuations in sensations present up to 6 months post-surgery in this group
[Ozdamar et al. 1999]	32 (64 eyes)	-Schirmer test -FTBUT	Significant decrease in Schirmer/FTBUT values post-surgery in comparison with the fellow eye (control) ($p=0.0001$) 6 weeks after the surgical procedure

Authors	Sample	Tests performed	Results
[Perez-Santonja et al. 1999]	18	Corneal sensitivity (Cochet-Bonnet aesthesiometer): Central zone and 2 mm from that central zone (nasal, inferior, temporal, and superior)	Return to pre-operative values at 3 months for central cornea and 1 month for the other corneal areas evaluated ($p>0.05$)
[Hong et Kim 1997]	220 eyes	Schirmer test TBUT	No significant changes in Schirmer test values were found at 6 months post-surgery 47.8% of eyes showed a reduced TBUT of which 72.7% complained of dry eye symptoms.
[Lee et al. 2000]	21 (36 eyes) eyes from 21 patients	Schirmer with anesthesia FTBUT	Significant decrease in Schirmer values at 3 months ($p=0.0011$) which tend to come back to normal values at 6 months ($p=0.3080$) Same trend for FTBUT values at 3 months ($p=0.0001$) and 6 months ($p=0.0678$)

Table 4. Prevalence of Dry Eye after PRK

- **LASEK**

This surgical technique is based on PRK procedure. The main difference with PRK is that the peeled corneal epithelium called an epithelial flap (which is discarded in the PRK technique) is repositioned after photoablation as for the stromal flap in the LASIK procedure [Ambrósio et Wilson 2003]. Alcohol is used to weaken adhesions between stroma and epithelium [Shah et al. 1998]. Factors such as alcohol concentration (usually between 18-25%) and exposure time play a key role in post-operative healing [Kim et al. 2002]. The detached epithelium is then moved to the periphery for the stromal ablation to be performed [Kim et al. 2002]. After ablation, the epithelium is repositioned with a spatula and a therapeutic bandage CL fitted in order to protect the vulnerable corneal epithelium. This technique is considered as well as a surface technique because no stromal flap is needed to perform corneal reshaping. Autrata et al. compared 184 eyes of 92 patients between PRK and LASEK with a 2 years follow-up and no post-operative complications occurred, no signs or symptoms of dry eye were found in this sample [Autrata et al. 2003]. Herrmann et al. found that LASEK patients obtained higher OSDI scores up to 2 months post-surgery but that these values returned to baseline at 3 months [Herrman et al. 2005] whereas Dooley et al. and Horwath-Winter et al. did not find any difference between baseline, 3 months, 6 months and 12 months [Dooley et al. 2012, Horwath-Winter et al. 2004].

Authors	Sample	Tests performed	Results
[Herrmann et al. 2005]	20 eyes from 10 patients	Schirmer test with anaesthesia Schirmer test without anaesthesia FTBUT Fluorescein staining of the cornea Corneal aesthesiometry (Cochet-Bonnet) Symptomatology	-Schirmer test with anesthesia was reduced at 3 months post-surgery ($p<0.05$) Schirmer test without anesthesia was reduced at 2 and 3 months after surgery ($p<0.05$) FBUT was reduced at 1 week and 1 month after surgery ($p<0.05$) Corneal staining was increased at 3 days and one week after surgery ($p<0.05$) Symptomatology was increased after surgery ($p<0.05$) excepted at 3 months
[Dooley et al. 2012]	35 eyes	OSDI Schirmer test with anaesthesic Osmolarity (TearLab)	OSDI values did not change during the follow-up period Schirmer values changed significantly at 12 months Osmolarity did not change across the follow-up period
[Horwath-Winter et al. 2004]	37 eyes from 21 patients	Symptoms Corneal sensitivity (Cochet-Bonnet) FTBUT Schirmer I Fluorescein staining of the cornea	No statistical difference in symptomatology was found. Corneal sensation reduced up to one month after the surgical procedure ($p<0.05$) FTBUT was significantly reduced at 1 week and 1 month ($p<0.05$ respectively) No changes in Schirmer results Significant increase in corneal staining at one week ($p<0.05$) No changes in lissamine green staining

Table 5. Prevalence of Dry Eye after LASEK

- **LASIK**

LASIK is a surgical corneal option for treating refractive errors [Sutton et Kim 2010] including presbyopia. This surgery technique is enjoying a growing popularity [Duffey et Leaming 2005] and presents a high success rate [Solomon et al. 2002, Liu et al. 2008, Miller et al. 2001, Marinho et al. 1996] as more than 90% of patients achieve 20/25 or better without glasses [Danasoury et al. 1999, Knorz et al. 1998]. However, DED is one, if not the most common adverse effects of LASIK surgery [Shoja et Besharati 2007, Chao et al. 2014, Miller et al. 2001, Salomão et al. 2009, Quinto et al .2008, Ang et al. 2001] even for people that did not show any signs or symptoms of the disease before the surgical procedure [Hovanesian et al. 2001, Mian et al. 2009].

LASIK is a surgical procedure in which a corneal flap (around 120-160 micrometers) is created by a blade called microkeratome/ or a femtosecond laser (the former inducing less DED signs and symptoms) [Salomão et al. 2009], and then reclined in order to proceed to the stromal ablation with an excimer laser (photoablation) which will reshape the cornea and modify the patient visual defect according to the amount of corneal tissue removed. LASIK-Induced neurotrophic epitheliopathy (LINE) [Wilson 2001, Ambrósio et al. 2008] refers to the neurotrophic component of this surgical procedure induced dry eye that mainly results from the nerve damage occurring during flap creation and stromal ablation. Indeed, the damage is so important that regrowth of subasal nerves takes up to five years to reach a density almost similar (but still inferior) to that before surgery [Erie et al. 2005]. Flap creation was initially performed using blades (microkeratome), but the emergence of newer technologies such as femtosecond lasers [Suga 2002] have allowed to reduce signs of dry eye. Indeed, flap creation is quite different in architecture: [Jagow et Kohnen 2009] based on the tool used to do it, the

peripheral shape will differ significantly: the blades from the microkeratome only allow for a single mechanical continuous cut whereas the femtosecond laser uses repeated impacts to photodisrupt the tissue providing a more regular peripheral flap shape [Tran et al. 2005, Durrie et Kezirian 2005], less aberrations and better visual outcomes [Tran et al. 2005, Durrie et Kezirian 2005, Kezirian et Stonecipher 2004]. Stromal reinnervation after corneal injury is eased by precise apposition of wound edges at the flap margin [Patel 2010] which is thought to be explained by the realignment of proximal and distal Schwann cell channels [Chan-Ling et al. 1987, Tervo et al. 1985] as no reinnervation after penetrating keratoplasty has been evidenced when no Schwann cell channel could have been affixed [Patel et al 2007].

Once the flap is reclined, ablation is performed and destroys mid stromal nerves; knowing that stromal nerves are limited to the anterior 60% of the corneal stroma [Al-Aqaba et al. 2010] it is expected that most of them are destroyed across the ablation process (although nerves that run through the hinge are not expected to suffer any damage). Thus, LASIK surgical process induces double damage to the cornea; during the flap creation where the subbasal nerves are cut, and during the excimer laser stromal ablation where stromal nerve trunks are destroyed by the laser. It is estimated a 90% reduction of central nerve fibers density in the first month following surgery [Denoyer et al. 2015].

Various studies investigated dryness symptoms after LASIK surgery and found that ocular symptoms of dryness tend to reach a peak between one week and three months after surgery, regardless of preexistent dry eye condition [Autrata et Rehurek 2003, Dooley et al 2012, Vroman et al 2005, Mian et al 2007, Mian et al 2009, Wildon 2001, Ambrósio et al. 2008, Erie et al. 2005, Sugar 2002, Jagow et Kohnen 2009, Tran et al. 2005, Durrie et Kezirin. 2005, Kezirian et Stonecipher 2004, Patel 2010, Chan-Ling et al. 1987, Tervo et al. 1985, Patel et al.

2007, Denoyer et al. 2015]. Hovasenian et al. obtained a 48% rate in self-reported DED at 6 months after surgery using a questionnaire [Hovasenian et al. 2001]. Patel et al. found that around 50 % of patients undergoing LASIK surgery will complain of dryness up to 6 months after the procedure [Patel et al. 2007]. Shoja et al. obtained an incidence rate of 20% for DED that lasted for more than 6 months after surgery [Shoja et Beshariti 2007].

Clinical signs post LASIK surgery are often highly variable [Feng et al. 2012]. When performed on DED patients, LASIK procedure worsens tear metrics and staining (reduced Schirmer test and BUT, increased rose Bengale and fluorescein staining) as reported by Toda et al. [Toda et al. 2001]. Tao et al found a decreased tear volume over time after LASIK surgery [Tao et al. 2010]. Various authors reported increased osmolarity values up to 6 months after LASIK [Autrata et Rehurek 2003, Lee et al. 2000] whereas Chao et al. only reported a peak at one day and a return to basis level at 6 months [Chao et al. 2015]. Chao et al. reported corneal sensitivity to reach baseline values between 6-12 months after surgery [Chao et al. 2014]. This is in agreement with previous studies that show that recovery of NFD 6 months after LASIK was less than 25 % [Chao et al. 2014] and could take, as said earlier, up to 2-5 years to reach basis levels [Patel 2010, Moilanen et al. 2008].

Authors	Sample	Tests performed	Results
[Vroman et al. 2005]	94 eyes from 47 patients	Corneal sensitivity (Cochet-Bonnet) Schirmer with anaesthesic TFBUT Ocular surface staining (NEI scale) OSDI	Significantly diminished at 1 week/1 month/ 3months/ 6 months ($p<0.001$) Schirmer values were significantly reduced only at 1 week post-surgery ($p<0.05$) TFBUT significantly reduced at 3 months post-surgery ($p<0.01$) No difference in ocular surface staining Significant increase in OSDI score at 1 week/1 month/ 3months/ 6 months ($p<0.01$)
[Mian et al. 2007]	66 eyes of 33 patients	Corneal sensitivity (Cochet-Bonnet) Schirmer test with anaesthesia FBUT Corneal fluorescein staining Lissamine green staining with Oxford scale OSDI	Significant reduction in corneal sensitivity at 1 week/1 month /3 months/ 6months/ 12 months ($p<0.0001$) Increase in Corneal fluorescein at 1 week post-surgery ($p=0.01$) FBUT/Schirmer test and conjunctival staining did not show significant changes after surgery. Increase in OSDI score at 1 week and one month ($p<0.0001$) respectively that stabilized at 3 months
[Shoja et Besharati 2007]	190 eyes	FBUT Schirmer I Corneal fluorescein staining Central corneal sensitivity Symptomatology	Significant decrease of Schirmer and TBUT at 1 month/ 3 months/ 6 months ($p<0.05$) Corneal sensitivity reduced at 1 month and 3 months but returned back to pre-operative values at 6 months

Table 6. Prevalence of Dry Eye after LASIK surger

-SMILE

The advent of lasers in the ophthalmic field to perform corneal refractive surgery lead to the concept of lenticule extraction. A precursor of modern techniques was called refractive lenticule extraction (ReLex) which consisted in the use of a picosecond laser in order to create a flap and an instrastromal lenticule removed manually; however, the lenticule created [Krueger et al. 2008, Ito et al. 1996] with the laser required further manual dissection leading to irregular surfaces. The apparition of femtosecond laser introduced a new procedure called Femtosecond Lenticule Extraction (FLEx) [Sekundo et al. 2008], leading to similar refractive results as LASIK [Shah et Shah 2011] but provided a longer recovery time due to laser related settings regarding energy delivered on corneal tissue between other things; however, further modifications lead to significant improvement in recovery times [Shah et Shah 2011].

Following this momentum, Small Incision Lenticule Extraction (SMILE), a refractive surgery technique using a femtosecond laser was developed to perform corneal reshaping [Reinstein et al. 2014]. This procedure aims to create an intrastromal lenticule (corresponding to the amount of power to remove) using the laser and then to extract it using a 2-3 mm tunnel incision usually located in the supero-temporal side of the cornea, eliminating the need to create a flap. This surgical procedure no longer needs excimer laser ablation nor the creation of a flap making this technique less invasive than LASIK. Since no flap is needed for SMILE procedure, it is expected that recovery is faster with this technique. Denoyer and al. found 80% of the 30 SMILE patients did not use any eye drops at 6 months post-surgery versus 57% of the 30 LASIK patients [Denoyer et al. 2015]. Furthermore, no patient from the SMILE group used any kind of eyedrops whereas 20% of the LASIK group were using tear substitutes

frequently. This data was accompanied by a higher osmolarity in the LASIK group. According to Li et al. SMILE patients reported less DED symptoms three months after surgery in comparison with LASIK patients [Li et al. 2013].

- Corneal onlays/inlays

The main advantage of this procedure over the previously described techniques is double: no tissue removal is needed, and it allows for the preservation of the more conventional options for correcting presbyopia [Lindstrom et al. 2013]. Corneal onlays/inlays are optical devices designed to alter corneal shape, they are inserted in the cornea of the patient. The use of highly biocompatible materials combined with surgical techniques at the edge of technology (i.e femtosecond laser) raised the positive outcome for the patients [Laroche et al. 1995, Waring et Klyce 2011]. Monovision is the most effective and common option to correct presbyopia [Fernandez et al. 2013] and it is the best-acknowledged approach regarding corneal inlays. Refractive power change is achieved through the alteration of the anterior corneal curvature, by the refractive index of the biomaterial, or by the combination of both [Evans et al. 2001]. If the lenticule is placed between the epithelium and the stroma it is called corneal onlay (epikeratoplasty/epikeratophakia); however, if it is placed within the corneal stroma it will be called corneal inlay (refractive keratoplasty). Three main types of corneal inlays exist to correct presbyopia and depth of placement in corneal stroma depends on each design: refractive inlays (alteration of the refractive index by the mean of bifocal optics), reshaping inlays (changes in corneal curvature) and inlays that use small aperture optics in order to increase depth of focus [Arlt et al. 2015]. Femtosecond laser is now widely used as it provides a more dependable flap than microkeratome [Papadopoulos et Papadopoulos 2014,

Binder 2010, Moarefi et al. 2017] and allows for the creation of stromal pockets improving accuracy of implantation depth and inlay centration.

Refractive inlays modify central corneal power to correct near vision, it is achieved through modification of the refractive index of the cornea centrally by the means of bifocal optics [Arlt et al. 2015, Papadopoulos et Papadopoulos 2014]. It is based on multifocality with a plano center surrounded by rings of changing addition to provide intermediate and near vision powers [Bouzoukis et al. 2012]. Surgical procedure uses a femtosecond laser to perform a lamellar cut at a depth of around 280 µm temporally, no flap is needed. Then, a tunnel (stromal pocket) is made in order to reach the pupil area where the inlay is injected and placed [Limnopoulou et al. 2013]. Cornea reshaping inlays present no intrinsic refractive power upon insertion as they are made of a material, which presents the same refractive index as the cornea, usually hydrogel, allowing fluids, nutrients and oxygen permeability, essential to maintain corneal homeostasis [Moarefi et al. 2017]. The reshaping of the cornea is achieved thanks to its positive-meniscus shape, which increases the central radius of curvature of the cornea overlaying the material due to the induced rise of corneal anterior surface profile [Arlt et al. 2015]. Since the edges are thinner than the center, it creates a continuous decrease in power from the center to the periphery of the implant giving to the overlying remodeled cornea a hyperprolate profile providing multifocality [Garza et al. 2013]. A flap is created using a femtosecond laser but unlike the previous inlay type, the disruption takes place at an inferior depth between 120-200 µm [Moarefi et al. 2017], the inlay positioned and the flap put back in place.

The small aperture optics inlays are a black film-like ring that increases the depth of focus (to restore near and intermediate vision) by blocking the peripheral light rays, it is basically a

pinhole placed in front of the pupil area [Tomita et al. 2013]. A femtosecond laser is used to create a lamellar cut at a depth of around 250 µm and the implant inserted and placed on the center of the constricted pupil area.

Dry eye after corneal inlay implantation is mainly due to the flap creation, which is the same technique as for LASIK surgery. Yilmaz et al. [Yilmaz et al. 2011] reported the same outcomes for the eye that was implanted with the inlay and the fellow eye that underwent LASIK surgery regarding dry eye. We already described the inflammatory mechanisms causes by surgical gesture and flap creation (damage to the afferent nerve bundles between other with a spared zone corresponding to the hinge) responsible for dry eye signs and symptoms. However, since no LASIK is applied to the corneal stroma, less deep nerve damage is expected to occur in comparison with LASIK. The stromal pocket technique is less invasive tan the flap technique and as such, a reduced incidence of dry eye post-surgery is expected as well as a shorter recovery period [Binder 2010, Limnopoulou et al. 2013]. However, the lamellar cut (flap creation) is still the more indicated technique as in cases of inlay decentration, the need to explantation, or when the inlay implantation is coupled with LASIK surgery, the flap allows for an easier access to the biomaterial and for the stromal zone to be treated by LASIK [Greenwood et al. 2016]. Further studies are needed to assess the long term outcomes of the lamellar cut and tunnel incision performed for the refractive inlay and the small aperture optics implants [Dexl et al. 2011] on dry eye signs and symptoms. Corneal inlays represent a good option for presbyopia correction and fulfill the requirement of an aging population willing to be spectacle independent. The continuous evolution of corneal inlays and their methods of insertion reduce the nerve damage to the cornea and the outcome of the surgery with faster recovery time and less signs and symptoms of dry eye.

Adverse ocular sensation in this age-based population, play a key role in CL wear, during the pre-operative assessment of the patient and following surgery; this is why understanding its onset and triggering factors will give new insights on patient's symptomatology as well as regarding the efficacy of treatments in DED. As reviewed in earlier, global knowledge regarding ocular sensation, damage and its associated pathways have significantly increased; however, the thorough mechanisms through which DED rises and further affects ocular surface homeostasis are not fully understood due to its high complexity and to the numerous mechanisms involved. Further research regarding the neuropathogenesis of impaired ocular sensation in DED is warranted in order to deepen the knowledge regarding homeostasis mechanisms, ocular response to nerve damage and its role in DED onset and perpetuation in a population that faces new challenges due to aging but also to the emergence of new refractive techniques.

CHAPTER 2

JUSTIFICATION

2.1 Actual situation

The scientific significance of epidemiological studies relies on a precise definition and classification of the disease, which, until recently, represented the main challenge for DED as no consensus was adopted regarding dry eye objective and subjective diagnostic criteria [Stapleton et al. 2017]. Furthermore, the absence of gold standard tests to diagnose the pathology, which goes hand to hand with an acknowledged heterogeneity between signs and symptoms, make the interpretation and comparison of different epidemiological studies more difficult to assess. The TFOS II Epidemiology Report reviewed epidemiological studies from around the world and found a prevalence ranging between 5-30% in population over 50 years old [Stapleton et al. 2017], lower values representing the more severe forms and the higher, mild to moderate stages of the disease. According to this literature review, symptomatic DED has a higher prevalence in women than men and more common in Asian than Caucasian.

However, even if DED is considered a symptoms-driven disease [DEWS 2007], epidemiological studies focusing only on clinical signs are source of a considerable variation in prevalence values. Standardization of diagnostic criteria and clinical tests are the great goal to achieve. The actual situation could explain the difficulties researchers are facing when it comes to diagnosis criteria; dry eye clinical tests evaluating the same parameter don't have the same sensibility and specificity in diagnosing the disease, tests used often only assess one aspect of the pathology, no gold standard or combination of tests have been chosen to evaluate clinical features; adding to the previous statements a great extent of DED signs, all of them with distinct severity, sensitivity to pain specific to each individual, age-related/ongoing ocular surface pathologies and systemic conditions with ocular impact or age-related changes taking place in the LFU, make a proper diagnosis based on both signs and symptoms challenging.

When coupling signs and symptoms, even with the discrepancies named above and the caution to take when looking at the outcomes of different studies, one important information stands out as specified by Stapleton et al.; women had 1.3-1.5 x the prevalence of men [Stapleton et al. 2017]. The overall prevalence of the disease was very similar (from 8.7-30.1%) to the studies only focusing on symptoms, confirming the 2007 hypothesis that DED is a symptom driven pathology [Stapleton et al. 2017].

According to the TFOS Epidemiology Report, prevalence of the disease based on symptoms and on clinical signs both show a gradual shift from aged 50 [Stapleton et al. 2017]. It seems very likely that important age-related changes take place in the LFU at this period of life (that could be due to a combination of aging eye and systemic changes), unbalancing the complex homeostasis mechanisms and leading to onset or excacerbation of signs and symptoms of dryness. Indeed, when it comes to risk factors for the disease, increased age, again depending on diagnostic criteria and variability of the definition of DED, appears to be the most consistent factor associated with dry eye [Schaumberg et al. 2009 , Ahn et al. 2014, Um et al. 2014, Lu et al. 2008, Moss et al. 2008, Jie et al. 2008, Viso et al. 2009, Hashemi et al. 2014, Vehof et al. 2014, Schaumberg et al. 2003, Moss et al. 2000 , Lee et al. 2002].

CL wear is recognized to play a role in setting up signs and symptoms of dryness [Paulsen et al. 2014, Tan et al. 2015]. CLD occurs in almost half of the CL wearing population [Dumbleton et al. 2013a]. It is considered, almost at the same level as dryness (24% and 20 % respectively) [Sulley et al. 2017] as the main reason for discontinuation. Discontinuation in CL wearers has been investigated and recent estimates give a large extent of values ranging from 12% to up to 43%, so that real dropout prevalence remains unclear [Weed et al.1993, Pritchard et al. 1999, Harknett et al. 2001, Jutai et al. 2003, Richdale et al. 2007, Rumpakis 2010, Dumbleton

et al. 2013b]. However, a recent study from Sulley et al. gives new insights regarding age-based CL retention rates showing that people over 45 years of age tend to discontinue more CL wear than the younger group (78% versus 63%); material, geometry, replacement schedule being additional factors influencing discontinuation [Sulley et al. 2017]. Age-related changes taking place in the LFU could potentially further increase dropout rates. Indeed, as it will be discussed in this work, CL insertion and its interaction with ocular surface induce changes in tear film metrics and ocular surface physiology that could trigger signs and symptoms of dryness or even worsen an already unbalanced state.

Dry eye assessment preceding ocular surgery (corneal refractive surgery, cataract surgery) is now a widely accepted and recommended practice among practitioners [Chao et al. 2016] as the pre-operative ocular surface state can influence outcomes of the surgical gesture. Both surgical procedures are invasive but to different extents and corneal damage (cellular and nerve damage) induced by the incision and laser application might never recover to preoperative state, giving rise to abnormal ocular surface tear dynamics and eventually to the initiation/exacerbation of signs and symptoms of dry eye.

The widespread use of VDTs for both professional and recreative purposes lead to eye fatigue and to reduced blinking frequency both potentially worsening signs and symptoms of patients with the disease [Ayaki et al. 2017, Uchino et al. 2013, Uchino et al. 2008]. Indeed, increased blinking interval leads to longer exposure time of the corneal and conjunctival epithelia more particularly in a region of meniscus induced thinning (corresponding to the black line seen with fluorescein sodium staining) where hyperosmolarity is expected to be much higher than in the rest of the ocular surface [Bron 2011a, Zubkov et al. 2013, McMonnies 2015]. Combined with limited eye movements, which occurs when performing activities requiring attention

such as reading a book, watching a movie on a tablet or working on a computer, more localized cellular damage is expected to occur inducing/exacerbating signs and symptoms of dryness.

DED has become a public health issue worldwide as its impact on healthcare systems is undeniable [Stapleton et al. 2017, Brown et al. 2009, Clegg et al. 2006, Galor et al. 2012, Mizuno et al. 2012, Patel et al. 2011a, Uchino et al. 2014, Waduthantri et al. 2012, Yamada et al. 2012, Yu et al. 2011, Fiscella et al. 2008, Wlodarczyk et Fairchild 2009, Bielory et Syed 2013, Farrand et al. 2016]. A striking example of the economic burden of DED is emphasized by a multicentric study designed to assess the annual cost of DED patients management by ophthalmologists in Europe: for 1000 patients with the disease in Europe ranged from USD 0.27 million in France to USD 1.10 million in United Kingdom [Clegg et al. 2006]. When it comes to United States, amounts reached USD 3.84 billion a year for the entire country [Yu et al. 2011] separated as follow: USD $678, $771, and $1267 for the mild, moderate and severe forms of the disease respectively. These patient-related costs also affects global productivity as the necessity of treatment and office visits generate an estimated productivity loss of USD $12 686, $12 569, $18 168 for the mild, moderate and severe forms of the disease respectively [Yu et al. 2012]. Interestingly, Mizuno et al. calculated the direct annual cost for the year 2010 and found that each DED patient spent USD $323±219 for drugs, USD $165±101 for healthcare, and USD $530±384 for punctal plug placement showing the impact of the disease on health expenses [Mizuno et al. 2012]. In addition to the economic cost, the social impact of the disease gained a foothold and showed reduced quality of life due to the major impact of the disease on patient's visual function with more frequent visits to the physician, higher frequency of depression and reduced workplace productivity.

2.2 Epidemiology of aging: an economic burden

Numerous studies have looked into the influence of aging on dry eye signs and symptoms and according to estimates from the Physician's Health Studies, the Women's Health Study, the Beaver dam offspring study, the Blues mountains study between others, age is a significant risk factor for the disease as people over 50 years old present a prevalence of dry eye increasing every 5 years steps with women being more affected [Schein et al. 1997, Moss et al. 2004, Schaumberg et al. 2003, Schaumberg et al. 2009, Schein et al. 1999, Paulsen et al. 2014, Chia et al. 2003]. The 15% prevalence estimates in the 1997 study from Schein et al. [Schein et al. 1997a] does not seem to represent adequately the actual situation as this value is now more than 20 years old and that overall population is expected to have increased significantly.

Indeed, the world population is expected to rise from 7.2 billion individuals in 2012 to 8.3-10.9 billion by 2050 [United Nations. World Population Prospects: The 2012 Revision. June 13, 2013]. This increase in world population is accompanied by significant aging, as recent estimates from the Lancet Series on Ageing expect 2 billion people over 60 years old by 2050 [The Lancet. Series on Ageing. 2014; November 6]. According to the Report of the Inaugural Meeting of the TFOS [Chao et al. 2016] increased prevalence of DED with age is widely acknowledged.

With the increasing aging population and according to estimates of number of people over 60 years old (2 billion people by the year 2050) [The Lancet Series in Ageing 2014] and an approximate prevalence of 25% for the disease [Stapleton et al. 2017], 500 million people will suffer from dry eye only in this age-based population. The burden to become for the society is thus undeniable.

2.3 Hypothesis and objectives

The aim of this project is to evaluate changes in tear film metrics and ocular signs induced by different types of refractive correction (corneal refractive surgery, intraocular lens implantation and contact lenses) focusing on the older population, since the prevalence of DED increases with age and due to presbyopia, most people over 45 need refractive correction for distance, intermediate or near vision, or all three.

The main goals of the study are as follow:

-Assess the impact of refractive means to correct presbyopia and their potential impact on ocular surface, signs and symptoms of dry eye, through two main research axis:

1-To assess the impact of CL material and wearing schedule on tear film metrics and ocular surface in a presbyopic population. To reach that goal, three research studies were set up:

- To investigate the clinical performance of a new contact lens (CL) material and physiological responses of tear film and ocular surface parameters in a presbyopic population over their first day of CL wear.
- To investigate the clinical performance of two multifocal soft contact lens materials and the physiological response of tear film and ocular surface parameters in a presbyopic population over a month of contact lens wear.
- To assess and compare the effect of the corneo-scleral lenses (C-ScL) and scleral lenses (ScL) on tear film parameters and central corneal thickness (CCT) in healthy presbyopic subjects.

2- Assess the impact of ocular surgery to correct presbyopia and their potential impact on ocular surface, signs and symptoms of dry eye:

- To assess the impact of cataract surgery on tear film metrics, ocular surface and MG function in a presbyopic population before and after cataract surgery and IOL implantation.

CHAPTER 3

GENERAL METHODOLOGY

3.1 General design of the studies

To implement this manuscript and form the doctoral thesis, a wide range of measurements were taken regarding optometric variables in a presbyopic population equipped/implanted with different refractive correction options. All of the participants were presbyopic, aged 40 or older and underwent all examination and surgery, if applicable, in the following research centers or clinical facilities:

- Oftalvist Clinic (Consultation).
- University of Valencia's Optometry Research Group (GIO) (Consultation and CL fitting).

To describe the changes in tear film metrics and ocular signs induced by different types of refractive correction, one literature review and four clinical studies were planned as follow:

- Review assessing the impact of all refractive means to correct presbyopia and their potential impact on ocular surface, signs and symptoms of dry eye.
- To investigate the clinical performance of a new contact lens (CL) material and physiological responses of tear film and ocular surface parameters in a presbyopic population over their first day of CL wear.
- To investigate the clinical performance of two multifocal soft contact lens materials and the physiological response of tear film and ocular surface parameters in a presbyopic population over a month of contact lens wear.
- To assess and compare the effect of the corneo-scleral lenses (C-ScL) and scleral lenses (ScL) on tear film parameters and central corneal thickness (CCT) in healthy presbyopic subjects.

- To assess the impact of cataract surgery on tear film metrics, ocular surface and meibomian gland function in a presbyopic population before and after cataract surgery and IOL implantation.

A prospective non-randomized study design was chosen for all aforementioned manuscripts.

The same optometrist practitioner (Edouard Lafosse) and the same Ophthalmologist (Francisco Pastor Pascual), who posteriorly performed the surgery, screened the patient to avoid bias in the results.

This set of prospective, studies were approved by the Institutional Ethics Committee of the University of Valencia. Participants were explained his/her rights as a research subject and then signed a statement of Informed Consent for the comprehensive ophthalmic examination as well as for the surgery and the subsequent collection of data for further analysis. Each of the previous study was performed according to the tenets of the Declaration of Helsinki.

Inclusion criteria were:

- Presbyopic participant
- Aged 40 or older
- Neophyte CL wearer
- Refractive defect between +6.00/-10.00 Spherical
- Corneal astigmatism inferior to 1.00 D
- Best Corrected Visual Acuity (BCVA) equal or better to 0.0 logMar
- Willing to comply with the constraints of appointments for the monitoring of participants

Refractive data will be expressed in diopters. Spherocylindrical refractive errors will be converted in vectors in order to be suitable for statistical analysis. [Mico et al. 2014, Thibos et Horner 2001].

To do so, spherocylindrical refractive errors (Sphere [S], Cylinder [C], and Axis [E] will be converted in coordinates of the refractive vector (M, J_0, J_{45}) using the following formulas:

$$M = S + C/2$$

$$J0 = -\frac{C}{2} * Cos(2E)$$

$$J45 = -\frac{C}{2} * \sin(2E)$$

M coordinate represents the spherical equivalent, whereas the others components, representing the cylindrical refractive defect, are basically two Jackson Crossed Cylinders with their respective axis a 0^0-90^0 (J_0) and 45^0-135^0 (J_{45}). The components of refractive vector give the location of the circle of least diffusion relative to the retina (M) and about the amount of astigmatism with the rule (WR)/against the rule (AR) (J_0) or skewed (J_{45}).

3.2 Tests used to evaluate symptomatology

Nociceptors, representing the great majority of corneal sensory neurons, are stimulated by inflammation and cellular damage, which is further worsened by the stimulation of mechano-nociceptors due to the increase in friction forces between eyelids and ocular surface [Belmonte et al. 2004]. Hyperosmolarity and cooling of the ocular surface following tear evaporation stimulate cold thermoreceptors inducing dryness sensation and discomfort

[Parra et al. 2010, Parra et al. 2014]. A comprehensive assessment of patient symptoms is mandatory as unpleasant dryness sensations (i.e. discomfort) are the most defining features of DED [DEWS 2007, Nichols et al. 1999]. Furthermore, a great number of patients present conflicting signs and symptoms of dry eye [Schein et al. 1997b, Begley et al. 2003, Nichols et al. 2004], making the diagnostic much more difficult. Most of the existing questionnaires were designed to identify the symptoms associated with the clinical findings and from the information collected, develop diagnostic tools according to them [Belmonte et al. 2017]. The difficulty to manage the disease is based on the discrepancy between clinical tests [Kallarackal et al. 2002, Moore et al. 2008] and patient-reported symptoms [Begley et al. 2003, Nichols et al. 2004, Mizuno et al. 2010, Sullivan et al. 2010, Fuentes-Paez et al. 2011]. When performing the patient case history in our everyday practice, patients self-expressed symptoms and sensations are difficult to quantify and standardize as no repeatable structure to the interview is preset [Wolffsohn et al. 2017] and the general term “discomfort” can be understood in many other ways making difficult addressing this aspect of the disease [Belmonte et al. 2017]. Besides, when translated to other languages, which was the case for the different studies forming part of the present thesis, words can take different meanings, which can impair the original purpose of the question and influence the answer [Begley et al. 2001, Uchino et al. 2006, Abetz et al. 2011]. According to Wolffsohn et al., assessing patients symptoms in a repeatable fashion is a key factor for its ability to serve various purposes: assessing if the patient requires further examination oriented towards clinical signs of the disease, monitor the evolution of symptoms over time and subjectively assess the efficacy of the treatment [Wolffsohn et al. 2017, Begley et al. 2003, Nichols et al. 2004, Sullivan et al. 2010]. The following questionnaires were chosen for the different studies that will be described in the present thesis.

3.2.1 OSDI

This questionnaire is the most commonly used for DED clinical trials [Wolffsohn et al. 2017]. It is a Patient Reported Outcome (PRO) questionnaire following the US Food and Drug Administration (FDA) requirements regarding psychometric testing .[Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance, [Guillemin et al. 2012]. Originally developed by the Outcomes Research Group at Allergan Inc (Irvine, California) [Walt et al. 1997] the OSDI is a 12-item questionnaire designed to assess the frequency of symptoms of ocular irritation consistent with DED and their impact on vision-related functions. DED can be graded using a score attributed to each question. Its validity has been acknowledged in the diagnosis of DED [Özcura et al. 2007]. The questions asked in the questionnaire refer to the "last week period" and present subscales allowing for the evaluation of treatment efficacy and impact on quality of life patients with different DED etiologies [Chang et al. 2009, Yuksel et al. 2010, Russo et al. 2007, Stevenson et al. 2000]. Three different subscales compose the questionnaire: the first one (6 questions), focusing on ocular symptoms (blurred vision, poor vision), the second one (3 questions) investigating vision-related function and limitations (for several activities such as reading, driving at night, watching TV, working on a computer), and the last one (3 questions) aiming to assess environmental triggers (wind, humidity levels, air conditioning). The OSDI is scored on a scale from 0 to 100, with higher scores representing higher symptomology. Each of the 12 questions can be scored based on the frequency of the symptoms from 0-4 points where 0 denotes "none of the time" and 4 indicates "all of the time". OSDI = [(sum of scores for all questions answered) × 100] / [(total number of questions answered) × 4]. Based on the score, patients symptoms can be classified as normal (0-12), mild DED (13-22), moderate DED (23-32) and a score and severe (33-100). Indeed, literature proved the efficiency of this

questionnaire for its discriminating abilities between severity levels: normal, mild-moderate and severe forms of DED, highlighting the significance differences (P<0.001) in subscales and total scores between the aforenamed groups [Simpson et al. 2008, Schiffman et al. 2000, Srinivasan et al. 2008]. Furthermore, OSDI questionnaire showed concomitance with other validated questionnaires such as: the Symptoms Assessment in Dry Eye (SANDE) [Amparo et al. 2015]; the Standard Deviation of Eye Dryness (SPEED) [Asiedu et al. 2017, Finis et al. 2014]; the five-item Dry Eye Questionnaire (DEQ-5) [Galor et al. 2015].

However, one of the limitations of this questionnaire is its moderate correlation with clinical findings [Simpson et al. 2008, Chalmers et al. 2012]. OSDI test is attached in Annex 1.

3.2.2 DEQ-5

Five-Item Dry Eye Questionnaire is a shortened version of the DEQ developed by Begley et al. [Begley et al. 2002(3)]. It is composed of 5 questions related to the severity of eye discomfort visual disturbance, dryness and tearing and how visual instability impacts the participant over a one-month recall period [Chalmers et al. 2010, Wolffsohn et al. 2017]. DEQ-5 is scored on a scale going from 0-22 with higher scores representing, higher symptomology. According to a previous study from Chalmers et al. 2010; [Chalmers et al. 2010] a score between 6 and 11 represents mild to moderate ocular symptoms, and values > 12 represents severe ocular symptoms. According to Galor et al. 2015 [Galor et al. 2015] the results obtained with this questionnaire are concurrent with the OSDI even if few manuscripts talk about the DEQ-5 in clinical practice or clinical trials. DEQ-5 is attached in Annex 2.

3.2.3 CLDEQ-8

CLD occurs in almost half of the CL wearing population [Dumbleton et al. 2013]. It is considered, almost at the same level as dryness (24% and 20 % respectively) [Sulley et al. 2017]

as the main reason for discontinuation. Therefore, it is logical that PRO questionnaire focused on this issue. CLDEQ-8 rises from a longer and older version initially called CLDEQ [Begley et al. 2000, Begley et al. 2001] that was designed at the same time as the longer version of the DEQ-5 (i.e DEQ). Its validity is based on its ability to correlate, through the 8 questions asked, to the overall opinion of CL wearers and to reflect CL wearers' degree of satisfaction [Chalmers et al. 2012]. CLDEQ-8 is attached Annex 3.

3.3. Techniques used for assessing tear meniscus parameters

Tear meniscus can be defined as the accumulation of tears between the lid margin and the bulbar conjunctiva; it is present on both superior and inferior lids [Santodomingo-Rubido et al. 2006]. It is believed that tear meniscus contains up to 90% of the total volume of the TF [Holly 1985], which makes it a useful clinical parameter to assess TF volume and its possible changes over time. The importance of the TM for the studies forming part of the present thesis requires a global knowledge of the background of TM assessment in order to justify the devices that were used to measure its parameters.

Several parameters can be extracted and analyzed from the simple triangular shape of the tear meniscus and give valuable information regarding total volume of the tears. Among them, tear meniscus height. TMH is defined as the straight-line distance between the upper and the lower edges of the tear meniscus. It is one of the most used TM metrics as a wide range of devices allow to measure this parameter from slit lamp to optical coherence tomography. However, it is important to underline that a wide range of values has been found in literature as it will be further described, depending on the delimitation of the edges of TM: some authors considered the height as being the distance between the upper limit of the TM and the upper limit of the inferior eyelid which has been defined as "Absolute" TMH (TMH-A) [García-Resúa,

et al. 2009, Mishima et al. 1966, Lamberts et al. 1979] and others as the distance between the upper limit of the TM and the brighter reflex of the meniscus [Port et Asaria, 1990, Santodomingo-Rubido et al. 2006]. Tables 7, 8, and 9 gather the main publications about this topic and underline the importance to know what parameter is being measured in order not to jeopardize results. Another TM parameter, TMR, is defined as the curved line joining the anterior profile/borderline of the TM. It has been demonstrated that evaluating this parameter is clinically accurate in diagnosis of dry eye [Mainstone et al. 1996, Bron et al. 1998, Shen et al. 2009, Yokoi et Komuro 2004]. TMD represents the distance between the most anterior part of the tear meniscus and the anterior part of the bulbar conjunctiva. TMA is defined as the triangular area formed by the anterior corneal boundary, anterior boundary of the lower eyelid and anterior borderline of the tear meniscus. [Czajkowski et al. 2012]. TMH, TMD, TMR, TMA parameters all refer to the tear meniscus at the center of the lower lid. We will see the main devices used to measure these parameters but also the correlation with each other and the importance to assess and follow-up these metrics in DED.

3.3.1 Slit lamp technique with graticule

It is possible to evaluate TMH vertically at 6-o'clock position (in other words, at the center of the lower lid), non-invasively using SL with a calibrated graticule inserted into the eyepiece [Santodomingo-Rubido et al. 2006] along with the appropriate magnification (usually 40x), giving TMH values between 0.12 mm and 0.35 mm in healthy subjects [Santodomingo-Rubido et al.2006, Miller et al. 2004, Lim et Lee 1991].

The following tables summarize mean values for TMH-A and TMH-R with the graticule technique and emphasize the importance of specifying which definition of the TMH is used in clinical practice.

Authors	Mean ± SD TMH	Parameter
[Santodomingo et al. 2006]	0.12 ± 0.05 mm	TMH-R
[Tomlinson et al. 2001]	0.35 ± 0.11 mm	TMH-A
[Jordan et Baum 1980]	0.30 ± 0.06 mm	TMH-A
[Miller et al. 2004]	0.22 ± 0.08 mm	TMH-A
[Papas and Vajdic 2000]	0.15 ± 0.04 mm	TMH-R
[Lim et Lee 1991]	0.19 ± 0.05 mm	TMH-A
[Lamberts et al.1979]	0.23 ± 0.09 mm	TMH-A
Mean ± SD TMH	**0,22 ± 0,07 mm**	TMH

Table 7. Mean TMH-R and TMH-A obtained with the SL graticule technique

3.3.1.1 Slit lamp with image analysis software

Another technique uses the SL beam height to measure TMH and gives a mean value of 0.32 mm [Guillon et al. 1997]. The image capture technique uses a video system coupled to the SL to take a picture of the tear meniscus (the edges of the meniscus are posteriorly bounded manually and the value calculated using a software that converts the number of pixel to a physical distance). The picture is then extracted to an image analysis software allowing precise measurement of the TMH. More repeatable values (between 0.17 and 0.43 mm in healthy eyes) have been found with this technique in comparison to the other SL techniques due to: the absence of eye movement when making the measurement and the higher resolution of the image (0,02 ± 0,05 mm p=0,01) (r=0,52, p< 0,0001) and (0,01 ± 0,03 mm, p=0,16) (r=0,56,

p=0,0001) for the graticule and image capture techniques respectively [Johnson et Murphy 2005]. Table 8 shows the Mean TMH-R and TMH-A values obtained with the image analysis technique and Table 9 shows the comparison between graticule and image analysis software systems.

Authors	**Mean ± SD TMH**	**Parameter**
[Johnson et Murphy 2005]	0.34 ± 0.05 mm	TMH-A
[Doughty et al. 2002]	0.19 ± 0.09 mm	TMH-R
[Glasson et al. 2006]	0.43 ± 0.11 mm	TMH-A
[Kwong and Cho 1998]	0.24 ± 0.07 mm	TMH-A
[Zaman et al. 1998]	0.18 ± 0.11 mm	TMH-R
[Santodomingo et al. 2006]	0.13 ± 0.04 mm	TMH-R
Mean ± SD TMH	**0,24 ± 0,07mm**	TMH

Table 8. Mean TMH-R and TMH-A obtained with the image analysis technique.

Parameter	TMH (Mean ± SD) Image analysis software system	TMH (Mean ± SD) Graticule technique
TMH-R	0,17 ± 0,07 mm	0,14 ± 0,05 mm
TMH-A	0,34 ± 0,08 mm	0,26 ± 0,08 mm

Table 9. Comparison between graticule and image analysis software systems.

Slit lamp technique for assessing TMH presents one limitation, which is the difficult limitation of the TM superior edge, which gave rise to TMH-A and TMH-R distinction. However, some authors tried to overcome this constraint by the use of fluorescein (TMH-F) defined as the distance between the lower lid margin and and the upper limit of the stained tear meniscus) which was proven to reduce tear film stability possibly leading to reflex lacrimation and overestimation of TMH values: the fluorescein volume instilled was not controlled and the strip potentially could induce reflex lacrimation [Mainstone et al. 1996, Johnson et Murphy 2005, Lime et Lee 1991, Patel et al. 1985].

3.3.2 Other existing devices

An optical pachymeter can also allow the assessment of TMH giving similar results (mean values between 0.16 and 0.38 mm) [Johnson et Murphy 2005, Port et Asaria 1990, Jones et al. 2002]. Eventually, TMH can also be evaluated using the Placido disc-based device corneal topographer (Oculus GmbH, Wetzlar, Germany). The technique is mainly the same as photographing with a SL but presents major advantages like for instance the infrared diodes used as a light source that prevent reflex tearing [Baek et al. 2015]. Reflective meniscometry is a non-invasive technique allowing to measure TMR; it relies on the projection of a network

of white and black stripes (of known dimensions) onto the meniscus at the lower lid margin. Using the inferior tear meniscus as a concave mirror it is possible to assess TMR after capturing the picture with a digital camera and exporting it to an image analysis software [Bandlitz et al. 2014]. Reflective meniscometry presents a sensibility of 88,9% and a specificity of 77,8% in measuring TMR [Yokoi et Komuro 2004] which makes it a valuable tool in the diagnosis and follow-up of dry eye. Furthermore this technique showed acceptable agreement with the SL technique (r=0,51 p = 0,001)[Ibrahim et al. 2010].

3.3.3 Optical Coherence Tomography

Details of the AS-OCT imaging technology have been described previously [Izatt et al. 1994, Radhakrishnan et al. 2001, Kiernan et al. 2010]. This non-invasive technique provides high-resolution images (4-10µm) [Kiernan et al. 2010, Maeda 2010] of the tear meniscus. An AS-OCT (High speed and tri-dimensional) coupled with a slit-lamp is performed in order to assess the tear meniscus parameters of the inferior eyelid using the B-scan mode and scanning at 6 o´clock the upper part of the inferior eyelid vertically to the apex of the cornea. The cross-section image obtained allow the visualization of the tear prism and can be bounded manually in order to assess TMA [Bitton et al. 2007, Czajkowski et al. 2012] defined as the triangular area formed by the anterior corneal boundary, anterior boundary of the lower eyelid and anterior borderline of the tear meniscus. These measurements can be realized from the images taken by the AS-OCT using an image software [http://imagej.nih.gov/ij/]. According to Czajkowski et al., anterior segment Spectral OCT presented sensitivity and specificity for dry eye diagnosis of 80.56% and 89.33% for TMH,86.11% and 85.33% for TMA, 77.78% and 52.7% for TMD respectively. Studies have shown that AS-OCT is a valuable tool for quantification of tear meniscus parameters and therefore this technique could be used in diagnosis and follow-

up of dry eye patients [Ibrahim et al. 2010, Qiu et al. 2011].

3.3.3.1 Slit lamp SL Scan-1 coupled with OCT (Topcon) (TMA)

In the present thesis, TMA images were acquired using the SL SCAN-1 (Topcon, Japan), a spectral-domain OCT integrated into a slit lamp using an 840 nm super-luminescent diode and providing 5000 A-scans/s with an axial resolution of 8-9 µm and a lateral resolution inferior to 20 µm. Tear meniscus cross-sectional area (TMA) of all participant was obtained manually using the B-scan mode and scanning at the 6 o'clock position of the cornea with a cross line centered on the inferior lid edge. Settings remained constant throughout the whole experiment for all subjects. Participants were asked to blink normally and then hold their blink during the acquisition of the scan.

Three consecutive scans were performed for each participant. Images were then exported to an image analysis software called image J [http://imagej.nih.gov/ij/] that allows, after manual delimitation of the edges of the central tear meniscus, to calculate TMA in mm^2. It is undoubtful that the best objectivity would be achieved with a program recognizing the borders [Tittler et al. 2011] as manual delimitation of TMA is dependent on the examiners' marking. However, Canan et al. [Canan et al. 2014] showed that TMA measurements with FD-OCT are reproducible and reliable.

Figure 3.1. An illustration of the slit-lamp SL SCAN-1 (Topcon, Japan)

3.4 Pachymetry: OCT (CCT) Visante Zeiss

Several devices and imaging techniques have been used over the years in an attempt to measure corneal thickness [Garcia-Resua et al. 2012]. Optical coherence tomography is a non-invasive high-resolution imaging technology that relies on the analysis of the interference between a signal coming from a structure under analysis and a reference signal [Podoleanu 2012]. It allows for the obtention of cross-sectionnal, two-dimensional images. Visante™ OCT [Carl Zeiss, Meditec, Dublin, CA, USA] is a TD-OCT which uses an optical source [infra-red light (1310nm)] to scan the anterior segment of the eye to construct a 2-dimensional image and an interferometer (Michelson interferometer) where a reference mirror and an optical splitter are used to produce a reference beam. The interference of light resulting from the difference between the reference optical source and the beam signal returned is processed to image the anterior segment of the eye, hence the AS-OCT.

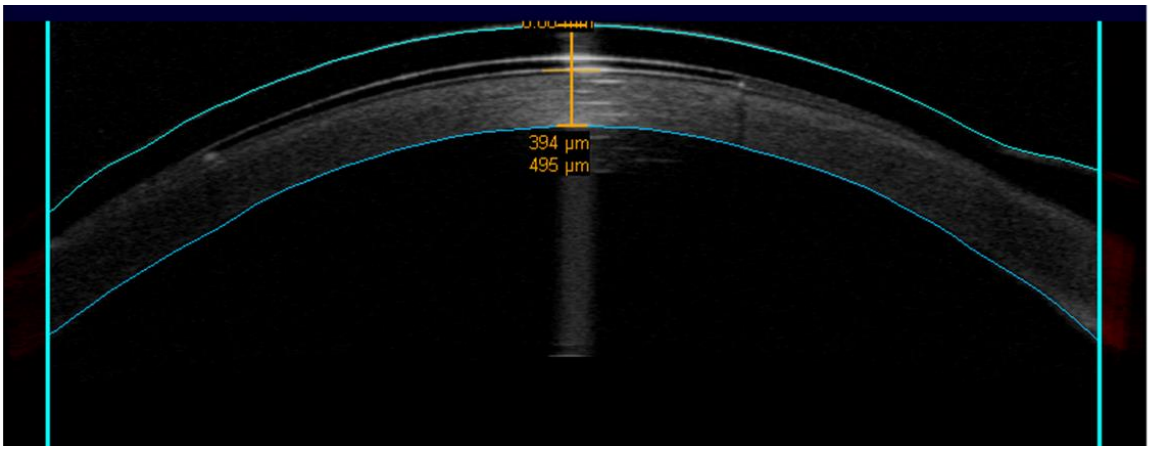

Figure 3.2. CCT obtained with Visante™ OCT [Carl Zeiss, Meditec, Dublin, CA, USA]

The axial resolution of the Visante™ is 18 µm and the transverse resolution is 60 µm. Various studies have looked into the repeatability of the device regarding pachymetric values [Otchere et Sorbara 2017, Mencucci et al. 2012, Mohamed et al. 2007] and OCT Visante™ showed good

repeatability and satisfactory agreement when compared with the former gold standard (ultra-sound pachymetry) and Scheimpflug imaging device both for normal [Sadoughi, et al. 2015] and diseased corneas [De Sanctis et al. 2007]. The global corneal "pachymetry map" protocol of the Visante OCT was used to capture 8 radial scans centered on the corneal vertex reflection [Radhakrishnan et al. 2001]. Three consecutive scans were carried out for each eye by the same examiner in order to calculate mean CCT.

3.5 Tear Osmolarity (I-Pen/TearLab)

Osmolarity can be defined as concentration of dissolved, active particles in a solution. These active particles, in tears, are called electrolytes [Taskapiliet al. 2015] and are mainly represented by cations sodium and potassium, anions chloride and bicarbonate: major contributors to osmolarity [Murube 2006, Stahl et al. 2012]. Tear hyperosmolarity is, along with loss of tear film stability, a key stone of the pathophysiology of DED [DEWS 2007/2017]. Objective measurement and monitoring of osmolarity data are as such a valuable source of information in the diagnostic of the disease. Mathematical models have estimated osmolarity values at the site of tear break up to be as high as 1900mOsm/L demonstrating the importance to monitor TF osmolarity values [Peng et al. 2014b]. Furthermore, an increased variability in osmolarity values has been evidenced in patients with DED [Keech et al. 2013]. Osmolarity at the TM normally is well defined and ranges between 270-400mOsm/L [Sullivan et al. 2010] and, according to mathematical models [Gaffney et al. 2010], is recognized to be very inferior to the mean values found at the ocular surface. Furthermore, in healthy subjects, osmolarity values taken from the lower meniscus are very stable and present a low variability [Lemp et al. 2011)]. Mean values of 302 ± 9.7 mOsm/L [Tomlinson et al. 2006] with an inter-eye variation of 6.9 ±5.9 mOsm/L [Sullivan et al. 2015] were reported at the TM [Bron et al. 2017] in healthy subjects.

Several existing devices are available on the market to measure osmolarity either by sampling of directly in situ. [Tomlinson et al. 2010]. The two following technologies will be briefly detailed, as they were not used in the present work; however, it is important to describe them as the devices used in the study rely on recent advances in technology and facilitate clinical use.

Vapor pressure technique [Terry et Hill 1978] relies on the principle that, at the same pressure and temperature, the vapor pressure of a solution is lower than that of the pure solvent. The more particles are present in a solution, the longer it will take to evaporate. The difference with water's time of evaporation gives osmolarity. It requires up to 5 µL of tears [Tiffany et al. 1994]. Given that the total amount of tears is 7-8 µL; even if the device performs the measurement fastly, DED patients are expected to have less tear available which could possibly enable the measurement. This technique has been relegated to a second option [Lemp 1995] and its clinical use requires practice in order not to trigger any reflex tearing that could jeopardize the measurement.

Freezing point depression is the second technique, it presents the advantage to require only a reduced amount of tears (0.2µL), which is suitable for DED patients; however, this device is space-consuming and is more indicated for research purposes [Gilbard et al. 1978]. Water freezes at 0° Celsius, but water mixed with different solutes (like in the tears) will freeze at lower temperatures hence the name "depression". The lower the freezing temperature, the higher the osmolarity values. This device can be used in DED but is subject to errors [Nelson et Wright 1986, Sullivan 2005] due to evaporation occurring directly from the sample; besides this device is space consuming and would hardly fit in an optometry practice.

The last technique, electrical impedance, is based on the recent advances in technology and allows taking measurements at the point-of-care, presenting the great advantage to be much more suitable than the previously described techniques for clinical practice. Electrical impedance relies on the electrical charges carried by the ions contained in a solution, for instance, the tear fluid. The higher the concentration of ions in a solution, the higher the osmolarity values.

3.5.1 TearLab Osmolarity System

Tear film osmolarity can be measured using a laboratory-on-a-chip system [TearLabTM Corp, San Diego, CA] in order to analyze the electrical impedance of a 50 nL tear sample from the infero-lateral tear meniscus. This device was commercialized in 2012 [US FDA. k083184, TearLab Osmolarity System. April 23, 2009] and has been the subject of numerous studies regarding its utility in the diagnosis, grading of severity and follow-up in DED [Farris et al. 1986, Versura et al. 2010, Tomlinson et al. 2010, Potvin et al. 2015].

Figure 3.3. An illustration of the TearLab osmolarity System (TearLabTM Corp, San Diego, CA)

The pen of the device is gently lowered towards the external third of the inferior lid until the tip of the pen touched the inferior tear meniscus and could collect the sample. An electronic

check card is used every morning in order to ensure accuracy of the measurements. In order to diagnose mild to moderate dry eye subjects, a thresold of 308 mOsm/L is now widely accepted in clinical practice [Lemp et al. 2011] and was used in the following studies as a cut-off value for DED. Readings between 308 and 325 mOsm/L are representative of mild-to-moderate dry eye, and values above 325mOsm/L indicate the severe state of the disease [Foulks et al. 2009].

3.5.2 I-Pen Osmolarity System

The other device used in the present work to assess tear osmolarity is the i-Pen Osmolarity System (I-Med Pharma Inc; 2016) commercially available since 2017 [Government of Canada. Medical Devices Active Licence Listing #94538. I-PEN, Life Care Ltd. Available from https://health-products. canada.ca/mdall-limh/index-eng.jsp. Accessed May 15, 2017]. This device also relies on electrical impedance to assess osmolarity of the ocular tissue on the inferior palpebral conjunctival membrane [i-Pen Osmolarity System User Manual. I-Med Pharma Inc, 2016]. The pen of the device is gently lowered towards the third middle of the everted inferior lid until the tip of the pen touched the inferior conjunctival epithelium and performs the measurement. The i-Pen device presents a cut-off value for DED at 300 mOsm/L [i-Pen Osmolarity System User Manual. I-Med Pharma Inc, 2016].

Figure 3.4. An illustration of the I-Pen Osmolarity System (I-Med Pharma Inc; 2016)

Various studies have looked into this device's ability to reproduce a range of normal values in a healthy samples [Nolfi et Caffery 2017, Rocha et al. 2017] in vitro data suggest that this device does not provide sufficient accuracy and precision in assessing osmolarity levels belonging to physiological ranges. Since it is a new device, it would be interesting to test it and evaluate its strengths and weaknesses.

3.5.3 TBUT / vital staining of the cornea and conjunctiva

Tear break up time is defined as the interval between a blink and the first occurrence of dry spots on the cornea [Norn 2009]. As TF impaired stability is a hallmark of DED, evaluating this parameter is valuable tool for diagnosis and follow-up of patients [Wolffsohn et al. 2017]. The present thesis focused on the assessment of TF stability using a staining dye which goal is to enhance visibility of TF [Wolffsohn et al. 2017], thus it will be named by the acronym FBUT standing for fluorescein BUT. TFOS Diagnostic and Methodology Report emphasizes that FBUT can be contemplated only when non-invasive techniques are not available, in other words, this is not the first intention test. On the other hand, it is still the most used clinical test for the disease in clinical practice [Cardona et al. 2011, Graham et al. 2010, Turner et al. 2005], and from that point of view, using this technique reflects the real conditions a practitioner is facing on a daily basis. Existing literature underlines the necessity of using controlled amounts

of fluorescein as this vital dye reduces TF stability [Mengher et al. 1985, Mooi et al. 2017] and could jeopardize the measurements.

Mooi et al. advise to use a fluorescein strip (a dry sterile applicator) previously soaked with saline solution (and immediately shaken so as to eliminate the excess of liquid) and apply the edge of the strip onto the outer canthus in order to avoid ocular surface damage [Mooi et al. 2017]. To optimize the visualization of fluorescein, we followed the recommendations from Peterson et al. [Peterson et al. 2006], that is, to wait between 1-3 minutes after instillation of the dye. Besides, the choice of an appropriate yellow filter, apart from the blue filter, is of great importance in the enhancement of fluorescence [Wolffsohn et al. 2017], in our case, a Wratten 12 short-wavelength barrier filter was used. Patient is asked to blink three times and then to hold blinking until instructed [Johnson et Murphy 2007]. Vitali et al. found a sensitivity and specificity of 72.2% and 61.6% respectively for a cut-off value < 10 s [Vitali et al. 1994]. Even if this parameter is assessed subjectively, a standardized procedure as described above, performed by the same examiner should ensure minimal variability and give reproducible results [Mooi et al. 2017]. A stopwatch was used to measure the interval between the last complete blink and the first appearance of a dry spot on ocular surface. The median of 3 consecutive measurements of the FBUT was calculated and presented as the final value for this parameter. Due to its invasiveness, this test was always performed after tear osmolarity measurement.

Vital staining of the cornea and conjunctiva was performed according to Efron's grading scale using fluorescein. EFRON grading scale for CL complications is attached Annex 4. Staining of ocular surface in a punctate pattern is not a specific feature of DED as many ocular conditions can induce those [Wolffsohn et al. 2017]; however, the distribution and location of the dye

uptake gives valuable information regarding its etiology [Bron et al. 2015]. Staining occurs whenever TJs are disrupted or glycocalyx is defective [Bron et al.2015] which basically represents local rupture of trans-cellular (mucins) and para-cellular (TJs) epithelial barrier.

This happens in physiological conditions, as epithelial cell turnover implies desquamation and shedding, which allows fluorescein uptake in the paracelular space. Thus, it is easily understandable to discard fluorescein uptake due to this renewing process. In DED, the pattern of staining is characteristic and distributed over the inter-palpebral area horizontally [Bron et al. 2017] and usually described as the "3 hours-9 hours syndrome". The TFOS II Diagnostic Methodology Report advise to use a solution of 2% fluorescein and 1% lissamine green increasing the likelihood of cellular damage observation as lissamine green dye produces staining only if the cell membrane is damaged irrespective of the presence of mucin [Bron et al. 2017]. In the present study, only fluorescein was used for corneal and conjunctival staining using a proper yellow filter (Wratten short-wavelength barrier filter) properly shaking the excess of saline solution (on a 1 mm strip and using a dry sterile applicator) on the fluorescein strip and having a single investigator applicating the strip onto the inferior conjuntiva steps that should ensures minimal variability and give reproducible results and good visibility of any, if present, conjunctival and/or corneal damage [Mooi et al. 2017].

3.6 Biometer (IOL Master 700): CCT

Various biometers are now available on the market [Holzer et al. 2009, Buckhurst et al. 2009, Hoffer et al. 2010, Goebels et al. 2015] and optical non-contact devices are now considered the gold standard for anterior segment measurements, supplanting the aging immersion ultrasound biometry in accuracy [Montés-Micó et al. 2011] and reproducibility [Findl et al. 2001, Goel et al. 2004], device that required contact with the patient's eye possibly source of

discomfort, and could lead to corneal complications [Haigis et al. 2000] and jeopardize further testing like in our case, TF metrics.

Accurate biometric measurements are essential in many areas of clinical practice such as ocular parameters follow-up for progressing ametropias, pre-operative assessment of patients undergoing cataract surgery (as visual outcomes rely on the precision of the measurements) and for the assessment of potential candidates for refractive surgery. The IOL Master 700 is one of the numerous optical laser systems for ocular biometry measurements available on the market. It uses a swept-source optical coherence tomography (SS-OCT) technology [Grulkowski et al. 2013] to obtain optical cross-sections (B-scans) necessary to provide biometric data of the eye. It enables measurements up to 44 mm in scan depth with 22µm resolution in tissue [Kunert et al. 2016]. Unlike its previous version (i.e IOL Master 500), this new device provides, in addition to : Axial length, anterior chamber depth, horizontal white to white corneal diameter, and keratometry, the central corneal thickness (CCT) and crystalline lens thickness (LT) [Kunert et al. 2016].

Figure 3.5. An illustration of the Biometer IOL Master 700 (Carl Zeiss Meditec, Jena, Germany)

To achieve measurements of CCT, the device uses an infrared light source varying from 1050nm to 1095 nm [Grulkowski et al. 2013]. This device showed good repeatability and

consistency of CCT measurement and provided the higher ICC with the lowest difference between each measurement when compared to similar devices [Kiraly et al. 2017].

3.7 Aberrometry (Atlas 9000)

TF stability is a keystone for the maintenance of the optical quality of the eye [Rieger 1992] as drying of the TF has a major impact on the quality of the optical system of the eye, increasing wavefront aberrations [Montés-Micó et al. 2004]. TF rupture at the break-up site induces variations in its thickness and above all in its curvature and resulting power, giving rise to High Order Aberrations (HoAs) [Montés-Mico et al. 2010]. Several studies have looked into the impact of DED on HoAs after blinking and found that changes in optical aberrations after break up contribute to reduce retinal image quality affecting visual function [Koh et al. 2008, Denoyer et al. 2012, Habay et al. 2014]. Among the HOAs, two individual ones stand out in DED patients: spherical- and coma-like aberrations are greater by a factor of about 2.5 compared with healthy subjects [Montés-Micó et al. 2010, Montés-Micó et al. 2005, Montés-Micó et al. 2004, Koh et al. 2008].

Figure 3.6. An illustration of the Atlas 9000 [software v3.0.0.39; Carl Zeiss Meditec, Jena, Germany]

The corneal front surface wavefront aberrations, derived from the Placido-based corneal topographer Atlas 9000 [software v3.0.0.39; Carl Zeiss Meditec, Jena, Germany] over a 6 mm central zone, was assessed with a non-dilated pupil for a pupil size of 4.5 mm and repeated three times between 3-6 seconds after blink in order to minimize the effect of lens movements and tear film stability on the measurements [Montes-Mico et al. 2004a, Montés-Micó et al. 2004b].

The choice not to control pupil diameter was deliberate, as studies of the thesis evaluating this parameter intended to assess the effect of the multifocal CL material in normal conditions of illumination, under the condition patients are usually assessed. Since the device used to quantify aberrometry is a Placido disk-based topographer, it uses the first Purkinje image, which is formed on the PLTF, to calculate topographic and aberrometric values. Image capture was timed for the same time post blink for each subject, as it has been found that TF stability is achieved approximately 6 seconds after blink, and overall aberrations tend to rise about 10 seconds after blink [Montés-Mico et al. 2004a].

CHAPTER 4

RESPONSE OF THE AGING EYE TO FIRST DAY OF MODERN CONTACT LENS WEAR

4.1 Introduction

CL fitting aims to provide good on-eye material stability, adequate vision for the required tasks, and comfort, all three ideally maintained throughout the period of wear. These are the main goals a practitioner intends to reach when fitting a new customer. This cannot be truer with young presbyopes, a growing population approaching a decisive turning point regarding their visual abilities, the progressive loss of focus coming hand to hand with a higher prevalence of age-related changes possibly leading to signs and symptoms of dry eye. This age-based population is highly demanding regarding the preservation of their quality of vision, willing to be spectacle independent maintaining high visual demands; and the more the visual loss advances, the more complex it is to provide statisfactory quality of vision at all distances [Pérez-Prados et al. 2016, Madrid-Costa et al. 2012]. CLs creating simultaneous images provide a good compromise for this age-based population expectations as these optical designs allow to achieve a corrected vision at all distances, avoiding monovision and its associated loss of stereopsis or the use of additional reading glasses [Pérez-Prados et al. 2016, Madrid-Costa et al. 2012]. The low use of CL designs to correct presbyopia was explained at the time by Morgan et al. by a lack of clinical knowledge from the practicioner and supported by a false idea that visual compromises inherent to their design are too great to achieve a good vision. Interestingly, a recent survey from Rueff et Bailey [Rueff et Bailey 2017] demonstrates the importance of considering the presbyopic population for CL fitting as it is acknowledged that presbyopic CL modalities are still under-prescribed worldwide [Morgan et al. 2011, Woods et al. 2007]. Furthermore, the advent of new technologies, materials and designs allowed enhanced CL comfort and quality of vision and were the presumed basis of the CL fitting increases during these last few years [Efron et al. 2015, Jones et al. 2016]. However, CL

discomfort is still identified as the primary reason for CL discontinuation [Glasson et al. 2006, Pritchard et al. 1999, Dumbleton et al. 2013a, Richdale et al. 2007]. CL material (silicone hydrogel [Sulley et al. 2017], parameters (lower sphere power [Pritchard et al. 1999] and wearing schedule (daily disposable [Sulley et al. 2017] have been reported as the main aspects associated with CL dropouts [Sulley et al. 2017].

According to a recent survey [Sulley et al. 2017], increased age is the main factor impacting retention rate, with multifocal CL fittings presenting the lowest continuation of use (57%) in comparison with other CL designs for the same age range population; poor achieved vision was identified as a key factor in multifocal CL wearers that stopped wearing CLs. Besides, Patel et al. suggest that the presbyopic population might be more susceptible to dryness-related comfort problems [Patel et al. 2000], mainly due to decreased TF stability, eventually leading to CL discomfort and dropout.

The purpose of this study was to assess the performance of a new daily disposable CL material on the ocular surface of a presbyopic population. To the best of our knowledge, this is the first study reporting the clinical outcomes of a water gradient daily CL material in a presbyopic population over their first day of CL wear. To achieve that goal, TF and ocular surface parameters were investigated at time intervals during a day of CL wear.

4.2 Methods

Forty subjects, neophyte CL wearers, were recruited. This prospective, non-randomized study was approved by the Institutional Ethics Committee of the University of Valencia. Informed consent was obtained for all subjects enrolled in the study. The clinical study adhered to the tenets of the Declaration of Helsinki.

Each of the subjects underwent a comprehensive ophthalmic examination as previously described in the methodology chapter, which included (in the following sequence): visual acuity, monocular and binocular refraction, anterior segment slit lamp biomicroscopy, osmolarity, measurement of the inferior TMA, topographic examination and TBUT assessment using fluorescein.

The room temperature was controlled and maintained between 20 and 25 degrees Celsius; the room humidity was maintained between 35 to 40%. The same investigator carried out all measurements and subsequent data analysis. Inclusion criteria were spherical equivalent refractive error between +6.00 to -10.00D, astigmatism ≤0.75D, monocular corrected distance visual acuity of 0.0 logMAR or better and normal binocularity. Patients who experienced any anterior segment pathology, previous corneal surgery, corneal abnormalities, self-reported DED or any general health condition were excluded from the study. Each subject underwent a comprehensive SL exam looking for any signs of inflammation of the anterior segment; cornea was assessed with different magnifications, using parallelepipedic and optical sections. CL fit quality was assessed according to Wolffsohn et al. critical fitting characteristics: centration, coverage, horizontal lag, movement on blink in up-gaze and push-up recovery speed [Wolffsohn et al.2009]. Tear osmolarity measurement was performed using the TearLab osmolarity system by collecting a minimal tear simple from the inferior lid tear meniscus (at the outer canthus).

Inferior TMA

Details of the AS-OCT imaging technology have been described previously [Izatt et al. 1994, Radhakrishnan et al. 2001]. The SL SCAN-1 is a spectral-domain OCT integrated into a slit lamp which details have been specified in the methodology. This device allows images of the inferior

tear meniscus to be obtained using the B-scan mode by scanning at the 6 o'clock ocular position with a cross line centered on the inferior lid edge. Measurements of the inferior TMA, defined as the triangular area formed by the anterior corneal boundary, anterior boundary of the lower eyelid and anterior borderline of the tear meniscus, were performed manually using image analysis software imageJ (http://imagej.nih.gov/ij/). In order to perform the measurement of this tear meniscus parameter, images acquired with the OCT were exported to an image analysis software. After determination of the number of pixels contained from one side of the image to another (each scan performed was 2 mm wide), and knowing the actual value of one pixel (by imaging an object of a known size with the same OCT settings), it was possible to calculate distances between the three points of the triangle formed by the tear meniscus and by extension to assess it surface. The previous explainations are illustrated in Figure 4.1.

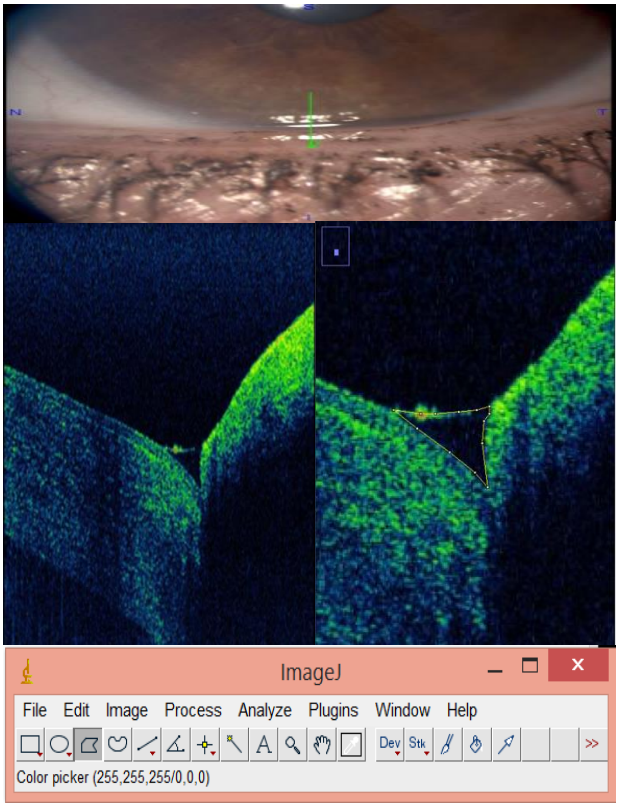

Figure 4.1. Images obtained with SL SCAN-1 (Topcon, Japan) Manual delimitation of TM edges using ImageJ Software (naked eye)

Aberrations Analysis

The corneal front surface wavefront aberrations derived from the Placido-based corneal topographer Atlas 9000 over a 6 mm central zone was assessed with a non-dilated pupil and repeated three times between 4-6 seconds after a blink [Montés-Micó et al. 2004a, Montés-Micó et al. 2004b]. Image capture was timed for the same time post blink for each subject, as it has been found that TF stability is achieved approximately 6 seconds after a blink, and overall aberrations tend to rise for about 10 seconds after a blink [Montés-Micó et al. 2004a]. Evaluating this parameter across a 8 hours period allowed information to be obtained about PLTF behavior on the CL material surface.

TBUT and Corneal-Conjunctival Staining Score

TBUT was measured subjectively with a slit lamp (equipped with a blue illumination filter and a yellow observation filter) by inserting into the lower fornix a fluorescein strip moistened with one drop of a nonpreserved saline solution. The strip was shaken in order to get rid of the saline solution in excess that could potentially jeopardize the measurement [Wolffsohn et al. 2017]. Patient was asked to blink three times and look forward during the procedure. The average of three consecutive TBUT measurements was then calculated. Corneal staining was evaluated after TBUT under blue illumination, between 1 and 3 minutes after fluorescein instillation. Corneal and conjunctival subjective assessment followed the grading scheme from Efron's scale (grades from 0-4 in 0.5 unit steps) observed with 16x slit lamp magnification.

Eligible patients (based on inclusion and exclusion criteria) were fitted binocularly with multifocal CLs (delefilcon A, Dailies Total1® Multifocal) in randomised sequence. CL material characteristics, according to manufacturer's data is displayed table 10. All baseline measures were repeated at 20 minutes and 8 hours after CL insertion.

Unites States Adopted Names Council (USAN)	Delefilcon A
Company	Alcon
Polymer type	Silicone Hydrogel
FDA group	I
Equilibrium water content (%)	Core 33% Periphery above 80%
Dk/t ([cm^2 s^{-1}][mL O_2/(mL × mmHg)] × 10^{-11})	159 @ -3.00D at a central thickness of 0.09 mm
Base Curve (mm)	14.1
Diameter (mm)	8.5

Table 10. Delefilcon A characteristics (Manufacturer's data)

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Science software [Version17.0, SPSS, Inc., Chicago, IL, USA]. Only right eye data was analyzed to avoid bias due to the similarities between the eyes of an individual. Friedman's nonparametric statistical test was used to detect differences over time of TMA, osmolarity and aberrations as they were not normally distributed (Kolmogorov-Smirnov). The Sign test was used to compare related intergroups for ordinal parameters (conjunctival and corneal staining), whereas a related samples average t test was used in the intergroup parameters with normal distribution (TBUT). Differences were considered statistically significant at $p \leq 0.05$.

4.3 Results

The average age of the participants was 50.0±4.4 years, ranging between 41 and 60 years old. Mean spherical equivalent refractive error was +1.11±0.35 D and ranged from -4.25 to +2.50 D. From the 40 eyes included, 18 were myopic (mean spherical equivalent error -2.80±0.72D) and 22 hypermetropic (+0.90±0.24D). Mean values and standard deviations of the parameters assessed at each visit over the day are presented in Table 11.

	Baseline (t_0)	**At 20 minutes (t_1)**	**At 8 hours (t_2)**	**P value**
Aberrations (µm)	0.38 ± 0.21	0.61 ± 0.04	0.64 ± 0.41	(t_0)/ (t_1) P< 0.01 (t_0)/(t_2) P< 0.01 (t_1)/(t_2) P=0.71
Osmolarity (mOsm/L)	306.9 ± 2.3	312.4 ± 2.4	310.4 ± 2.3	(t_0)/ (t_1) P=0.02 (t_0)/(t_2) P=0.09 (t_1)/(t_2) P=0.71
TMA (mm^2)	0.020 ± 0.003	0.019 ± 0.002	0.017 ± 0.003	P=0.061
TBUT (s)	10.4 ± 0.4	-	9.0 ± 0.3	P <0.01

Table 11. Comparison of the objective measurements of the non-previous CL wearers at the initial visit (t_0), 20 minutes (t_1) and 8 hours (t_2) after CL insertion (mean ± SD). TMA: tear meniscus area; TBUT: tear break-up time.

Osmolarity showed significant changes between baseline (306.9±2.3 mOsm/L) and 20 minutes (312.4±2.4 mOsm/L) (P=0.02) (Figure 1). No statistically significant changes were found between baseline (306.9±2.3 mOsm/L) and 8 hours (310.4±2.3 mOsm/L) (P=0.09). TMA values diminished across the day (from 0.020±0.003 mm^2 to 0.017±0.03 mm^2) (P=0.061) but was not statistically significant.

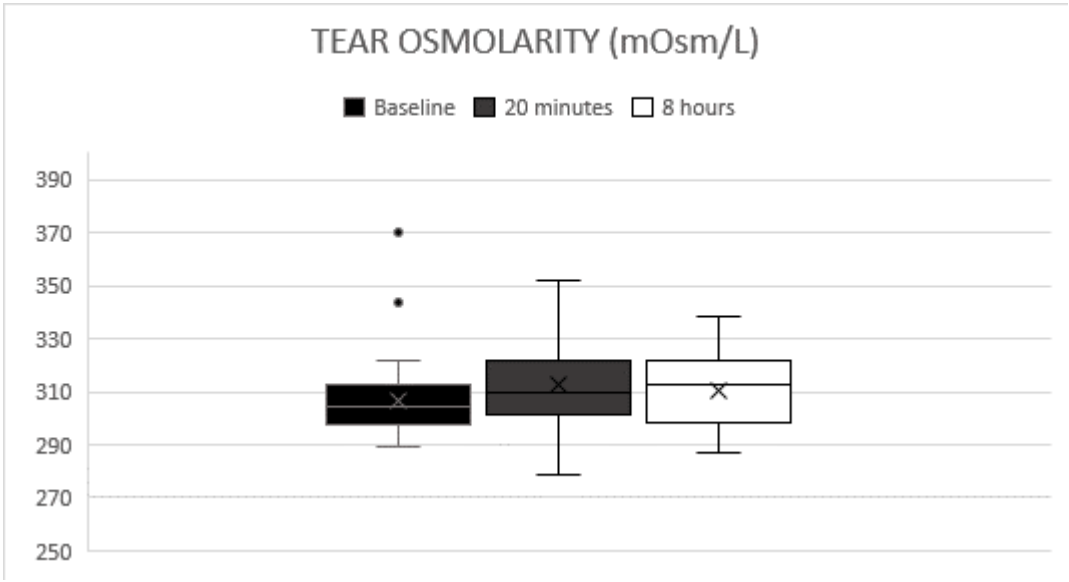

Figure 4.2. Box-plot of osmolarity at baseline, 20 minutes and 8 hours of Cl wear. Medians are represented for each plot; quartiles are shown as boxes, ranges as whiskers and outliers as dots.

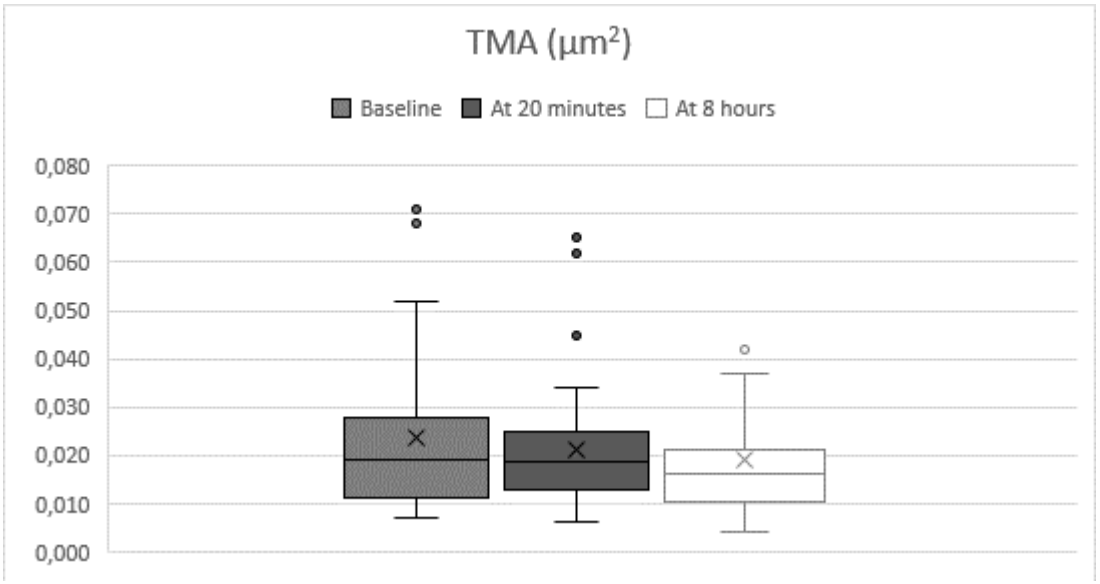

Figure 4.3. Box-plot of TMA values at baseline, 20 minutes and 8 hours of Cl wear. Medians are represented for each plot; quartiles are shown as boxes, renges as whiskers and outliers as dots.

Figure 4.3 displays aberrometric RMS data before CL adaptation at 20 minutes and 8 hours after CL insertion. Ocular surface higher order RMS aberrations showed a statistically significant increase between baseline (0.38±0.21 µm) and 20 minutes (0.61±0.44 µm) (P≤0.001) and between baseline and 8 hours (0.64±0.41 µm) (P≤0.001).

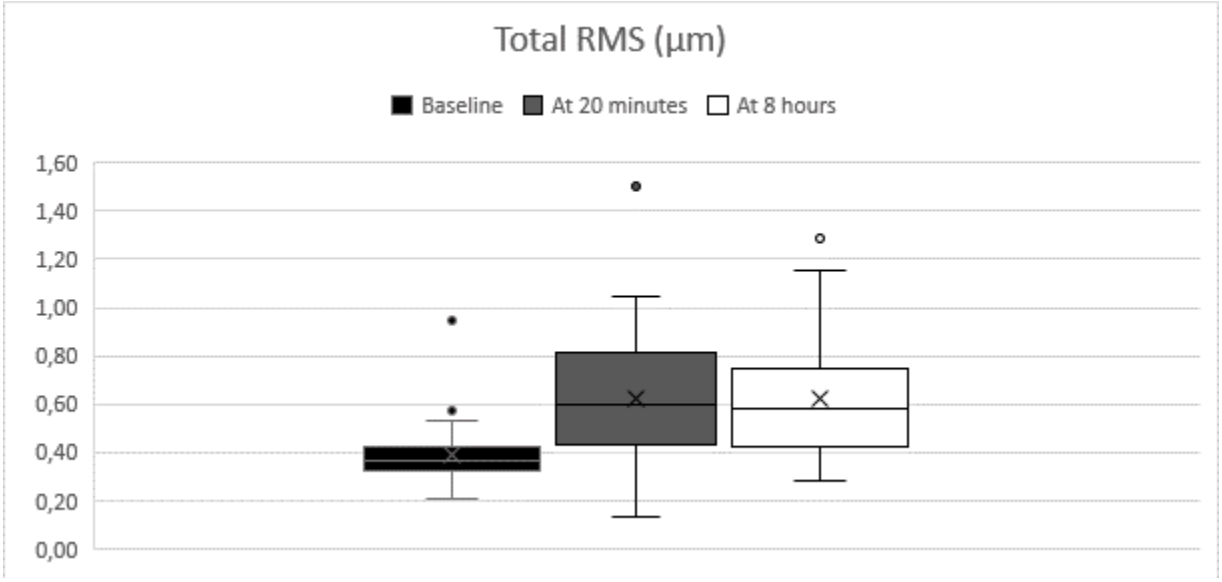

Figure 4.4. Box-plot of osmolarity at baseline, 20 minutes and 8 hours of Cl wear. Medians are represented for each plot; quartiles are shown as boxes, ranges as whiskers and outliers as dots.

No statistically significant changes were found between 20 minutes (0.61±0.44 µm) and 8 hours (0.64±0.41 µm) (P=0.711). TBUT worsened by the end of the day from 10.4±0.4 seconds at baseline to 9.0±0.3 seconds after 8 hours of CL wear (P<0.05) (Figure 4). No statistically significant differences were found between the measurements at baseline, and after 8 hours of CL wear regarding fluorescein corneal (P=0.727) and conjunctival staining (P=0.092).

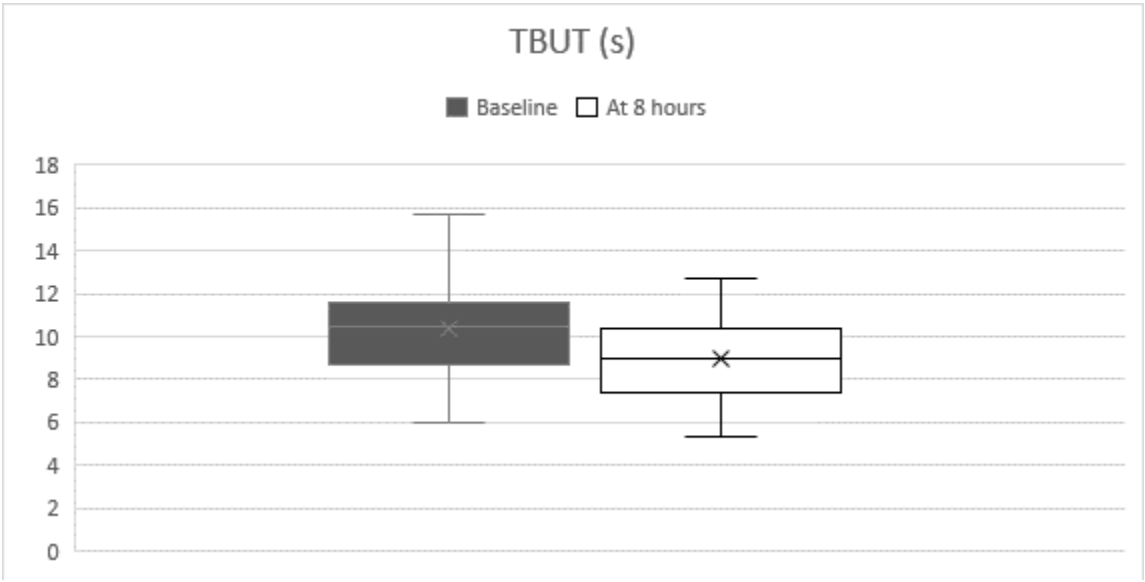

Figure 4.5. Box-plot of FBUT at baseline, 20 minutes and 8 hours of Cl wear. Medians are represented for each plot; quartiles are shown as boxes, ranges as whiskers and outliers as dots.

4.4 Discussion

A healthy tear film is a key factor in order to maintain a functional and efficient ocular surface. Ocular dryness and discomfort represent the main complaints in CL wearers [Pritchard et al. 1999, Dumbleton et al. 2013, Richdale et al. 2007, Young et al. 2002]; CL discomfort (CLD) (24%) and dryness (20%) being the primary reasons for discontinuation [Pritchard et al. 1999, Dumbleton et al. 2013, Sulley et al. 2017]. According to Dumbleton et al., "discomfort" is the most frequently cited reason for CL dropout [Dumbleton et al. 2013], but its precise meaning to the individuals is more complex to assess. Indeed, the terms dry eye and CL discomfort closely interlace, since a patient that presents signs and symptoms of dry eye has more propensity to have CL discomfort when fitted with CLs [Begley et al. 2001].

Tear hyperosmolarity is a key mechanism of ocular surface inflammation leading to dry eye clinical features [Suzuki et al. 2010, Sullivan et al. 2010]. Environment, CL materials and parameters, and TF factors such as stability have been described as triggers for the rise of

osmolarity [Nichols et Sinnott 2006, González-Méijome et al. 2009, Gilbard et al. 1986]. TF stability is altered by CL wear regardless of the lens type as CLs induce changes in TF structure, creating a PLTF and a postlens TF, that is, new interfaces within the ocular environment [Glasson et al. 2006]. PLTF is mainly responsible for the hydration and wettability of the CL front surface, facilitating the interaction with palpebral conjunctiva, by reducing friction forces and hence providing a smooth optical surface [Koh et al. 2016, Nichols et King-Smith 2003]. PLTF instability can be found in hydrogel high water content and thin CLs, leading to a rise of osmolarity, since it has been suggested that this type of lens can dehydrate easily partly due to its elevated water content [González-Méijome et al. 2009, Ramamoorthy et al. 2010].

Previous studies demonstrated that refractive index (RI) of a CL material and its water content are closely related, showing the interest of evaluating RI to assess lens water content [Brennan 1983]. Delefilcon A provides a water gradient and a surface water content corresponding to a high-water content hydrogel material, and as such, it may be expected to induce a rise in osmolarity values when fitted, due to partial dehydration of the outermost part of the CL material. This hypothesis seems robust since in Schafer et al. study, an index change was found to occur on the CL surface after 15 minutes of lens wear, shifting from a high-water content RI to a level compatible with a low water content material RI [Schafer et al. 2015]. However [Szczesna-Iskander et al. 2014] found that this water gradient material provided a better end of the day TFSQ than a high-water content hydrogel material. This finding implies that the rate of superficial dehydration of this material is lower than other CLs [Szczesna-Iskander et al. 2014].

Previous studies of existing, largely young, CL wearers reported significant rises in tear osmolarity in CL wearers during the time of use [Farris 1985, Iskeleli et al. 2002, Sarac et al.

2012]. Iskeleli et al. found that monthly hydrogel soft CLs induced a raise in osmolarity values between 1-2 hours after insertion [Iskeleli et al. 2002]. Sarac et al. evaluated osmolarity with daily wear silicone-hydrogel CLs over the course of a day and found a rise in tear osmolarity after 4 hours of CL wear, followed by an insignificant reduction in osmolarity values at the end of the day [Sarac et al. 2012]. These results are in agreement with the present study. Indeed, statistically significant differences have been found between baseline and 20 minutes showing that an increase in osmolarity values occurs even sooner than evaluated before; while over the course of the day a reduction in tear osmolarity values could be observed, although not statistically significant, but consistent with the findings of Sarac and al [Sarac et al. 2012].

According to Nichols et al. the on-eye CL sits in and not on the TF [Nichols et King-Smith 2003]; CLs are many times thicker than the TF so its insertion is expected to induce perturbation to the ocular surface as noted earlier [Mann et Tighe 2013]. Furthermore, CL interaction with the eyelid and cornea can modify tear composition and electrolytes levels, as shown by Tighe [Tighe 2013]. The hypothesis explored in the present study was that CL initially disturbs the newly formed PLTF (by inducing reflex tearing), leading to decreased TF stability and increased evaporation, resulting in elevated tear osmolarity values at 20 minutes. Besides, it is speculated that increases in osmolarity at 20 minutes might also be partly due to both an ocular surface response to CL insertion, and an individual tear interaction with the CL material.

At the end of the day (i.e after 8 hours of CL wear), osmolarity values were lower than those obtained at 20 minutes, but did not reach the baseline level. Furthermore, both values obtained at 20 minutes and after 8 hours of CL wear were higher than the cut-off value of 308mOsm/L, which, according to Foulks, can be considered as a mild form of dry eye [Foulks et al. 2009].

It is important to emphasize that no significant changes were found regarding corneal or conjunctival staining by the end of the day, which means that even if osmolarity was above cut-off values, it was not clinically significant with short term wear since there was no significant cellular damage. Osmolarity values did not change over the time of wear, which may imply that CL surface properties remain rather stable during the 8 hours of CL wear and provide enough oxygen transmission and lubrication to the ocular surface in order not to induce any additional staining. However, if the osmolarity changes occur in a similar pattern over longer-term wear, corneal integrity could well be compromised.

It is known that tear hyperosmolarity induces epithelial cell hyperosomolarity [Baudouin et al. 2016, Baudouin et al. 2013, Li et al. 2004, Luo et al. 2007], leading to intracelular activation involving MAP Kinase and NFκB pathways and therefore liberation of pro-inflammatory cytokines, which eventually induce epithelial cell apoptosis [Downie et Keller 2015, Li et al. 2004, Luo et al. 2007]. Further investigation is needed in order to assess the rise in osmolarity values from baseline and the duration of this elevation that could trigger an inflammatory response from the ocular surface, leading to cellular apoptosis and the corresponding positive vital dye staining.

Tear meniscus can be defined as the accumulation of tears between the lid margin and the bulbar conjunctiva; it is present on both superior and inferior eyelids [Holly 1985, Garcia-Lázaro et al. 2012]. It is believed that tear meniscus contains 75%-90% of the total volume of the TF [Holly 1985], which makes it a useful clinical parameter to assess TF volume and its possible changes over time. AS-OCT is a useful device for in vivo non-invasive quantification of tear meniscus parameters, with [Garcia-Lázaro et al. 2012, Del Águila-Carrasco et al. 2015] or without CLs [Wang et al. 2006, Chen et al. 2009]. Czajkowski et al. showed that AS-OCT

presents sensitivity and specificity for dry eye diagnosis (prior to the standardisation of TFOS DEWS II) of 86.1% and 85.3% for TMA and a strong positive correlation to tear meniscus height ($r=0.763$, $p<0.0001$), making this device a valuable tool for diagnosis and follow-up of patients with dry eye disease [Czajkowski et al. 2012].

In the present study, TMA values did not show significant changes across the day. It suggests that short-term CL wear may have limited impact on tear volume in a non-dry eye presbyopic population, which is in agreement with Wang et al. work on the influence of CL wear on upper and lower meniscus in a normal young adult population [Wang et al. 2009]. Chen et al. evaluated CL wearers with self-reported dryness, asymptomatic wearers and asymptomatic non lens wearers [Chen et al. 2009]. No significant statistical changes were found between baseline and after 30 minutes for the asymptomatic wearers, which is in agreement with the results obtained in this study. According to our results, it seems very likely that CL insertion induces reflex lacrimation responsible for an immediate increase of tear volume and decreased TF stability, but it tends to return back to normal values by 20 minutes after CL lens insertion. PLTF quality mainly relies on surface wettability and the water content of CL materials [Tonge et al. 2001, Jones et al. 2002b].

In this study, no difference was found at the end of the day in comparison to baseline, even if TMA diminished over the day, which suggests that PLTF surface quality remained stable over time. Higher-order aberrations are believed to contribute up to seven percent of retinal image quality [Porter et al. 2001, Guirao et al. 2002]. The main difference between a perfect wavefront and the one displayed by the human eye mainly is due to higher order aberrations, more precisely third order coma-like and fourth-order spherical aberrations [Charman 2005, Thibos et al. 2002a, Thibos et al. 2002b]. It is known that the effect of coma and spherical

aberrations is pupil dependent, the greater the pupil size, the greater the aberrations and the depreciation of the final retinal image [Patel et al. 2002].

In this study, the CL geometric characteristics were a front and back surface aspheric center-near multifocal design, which is expected to induce a certain amount of spherical aberration [Peyre et al. 2005]. Moreover, decentration of a CL on the eye due to eye movement or to the lag in the replacement of the CL after blink are expected to induce coma-like aberrations proportional to the amount of decentration from the visual axis [Patel et al. 2002, Kollbaum et al. 2011, Gatinel 2003]. For these reasons it was decided to only assess ocular surface high order RMS of coma-like and spherical aberration in this study. Data were converted into RMS values for spherical aberrations and coma combined [Patel et al. 2002, Gatinel 2003] in order to follow-up changes of the total RMS over time and to assess the influence of the CL insertion over this parameter.

A statistical significant increase in ocular surface higher order RMS was found between baseline and 20 minutes, i.e from the CL insertion. In the majority of participants, the set of ocular surface higher order RMS increased 20 minutes after CL insertion, but remained stable over the day; no significant difference was found between 20 minutes and 8 hours of CL wear. This could be explained by the behaviour of the lens on the eye, remaining stable throughout the day, and the time the lens took to centre after a blink, which was approximately the same at 20 minutes and 8 hours, thus obtaining similar aberrations values for all participants.

Tear quality, stability and dynamics play a key role in optical performance of CLs [Montés-Micó et al. 2004a, Erdélyi 2006, Zhu et al. 2007]. Indeed, local variation of PLTF thickness influences the amount of ocular aberrations being measured [Rae et Price 2009]. DED, according to its severity, is also known to induce a significant rise in aberrations, so the fact that corneal high

order RMS remained rather stable during the day may imply that the pre-lens TFSQ and dynamics were minimally impacted over the course of the day. TBUT is one of the clinical methods used to assess compromised tear film stability [Pflugfelder et al. 1998]. In the present study, a significant decrease in TBUT was found between baseline and 8 hours of wear. This decrease in TF stability was an expected outcome, since TF structure is altered by CL (increased evaporation and perturbation in TF spreading) [Glasson et al. 2006, Pritchard et al. 1999, Dumbleton et al. 2013, Richdale et al. 2007]. Since measurement was carried out just after CL removal, it was expected that complete recovery of the TF would not yet have been achieved at that moment. So, even if a statistical decrease in TBUT was evidenced, it is unlikely to have any clinical significance. Fluorescein dye is not the first option to assess TF stability (since its efficiency relies on a controlled amount of fluorescein instilled and on the practitioner's experience to detect the first dry spot on corneal surface), as objective, non-invasive methods are now available [Wolffsohn et al. 2017]. The topographer used in the current study was the Atlas 9000, which although it utilises a Placido disc, does not include in the software an automatic delimitation of the BUT. Instead the TFOS DEWS II standardized methodology for use of fluorescein to assess subjectively tear film stability was adopted [Wolffsohn et al. 2017] using a single investigator applicating the strip onto the inferior conjunctiva to ensure minimal variability and give reproducible results. The subjective assessment of TBUT and vital staining, as discussed before, could be limitations of the study along with the time between visits that was not masked to the investigator and could have influenced the results. Duration of wear might be another limitation of the current study as previous works reported a longer average time of wear with up to 25% of the patients wearing their lenses up to 16 hours [Riley et al. 2006, Long et McNally 2006]. The duration evaluated in this study is more in agreement with a recreational wear including hobbies or social activities [Riley et al 2005, Wolffsohn et al.

2015], which gives valuable information, but does not represent a typical day for usual CL wearers.

4.5 Conclusions

This study reports the clinical performance of a water gradient daily disposable soft CL on the ocular surface and the TF in a neophyte presbyopic population over their first 8 hours of wear. CL insertion induces an initial decrease in TF stability observed by osmolarity values rising after 20 minutes of wear, but it did not impact tear meniscus metrics and seemed to be transitory, as a decrease, without reaching baseline values, occurred by the end of the wearing period. Ocular surface aberrations remained largely stable from CL insertion, demonstrating an even repartition of TF over the CL material surface.

CHAPTER 5

CLINICAL PERFORMANCE OF TWO SILICONE HYDROGEL MULTIFOCAL MATERIALS ACROSS A MONTH OF WEAR IN A PRESBYOPIC POPULATION

5.1 Introduction

Optical devices to correct presbyopia such as multifocal designs in soft CL materials have boomed over the last decades mainly due to increased demand of visual solutions for this age-based population [Pérez-Prados et al. 2016]. These designs provide at least two refractive zones with different powers in order to create simultaneous images: distance and near powers are positioned within the pupillary area at the same time. The wearer is expected to receive superimposed multiple images on the retina and their neural processing select the clearest one for a given task. Several modalities of wear are now available in soft CLs, daily and monthly disposable being the most popular [Morgan et al. 2011]. Practitioners tend to favor daily disposable wear as no cleaning or storing is necessary and above all, it avoids the use of chemicals. New CL materials constantly appear on the market aiming to provide more and more ease of wear and biocompatibility with the ocular surface in order to improve signs and symptoms of dryness and discomfort.

However, CL material interaction with TF and ocular surface is wearer-dependent and could be further influenced by the age-related changes taking place in the LFU, the geometry of the lens and modalities of wear. CL interaction with tear variables (lipid layer integrity, tear film stability and tear volume among others) is a key factor on which relies the success of the fit and the end-of-day comfort. The 2013 report of the TFOS International Workshop on Contact Lens Discomfort [TFOS CLDW] defined CLD as “a condition characterized by episodic or persistent adverse ocular sensations related to lens wear, either with or without visual disturbance, resulting from reduced compatibility between the contact lens and the ocular environment, which can lead to decreased wearing time and discontinuation of contact lens wear” [Nichols et al. 2013]. As specified in the introduction of this thesis, discomfort is one of

the main factors of CL discontinuation [Dumbleton et al. 2013, Richdale et al. 2007]. Thus, identifying the factors influencing comfort and understanding the underlying mechanisms is a crucial step towards improving CL material characteristics.

The purpose of this study was to assess the effect of lens wearing modality on the ocular surface physiology across a month in a presbyopic population. To the best of our knowledge, this is the first study to look into the effect of lens wearing modality on the ocular surface physiology in presbyopic subjects. To achieve that goal, TF, ocular surface parameters and symptoms were investigated along a typical month of CL wear.

5.2 Methods

A total of forty eyes of 40 subjects, no previous CL wearers, aged between 41 and 60 years old, were included in this study. Only right eye data was analyzed to avoid bias due to the similarities between the eyes of an individual [Mcalinden et al. 2011]. This prospective, cross-over study was approved by the Institutional Ethics Committee of the University of Valencia. Participants were explained his/her rights as a research subject and agreed to take part by signing a statement of informed consent. The study was performed according to the tenets of the Declaration of Helsinki. As part of the study screening, each of the participants underwent a baseline comprehensive ophthalmic examination, which included, in the order as follow: OSDI, CLDEQ-8, visual acuity, refraction, slit lamp biomicroscopy, topographic examination using the topographer Atlas 9000, ocular fundus examination, horizontal visible iris diameter measurement using a ruler to nearest 0.5 mm and CCT measurements using OCT and a swept-source biometer, osmolarity measurement and FBUT and TMA using SL integrated OCT SL SCAN-1. Patients who experienced any anterior segment pathology, previous corneal surgery,

corneal abnormalities, chronic self-reported DED or ocular fundus diseases, conjunctival staining present ≥2, corneal staining present ≥2 were excluded from the study. Participants were randomly assigned to be initially fitted with either Dailies Total One Multifocal (center-near aspheric; Alcon, Texas, U.S.A.) or Air Optix Aqua multifocal (center-near aspheric; Alcon, Texas, U.S.A.). CL characteristics are summarized in table 12. Before dispensing the lenses, all participants were taught appropriate lens insertion, removal, and cleaning techniques for the EW lenses (which are basically daily wear monthly replacement schedule CLs), with preservative-free multipurpose solution (Optifree Replenish (Alcon). Previously described parameters were measured at: baseline (t0), 20 min margin (t1) and 8 hours margin after insertion (t2), in morning hours (t3) and in the afternoon (t4) of the 30^{th} day except for OSDI/CLDEQ-8 that were assessed at the end of the wearing period for each CL material. CL wear was discontinued for four days between each period of one month of wear in order for the eyes to fully recover (wash-out period).

Unites States Adopted Names Council (USAN)	**Delefilcon A**	**Lotrafilcon B**
Company	Alcon	Alcon
Polymer type	Silicone Hydrogel	Silicone Hydrogel
FDA group	I	I
Equilibrium water content (%)	Core 33% Periphery above 80%	33%
Dk/t ([cm^2 s^{-1}][mL O_2/(mL × mmHg)] × 10^{-11})	159 @ -3.00D at a central thickness of 0.09 mm	138 @ -3.00D at a central thickness of 0.08 mm
Base Curve (mm) / Diameter (mm)	14.1/8.5	14.2/8.6
Wearing Schedule	Daily Disposable	Daily Wear Monthly Replacement Schedule

Table 12. Contact lenses characteristics according to manufacturer's data

- Symptomatology questionnaires (OSDI and CLDEQ-8) were administered as described in general methodology.
- Slit Lamp Examination was performed for each subject of the oculus uterque (OU) looking for any signs of inflammation of the anterior segment; the cornea was assessed with different magnifications, using parallelepipedic and optical sections. CL fit quality was assessed according to Wolffsohn et al. critical fitting characteristics: centration, coverage, horizontal lag, movement on blink in up-gaze and push-up recovery speed [Wolffsohn et al. 2009]. Tear osmolarity measurement was performed using the TearLab osmolarity system by collecting a minimal tear simple from the inferior lid tear meniscus (at the outer canthus).
- Tear osmolarity was performed as explained in the general methodology before FBUT and vital stainings.
- Inferior Tear Meniscus Area: Images obtained with SL-Scan 1 were then exported to an image analysis software called imageJ [http://imagej.nih.gov/ij/] that allows, after manual delimitation of the edges of the central tear meniscus, the calculation of TMA in mm^2 as illustrates Image 2.

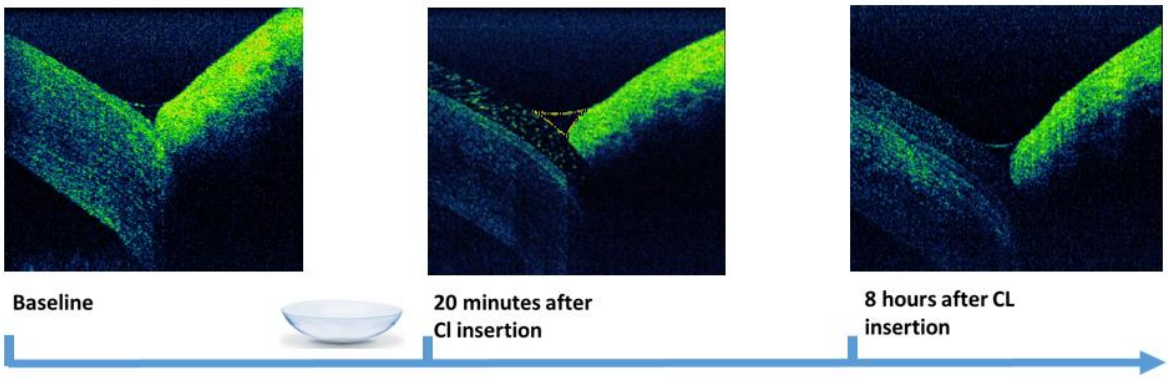

Figure 5.1. TMA measurement performed on the first day of CL wear (delefilcon A)

- Aberrations Analysis was performed as detailed in Chapter 3.
- CCT: Optical Coherence Tomography was used for assessing corneal-CL Pachymetry AS-OCT Visante. The IOL Master 700 uses swept source OCT (SS-OCT) to measure corneal-CL pachymetry. Corneal thickness is known to increase over night [(Mertz 1980] reaching a peak upon waking [Mandell et Fatt 1965]. According to this, baseline (t0) and morning measurements (t1/t3) were performed at least two hours after awakening so as to allow the cornea to return to its basal thickness.
- Tear Film Breakup Time and Corneal-Conjunctival Staining Score (Fluorescein Sodium) was performed as detailed in Chapter 3.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Science software (Version17.0, SPSS, Inc., Chicago, IL, USA). Friedman's non-parametric statistical test was used to detect differences over time for TMA, osmolarity, CCT and aberrations as they were not normally distributed (Kolmogorov-Smirnov $p < 0.05$). Wilcoxon test was used in order to compare related intergroups for ordinal parameters, whereas Mann-Whitney test was used to compare parameters not normally distributed between the two CL materials. Correlations between the questionnaires responses were assessed by the Spearman coefficient of correlation. Differences were considered statistically significant at $p \leq 0.05$.

5.3 Results

Forty right eyes from 40 presbyopic subjects (50.0 ± 4.4 years) completed the study. Mean spherical equivalent refractive error was +1.1 ± 0.4 D.

OSDI scores obtained at (t0) an (t4) for the daily and extended wear (EW) lenses were 8.5, 13.2 and 24.4 points respectively and showed significant differences only regarding the EW lens (p=0.042; Figure 1.a).

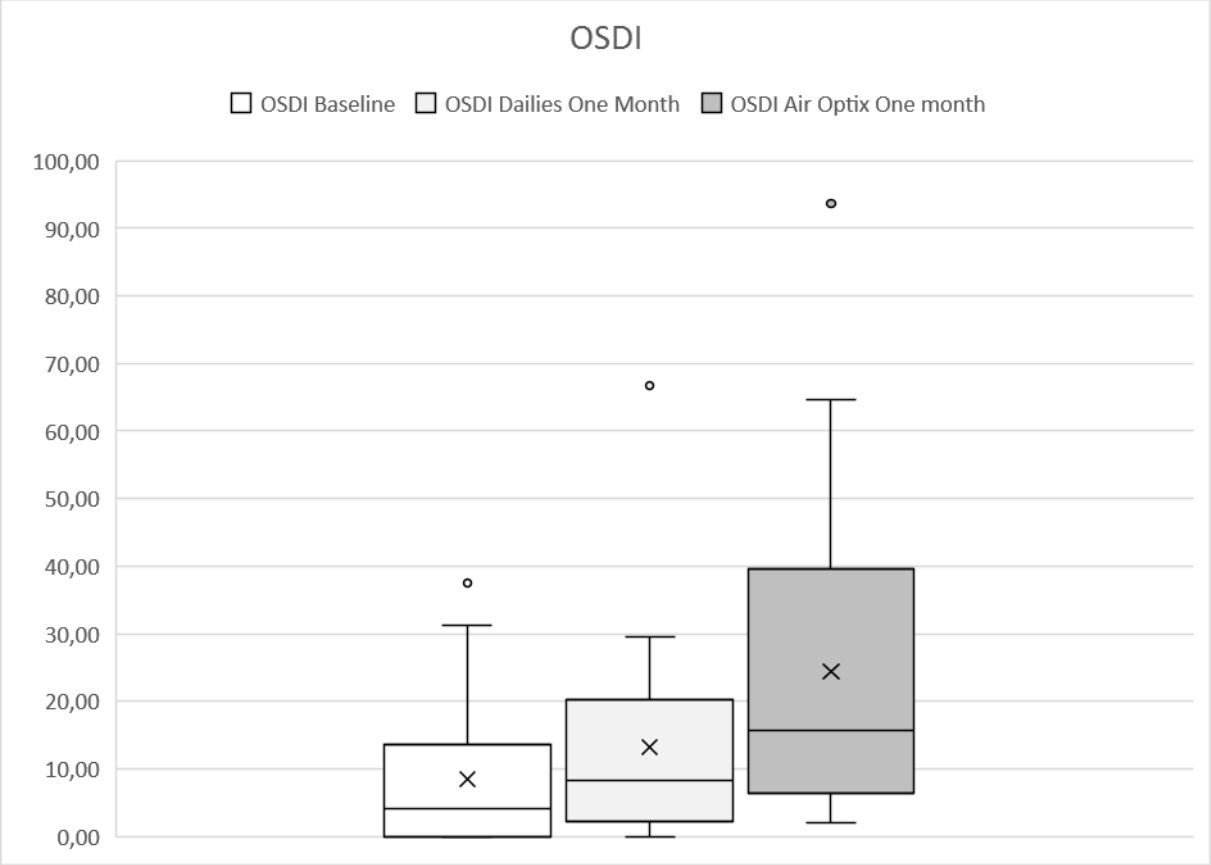

Figure 5.2.a. Box-plot of OSDI scores the month of CL wear for each lens. Medians are shown for each plot, quartiles are shown as boxes, ranges as whiskers and outliers as dots.

CLDEQ-8 scores obtained at (t0) and (t4) for the daily and extended wear (EW) material were 6.2 ± 3.8 points, 10.6 ± 8.5 points and 18.1 ± 9.8 points respectively and showed significant differences lotrafilcon B giving the higher scores (P=0.012)(Figure1.b).

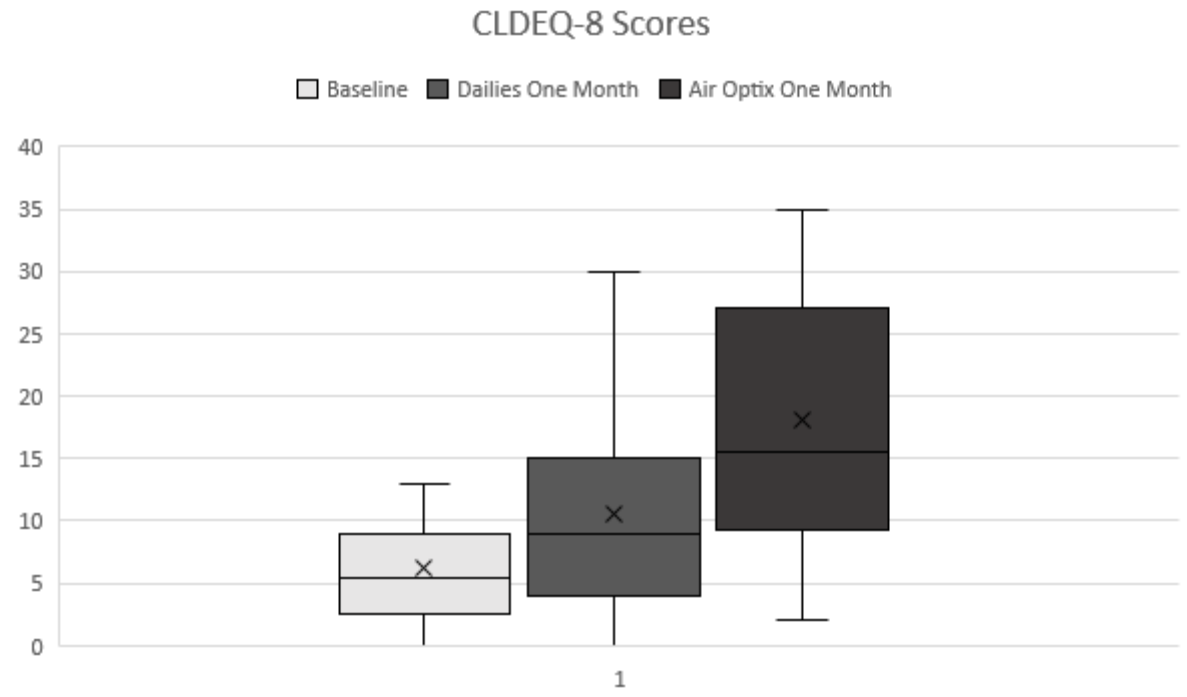

Figure 5.2b. Box-plot of CLDEQ-8 scores at the end of CL wear for each lens. Medians are shown for each plot; quartiles are shown as boxes, ranges as whiskers and outliers as dots

Spearman correlation coefficient results revealed a strong correlation between the OSDI and CLDEQ-8 scores at baseline visit ($R = 0.76$; $P < 0.0001$), at one month for delefilcon A ($R = 0.65$; $P < 0.002$), but it was not significant regarding the lotrafilcon b material ($R= 0.3$; $P < 0.203$).

For both lenses, TMA decreased with time ($p<0.001$) and ($p<0.002$) respectively (Figure 2). The post-hoc analysis revealed only significant differences for the daily lens between the measurements taken at baseline (t0)/(t2), (t0)/(t3), (t0)/(t4), as well as between (t1)/(t2) and (t1)/(t4) ($p<0.05$). For the EW lens, significant differences were found between (t0)/(t1) ($p=0.016$), (t0)/(t3) ($p=0.009$), (t0)/(t4) ($p=0.001$) and (t1)/(t4) ($p=0.017$).

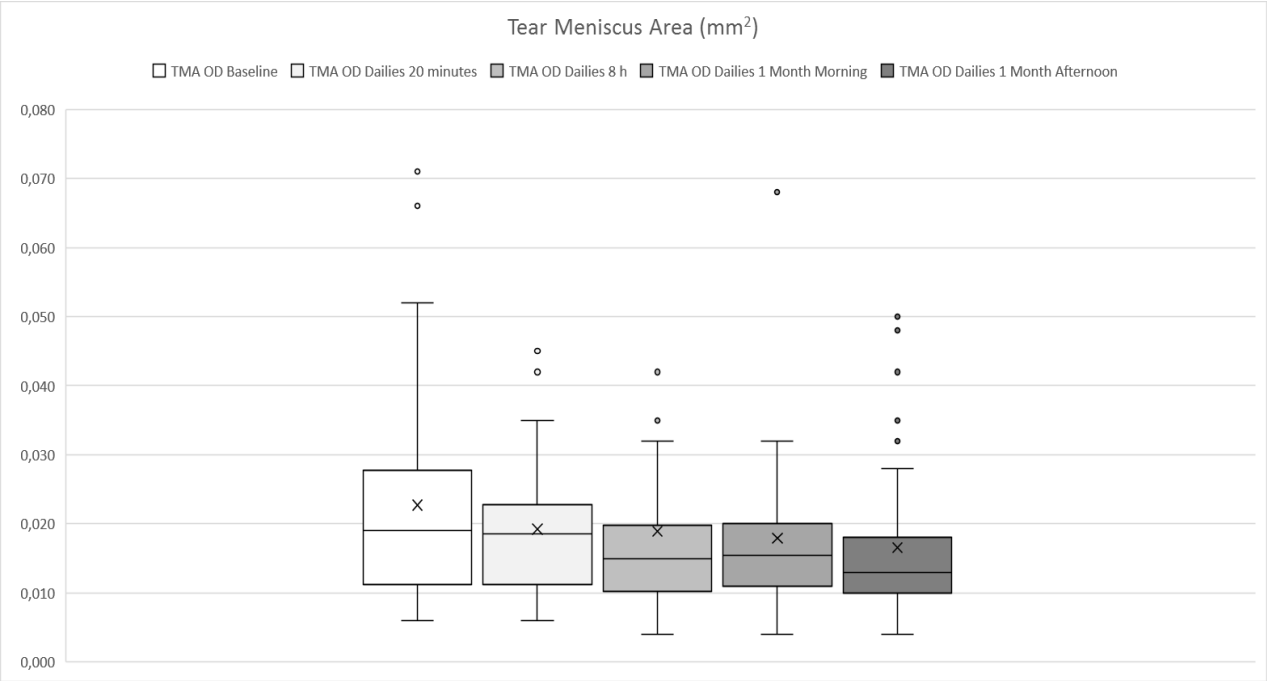

Figure 5.3.a. Box-plot of tear meniscus area at baseline, 20 minutes, 8 hours, one month morning and afternoon of CL wear for Delefilcon A. Medians are shown for each plot, quartiles are shown as boxes, ranges as whiskers and outliers as dots.

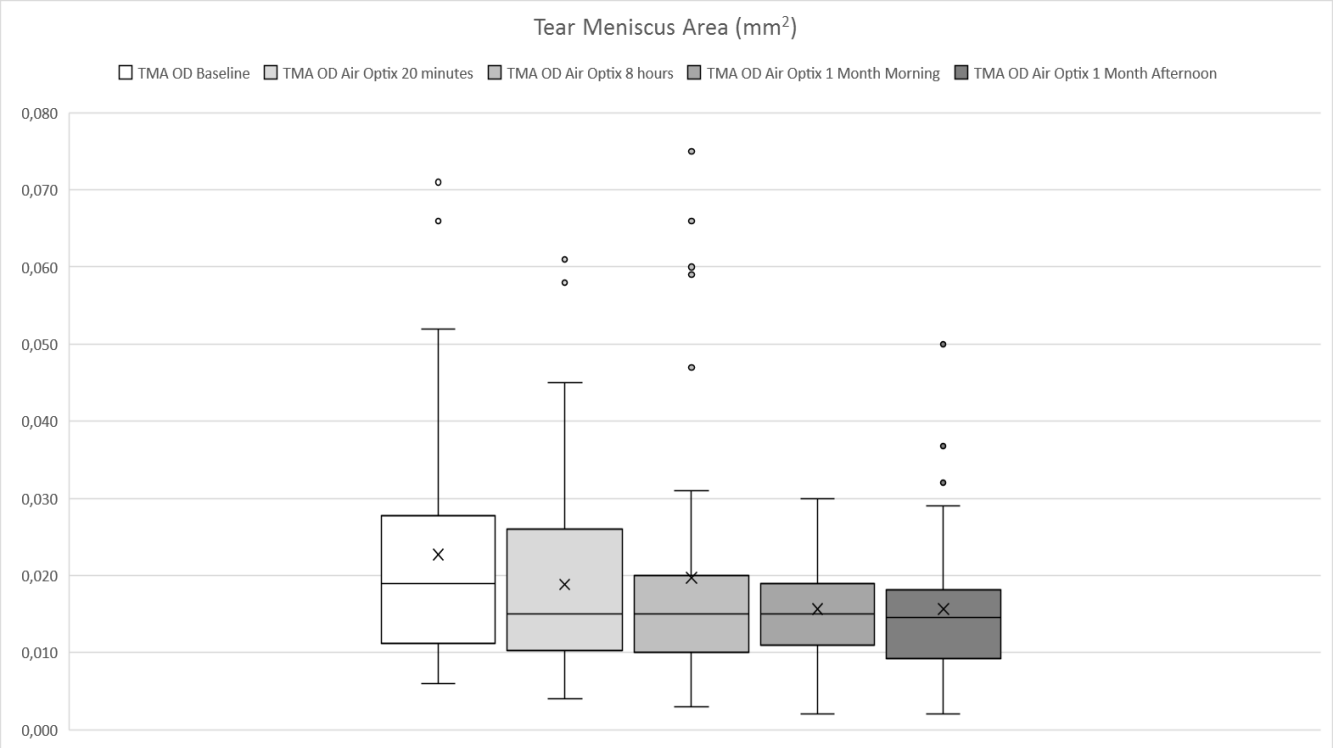

Figure 5.3.b. Box-plot of tear meniscus area at baseline, 20 minutes, 8 hours, one month morning and afternoon of CL wear for Lotrafilcon B. Medians are shown for each plot, quartiles are shown as boxes, ranges as whiskers and outliers as dots.

No statistical significant differences in osmolarity were found across the day and at the end of the month for each lens (Figure 3). When comparing both lenses, significant differences exist at (t1) (p=0.006) and at (t2) (p=0.002) values being greater for Delefilcon A.

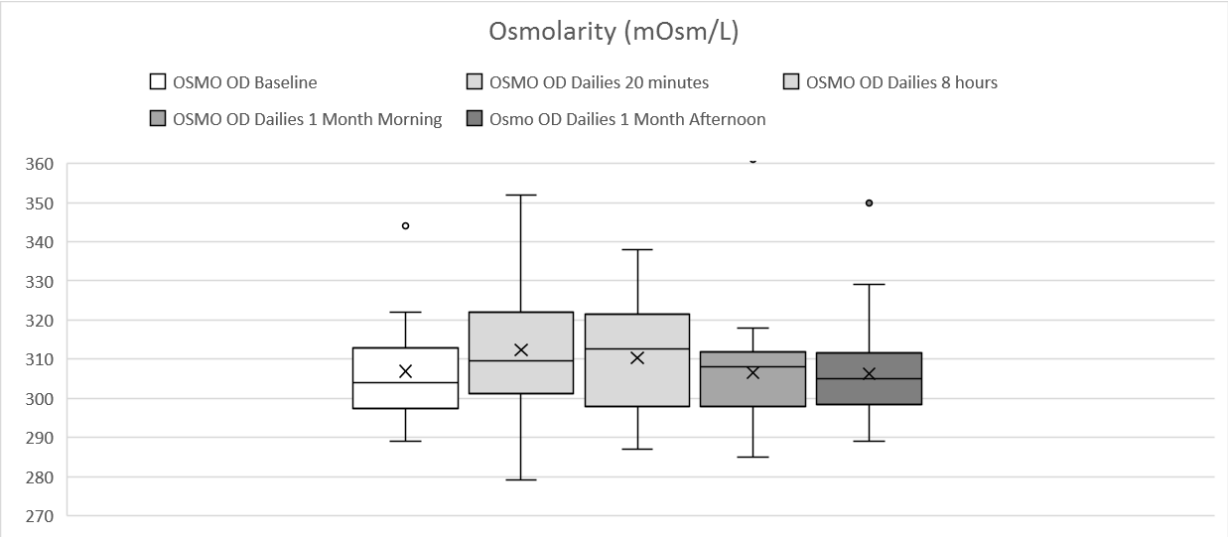

Figure 5.4.a. Box-plot of osmolarity at baseline, 20 minutes, 8 hours, one month morning and afternoon of CL wear for Delefilcon A. Medians are shown for each plot, quartiles are shown as boxes, ranges as whiskers and outliers as dots

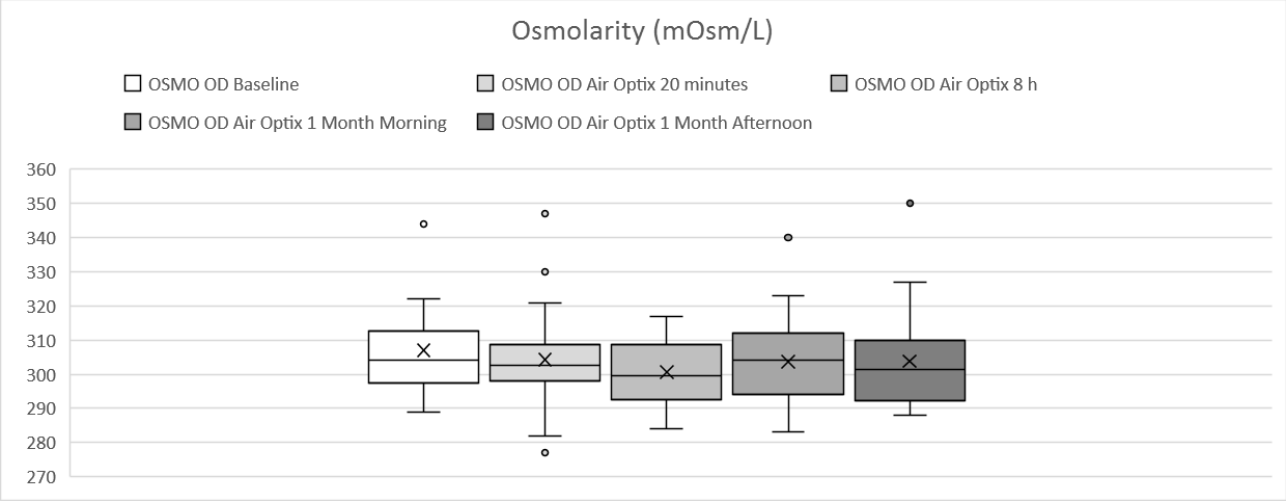

Figure 5.4.b. Box-plot of osmolarity at baseline, 20 minutes, 8 hours, one month morning and afternoon of CL wear for Lotrafilcon B. Medians are shown for each plot, quartiles are shown as boxes, ranges as whiskers and outliers as dots

4. Figure 4 shows the boxplot obtained for the total higher order root means square changes for both lenses with time. For the daily lens, mean values for (t0), (t1), (t2), (t3) and (t4) were

0.39, 0.63, 0.63, 0.68, 0.69 µm respectively. Regarding EW lens, mean values for (t0), (t1), (t2), (t3) and (t4) were 0.39, 0.61, 0.57, 0.63, 0.66 µm respectively. For both lenses, higher order aberrations were significant differences with time whereas Wilcoxon test found significant differences between (t0)/(t1), (t0)/(t2), (t0)/(t3) and (t0)/(t4) ($p<0.001$) for each lens respectively. No differences were found between lenses across the month of lens wear.

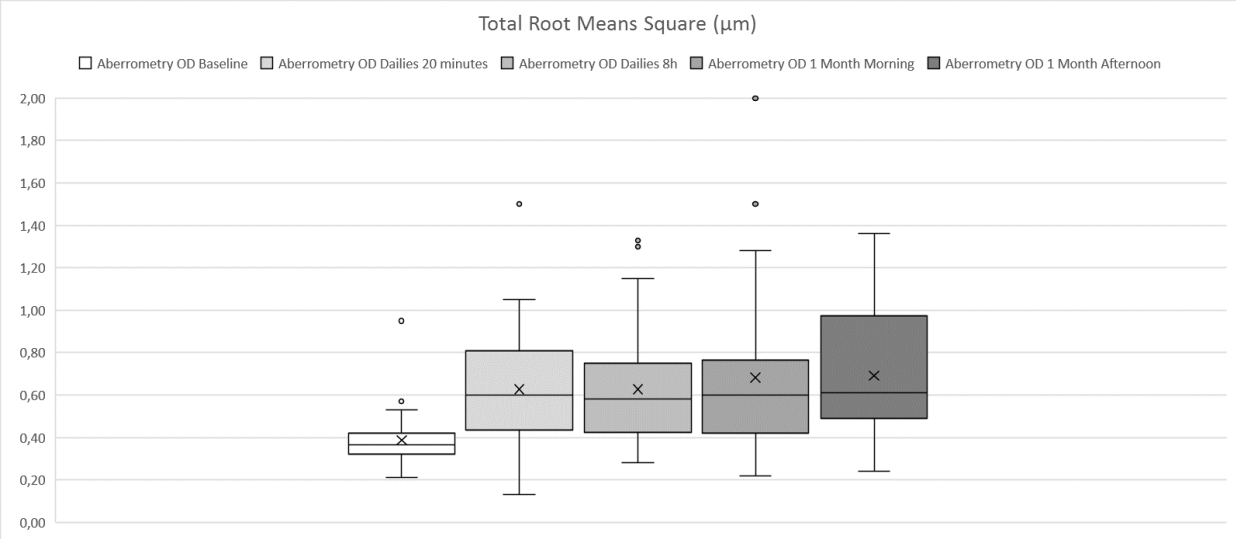

Figure 5.5.a. Box-plot of high order root means square at baseline, 20 minutes, 8 hours, one-month morning and afternoon of CL wear for Delefilcon A. Medians are shown for each plot, quartiles are shown as boxes, ranges as whiskers and outliers as dots

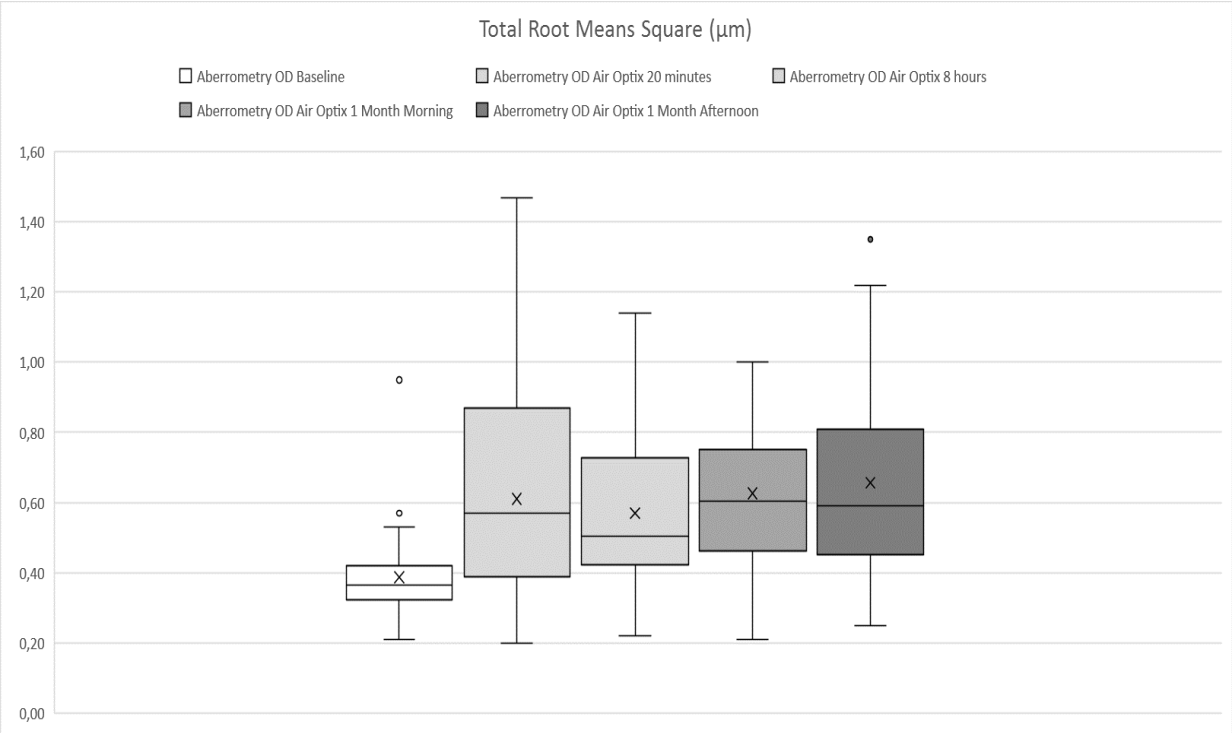

Figure 5.5.b. Box-plot of high order root means square at baseline, 20 minutes, 8 hours, one-month morning and afternoon of CL wear for Lotrafilcon B. Medians are shown for each plot, quartiles are shown as boxes, ranges as whiskers and outliers as dots

Significant differences in corneal thickness were found from lens insertion for both lenses as expected while the post-hoc analysis revealed statistically significant differences for all paired comparisons ($p<0.001$) for the daily lens excepted between (t1) and (t3) ($p=0.2$; Table2).

	Visante OCT				
DAILIES (Mean value± SD µm)	Baseline (t0)	20 minutes (t1)	8 hours (t2)	1 month morning (t3)	1 month afternoon (t4)
	526±28	660±43	653±41	657±41	655±41
	IOL Master				
	532±30	675±46	666±44	673±45	666±44

AIR OPTIX (Mean value ± SD µm)	Visante OCT				
	Baseline (t0)	20 minutes (t1)	8 hours (t2)	1 month morning (t3)	1 month afternoon (t4)
	526±28	625±34	622±34	626±34	623±35
	IOL Master				
	532±30	638±38	630±34	637±39	630±37

Table 13. Pachymetric measurements obtained with both devices.

Regarding EW lens, significant differences were found for all paired comparisons excepted for (t1)/(t3), (t1)/(t4), (t2)/(t4) pairs ($p>0.05$). When comparing both lenses, significant differences were found between all paired comparisons ($p<0.001$). The IOL Master 700 gave higher mean values for (t0), (t1),(t2), (t3) and (t4) of 532, 674, 666, 673, 666 µm and 532, 638, 630, 637, 630 µm for daily and EW lenses respectively. All paired comparisons showed significant differences ($p<0.001$) excepted when comparing (t1)/ (t3) and (t2)/(t4) values for both lenses ($p>0.05$). When comparing both lenses, significant differences were found between all paired comparisons ($p<0.001$).

5.4 Discussion

CLD, contributes almost at the same level as dryness (24% and 20% respectively) as the primary reasons for CL discontinuation [Nichols et al. 2013, Sulley et al. 2017]. Chao et al. identified various factors including ageing, female sex, and the medication used to treat systemic conditions as increased risk factors for DED, these factors being encountered as well in the “inherent patient factors” classification of CLD (Chao et al. 2016, Moss et al. 2008).

During CL wear, the interaction of the material with the TF separates it into PLTF and PoLTF. This affects its stability by modifying the lipid layer spread hence influencing TF evaporation, these series of events being directly linked to CLD [Markoulli et Kolanu 2017, Craig et al. 2013]. Friction plays as well a key role in CLD, as repeated interactions of CL material with conjunctiva during blink and eye movement (when the lid border moves over CL rim and along the anterior surface) has been shown to induce changes over the limbal and conjunctival area, possibly leading to positive vital staining of both corneal and conjunctival tissues as well as symptoms of ocular dryness [Efron et al. 2013].

The results of the OSDI questionnaire showed an average increase of 4.7 points across the month for the daily lens. However, as this increase was not statistically significant, this could be attributed to a noise in measurement and not a real effect of the CL material. Furthermore, the mean value of OSDI score (13.1 points) was just above the cut-off value (i.e 13.0 points) for dryness as defined by Wolffsohn et al. [Wolffsohn et al. 2017] which supports the hypothesis that comfort remained rather stable across the month of wear for this lens material. Regarding the EW lens, a significant increase in OSDI score occurred across the month of wear: from 8.5 to 24.4 points, which would correspond, according to the cut-off values previously described, to moderate ocular surface disease. CLDEQ-8 scores were 6.2 ± 3.8 points at baseline, 10.6 ± 8.5 points and 18.1 ± 9.8 points at one month for delefilcon A and lotrafilcon B respectively, and significantly different (P=0.01). Delefilcon A scores were below the cut-off value for CLD (i.e $\geqslant$12) [Chalmers et al. 2016], which was not the case with lotrafilcon B material, showing that the former indeed induced discomfort across the month of wear. Patients were randomly fitted with one of the two CL materials so as no bias was induced during the study.

According to Sulley et al. [2017b], overall performance of a CL material can be anticipated based on material physical characteristics such as modulus, oxygen permeability and thickness. Indeed, it is known that higher moduli silicone hydrogel CL materials are related to a higher rate of mechanical events, as greater stiffness is expected to impact CL edges and its interaction (mainly friction) with both bulbar and palpebral conjunctiva [Ozcan et al. 2010].

According to manufacturers' data, delefilcon A presents a very low surface modulus of 0.025 MPa (core of 0.76 MPa) whereas lotrafilcon B material has an overall modulus of 1.2 MPa making it more rigid. This could induce increased discomfort across the period of study compared to the daily CL material (as lens design affects lens comfort) and this partly explains the higher symptomatology scores obtained for the EW CL material. This will be discussed later with vital stainings.

TMA

Tear meniscus is believed to contain up to 90% of the TF [Holly 1985], which makes it a key parameter to assess the impact of CL wear on tear volume. AS- OCT is a valuable device to assess TF parameters changes over time non-invasively [Wang et al. 2006, Del Águila-Carrasco et al. 2015] due to the use of a light source outside the visible spectrum reducing photostimulation and thus possible induced reflex tearing [Shinzawa et al. 2017]. Besides, a high sensitivity and specificity for TMA has been found in diagnosing dry eye disease, 86.1% and 85.3% respectively [Czajkowski et al. 2012], make this device a valuable tool for diagnosis and follow-up of DED patients [Akiyama et al. 2017]. The goal of evaluating TMA in the present study was to assess in which extent CL wear alters this parameter. Baseline values were 0.023 ± 0.015 mm^2 which are in agreement with Wang et al. work (22,732 ± 11,974 μm^2 for healthy subjects) [Wang et al. 2006]. For both the daily and EW lenses, TMA decreased gradually from

baseline to the last visit, changes being significant only after 8 hours or longer. No significant difference occurred between 8 hours and 1 month of wear, which indicates that TMA remained rather stable over this period and both lenses performed similarly regarding this parameter. Previous works have studied tear meniscus volumes variation across the day in healthy and dry eye subjects finding stable diurnal values for both populations with however reduced values in the dry eye group [Shen et al. 2008] and in CL wearers [Del Águila-Carrasco et al. 2015]. Shen et al. [Shen et al. 2009] measured upper and lower TMA comparing two different soft CL materials with the naked-eye (i.e no CL). As with this study, 20 minutes from CL insertion, they found no significant differences in TMA values in comparison with the naked eye scenario. These results are partly in agreement with the current study; it is believed that this time interval is sufficient to stabilize reflex tearing that occurs in response to insertion. This was the case for the daily lens as no significant changes occur during the first day (t1 and t2) nor during the 4 weeks of wear (t3 and t4). Regarding both lens materials, a significant reduction in TMA values occurred from the first to the 30th day of wear (from 0.019 mm^2/0.020 mm^2 on the first day of wear to 0.017mm^2/0.016 mm^2 on day 30 for the daily and EW lens materials respectively). Since every participant of the study did not present any signs and symptoms of DED, it seems reasonable to surmise that the reduction in TMA values found in the present study might be due to: the destabilization of TF by CL material regardless of lens type as well as to the large day to day variability of this parameter. Indeed, CL wear directly impacts tear meniscus characteristics [Downie et Craig. 2017], and it is known that tear meniscus volume is significantly reduced from the time of lens application to end-of-day removal [Chen et al. 2009, Chen et al. 2010] by an order of approximately one-third [Craig et al. 2013]. In the present study, even if TMA values significantly decreased across the month of wear, these changes were clearly inferior to the values found by [Craig et al. 2013], which

allow us to hypothesize that both CL materials minimally impacted this parameter during the study. Since some factors, being controlled during the measurements sessions such as time of day, time after blink, temperature, humidity, air speed and illumination can influence TMA values [DEWS 2007, Johnson et Murphy 2007, Bandlitz et al. 2014b], the outliers found during the experiments could be due to remaining influencing factors such as measurement locus along the lid margin (it is indeed really difficult that the row of three measurements be exactly on the same locus) and biasing parameters such as conjunctivochalasis, disorders of lid margin congruity and apposition between lid margin and ocular surface [Ibrahim et al. 2010, Pult et Pult 2015]. No conjunctivochalasis or apposition issues were noted in the subjects enrolled in the study. However, lid margin congruity disorders (found in 4 participants), corresponds to MG atrophy and it is obvious that if this abnormality is located at 6 o'clock vertically to the corneal apex, the measurement could be easily jeopardized the TMA measurement since it is expected a superior amount of fluid to accumulate in the depression made by the atrophy and thus give greater values of TMA.

Osmolarity

Tear osmolarity is considered by some as the best single metric to diagnose, classify and monitor DED [Tomlinson et al. 2006, Lemp et al. 2011]. According to Potvin et al. 2015, [Potvin et al. 2015] hyperosomolarity of the ocular surface induces the activation of inflammation pathways leading to epithelial cell apoptosis and positive vital staining of the ocular surface, these series of events possibly challenging CL comfort. According to Keech et al. [Keech et al. 2013], a healthy population is expected to exhibit little day-to-day and visit-to-visit variation of osmolarity values. However, raised osmolarity in CL wearers is associated with CL increased symptomatology [Stahl et al. 2009]. In order to diagnose mild to moderate dry eye subjects, a

thresold of 308 mOsm/L is now widely accepted in clinical practice [Lemp et al. 2011]. Readings from the measuring device are expected to fall within a +/- 5 mOsm/L interval in healthy subjects according to the TearLab® device standard deviation [Wilson et Canavan 2013]. Previous studies have related CL use to low or moderate variations in tear osmolarity [Chao et al. 2016, Wolffsohn et al. 2017, Miller et al. 2004]. In the present study, only first-time CL users were included with no diagnosed DED and mean baseline value of osmolarity (i.e 307 mOsm/L) was below the cut-off value set up for the present experiment. Delefilcon A only showed a significant difference between (t1) (312mOsm/L) and (t4) (306mOsm/L), which however stays within the standard deviation of the device and just above the cut-off value for DED. Anyhow, this slight punctual raise in osmolarity is not clinically significant since it came back to baseline levels across the month of wear and did not lead to any significant changes in vital stainings. The EW material showed constant values of osmolarity between each visit as well, which allow us to hypothesize that both materials provide high compatibility and minimum disturbance with the ocular surface of first time presbyopic CL wearers.

Aberrations

Optical aberrations of the eye play a key role in the final retinal image quality [Liang et Williams 1997]. Assessing optical performance of modern multifocal CL materials is of great relevance as numerous presbyopic wearers complain of halos and contrast sensitivity reduction being the result of the sum of aberrations from both optical systems (i.e CL and eye) taken together [Lopez-Gil et al. 2002]. Once defocus and astigmatism are corrected by the CL, differences between a perfect wavefront and the human eye relies on HOAs mainly third order coma-like and fourth-order spherical aberrations [Patel et al. 2002, Peyre et al. 2005]. Both CL materials used in the present study provide the same geometry, i.e front aspheric center-near multifocal

design. This design, is expected to generate SA induced by the gradient power change from center to periphery of the optical zone which is originally designed by the manufacturers to increase the depth of focus in presbyopes. The induction of coma-like aberration is in direct relationship with the amount of decentration of CL material from the pupil center [Patel et al. 2002, Gatti et Lipener 2008]. Indeed, blinking and in a lesser extent, eye movement, displace the optical center of the lens from the visual axis. The association of raised SA (within the CL material) and coma gives an overall decrease of optical quality that was assessed in the present study as an RMS combination of both aberrations in order to follow-up changes of the total high order RMS and the influence of CL insertion on this parameter across a month of wear. In the present study, total RMS, regardless of CL material, significantly increases from CL insertion (REF). This was an expected outcome given both CL designs. At 20 mn after CL insertion, the set of high order RMS rose from 0.39 µm (i.e no CL/(t0)) to 0.60 µm (t1) for the daily lens and remained rather stable across the month of wear. Lotrafilcon B showed a similar behavior, total RMS rising from baseline/(t0) (0.39 µm) to 0.61 µm at (t1) and remained statistically unchanged during the study period except for the end of the day values ((t2)/(t4)) where a significant difference has been found (0.57 µm versus 0.66 µm respectively). One interesting point to raise here is that, when a CL is inserted on eye, the separation of TF into two layers makes it more prone (overall the pre-lens TF (PLTF)) to disruption and evaporation. Indeed, the normal pre-corneal tear film is expected to be around 3 µm thick whereas PLTF is expected to be 1 µm thinner [Chen et al. 2010, Nichols et King-Smith 2003]. Tear film quality/quantity, stability and dynamics play a key role in optical performance over the course of CL wear [Downie et Craig 2017] hence PLTF surface quality is an excellent indicator of the TF ability to prevent CL surface dehydration.

Surface wettability and water content of the CL material are the main parameters that can impact PLTF quality [Tonge et al. 2001, Jones et al. 2002b] as local variations of PLTF thickness directly impacts the amount of aberrations being measured [Montés-Micó et al. 2004a, Erdélyi et al. 2006]. In the present study, the CL materials are different and, even if both are silicone-hydrogel lenses, their water content and core structure do differ. On the basis of this observation, significant differences were expected to be found across a month of wear regarding PLTF quality. However, no disparities were found when comparing lenses, except for the end of the day values ((t2)/(t4)) which suggests that PLTF might have showed local end of the day variations regarding lotrafilcon B. Pre-lens TFSQ and dynamics were minimally impacted across a month of CL wear. However, it would have been interesting evaluating this parameter over a longer period of wear as previous works reported that up to 25% of the patients wearing their lenses up to 16 hours [Riley et al. 2005]. The duration evaluated in this study gives valuable information, but does not represent a typical day for usual CL wearers [Riley et al. 2005, Wolffsohn et al. 2015].

Pachymetry

New high Dk soft CL silicone-hydrogel materials minimally impact corneal swelling [Covey et al. 2001, Keay et al. 2000, Stapleton et al. 2001, Dumbleton et al. 2001, Nilsson 2001, Papas et al. 1997] and hypoxic effects of those silico-hydrogel materials are considered to be negligible. Both CL materials have been worn for a limited period of one month and no or minimal corneal changes were expected to occur. Furthermore, as CL edges (back surface) are very difficult to delimitate using the Visante device due to the reduced resolution of the back surface of the CL (index changes from CL material to TF and anterior corneal surface) and given that the IOL master does not allow for a manual delimitation of the central CL edges, it was

decided to consider the complex Cornea-CL as a whole and baseline CCT as a constant in order to evaluate and compare variation of lens thickness across a month of CL wear. The main goal here was to assess the evolution of CL material thickness over time and to explain the possible causes of it. According to previous studies [Hong et al. 2012, Huang et al. 2010, Li et al. 2008, Rao et al. 2011, Mohamed et al. 2007], baseline CCT values acquired with OCT in healthy eyes ranges between 520 – 545 µm, comparable to the values obtained in this study, i.e, 526 ± 28 µm. Values obtained with both devices are summarized Table 2.

Regarding the daily lens using the IOL Master device, mean CCT varied from an average 675 µm at (t1) to 666 µm (t2) and from 673 µm (t3) to 666 µm (t4). This corresponds to a 1.33% and 1.04% decrease respectively in cornea-Daily CL central thickness and differences between each morning as well as between each afternoon were not statistically relevant. This allow us to hypothesize that CL material do dehydrate during wearing time and that the dehydration rate remain rather stable from one daily lens to another across the month of wear. The Visante OCT gave similar results and lead to similar conclusions; mean CCT varied from an average 660 µm (t1) to 653 µm (t2) and from 657 µm (t3) to 655 µm (t4). This corresponds to a 1.1% and 0.3 % decrease respectively in CL central thickness of the daily lens and the difference between each morning as well as between each afternoon were not statistically relevant. IOL Master device for the EW lens showed a decrease in overall thickness across the month: mean Lotrafilcon B-CCT varied from an average 638 µm (t1) to 630 µm (t2) and from 637 µm (t3) to 630 µm (t4). This variation was for the Visante from an average 625 µm (t1) to 622 µm (t2) and from 626 µm (t3) to 623 µm (t4).

This corresponds to a 1.3% and 1.1 % decrease for the IOL Master and 0.5% for the Visante in CL central thickness of cornea-monthly CL and the difference between each morning as well

as between each afternoon were not statistically relevant for both devices. An interesting fact is the slight superior in-vivo dehydration rate of the Delefilcon A lens that was found in the current study. Delefilcon A is a layered material composed of a silicone core (water content 33%) and a silicone free (or hydrogel) outermost part with a water content superior to 80%. Lotrafilcon B is a polymer that requires surface treatments to hide the silicone from the surface of the lens to keep it wettable. According to the model developed by Fornasiero et al. 2006 [Fornasiero et al. 2006], in vivo hydrogel CL dehydration takes place during blink cycle. A fresh PLTF is deposited on the CL upon each blink [Miller et al. 2004, Wong et Fatt 1996] which allows for the hydration of the CL. However, water evaporation mainly due to the environment induces decrease in PLTF thickness to the point that it finally ruptures, and if that break occurs during the blink interval, the exposed CL surface loses water. Water content of the anterior surface of the CL decreases inducing water flow from the PoLTF giving rise to lens dehydration. This is partly what is thought to happen in the delefilcon A scenario as the dehydration process could be divided into two different stages: a continuous and progressive dehydration across the day as explained earlier since the outermost part of the CL (in contact with environment on one side and PoLTF on the other side) can be considered as a hydrogel material on a behavioural point of view, but also an immediate surface water loss upon material insertion as reported by Schaffer et al. [Schaffer et al. 2015]. Indeed, previous studies evidenced a rapid surface dehydration of this material upon insertion, the surface refractive index swiftly shifting towards the silicone core water content index [Schaffer et al. 2015, Szczesna-Iskander et al. 2014].

However, these events must be taken with caution as in the present study, the dehydration process, although present, was really limited and did not present any statistical significance. Furthermore, as discussed before, TFSQ remained stable across the day and month of wear

showing that CL anterior surface maintained the same slighty reduced water content from lens insertion to the end of the day. Lotrafilcon B showed an inferior overall dehydration rate during the month of study which leads to one of the possible limitations of the present study. Indeed, dehydration estimates for this CL material were obtained without taking into account the possible depositions on the CL material [González-Méijome et al. 2013] that could possibly influence central CL thickness measurements and surface wettability. However, existing literature and clinical experience of the examiner showed a certain trend: lotrafilcon B has one of the lowest affinity for tear lipids [Carney et al. 2008] and protein adsorption such as lysozyme among silicone-hydrogel materials [Chow et al. 2009, Zhao et al. 2009]. Lens care system used in this study was Optifree Replenish and it could be hypothesized that the non significant decrease in dehydration across the month could partly be attributed to the lens care-induced increased capacity of retaining water [González-Méijome et al. 2013]. More studies are needed to better understand the influence of lens care systems on overall behavior of the CL materials on-eye. Values of dehydration obtained in the present study, regardless of the lens type, were inferior to the values reported by Morgan and Efron 2003 or by Gonzalez-Meijome et al. [Morgan et Efron 2003, González-Méijome et al. 2013]. One explanation for these differences is wearing time as in their studies CL were worn for a 10 hours period and more evaporation is expected to occur during this time span.

TFBUT and vital staining

Due to the lack of non-invasive methods to assess TF stability, it was decided to evaluate this parameter using a fluorescein dye according to Mooi and al. standards in order to minimize the impact of fluorescein on clinical measurements [Mooi et al. 2017]. In the current study, mean values of baseline TFBUT were 10.4± 2.3 seconds above the cut-off values for dry eye

[Mooi et al. 2017] significant differences were found between baseline, 8 hours and the end of the month for the daily CL material with a gradual decrease of FBUT values across the month of wear. This was the case for the EW lens even if no difference was found when comparing values at 8 hours and at the end of the month. No difference between each CL material has been evidenced which seems be due to the very ressembling parameters and on-eye behaviour of both CL materials.

Corneal and conjunctival staining decreased from baseline across the month of wear for both lenses. However, from the 40 patients included in the study, 18 reported end of the day discomfort (t2 and t4) with mild symptoms when wearing the EW lens resulting in positive staining described by the investigators as a “Circumlimbal staining sometime continuous, sometime discontinuous corresponding to CL edges located at 1-3 mm from the limbus ”. It seems reasonable to hypothesize that interaction of the conjunctival epithelia with CL edges design and modulus directly impacts superficial cells giving rise to positive staining as it has been suggested by Sapkota et al.2016 and Radford et al. 2009 [Sapkota et al. 2016, Radford et al. 2009]. Chao et al. [Chao et al. 2017] found an association between EW CLs wear and an increase in tear CKs and conjunctival staining in comparison with daily disposable wearers. This could be induced by the use of multipurpose solutions with EW CLs which are associated with an increase in CKs levels [Kalsow et al. 2013] and the possible accumulation of debris across the month of wear, which could increase friction forces at the edges of the lens giving rise to this pattern. However, it is unlikely to have occured in our study since circular staining was already visible after 8 hours of wear and it is thought to be due to CL material edges interaction with the conjunctival epithelia.

5.5 Conclusions

Attempts to target unmet needs for a growing presbyopic population especially regarding CL fitting strategies require previous identification of the changes taking place in the LFU, how they affect the ocular surface and in which extent the insertion of a CL would affect this set of structures or worsen an already unbalanced ocular environment. Both CL materials fitted in this study provided satisfactory and similar objective on-eye behaviour and remained rather stable along the experiment period. However, subjective symptoms showed a greater increase from baseline regarding the extended wear lens. Comfort seems to be impacted by CL material modulus, parameters of both CLs being otherwise very ressembling.

CHAPTER 6

COMPARISON OF THE INFLUENCE OF CORNEO-SCLERAL AND SCLERAL LENSES ON OCULAR SURFACE AND TEAR FILM METRICS IN A PRESBYOPIC POPULATION

6.1 Introduction

ScLs are rigid gas permeable devices that are supported entirely by the conjunctival tissue overlying the sclera and vault the cornea and limbus [Schornack et al. 2015]. Their major advantage lies in the vaulting of the cornea (and the subsequent apical clearance) that avoids direct mechanical stress to this ocular tissue. The development of new lens materials, computer-generated lens devices as well as new insights into the anterior scleral shape and corneo-scleral junction have contributed to improve designs and oxygen transmissibility allowing better ocular health, longer wearing time and ease of lens fit [Pearson 2007, Ezekiel 1983, Bavinger et al. 2015, Van der Worp 2015]. ScLs are typically prescribed for corneal ectasia (primary corneal ectasia like keratoconus) [Barnett et Mannis 2011] and ocular surface diseases when a patient's corneas shows intolerance to other forms of vision correction (rigid gas permeable and soft lenses materials) and does not provide adequate visual acuity to the patient [Schornack 2015]. ScLs have shown good results in patients with graft versus host disease, DED and exposure keratopathy among others [Schornack 2015], but also for high ametropias [Visser 1997] and for cosmetic purposes such as in atrophia bulbi [Van der Worp 2015, Tan et al. 1995].

As well as the prevalence of DED increasing with age, systemic disorders (and the medication associated with them) are recognized as risk factors that might jeopardize ocular surface homestasis and induce dry eye signs and symptoms [Chao et al. 2016]. Fitting CLs in a presbyopic population is as such expected to be more challenging in comparison with a younger sample. However, presbyopics patients could benefit from wearing ScLs; multifocal designs such as centre near or centre distance vision exist and these present a great advantage over conventional rigid gas permeable lenses devices (lens stability on eye due to reduced movement) and in a lesser extent over multifocal soft CLs (optical quality and resulting higher

contrast sensitivity) [Van der Worp 2015]. ScLs allow for a better centration of the lens and an easier adaptation to simultaneous images due to the stability of the image provided by the scleral design. Furthermore, ScLs have demonstrated interesting qualities in maintaining homeostasis beneath the lens [Bavinger et al. 2015, Van der Worp 2015, Barnett et Mannis 2011].

However, even if a larger CL diameter would provide more stability regarding multifocal designs, to the best of our knowledge academic literature is missing in the matter of how CL diameter changes affect ocular surface physiology as well as tear quality/quantity of presbyopic patients. Thus, it may be interesting to research into the differences between a full ScLs and a smaller diameter lens that partly rests on the sclera [corneo-scleral lenses (C-ScL)]. Theses CLs offer more consistent visual performance, due to the larger optic zone and increased stability, than corneal CLs.

Thus, the aim of this study was to assess and compare the effect of the C-ScL and ScLs on TF parameters and corneal thickness in healthy presbyopic subjects.

6.2 Methods

This prospective study was conducted in the Valencia's University laboratory facility, Valencia, Spain. The project was approved by the Ethical Committee of our institution. Patient's consent forms were obtained for all participants. The clinical study adhered to the tenets of the Declaration of Helsinki. As part of the study screening, each of the participants underwent a comprehensive ophthalmic examination, which included, in the order as follow: visual acuity, refraction, slit lamp biomicroscopy, topographic examination using the topographer Atlas 9000, ocular fundus examination, horizontal visible iris diameter measurement using a ruler to nearest 0.5 mm and CCT measurement using OCT. Patients who experienced any anterior

segment pathology, previous corneal surgery, corneal abnormalities, chronic DED or ocular fundus abnormalities were excluded from the study. The subjects wore two contact lenses, randomly assigned, with neutral power and different diameters [12.7 mm (C-ScL), 18 mm (ScL) Figure 6.1] and being the samefor the other parameters: material (HS100) and central thickness (0.29mm) (Tiedra Farmacéutica SL, Alcorcón, Spain).

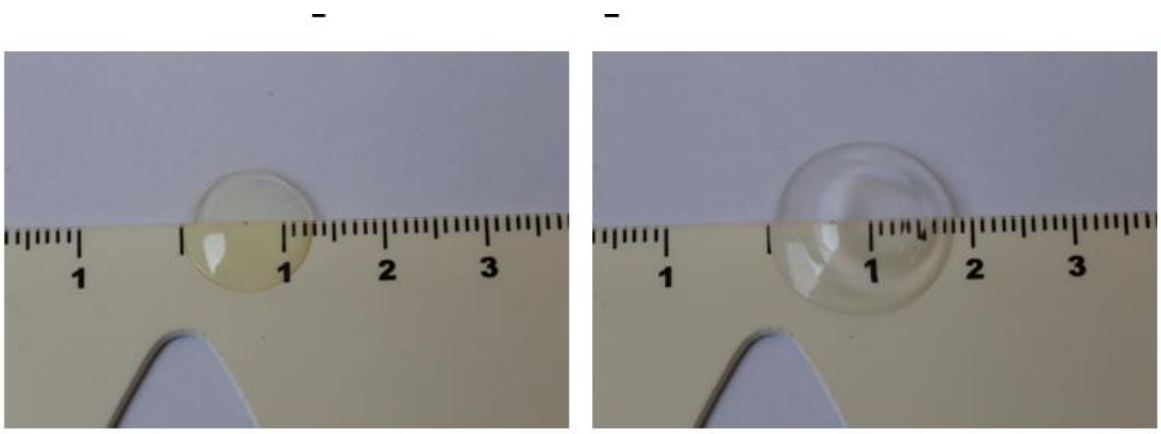

Figure 6.1. C-ScL diameter: (12.7 mm), ScL (diameter 18 mm)

At baseline, 20 min margin (t1) and 8 hours margin after insertion (t2), the area of the tear meniscus was evaluated with OCT (SL SCAN-1, Topcon) as well as CCT and tear osmolarity. CL wear has been discontinued for four days between each measurement in order for the eyes to fully recover.

Details of the AS-OCT imaging technology have been described previously (Izatt et al. 1994; Radhakrishnan et al. 2001). An anterior segment OCT [coupled with a slit-lamp was performed in order to assess the tear meniscus parameters of the inferior eyelid using the B-scan mode and scanning at 6 o´clock the inferior eyelid right below the centre of the pupil. TMA [Czajkowski et al. 2012], the triangular area delimited by the anterior corneal boundary, anterior boundary of the lower eyelid and anterior borderline of the tear meniscus was calculated using an image analysis software imageJ (http://imagej.nih.gov/ij/). The same

examiner carried out all of the three measurements for each patient as well as manual demarcation of the boundaries of the TM.

The global corneal “pachymetry map” protocol of the Visante OCT was used to capture 8 radial scans centered on the corneal vertex reflection. Each scan line was 10 mm long, with a transverse resolution of 60 µm and a vertical resolution of 18 µm. Three consecutive scans were carried out for each eye by the same examiner.

Tear film osmolarity was measured using a laboratory-on-a-chip system which analyzes the electrical impedance of a 50 nanoLiter (nL) tear sample taken from the inferior lateral meniscus of both eyes of the patient. Osmolarity values below 308mOsm/L are considered as normal [Lemp et al. 2011]; readings between 308 and 325 mOsm/L are representative of mild-to-moderate dry eye, and values above 325mOsm/L indicate the severe state of the disease [Foulks et al. 2009].

Statistical analysis

Measurements were evaluated using SPSS v.22 (IBM Corp., New York). Normality was evaluated by the Shapiro-Wilk test. To analyze the results as a function of the lens wearing time a repeated measures analysis of variance (rANOVA) was performed to reveal significant differences among time periods; Greenhouse-Geisser correction was applied when the rANOVA sphericity assumption checked using the Mauchly's test was breached [Box 1965]. Bonferroni correction was applied to post-hoc tests for comparisons between time periods. When normality of data groups could not be assumed, a non-parametric Friedman test was performed. Then, if needed, a Wilcoxon signed-rank or a Sign test, depending on the symmetry of the differences distribution, was performed as a post-hoc test. To analyze the results as a function of the diameter of the lens, a Student’s t test for related samples was

used when normality can be assumed, while a Wilcoxon signed-rank or a Sign test was used when normality could not be assumed. The statistical significance limit was set at $p<0.05$.

6.3 Results

Thirty eyes from thirty presbyopic subjects (average age from thirty presbyopic subjects (average age 54 ± 4 years, range: 46-63 years) completed the study.

Analysis as a function of the lens wearing time

Boxplots obtained for the tear meniscus area for the both designs are shown in Figure 6.2. For the C-ScL, median values for basal, 20 min, and 8 hours were 0.0213, 0.0216, and 0.0152 mm^2, respectively. For the ScL, median values obtained for basal, 20 min, and 8 hours were 0.0213, 0.0205, and 0.0137 mm^2, respectively. For both lenses, Friedman test revealed statistically significant differences with time ($p<0.001$), while the post-hoc analysis revealed only significant differences between the measurements taken at 8 hours and the other two earlier time periods ($p<0.001$).

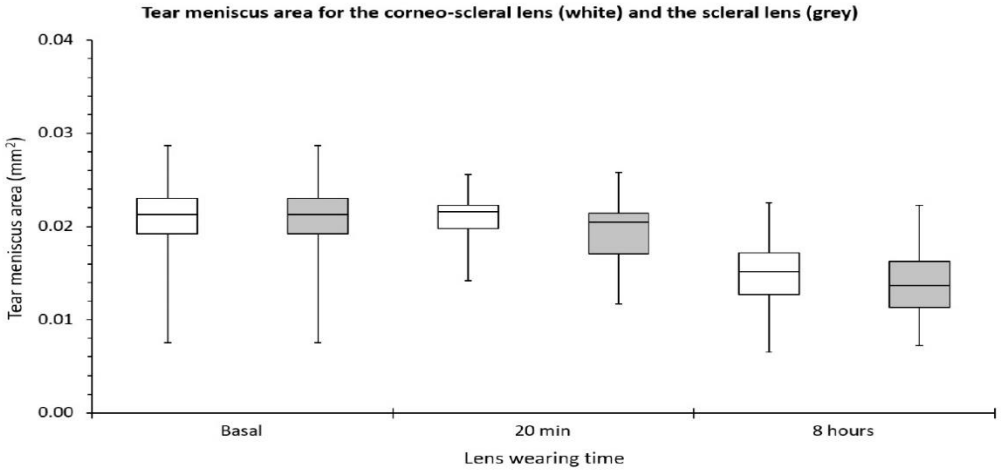

Figure 6.2. Boxplots over time obtained for the tear meniscus area for the corneo-scleral lens (white) and the scleral lens (grey)

Boxplots for the central corneal thickness for the both designs are shown in Figure 6.3. For the C-ScL, median values for basal, 20 min, and 8 hours were 549, 555, and 563 µm, respectively. For the ScL, median values obtained for basal, 20 min, and 8 hours were 549, 556, 577 µm, respectively. For both lenses, Friedman test was statistically significant between visits ($p<0.001$), while the post-hoc revealed statistically significant differences for all paired comparisons ($p<0.001$).

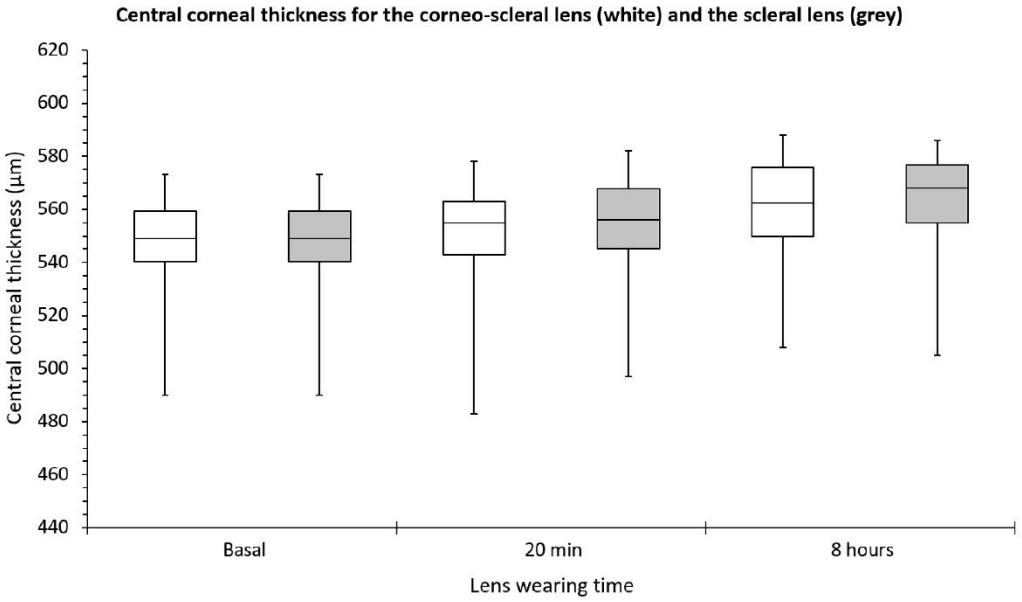

Figure 6.3. Boxplots over time obtained for the central corneal thickness for the corneo-scleral lens (white) and the scleral lens (grey).

Figure 6.4 shows the boxplots obtained for the osmolarity changes for both lens designs with time. For the C-ScL, mean values for basal, 20 min, and 8 hours were 296, 298, and 305 mOsm/L, respectively. For the ScL, mean values for basal, 20 min, and 8 hours were 296, 299,

and 306 mOsm/L, respectively. For both lenses, the rANOVA procedure revealed statistically significant differences between visits ($p<0.001$), while the post-hoc revealed statistically significant differences between all paired time periods ($p\leq0.002$).

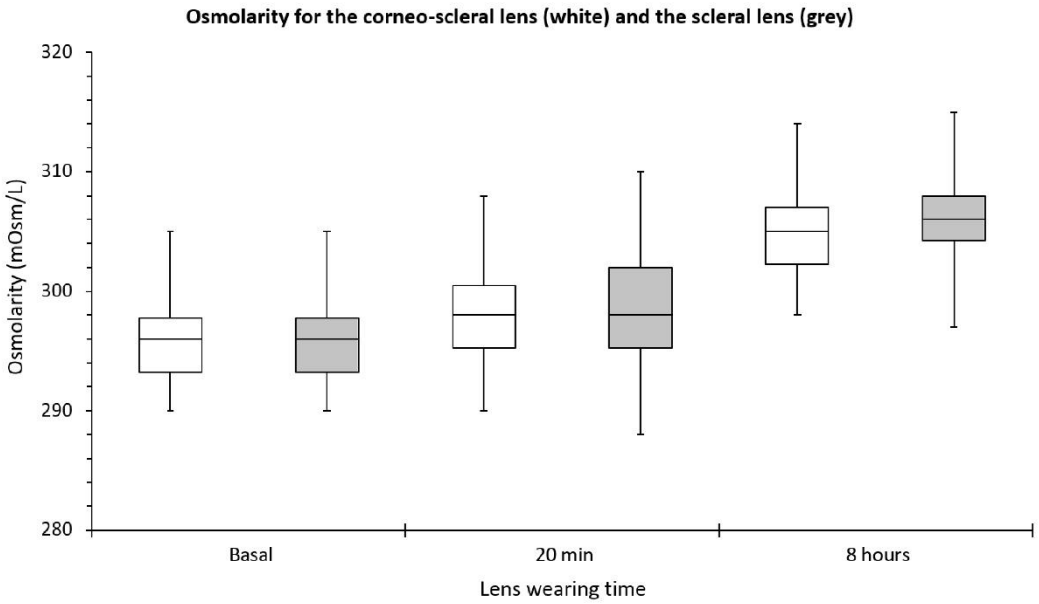

Figure 6.4 Boxplots over time obtained for the osmolarity for the corneo-scleral lens (white) and the scleral lens (grey).

Analysis as a function of the lens diameter

The tear meniscus area revealed statistical differences for both lenses at 20 min ($p<0.001$), and also at 8 hours ($p=0.003$), being greater for the C-ScL. The central corneal thickness revealed statistical differences for both lenses at 20 min ($p=0.002$), and also at 8 hours ($p=0.001$), being lower for the C-ScL. Osmolarity did not reveal statistical differences at

20 min (p=0.29), while it was statistically different at 8 hours (p=0.03), being lower for the C-ScL.

6.4 Discussion

The aim of this study was to assess and compare the effect of the C-ScL and ScLs on TF parameters and corneal thickness in healthy presbyopic subjects. In this study, statistical significant decreased occurred in TMA regarding both CLs being more marked for ScL. CL wear induces decreases of tear meniscus values across the day [Chen et al. 2009; Chen et al. 2011), Wang et al. 2009, Le et al. 2009]. Moreover, CL wear is known to negatively impact the TF, separating it into two parts; pre and post lens TF, making it thinner and more susceptible to evaporation [Guillon et Maissa 2008, Tomlinson et Cerdastaff 1982] and disruption [Muntz et al. 2015]: C-ScL showed a 29% decrease in TMA across the day whereas the diminution was up to 36% regarding the ScL. When a ScL is fitted on an eye, little to no movement is expected which is not the case with a C-ScL, the latter providing greater mobility and tear exchange under the lens. This is a very important point to take into account when comparing both designs. Indeed, movement and tear exchange (C-ScL) versus an almost sealed post-lens TF (ScL), coupled with increased instability of the tears induced by the insertion of the material and its interaction with TF, could explain the significant differences in TMA found at the end of the day.

Failure to deliver proper amounts of oxygen to the cornea during CL wear might induce corneal oedema, observed as increased CCT, as one of the numerous complications [Klyce 1981, Michaud et al. 2012] that can occur secondary to CL induced hypoxia. It is acknowledged that the great majority of ScCLs available on the market, once placed on eye and thus forming

a tear reservoir beneath the lens, do not meet either the Holden and Mertz (central cornea) or Harvitt and Bonanno's (limbal area) criteria for oxygen permeability [Harvitt et Bonano 1999, Bland 2012, Dalton et Sorbara 2011, Tan et al. 1995]. However, clinical manifestation of corneal oedema is seldom seen in clinical practice [Klyce 1981, Michaud et al. 2012].

ScLs, once settled on the sclera, have a tear reservoir beneath the lens which is believed to be almost sealed [Tan et al. 1995, Fatt 1997, Weissman et Ye. 2006, Bergmanson et al. 2015, Cotter et Rosenthal 1998]. Hence the perpendicular outflow of oxygen through the material and its further mixing with the tear reservoir is more important than transversal tear exchange that could occur between tear reservoir and peripheral tears [Bergmanson et al. 2015] Michaud et al. calculated that a lens would need parameters of central thickness of 250 µm, Dk 100 and central clearance of no more than 100 µm to give Dk/t of 26.5, above the cut-off value of Holden and Mertz [Michaud et al. 2012, Fatt 1997, Weissman et Ye 2006] and the more recent findings of Morgan et al [Morgan et al. 2010] for daily wear. Previous studies have investigated the correlation between tear clearance, central lens thickness and corneal hypoxia [Morgan et al. 2010, Jaynes et al. 2015].

In our study, an average 2.6% (C-ScL) and 5.1% (ScL) CCT increase occurred across the day of lens wear. CCT changes can be directly related to patient specific corneal physiology as it is acknowledged that corneal response to hypoxic stress is specific to each individual and is subject to a great variability [Benjamin et Hill 1988]. However, the 2.6% increase found in this study is in agreement with Mountford et al. and corresponds to 1µm per hour CCT increase, result obtained in the former study with a 120 Dk material [Mountford et al. 1994]. It allows us to hypothesize that since the lenses were of the same material and transmissibility, the combination of movement induced tear exchange beneath the lens on one hand and a

sufficiently low tear clearance on the other hand, explain lower values of CCT increase across the day by bringing (laterally) more oxygen to the area under the lens and by efficiently mixing (transversally) the transported oxygen to the underlying tear pool to nourish properly corneal tissue.

Tear film osmolarity assessment is proven to be an effective diagnostic tool for dry eye disease [Chen et al. 2009, Chen et al. 2011, Wang et al. 2009, Tsubota et Yamada 1992, Gaffney et al. 2010; Gilbard et Farris 1979, Baudouin et al. 2017]. Tear osmolarity increases have been associated with CL wear in some studies [Muntz et al. 2015, Iskeleli et al. 2002, Stahl et al. 2009], whereas other studies evidenced no changes [Sarac et al 2012, Benjamin et al. 1983]. According to Efron and colleagues, it is thought increase tear evaporation inducing electrolyte concentration changes could explain tear osmolarity build up associated with CL wear [Tomlinson et Cedarstaff 1982, Romero-Rangel et al. 2000].

Over the past decade, there has been a growing interest in using ScL for the treatment of DED by protecting the ocular surface [Rosenthal et Cotter 2003, Rosenthal et Crotteau 2005, Rosenthal et al. 2000, Schornack et al. 2014, Weyns et al. 2013, Takahide et al. 2007, Pullum et Buckley 2007, Alipour et al. 2012, Papakostas et al. 2015] due to advances in CL materials and oxygen permeability [Bland 2012, Bergmanson et al. 2015, Weyns et al. 2013, Takahide et al. 2007, Pullum et Buckley 2007, Alipour et al. 2012, Papakostas et al. 2015]. Weber et al found a significant decrease of osmolarity in severe dry eye patients adapted with ScLs for 6 months; the vaulting of the cornea and conjunctiva is believed to prevent evaporation and the tear reservoir maintains direct contact between tears and corneal tissue in addition to playing the role of interface protecting the cornea from possible abrasion from eyelid conjunctiva irregularities or trichiasis [Benjamin et Hill 1988, Weber et al. 2016]. In our study, only healthy

presbyopic patients were recruited without any anterior segment signs or symptoms of DED; baseline osmolarity was below the cut-off value for the disease and this remained the case even with the significant increase in osmolarity over the 8 hours of wear. Further studies are needed to better assess the influence of lens diameter over this parameter over a longer period of wear. Furthermore, as suggested by Carrecedo et al., it would have been interesting comparing osmolarity measurements just before and after removal of the ScL as it is expected that the release of the tears held under the scleral lens vault might increase tear meniscus volume and thus modify the final value of osmolarity, giving further information about the retained volume of tears beneath the lens [Carracedo et al.2016].

6.5 Conclusion

Ageing population is more prone to develop DED as increased aged is associated with higher prevalence of systemic and ocular disorders that may disturb anterior segment homeostasis. ScLs present a double advantage for this population as ScL can be a good optical platform for correcting presbyopia through multifocality as well as protecting the ocular surface by vaulting the cornea. Further studies are needed to better identify the benefits of the ScL could bring to an older population with anterior segment pathologies and to better understand ScL potential role in restoring/maintaining ocular surface homeostasis over longer periods of time.

CHAPTER 7

THE IMPACT OF CATARACT SURGERY ON TEAR FILM METRICS, OCULAR SURFACE AND MEIBOMIAN GLAND FUNCTION

7.1 Introduction

The increase in world population is accompanied by significant aging, as recent estimates from the Lancet Series on Ageing expect 2 billion people over 60 years old by 2050 [The Lancet. Series on Ageing. 2014; November 6]. Because the incidence of cataract increases with age, the growing elderly population is expected to lead to a significant increase in cataract prevalence [Gupta et Ram. 2017]. For instance, from the 26 million Americans affected by cataract [Wittenborn et Rein. 2014], one out of four is aged between 65 and 69 years old, this proportion increasing to almost seven people out of 10 for people aged 80+ years [Friedman et al. 2012]. Social and economic burden of this age-related condition is undeniable in developed countries [Abraham et al. 2006, Resnikoff et al. 2004] as recent estimates from 2015 evaluate direct costs of cataract in the United States to approach $ 12 billion [Mariotti 2012]. Besides, cataract surgery remains an important healthcare expense in Europe [Prokofyeva et al. 2012]. The prevalence of cataract in Europe increases with age from 5% for aged based population between 52-62 years old [Moshetova et al. 2009], to 30% for 60–69 years old and up to 64% for the population over 70 years [Das et al. 1990]. Cataract surgery is the most commonly performed ophthalmic procedure worldwide with more than 23 million operations in 2014 [Freeman 2014]. According to the WHO, this number is very likely to reach 32 million by the year 2020 as the population over 65 years old is expected to double between 2000 and 2020 [Brian et Taylor 2001].

Phacoemulsification is the main technique used for cataract surgery accounting for 90% of the procedures in developed countries [Leaming 2004]. The goal of the surgery is double: to restore quality of the optical media and change the refractive power of the eye with the possibility to correct presbyopia with the use of foldable IOLs [Skiadaresi et al. 2012]. Phacoemulsification technique remained almost unchanged through the years as introduced

by Charles Kelman in the 1970s including: manual minimal corneal incision, capsulorrhexis and phacoemulsification using ultrasound energy [Nagy et al. 2009] making this surgery an efficient and safe procedure. However, the introduction of femtomsecond laser for cataract surgery in 2009 [Nagy et al. 2009] is considered a breakthrough in ophthalmic surgery: its combination with a computer controlled delivery systems allow for precise incisions with limited collateral damage to surrounding tissues [He et al. 2011, Seitz et al. 2003, Sugar 2002]. The main drawback of this advanced technology relies on its high cost. A recent review comparing both techniques underlies the fact that femtomsecond laser improves reproducibility and precision of corneal incision [Dick et Schultz 2017] possibly reducing corneal nerve damage and a major potential adverse effect of the surgery: DED. Dry eye after cataract surgery or worsening of signs and symptoms of dryness are not uncommon as this procedure is invasive and the limbal incision necessary to gain access to the posterior chamber where the clouded lens is located, induces damages to the corneal nerves and cells. However, pre-existing MGD, the most common cause of evaporative dry eye [Foulks et Bron 2003, Bron et Tiffany 2004] could be an important factor influencing surgery outcomes as suggested by Han et al. [Han et al. 2014]. Indeed, it is recognized that increasing age goes hand to hand with an increased loss of meibomian glands acini. From the 236 patients aged 4-98 years old evaluated by Arita et al. using meibography , gland dropout was found to be significant for participants over 20 years old [Arita et al. 2008]; in contrast, Villani et al. [Villani et al. 2013] found the decrease in the number of acini to be most noticeable at 50 and 60 years of age. These results are consistent with previous studies from Norn and Den et al. reporting increased changes in meibomian glands after 40 years of age [Norn 1987, Den et al. 2006]. These works suggest that age-related acinar atrophy leads to an initial loss of acini followed by further obstruction of meibomian glands, the former leading to obstructive MGD [Bron et

al. 2017]. Three main forms of MGD have been identified, hyposecretevive, hypersecretive and obstructive, the latter being the most common type [Foulks et Bron 2003, Knop et al. 2011]. The obstructive subtype is the main factor responsible for a reduced amount of meibum delivered on the ocular surface eventually giving rise to EDE, or "MGD-dependent EDE" [Bron et al.2017] considered as the most frequent form of DED [Nichols et al. 2011, Lemp et al. 2012, Schaumberg et al. 2011]. Han et al. found that patients without preexisting MGD developed it after uncomplicated cataract surgery showing, on one hand, the potential impact of the surgery on meibomian gland function [Han et al. 2014] and on the other, the interest to evaluate changes and the short-term impact of the surgery on meibomian gland function in an aging population more prone to MGD.

The goal of the present study was to evaluate the short-term influence of cataract surgery on tear film metrics and meibomian glands function in an aging population.

7.2 Methods

This prospective study was performed according to the tenets of Helsinki. The protocol was approved by the ethical committee of the University of Valencia and Oftalvist clinic in Valencia. All subjects were given written information about the study before they signed a written statement of consent to participate. Eleven patients with cataract (mean [±SD] age 62.10 [±10.7] years (range 40 – 75 years, median 63.5 years) were included in the present study.

Cataract surgery

Cataract surgery was performed using the FEMTO LDV Z8 [Ziemer Ophthalmology (Deutschland) GmbH]. The cutting device of the Femto LDV is integrated into a hand piece and positioned onto the eye during the docking procedure directly by the hands of the surgeon.

Femto LDV lasers have a suction ring and a central transparent part that are merged into one piece in association with a spectral-domain OCT. The former device is used to image anterior segment, centre the cornea and mark corneal incisions location and capsulorrhexis pattern which must remain within the pupillary border (generally 5.0 mm) [Donaldson et al. 2013]. Laser energy is absorbed by the tissue resulting in plasma formation and disruption induced by the cavitation bubbles. Ultra-short duration of the pulses (10^{-15} seconds) [Kullman et Pineda 2010] allows for a limited strength of the shock waves induced by the photodisruption and the creation of spots of 3 µm diameter and with an accuracy of 5 µm in depth. Capsulorrhexis was performed first by the surgeon (F.P.P) followed by lens fragmentation and corneal incisions (paracentesis and primary incision) the phacoemulsification through a 2.2 mm clear corneal temporal incision under topical anesthesia. The IOL implant was the PodEye Monofocal (Physiol, Advanced Optical Solutions, Liège, Belgium). At the end of surgery, the corneal incision was sealed with stromal hydration. There were no intraoperative or postoperative complications. Postoperatively, topical moxifloxacin 0.5% (Alcon Laboratories, Inc. Fort Worth, Texas 76134 USA) and dexamethasone 0.1% (NOVARTIS PHARMA SA) were instilled 4 times daily for 4 weeks..

Clinical examination included the following exams:

Patients were seen on two occasions: seven days before cataract surgery, and 7 days after the surgical procedure. At each visit, the following tests were performed. Symptomatology was evaluated according to the TFOS DEWS II Diagnostic methodology report [Wolffsohn et al. 2017] using the OSDI due to the strong acceptance among professionals [Wolffsohn et al. 2017] and the DEQ-5 for its quick instruction and high discriminative capacity [Chalmers et al. 2010].

The I-Pen device was used to assess the osmolarity of the ocular tissue on the inferior palpebral conjunctival membrane [i-Pen Osmolarity System User Manual. I-Med Pharma Inc, 2016]. The pen of the device is gently lowered towards the third middle of the everted inferior lid until the tip of the pen touched the inferior conjunctival epithelium and performs the measurement. As previously described in the general methodology, a cut-off score of 300 mOsm/L for DED was chosen for the study.

As non-invasive methods were not available, FBUT was evaluated by using blue illumination and a yellow filter (Wratten #12), and placing a single fluorescein strip (previously shaken) at the outer canthus of the inferior eyelid [Mooi et al. 2017]. After a time laps between 1 and 3 min [Peterson et al. 2006], the time from the last blink to the first appearance of a randomly distributed dry spot on the cornea was recorded in seconds using a stop watch. The mean time for 3 consecutive attempts was recorded. After measuring TBUT, corneal and conjunctival staining were assessed by evaluating the extent of the staining of conjunctiva and cornea (central, superior, temporal, inferior, and nasal) was graded from 0 (none) to 4 (severe), according to the Efron's grading scale for ocular surface staining [Bronet al. 2003]. Lower TMH was evaluated using a Slit-Lamp (SL-Scan, Topcon, Japan). Biomicroscope observation system was aligned with the illumination system, tangential to the inferior tear meniscus. Patients were asked to look straightforward. TMH was measured as the distance between the darker edge of the lower eyelid and the tear strip. Beam width and height were settled on the patients closed eye in order not to induce reflex lacrimation, in other words the height of the beam was always sufficiently low so as not to enter the pupil area, an event that would jeopardize TMH measurements. At a magnification of 32x, TMH measurement was performed by coupling the width to the absolute height of the tear meniscus [Guillon et al. 1997] (TMH-

A as described by Santodomingo-Rubido et al. 2006) in order to form a square. The test bar was then placed on its support and TMH measured using a ruler to the nearest 0.05 mm.

Expressibility of the meibum was scored by the application of digital pressure to the central third of the upper tarsus. The ease of meibum secretion was graded as follow: 0 (clear meibum easily expressed); 1 (cloudy meibum expressed with mild pressure); 2 (cloudy meibum expressed with more than moderate pressure); and 3 (meibum not expressed, even with heavy pressure) [Shimazaki et al. 1995]; higher scores represented a more obstructive status. Meiboscore ranges as follow: from 0 to 3 for each eyelid giving an overall score ranging from 0 to 6 [Arita et al. 2017]. The cutoff value of the meiboscore as a criterion for the diagnosis of MGD was found to be ≥3 [Arita et al. 2009].

The meibography system was composed of a SL (SL-D701, Topcon, Japan) equipped with an infra-red transmitting filter (BG-5; Topcon, Japan) coupled with a digital camera (DC-4; Topcon, Japan) allowing still images or videos to be captured of the morphology of meibomian glands. The upper and lower eyelids were everted and images were obtained in which intact glandular tissue appears pale against a dark background. Areas where glandular tissue could not be visualized were considered areas of meibomian gland dropout.

Meibography scores, which quantify obstruction of meibomian glands, were obtained using the following grades for each eyelid: 0 (no loss of meibomian glands); 1 (meibomian gland loss involving less than one third of the total meibomian gland area); 2 (area lost between one third and two thirds of the total meibomian gland area); and 3 (area lost more than two thirds of the total meibomian gland area). The total meibography score was the sum of the scores of the upper and lower lids and was recorded as 0 to 6 [Arita et al. 2009, Arita et al. 2013].

Figure 7.1. Infrared meibography of superior eyelid at baseline

Figure 7.2. Infrared meibography of superior eyelid 7 days after the surgery

Figure 7.3. Infrared meibography of inferior eyelid at baseline

Figure 7.4. Infrared meibography of inferior eyelid 7 days after the surgery

Statistical analysis

All statistical analyses were performed using SPSS V.21.0 (SPSS, Chicago, Illinois, USA). Descriptive statistics were used to summarise patient demographic and clinical information. Shapiro-Wilks test was used to assess distribution of the variables included in the present study. Wilcoxon's test was used for the data which was not normally distributed whereas paired sample t-test was used for the data normally distributed. Pearson's and Spearman's correlations were used to evaluate the strengths of association between questionnaires.

7.3 Results

Eleven eyes from 11 patients participated in the study. The mean Five-item DEQ score was 9.82 (SD 1.9 range 1 to 18) before the surgery of which 63% (n=7) had a baseline score greater than 6 (indicative of mild or greater DED symptoms). Post-surgery, mean DEQ score was 14 (SD 1.9 range 3 to 20) of which 82% (n=9) had a score greater than 6. A significant increase in DEQ-5 score was found after surgery (Wilcoxon test p= 0.017).

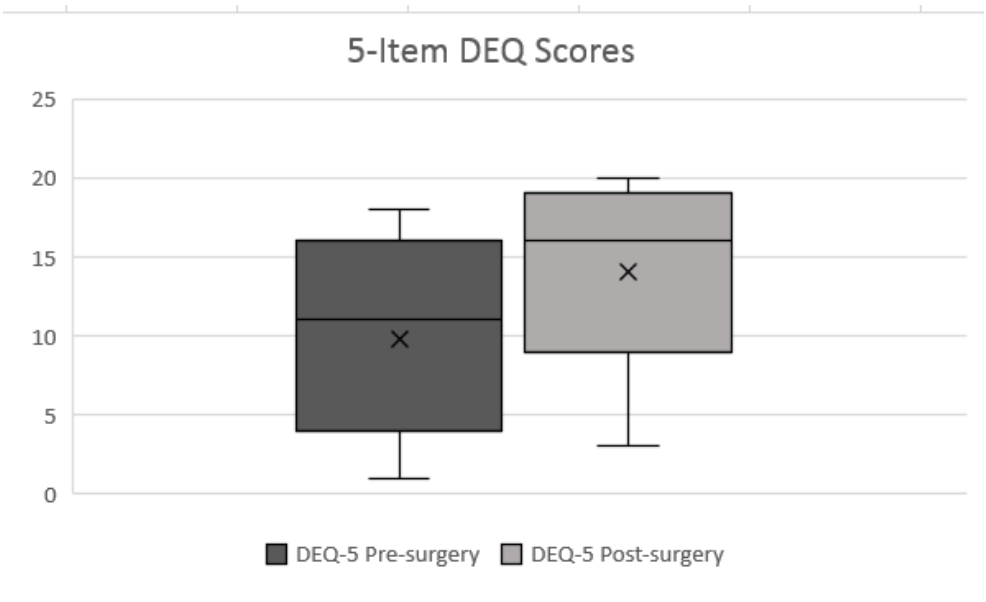

Figure 7.5. Boxplot over time of Five-Item Dry Eye Questionnaire

Mean OSDI score at baseline was 36 (SD 4.8 range 4 to 62) of which 91% were above the cut-off score for DED. Post-surgery, mean OSDI score was 42.4 (SD 5 range 8 to 67) of which 91% were above the cut-off score for DED. A significant increase in OSDI score was found after surgery (Paired sample t-test p=0.03).

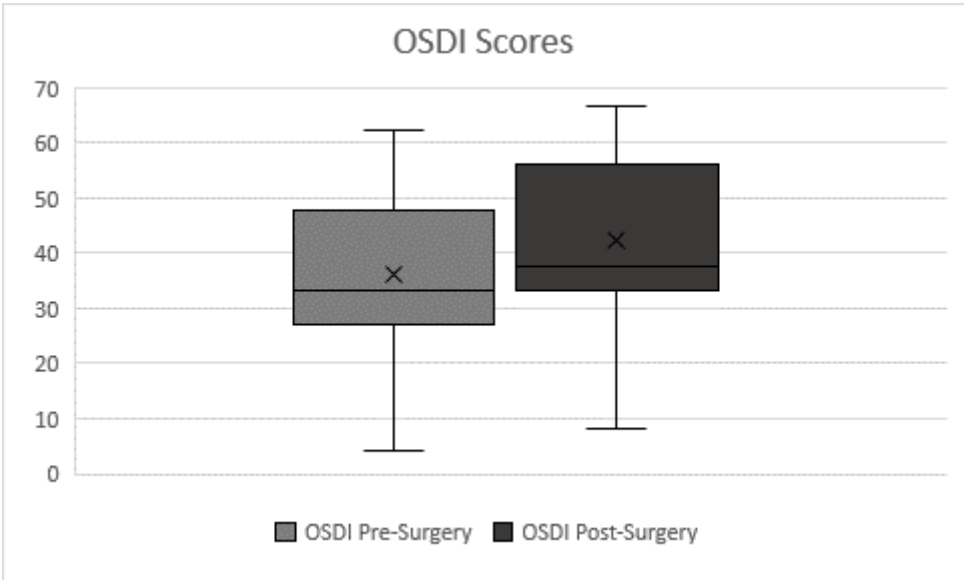

Figure 7.6. Boxplot over time of OSDI score

The correlation between these two questionnaires was moderate (Pearson's r= 0.60, Spearman's ρ= 0.57 p=0.05). Mean TBUT values were 8.6 s (SD 0.5 range 6 to 11 s) before surgery and 8.4s (SD 0.6 range 6 to 11 s). No significant differences were found between pre- and post-surgery values (p= 0.608). Mean staining scores were 0.3 (SD 0.5 range o to 1) and 1.3 (SD 0.5 range 1 to 2) pre- and post-surgery respectively. Vital staining significantly increased through the surgery (p=0.004). Mean TMH values were 0.26 mm (SD 0.03 range 0.10 to 0.40 mm) and 0.27mm (SD 0.03 range 0.15 to 0.40mm) pre- and post-surgery respectively. No differences could be evidenced between the appointments. Mean osmolarity values were 299.2 mOsm/L (SD 4.6 range 282 to 333 mOsm/L) and 294 mOsm/L (SD 2.3 range 275 to 303 mOsm/L) pre- and post-surgery respectively. Osmolarity values did not show significant changes during the study (p= 0.66). Mean MGs expressibility scores were 1.0 (SD 0.3 range 0 to 2) and 1.7 (SD 0.3 range 0 to 3) pre-and post-surgery respectively. From the 11 patients included in this study, 6 presented a pre-surgery meiboscore ≥3 which classified them as having MGD. MG expression was significantly more difficult to perform after the surgery (p= 0.011). Regarding IR imaging of MGs, mean grades were 2.5 (SD 0.4 range 1 to 4) for pre- and post-surgery respectively. No statistical differences were detected between appointments for this parameter.

7.4 Discussion

Numerous factors can induce signs and symptoms of DED following cataract surgery despite uncomplicated procedure. Ocular discomfort following cataract surgery has been attributed to exacerbation of preexisting DED or to its onset [Li et al. 2007, Ram et al. 1998, Oh et al. 2012, Cho et Kim 2009, Chung et al. 2013] mainly due to surgery-related events: corneal nerve section that is recognized to reduce corneal sensitivity and thus the efficiency of the feedback

loop of the LFU; toxic changes at the ocular surface induced by preservatives found in topical eyedrops used consistently before, during and following the procedure and repeatedly insulting corneal and conjunctival tissue [Salomão et al. 2009, Walker 2004]; a drastic reduction in blinking rate during the surgery coupled with repeated irrigations of the ocular surface are thought to snatch goblet cells and further impact TF stability [Salomão et al. 2009, Walker 2004, Cho et Kim 2009, Nakamori et al. 1997], a long time of exposure of the ocular surface to the light of the microscope leading to thermal damage [Salomão et al. 2009, Walker 2004, Cho et Kim 2009]. Ocular surface structures are fundamental for the proper functioning of the LFU and as such, their insult is expected to generate signs and symptoms of DED [Baudouin et al. 2013]. Thus, numerous patients candidate for cataract surgery and presenting MGD often present a fairly wide range of symptoms [Arita et al. 2008]. Previous studies focusing on the impact of surgery on dry eye signs and symptoms, found an aggravation of the evaluated parameters after the surgical procedure [Ram et al. 2002, Cho et Kim. 2009]. Oh et al. found that even if TF function gradually improved after the surgery, increased ocular symptomatology could last more than three months after the procedure before returning to levels approaching the pre-operative state [Oh et al. 2012]. In the present study, a significant increase in OSDI scores was found 7 days after the procedure, which is in agreement with previous studies [Ram et al. 2002, Cho et Kim. 2009, Oh et al. 2012]. The 5-Item dry eye questionnaire also showed an increased score after the surgery but only a moderate correlation was found between both questionnaires.

This moderate correlation could be due to two main factors: the low number of participants to the study and the fact that on the contrary to what was previously done regarding OSDI testing in patients undergoing cataract surgery [Park et al. 2016], items 4 and 5 were not removed from the questionnaire. These questions evaluate the blurred vision and it is indeed

difficult to seclude vision-related symptomatology changes due to cataract removal from the dry eye induced symptoms related to surgery itself, which could undoubtedly lead to some degree of bias. However, this “r” value obtained in the present study is consistent with literature, as similar moderate correlation has been found when comparing both questionnaires [Galor et al. 2015]. Further research is needed in order to develop a definite cataract and corneal surgery questionnaire evaluating dry eye symptoms with a specific focus on surgery associated changes in vision (separating the ones expected from the surgery and the unwanted dry eye induced changes).

Regarding the influence of cataract surgery on TF stability, existing literature gives inconsistent results. Li et al. [Li et al. 2007, Liu et al. 2002] both found a significant decrease in TBUT values along with other TF parameters such as Schirmer test 1 and lower TMH. In the study from Li et al., TBUT, evaluated at one week, one month and three months showed a significant decrease only after 3 months, which is consistent with the present study. However, Liu et al. found a significant decrease in TBUT values from day 1 post-surgery that came back to pre-operative value after one month.

In the current study, no significant differences were found before and after the surgery, these results are in agreement with Ram et al. study [Ram et al. 2002]. Discrepancies between studies might come from differences in the study design, methodology (all of the previous studies did not evaluate MG function and structure before and after the surgery) as well as sample used, as prevalence of MGD increases with age. In this study, it is thought that a small corneal incision of 2.2 mm caused a very limited focal reduction in corneal sensitivity, retaining intact the majority of corneal nerve architecture, which undeniably resulted in token short-term changes in tear secretion and tear film stability. Indeed, a previous study indicates that

recovery times are directly related to incision size [Oh et al. 2012]. Besides, patients were seen seven days after the surgical procedure, and initial post-surgery TF instability as evidenced by Li et al. and Liu et al. occurred only a few hours after the surgery [Li et al. 2007, Liu et al. 2002]. However, long-term follow-up of this parameter, as performed by Li et al. would give valuable information on TF stability over time as significant decrease in stability have been highlighted at three months post-surgery [Li et al. 2007]. We hypothesize that surgery-related functional changes taking place in MGs could positively impact TF stability, with a lag time for setting it up post-surgery which might depend on MG degree of dropout at baseline. Further studies are needed in order to better understand which factors can influence TF stability values over time following cataract surgery as the TFOS Workshop on MGD [Schaumberg et al. 2011], emphasize that TBUT is considered "as a secondary or surrogate measure of MGD and therefore is a less specific indicator of disease status" .

The important role played by the long-term use of preservative-containing eyedrops on TF stability, epithelium barrier disruption, goblet cell loss and ocular surface cells apoptosis is well recognized [Baudouin et al. 2010]. BAK is the most commonly used preservative in ophtalmic drug formulations and its role is double. First, for its preservative intrinsic qualities, but also because the epithelium barrier disruption induced by quaternary ammoniums enhances the penetration of drugs into the anterior chamber. The precise mechanisms through which its use induces inflammatory processes leading to pro-inflammatory CKs expression and ocular surface damage are yet to be elucidated; however, its toxic effects are known to be dose- and time-dependent [Baudouin et al. 2010]. Dry eye models in rats [Lin et al. 2010] suggest that the use of BAK for 7 days is sufficient to induce inflammatory cascades at the ocular surface leading to the liberation of pro inflammatory CKs such as TNF-α which effects have already been described in the introduction of this manuscript. The following

ocular surface cells apoptosis gave a pattern very similar to the one that can be found in dry eye patients suggesting that this preservative potentially could aggravate or induce signs and symptoms of dry eye on its own. In the present study, patients used Vigamox and Diclofenac-Lepori eyedrops, which are preservative-free and with very limited adverse effects [Miller 2008]. The other drops used just after the surgery were Maxidex, known to contain BAK. However, its use was too limited in time and dose to have induced further corneal staining that would have maintained until the seventh day following the surgery. Thus, the significant increase in vital staining found in the present study cannot beattributed to the use of eyedrops. A recent study focused on the in-vitro effect of light exposure on conjunctival cells and shown that even a quarter of the amount of microscopic light used during the surgery was sufficient to induce cellular damage that could slow down the wound healing process [Ipek et al. 2018] possibly leading to short-term increased positive vital staining. Further studies are needed to better understand the role played by microscopic light illumination in post-surgery signs and symptoms of dryness.

According to the TFOS Diagnostic Methodology report, tear osmolarity is the tear parameter that provides the strongest correlation to DED severity among all other tests [Sullivan et al. 2010, Wolffsohn et al. 2017]. Besides, it is considered the best tear film metric to diagnose and classify the disease [Tomlinson et al. 2006, Lemp et al. 2011, Potvin et al. 2015]. Few studies focused on the impact of cataract surgery on osmolarity values [Khanal et al. 2008, González-Mesa et al. 2016]. Khanal et al. found an early post-operative (at 3 days) significant increase in comparison with pre-operative values, and even if osmolarity remained higher than baseline at 10 days, the difference was not sufficient to be significant [Khanal et al. 2008]. The device used in this study was based on freezing point depression to determine osmolarity values and nowadays, higher specificity “lab-on-a-chip” devices using electrical impedance

exist to perform the measurement [Tomlinson et al. 2010]. The device used in the present study is the i-Pen, one of the both "lab-on-a-chip" devices available on the market along with the TearLab. The former has demonstrated its usefulness through numerous studies for diagnosis, grading of severity, and follow-up of DED patients [Farris et al. 1986, Versura et al. 2010, Tomlinson et al. 2010, Potvin et al. 2015]. However, the i-Pen system, appeared recently on the market and little is known about its ability to properly diagnose and grade patients with the disease. Few studies have looked into this device's ability to reproduce a range of physiological values [Nolfi et Caffery 2017, Rocha et al. 2017] and both in vitro and in vivo data suggest that this device does not provide sufficient accuracy and precision in assessing osmolarity levels belonging to physiological ranges [Nolfi et Caffery 2017, Rocha et al. 2017]. The present study did not find any statistical change in osmolarity values before and after the surgery, which is in agreement with González-Mesa et al., and even if a different "lab-on-a-chip" device was used, it lead to similar conclusions [González-Mesa et al. 2016]. It seems that ocular surface discomfort increase, as evidenced by both questionnaires in this study, cannot be attributed to osmolarity changes. The i-Pen device was designed to sample the inferior eyelid conjunctival epithelium, which could very possibly be at the origin of differences between devices. However, Rocha et al. already looked into the reasons for differences between devices displayed values: if the i-Pen really measures tissue impedance (which is expected to give much higher values than a solution like the tears [Pethig 1987]), little is known about what happens in clinical practice when some of the tear accidentally bridges the tip of the pen, which occurred almost every time during the present study [Rocha et al. 2018]. Osmolarity values obtained should be far out of the normal human osmolarity range [Rocha et al. 2008] as this device was calibrated to measure a tissue with electrical resistance greater

than the tear film. Further research is needed to better understand the measurements taken by this device.

Data regarding changes induced by cataract surgery in TM measured using SL and Schirmer test gave discordant results [Ram et al. 2002, Kim et al. 2009, Oh et al. 2012, Sanchez et al. 2010, Cho et Kim. 2009; Lim et al. 2007]. We measured subjectively TMH using SL and graticule, which has shown acceptable repeatability and high reproducibility between visits [Santodomingo-Rubido et al. 2006, Imamura et al. 2017]. As underlined by García-Resúa [García-Resúa et al. 2009], measuring TMH with SL requires a learning-curve as identifying TMH superior edge might not be as easy as it seems. However, the practitioner (i.e. E.L) is an experienced optometrist and has been practicing this technique for several years. Measuring this parameter did not show significant changes between visits. Even if newer, more precise and reproducible techniques exist, a previous work by Han et al. [Han et al. 2014] evaluating TMH using OCT before and after cataract surgery was not able to show any significant influence of cataract surgery on this parameter [Han et al. 2014]. The hypothesis explored by the authors to which we adhere is that ocular symptoms following cataract surgery cannot be attributed to a decrease in aqueous tear production alone as increased symptomatology is still present more than 3 months post-surgery and literature reports that corneal sensitivity could take between one and 3 months to go back to pre-operative levels .

Among the age-related changes taking place in MGs, recent studies identified, in addition to already acknowledged alterations (i.e gland atrophy and decreased acinar cell proliferation) [Jester et al. 2015] a significant decrease in the expression and localization of a receptor, a major regulator of lipogenesis called proliferator-activated receptor gamma (PPARγ) [Nien 2011, Nien et al. 2009]. This receptor plays a key role in meibocytes differentiation and thus

in lipid synthesis, so the decrease in PPARγ expression is directly linked to age-related MGD leading to gland dropout and changed lipid composition and protein to lipid ratio [Jester et al. 2015]. Indeed, studies based on animal models suggest that, in normal conditions, lipids synthesized by the MGs are subject to a maturation process as they migrates along the ductule to reach the main duct and then the meatus of the MG during which, they progressively lose their associated proteins before leaving the lumen [Suhalim et al. 2014]. Sulajhim et al. found that this protein to lipid ratio remains almost unchanged in prolonged dessicating stress conditions indicating the impact of this environmental change on MG function. Interestingly, Ong et al., Palaniappan et al. and Millar et al., found that the incorporation of protein to normal MG secretion possibly increases lipid rigidity and viscosity making it more fragile and prone to rupture by reduction of surface tension when incorporated to the TF [Ong et al. 1991, Palaniappanet al. 2013, Millar et al. 2009]. The protein very likely to be responsible for MG obstruction is keratin and its derivatives as they are the major proteins found in meibomian secretions [Tsai et al. 2006, Ong et al. 1991]. This theory seems to be robust as some authors confirmed that keratin found in MGs secretions originates from the shedding of the epithelial cells upholstering the ducts [Ong et al. 1991, Knop et Knop. 2009] but also MG acini [Liu et al. 2010]. Therefore, mechanisms of accumulation of cellular debris and lipids create an obstruction further leading to duct dilation and gland atrophy [Blackie et al. 2010, Korb et Henriquez 1980].

As suggested by Jester et al., the overall mechanism of age-related obstruction would be as follow; an initial environmental trigger increases epithelial duct and acinar cells turnover that leads to accumulation of desquamated cells and proteins in the ducts affecting lipid properties and possibly inducing mechanical obstruction [Jester et al. 2015]. However, it is necessary to take into account the interesting theory that could combine to, and further promote

keratinization at the main ducts: the recent TFOS DEWS II pathophysiology report [Bron et al. 2017] mentions the possibility that the incomplete apposition of the lid margins with every blink [Pult et al. 2015], possibly further aggravated by the surgery, would make Marx's line a permanent hyperosmolarity site allowing the diffusion, up to the terminal MG ducts, of low molecular weight proteins such as pro-inflammatory CKs among which IL-1β and INFγ, CKs that provide the ability to induce the expression of precursors of cornifying proteins that could possibly, with time, induce further hyperkeratinization, a keystone of the pathophysiology of the disease. Besides, let us not forget that pre-existing DED permanently drops at the ocular surface and thus over MCJ site, the same pro-inflammatory CKs (among others) that could accelerate the keratinization process and excacerbate obstruction and lipid delivery reduction.

As defined by Korb and Blackie, MG expressibility is used to depict "the ease with which secretion can be physically expelled from the gland" [Korb et Blackie 2008] and scientific literature demonstrated the importance of the efficacy of such glands in preventing dry eye signs and symptoms [Bron et al. 2017]. In the present study, a significant reduction in glands expressibility was found after cataract surgery. Interestingly, ocular surface and adjacent structures such as eyelids and the glands they enclose are subject to the same general inflammatory response following surgery as the liberation of pro-inflammatory signaling molecules is ubiquitous and could very easily amplify age-related changes leading to keratinization and epithelial cells turnover. Interestingly, MG expressibility worsening through the surgery should be considered as an enhancement of an already on-going process that could be related to aging, to DED alone, or the combination of both. Furthermore, the amount to which feedback loop damage, secondary to corneal nerves harm, impacts MG function is

difficult to assess as the effect of nerves on MGs is still unclear and requires further investigation [Cox et Nichols 2014].

From the 11 patients included in this study, 55% (n=6) were initially diagnosed with MGD. Even if the number of patients is reduced, MGD prevalence in this group was almost the same as the ones reported in previous epidemiological reports, i.e 61.9% according to Uchino et al. study [Uchino et al. 2006] based on gland dropout, expressibility and nature of meibum secretion; and 60.8% in the Shihpai Eye Study [Lin et al. 2003]. However, vigilance is required when looking at these numbers as ethnicity varies between studies and, as shown in the Salisbury Eye Evaluation, even if parameters evaluated largely differ, prevalence in Caucasian population was found to be much lower than the group evaluated in the present study [Schein et al. 1997].

7.5 Conclusions

We hypothesize that cataract surgery further promotes short-term MG obstruction, as only functional changes (reduction in MG expressibility) could be evidenced and IR meibography did not show any significant structural change. As proposed by Han et al., it is more likely that structural changes impacting MGs, which were not found in the present study, are more the result of a chronic dysfunction than a part of the short-term cataract surgery outcomes [Han et al. 2014]. The present study could not elucidate the exact mechanisms by which functional short-term changes occur in MGs following the surgery; however, it is very likely that even without significative signs of MG structure damage, cataract surgery seems to impact MG function. Previous litterature suggest that surgery-induced inflammation, bacterial infection from breached ocular surface, preservative-containing postoperative medications or

combination of the former, are thought to play a role, even if in different extents [Sutu et al. 2016, Li et al. 2009, Akyol-Salman et al. 2012]. Besides, it would be interesting to follow-up changes taking place in both upper and lower MCJ and Marx's line, as widening and anterior displacement of Marx's line is a good indicator of meibomian glands orifices status.

This study has some drawbacks. First, it was conducted in a relatively small number of subjects and did not have a control group that had not undergone cataract surgery. Second, the lid hygiene status was not studied and Marx's line and MCJ not evaluated which could have given valuable information on the impact of the surgery on these parameters; indeed, a previous study showed significant changes in lid margin vasculature and irreversible MCJ displacement through the surgery [Han et al. 2016]. Third, meibum expressibility was not objectively measured using a device that delivers standardized pressure on the lid [Korb et Blackie 2008]. Promizing therapies are emerging in order to treat MGD, such as Intense Pulsed Light (IPL) systems used to treat the disease (REFs). Further investigation is needed to assess the impact of this therapy in MGD patients on surgery outcomes

CHAPTER 8

GENERAL CONCLUSIONS

The clinical studies presented in this doctoral tesis with patients corrected for presbyopia with different refractive modalities allow us to draw the following conclusions:

1. The eye, as well as the entire human body, is subject to the process of aging, the most remarkable manifestations of which are presbyopia and opacification of the lens, in other words, cataract. Almost every anterior segment structure undergoes age-related functional and morphological changes, from the lacrymal glands (main lacrymal gland, meibomian glands, and goblet cells) to eyelids and conjunctiva. These changes reduce both quantities and quality of tear secretion, prevent an optimal repartition of the tear film on the ocular surface potentially leading to/ worsening signs and symptoms of dryness.

   DED prevalence increases with age, because of the aforementionned aging processes, and compensating for presbyopia or getting rid of crystalline opacities require a comprehensive previous assessment of the Lacrymal Functionnal Unit and more generally of the anterior segment. The great majority of refractive options available, apart from eyeglasses, are considered as invasive and could easily perturb the ocular surface homeostasis. Multiple approaches can be considered when correcting presbyopia and cataract, the common goal being to restore vision and give sustainable comfort to the patient.

   Presbyopia correction can be achieved through eyeglasses (monofocal, bifocal, trifocal and multifocal lenses) and the former approaches are not expected to induce or worsen signs and symptoms of dryness. Presbyopia correction through CLs is another option that includes: rigid gas permeable contact lenses (from corneal RGPs to semi-

scleral and scleral designs with different geometries such as monofocal, bifocal, soft contact lenses). However, CLs, once upon eye, sits in the tear film (TF), disturbing its normal structure and interact with the ocular surface possibly worsening an already unbalanced environment. Refractive surgery is another option available (cataract surgery with implantation of different geometry intra ocular lenses (IOL) (monofocal, bifocal, trifocal), corneal refractive surgery) but its invasiveness, even if great steps forwards have been made, disturbs as well the ocular surface and can worsen or induce signs and symptoms of dryness.

2. Clinical performance of a water gradient daily disposable soft CL on the ocular surface and the TF in a neophyte presbyopic population over their first 8 hours of wear induced an initial decrease in TF stability from CL insertion observed by osmolarity values rising after 20 minutes of wear; however, it did not impact tear meniscus metrics and seemed to be transitory, as a decrease, without reaching baseline values, occurred by the end of the wearing period. Ocular surface aberrations remained largely stable from CL insertion, demonstrating an even repartition of TF over the CL material surface.

3. Attempts to target unmet needs for a growing presbyopic population especially regarding CL fitting strategies require previous identification of the changes taking place in the lacrimal functional unit, how they affect the ocular surface and in which extent the insertion of a CL would affect this set of structures or worsen an already unbalanced ocular environment. Both daily disposable and extended wear soft CL material fitted provided satisfactory and similar objective on-eye behavior and remained largely stable along the experiment period. However, subjective symptoms showed a greater increase from baseline regarding the extended wear lens in

comparison with the daily lens. Comfort seems to be impacted by CL material modulus, parameters of both CLs being otherwise very similar.

4. Ageing population is more prone to develop DED as increased aged is associated with higher prevalence of systemic and ocular disorders that may disturb anterior segment homeostasis. ScLs present a double advantage for this age-based population as ScL can be a good optical platform for correcting presbyopia through multifocality as well as protecting the ocular surface by vaulting the cornea and limbo. Further studies are needed to better identify the benefits of the ScL could bring to an older population with anterior segment pathologies and to better understand ScL potential role in restoring/maintaining ocular surface homeostasis over longer periods of time.

5. The results of this pilot study suggest that cataract surgery further promotes short-term MG obstruction, as only functional changes (reduction in MG expressibility) could be evidenced and IR meibography could not evidence any significant structural modification. As mentionned in other studies, it is more likely that structural changes impacting MGs, which were not found in the present study, are more the result of a chronic dysfunction than a part of the short-term cataract surgery outcomes. The results obtained did not allow the exact mechanisms to be elucidated by which functional short-term changes occur in MGs following the surgery; however, it is very likely that even without significative signs of MG structure damage, cataract surgery impacts MG function. MG expressibility worsening through the surgery is thought to be an enhancement of an already on-going process that could be related to aging, to DED alone, or the combination of both.

CHAPTER 9

FUTURE LINES OF INVESTIGATION

From the data analyzed in the clinical studies forming part of this doctoral thesis, we arrived at various conclusions concerning the different types of refractive corrections in a presbyopic population and their impact on dry eye signs and symptoms. These conclusions raise a number of questions that deserve further investigation. Here are the main topics requiring further research:

- Questionnaires

Evaluating symptomatology in a comprehensive way is a very difficult goal to achieve. Indeed, as reviewed in this manuscript and through the different clinical studies performed, ocular sensation is very subjective and given symptoms can be described in many different ways by the patient. Even if considerable efforts have been made to design and validate questionnaires aiming to assess general and contact lens associated symptomatology, we realized that information is still lacking regarding specific DED induced symptomatology like for instance the specific impact of corneal refractive and cataract surgeries. Indeed, this scientific vacuum has been highlighted in **Chapter 7** where generic questions related to vision quality were not appropriate in the case of media opacities as for instance: cataract surgery with IOL implantation would definitely improve those symptoms (thus reduce the overall score of the questionnaire) no matter if DED was already present before the surgery; which means that those questions, in their actual formulation, fail to properly quantify/segregate cataract associated symptomatology/ DED associated decrease in quality of vision and should be removed (or re-formulated towards pre-surgery DED symptomatology and surgery-induced possible symptomatology). Both corneal refractive and cataract surgeries are rapidly expanding, and the impact of these techniques on DED signs and symptoms needs to be

precisely assessed. Hence the necessity to design new screening tools such as ocular surgery-oriented questionnaires to compare pre- and post-surgery outcomes.

- CL materials biocompatibility

Considerable efforts have been made in the last few years to describe corneo-scleral and scleral profiles principally due to recent technologic advances in anterior segment-OCT imaging. This device helped to design scleral lenses with customized periphery in order to fit as best as possible the chiral nature of the sclera, thus increasing comfort and stability of vision. However, little is known regarding the long-time effect of these new designs and the benefits that could arise for patients in terms of, comfort, quality of vision, maintaining/restoring ocular surface homeostasis but also the gain of office-time for the practitioner with a set of trial scleral lenses which would accelerate the fitting process.

- Inflammatory cascades in response to osmolarity changes

Inflammatory processes taking place at the ocular surface are highly complex and involve many inflammatory mechanisms and immune cells. Great advances have been made to identify and describe inflammatory markers responsible for the spread of the inflammation signal triggered by the multifactorial etiology of the disease. This lead to the development of new anti-inflammatory strategies that intend to block key interactions between immune cells and thus prevent the propagation of the inflammation signal. Even if some of these new therapies are still in development, they gave promising results in clinical trials and showed the importance to study cellular interactions in DED associated immune responses. Future lines of investigation in this domain should focus on how to modify/counteract the intracellular activation cascade induced by raised osmolarity, or cellular damage, like for instance the Toll-receptors. These latter are able to: recognize auto-Antigen, internalize them and present part

of them to APCs. Blocking that interaction by a system of competitive ligand (mimicking the human body) as for the IL-1 RA which union to IL-1 receptor (IL-1 R) induces no effect, preventing effectory IL-1 to bind to this receptor and promote inflammation signal.

Besides, further research is needed regarding the impact of a raised osmolarity on ocular surface: the duration of an increased osmolarity and the amount of this increase from baseline values that will induce cellular damage.

Evaluate if, before cellular damage takes place, there is warning signs like for instance a change in cellular function or metabolism that could be used as an early marker of ocular surface loss of homeostasis.

Assess type cells sensitivity to osmolarity (bulbar conjunctival cells versus corneal cells versus palpebral conjunctiva cells) in order to establish a sequence, if applicable, of cellular damage that could be a pharmaceutical target for dry eye eyedrops in order to palliate the decrease in some cell type function that would strengthen TF composition and stability on ocular surface.

- Tear meniscus parameters

Assessing tear meniscus parameters (TMH, TMA, TMV) non-invasively using OCT has been proven to be of great value in the diagnosis and monitoring of DED patients. However, these parameters are generally evaluated in the center of the eyelid, typically called “six o’clock position” below the pupil center, and in both nasal and temporal locations in a reproducible way [Pult et Riede-Pult 2015]. Previous studies proposed a mathematical model to extrapolate from TMA values at the center of the inferior eyelid including in the formula a compensation factor for the eyelid’s curvature [Del Águila-Carrasco et al. 2015, Palakuru et al. 2007, Bandlitz

et al. 2016]. However, this formula, even if giving interesting data regarding the overall TMV, does not take into account biasing lid and conjunctiva disorders such as LIPCOF, conjunctivochalasis disorders of the lid margin congruity and apposition between the lid and ocular surface [Ibrahim et al. 2010, Pult et Riede-Pult 2015, Wolffsohn et al. 2017]. Understanding the influence of these disorders on tear meniscus parameters from canthus to canthus would give valuable information regarding total TMV for diagnosis and follow-up of DED patients. To do so, further research is needed in order to find a way to visualize/ map continuously from canthus to canthus the entire shape of the inferior tear meniscus. The investigation should focus on built-in softwares that can mark the area of the inferior meniscus already scanned and, with an additional image analysis software unite every scan in order to form a tridimensional image that would give an information on every tear meniscus parameter and how it is modified by lid margin disorders and DED.

- Refractive surgery

Further investigation should focus on the impact of corneal refractive surgery to correct presbyopia (the different techniques described in the introduction) as new techniques constantly appear. Evaluate the impact of the surgery approach and the technique used in inducing/ worsening signs and symptoms of DED would give new sight on the pathophysiology of the disease. Again, this goes in pair with the design of new questionnaires dedicated to segregate visual symptoms due to refractive defects from those induced by DED, and be able to evaluate the impact of the surgery on those symptoms. Besides, the advent of new promising therapies to improve surgery outcomes such as IPL devices deserve further research as some studies already showed the positive impact of this technology on MG function and

expressibility, this could be used as a preventive/ prophylactic treatment for every patient over 40 years old in order to preserve/enhance MG function.

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Appendix

Annex 1: Ocular Surface Disease Index questionnaire (OSDI)

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

Please circle your answers

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

Subtotal score for answers 1 to 5 [A]

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

Please circle your answers

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

Subtotal score for answers 6 to 9 [B]

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

Please circle your answers

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

Subtotal score for answers 10 to 12 [C]

ADD SUBTOTALS A, B, AND C TO OBTAIN D (D) TOTAL NUMBER OF QUESTIONS ANSWERED (E)

Annex 2: Five-Item Dry Eye questionnaire (DEQ-5)

DEQ 5

1. Questions about **EYE DISCOMFORT**:
   a. During a typical day in the past month, **how often** did your eyes feel discomfort?

      0 Never
      1 Rarely
      2 Sometimes
      3 Frequently
      4 Constantly

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

Never have it	Not at All Intense				Very Intense
0	**1**	**2**	**3**	**4**	**5**

2. Questions about **EYE DRYNESS**:
   a. During a typical day in the past month, **how often** did your eyes feel dry?

      0 Never
      1 Rarely
      2 Sometimes
      3 Frequently
      4 Constantly

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

Never have it	Not at All Intense				Very Intense
0	**1**	**2**	**3**	**4**	**5**

3. Question about **WATERY EYES:**
   During a typical day in the past month, **how often** did your eyes look or feel excessively watery?

      0 Never
      1 Rarely
      2 Sometimes
      3 Frequently
      4 Constantly

Score: 1a + 1b + 2a + 2b + 3 = Total
___+___+___+___+___=___

Annex 3: EFRON grading scale for CL complications

Annex 5 : Publications related to the doctoral thesis

The following publications have been derived from the clinical work and research carried out for the present doctoral thesis :

Articles in research journal :

-Lafosse E, Romín DM, Esteve-Taboada JJ, Wolffsohn JS, Talens-Estarelles C, García-Lázaro S. *Comparison of the influence of corneo-scleral and scleral lenses on ocular surface and tear film metrics in a presbyopic population.* Cont Lens Anterior Eye. 2018;41(1):122–7. doi: 10.1016/j.clae.2017.09.014.

-Lafosse E, Martinez-Albert N, Wolffsohn J, Cerviño A, García-Lázaro S. *Response of the aging eye to first day of modern material contact lens wear.* Eye Contact Lens. 2018 In Press.

Submitted to Ocular Surface Journal: Literarure Review Aging eye, presbyopia: Existing refractive approaches and their potential impact on dry eye signs and symptoms.

Communications in congresses :

-Edouard Lafosse. “Pathophysiology of dry eye: Role of inflammation in the onset of the disease”. 37th Congress of Optometry and Contactology, Paris, France. Starting date: 28 th January 2018. Ending date: 29 th January 2018. Oral Communication.

-Edouard Lafosse. “Purinergic receptors and inflammatory factors in dry eye”. 16th International Optometry Conference. Starting date: 4th August 2017. Ending date: 6 August 2017, Bogotá, Colombia. Oral Communication.

-Edouard Lafosse. “New insights on current dry eye diagnosis methods: meniscometry and osmolarity”. 16th International Optometry Conference Bogotá, Colombia.. Starting date: 4th August 2017. Ending date: 6 August 2017. Oral Communication.

-Edouard Lafosse, James S. Wolffsohn, Teresa Ferrer Blasco, Noelia Martínez, Santiago García-Lázaro. “Tear Film Changes over a Day of Daily Disposable Contact Lens Wear”. BCLA Clinical Conference & Exhibition 40th Clinical Conference & Exhibition ACC Liverpool,UK. Starting date: 9 th June 2017 Ending date: 11 th June 2017. Oral Communication.

-Edouard Lafosse, Santiago Garcia-Lazaro, Teresa Ferrer-Blasco, Jose Juan Esteve-Taboada, Izabela Garaszczuk. “Técnicas no invasivas para la evaluación del menisco lagrimal”. 24th Congreso Internacional de Optometría, Contactología y Óptica Oftálmica Madrid, Spain. Starting date: 8 th April 2016, Ending date: 10 th April 2016. Oral Communication.

-Edouard Lafosse, Santiago García-Lázaro, Alejandro Cerviño Expósito, Teresa Ferrer-Blasco, Robert Montés-Micó. “Daytime tear film and corneal thickness variations with several scleral contact lens diameters”. 8th Tear Film and Ocular Surface (TFOS) Congress. Starting date: 7 th September 2016, Ending date: 10 th September 2016, Montpellier, France.