VNIVERSITAT DE VALÈNCIA

The role of dry eye disease in cataract and refractive surgery

PROGRAMA DE DOCTORADO

EN OPTOMETRÍA Y CIENCIAS DE LA VISIÓN

Doctorando:

Alberto Recchioni

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Thesis presented by

Alberto Recchioni

To apply for the Degree of

DOCTOR OF PHILOSOPHY

in

OPTOMETRY AND VISION SCIENCES

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DECLARATION

This dissertation is the result of my own work and includes nothing, which is the outcome of work done in collaboration, except where specifically indicated in the text. No portion of the work referred to in the following dissertation has been submitted in support of an application for another degree or qualification of this or any other University or other institution of Learning.

_____

Alberto Recchioni, MSc

Birmingham, April 2019

Prof. Alejandro Cerviño-Esposito from University of Valencia and **Dr. Clare O'Donnell**, PhD and **Prof. James S. Wolffsohn**, from Aston University, CERTIFY that the present report entitled: "The role of dry eye disease in cataract and refractive surgery", summarizes the research work carried out under their supervision, by Alberto Recchioni, MSc and constitutes his thesis to apply for the double interdisciplinary degree of Doctor of Philosophy in Optometry and Vision Sciences at the University of Valencia and Aston University.

And to make it be on record, and complying with current legislation, they sign the present certificate in _____, on the _____ day of _____ of the year_____

Alejandro Cerviño-Expósito	Clare O'Donnell	James S. Wolffsohn

UNIVERSITY OF VALENCIA

The role of dry eye disease in cataract and refractive surgery

ALBERTO RECCHIONI

Doctor of Philosophy

April 2019

Resumen

El síndrome de ojo seco (DED) puede jugar un papel importante en las cirugías oftálmicas con fines refractivos tanto corneales (tratamiento corneal laser) como cristalinianas (cirugía de catarata) pero también en aquellas cuyo fin es controlar la presión intraocular en pacientes que sufren de glaucoma. El objetivo principal de esta tesis se refiere a la aplicación de una serie de pruebas diagnósticas, de mínimamente a no-invasivas, sugeridas por el Tear Film & Ocular Society Dry Eye WorkShop II (TFOS DEWS II) que pueden ayudar a mejorar los resultandos refractivos y visuales en la cirugía oftálmica actual.

La cirugía de cristalino, particularmente la cirugía moderna de catarata y la *refractive lens exchange* (RLE), centra la primera sección de la tesis. En realidad, el DED no está presente solo como complicación post-operatoria, sino que también es responsable de resultados refractivos y visuales no deseados dado que parte del examen pre-operatorio en la cirugía del cristalino puede verse influida por una película lagrimal deficiente (por ej. biometría ocular y topografía corneal). La literatura revisada ha demostrado poca información en el uso de técnicas avanzadas para evaluar la película lacrimal en pacientes que se someten a cirugía de cristalino, siendo estos hallazgos los más importantes para evitar resultados subóptimos después de la intervención.

Posteriormente, en la cirugía refractiva corneal moderna, a pesar de la seguridad y efectividad en la corrección de errores refractivos tales como miopía, hipermetropía y astigmatismo, el DED post-quirúrgico sigue siendo un problema recurrente y unas de las complicaciones más referidas por los pacientes. Recientemente, nuevas técnicas (por ej. small incision lenticule extraction (SMILE)) han sido introducidas con el fin de reducir el desarrollo de DED. El uso de la microscopia confocal in-vivo, así como un programa automático de análisis, has sido incluidos para proporcionar resultados objetivos más rápido que puedan ser comparados con la cirugía de la córnea tradicional (e.g. laser-assisted in situ keratomileusis (LASIK)).

El manejo de glaucoma mediante colirios oculares con preservantes puede llevar a deterioro de la superficie ocular con una larga proporción de pacientes con quejas del DED tanto como signos (como enrojecimiento ocular) tanto como síntomas (como incomodidad ocular, fotofobia, etc.). De los nuevos procedimientos oculares para controlar la presión intraocular reduciendo la necesidad del manejo tópico, la cirugía de glaucoma minimamente invasiva (MIGS) es prometedora también en mejorar la homeostasis de la superficie ocular. Sin embargo, muy poco ha sido investigado y la necesidad de una mejor comprensión ha llevado a administrar una serie de pruebas avanzadas para el diagnóstico de ojo DED con objeto de revelar los resultados a corto plazo sometidos a MIGS.

Los estudios de investigación detallados en esta tesis evalúan una serie de técnicas avanzada de diagnóstico para comprender el papel de la DED en los procedimiento actuales de cirugía oftálmica con propósitos refractivos y visuales pero también para el manejo de enfermedades como el glaucoma. Asimismo, dichos estudios tratan de descubrir cual son las pruebas más importantes, mínimamente o no-invasivas, capaces de revelar el papel del DED en la cirugía oftálmica que llevarían a una mejora en los resultados tanto refractivos como visuales, así como los referidos por los pacientes.

Palabras clave: ojo seco, cirugía refractiva de la córnea, cirugía del cristalino, cirugía de glaucoma, superficie ocular

Summary

Dry eye disease (DED) can play an important role in ophthalmic procedures with refractive aims such as those involving the cornea (corneal laser surgery) or the crystalline lens (refractive lensectomy or cataract surgery) but also in the treatment of other conditions such as glaucoma. This thesis describes the application of a series of minimally to non-invasive diagnostic DED tests recommended by the recent Tear Film & Ocular Society Dry Eye WorkShop II (TFOS DEWS II) to help to improve the understanding of the impact of dry eye on the refractive and visual outcomes in the ophthalmic surgery and the impact of ophthalmic surgery on the ocular surface.

Intraocular lens surgery, in particular modern cataract and refractive lens-exchange (RLE) surgery, is the focus of the first section of the thesis. In fact, DED is not only present as a post-operative complication but can also be responsible for sub-optimal refractive and visual outcomes since parts of the pre-operative examination pathway can be influenced by a depleted tear film (e.g. biometry and corneal topography). A literature review suggests little evidence of the routine use of advanced tear film assessments in patients undergoing intraocular lens surgery and there is little information on which DED findings are most important to avoid suboptimal clinical outcomes. Studies were carried out to explore the most relevant DED tests as recommended by the TFOS DEWS II. The key findings were validated questionnaires such as Ocular Surface Disease Index (OSDI) and Dry Eye Questionnaire 5-items (DEQ-5) and tear metrics such as non-invasive keratograph break-up time (NIKBUT), tear film volume (TMH) and tear osmolarity.

In modern corneal refractive surgery, despite numerous publications and studies demonstrating the safety and efficacy in correcting refractive errors such as myopia, hyperopia and astigmatism, post-operative DED is still problematic and of the most common complications after surgery. Recently, newer techniques (e.g. small incision lenticule extraction (SMILE)) have been introduced with the aim of providing excellent visual outcomes whilst overcoming some of the limitations of more established procedures including undesirable alterations to corneal nerve structure and function and DED development. The use of in-vivo confocal microscopy was used to compare corneal nerve structure after SMILE with that seen after traditional laser-assisted in situ keratomileusis (LASIK). The results showed FS-LASIK surgery had more impact on DED symptomatology, TMH and NIKBUT and has led to significant change to the corneal nerve fibre metrics considered than SMILE surgery.

Glaucoma management with topical preserved eyedrops can lead to deterioration of the ocular surface in a large proportion of patients with DED issues in terms of signs (e.g. ocular redness) and symptoms (grittiness, photophobia, etc.). Of the newer surgical procedures designed to control intraocular pressure reducing the need for topical management, minimally-invasive glaucoma surgery (MIGS) seems to be promising and could improve the homeostasis of the ocular surface in glaucoma patients. However, very little research on this topic has been published and an advanced pilot investigation to explore the use of a diagnostic battery of tests for DED after MIGS was carried out. Reduction in IOP was achieved by the procedure together with the reduction in DED symptomatology, increase of stability of the tear film and improvement of the ocular surface staining.

In summary, the research studies detailed in this thesis use a series of advanced diagnostic techniques primarily to understand the role of DED in patients undergoing ophthalmic procedures for refractive and visual indications but also in patients being treated for glaucoma. They also explore which are the most important tests, in terms of identifying the impact of DED in ophthalmic surgery. Better diagnosis and management of DED in patients undergoing ophthalmic surgery will lead to optimal refractive, visual and patient-reported outcomes.

Key words: Dry eye, corneal refractive surgery, lens surgery, glaucoma surgery, ocular surface.

Dedication

I dedicate this thesis to the women who made me the man I am.

"A n'ò mai imparà gnént da ûn che e'n sa meno che mé

Popular proverb, around 1943.

Acknowledgements

In the dedication, the sentence (translated) says "*I never learned anything from someone who knows less than me*". I have been lucky to learn a lot from many people during my postgraduate studies. In first instance, I want to thank to my supervisors Dr Clare O'Donnell, Professor James Wolffsohn and Professor Alejandro Cerviño for their counsel, competence and guidance throughout the course of the thesis and beyond. I could not have imagined having better advisors in my PhD study.

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Contents

List of abbreviations

1M - 1 month

3M - 3 months

6M - 6 months

ACNBD- Automated corneal nerve branch density

ACNFD- Automated corneal nerve fibre density

ACNFL- Automated corneal nerve fibre length

ACNFrD- Automated corneal nerve fibre fractal dimension

ADDE - Aqueous deficient dry eye

AH - Aston Halometer

ALT - Argon laser trabeculoplasty

AM - Ante meridiem

AR - Alberto Recchioni (author)

BAK - Benzalkonium chloride

BCVA - Best-corrected visual acuity

CDVA - Corrected distance visual acuity

CI - Confidence interval

CL - Contact lens

DALK - Deep anterior lamellar keratoplasty

DCWT - Dual-tree complex wavelet transform

DED - Dry eye disease

DEQ - Dry eye questionnaire (21 items)

DEQ-5 - Dry eye questionnaire (5-items)

DEV_PPOR - Deviation from the predicted post-operative refraction

DEWS I- Dry eye workshop I

DEWS II- Dry eye workshop II

DLS - Dysfunctional lens syndrome

DMF - Dual-model filter

EDE - Evaporative dry eye

EDOF - Extended depth of focus

EMR - Electronic medical records

Epi-LASIK - Epithelial laser-assisted in-situ keratomileusis

EPP - Estimated pool prevalence

EQ-5D - EuroQol 5-dimensions questionnaire

EQ-VAS- EuroQol visual analog scale

EU - Europe

F - Female

FDA - Food and drugs administration

FLEX -Femtosecond lenticule extraction

FS-LASIK- Femtosecond laser-assisted in-situ keratomileusis

fTBUT - Fluorescein tear break-up time

GP - General practitioner

GVHD - Graft-versus-host disease

HCT - Health care technician

HOA - High order aberration

HP - Hydroxypropyl

HRT-RCM - Heidelberg retina tomograph rostock cornea module

IBM - International business machines

IDEEL - Impact dry eye on everyday life

IL - Interleukin

IOL - Intraocular lens

IOP - Intraocular pressure

IVCM - In-vivo confocal microscopy

K5M - Keratograph® 5 m

KCS - Keratoconjunctivitis sicca

LASEK- Laser-assisted subepithelial keratomileusis

LASIK - laser-assisted in-situ keratomileusis

LCD - Liquid crystal display

LED - Light emitting diodes

LFU - Lacrimal function unit

LLT - Lipid layer thickness

LVC - Laser vision correction

M - Male

MAX - Maximum

MG - Meibomian gland

MGD - Meibomian gland dysfunction

MIGS -Micro-invasive glaucoma surgery

MIN - Minimum

MM - Manual microkeratome

MUC - Mucin

NA - Not applicable

Nd-YAG- Neodymium-doped yttrium aluminium garnet

NEI - National Eye Institute

NEI-RQL - National eye institute refractive error quality of life instrument

NEI-SES- National eye institute socioemotional scale

NEI-VFQ- National eye institute visual function questionnaire

NHS - National health service

NIBUT - Non-invasive break-up time

NICE - National institute for clinical excellence

NIKBUT- Non-invasive keratograph break-up time

NIKBUT-Avg - Non-invasive keratograph break-up time average in 25-seconds

NIKBUT-First - Non-invasive keratograph break-up time firstly observed

NSAID - Nonsteroidal anti-inflammatory drugs

OCT - Optical coherence tomography

OHT - Ocular hypertension

OSDI - Ocular surface disease index

PCAG - Primary closed-angle glaucoma

PHACO- The prospective health assessment of cataract patients' ocular surface

PIS - Patient information sheet

POAG - Primary open-angle glaucoma

POST - Post treatment / post surgery

PRE - Pre treatment/ pre surgery

PRK - Photorefractive keratotomy

Q - Question

QoL - Quality of life

RCOphth -Royal College of Ophthalmologists

REC - Research ethics committee

REF - Reference

ReLEx - Refractive lenticule extraction

ReLEx - see SMILE

RLE -Refractive lens exchange

RMS - Root mean square

SD - Standard deviation

SEQ - Spherical equivalent refraction

SimK - Simulated keratometry

SLT - Selective laser trabeculoplasty

SMILE - Small incision lenticule extraction

SPSS - Statistical package for the social sciences

SS - Sjögren syndrome

TBUT - Tear break-up time

TCR - Tear clearance rate

TF - Tear film

TFOS - Tear film & ocular surface (society)

TMH - Tear meniscus height

TNF - Tumor necrosis factor

UDVA - Unaided distance visual acuity

UK - United Kingdom

US - United States

UV - Ultraviolet

VA - Visual acuity

VDT - Visual display terminal

VF - Visual function index

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Chapter 1: Literature Review

1.1 Introduction to the literature review

Dry eye disease (DED) is one of the most common eye condition in the World that could potentially affect patients' quality of life and vision if it is not resolved (McDonald et al., 2016). Despite a remarkable effort in the research field, with an increasing number of publications related to the ocular surface and its conditions (Baudouin et al., 2017; Conrady et al., 2016; Gomes et al., 2019; Milner et al., 2017; Ong et al., 2018; Vehof et al., 2017), many aspects remain unclear about DED with poor understanding about the causes and solutions (Galor et al., 2015b). Although the literature covers a wide variety of possible theories, this review aims to consider all the most relevant scientific evidence in terms of ocular surface disease, such as dry eye, and its relationship with ophthalmic procedures.

The literature review details the anatomy of the ocular surface that is a complex network made of several structures with the vital functions to maintain the eye's homeostasis. The same equilibrium could be potentially lost in DED. An updated scientific approach has been detailed along the text following the recommendations of the first Tear Film & Ocular Surface Society Dry Eye WorkShop I (TFOS DEWS) and from the more recent Tear Film & Ocular Surface Society Dry Eye WorkShop II (TFOS DEWS II) in terms of DED definition, classification and diagnosis. Therefore, the cornerstone of the thesis in which are described the most common ophthalmic surgeries with their relationship with DED. In conclusion, the literature review ends with the aims of the thesis addressing the differences in the literature and the justification of the studies planned.

1.2 Methods

The basic knowledge such as anatomy, physics, bio-chemistry, pharmacology, visual optics, optometry, ophthalmology, ocular pathology and eye surgery procedures have been consulted using the books available in the Aston University Library.

The following reports have been considered for their scientific contribution to the field of DED:

- Report of the National Eye Institute/Industry WorkShop in Dry Eye - 1995
- Report of the International Tear Film & Ocular Society Dry Eye WorkShop (TFOS DEWS) – 2007
- Report of the Tear Film & Ocular Society Dry Eye WorkShop II (TFOS DEWS II) - 2017

Additionally, two different databases were continuously used for the review: PubMed for scientific literature from MEDLINE and Web of Science™ Core Collection by Aston University.

The following search terms were used:

1. dry eye disease or ocular surface disease or dry eye
2. lacrimal functional unit
3. corneal refractive surgery or laser refractive surgery or refractive surgery or corneal laser surgery
4. lens surgery or intraocular surgery or cataract surgery or lensectomy
5. refractive lens exchange or clear lens exchange or RLE surgery
6. photorefractive keratotomy or PRK
7. laser-assisted sub-epithelial keratomileusis or LASEK
8. epithelial laser-assisted in situ keratomileusis or EPI-LASIK
9. laser-assisted in situ keratomileusis or LASIK or mechanical LASIK or femtosecond LASIK or FS-LASIK
10. femtosecond lenticule extraction or FLEX or ReLEx FLEX
11. small incision lenticule extraction or SMILE or ReLEx SMILE
12. corneal nerves or subbasal corneal nerve or corneal nerves loop or corneal nerves plexus
13. in-vivo confocal microscopy or IVCM
14. glaucoma or glaucoma surgery or minimally-invasive glaucoma surgery or MIGS

The electronic sources were last searched in April 2019.

1.3 Ocular surface

Following the recent TFOS DEWS II (2017), the ocular surface includes the following structures: cornea, conjunctiva, eyelids, eyelashes, tear film, main and accessory lacrimal glands, and the Meibomian glands (Craig et al., 2017b). In the next sections, the ocular surface structures and their links to DED are explained.

1.3.1 Cornea

The cornea is the transparent and avascular structure of the anterior part of the eye that covers the anterior chamber, the iris and the pupil. It represents approx. 70% of the total dioptric power of the eye which in humans is approximately 43 Diopters, considering a refractive index of n=1.376 (Ayres et al., 2006). The average diameter of the cornea is 11 mm and the average central thickness is 500 µm increasing to around 700 µm in the periphery (Kanski et al., 2011; Snell et al., 2013). According to Sridhar (2018), the anterior surface of the cornea has a mean radius of curvature of approximately 7.8 mm while the posterior radius is approximately 6.5 mm.

The corneal homeostasis is maintained by the tear film, the aqueous humour and the limbal vessels. The tear film provides oxygen to the cornea transported by the external environment (air) while the aqueous humour delivers amino acids and vitamins to this layer. The limbal blood vessels remove catabolites from the adjacent tissues as they are passing through the transition area between the cornea and the sclera (the limbus).

The cornea is composed of different layers as pictured in Figure 1.

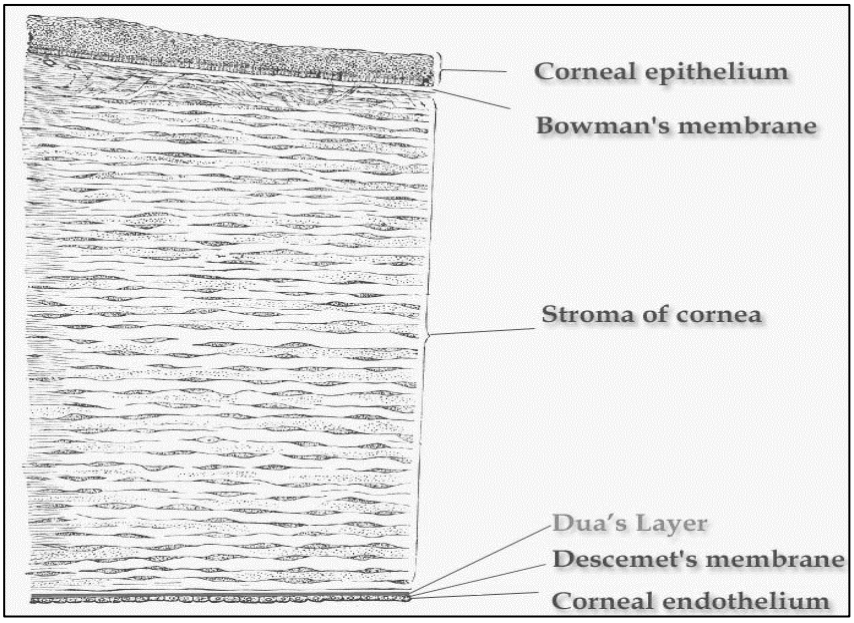

Figure 1 Vertical section of the human cornea. Adapted from Gray's Anatomy book (2009)

The epithelium is the stratified non-keratinized outer layer of the cornea. Its thickness has an average value of 50 to 60 microns formed by 5 to 7 cells' layers (Kanski et al., 2011). Due to the high rate of cell regeneration, the epithelium provides a continuous defence against the external environment even when the cornea is superficially wounded. This mechanism is guided by the thin basal membrane that regulates corneal homeostasis and cell growth (Torricelli et al., 2013). Complete 's turnover takes usually 7 to 10 days (C. Liu et al., 2015a).

The cornea is hydrophobic and the mucins, made of high-molecular-weight glycoproteins, allow the aqueous layer to adhere and hydrate the cornea (Sharma, 1993). Additionally, mucins are able to protect the corneal surface acting as an antimicrobial barrier (Mantelli et al., 2008). In humans, there are approximately 20 different mucin genes with approximately 7 to 8 identified in the ocular surface (Hodges et al., 2013). In DED, the reduction of certain mucins (MUC1, MUC2, MUC4, MUC5A and MUC7) affects the quality of the tear layers and patients may report discomfort (Carracedo et al., 2015). In a recent review by Y. Uchino (2018), the author remarked on the importance of transmembrane mucins (MUC1, MUC4, MUC16 and MUC20) to lubricate the ocular surface reducing the frictional stress. Additionally, these mucins act in conjunction with glycocalyx to protect against external agents (e.g. external microorganism) and to enhance the corneal epithelium wettability. However, despite the role played by mucins in DED, especially in being targeted by the inflammatory process provoked by tear film hyperosmolarity (see section 1.4.3), their clinical evaluation is still a challenge due to the lack of availability of all-in-one device for analysis and further research is needed.

Bowman's membrane is the anterior part of the corneal stroma with a 6 to 9 micron thickness and a particularly organised structure. The smooth anterior surface is comprised of collagen type 1 fibrils facing the epithelium, while the posterior surface is combined with the anterior stroma. Currently, its function is unclear but following the work of Lagali et al. (2009), it seems that it could help to regenerate stromal cells, for example after corneal laser refractive surgery. Additionally, this research has suggested that Bowman's membrane could potentially provide protection of the corneal nerves under the epithelium that influence tear secretion.

The transparency of the cornea is guaranteed by the well-organized structure of the stroma and its collagen fibrils (collagen V and IV). However, the stroma has not only an optical function but it maintains proper curvature of the cornea resisting against the mechanical strength of the intraocular pressure (IOP). The stroma accounts for approx. 90% of the total corneal thickness and it is the main tissue altered during corneal refractive surgery (Ambrosio et al., 2003b). Thus, DED and stroma have a direct relationship as several authors have showed how corneal refractive surgery, especially radial keratotomy, photorefractive keratectomy (PRK) and

laser assisted in-situ keratomileusis (LASIK) damage corneal nerves in the stroma inducing ocular surface disturbance (Demirok et al., 2013; Denoyer et al., 2015; Gao et al., 2014; McAlinden, 2012; Toda, 2018).

During recent years, an additional layer was discovered by Dua et al. (2013) (now formally named “Dua’s layer”) that is located between the stroma and Descemet’s membrane. The layer has shown an ability to resolve corneal edema provoked by intraoperative trauma after cataract surgery (Dua et al., 2016). Kocluk et al. (2016) mentioned its presence in a report on deep anterior lamellar keratoplasty (DALK) surgery confirming its clinical existence in the cornea.

Descemet’s membrane is located in between the corneal endothelium and the posterior stroma. The thickness is approx. 10 microns in adults and the composition is different from the stroma with a single collagen VII fibrils. Descemet’s membrane acts as an intermediate interspace with an anterior banded layer in contact with the stroma and an un-banded layer in contact with the endothelium (Eghrari et al., 2015).

Maintenance of corneal hydration is carried out by the endothelium, acting as a metabolic sodium pump to keep the water content at approximately 70-78% of the whole composition. The hydration is continuously kept at an adequate level to nourish the adjacent structures, providing amino acids and glucose. Moreover, the corneal hydration is controlled to avoid corneal swelling (oedema) and loss of transparency (Sridhar, 2018). Kheirkhah et al. (2015) reported that patients who suffer from DED have a significant reduction in central corneal endothelial cell density and corneal subbasal nerve density compared with patients not diagnosed with DED. In a retrospective study, the authors were able to confirm these changes also in DED patients (Kheirkhah et al., 2017).

1.3.2 Conjunctiva

The conjunctiva is a membrane of non-keratinized squamous epithelial cells and goblet cells whose role is to deliver mucins that are important to support the tear film and maintain its integrity (Bhattacharya et al., 2017). Part of the conjunctiva covers the sclera up to the junction between the sclera and the cornea (bulbar conjunctiva) while the rest covers the inner surface of the upper and lower eyelids.

By protecting the eye from any external hazards (e.g. dust. debris, infections, etc.), the conjunctiva also nourishes the eye through the blood supply that originates from the ophthalmic artery and from the external carotid artery (tarsal conjunctiva) (Shahidi et al., 2010). Spread over the conjunctiva, there are mucins that lubricate and protect the cornea produced by the goblet

cells, creating a solid junction between the corneal epithelium and the aqueous tear film otherwise the cornea is hydrophobic (Davidson et al., 2004).

Hyperosmolarity of the tear film was observed as a risk factor on inducing the inflammatory response (e.g. T-cells) which can damage and reduce the conjunctival goblet cells (Yamaguchi, 2018).

1.3.3 Eyelids and eyelashes

Eyelids and eyelashes cover and protect the anterior part of the eye. While the eyelids play an important role to keep the ocular surface wet through the action of blinking (Snell et al., 2013), the eyelashes keep dust and debris away from the ocular surface and make the eye sensitive to external contact by providing additional protection through the fine hairs. Moreover, the structure of the eyelids allows the tear film to be drained through the upper and lower puncta (nasal side) and via the adjacent canaliculi into the nasolacrimal duct for its expulsion into the nose (Hasner's valve) (Kanski et al., 2011).

Every blink allows the lipid layer, secreted by the tarsal glands (Meibomian glands) in both portions of the eyelids, to be spread over the ocular surface helping to increase the resistance of the muco-aqueous gel from evaporation (Knop et al., 2011). The blink rate and its completeness is an important factor to consider to disclose any potential DED development. Previous studies have reported that an incomplete spreading of the lipid layer could induce staining of the ocular surface and an increase in DED symptoms (Lowgren et al., 2017; Pult et al., 2013b). Additionally, in the case of Meibomian glands dysfunction, tear film lipids are reduced causing an evaporative form of DED that is discussed in section 1.4.2.2.

1.3.4 Tear film

The tear film (TF) is a multi-layered structure on top of the outer mucosal surfaces of the cornea and conjunctiva that has several functions: to provide homeostasis of the superficial cells (epithelium and conjunctiva) by ensuring a wet environment, reducing the frictional forces experienced with every blink, to determine the optical power of the cornea and keeping a regular profile, to nourish the conjunctiva and cornea while protecting them from external agents such as bacteria, to eliminate catabolites and foreign bodies and to regulate changes in temperature and ocular surface pH (Coles et al., 1984; Tiffany, 2008).

The TF is composed of a lipid layer that is in contact with the external environment (outer) and an aqueous layer (intermediate) that is mixed with the mucinous compound (inner) in contact with the corneal epithelial cells forming the muco-aqueous gel layer (Dohlman et al., 2016; Willcox et al., 2017). Wolff (1946, 1954) was one of the first authors to describe the characteristics of the TF as a three-layer system (lipid-aqueous-mucous), without specifying the

thickness. Recent findings from Werkmeister et al. (2013) reported the average central TF thickness is approximately 4 to 5 μm assessed by the means of spectral domain optical coherence tomography (OCT). However, even if TF is generally assumed as a three-layer structure, Doane (1994) remarked that has a more complex structure as reported by Willcox et al. (2017) in the TFOS DEWS II chapter dedicated to the TF composition (Figure 2).

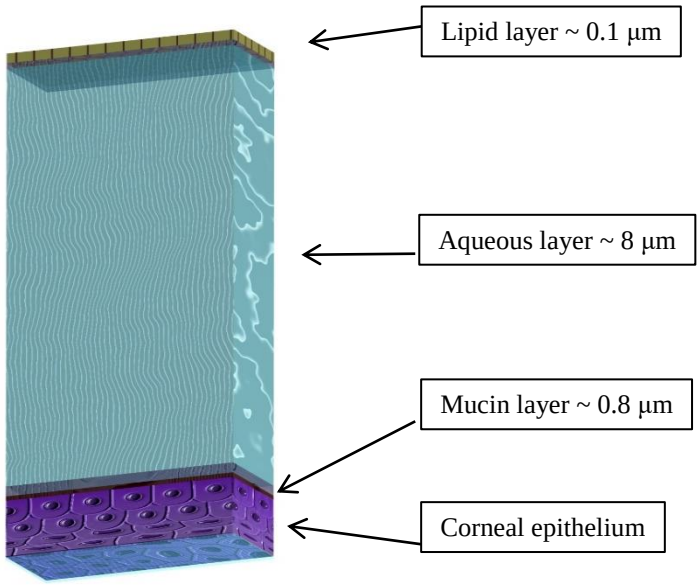

Figure 2 Schematic representation of the tear film (TF) (Courtesy of Professor Jesús Pintor Just, University Complutense of Madrid, Spain)

The lipid layer carries out several functions such as reducing evaporation, lowering TF surface tension and lubricating the eyelids. It consists of lipids of low polarity (e.g. wax and cholesterol esters) and high polarity (e.g. phospholipids) produced in the Meibomian glands located in the upper tarsal conjunctiva and in the inferior tarsal conjunctiva (Willcox et al., 2017). The number of these glands varies from 20 to 30 depending on the study (K. Nichols et al., 2011). In addition, Zeiss and Moll glands (also known as ciliary glands) supply additional lipids to the TF, retarding its evaporation. Normally, it is observed that a healthy TF resists evaporation for approx. 15 to 40 seconds (also called tear film breakup time, see 1.4.4.2.2.1) with open eyes, while in DED the time decreases to below 5-10 seconds (Savini et al., 2008). However, the automatic eye response to TF evaporation is blinking. This avoids the perception of any symptoms of dryness over the ocular surface (for more details see section 1.3.3).

The aqueous layer (approx. 90% of the total TF thickness) contains important chemical protective factors such as albumin, lysozyme, lactoferrin, lipocalin, cytokines and immunoglobulin A, but also elements which help to nourish the corneal tissues providing inorganic salts, glucose, urea, enzymes, protein and glycoproteins. The dedicated sites of

production of the aqueous part are the lacrimal gland and the accessory glands (Krause and Wolfring).

The main lacrimal gland is located in a cavity above the super-temporal eye orbit, while the accessory glands are on the peripheral side of eyelid conjunctiva (tarsus and fornix) (Conrady et al., 2016). The combination of the aqueous layer and the eyelids is recognized to be the most effective tool for protecting and cleaning the ocular surface and to maintain the ocular surface smooth which is important for clear vision (Kaido et al., 2007). In fact, a depleted TF reduces the quality of life due to the poor visual outcomes associated with DED (Benitez-del-Castillo et al., 2016). Additionally, as the corneal epithelial cells are continuously in apoptosis (programmed cell death), the TF and eyelids help to remove metabolic components and dead cells produced by the physiological turnover that is usually observed after 7-10 days starting from the outermost cell layer to the innermost layer (Hanna et al., 1961).

The aqueous layer is combined with the mucous layer formed by mucins such as MUC1, MUC 2, MUC5AC, etc. These mucins are produced in the goblet cells that are apical cells of the conjunctiva and cornea but there are also mucins produced in the lacrimal gland (H. Watanabe, 2002). Together with the aqueous layer, the mucins form a thick compound that covers the ocular surface. As the corneal epithelium surface is hydrophobic, the mucins made of high-molecular-weight proteins (glyoxylate) allow the TF to anchor the corneal epithelial cells. The mucin layer also avoids shearing forces on the ocular surface due to the action of the eyelids as absorbs some pressure (Mantelli et al., 2008).

A healthy and intact TF is important to maintain the homeostasis of the ocular surface and avoid disturbance in quality of life metrics such as vision and comfort. However, as the TF could be affected by several disorders, in the next sections the report will focus on DED classifications and factors responsible for this condition.

1.3.5 The lacrimal functional unit

The ocular surface innervation is provided by the trigeminal nerve (fifth cranial nerve, V) and its branches through the lacrimal nerve that connects to the lacrimal gland within the orbit (Sridhar, 2018). Additionally, underneath the cornea there are nerves derived from the ophthalmic branch of the trigeminal nerve. The majority of these nerves pass through the corneal stroma and through the subbasal plexus under the corneal epithelium: an estimated 7000 corneal receptors per mm^2 are observed at this level (Muller et al., 2003). The cornea is highly innervated with receptors that are activated by pain (nociceptors), contact (mechanoreceptors) or thermic (thermoreceptors) stimulation leading to lacrimal secretion (Bron et al., 2017). One of the principal roles of the lacrimal functional unit, formed by the structures detailed in the previous sections together with

the connecting innervation, is to maintain a stress-free environment that avoids any potential trigger events (e.g. tear film evaporation, tear film flow reduction, etc.) that could potentially start the development of DED (Stern et al., 2004).

1.4 Dry eye disease

1.4.1 Definition, prevalence and risk factors

The first definition of DED was agreed during the National Eye Institute (NEI) workshop in 1995. At that time, a panel of experts coined the definition as follows: "*Dry eye is a disorder of the tear film due to tear deficiency or excessive evaporation, which causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort*" (Lemp, 1995). More than 10 years later, in 2007, the definition was revised due to the new research which had revealed that tear film osmolarity and ocular surface inflammation were involved in DED development causing deterioration in visual function. Thus, the TFOS DEWS report stated: "*Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface*" (Lemp et al., 2007). In 2017, TFOS DEWS II report provided the current and updated version of DED definition. It takes into account the multifactorial origin of the condition together with the TF loss of homeostasis which has collected all the elements underlying DED. Additionally, ocular symptoms have included visual and discomfort aspects affected by DED. TF osmolarity, together with TF stability, were reported as the triggers in starting the DED process. Finally, aetiology factors such as inflammation and damage of the ocular surface were included, together with the neurosensory response. The current definition is detailed as follows:" *Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles*" (Craig et al., 2017b).

In 2007, the first TFOS DEWS report indicated that the prevalence of the condition was between 5 and 30% (Chia et al., 2003; Lemp et al., 2007) in population older than 50 years while the latest TFOS DEWS II report indicate higher percentages up to 50% with peaks up to 75% in certain populations (Stapleton et al., 2017). The reason behind the difference depends on which clinical assessment has been considered in determining DED, if based on symptoms, signs or both. DED prevalence based on symptoms ranges from 5% to 50% where the most common symptoms reported were increased sensibility to light (photophobia), sensation of sand in the eyes, watery eyes, burning, aching, itching, dryness and a general feeling of ocular discomfort (Fiscella, 2011). In studies performed in South East Asia based on DED symptomatology, the

prevalence of the condition ranges from 20 to 52.4% while in other countries such as the US, UK and Spain the prevalence is approximately 15-20% (Moss et al., 2000; Vehof et al., 2014; Viso et al., 2009). DED prevalence based on signs varies according to the test considered in the study: for example, when the stability of the tear film is considered with a cut-off below 10 seconds, the range is quite broad (from approximately 16 to 85%) (Guo et al., 2010; Lu et al., 2008; Malet et al., 2014). Otherwise, if the volume of the tear film is considered with a cut-off below 5 mm obtained with a Schirmer test, the prevalence varies from approximately 20 to 37% while if the corneal staining is considered, the prevalence varies from approximately 6 to 77% (Gong et al., 2017; M. Uchino et al., 2008; M. Uchino et al., 2006).

Risk factors such as gender, race and age could potentially influence DED prevalence. In terms of gender, the prevalence of DED symptoms is higher in women than men (Hashemi et al., 2014; Song et al., 2018). A lack of oestrogens, especially during the post-menopausal period, has been reported as a cause of DED in women and should be taken into account during the eye examination (Hessen et al., 2014). However, additional studies are required to clarify the role of sex hormones (androgens and estrogens) on the ocular surface homeostasis (Truong et al., 2014). In terms of race, data from Women's Health Study suggest that Hispanics and Asians are more affected by DED compared to Caucasian women (Schaumberg et al., 2003), as recently remarked by Kim et al. (2019a) comparing Asian an Caucasian population. Another factor related to DED development is age. In a study by Ezuddin et al. (Ezuddin et al., 2015), DED was mainly reported in adults aged 50 years or older (up to 30%). In support of these findings was the Beaver Dam Eye Study (Moss et al., 2000), which gave a percentage in DED prevalence of 8.4% in patients younger than 60 years and a two-fold increase in those older than 80 years. Additionally, as aging of the eye is linked to Meibomian gland dysfunction (MGD) and MGD is one cause of DED, it is easy to understand the relationship between age and DED (Cochener et al., 2018; Pult, 2018; Rico-Del-Viejo et al., 2018).

1.4.2 Classification of dry eye disease: past and present outlook

The following sections aim to describe how the evolution of DED classification has changed in 10 years from TFOS DEWS to TFOS DEWS II report. In fact, several publications were published between the two reports and therefore many eye professionals and general clinicians have increased their interest in discovering more about DED (Figure 3).

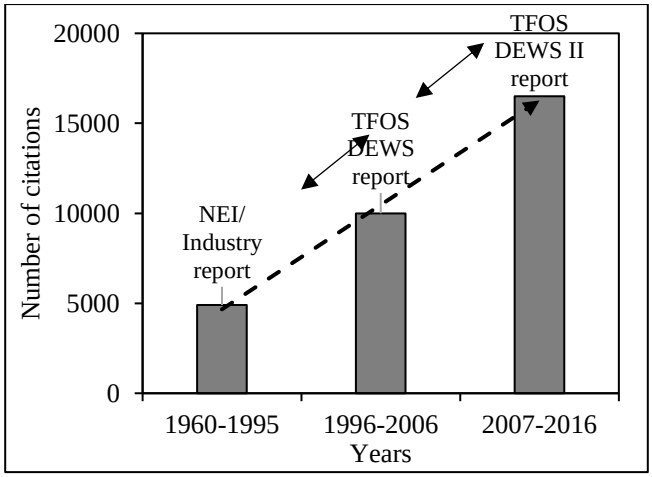

Figure 3 The number of dry eye citations prior to the NEI/Industry Report (1960–1995); new citations between the NEI/Industry Report and the Tear Film & Ocular Surface Society Dry Eye WorkShop (TFOS DEWS) report (1996–2007); new citations between the TFOS DEWS report and the TFOS DEWS II report (adapted from the TFOS DEWS II report Introduction).

From TFOS DEWS Dry Eye Classification (2007), two main categories were recognized: the hypo-production of the tear film (aqueous deficient dry eye or ADDE) and the irregular evaporation of the tear film (evaporative dry eye or EDE).

ADDE could be due to a reduction in tear flow over the ocular surface provoked by any failure of the lacrimal glands (e.g. Sjögren syndrome), obstruction of the tear ducts, disruption of the sensory innervation that leads to tear secretion and the influence of systemic drugs (Conrady et al., 2016). EDE could be due to an unstable ocular surface composition (e.g. lipid layer instability), irregular eyelid aperture (e.g. eye anatomy and dynamics) or Meibomian glands dysfunction (Bron et al., 2017; Tomlinson et al., 2011).

1.4.2.1 Aqueous deficient dry eye

Reduction in the tear volume can be due to different factors described in the following sections.

1.4.2.1.1 Sjögren's syndrome

In case of Sjögren's syndrome (SS), which is an autoimmune disease that causes general dryness in the body (e.g. mouth, skin, etc.), a long-term DED is observed. In fact, the tear volume is reduced as both lacrimal and salivary gland functions are reduced (Thomas et al., 1998). DED is also present in secondary SS where the condition is associated with autoimmune connective disease such as rheumatoid arthritis, lupus erythemalosis, etc. (Wiik et al., 2006).

1.4.2.1.2 Non-Sjögren's syndrome

ADDE can be caused by the hypo-production of the tear film that can be observed due to aging (Rico-Del-Viejo et al., 2018): the physiological changes over the lacrimal gland structure (e.g. acinar atrophy, acinar fibrosis, ductal dilation and proliferation) have shown a negative effect

over the tear volume with potential inflammation of the lacrimal functional unit (LFU) (see 1.3.5). Congenital alacrima is related to a series of conditions where the lacrimal secretion is absent or reduced with severe damage to the ocular surface. In fact, the lack of gene encoding produces the dysfunction that induces DED in younger populations (Alwohaib et al., 2017). Familial dysautonomia is a sensory and autonomic neuropathy in which gene deficiency is responsible for causing problems of sensitivity to parasympathetic and sympathetic innervation. The neuropathy affects the nerve stimulus causing a reduction of tear production and DED (Scanzera et al., 2018).

ADDE can be provoked by a blocked tear duct: patients describe the symptoms as sand in the eye or a foreign body sensation. In fact, the production of the tear film is not changed but the cicatrisation of the ducts forces the tears to remain longer over the ocular surface increasing the catabolites (waste products) with potential inflammation or infection (Mainville et al., 2011). The aetiology includes poor eyelid hygiene, eyelid surgery, frequent eye infection, injury or trauma, tumour, topical treatment (e.g. glaucoma), cicatricial disorders and ageing (Mishra et al., 2017).

As mentioned in section 1.3.5, the neural innervation of the cornea is provided by the trigeminal branch that innervates the ocular area (head and face). It controls the nasolacrimal passages together with tear secretion. Nevertheless, DED may affect the function of trigeminal branch neurons and reduce TF secretion (Lemp et al., 2007). In the presence of a prolonged state of DED (e.g. chronic condition), corneal morphological differences (nerve tortuosity) were found by Benitez (2007) together with reduced corneal sensitivity but without giving a clear explanation of the findings. Meng et al. (2013) discovered the corneal thermoreceptors were active even in the absence of the lacrimal gland innervation (e.g. nerves severed for the experiment). Thus, the activation of these thermoreceptors, without causing damage to the ocular surface (e.g. modifying temperature), could be considered as a novel approach to treat DED. However, future studies are needed to underlay the mechanism that links the thermoreceptor with DED treatment.

A series of different systemic medications are recognized to affect the ocular surface leading to DED development as they reduce tear production (Gomes et al., 2017): nonsteroidal anti-inflammatory drugs (NSAIDs), diuretics, antidepressants, anxiolytics, antihistamines, analgesics, etc. Evidence for what the impact of medications on DED has been provided by several studies such as The Beaver Dam Offspring Study. In the research, more than 3700 subjects who were taking systemic antihistamines and diuretics were more prone to DED (Paulsen et al., 2014). In most cases, systemic medications (e.g. hydrochlorothiazide) alter tear film production directly by affecting the lacrimal glands (Bergmann et al., 1985) or indirectly by acting on the sensitivity of the corneal nerves reducing reflex secretion (e.g. diclofenac sodium) (Szerenyi et

al., 1994) or inducing inflammation of secretory glands (e.g. rifampicin) (Fraunfelder et al., 2012; Tiffany, 2008).

Topical drugs are important risk factors for developing DED: in fact, a drug applied over the ocular surface interacts with the related tissues depending on its concentration, frequency of application and whether a preservative is included in the formulation (Fraunfelder et al., 2012). DED is highly correlated with glaucoma, both conditions are frequently present in elderly patients and most glaucoma is managed with topical drops (e.g. betaxolol, travoprost etc.) (Anwar et al., 2013; Leung et al., 2008). Further details on glaucoma and DED are included in section 1.6.2.

1.4.2.2 Evaporative dry eye

The following sections will describe the principal causes of evaporative DED.

1.4.2.2.1 Intrinsic factors

A key role of the lipid layer is to protect the tear film from evaporation. As lipids are produced by the Meibomian glands (MG) located in the tarsal plate, any kind of threat to the secretory glands may accelerate tear film evaporation leading to DED (O'Brien et al., 2004). For example, any disease which alters the skin around the eyelids (e.g. acne rosacea) could also induce DED (K. Nichols et al., 2011; Schaumberg et al., 2011).

Korb et al. (1980) were the first to explore the MGs in patients reporting discomfort while wearing contact lenses. In 2011, a panel of experts reported that MGD prevalence varies between 3.5% and 68% with elderly populations more affected (Nien et al., 2011; Nien et al., 2009; Norn, 1987; Tomlinson et al., 2011) with a higher prevalence after 40 years (Han et al., 2011; Jie et al., 2009; Rico-Del-Viejo et al., 2018). Furthermore, Nien et al. (2011) identified through two different samples of young and old eyelid tissue (ages, 18 and 44 years) that in the older sample there was a significant reduction in cell differentiation responsible for the development of MGD. However, the study was conducted in only 36 tissues and the analysis was performed *ex vivo*. In a study by Guillon et al. (2010), the authors analysed two different age groups: younger and older than 45 years. Using an evaporimeter (Oregon Health Sciences University Evaporimeter) set with different percentage of humidity (30% and 40%), the researchers showed a higher evaporation rate in older patients suggesting that age is a contributing factor for developing DED. In a recent study by Amano et al. (2017), the authors, considering a study population older than 50 years, revealed a significant relationship between age and MGD. As remarked in section 1.4.1, age is a consistent risk factor in DED development. In terms of sex, the results are inconclusive: some researchers have found higher MGD incidence in females (Pult et al., 2012) while others did not (Arita et al., 2008; Asiedu et al., 2018; Den et al., 2006). Asian populations are more prone to MGD with a prevalence rate ranging from 46% to 70% (P. Lin et al., 2003; M. Uchino et al.,

2006) and for Caucasian populations prevalence ranging from 3.5% to 20% has been reported (K. Nichols et al., 2011).

As mentioned in section 1.3.3, the TF is spread over the ocular surface by the action of the eyelids. The portion of the eye covered by the conjunctival tissue of the eyelids reduces the TF area exposed to air and guarantees a better resistance to evaporation together with protecting the ocular surface. In ptosis (blepharoptosis), one or both eyes are completely or partially covered by the eyelids because the levator muscle does not work properly. The visual field can also be limited (A. Watanabe et al., 2014). However, also ptosis surgery could promote DED: in a study by Bagheri et al. (2015), the authors measured TF signs such as Schirmer test and tear break-up time (TBUT) and found a reduction of these parameters after ptosis surgery. However the results should be considered carefully as both measurements are considered invasive (e.g. Schirmer test strip and fluorescein TBUT) (Savini et al., 2008). In contrast, other authors found ptosis surgery improved the condition of patients suffering from filamentary keratitis provoked by DED but with a sample size of only two cases (Kakizaki et al., 2003).

Eyelids surgery can also be considered for cosmetic purposes. In a recent review by Yang et al. (2017), the authors remarked that blepharoplasty surgery could induce DED leading to iatrogenic lagophthalmos, lacrimal gland injury and corneal wounds. However, other authors found that in the majority of DED patients undergoing blepharoplasty without denervation of the orbicularis muscle, DED did not worsen (Saadat et al., 2004).

Blinking allows the restoration of the TF. Normal blink rate is between 4.5 to 26 times per minute depending on the task being completed (Belmonte et al., 2017; Nosch et al., 2015). Corneal innervation is responsible for the reflex blink after tactile stimuli, optical stimuli or auditory stimuli. When corneal sensitivity is reduced, the blink rate could be reduced causing an improper spreading of the lipid layer over the ocular surface that induces TF evaporation. The connection between blinking rate and DED was investigated by Portello et al. (2013) in a study cohort of patients performing a 15-minute task with a computer. The researchers recorded blink rate and the amplitude of the eyelids with and without an audible-tone to remind them to blink every 4 seconds. At the end of the task, patients were invited to complete a questionnaire on ocular symptomatology. The results showed no significant changes comparing the forced blink (audible-tone) with the natural blink, suggesting that blinking may not be associated with DED symptoms. However, the results were produced considering a non-validated questionnaire such as the Ocular Surface Disease Index (OSDI) questionnaire or the Dry Eye Questionnaire 5-Items (DEQ-5). Additionally, Hirota et al. (2013) reported that incomplete blinking rather than blinking rate in visual display terminal (VDT) users was more critical because the exposed ocular surface could potentially show DED signs. Further research is needed to confirm these findings.

1.4.2.2.2 Extrinsic factors

Vitamin A is crucial to improve cell activity in the cornea and to avoid xerophthalmia with potential loss of vision, especially during night time (Bron et al., 2017). Moreover, a lack of vitamin A absorption is one of the causes of DED related to nutrition. Patients with vitamin A deficiency may develop DED due to the reduced goblet cell expression (MUC1, MUC4 and MUC 16) and a decreased aqueous layer production (Baudouin et al., 2018). The lack of vitamin A could also lead to an abnormal differentiation process of the corneal surface (e.g. keratinization of conjunctival and epithelial cells) with negative influence over the ocular surface (Hori et al., 2004). In developing countries, such as Asia, Africa and Latin America, malnutrition is still a considerable problem. A study analysed vitamin A levels of Brazilian children aged between 6 and 59 months: the authors found that vitamin A levels were insufficient in 16% of the study population (Faustino et al., 2016). Therefore, an assumption can be made considering part of the population who can potentially develop DED due to a loss of vitamin A.

A depleted TF could affect contact lens (CL) wear by generating DED. Based on a CL trends survey carried out every year between 2002 and 2014, there are around 140 million CL wearers worldwide (Efron et al., 2015). From a large study cohort performed in multiple sites study across North America, C. Begley et al. (2001) reported that the prevalence of ocular discomfort in CL wearers was 79% and dryness was 77%. In support of these findings, later data extracted from the *"2016 CL survey results Contact Lens Category Retention White Paper"* by CooperVision (The Cooper Companies Inc., Lake Forest , US) reported that the CL dropout rate is around 49% and most patients stop using CL due to comfort issues. Thus, DED is recognized as one of the most recurrent causes of ceasing CL wear by many studies (Dumbleton et al., 2013; Masoudi et al., 2016; Young et al., 2002). Two of the most common reasons for CL discomfort are the reduction in corneal sensitivity (Lum et al., 2013) and the increase in tear osmolarity (Panaser et al., 2012; Stapleton et al., 2013). Corneal sensitivity is reduced by CL wear because of their mechanical impact over the ocular surface (e.g. interaction between blinking rate, CL wear and corneal epithelial cells) while tear film osmolarity is increased by the increased evaporation rate provoked by wearing a CL (Iskeleli et al., 2013).

Reduction of corneal sensitivity can be observed after long-term CL wear (Lum et al., 2013) and in the presence of reduced oxygen CL transmissibility (Golebiowski et al., 2012). However, one of the most recognized risk factors that affects corneal innervation is the impact of the corneal refractive surgery that could potentially lead to DED development (Demirok et al., 2013; Denoyer et al., 2015; Toda, 2018) (see section 1.5.1.1 for more details). The ocular surface may be temporarily less receptive due to the reduction of corneal nerve fibre density after surgery (He et al., 2015). The consequent effect is a drop in tear secretion followed by a reduction in blink

rate which is important to maintain corneal integrity (Rahman et al., 2015). In a study by Zhang et al. (2005), the researchers considered 8 patients with SS and 30 healthy patients by analysing slit scanning confocal microscopy images and ocular staining. The results indicated a positive correlation between the corneal staining (epithelial cells fragility) and corneal nerve fibre reduction with a potential decrease in corneal sensitivity. Rahman et al. (2015) hypothesised (based on Zhang et al.'s findings) that the corneal epithelium damage is related to diminished corneal sensitivity as the ocular surface is less sensitive to potential threats. The reduced corneal sensitivity after surgery can be recovered after 3 to 6 months, depending on which type of surgery is considered (Gogate et al., 2005; J. B. Lee et al., 2001). However, other authors reported up to 1 year due to the different DED tests considered (Shtein, 2011).

In comparison with the first TFOS DEWS report, the recent TFOS DEWS II report aimed to improve DED diagnosis considering both forms of DED (ADDE and EDE) as "*continuum rather than as separate entities"* (Craig et al., 2017b). TFOS DEWS II report suggests considering a series of triaging questions to exclude conditions which are not DED (e.g. SS) followed by a DED diagnostic test battery including symptoms and signs. The information obtained from those DED metrics aim to improve the management of the condition (Jones et al., 2017).

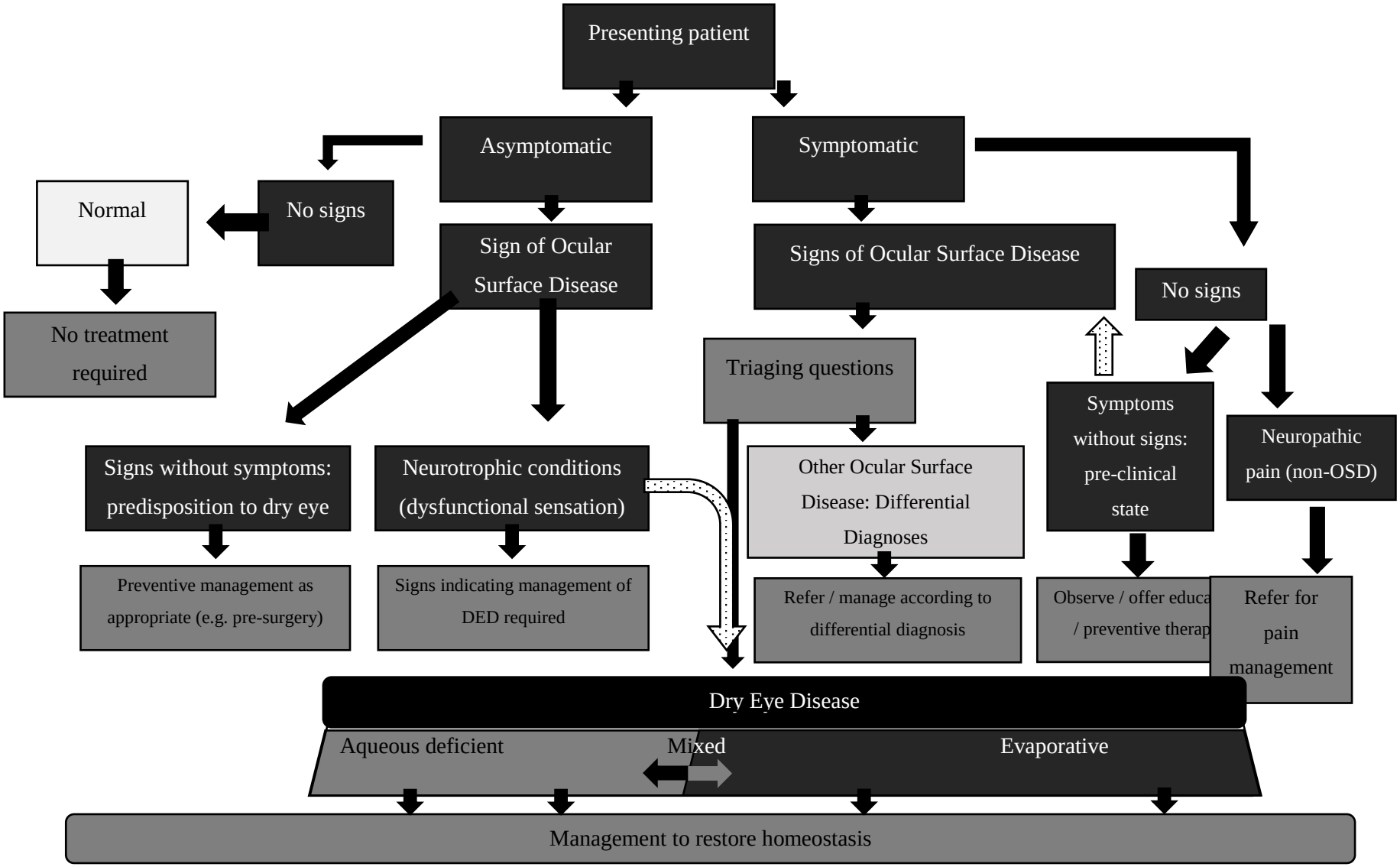

Figure 4 Classification of DED from Tear Film & Ocular Surface Society Dry Eye WorkShop II (TFOS DEWS II) report.

Figure 4 shows the classification of DED obtained by the last TFOS DEWS II report (Craig et al., 2017a): the upper portion is related to the clinical decision algorithm that starts with the assessment of symptoms followed by determination of signs. In the presence of both DED characteristics, using the triaging questions DED can be differentiated from other conditions (e.g. SS, CL discomfort, ocular allergy, etc.) and therefore the treatment improved. Patients reporting symptoms but no signs are currently not considered to be DED patients but should be referred for pain management to other professionals (e.g. general practitioner (GP) or ophthalmologist) or followed-up to monitor changes that potentially can worsen (e.g. pre-clinical state). For asymptomatic patients, Figure 4 indicates that patients interested in having surgery, for example, may develop DED after the procedure or those with reduced sensitivity could experience DED if not managed properly. Finally, the lower part shows that both subtypes, ADDE and EDE, can be present at the same time, especially in the early stage. If DED increases in severity, it is easier to diagnose whether ADDE or EDE is present and which helps to plan appropriate treatment (Wolffsohn et al., 2017).

1.4.3 Pathophysiology of dry eye disease

The core mechanism of DED is TF hyperosmolarity (Lemp et al., 2011; Sullivan et al., 2010). The increased "saltiness" of the TF is responsible for starting a cascade of inflammatory processes whose primary targets are corneal epithelial cells, conjunctival goblet cells (columnar epithelial cells) and the epithelial glycocalyx (peri-cellular matrix) (Bron et al., 2017). In this aspect, both DED subtypes (ADDE and EDE) have hyperosmolarity in their aetiology: ADDE because of the reduced lacrimal secretion and EDE because of the hyper-evaporative state. Thus, in other words, the TFOS DEWS II report supported the hypothesis that both DED subtypes are intrinsically evaporative forms.

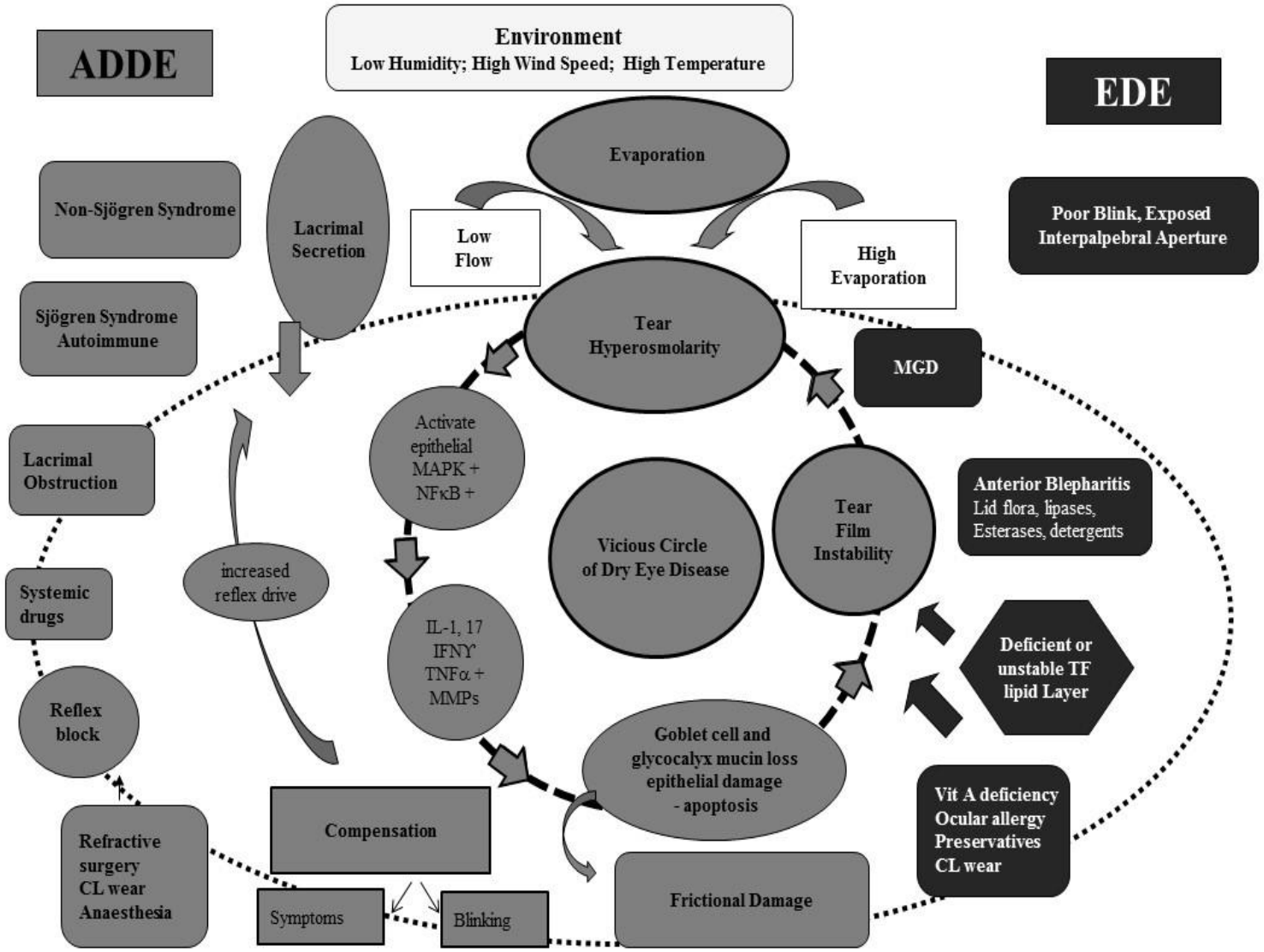

Figure 5 The "*Vicious Circle of Dry Eye Disease*" (Adapted from Bron, "Definition of dry eye disease", 2015, Springer)

As remarked previously, damage to the ocular surface tissues due to inflammation worsens the stability of the TF, leading to a depletion of the quality, which in turn increases the osmolarity of the TF, perpetrating the so-called "*Vicious Circle of Dry Eye Disease*" (Figure 5). However, inflammation is not the only factor that can potentially destabilize the TF, but several causes can intervene such as vitamin A deficiency, ocular allergy, CL wear, etc., but especially MGD (Baudouin et al., 2016; Chhadva et al., 2017; McMonnies, 2018).

As shown in Figure 5, there are several factors responsible for ADDE and EDE (see sections 1.4.2.1.1, 1.4.2.1.2 and 1.4.2.2). However, the pathophysiology of DED covered in this section is focused on the mechanisms underlying the impact of different ophthalmic surgery procedures in the development of DED. This is an area of focus in this PhD thesis.

Several studies have reported the incidence of DED after refractive surgery. In a survey from Jabbur et al. (2004) "dry eyes" was reported in 21.1% of 101 patients supported by similar findings after 3 months by De Paiva et al. (2006). However, both studies were performed previous the release of the first TFOS DEWS report and a diagnostic protocol based on a general consensus was not considered. Additionally, the researchers suggested that the depth of ablation together with the pre-operative amount of myopia could be linked to increase DED after the procedure. In a survey sent to more than 8800 members of the American Society of Cataract and Refractive Surgery, 1053 were returned addressing that the most common complication after LASIK surgery was dry eye (95.2% of the total respondents) (Sandoval et al., 2005). Nevertheless, details on the diagnostic protocol considered to define "dry eye" were not included. More recently, Bower et al. (2015) reported the results after 12 months with DED incidence in 5% and 0.8% operated with PRK and LASIK, respectively. Considering modern corneal refractive techniques such as SMILE, Moshirfar et al. (2018a) published data where patients with pre-operative DED (45%) returned to pre-operative prevalence 3-months after SMILE surgery but again the researchers did not follow the recent DED diagnostic test battery proposed by TFOS DEWS II (e.g. minimally invasive tests).

As DED has a high prevalence in the global population (see section 1.4.1), a considerable number of patients presenting for refractive surgery may show DED signs, symptoms or both before the procedure. Nevertheless, refractive surgery has been shown not only to impact in DED metrics related to ADDE such as tear meniscus height or Schirmer test (Tao et al., 2010; Toda, 2018) but also to reduce the metrics that represent the quality of the TF such as osmolarity, TBUT, lipid layer thickness (LLT) and MG aspects (anatomy, secretion, expressibility, etc.) (Hassan et al., 2013; Jung et al., 2017; Kacerovska et al., 2018).

The results from the available literature suggest that the diagnosis and treatment of DED before refractive surgery should be included in the routine clinical pathway as many patients are asymptomatic or with "acceptable" DED signs which could deteriorate after surgery. Additionally, screening and

management of DED pre-operatively reduces the risk of unwanted refractive and visual outcomes together with post-operative complaints. Future studies with minimally invasive and reliable devices are needed to address the reason behind DED development after refractive surgery even when modern surgical (e.g. SMILE) techniques are considered and as mentioned above is the area of focus in this PhD thesis.

1.4.4 Diagnosis of dry eye

TFOS DEWS II presented a quick and reliable approach to detecting the presence of DED (Figure 6). A proper DED diagnosis should be made, excluding conditions that are not DED (e.g. SS, CL wear, allergy, etc.). For this purpose, experts proposed to test symptomatology using validated questionnaires (see sections 1.4.4.1.1 and 1.4.4.1.2) followed by the evaluation of one homeostasis marker that can be chosen from TBUT, tear film osmolarity or via vital dyes assessment that defines if ocular surface staining is present (Wolffsohn et al., 2017).

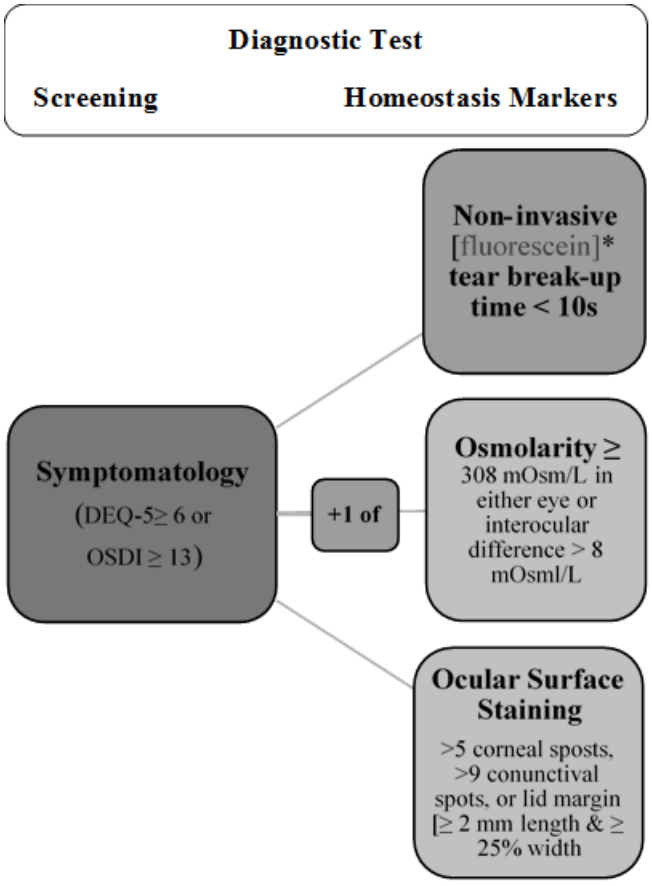

Figure 6 Diagnostic tests comprise of screening (symptomatology) and homeostasis markers. *only to be used if non-invasive TBUT is not available. Dry Eye Questionnaire 5-items (DEQ-5) and Ocular Surface Disease Index (OSDI).

Using this simplified diagnostic approach, clinicians should be able to improve their accuracy in determining the presence of DED by choosing the most appropriate test available in their practice or by referring patients to another practitioner (e.g. GP, ophthalmologist, optometrist). However, to be able

to disclose and identify the subtype of DED, different subjective and objective tests are detailed in the following sections.

The successful completion of a series of clinical tests (subjective and objective) is crucial to identify which subtypes of DED the clinicians is facing and to plan a treatment to better tackle the condition (Savini et al., 2008). In the scientific literature, a debate about the relationship between signs and symptoms is ongoing as many studies involve patients with reduced tear functions (TBUT or Schirmer test) but without complaints and vice versa (Johnson, 2009; K. Nichols et al., 2004b; Pult et al., 2011). In the next sections, the chapter describes the most common clinical tests for subjective and objective assessments.

1.4.4.1 Subjective evaluation

The subjective evaluation in DED is carried out by oral or written questionnaires that consider a series of metrics such as quality of life, health outcomes, visual function, comfort, severity and activities dependent upon vision (J. Smith et al., 2007). This section summarises the most common questionnaires used for clinical and scientific purposes.

1.4.4.1.1 Ocular Surface Disease Index questionnaire

The OSDI questionnaire was developed by Allergan Inc. (Irvine, US) based on internal research derived from the experience of patients and clinicians. Initially, the questionnaire was composed of 40 items and then shortened to 12 questions in a subsequent version that evaluates ocular soreness due to DED and its relationship with the visual functions (Ozcura et al., 2007). In fact, OSDI has 6 questions based on visual disturbance and visual functions that help the clinicians to appreciate not only DED patients but also the visual outcomes differences with a normal healthy group (Amparo et al., 2015). Additionally, it is also able to measure the frequency of symptoms and environmental triggers such as windy conditions, low humidity and air-conditioned areas. The 12 questions are scored from 0 to 4 that correspond to "*none of the time"*, "*some of the time", "half of the time", "most of the time", "all of the time",* respectively. Then the total score is calculated using Formula 1:

$$OSDI = \frac{[(sum\ of\ scores\ of\ all\ questions\ answered) \times 100]}{[(total\ number\ of\ question\ answered) \times 4]} \qquad \text{Formula 1}$$

In a study by Schiffman et al. (2000), the authors reported a good to excellent results in terms of the reliability, validity, sensitivity and specificity. However, a moderate agreement with clinical signs was observed only in DED patients with reduced tear secretion. In a review conducted by Grubbs et al. (2014), the comparison between OSDI and the Impact Dry Eye on Everyday Life (IDEEL) questionnaire revealed the validity and the reliability of both questionnaires to estimate the clinical impact of DED on quality of life (QoL). McAlinden et al. (2017) reported a lack of correlation between OSDI and visual acuity (VA), fluorescein TBUT, Schirmer test, corneal staining and MG grading. Vehof et al. (2017), in

support of McAlinden et al.'s results, found poor agreement between the questionnaire and clinical signs in a large study cohort where 648 patients with DED were evaluated.

OSDI can be used to subjectively evaluate post-operative outcomes after ocular surgery. In a previous study with 511 patients after LASIK, Hays et al. (2017) suggested using OSDI questionnaire together with other visual symptoms scale questionnaires such as NEI-RQL-42 (National Eye Institute Refractive Error Quality of Life Instrument) and NEI-VFQ (National Eye Institute Visual Function Questionnaire) to improve the understanding of the impact of the procedure on patient satisfaction. In the case of cataract, OSDI questionnaire may be used to understand the subjective impact of the technique. Kim et al. (2016) examined 43 patients before and after cataract surgery. The results showed a significant increase in OSDI score after 1 month that returned to pre-operative values 3 months after the procedure. Finally, OSDI questionnaire is one of the most commonly used subjective tools in DED diagnosis due to its wide availability in different clinical settings (e.g. hospitals and high street practices). It is easy to complete but may show no agreement with clinical signs (Kyei et al., 2018; Sullivan et al., 2014).

1.4.4.1.2 Dry Eye Questionnaire and Dry Eye Questionnaire 5-items

The Dry Eye Questionnaire (DEQ) was initially proposed as a set of 21 items that aim to evaluate the presence of DED and its severity including CL wear, age and sex. A shorter version (5 questions) was validated by Chalmers et al. (2010) and it is known as DEQ-5. In contrast to other questionnaires, DEQ and DEQ-5 consider the time of day when the symptoms are more prevalent (diurnal severity). Thus, the final score is obtained by the sum of each score in frequency and intensity of dryness and discomfort in addition to the score returned by the frequency of "*watery eyes*". The score ranges from 0 to 22, where the high values report the increased severity of the condition.

In a study by Begley et al. (2002), the sensitivity of DEQ was evaluated in 100 patients, 30 with SS, 30 with keratoconjunctivitis sicca (KCS) and 40 healthy controls. The authors found the majority of patients were complaining during the morning in the SS group with 60% of them stopping performing any type of daily activities due to the severity of the sensation (e.g. dryness, itchy eyes and light sensitivity). However, as previously observed with other questionnaires, DEQ scores did not correlate with clinical signs indicating that patient's symptomatology in DED has to be considered carefully (C. Begley et al., 2003). For the shorter version, DEQ-5 questionnaire was compared with TF osmolarity with no significant correlation found but DEQ-5 was able to discriminate between self-assessed severity ratings and patients with DED diagnosis. Nevertheless, the researchers suggested that a score >6 may indicate DED while >12 could be related to SS. However, as per OSDI, a difference between the results in subjective and objective DED metrics has been observed supporting the hypothesis of a lack of agreement (Caffery et al., 2014). Additionally, other studies found OSDI and DEQ-5 to be well correlated (Caffery et al., 2011; Galor et al., 2015a) with a slight preference in using DEQ-5 to

distinguish between normal and non-SS patients with keratoconjunctivitis while others did not report the same findings indicating that OSDI had a better ability to discriminate (M. Wang et al., 2018).

1.4.4.2 Objective evaluation

1.4.4.2.1 Assessment of tear volume

TF volume plays an important role in the homeostasis of the ocular surface. In fact, as detailed in section 1.4.2.1 and section 1.4.3, ADDE subtype is less common than EDE but represents an important proportion in DED diagnosis. In the last decade, advanced technologies were developed to assess TF characteristics with minimal impact on the eye.

The Oculus Keratograph® 5M (K5M) (Oculus, Wetzlar, Germany) is a promising device in the field of DED assessment. It provides non-invasive or minimally invasive measurements of TF parameters by the means of different lights (white, blue and infrared illumination, see Chapter 2.4). Additionally, it can measure corneal topography using the common reflection from a Placido disc projected onto the eye.

K5M estimates TF volume considering the height of the tear meniscus measured perpendicularly to the lid margin in a position that is centrally aligned with the pupil (6 o'clock). The measurement, that is subjectively detected by the means of a built-in calliper, relies on the observer to correctly place the calliper (Figure 7).

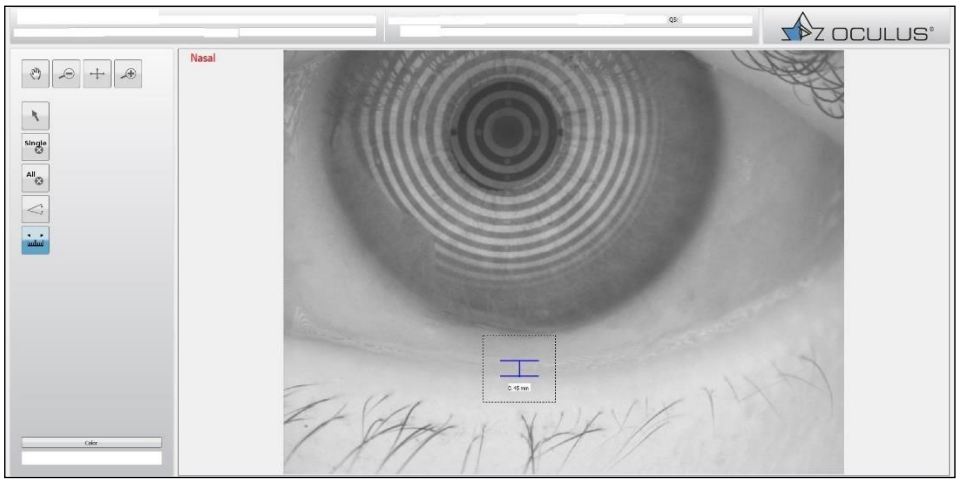

Figure 7 Infrared illumination scan of tear meniscus height (TMH) measurement using the built-in calliper (blue line) assessed with the Oculus Keratograph® 5M (K5M).

One of the first published studies to include the K5M ocular assessment tools was by Abdelfattah et al. (2015). The researchers described that the automatic TMH measurements were higher in the DED group than in the control group. The findings reported were conflicting as patients with DED usually show less TF volume than normal subjects (Yuan et al., 2010). However, details in the classification of DED patients were missing in the methods of the study. In contrast, results from K. Lee et al. (2017) assessed with a K5M obtained non-invasive measurements able to distinguish healthy from

DED patients. Nevertheless, as suggested by Koh et al. (2015), the measurement of TMH should be performed before measuring TBUT to avoid any bias due to reflex tearing. In point of fact, for the dry eye assessment performed in all the experimental chapters considered in this thesis, TMH was performed before the non-invasive Keratograph® break-up time (NIKBUT). Another possible limitation observed with K5M is the influence of eye movements. In a previous study by Szczesna-Iskander et al. (2012), the authors suggesting to include new functions to track the eye during the measurements to avoid errors during the TF evaluation.

1.4.4.2.2 Assessment of tear stability

1.4.4.2.2.1 Tear break-up time: invasive and minimally to no-invasive techniques

One of the most common procedures in clinical practice to test the stability of the TF is the TBUT test (P. Cho, 1993; Doughty, 2014; Iskander et al., 2005; Tutt et al., 2000). TBUT is measured in seconds and it is determined by the time passed from the last complete blink and the appearance of the first disruption in the TF. Two different techniques are normally considered in clinical practice: invasive and no-invasive TBUT (Zeev et al., 2014).

The invasive technique requires the observation with a slit lamp through the instillation of a minimum quantity of a vital dye, approximately 15 to 30 µl if the fluorescein-impregnated strip is considered (Mooi et al., 2017). The clinician is able to estimate the appearance of dark spots, corresponding to the break-up of the tear film projecting with the slit lamp the blue light in combination with a yellow filter (Kodak Wratten 12) to enhance the observation (Figure 8).

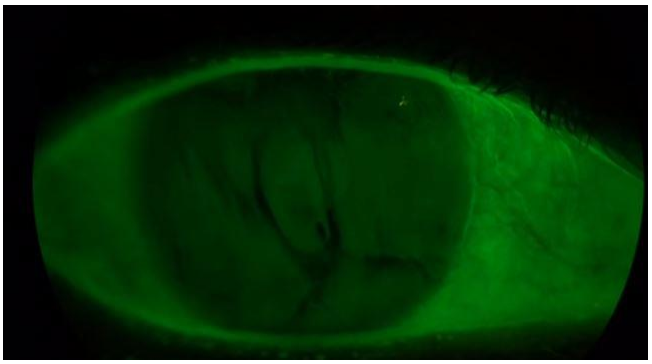

Figure 8 Fluorescein tear break-up time (TBUT) observed with a digital slit lamp with blue light and yellow filter (Kodak Wratten 12).

Due to the invasiveness of the test, the results are difficult to standardize but values below 10 s are indicative of DED (McMonnies, 2018). TBUT has high variability, especially in DED patients and therefore several investigations have suggested perform TBUT without the use of any vital dyes by the means of non-invasive devices as adopted using the K5M infrared illumination NIKBUT in this thesis (Brown et al., 1994; Tong et al., 2018b; Yokoi et al., 2015).

Tearscope® (Keeler, Windsor, UK) is a hand-held device invented by Guillon (1998b) that can be used no-invasively, in conjunction with the slit lamp, to measure TBUT. The device is able to emit a

white cold light that is diffused from its inner cup surface over the ocular surface displaying changes in TF (dry spots). To improve TBUT detection, the device has a removable grid pattern to insert in the inner cup surface. Any modification of the grid pattern perceived by the clinician is considered to be the TBUT (Figure 9). Currently, the device has not provided evidence of reliability as the measurements are graded accordingly to the clinician's experience (subjective assessment). Recently, in a comparison performed by Markoulli et al. (2018), the findings were not comparable with the TBUT measurements obtained with two different non-invasive devices: K5M and LipiView interferometer (TearScience, Morrisville, US).

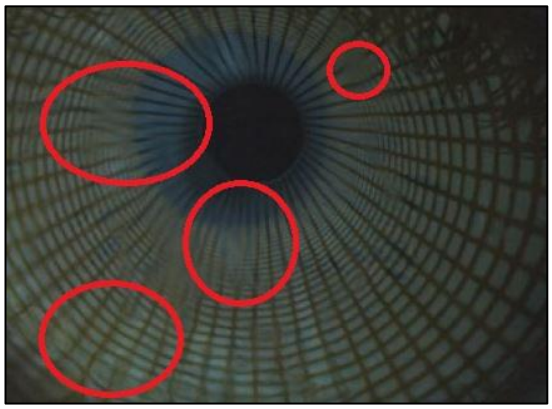

Figure 9 Grid pattern projected over the tear film (TF) by the means of a Tearscope®: in the red circle the perceived dry spots that correspond to tear break-up time (TBUT).

K5M is equipped with a software that automatically detects and maps the dry spots over the TF providing the readings in seconds without causing any harm to the patients' eyes (infrared illumination) (Figure 10).

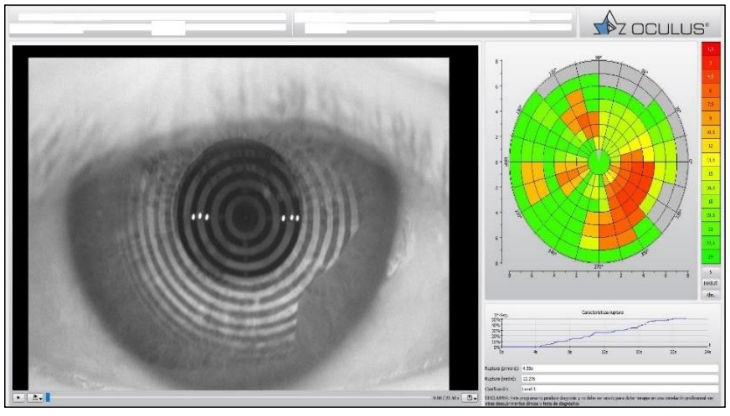

Figure 10 Infrared illumination scan of NIKBUT assessed with the Oculus Keratograph® 5M (K5M)

The measurement is defined as non-invasive Keratograph® tear breakup time (NIKBUT-First) when the device detects the time in seconds where the first break in the tear is observed. Additionally, it is also possible to automatically detect the NIKBUT-Average that is the average of the tear break-up observed in 25 seconds of measurements. Abdelfattah et al. (2015) reported different results when

traditional TBUT measurements were compared with automated measures, making it difficult to correlate the techniques when DED and healthy subjects are considered. In contrast, in a cross-sectional study by Tian et al. (2016), the authors promoted the K5M as a powerful non-invasive screening tool in DED assessment, especially to consider both TMH and NIKBUT. In support, Zhu et al. (2016) reported K5M to be an accurate way to provide non-invasive TMH, NIKBUT-first and NIKBUT-Average, distinguishing DED patients from healthy patients. Hong et al. (2013) reported good results measuring NIKBUT with K5M in patients with and without DED; the percentages of sensitivity (ability to correctly identify patients with DED or true positive rate) and specificity (ability to correctly identify patients without DED or true negative rate) were 84.1% and 75.6% respectively.

1.4.4.2.3 Assessment of ocular integrity

1.4.4.2.3.1 Damage to ocular surface

The use of slit lamps allows the clinician to observe not only the TF metrics (quantity and quality) but to investigate the status of the cells that form the ocular surface by the means of vital dyes (e.g. colorants) (see section 1.4.4.2). The most common dyes considered in clinical practice and in research are sodium fluorescein and lissamine green (Korb, 2000). The dyes are available on the market as liquid or via moistened strips: the dyes are mixed within the tears to lighten the intercellular spaces, damaged or dead cells of the corneal and conjunctival epithelium. Additionally, the vital dyes are used to evaluate the eyelids and the tarsal plate (e.g. MG) (Efron et al., 2016).

Fluorescein sodium is generally well tolerated by the eye but some cases have revealed that fluorescein 2% drops could potentially induce an anaphylactic response (Shahid et al., 2010). In the case of fluorescein in paper strip (1mg), the colorant is moistened with sterile saline, better if without preservatives to avoid influences in TF (Huntjens et al., 2018). The strip is then shaken to avoid an excessive amount of instilled colorant, as this could lead clinicians to make the wrong diagnosis due to oversaturation of the tinted epithelium (false positive) (Abelson et al., 2002). After instillation, the vital dye can be observed using blue light (450 nm) adding a yellow filter (Kodak Wratten 12, 500 nm) (Kristoffersen et al., 2018). Recently the TFOS DEWS II report has recommended applying the vital dyes diluted from the strips in the lower temporal canthus to avoid damage to the conjunctiva and lid margins (Wolffsohn et al., 2017) (Figure 11).

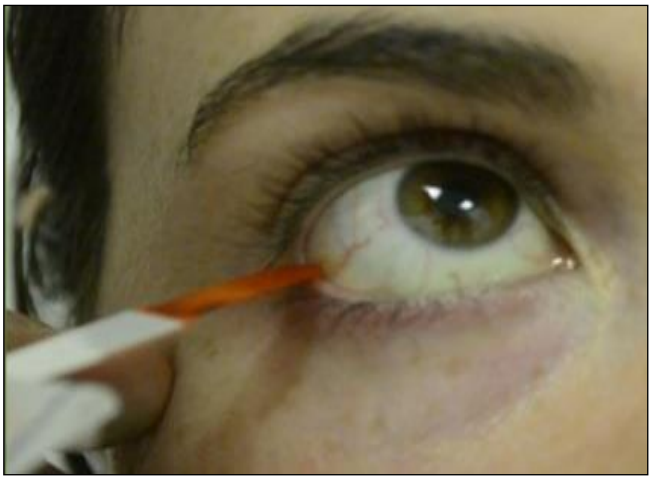

Figure 11 Suggested location from Tear Film and Ocular Surface Society Dry Eye WorkShop II (TFOS DEWS II) report to instil vital dyes in the eye.

However, clinicians should be aware that the normal TF turnover reduces the efficacy of the staining visibility and grading, therefore, the measurements should be collected within minutes.

Lissamine green has replaced the use of Rose Bengal during the last years in clinical practice (Doughty, 2013; Korb et al., 2008): Tseng (1994) confirmed its ability to stain only damaged and dead cells without any toxic effect on the corneal epithelium. In a review by Korb et al. (2008), the authors found that the lissamine green concentration to avoid burning and discomfort was 1% and it could be mixed with 2% fluorescein to perform the DED assessment. The main advantage of using a combination of both dyes is reducing clinical evaluation time without altering corneal epithelial cell homeostasis. In a retrospective analysis performed on 344 subjects where the majority of the participants were women, Sullivan et al. (2014) reported a lack of agreement between signs and symptoms in DED diagnosis: conjunctival staining only correlated with corneal staining but not with other tests such as TF osmolarity, Schirmer test and meibography. Additionally, Eom et al. (2015) suggested that conjunctival staining was better assessed with fluorescein viewed with a yellow filter than with lissamine green. Using fluorescein, the clinician is able to observe corneal and conjunctival staining at the same time. In contrast, Hamrah et al. (2011) report good results in terms of observer reliability and variability suggesting that 10 μl volume of lissamine green is the right quantity. Additionally, the TFOS DEWS II report advises retaining a whole drop of saline at least 5 s to elute the colourant and obtain a better staining of the ocular surface, as the present thesis has considered (Wolffsohn et al., 2017).

Ocular staining is graded using different systems and scales such as the van Bijsterveld system (van Bijsterveld, 1969), the National Eye Institute/ Industry Workshop guidelines (Lemp, 1995), the Collaborative Longitudinal Evaluation of Keratoconus schema (Barr et al., 1999), the Oxford Scheme (Bron et al., 2003), the area-density combination index (Miyata et al., 2003) and the SS International Collaborative Clinical Alliance ocular staining score (Whitcher et al., 2010). Despite the lack of

correlations between grading score and disease severity in mild/moderate DED patients, TFOS DEWS II suggested considering using grading scales especially in severe DED (Wolffsohn et al., 2017).

Of particular interest is the log scale with the Oxford Scheme that can be used with fluorescein and lissamine green (Bron et al., 2003). The scale ranges between 0 to 5 depending on the intensity of the punctate staining considering both cornea and conjunctiva. The grading scale was adopted in different clinical trials due to its capacity to improve the classification of both corneal and conjunctival staining (Boujnah et al., 2018; Morton et al., 2015). The Oxford Scheme was used in all the experimental chapters considered in this thesis.

1.4.4.2.3.2 In vivo confocal microscopy

In vivo confocal microscopy (IVCM) is a powerful tool to assess a series of different parameters related to the ocular surface: conjunctival epithelial cells, goblet cells, corneal nerves, etc. (Matsumoto et al., 2018). Additionally, it can provide precise scans to early detect and confirm the diagnosis of a severe keratitis infection such as Acanthamoeba and fungal keratitis (McKelvie et al., 2018), changes in the eye due to diabetes (Petropoulos et al., 2015), fibre neuropathy (Tavakoli et al., 2010a) and comorbidities due to Parkinson's disease (Kass-Iliyya et al., 2015).

The optical principles behind IVCM are three: the tandem scanning-based, the scanning slit methods and the laser scanning confocal microscope. Among them, the laser scanning techniques which uses the coherent laser light has demonstrated to provide fast scans of the anterior eye (e.g. cornea layers, nerves, etc.) and therefore is one of the most adopted (Guthoff et al., 2009; Oliveira-Soto et al., 2001)

One of the most common IVCM applications is to track changes in the corneal nerve structure, particularly, nerve fibre length, nerve fibre density, nerve tortuosity and relative branches (Guthoff et al., 2009). For example, if monitoring changes due to corneal refractive surgery, comparing before and after the procedure, IVCM can be used to report the impact of LASIK surgery (lamellar cutting of the nerves due to flap creation/ablation). Additionally, IVCM was able to demonstrate that even if the corneal nerves were not completely restored, the corneal sensation was returned to the pre-operative level within 6 months comparing the images analysed with the corneal sensitivity measured with a Cochet-Bonnet esthesiometer (Bragheeth et al., 2005). The diminution of subbasal nerve density was found in several studies using IVCM, especially after refractive surgery such as PRK (Tomas-Juan et al., 2015), LASIK (Toda, 2018), SMILE (M. Liu et al., 2015b) and when the surgeries were compared (Cai et al., 2017; Demirok et al., 2013; Denoyer et al., 2015; M. Li et al., 2013a). In a review by Alhatem et al. (2012), the researchers mentioned increasing interest in applying IVCM to the tarsal glands. The laser scanning confocal microscopy was able to describe the morphologic irregularities observed in MGD patients, underlying the inflammatory cell infiltration. However, the clinical significance of the observation will need further studies to increase the adoption of this technique in the clinical setting.

In summary, IVCM has not yet become a standard tool in the clinical DED routine, but its promising results in assessing aspects of the ocular surface, may help clinicians to improve DED diagnosis and management in the future. For this reason, IVCM has been selected to be included in the analysis of the impact of FS-LASIK and SMILE surgery in Chapter 8.

1.4.4.2.4 Assessment of tear film composition

1.4.4.2.4.1 Tear film osmolarity

The osmolarity of the TF is defined as the concentration of an osmotic solution measured in litres of the solution. In order words, TF osmolarity is an estimation of the "saltiness" of the tears that range in healthy human subjects between 289 to 304 mOsm/l, depending on the study considered (Jacobi et al., 2011; Messmer et al., 2010). Following both TFOS DEWS reports, TF osmolarity become recognised as an important metric because it has been recommended as being "*one of the two core mechanism of dry eye*" (Lemp et al., 2007) and because it has been defined as "*the single best metric to diagnose and classify DED"* (Lemp et al., 2011; Potvin et al., 2015). In the case of values over 308 to 312.7 mOsm/l, patients may be diagnosed with DED due to hyperosmolarity of the TF (Caffery et al., 2014; Dohlman et al., 2016). However, recent findings suggested adopting osmolarity values as a clinical sign of DED if ≥ 308 mOsm/L (Jacobi et al., 2011; Lemp et al., 2011) or with a difference between eyes of >8 mOsm/L (Sullivan, 2014). In various studies, TF hyperosmolarity is defined as a DED marker (Caffery et al., 2014; Kanellopoulos et al., 2016; Vehof et al., 2017). Increased values of TF osmolarity could be due to the reduction in TF secretion by the lacrimal gland and accessory glands that provokes TF instability due to evaporation (Potvin et al., 2015). Following the "*Vicious Circle of Dry Eye"* (see section 1.4.3), in the presence of TF hyperosmolarity, the ocular surface may respond with inflammation. In a review by Brocker et al. (2012) increased cytokine levels were reported in DED patients. Most of those substances secreted by the immune system such as Cytokines IL-1α, IL-1β and TNF-α are responsible for damage to the epithelial surface cells, goblet cells and the glycocalyx functions. To improve DED diagnosis a device was introduced to measure the TF osmolarity without the need of a chemical laboratory to analyse the TF. The TearLab® Osmolarity System (TearLab® Corporation, US) works with a chip-reader to evaluate osmolarity. The device collects tears samples around 50 nl and using the electrical conductance is able to provide the results of the analysis in less than 10 seconds. However, each chip used for the measurement is for single use and there still a limitation in its availability in many clinical practices due to the cost of the chips (ranging from 12 to 20£ each). In a study by Jacobi et al. (2011), the authors compared the osmolarity values between patients with KCS and controls. As expected, TearLab® returned increased values of osmolarity in KCS patients compared to the control group but a higher variability was observed associated with the severity of the condition. In fact, in a study based on repeated measurements done with TearLab®, Szczesna-Iskander (2016) reported that at least 3 measurements are needed to obtain clinically reliable values limiting the variability.

1.4.4.2.5 Assessment of the eyelids

1.4.4.2.5.1 Interferometry

Interferometry belongs to the non-invasive techniques that are able, by the means of broadband illumination, to display the lipid layer of the tear film and its thickness (M. Guillon et al., 1997). The colour fringes visualized through this technique correspond to the lipid layer thickness that can vary in patients with MGD or DED: in a study by Hosaka et al. (2011), the authors analysed the TF thickness in a group of aqueous deficient patients showing a reduction compared to healthy subjects. Additionally, the study found a good correlation with other clinical tests performed in DED assessment such as fluorescein and Rose Bengal staining, TBUT and Schirmer test.

In order to provide useful information of the tear lipid, the pattern assessed through interferometry, clinically known as lipid layer thickness (LLT), is recorded and graded using a comparison grading scale. One of the most commonly adopted scale is the Guillon's clinical scheme (J. Guillon, 1998a) where a series of sampled images are associated with the thickness of the lipid layer. As remarked by J. Nichols et al. (2002), the subjective evaluation of LLT could be difficult to interpret and takes time to learn how to differentiate. For this reason, Garcia-Resua et al. (2014a) reported that the lack of a vast bank of LLT patterns to use as a reference, has forced many clinicians to discard LLT analysis in their practice. However, recent progress was made to include automatic evaluation of the interferometric patterns related to LLT. In a study by Remeseiro et al. (2013), the researchers considered the analysis methods in three colour spaces using different machine learning algorithms. Thus, the automatic classifications were better in classifying LLT compared to Guillon's clinical scheme as the tear film lipid layer is very heterogeneous to be associated with a single image only. Newer devices are currently on the market with the aim to improve LLT analysis. The LipiView has demonstrated its ability to detect LLT in healthy eyes (Markoulli et al., 2018) as the lateral shearing interferometry did (Szczesna-Iskander et al., 2012).

1.4.4.2.5.2 Meibography

Meibography is the observation and classification of the MG structure. The images are acquired by the means of different illumination such as trans-illumination, video meibography systems (infrared with a charge-coupled device) and, more recently, non-contact meibography (Arita et al., 2008; Ngo et al., 2013). Through the scans of both tarsal plates, the clinician is able to estimate the area of drop-out (atrophy) of the MG using several different grading scores (Chhadva et al., 2017; K. Nichols et al., 2011). The Meiboscore, developed by Arita et al. (2015), requires counting manually the MG of the upper and lower eyelids and then their sum to obtain a value that ranges between 0 to 6 (max 3 for the upper + 3 for the lower), where 0 correspond to no loss of MG and 6 a lost area of more than 67% of the total MG area (Figure 12).

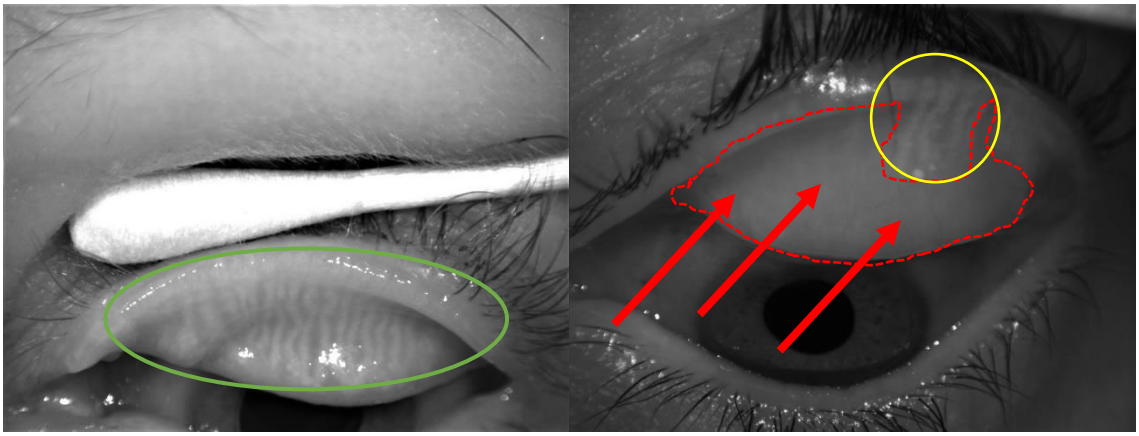

Figure 12 Meibography scan obtained by an healthy subject without Meibomian gland dysfunction (MGD) (pictured left inside the green circle) and MG scan obtained by grade 4 Meiboscore patient with MGD (pictured right, inside red dot line indicated by red arrows = area of dropout, inside yellow circle = few residual MG).

Meibography has proved to be a significant indicator of EDE as the change in MG atrophy was less relevant in ADDE (Arita et al., 2015; Lemp et al., 2012). However, Meibography did not show a correlation with DED symptomatology (Kyei et al., 2018), although MG atrophy of the lower eyelid was correlated with age and DED severity of the study cohort (Pult, 2018).

1.4.4.2.6 Inflammation of the ocular surface

1.4.4.2.6.1 Ocular and conjunctival redness

The redness of the eye is frequently associated with the presence of ocular inflammation. In a review by Hessen et al. (2014), the mechanism which contributes to ocular inflammation is the hyperosmolarity of the TF (also discussed in section 1.4.3). The hyperosmolarity leads to modification in the limbal epithelial cells which are exposed to increased levels of cytokines and chemokines such as IL-1β, TNF-α and the C-X-C chemokine IL-8. The inflammation produces vascular engorgement and redness that can be detected subjectively by the means of a slit lamp or with automatic assessment using K5M (Figure 13).

Figure 13 Ocular redness scans from a healthy eye (top) and glaucomatous eye (bottom).

In fact, previous studies have shown that subjective grading of the hyperaemia of bulbar conjunctiva could suffer from variability due to the operator (Schulze et al., 2009) whereas with a K5M

used in a glaucoma cohort hyperaemia was shown.as being able to detect the impact of topical drugs for intraocular pressure control (Perez Bartolome et al., 2018). However, in another study by Perez-Bartolome et al. (2018), the K5M was reported to be inaccurate in the automatic grading of ocular redness with significantly higher scores than the subjective grading method. Despite the contrast in the findings, the measurement was implemented in the Chapter 9 dedicated to glaucoma surgery.

1.4.5 Staged management algorithm

The multifactorial nature of the condition, together with the mixed subtypes classification (ADDE and EDE) makes it desirable to approach DED treatment, as recommended by TFOS DEWS II, by considering a step by step process (Bron et al., 2017; Jones et al., 2017; Wolffsohn et al., 2017) (Figure 14).

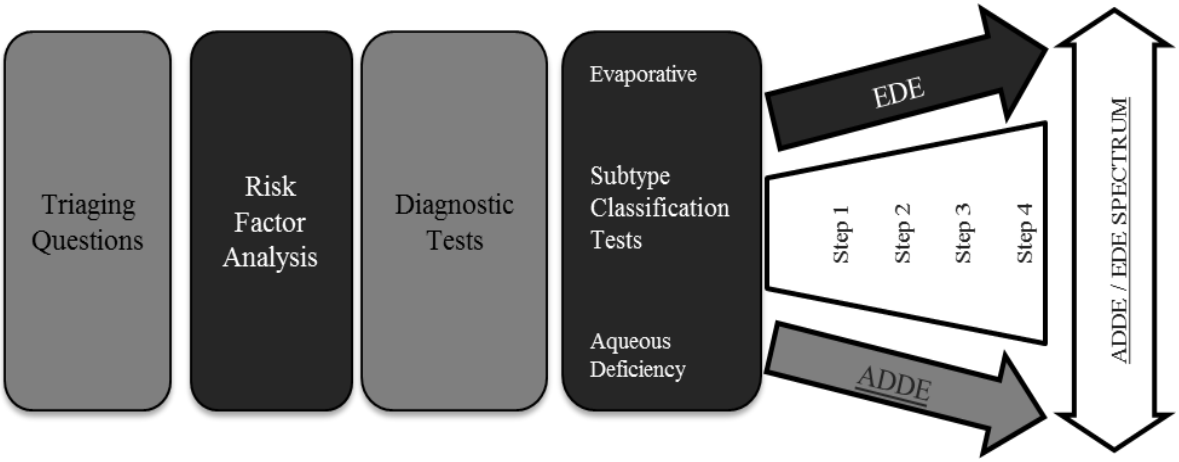

Figure 14 Schematic description of the recommended TFOS DEWS II about DED treatment.

The recommended approach should be based on a detailed methodology able to identify whether ADDE or EDE is more preponderant. The main aim in creating a DED treatment plan is to restore the homeostasis of the ocular surface avoiding the perpetuation of the *"Vicious Circle of Dry Eye* (see section 1.4.3) and preventing any recurrence of the condition (Rhee et al., 2017). However, clinicians should be informed that the management of DED is an ongoing process, it requires patients compliance to understand that one or more strategies can be valid at the same time. Additionally, due to the chronic processes related to DED, it might take time to obtain a solution or a more bearable situation. In a review from Gomes et al. (2019), the researchers found that higher DED severity was associated with lower levels of satisfaction in quality of life and most of the studies considered were unable to be compared due to the lack of a universally accepted way to measure the patients' response (Guillemin et al., 2012). The management algorithm presented by TFOS DEWS II should be considered with some flexibility. In patients that do not respond to a previous treatment alone, perhaps its combination with other treatments should offer some benefits. Thus, more than a rigid stepwise process, DED treatment should be seen as a range of different solutions that can be customised depending on the patient's feedback. In DED treatment, the clinician's role is not only to determine and prescribe a solution but to plan a series

of follow-up that can establish the improvements reached. A series of studies have reported that the most successful results in DED are achieved in 1 to 3 months (Jones et al., 2017). In summary, DED management should follow an evidence-based algorithm that can be customised to reach the best patient compliance with all the necessary follow-up planned by the clinician to maximise the benefits.

1.5 Refractive eye surgery

Refractive surgeries describes procedures with the intention to modify the refractive power of the eye by altering the cornea (corneal refractive surgery or keratorefractive surgery), by replacing a crystalline lens with a new artificial intraocular lens either due to its opacification (refractive cataract surgery) or by placing an intraocular lens with (usually with multifocal design) (refractive lens exchange, RLE). However, the general aim of these procedures is to restore vision, especially if cataract is present and/or to allow patients to be less dependent on spectacles or CLs.

No surgical procedure is risk-free. One of the most common conditions experienced after refractive eye surgery is DED (Gomes et al., 2017).

The following sections give a description of refractive surgical procedures and the relationship with DED, identifying any potential disparity in the current knowledge.

1.5.1.1 Corneal refractive surgery

1.5.1.1.1 Refractive error prevalence

In a systemic review by Hashemi et al. (2018), the authors collected data from 143 different articles and investigated the estimated pool prevalence (EPP) of refractive error across different regions such as Africa, the Americas, South-East Asia, Europe, Eastern Mediterranean and Western Pacific. With evidence from 800.000 subjects, myopia was reported 11.7% and 26.5% in children and adults, respectively. Additionally, myopia showed EPP higher in Western Pacific region in children (18.2%) than South-Est Asia (4.9%) while adult myopes were predominantly located in Myanmar (Asia) with the highest prevalence (51%) compared to India with the lowest prevalence (4.4%). The findings revealed a EPP of hyperopia from slightly less than 400.000 subjects where the refractive error was 4.6% and 30.6% in children and adults, respectively. Nevertheless, the regions with the lowest EPP of child hyperopes was South-Est Asia (2.2%) while with the highest was the Americas (14.3%). In adults, Africa demonstrated the highest EPP of hyperopia (38.6%) followed by the Americas (37.2%) and Europe (23.1%). From the 135 studies analysed, the authors reported an EPP of astigmatism with more than 250.000 subjects considered: 14.9% and 40.4% in children and adults, respectively. EPP of astigmatism in children was the lowest in South-East Asia (9.8%) and the highest in America (27.2%) while in adults, with only one study included from Americas, the highest EPP was 45% and the lowest 11.4% in the Americas and Africa, respectively. Otherwise, South-East Asia revealed the highest EPP of astigmatism with 44.8%.

From the American Academy of Ophthalmology in their "*Refractive Errors & Refractive Surgery Preferred Practice Pattern*®", the authors stated that the aim for treating refractive errors are to "*improve a patient's visual acuity, visual function, and visual comfort."* (Chuck et al., 2018).

The goal of corneal refractive surgery is to correct a refractive error using "Light Amplification by the Stimulated Emission of Radiation" (LASER). The laser is focused on the stroma to obtain a controlled remodelling, depending on the refractive error considered. For example, for a myopic eye the basic principle is to flatten the central cornea obtaining a reduction of the total refractive power of the eye. For hyperopia, the laser steepens the central cornea relatively and increases the refractive power. Generally, most surgeons will treat a refractive error within the ranges -14 to +8 Diopters but it depends on the individual's characteristics as well as the technology being used and approved by the national and international agencies (e.g. Food and Drugs Administration (FDA)). Pre-operative examinations like corneal topography and pachymetry are mandatory to assess whether is safe to treat (e.g. if there is sufficient corneal thickness) and to exclude any contraindications (e.g. keratoconus, pellucid marginal degeneration, etc.) (Ambrosio et al., 2003a). Several authors reported that the residual stromal thickness after a hypothetic laser surgery should be approximately 250-300 µm to avoid future keratectasia (Bamashmus et al., 2010; Tae et al., 2007). Furthermore, it should be considered that in the case of hyperopia the treatment area is larger than that for myopia because the amount of refractive error corrected is directly proportional to the diameter and depth of the dissection (O'Keefe, 1998). In summary, corneal refractive surgery is based on the individual's characteristics (e.g. pre-operative refractive error, corneal thickness, etc.) but also limited by different parameters including patient's pupil size, diameter of the effective optical zone and quality of the optical zone considered. A pre-operative evaluation should take into account these metrics to avoid any drawback on the refractive outcomes but also consider the homeostasis of the ocular surface to limit the occurrence of post-operative DED.

The following surgical techniques are detailed in the next section: photorefractive keratotomy (PRK), laser-assisted subepithelial keratomileusis (LASEK) and epithelial laser-assisted in-situ keratomileusis (Epi-LASIK) and laser-assisted in-situ keratomileusis (LASIK) using a microkeratome or a femtosecond-laser. More recently, flap-less surgeries have been introduced such as femtosecond lenticule extraction (ReLEx) and the small-incision lenticule extraction (ReLEx SMILE).

There are a series of contraindications to corneal refractive surgery. As suggested by Chuck et al. (2018) these include unstable refraction, eye abnormalities (irregular cornea, extensive vascularization, etc.), uncontrolled glaucoma, external or autoimmune disease, unrealistic patient expectations, inadequately controlled DED, etc.

1.5.1.1.2 PRK

PRK is one of the most common types of corneal refractive surgery invented by three different IBM® researchers in the 80s. Trokel et al. (1983) tested the excimer-laser in 1983 on bovine eyes while

McDonald was the first surgeon who used it for humans (J. Liu et al., 1990). Nonetheless, the F.D.A. approval for refractive correction was granted in 1995.

PRK includes a series of steps under topical anaesthesia starting from the de-epithelialization of the cornea using a spatula (mechanical removal) or alcohol (chemical debridement) followed by the action of the excimer-laser on the stroma (Ghoreishi et al., 2010). It is a painful approach because the post-operative recovery takes longer than for other techniques (e.g. LASEK and Epi-LASIK) due to the long period needed for corneal epithelial regeneration. However, the recovery of epithelial tissue is usually observed in 2-5 days and the surgeon often applies a bandage CL to protect the corneal surface, promoting wound healing and increasing patient comfort (Mohammadpour et al., 2016). The bandage CL is followed by antibiotic and anti-inflammatory therapy (ofloxacin 0.3% and diclofenac 0.1%) (Alio et al., 1998).

As mentioned in section 1.4.3, several studies have been published regarding the DED prevalence after corneal refractive procedures. PRK surgery leads to a reduction of subbasal nerve density for up to 1 year after surgery with a complete recovery observed after 2 years (Erie, 2003). During the period of nerve fibre regeneration, DED symptoms can exacerbate due to the reduction of the corneal sensitivity. Ozdamar et al. (1999) measured TBUT with fluorescein and Schirmer test and found the results were reduced by about 50% in the operated eye compared to the contralateral non-operated eye 6 weeks after surgery. Due to the relationship between corneal innervation and corneal sensitivity, different studies have found corneal sensitivity to be reduced for up to 3 months after surgery (Campos et al., 1992; Ishikawa et al., 1994). In a longitudinal study by Hong et al. (1997) more than 73% of the patients complained about DED and 48% of these eyes showed a reduction of TBUT after surgery. Another study analysed the subjective response using a non-validated questionnaire for 231 patients after PRK in which “ocular discomfort” was felt by 43% of the subjects (Hovanesian et al., 2001). Long-term results were reported by Rajan et al. (2004), where approximately 3% of the total study cohort (n=65) reported DED symptomatology even after 12 years. In a study by Tanbakouee et al. (2016), all the subjects had a statistically significant decrease of the Schirmer test and TBUT 3 months post-operatively while the change in the subjective questionnaire scores (OSDI) were not statistically significant. The difference in the prevalence rate between studies could be due to the heterogeneity in the clinical protocols adopted since some studies have included only symptomatology while others only signs (S. Shah et al., 2015). Additionally, it is important to reflect on which tests are the most suitable for the evaluation as the more invasive the more variability in the findings (Wolffsohn et al., 2017). An example is the Schirmer test which has been used for several years in research and clinical field. P. Cho et al. (1993) obtained inconsistent results to the invasiveness of the test while for other authors remains a standard approach used in clinical practice (Serin et al., 2007).

Compared with other corneal refractive procedures, PRK surgery has demonstrated worse visual outcomes, higher total higher-order aberrations (HOA) and a general reduction in contrast sensitivity compared to SMILE (Ganesh et al., 2017). Additionally, PRK surgery was shown to induce staining of the ocular surface after surgery (Jung et al., 2017) but with a faster recover in corneal sensitivity compared to LASIK surgery (Bower et al., 2015).

In summary, PRK tends to reduce tear function in patients with pre-operative low and normal Schirmer test and TBUT values, causing ocular staining after surgery up to 3 months and reducing corneal sensitivity up to 1 post-operatively. Despite several research where PRK was considered inducing post-operative DED (Beheshtnejad et al., 2015) or approached with newer treatments (Schallhorn et al., 2017a), at the current date further research can be addressed to the relationship between PRK surgery and MGD.

1.5.1.1.3 LASEK

A modification of PRK surgery called LASEK was introduced to preserve the corneal epithelium (Camellin, 2003). The technique separates the epithelium from the underlying stroma using alcohol (concentration usually between 18 and 25%). The duration of alcohol deposition on the corneal surface is the key to weaken the adhesions between the epithelium and the stromal layer, but the effect varies among patients (Ambrosio et al., 2003b). To obtain an adequate position for the epithelial flap, the cornea is labelled prior to the excimer-laser with a special marker. After laser ablation of the stroma, the flap is repositioned using a spatula and a soft bandage CL is fitted to improve corneal wound healing.

In terms of post-operative findings, corneal haze (e.g. blurry vision due to inflammation) was reported less frequent after LASEK due to a reduced production of corneal myofibroblast cells (Ambrosio et al., 2003b) but DED patients after LASEK experienced increased HOA (root mean square (RMS), coma and trefoil).

In terms of DED metrics, PRK and LASEK surgery demonstrated slightly better post-operative tear volume measured with Schirmer test compared to LASIK (Mrukwa-Kominek et al., 2006). As mentioned before, the results using the Schirmer test are not clear due to its invasiveness but also because of the several diagnostic cut-off values have been proposed in the literature to diagnose DED (e.g. $\leq$5 mm in 5 min (Lemp, 2007), $\leq$10 mm in 5 min (de Monchy et al., 2011), etc.). However, the results were confirmed by Dooley et al. (2012) with improved Schirmer values in LASEK compared to LASIK surgery, although not statistically significantly different. LASEK showed lower DED incidence compared to PRK with no reported post-operative DED at the 24-months appointment after (Autrata et al., 2003). Considering modern devices (e.g. K5M) in evaluating DED metrics after LASEK/PRK and LASIK, non-invasive TF stability and fluorescein ocular staining shown better results with LASEK/PRK than with LASIK (Jung et al., 2017).

1.5.1.1.4 Femtosecond laser technology

Femtosecond laser in corneal refractive surgery has introduced several improvements following FDA approval for LASIK (2010) and thereafter associated with refractive lenticule extraction (2016). Its application has given increased precision, versatility and safety (Marino et al., 2017). In fact, it has demonstrated its efficacy in residual astigmatism after corneal transplantation (Alio et al., 2015), tunnelling of intrastromal corneal ring segments (Ratkay-Traub et al., 2003) or during cataract surgery (Qian et al., 2016). Additionally, a study from Kanellopoulos (2009), demonstrated the potential application of the femtosecond laser for collagen cross-linking in irregular corneas (e.g. keratoconus).

The optical principle behind the femtosecond laser is the use of infrared light (approximately 1050 nm) that causes photodisruption of the targeted tissue, without compromising the adjacent layers (Kohli et al., 2005). The short laser pulses (0.001mm diameter in 1 femtosecond, 10^{-15}s) lead to the photodisruption process. The energy penetrates and ionizes the tissue producing plasma (CO_2 and water) which creates a cavitation bubble. The bubble is responsible for the separation of the tissue and its dimension relies on the energy utilised (e.g. high energy for big cavitation bubble): different cutting templates are available depending on the device considered.

The application of femtosecond laser technology is detailed in the following sections: LASIK, ReLEx FLEX and ReLEx SMILE.

1.5.1.1.5 LASIK or femtosecond laser LASIK

LASIK surgery was invented by Dr Ioannis Pallikaris who performed the first LASIK procedure in a human eye in 1989. In 1998, F.D.A. approval for treating human eyes was received. Compared to PRK surgery, LASIK surgery aims to preserve the epithelium using a microkeratome or a femtosecond laser that creates a thin central flap (approximately less than 200 µm depth) of the cornea. The corneal epithelium is less affected by LASIK surgery allowing better post-operative outcomes in terms of VA and subjective comfort (Slade, 2008). Therefore, the action of the excimer-laser is concentrated on the corneal stroma (laser ablation), as in PRK, followed by the flap repositioning onto the cornea. As previously observed, the healing process normally takes less time than PRK (Shortt et al., 2013). The surgeon can choose to apply a bandage soft CL in the case of epithelial defects and the flap position is normally verified in the first post-operative hours (24 to 48 hours).

A series of studies demonstrated that LASIK surgery had higher post-operative DED prevalence compared to PRK surgery (Bower et al., 2015; Murakami et al., 2012), while other reported the contrary in terms of DED metrics and corneal nerves structure (Darwish et al., 2007; H. Lee et al., 2005; Torricelli et al., 2014). As before mentioned, especially before the introduction of the recent TFOS DEWS II report, there was a lack of agreement in DED diagnosis and which test to consider. Thus, the prevalence estimated can potentially vary between studies depending which metric is considered leading to a

reduction in the accuracy of DED diagnosis. Hovanesian et al. (2001) found a DED incidence rate of 48% using a non-validated questionnaire after 6 months while Toda et al. (2002b) confirmed precision and safety of the procedure even when performed on DED patients. Despite preserving the epithelium compared to PRK surgery, the flap creation in LASIK surgery causes transection of the subbasal corneal nerves (Xie, 2016). Studies reported that the corneal epithelium regrowth is observed 1 month after LASIK surgery while it could take up to 12 months after PRK surgery (Erie, 2003; Mitooka et al., 2002). E. Donnenfeld et al. (2003) reported the hinge position as a significant intraoperative risk factor to increase DED exacerbating the loss of corneal sensitivity while Ambrosio et al. (2008) and Battat et al. (2001) found the flap re-lifting/re-positioning as significant post-operative DED risk factor. As disclosed in section 1.5.1.1.4, femtosecond-assisted LASIK (FS-LASIK) surgery revealed a new horizon in terms of safety, predictability and accuracy compared to the previous microkeratome flap creation (Aristeidou et al., 2015). The safety is provided by the possibility of thinner LASIK flaps and also a thickness uniformity compared to microkeratome flaps (Slade, 2007). When compared the traditional LASIK surgery with FS-LASIK surgery, researchers reported that both techniques impacted ocular surface homeostasis reducing corneal sensitivity, TBUT and symptoms but FS-LASIK surgery gave less reduction in TBUT after surgery (C. Sun et al., 2013). More recently, the two techniques were considered in a study by Shaaban et al. (2018). The patients operated by the means of a microkeratome blade experienced the most substantial drop in TMH and in tear meniscus depth and area assessed with an OCT device. In contrast, the report from the American Academy of Ophthalmology, reviewing several studies, did not report a significant difference between the techniques in DED development (Farjo et al., 2013; Sutton et al., 2014). However, due to the current availability of newer devices able to establish the status of the ocular surface with minimally to non-invasive techniques, the outcomes should be updated to reflect the those changes as discussed in Chapter 8.

1.5.1.1.6 ReLEx FLEX and ReLEx SMILE

Femtosecond lenticule extraction (ReLEx FLEX) and ReLEx SMILE techniques are based on the application of the femtosecond-laser to create a slice of stromal tissue called lenticule. To perform both procedures and obtain a precise correction of the targeted refractive error, the device adopts a unique curved applanation plate (firstly developed by Carl Zeiss Meditec AG, Jena, Germany) (Figure 15) that maintains the eye firm (“docks”) allowing the creation of the lenticule during the first steps of the procedure.

Figure 15 Curved applanation plate used with the VisuMax all-in-one platform to perform ReLEx FLEX and SMILE (Courtesy of Carl Zeiss Meditec AG, Jena, Germany).

The main difference between FLEX and SMILE is the presence of the lifting flap: the FLEX technique incorporates a flap while the ReLEx SMILE technique a tunnel is created ("small incision") (Figure 16). The lenticule is created by the means of a posterior circular dissection followed by the anterior creation of the lenticule surface with the femtosecond laser. The sidecut (between 2.5 and 5 mm) allows the extraction of the lenticule avoiding any flap complications (Figure 16). Both methods are indicated as an alternative to LASIK in myopia (Sekundo et al., 2014) and several clinical trials have reported the use of femtosecond laser procedures in hyperopia (Blum et al., 2013; Reinstein et al., 2017a; Reinstein et al., 2017b; Zhao et al., 2016). The possible complications during both ReLEx surgeries include epithelial defects, lenticule misdissection, suction loss, cap rupture, bubbles in the interface, opaque bubble layer that impedes the laser treatment. However, all those complications may be reduced by the surgeons' training and experience (Ramirez-Miranda et al., 2015) (see Chapter 7).

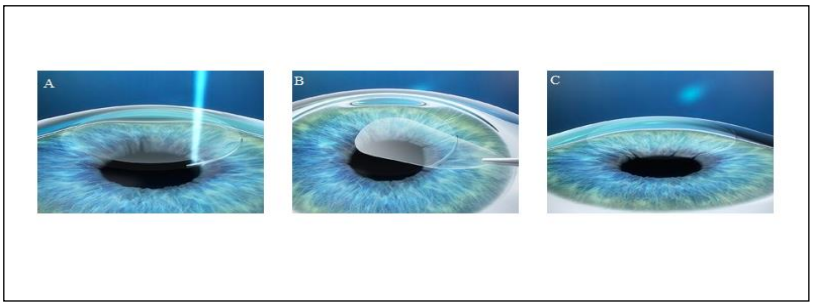

Figure 16 ReLEx SMILE extraction procedure: side cut (A), forceps extracting the lenticule (B) checking of the corneal integrity and its stromal lenticule (C) (Courtesy of Carl Zeiss Meditec AG, Jena, Germany).

In terms of DED, SMILE surgery has proven to be one of the less invasive techniques among the corneal refractive procedures (De Paiva et al., 2006; Demirok et al., 2013; Denoyer et al., 2015; Kacerovska et al., 2018; Marino et al., 2017; Toda, 2018). When compared with traditional corneal refractive procedures, SMILE gave better post-operative results than PRK and LASIK surgery in

refractive predictability and less foreign body sensation assessed by a subjective questionnaire developed by the researchers (Vestergaard, 2014). Ganesh et al. (2017) found better post-operative patients 'satisfaction with SMILE surgery versus PRK surgery. Moreover, SMILE surgery permitted a better conservation of the biomechanical properties of the cornea with preserving the corneal nerves (J. K. Lee et al., 2015) and with a faster recovery than FS-LASIK surgery (Cai et al., 2017; He et al., 2015). In a comparative study, 74% of patients that had FLEX surgery reported DED discomfort while only 9% reported the existence of DED with SMILE surgery considering DED metrics such as tear osmolarity, NIKBUT and TMH assessed with an anterior segment OCT (Vestergaard et al., 2013a) suggesting the benefit of a flap-less procedure (Chiche et al., 2018).

1.5.1.2 Lens surgery

1.5.1.2.1 Crystalline lens

The crystalline lens is situated behind the iris, in the posterior chamber (Figure 17). It consists of three transparent structures: the external capsule (or capsular bag) above the epithelium, the cortex and the nucleus. The capsular bag is the external layer and is attached to the zonular fibers. The inner structure is the core lens made of proteins. The nucleus is situated in the centre of the lens (Kanski et al., 2011). The primary role of the crystalline lens is to focus light rays of an object at varying distances at the retina, this function is known as accommodation. The optical power of the lens is changed by the action of the ciliary muscle which is linked to the lens by the zonular fibers. The ability of the eye to accommodate varies with age and the loss of the same is called presbyopia. It was predicted that presbyopia will affect 41% of the global population by 2030 (Hickenbotham et al., 2012).

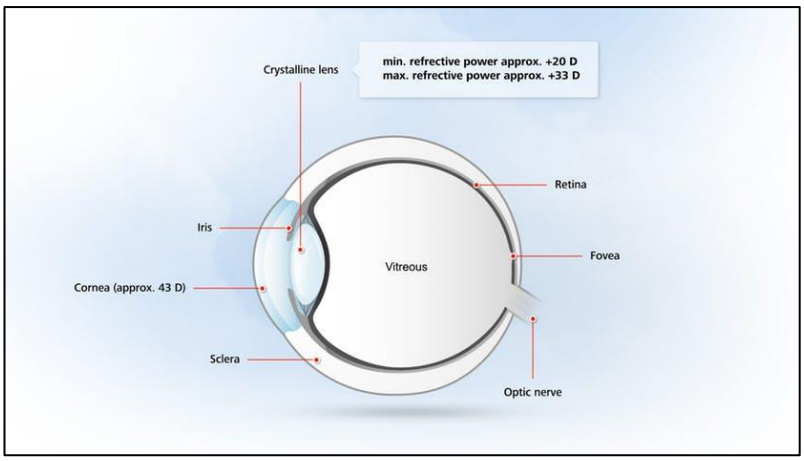

Figure 17 The structure of the human eye (Courtesy of Carl Zeiss Meditec AG, Jena, Germany).

1.5.1.2.2 Dysfunctional lens syndrome

In a recent review by Fernandez et al. (2018), the researchers suggested the use of the term dysfunctional lens syndrome (DLS) as a useful tool in helping clinicians to understand changes in the crystalline lens

due to ageing. Through a three-stage approach, the review included both presbyopia and cataract as fundamental conditions of the ageing of the crystalline lens. In stage 1, includes people from 42 to 50 years and constitutes the presbyopes group while in stage 2 (50 to 65 years) and 3 (over 65 years), the patient's sight can be affected by visual phenomena such loss of contrast sensitivity, VA and scattering, mainly referred to cataract. To help in defining presbyopia, in a recent review by Wolffsohn et al. (2018), the investigators stated: "*presbyopia occurs when the physiologically normal age-related reduction in the eye's focusing range reaches a point, when optimally corrected for distance vision, that the clarity of vision at near is insufficient to satisfy an individual's requirements*". In other words, in presbyopia (stage 1), the patient suffers from a progressive loss of accommodation of the crystalline lens where focusing near objects is limited. There are several strategies to help to resolve presbyopia: monofocal spectacles for near distance or progressive ophthalmic lenses (bifocal, trifocal) or different CL options (monovision, bifocal and progressive) (Charman, 2014). Additionally, patients who want to be independent of spectacle or CLs can choose surgery as an option. The most common procedures are monovision/blended vision achieved approaches on the cornea by the means of laser treatment (Vargas-Fragoso et al., 2017) or by replacing the crystalline lens with monofocal (monovision), extended depth of focus (EDOF) intraocular lens (IOL) or multifocal IOL designs (see section 1.5.1.2.5) (Alio et al., 2017; Kelava et al., 2017). Refractive lens exchange or clear exchange has the same surgical pathway considered as cataract surgery (see sections 1.5.1.2.3 and 1.5.1.2.4). However, while a dynamic solution that restores the accommodation to the same extent of that from a young eye remains unfeasible, the aim is to reduce the need for aids to see at one distance (if a monofocal IOL is implanted) or at different distances (if a multifocal IOL is implanted) where the DLS age-range is stage 2 and 3 (see also 1.5.1.2.5).

Cataract is defined as a progressive increase in opacification of the crystalline lens or its capsule and is one of the most prevalent causes of reversible blindness in the world (Thompson et al., 2015). The opacification of the crystalline lens is normally due to a oxidation in lens proteins (cysteine and methionine) caused by ageing (normally after 50 years) but also influenced by environmental factors such as ultraviolet (UV) light radiation and lack of lens cells homeostasis (Steinert, 2010). Cataract usually causes a progressive reduction of functional vision and contrast sensitivity related to the lens opacification process (Shandiz et al., 2011). In developed countries, cataract is treated by phacoemulsification followed by IOL implantation with positive outcomes in terms of safety and vision (Donaldson et al., 2013; Gogate et al., 2005) whereas in the developing countries cataract still remains one of the most common eye condition that leads to blindness in up to 75% of patients affected due to the fact that it is not treated (Tabin et al., 2008). Among the surgical management options, small incision phacoemulsification is typically offered for the treatment of cataract in developed countries (Packer et al., 2005). Femtosecond lasers can be used to automate some steps of the surgery so-called "femtosecond laser-assisted cataract surgery" (Roberts et al., 2013).

1.5.1.2.3 Small incision phacoemulsification

Cataract surgery has consistently evolved over the last decades. Prior to 1950, intracapsular cataract extraction was the preferred technique followed by the extracapsular techniques (after 1950). Dr Charles D. Kelman introduced phacoemulsification (1967) reducing the size of the incision with fewer ocular surface issues and complications (Gurung et al., 2008). In a recent study, the Royal College of Ophthalmologists reported that posterior capsule rupture and zonule rupture without vitreous loss were among the most common intra-operative complications with a prevalence of 3.3% and 0.4% respectively (2017). Similar findings were described by the National Institute for Clinical Excellence (NICE) when the cataract guidelines were released in 2017 reporting also the occurrence of anterior capsule tear and cystoid macular oedema.

1.5.1.2.4 Femtosecond laser-assisted cataract surgery

Femtosecond laser for cataract surgery, firstly used in 2009 and then approved in 2010 by FDA, aimed to use a femtosecond laser to achieve higher operative precision with less ultrasound energy to cause stress to the corneal endothelium and improve outcomes for patients (N. Baig et al., 2017; Nagy et al., 2009). In summary, both techniques are available nowadays to restore clear transparency by the means of an artificial IOL implantation in eyes with cataract. However, Popovic et al. (2016) did not found significant differences in terms of surgical procedure time: femtosecond laser procedure time was slightly shorter (approx. 3 s) than manual cataract surgery. In terms of refractive outcomes, the femtosecond laser allows a better centering of the IOL due to the high precision during the bag capsulotomy compared to manual phacoemulsification (Kranitz et al., 2011; Roberts et al., 2016). In fact, the precise placement of the IOL becomes more important when multifocal and trifocal IOLs are considered as the geometry of the lenses should be aligned with the visual axis of the eye (Friedman et al., 2017). However, several authors reported no significant differences between the two procedures in terms of visual and refractive outcomes, while the postoperative complication rates were lower using the conventional technique (Manning et al., 2016; Popovic et al., 2016). Finally, the small incision phacoemulsification remains the most common surgical technique to operate cataract due to the cost-effectiveness of the treatment compared to femtosecond laser-assisted cataract surgery (Abell et al., 2014).

1.5.1.2.5 Types of intraocular lenses

The refractive changes in lens surgery are achieved by the implantation of an artificial IOL made from acrylic or silicone that replaces the crystalline lens (pseudophakic eye) (Kelava et al., 2017; Thompson et al., 2015). IOL can be implanted in the anterior or posterior chamber or in the capsular bag depending on the state of the lens capsule. In the event of capsule tearing, the surgeon can place the IOL in the anterior chamber, especially if a dense nuclear cataract is removed or the patient has weakened zonules, etc. (Zare et al., 2009). Additionally, the surgeons may also decide to place the IOL in the posterior

chamber (PCIOLs) using the space in the ciliary sulcus (Kwong et al., 2007). However, if the posterior capsular structure is intact, the preferred location to place the IOL is inside the capsular bag.

In terms of IOL geometry, different designs are available: monofocal IOL (MIOL), Accommodative (AIOL), Multifocal (MFIOL) and Toric. Monofocal IOLs are most frequently used (Foster, 2000). Accommodative IOLs can change their effective power due to the haptics used which can vary their axial position, shape or curvature or the changes in refractive index or power (Pallikaris et al., 2011). However, the amplitude of accommodation achieved by accommodating IOLs is very limited (around 1 Diopter) (Pepose et al., 2017).

MFIOL can offer two or more focuses allowing patients to see distance and near. Bifocal designs allow clear vision at distance and intermediate or near whereas trifocal designs allow clear vision at distance, intermediate and near. The predominant MFIOL designs available in the market are diffractive and refractive. Diffractive IOLs are based on diffraction principle as they are made of different diffractive steps that distribute the incoming light rays into two or more foci while refractive IOLs are designed with several refractive zones with different focal points (distance, intermediate and near vision) (Barisic et al., 2008). For astigmatic eyes, surgeons can implant toric IOLs. However, these lenses need to be aligned according to the axis of the corneal power to avoid loss of visual quality (Carey et al., 2010). Patients' selection is crucial to understand suitability, individual visual requirements and desire to proceed with a MFIOL implantation. In fact, due to the complexity of MFIOL designs, a series of complications such as blurred vision, glare, residual refractive error, dry eye, posterior capsule opacification are possible (Woodward et al., 2009). However, in terms of refractive outcomes and patients' satisfaction, Salerno et al. (2017) reported high spectacle independence (80%), binocular uncorrected vision of 0.30 logMAR in 100% for distance VA, 96% for intermediate VA and 97.3% for all the participants enrolled.

1.5.1.2.6 Lens surgery and dry eye disease

The relationship between lens surgery and DED can be described at two different time points: pre-operative and post-operative DED. Preoperatively, as cataract condition is normally more prevalent in people older than 50 years (Thompson et al., 2015), DED can occur before surgery as it is more prevalent after that age with a peak of prevalence higher than 50% of the global population (Stapleton et al., 2017). Despite a plethora of studies performed relating aging and DED due to antigen-presenting cell alteration, changes in hormones, hypercholesterolemia, sleep deprivation, reduction in tear production, MGD, and so on (Bian et al., 2019; Borchman et al., 2018; K. I. Kim et al., 2019b; Pult, 2018; Rico-Del-Viejo et al., 2018; Song et al., 2018; Yamaguchi, 2018) not many studies have considered populations undergoing lens surgery with potential presence of DED. In a study by Epitropoulos et al. (2015), patients attending lens surgery with ocular surface disturbance had keratometry readings with a variability of 1 D in the measured corneal astigmatism which could have influenced the final IOL

calculation by more than 0.5 D. Indeed, tear film osmolarity was found a useful DED metric to quantify the variation in the refractive outcomes after surgery as adopted in Chapter 5. DED could alter the precision of the biometry resulting in an incorrectly calculated IOL power and leading to an unexpected residual refractive error: D. Goldberg (2011) reported the results from the "Prospective Health Assessment of Cataract Patients' Ocular Surface" (PHACO) study in which patients undergoing intraocular surgery were found with reduced tear film stability (50%, n= 136 patients) and ocular surface staining (45%). Additionally, Trattler et al. (2017) reported only less than 15% had positive symptomatology (e.g. self-assessment of foreign body sensation) confirming a lack of agreement between signs and symptoms in DED (K. Nichols et al., 2004b). Gupta et al. (2018) remarked the results from the PHACO study as during pre-operative screening of patients undergoing intraocular surgery. The researchers found 56.7% with hyperosmolarity along with positive fluorescein staining (39.2%). Moreover, Cochener et al. (2018) found 52% of their study cohort with MGD but with a normal lipid layer thickness (approx. 80 nm) not correlated with the subjective responses (Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire). In a review by Sutu et al. (2016), the authors suggested the importance to clinically assess the state of the ocular surface, before the surgery, considering subjective and objective metrics.

Surgery can increase the severity of DED potentially due to corneal incisions' and inflammatory factors (Sutu et al., 2016). Additionally, the ultrasound probe involved in the phacoemulsification procedure may also be responsible for DED by inducing histological changes (e.g. epithelial cell oedema, collagen disorganization, severe stromal oedema etc.) with increased temperature up to 60 degrees C for 10 seconds (Mencucci et al., 2005). In contrast, in a study by Y. Cho et al. (2009), the phacoemulsification probe did not induce an increase in DED severity but the researchers pointed out that corneal incision and microscope light exposure were the most common causes of DED, even in patients without ocular surface disturbance before IOL surgery.

The second step that relates cataract and DED is the impact of the surgical procedure and the consequent post-operative DED. In a prospective study by Kasetsuwan et al. (2013) different factors were listed for developing DED after cataract surgery: transection of corneal nerves, corneal epithelial cells loss, topical anaesthesia, etc. Nevertheless, light exposure during the ophthalmic procedure can be considered another relevant area research. In a study by Ipek et al. (2018), wound closure in conjunctival fibroblast cells was slower in the cells exposed to 10 minutes of microscope light (halogen bulb) compared to cells group not exposed to light. Additionally, post-surgical drug regime is a potential risk factor for DED development: in a review published by Shoss et al. (2013), the investigators indicated the preserved drugs, typically prescribed after lens surgery to avoid infection and reduce inflammation, might be responsible for loss of homeostasis of the ocular surface and promoting DED.

In summary, DED and lens surgery are associated. Despite increasing awareness of postoperative dry eye issues, a pre-operative DED screening is not always included in the preoperative clinical pathway and therefore many patients undergoing lens surgery could potentially risk unwanted refractive outcomes due to dry eye issues (e.g. sub-optimal VA). Hence, the usefulness of some DED tests in predicting the visual outcomes after intraocular lens surgery will be assessed in Chapter 4 of this thesis.

1.6 Glaucoma

1.6.1 Definition, prevalence, management

Glaucoma is a neuropathy that produces changes in the optic nerve disc of the eye with visual field modifications with or without the influence of elevated intraocular pressure (IOP). The worldwide glaucoma prevalence reaches 3.54% for population aged 40-80 years and it is the second cause of blindness after cataract: following the World Health Organisation source, more than 12 million people are blind because of glaucoma disease. Tham et al. (2014) estimated a dramatical increase of glaucoma patients to 111.8 million in 2040. However, the prevalence of undetected glaucoma is about 50% in Europa and Australia (Mitchell et al., 1996) where in Asia and Africa can reach up to 90% (Vijaya et al., 2005). Glaucoma treatment has the aim to preserve patients 'visual functions through their life and several options are available: medication (topical drops), laser trabeculoplasty and filtering surgery. In particular, the management of ocular hypertension (OHT), the NICE guidelines in glaucoma treatment suggested to offer prostaglandin analogue to people with IOP with 24 mmHg or more to avoid the risk of visual impairment. Additionally, in case patients are already under prostaglandin analogue, it may require to switch to other therapeutic class (beta-blocker, carbonic anhydrase inhibitor or sympathomimetic) or to combine both medications (Conlon et al., 2017). However, if medications to control IOP fail there are several surgical alternatives to discuss between the clinician and the patient.

One of the most common surgeries used in primary open-angle glaucoma (POAG) is using laser trabeculoplasty: argon laser trabeculoplasty (ALT) or selective laser trabeculoplasty (SLT). Both lasers have the scope to target the trabecular meshwork, enhancing the aqueous outflow and reducing IOP. The advantages between the laser techniques are in favour of SLT as it was observed to be less invasive and more precise selecting only melanin pigment in the trabecular meshwork thanks to the Nd:YAG laser, a solid-state laser that uses a neodymium-doped yttrium-aluminium-garnet crystal as the lasing medium (Hutnik et al., 2019). Alternatively, Nd-YAG laser can be used to open a passage in the iridotrabecular space allowing more flux of aqueous fluid but it exposes to the risk of primary closed-angle glaucoma (PCAG) due to pupillary block (Theinert et al., 2017).

Among the filtering surgery, trabeculectomy is one of the most performed (Koike et al., 2018). The surgery aims to create a filtration passage via a scleral incision (flap) that allows the aqueous flow to pass from the anterior chamber throughout the conjunctival tissue. The result is an aperture of the

tissue that has the shape of a scleral engorgement, covered by the upper eyelid. Trabeculectomy can be performed with mitomycin-C and 5-fluorouracil that reduce tissue fibrosis extending the duration of the treatment in filtering and controlling the IOP. However, due to the invasiveness of the surgery and the fact that could potentially have a limited duration (scleral fibrosis) in controlling IOP, nowadays microinvasive glaucoma surgery (MIGS) has gained attention in the surgical treatment of glaucoma (Richter et al., 2016). In fact, MIGS showed to be a valid alternative to traditional glaucoma surgery by reducing IOP and the invasiveness of the procedure (e.g. avoid conjunctival dissection), with the aim to reduce topical drops doses and dependency. There are several MIGS devices available which target the juxtacanalicular portion of the trabecular meshwork, however, for the scope of the review in supporting of Chapter 9, only the trabecular micro-bypass surgery performed using the iStent Inject® (Glaukos Corporation, Laguna Hills, US) is detailed as follow.The iStent procedure was approved by the FDA in 2012: in the US is only used in combination with cataract surgery, while in Europe it can be used stand alone. iStent is contraindicated to treat PCAG, neovascular glaucoma and other episcleral venous pressure with high IOP. The second generation, called iStent Inject® GTS400 device, is made of titanium with 360 μm length with a head to be implanted in the Schlemm's canal of 230 μm (Figure 18). To insert the pre-loaded tool carrying 2 iStent devices, a small incision (approx. 1,7 mm) in the cornea is required. The surgeon uses a surgical gonioscopy lens to reach the points of implantation and locate the devices. In a multicentre, prospective study Voskanyan et al. (2014) reported that 66% of patients implanted with iStent reduced to ≤ 18 mmHg their IOP at 12 months, with 81% of them with no need of medication or with one medication only. Similar findings were found by Arriola-Villalobos et al. (2013) where the researchers reported that 75% of the study cohort stopped to use medication after the implantation of iStent at the 1-year follow-up.

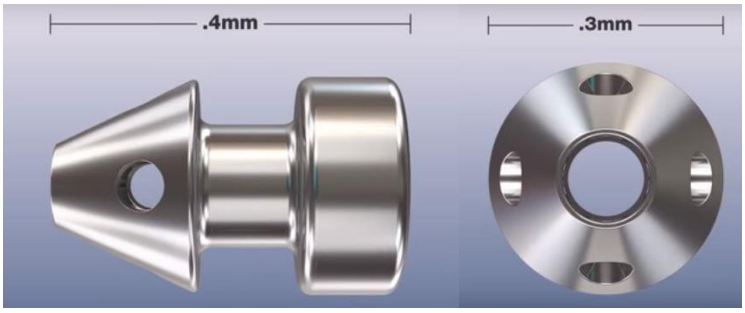

Figure 18 iStent Inject® side view (pictured left) and front view (pictured right) (Courtesy of Glaukos Corporation, Laguna Hills, US).

The complications observed with iStent Inject® are in general: corneal oedema, anterior chamber inflammation, discomfort, epithelial defect, macular oedema, posterior capsular opacification, etc. (Craven et al., 2012). No visual modifications were observed in patients with or without iStent implantation in terms of best-corrected visual acuity (BCVA) and visual-field mean deviation (Samuelson et al., 2011).

1.6.2 Glaucoma and dry eye

The relationship with glaucoma and DED is mostly based on how the preservative topical drugs used to control IOP interacting with the ocular surface (Gomes et al., 2017). In a multicentre cross-sectional epidemiologic survey across Europe (n= 9658), Jaenen et al. (2007) reported that 74% patients using preservative eye drops for glaucoma had complaints of discomfort during instillation (48%), foreign body sensation (42%), stinging or burning (48%) and dry eye sensation (35%). In another epidemiological study performed by Pisella et al. (2002), the researchers found 84% patients using preservative eye drops for glaucoma had discomfort upon instillation (43%), burning-stinging (40%), foreign body sensation (31%), dry eye sensation (23%), tearing (21%) and eyelid itching (18%).

There are several mechanisms which lead to ocular discomfort and DED using topical drops, especially if with preservatives: chemical interaction with TF, damage of corneal and conjunctival epithelial cells and goblet cells, corneal nerve neurotoxic effects and inflammation of the MG and eyelid skin. The amount of benzalkonium chloride (BAK), a preservative frequently included in topical drops associated with IOP control, has been shown to increase TF osmolarity leading to inflammation suggesting patients with DED signs and symptoms to switch to no-preservative drops (Radenkovic et al., 2016; Uusitalo et al., 2010; Warcoin et al., 2017) Additionally, BAK provokes the disruption of the tight junctions of the corneal epithelial cells leading to staining of the ocular surface, ocular redness and inflammation (Baudouin et al., 2010; Perez-Bartolome et al., 2018; Perez Bartolome et al., 2018) (Figure 19).

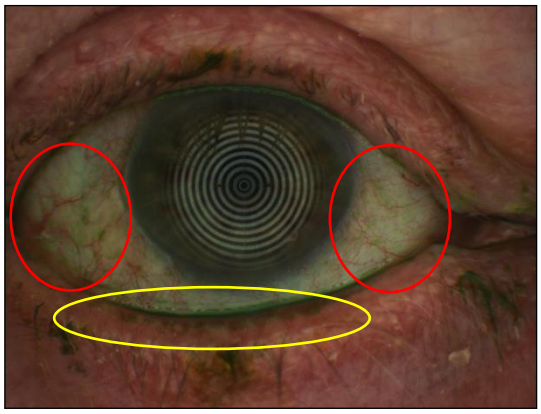

Figure 19 Glaucoma patient's eye managed with topical drops: note the presence of ocular staining (yellow circle) and ocular redness (red circles).

Preservative topical drops in glaucoma treatment not only affect DED signs but also symptoms measured with validated questionnaires. In a study by Camp et al. (2015) 33% of the subjects considered (n= 467) reported DEQ-5 scores > 12 where in a study by Costa et al. (2013) more than 62% of study cohort answered with mild (20) to severe (>25) OSDI scores. Thus, patients using preservative drops to control IOP in glaucoma disease are more likely to develop DED (Lemij et al., 2015), especially in long-

term treatment and several studies have demonstrated that switching from preservative topical drops to non-preservative drops might increase tear film stability, reduce prevalence of ocular surface staining and conjunctival hyperemia, improve DED symptomatology without altering the efficacy on lowering IOP (Aihara et al., 2012; I. Goldberg et al., 2015). Finally, patients with severe DED and glaucoma are more likely to improve the state of their ocular surface considering laser trabeculoplasty and filtering surgery.

Most of the studies that relate DED and glaucoma management describe the role of preservatives and their impact over the ocular surface. However, in recent years MIGS has demonstrated to be a safe and effective alternative way to control IOP but no studies have been carried out to investigate the impact of MIGS on the ocular surface. Thus, Chapter 9 of this thesis will address this issue.

1.7 Aim of thesis

Despite progress in research and clinical settings during the last years, consensus for the optimal approach to the diagnosis of DED has been not reached (Stapleton et al., 2017). However, the latest TFOS DEWS II report has recommended a series of clinical guidelines based on scientific evidence with the aim of improving key aspects relating to DED: definition, classification, prevalence, risk factors, diagnosis, etc. Nevertheless, a "*gold standard*" test that correlates with DED signs and symptoms does not currently exist due to the multifactorial nature of the condition where patients may manifest symptoms without signs and vice versa (Wolffsohn et al., 2017). To reduce test variability in defining DED with the intention of increasing the diagnostic power in terms of sensitivity (ability to correctly identify patients with DED or true positive rate) and specificity (ability to correctly identify patients without DED or true negative rate), researchers and clinicians should base their approach on both subjective and objective metrics, influenced by robust randomized clinical trials.

In corneal refractive and lens surgery, DED could potentially occur as a temporary post-operative complication due to the impact of the procedures on the ocular surface. However, little research has been done on understanding the wider impact of DED before undergoing these procedures. In fact, a depleted tear film could be responsible for unreliable pre-operative measurements which can lead to unexpected post-operative outcomes affecting patients satisfaction. In order to improve the understanding from a patient's perspective of satisfaction before and after a treatment, patient-reported outcomes measures (PROMs) are increasingly being considered a key outcome measure in healthcare. PROMs are also useful to improve the clinicians' knowledge of some of the most common complaints after intraocular lens surgery such as vision fluctuations and DED. However, to date, little research has been done regarding PROMs in intraocular lens surgery, especially over longer-term periods, and therefore understanding the likelihood of patients experiencing issues such as dysphotopsia and dry eye in the longer terms is challenging. This was explored in Chapter 3. In support of this, there is also a need for pre-operative DED screening as it could potentially predict the post-operative refractive and visual outcomes. This aspect was studied in Chapter 4. Moreover, newer DED metrics that incorporate validated scoring of symptoms or the composition of aspects of the tear film (e.g. osmolarity), may be used to determine the refractive predictability in refractive lensectomy with advanced technology IOLs (Chapter 5) or to assess their role in light scattering using novel evaluations of visual quality in cataract surgery (Chapter 6). Similarly, newer DED metrics can be considered in assessing whether newer modes of corneal refractive surgery (e.g. SMILE) have less impact on the ocular surface (Chapter 7) and whether the use of novel software can improve the detection of changes to corneal nerve structure that may correlate with DED (Chapter 8). Finally, the change from preserved eyedrops to minimally-invasive surgery (e.g. microsurgery) in glaucoma patients has been shown to be efficacious in controlling intraocular pressure, however the potential improvement in the ocular surface homeostasis, has not yet been detailed. This was explored in the study reported in Chapter 9.

1.7.1 Hypotheses and objectives of the thesis

The hypotheses of this thesis are:

- DED leads to higher variability in the pre-surgical assessments for IOL calculation in patients undergoing cataract surgery causing less accurate refractive and visual outcomes.
- Hyperosmolarity of the tear film, as a core mechanism of DED, can lead to suboptimal visual outcomes in patients undergoing intraocular surgery.
- Newer ophthalmic procedures such as SMILE impact less on the ocular surface compared to traditional approaches such as LASIK.
- Topical management of glaucoma may affect the ocular surface leading to DED development. MIGS reduces dependence on preserved topical drugs to control IOP and therefore can potentially improve the homeostasis of the ocular surface reducing the symptoms and signs associated with ocular surface disease.

The objectives of this thesis are:

- Chapter 3: To report on the results of a study of longer term patient reported outcomes after refractive lensectomy in a large cohort and to explore possible relationships between age, vision fluctuations and DED.
- Chapter 4: To assess whether pre-operative dry eye disease (DED) tests can be used to predict post-operative refractive and visual outcomes after laser vision correction and intraocular lens surgery.
- Chapter 5: To evaluate the post-operative refractive predictability and visual outcomes in normal and hyperosmolar populations presenting for lens surgery.
- Chapter 6: To determine whether DED signs and symptoms, prior to small incision phacoemulsification surgery, followed by IOL implantation, affect post-operative refractive outcomes, dryness symptoms and light scatter.
- Chapter 7: To present the clinical outcomes and tear film stability before and after SMILE undertaken by surgeons in the early learning curve.
- Chapter 8: To report on the clinical outcomes in patients undergoing FS-LASIK and SMILE surgery and to provide a comprehensive DED analysis using minimally invasive clinical tests as well as performing an analysis of the subbasal corneal nerve structures using in-vivo confocal microscopy before and after the surgery.
- Chapter 9: To detail the short-term changes in ocular surface disease in patients switching from topical preserved eyedrops to minimally invasive surgery in the treatment of glaucoma.

Chapter 2: General methodology

In this chapter, the number of participants, inclusion and exclusion criteria. clinical and DED assessments together with the statistical analysis performed for each study are described.

All clinical assessments were performed by the Optegra Eye Hospital Staff while the study procedures (dry eye assessments) were performed by Alberto Recchioni (AR).

2.1 Ethics and subjects

The research followed the tenets of the Declaration of Helsinki (Forster et al., 2001) and the studies were approved by the Aston University Ethics Committee on 01.06.2017 with REF. REC. 1050, by the South East Scotland Research Ethics Committee 02 and by Aston University Ethics Committee on 27.11.2017 with REF. REC 1185 (see Appendices 12).

All subjects were English speakers assigned with an alphanumeric digital code to protect their privacy (e.g. 1000, 1001, etc.). Informed consent was taken prior to any study procedures (see Appendices 12). A patient information sheet (PIS) was given to the patients with all the information regarding the study (see Appendices 12). The patients enrolled in the study were evaluated before and after corneal refractive or lens surgery. The pre-operative evaluation was used to determine suitability for surgery and to be enrolled in the study, while the post-operative evaluation was set for the mandatory follow-up in the clinical pathway together with the study follow-up visits, up to the discharge appointment (approximately 3 months after surgery).

A total of 940 participants were considered for the studies as detailed in Table 1:

Study in	No of subjects	Design of the study
Chapter 3	728	Retrospective
Chapter 4	100	Prospective, longitudinal and observational
Chapter 5	27 from Chapter 4	Prospective, longitudinal and observational
Chapter 6	41	Retrospective
Chapter 7	37	Retrospective
Chapter 8	29	Prospective, longitudinal and observational
Chapter 9	5	Prospective, longitudinal and observational

Table 1 Details of the number of participants who have successfully completed the research studies.

All studies were carried out in the facilities of Optegra Eye Hospitals in Birmingham and London, United Kingdom.

2.2 Inclusion and exclusion criteria

For Chapter 3 the participants were eligible to take part in the study if the following conditions were satisfied:

- patients identified on the electronic medical records (EMR) of the eye hospital group
- patients who were discharged from the hospitals more than 18 months

For Chapter 4, 5, 8 and 9 the participants were eligible to take part in the study if the following conditions were satisfied:

- Legal age (16 years) or older and undergoing corneal refractive, lens or glaucoma surgery
- Willing and able to adhere to any study instructions and complete all specified evaluations
- Willing and able to give informed consent

Any potential subject who met any of the following criteria was excluded from participating in the study:

- Prior surgery on the selected eye
- Previous uveitis or trauma to the selected eye, anterior or posterior synechiae
- Previous DED diagnosis
- Potential for best corrected VA worse than 6/9 (since this may indicate other causes of ocular pathology)
- Partial or total paralysis, Parkinson's syndrome, cerebrovascular accident or other condition that could impact on the results of the study
- Subject over 85 years of age (ocular pathology is more common in this age group)
- Subjects without adequate physical and mental capacity to enable participation in the study
- Subject unwilling to participate
- Systemic or topical medication known to influence visual function measures (except for Chapter 9)

For Chapter 6 the participants were eligible to take part in the study if the following conditions were satisfied:

- Age 45 years or older
- Phacoemulsification surgery with implantation of a hydrophilic acrylic monofocal IOL (Rayner 800s, Rayner Intraocular Lenses Ltd, UK)
- Willing and able to adhere to study instructions and complete all specified evaluations up to 6 months
- Willing and able to give informed consent

Any potential subject who met any of the following criteria was excluded from participating in the study:

- Previous ocular surgery in the selected eye
- Iatrogenic or drug-induced cataract
- Pre-existing corneal pathology (e.g. history of recurrent keratitis), ocular surface disease, dry eye and/or decreased corneal sensation
- Glaucoma
- Uveitis
- Meibomian gland dysfunction
- Naso-lacrimal anomalies
- Autoimmune disease
- Subjects without adequate physical and mental capacity to enable participation in the study
- Subject unwilling to participate

For Chapter 7 and Chapter 8 the participants were eligible to take part in the study if the following conditions were satisfied:

- Myopia up to -10 D with ocular astigmatism up to -5 D
- Motivated to reach spectacle independence by the means of an advanced corneal laser refractive technique

Any potential subject who met any of the following criteria was excluded from participating in the study:

- Unstable refractive error
- Previous ocular surgery or trauma
- Ocular abnormalities or disease
- Progressive myopia or astigmatism
- Systemic disease which could affect wound healing such as diabetes

2.3 Clinical assessment

Except for Chapter 3 which was a retrospective questionnaire audit, the rest of the studies have adopted all or part of the following clinical protocol to determine patients' suitability for surgery, the presence of any ocular abnormalities or disease and the consequent follow-up after surgery (Figure 20).

The first part of the clinical protocol involved acquiring ocular scans and measurements performed by a healthcare technician (HCT) at the hospitals. This included the Topcon KR-800 autorefractor (Topcon Tokyo, Japan), NT-530 non-contact tonometer (Nidek, Gamagori, Japan), IOL Master 700 ocular biometer (Carl Zeiss Meditec AG, Jena, Germany), Oculus Pentacam corneal

topography and Scheimpflug camera (Oculus, Wetzlar, Germany), Colvard pupilometer (Oasis, Glendora, US), Topcon SP-3000p automated endothelial cell count (Topcon, Tokyo, Japan) and a Heidelberg Engineering Spectralis macular and optic nerve optical coherence tomographer (Heidelberg Engineering GmbH, Dossenheim, Germany). However, for the scope of the studies, only the scans or the measurements considered for calculating the refractive and the visual outcomes such as refraction and VA were included in the analysis.

Thereafter, all patients had a general medical history taken which included past and current illnesses and the general health conditions of the patients. Patients were asked about any type of past general surgery procedures and if they were taking any type of medications and the prescribed regime. Additionally, the patients were asked about past and current ocular surgeries or any ocular conditions. A detailed ocular medication history was taken and recorded for reference.

The optometrist performed a pre- and post-operative eye examination where VA, subjective refraction, binocular and accommodative visual assessment were carried out. To avoid any interference (e.g. post slit lamp glare) partial with the visual metrics recorded, the Optometrist performed the anterior and posterior segment slit-lamp evaluation at the end of the consultation. For the study, monocular unaided distance visual acuity (UDVA) and monocular corrected distance visual acuity (CDVA) were measured in logMAR at 4 meters and then recorded. LogMAR VA data was collected following a standard operating procedure that describes VA assessment using a Topcon CC-100 computerized test charts (Topcon, Tokyo, Japan). The spherical equivalent refraction (SEQ) considered in the study, was determined before and after surgery considering the subjective refraction measured at each up follow-up and depending on the study considered, up to 6 months after surgery. SEQ was calculated by adding the sum of the sphere power with half of the cylinder power (Benjamin, 2006). Deviation from the predicted post-operative refraction (DEV_PPOR) was calculated considering SEQ (up to 6-months) after surgery and the planned target refraction (0 D). At the end of the appointment, the patients were seen by the consultant ophthalmic surgeon to discuss the different types of surgery available and their suitability to proceed with the operation.

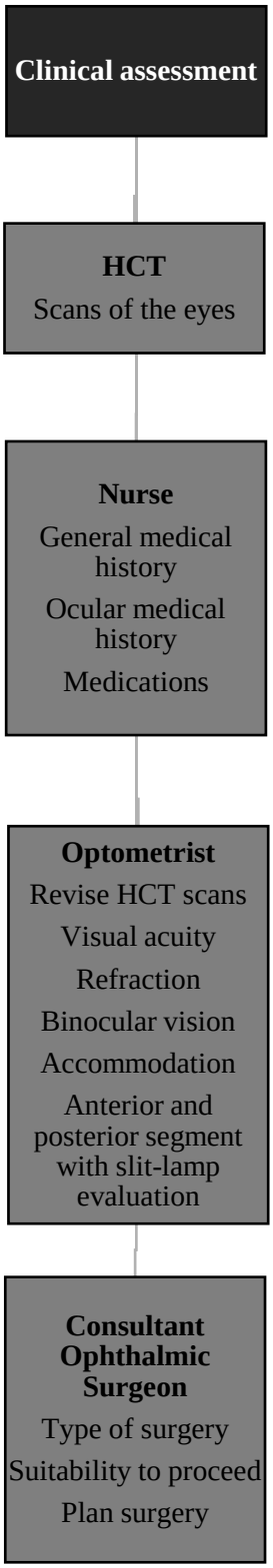

Figure 20 Flow diagram of the clinical assessment pathway.

2.4 Dry eye assessment

Except for Chapter 3 where no dry eye assessment was performed, the rest of the studies adopted all or part of the following dry eye protocol with the aim of assessing the status of the ocular surface before and, if surgery took place, also after surgery at follow-up (Figure 36). All the patients were seen at the end of the clinical assessment pathway based on the patients' willingness and ability to adhere to any of the study instructions and to complete all the specified evaluations. For this purpose, patients were provided with a copy of the PIS. Thereafter, signed informed consent was taken before starting any of the measurements (see Figure 36).

The battery of DED assessment tests was planned following the latest suggestions from the Tear Film Ocular Society Dry Eye WorkShop II (TFOS DEWS II) diagnostic methodology report (Wolffsohn et al., 2017). The tests were performed by the author (AR) starting with the least invasive to the most invasive test to minimize the potential influence of the measured DED metrics and to obtain reliable measurements. The eye with better VA or the dominant eye assessed considering motor and sensory dominance tests in case of equal VA, was chosen for evaluation (McAlinden et al., 2011b). Additionally, only one eye was included to design a reasonable clinical protocol in terms of time and tests for the patients who have participated in the study. All measurements were preceded by hand decontamination techniques following the World Health Organization recommendation and NHS guidelines (Loveday et al., 2014) (Figure 21). To minimise infections, a disinfectant solution and/or wipes were used (Clinell Universal Spray and Alcoholic 2% Chlorhexidine wipes). The surfaces and devices used were disinfected before and after use (chinrest, forehead, tables, chair armrests, etc.).

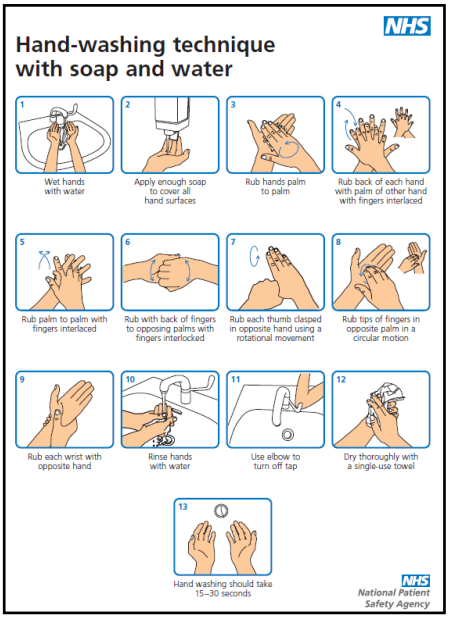

Figure 21 NHS guidelines for washing hands.

2.4.1 Symptoms and visual disturbance

The symptomatology questionnaires considered in the study were the OSDI and DEQ-5 questionnaires (Chalmers et al., 2010; Schiffman et al., 2000).

The reason for including both questionnaires was because while OSDI measures three different subscales between ocular symptoms, vision-related functions and environmental triggers over the last week, DEQ-5 is able to track the visual disturbance during the day and how much visual fluctuations affect the patients over the last month. Additionally, as previously reported by Caffery et al. (2011) both diagnostic tools are well correlated in DED diagnosis but they showed different correlations when compared with DED signs as the lack of relationship between symptoms and signs (K. Nichols et al., 2004b).

For ease of the data management, both questionnaires were collated on the same sheet (see Appendices 12.8) and were handed to the patients immediately after reading the study PIS and after written informed consent was obtained.

2.4.2 Eyelids aspects

Two different aspects of the blinking process were recorded: the number of blinks in 30 seconds and their completeness. To report these characteristics, AR was counting, using a manual counter (clicker) and a stopwatch, while exploring the blinking aperture-closure phase when the patients, not aware of the procedure, were completing the aforementioned questionnaires (See section 2.4.1). Finally, the presence of any crease over the eyelids was recorded as the presence of anterior blepharitis is important to define the diagnosis of DED.

2.4.3 Tear film composition

A tear film sample collection in both eyes (approximately 50 nl of tears) using the TearLab® Osmolarity System (TearLab® Corp, San Diego, US) allowed the calculation of the tear film osmolarity in the eyes with minimal impact on the ocular surface (Figure 22). Due to the nature of the test, it was performed first to avoid any influence from the other DED tests (e.g. TBUT or ocular staining) and following the instructions from the manufacturer. The sample of tears was collected from the temporal side of patients' lower eyelids while looking upwards. AR ensured the Osmolarity Test card, which is clipped into the top of the pen, was not touching the eye but only collecting the minimum quantity of tears from the inferior tear reservoir (Figure 22). The room temperature was controlled and maintained between 20° and 24°C.

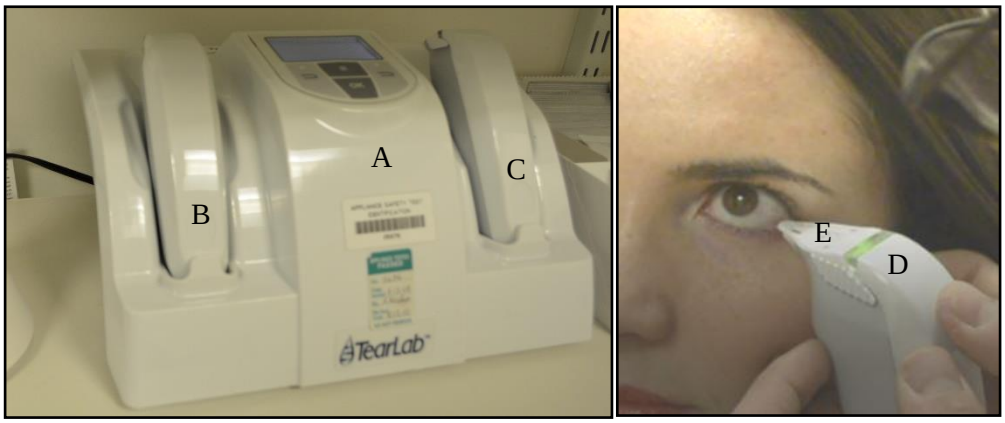

Figure 22 TearLab® Osmolarity System (A) with the Osmolarity Test pens (B and C) and during the collection (D) of a sample of tear film through the Osmolarity Test card (E).

After collecting the samples, the Osmolarity Test pens were repositioned over the Osmolarity System (reader unit) to process the measurements that were displayed in the small liquid crystal display (LCD) screen. As suggested by the manufacturer (Figure 23) and from the scientific literature (Sullivan et al., 2010), the range of the measurements vary with disease severity (270 to 400 mOsm/L): normal (302.2 ± 8.3 mOsm/L), mild-to-moderate (315.0 ± 11.4 mOsml/L) and severe (336.4 ± 22.3 mOsm/L). The manufacturer recommends to test both eyes and then consider the eye with the higher osmolarity reading while Szczesna-Iskander (2016) found that three consecutive acquisitions are required for the measurement to be reliable. However, for the current research, only the results from the eye with better VA or the dominant eye were included and only considering one single repeat: the reasons behind this decision was to design a reasonable clinical protocol in terms of time and tests for the patients who have participated in the study (see Appendices 12). Moreover, to understand if a single repeat of the tear film osmolarity could be a reliable test in our study population and to be included in the standard assessment of the hospitals matching the benefit-cost analysis of the procedure (Sullivan, 2014). After the readings of both eyes, the chips were discarded as single-use.

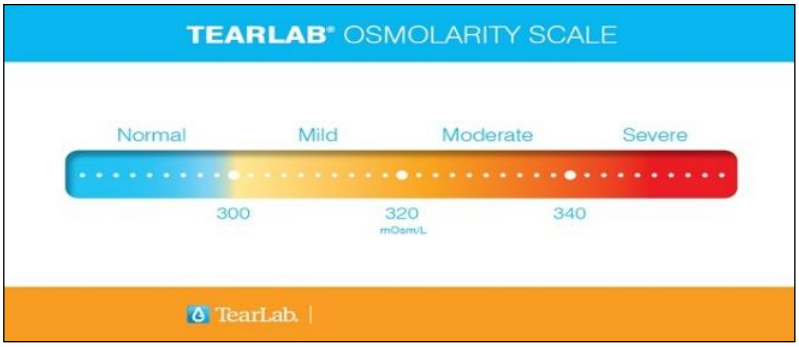

Figure 23 TearLab® Osmolarity Scale provided by the manufacturer.

2.4.4 Objective tear film analysis

As mentioned in section 1.4.4.2, the K5M is an advanced corneal topographer equipped with a Placido disc illumination system and a series of different light emitting diodes (LED) (Figure 24) to obtain a

detailed description of the cornea (keratometry readings). Additionally, it is able to obtain the measurements of ocular surface parameters such as ocular redness, TMH, LLT, NIKBUT and ocular surface staining (fluorescein and lissamine green). With a supplementary set of infrared illumination lights, it is also able to assess the meibography of the eyelids.

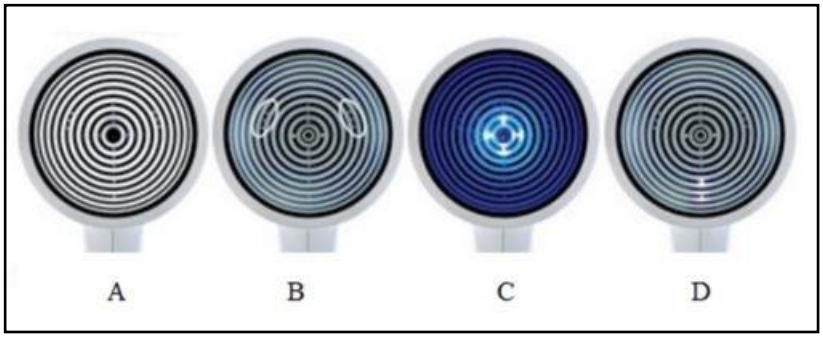

Figure 24 Different sets of emitting diodes/lights and functions with the Oculus Keratograph® (K5M) considered in the study: white and infrared Placido ring for non-invasive Keratograph® break-up time (NIKBUT), tear meniscus height (TMH) and lipid layer thickness (LLT) (A); infrared LED for Meibography (B); blue LED for fluorescein staining (C); white LED for ocular redness and lissamine green staining (D).

In the current research, the device was installed over a height-adjustable table with a dedicated chin and forehead rest (Figure 25A) where the patients were comfortably seated and adjusted at the correct height for acquiring the measurements (Figure 25B). However, before taking any measurements, the device, its base, the chin and the forehead were cleaned following the NHS guidelines (Loveday et al., 2014).

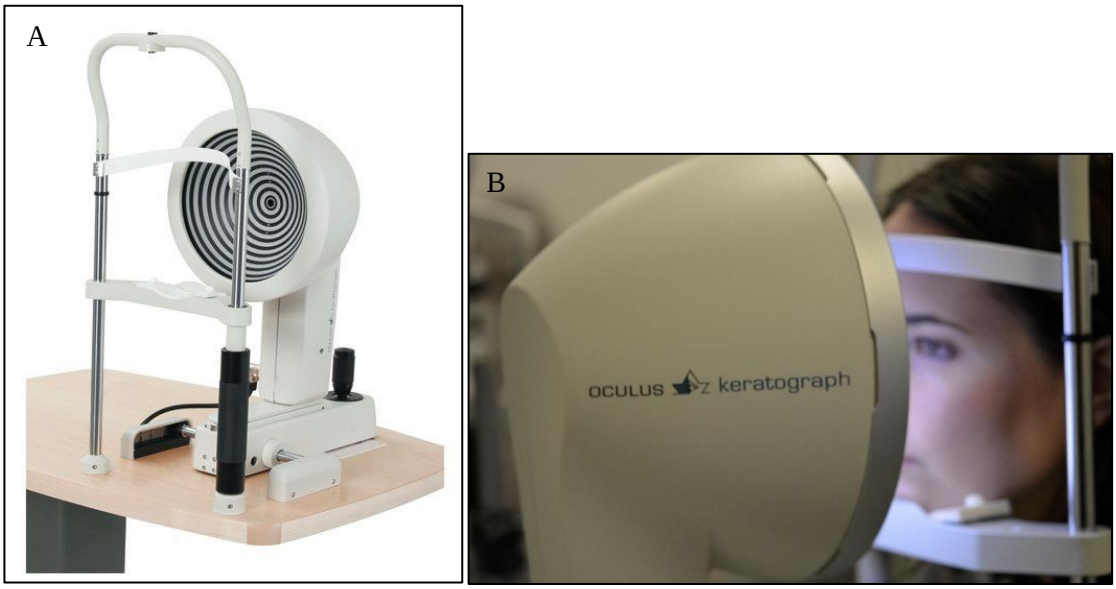

Figure 25 The Oculus Keratograph® 5M (K5M) mounted over a height-adjustable table and a patient comfortably sit with her chin and forehead rest correctly positioned.

The ocular redness was classified by considering the bulbar and the limbal area as the device is able to detect the vessels in the conjunctiva and extrapolate a degree of redness (Figure 26, A and B). A single image was collected while patients were instructed to look inside the device fixing a red dot target,

while blinking naturally. Therefore, the values of redness for both areas were noted. In general, the less red the eye, the less chance to inflammation of the ocular surface was present, although redness is also associated with other conditions such as ocular injuries and conjunctivitis (Hessen et al., 2014). The range of the values obtained from the internal grading scale was from 0.0 (no redness) to 4.0 (maximum level of redness) for both bulbar and limbal area. However, a validated scale to correlate with DED diagnosis and severity still not available (Bose et al., 2017) but, as an indirect measure of inflammation, the ocular redness can be associated with other DED metrics such as tear film osmolarity and ocular staining (Nitoda et al., 2018; Rico-Del-Viejo et al., 2018).

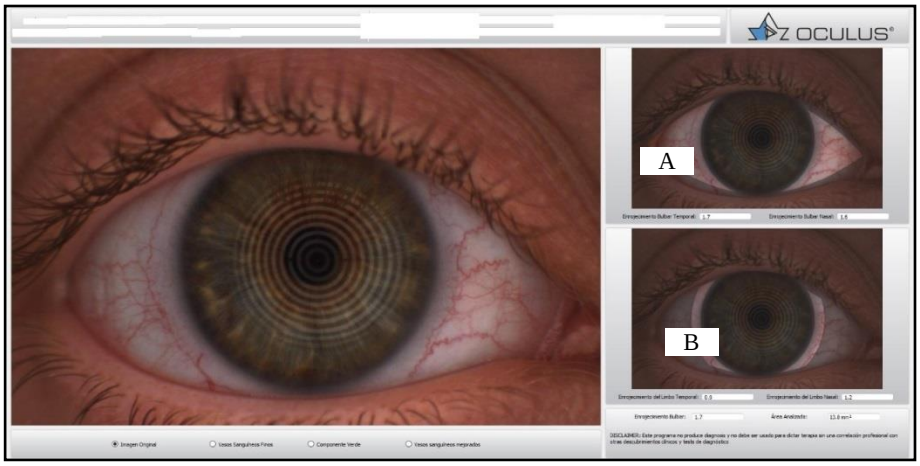

Figure 26 Ocular redness evaluation with the Oculus Keratograph® 5M (K5M) using white LED source: bulbar area (A) and limbal area (B).

TMH is an estimation of the tear film volume of the eye (M. Shen et al., 2009). In the current research, it was measured using the K5M set up with the infra-red illumination to avoid any influence over the measurements as the type of illumination does not provoke reflex tearing. The patients were instructed to fix on a red dot target while a single scan was acquired in a central location between the cornea and the inferior eyelid from the selected eye, immediately after blinking. The average values of three repeats were analysed and measured in millimetres considering the area located approximately at 6 o'clock. The device by means of an in-built software calliper, it is able to provide the height of the tear film between the margin of the lower eyelid and the upper limit of the reflective zone (bulbar conjunctiva) (Figure 27). Following Baek et al. (2015), a value is considered normal when greater than 0.20 mm.

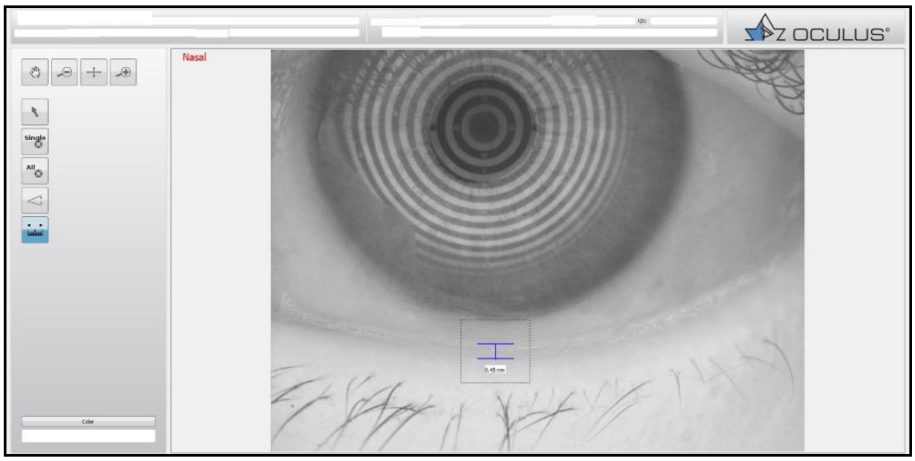

Figure 27 TMH measurement using the built-in calliper (blue line) provided with the Oculus Keratograph® 5M (K5M) software.

LLT was derived using the evaluation of the interferometric patterns generated by the K5M white light source (Figure 28). The patients were asked to blink naturally while recording a short video (up to the third non-forceful blink or approximately 15 to 20 seconds) and then subjectively graded using the scale published by J. Guillon (1998a). In fact, in Guillon's clinical scheme (Figure 28B), the interferometric pattern corresponding to LLT uses the following classifications: open meshwork (~15 nm), closed meshwork (~30 nm), wave pattern (~30-80 nm, pictured in Figure 28G), amorphous (~80 nm), colour fringes (~80-300 nm) and abnormal colour fringes (~600 nm). A normal human tear LLT is approximately 40 nm (King-Smith et al., 2010) (Figure 28, H).

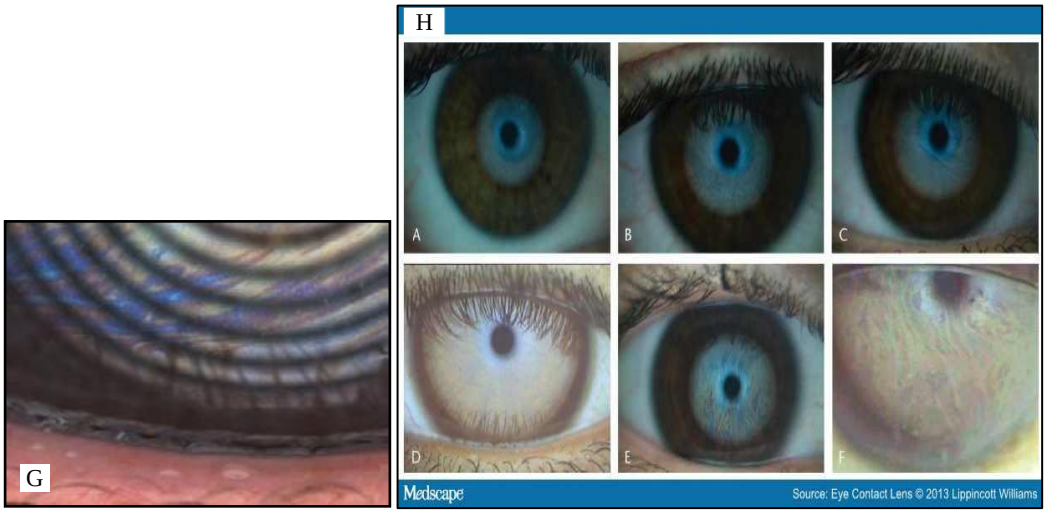

Figure 28 Magnified image of the interferometric pattern (wave) (G) extrapolated from a recording using the Oculus Keratograph® 5M (K5M) and the Guillon clinical scheme adapted from Remeseiro et al. (H).

NIKBUT was assessed through the projection of a Placido disc (22 ring pattern with 22.000 analysed points) sourced with an infrared light of 880 nm of wavelength over the ocular surface (Figure 29A). Patients were instructed to perform two complete blinks before staring at the red dot target displayed. The device was able to automatically detect changes in the regularity of the projected rings indicating the rupture of the tear film in seconds (Figure 29) (Tian et al., 2016). Immediately after the

successful recording of the rupture (break-up time), patients were invited to blink freely and taking a 1-minute rest before performing two consecutive measurements, each spaced by one minute. Then the NIKBUT-First results (appearance of the first break in seconds) were averaged. NIKTBUT-First values below 10 secs were considered as a sign of DED (Markoulli et al., 2018).

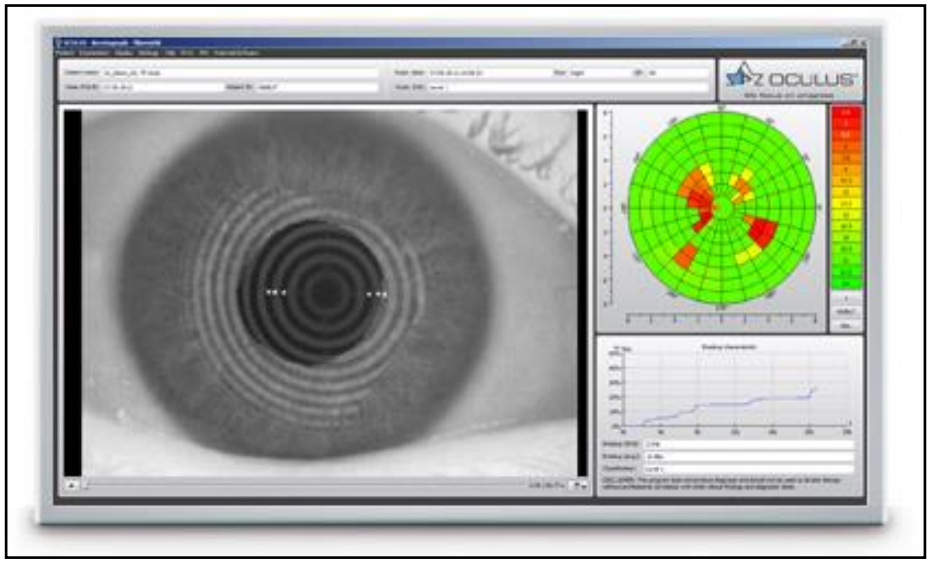

Figure 29 Infrared illumination scan of non-invasive Keratograph® break-up time (NIKBUT) assessed with the Oculus Keratograph® 5M (K5M): the image shows the software window appearance during acquisition.

For Chapter 6, only the Tearscope® (Keeler Ltd, Windsor, UK) was available for the measurement of TBUT. The device is a hand-held instrument used in conjunction with a slit-lamp to examine the tear film non-invasively (J. Guillon, 1998b) (Figure 30).

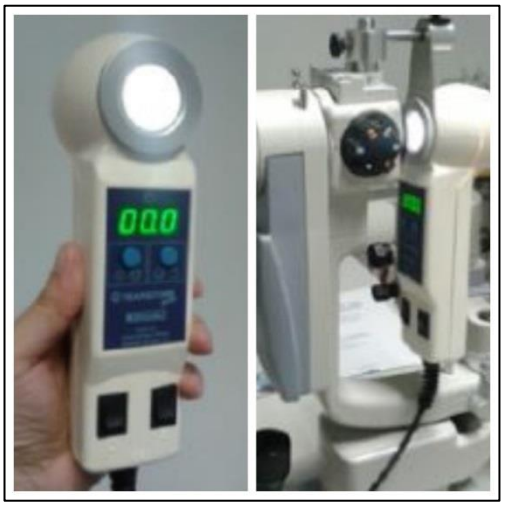

Figure 30 The Tearscope® device mounted with a slit lamp (Courtesy of Keeler Ltd).

To detect NIBUT, the Tearscope® grid pattern, similar to the K5M Placido disc, was projected over the patients' cornea. Therefore, patients were instructed to perform two complete blinks before holding the eyes open for as long as possible while the examiner was using the integrated stopwatch to measure the time of the appearance of any irregularity of the projected rings indicating the first rupture of the tear

film in seconds. Immediately after the successful recording of the rupture (break-up time), patients were invited to blink freely and taking a 1-minute rest before performing two consecutively measurements, each spaced by one minute. Then the results were averaged (Figure 31).

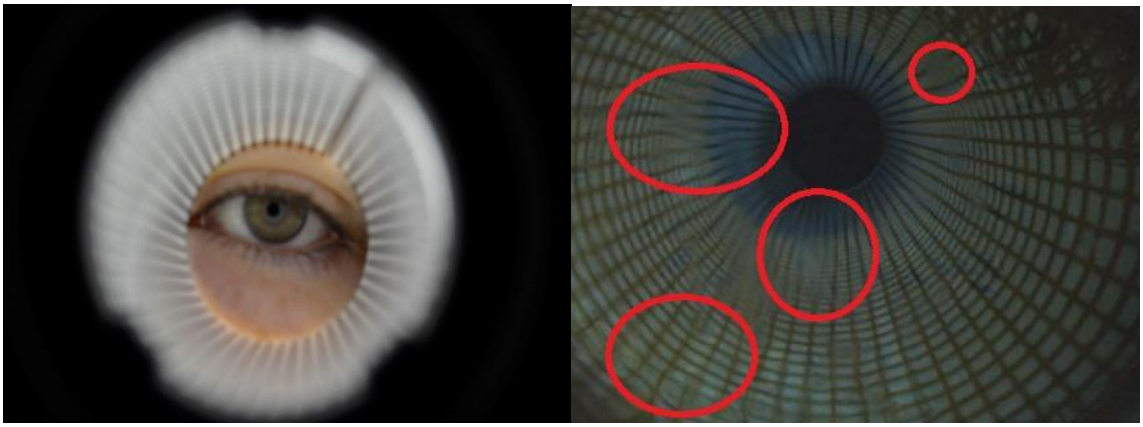

Figure 31 Image of the Tearscope® (left) and the distortions (red circles) observed on the specular image (right).

For Chapter 7, a digital slit lamp with vital stains was available to assess tear film stability. Before the start of the measurements, patients were comfortably sat with their chin and forehead on the rest of the slit-lamp. Fluorescein colorant was applied to the eye through a strip of Bio Fluoro fluorescein (Bio-Tech, Gujarat, India) eluted with a drop of non-preserved single-use saline B&L Minims Saline 0.9% (Bausch & Lomb, Aubenas, France). Thereafter, the patients were asked to perform two complete blinks before holding the eyes open for as long as possible while the optometrist detected the appearance of the first dry spot in the tear film indicating the first rupture of the tear film in seconds (Figure 32). Immediately after the successful recording of the rupture (break-up time), patients were invited to blink freely and taking a 1-minute rest before performing two consecutive measurements, each spaced by one minute. Then, the results were averaged.

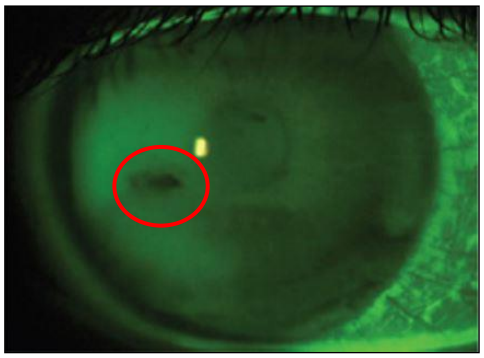

Figure 32 Fluorescein tear break-up time (TBUT): the red circle indicates the dry spot (black area) that corresponds to the break of the tear film.

Ocular surface staining was performed using two vital dyes in single-use strips (Bio Fluoro fluorescein and GreenGlo lissamine green) (HUB Pharmaceuticals, California, US). Both strips were activated using non-preserved single-use saline B&L Minims Saline 0.9% and then applied to the eye together. However, for fluorescein only the minimum quantity was used and in case of excess, the strip

was shaken over a tissue before applying while for the lissamine green, a couple of drops were left for at least 5 s to help with eluting the colorant before applying into the eye. The recommended location to apply the vital dyes using the strips into the eye was the temporal lower eyelid to avoid or at least reduce damage to the conjunctival tissue and lid margin (Wolffsohn et al., 2017) (Figure 11). Patients were instructed to blink naturally several times, without excessive squeezing, to distribute the colorants before the measurements. The corneal staining using the fluorescein was detected using the K5M blue LED light equipped with a yellow filter (465 nm of wavelength, Figure 33 left), while the lissamine green staining was detected using the white LED light. The images were graded according to the Oxford grading scheme comparing the staining represented by punctate dots with the grading panel provided (Bron et al., 2015) (Figure 33 right and Figure 34).

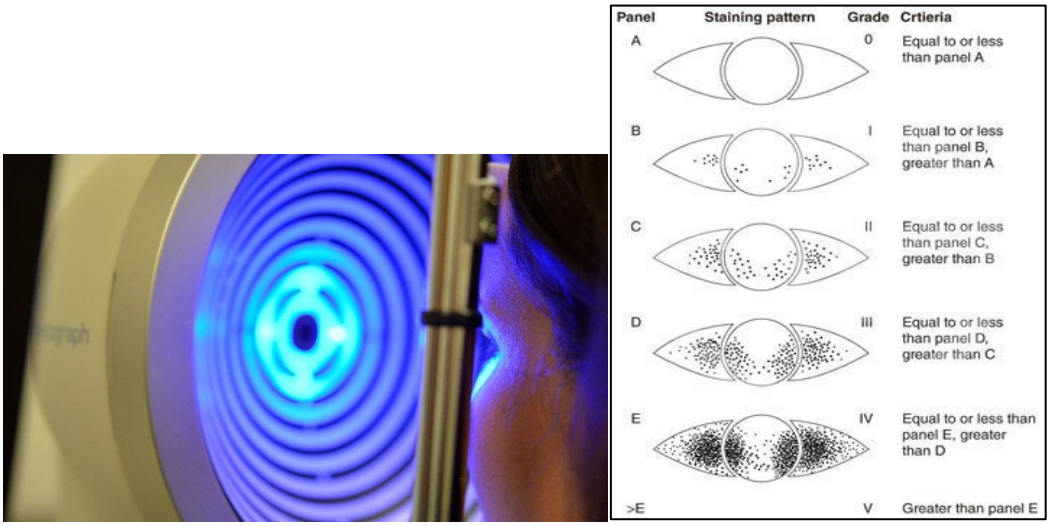

Figure 33 Blue LED light emitted from the Oculus Keratograph® 5M (K5M) to assess fluorescein staining of the ocular surface (left) and the Oxford grading scale for corneal and conjunctiva staining (right).

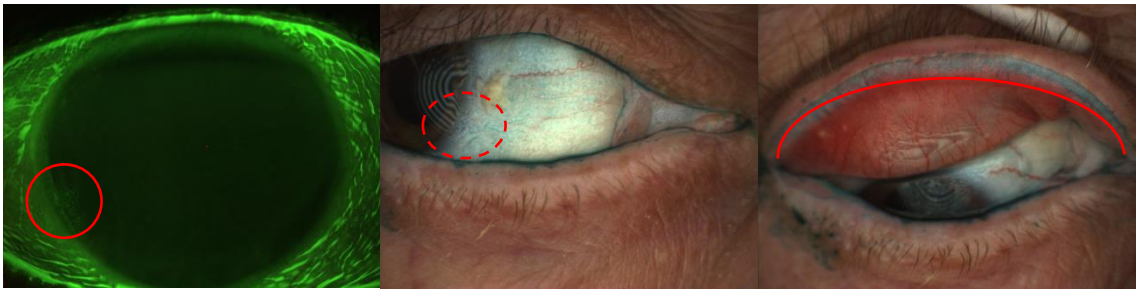

Figure 34 Images from corneal staining (left in the red circle), conjunctival staining (centre in the red dashed circle) and lid margin length staining (right in the red arch).

2.4.5 Meibography

The tarsal glands also commonly known as MG, were analysed using the K5M infrared LED light (840 nm of wavelength) acquiring scans from the upper and lower eyelids. In both cases, the eyelids were gently everted using a single-use sterile cotton swab (Applimed SA, Chatel-St-Denis, Switzerland) to evaluate the morphological changes in the Meibomian glands through the scans (meibography). Patients were instructed to look upward for the lower eyelid (and vice versa) while the device was acquiring

images, firstly from the lower eyelid and secondly from the upper eyelid, using the foot pedal. Therefore, the scans were graded using the Meiboscore from Arita et al. (2008): grade 0 = no glands loss, grade 1 = area of glands loss < 33% of the total surface analysed, grade 2 = area of glands loss 33%-67% and grade 3 = area of glands loss > 67%. The sum of the lower and the upper eyelid was defined as the total Meiboscore (Figure 35 A and B).

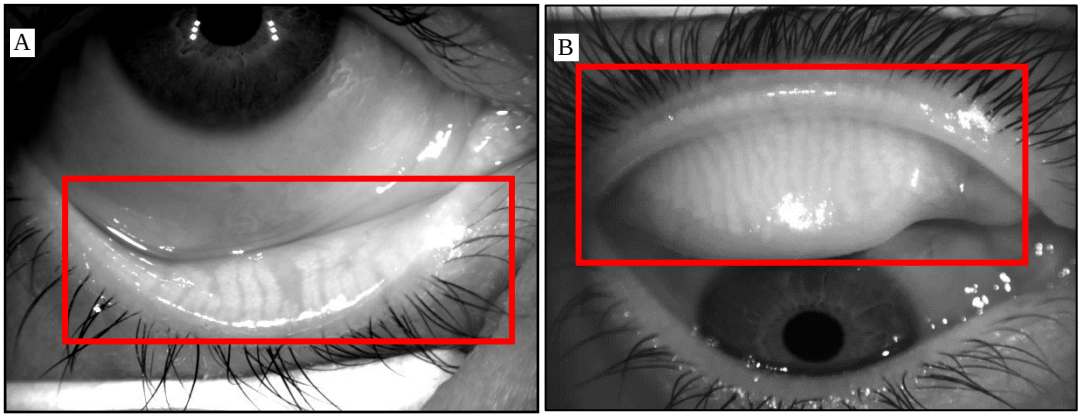

Figure 35 K5M Meibography scans acquired from the lower (A) and upper (B) eyelids of the same patient. Please note the tarsal glands marked inside the red boxes

At the end of the Dry eye assessment, patients' ocular surface was cleaned using non-preserved single-use saline B&L Minims Saline 0.9% to remove any traces of the previously applied colorants.

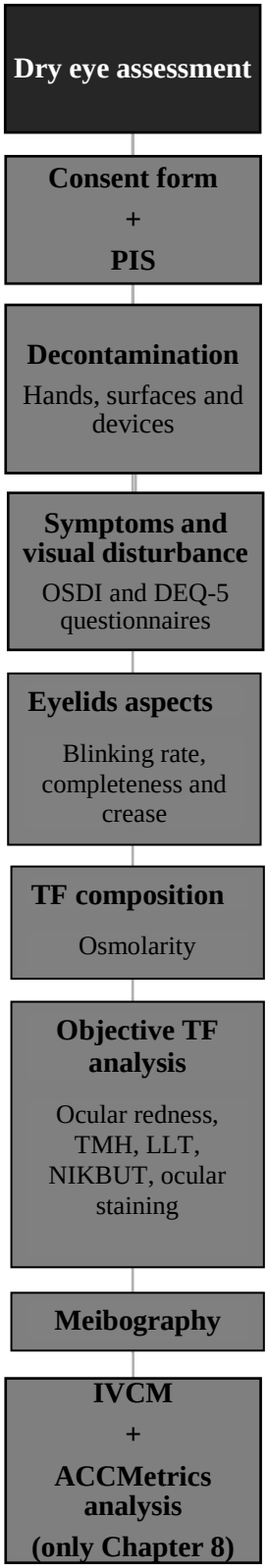

Figure 36 Flow diagram of the dry eye assessment steps followed by IVCM and ACCMetrics analysis.

2.5 Statistical analysis

All the statistical analysis was performed using the software package IBM® SPSS Statistics v23 (IBM Corp, Armonk, US). For all chapters, data normality was tested considering the Shapiro-Wilk test or Kolmogorov-Smirnov test and rejected in case of a p-value (p) < 0.05. Statistical significance was set on alpha of 0.05. In presence of data normally distributed a paired samples *t*-test was considered whereas data were not normally distributed a Wilcoxon Signed Rank test (related sample) or Mann-Whitney U (in case of independent samples) were used. Additionally, non-parametric data were also compared using the Kruskal-Wallis test by ranks (e.g. group analysis by age). Correlations between refractive and visual metrics with DED metrics were carried out using Pearson and Spearman coefficients (Y. H. Chan, 2003). A guide to interpreting correlations was deducted by Navarro (2015), following Table 2:

Correlation	Strenght	Direction
-1.0 to -0.7	Strong	Negative
-0.7 to -0.4	Moderate	Negative
-0.4 to 0	Weak	Negative
0 to 0.4	Weak	Positive
0.4 to 0.7	Moderate	Positive
0.7 to 1.0	Strong	Positive

Table 2 Correlations suggested by Navarro et al. (2015) in the book "*Learning Statistics with R*" (self-published).

2.5.1 Sample size calculation

The minimum sample size recommended by the TFOS DEWS II report is for normal data based on 2-sample t-test comparisons with 80% power and p < 0.05 significance level. Thus, as the initial aim of the current research was to evaluate DED metrics before and after surgery, a G-Power sample size calculation assuming an effect size of 0.5, an alpha error of 0.05 and a power of 80% was performed. The minimum sample size required is detailed below, except for the retrospective study analysis and for Chapter 9 that was designed as a pilot investigation (n= 5 eyes, before and after surgery). Nevertheless, whereas possible, all the samples sizes were increased by 30% to account for discontinuations (e.g. patients who decided to do not proceed with the surgery, etc.).

Following the latest TFOS DEWS II report (Wolffsohn et al., 2017), symptoms and visual disturbance measured using OSDI questionnaire should have a standard deviation (SD) of repeated measurements equal to 6.7 on 100 point scale, as reported by Schiffman et al. (2000). Bases on their findings, a clinical difference to detect DED was 4.5 to 7.3 in case of mild/moderate DED and 7.3 to 13.4 in presence of severe condition with a minimum suggested study sample size to consider between 14 to 35 subjects (Miller et al., 2010). However, for DEQ-5 questionnaire, the clinical difference to detect were 6 points but without published evidence to support the minimum sample size required. Tear film osmolarity was found with 4.8 SD by Gokhale et al. (2013) with a clinical difference to detect of 5

mOsm/L and a minimum suggested sample size of 15 subjects. In terms of ocular staining, due to high variability based on the clinician experience there are no reference to clinically differentiate and to support the minimum sample size required. Non-invasive TBUT measurements were considered with 7.2 SD and 2.0 SD using Tearscope® and K5M, respectively. The clinical difference to detect is set to 5 s: while the minimum sample size suggested is 33 and 3 with Tearscope® and K5M, respectively. The meibography has an SD of 0.9 calculated from the study by Pult et al. (2013a) that have calculated with a minimum sample size required of 14 subjects. IVCM assessment has followed the suggestion by Vestergaard et al. (2013a) 4 or more representative and complete images of the central corneal subbasal nerve fibres with a minimum sample size suggested to be 15.

2.5.2 Intra-observer repeatability on dry eye assessment tests

The dry eye assessments in the studies included a series of subjective and objective measures collected and analysed by AR. However, in order to test the agreement on grading the subjective DED metrics such as TMH, LLT, ocular staining and Meibography, Bland-Altman analysis with respective limits of agreement (LoA) and 95% confidence intervals (CI) was performed (Bland et al., 1986, 1997, 1999; McAlinden et al., 2011b). For the ease of reading, the subjective metrics tested are gathered from Chapter 8 because this chapter has included all the subjective DED metrics considered in this thesis. The Bland-Altman analysis was performed between two different acquisition defined as run 1 (or first evaluation) and run 2 (or second evaluation). The subjects considered in Chapter 8 belonged to two different groups: FS-LASIK and SMILE. The FS-LASIK group was composed of 16 subjects (7 males; 9 females) with a mean age of 32.6 ± 9.1 years and pre-operative refraction of -3.48 ± 2.89 D (range from -7.50 to 2.38 D) while SMILE group was composed of 13 subjects (5 males; 8 females) with a mean age of 32.2 ± 5.3 years and pre-operative refraction of -4.67 ± 2.12 D (range from -8.50 to -1.75 D). The time between run 1 and run 2 in evaluating the results was two weeks without intervention in between and the time of day was matched and the researcher was masked.

2.5.2.1 Agreement in tear meniscus height

Agreement in tear meniscus height (TMH, mm)				
Group	FS-LASIK		SMILE	
	Before surgery	After surgery	Before surgery	After surgery
run 1	0.32 ± 0.13	0.31 ± 0.12	0.30 ± 0.07	0.31 ± 0.06
run 2	0.22 ± 0.09	0.21 ± 0.08	0.30 ± 0.07	0.31 ± 0.06

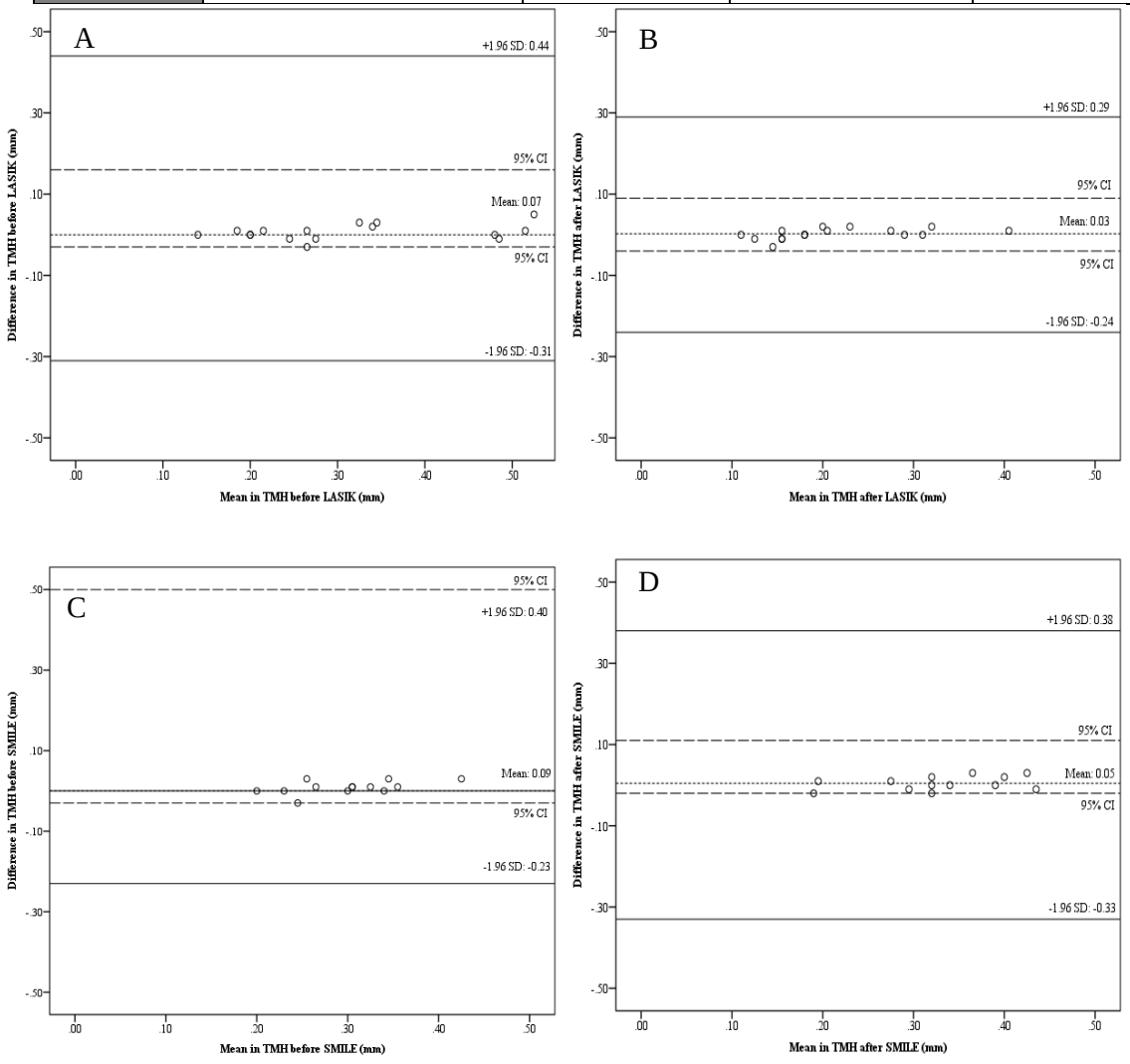

Figure 37 Tear meniscus height (TMH) Bland–Altman plots (difference plot) (average of the two runs against the difference) comparing the run 1 and run 2. The mean difference is shown by the dotted line, the limits of agreement by the solid lines and the 95% CI by the dashed line. A) pre-surgery FS-LASIK B) post-surgery FS-LASIK C) pre-surgery SMILE D) post-surgery SMILE.

2.5.2.2 Agreement in lipid layer thickness

Agreement in lipid layer thickness (LLT, grade)				
Group	FS-LASIK		SMILE	
	Before surgery	After surgery	Before surgery	After surgery
run 1	3.69 ± 1.01	3.38 ± 0.81	2.46 ± 0.97	2.46 ± 0.88
run 2	3.31 ± 0.95	2.94 ± 1.00	2.23 ± 0.73	2.31 ± 0.75

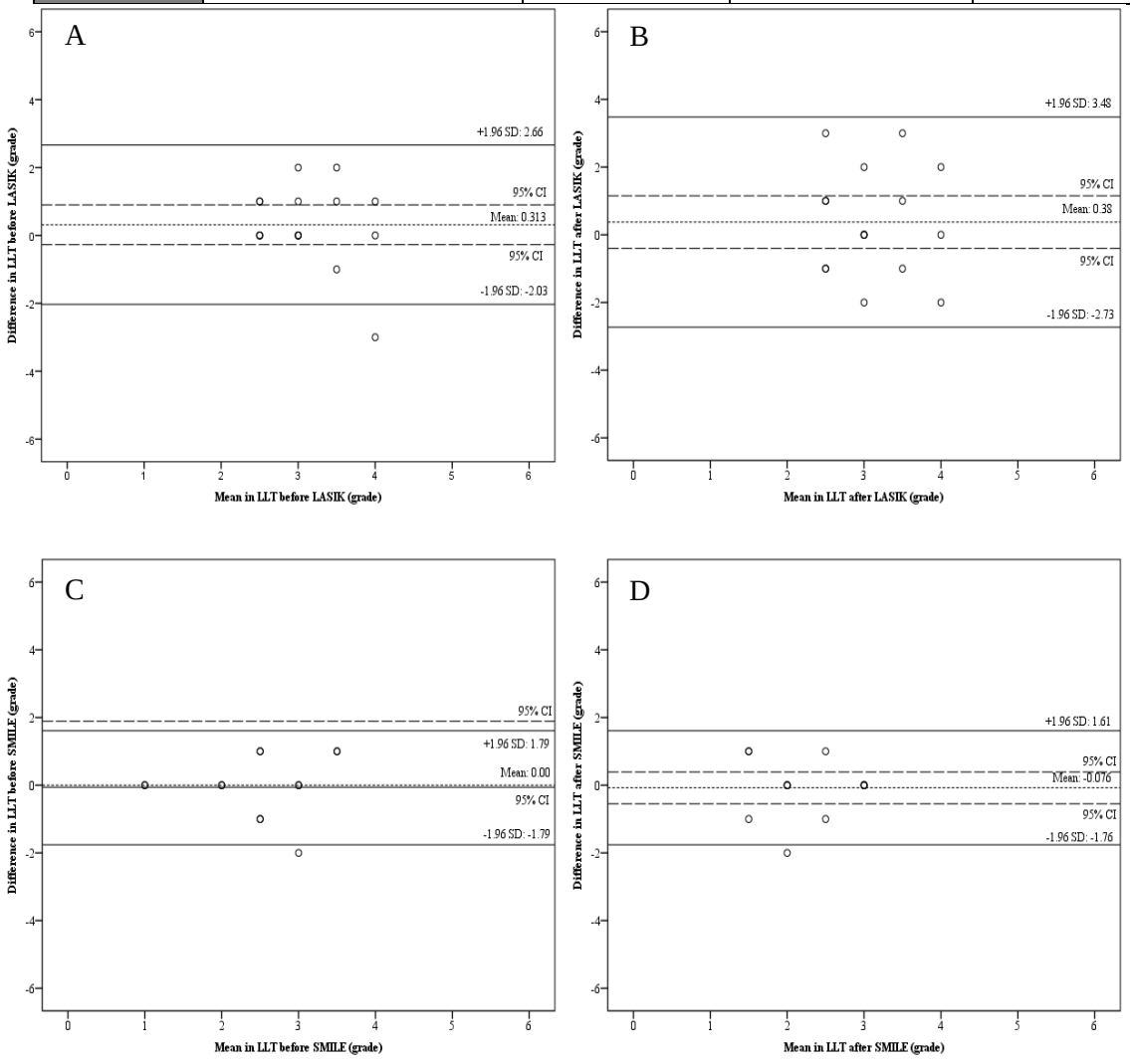

Figure 38 Lipid layer thickness (LLT) Bland–Altman plots (difference plot) (average of the two runs against the difference) comparing the run 1 and run 2. The mean difference is shown by the dotted line, the limits of agreement by the solid lines and the 95% CI by the dashed line. A) pre-surgery FS-LASIK B) post-surgery FS-LASIK C) pre-surgery SMILE D) post-surgery SMILE.

2.5.2.3 Agreement in ocular staining

Agreement in ocular staining (grade)				
Group	FS-LASIK		SMILE	
	Before surgery	After surgery	Before surgery	After surgery
run 1	0 ± 1	0 ± 1	0 ± 1	0 ± 1
run 2	0 ± 1	1 ± 1	0 ± 1	0 ± 1

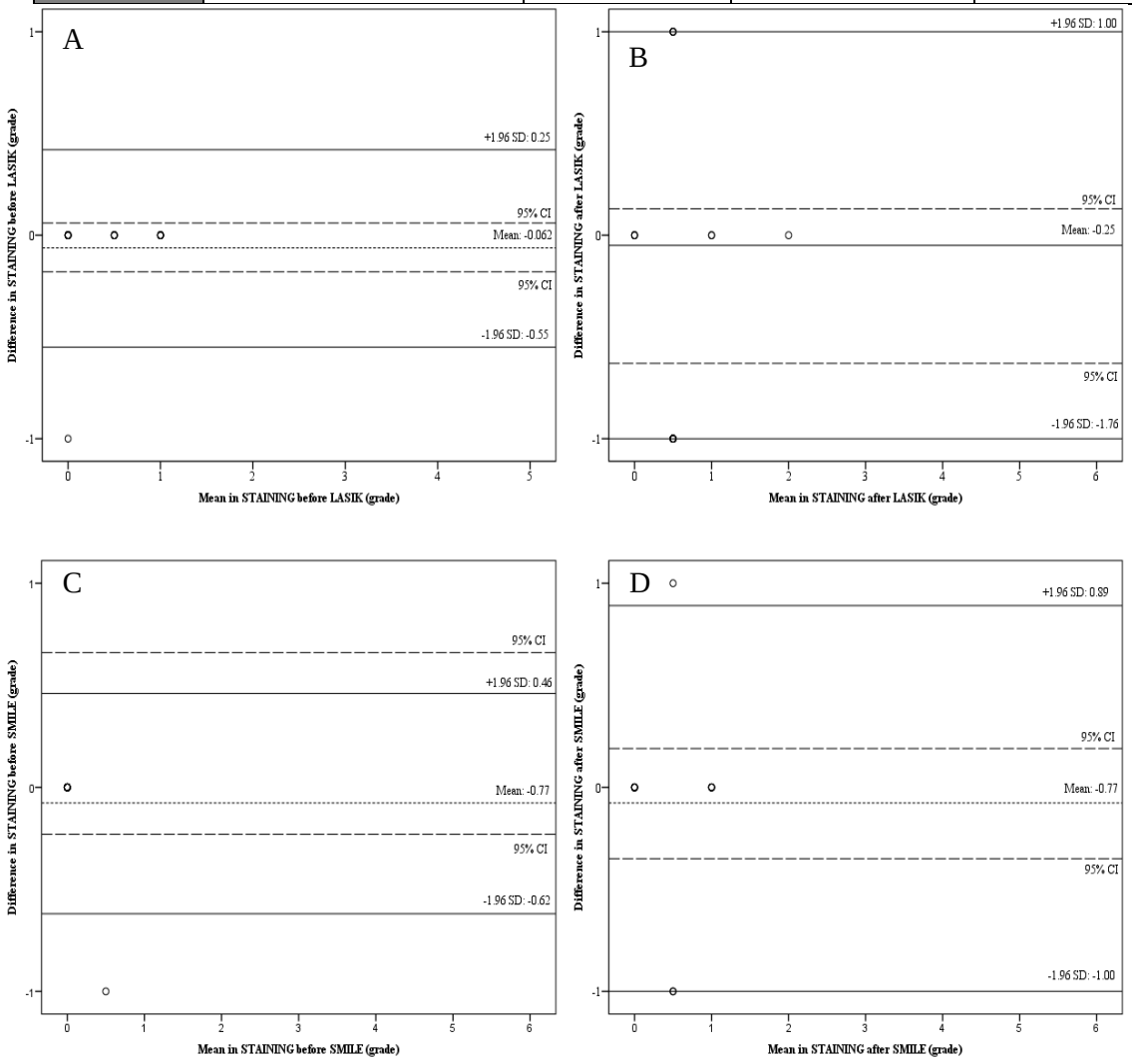

Figure 39 Ocular staining Bland–Altman plots (difference plot) (average of the two runs against the difference) comparing the run 1 and run 2. The mean difference is shown by the dotted line, the limits of agreement by the solid lines and the 95% CI by the dashed line. A) pre-surgery FS-LASIK B) post-surgery FS-LASIK C) pre-surgery SMILE D) post-surgery SMILE.

2.5.2.4 Agreement meibography

Agreement in meiboscore (grade)				
Group	FS-LASIK		SMILE	
	Before surgery	After surgery	Before surgery	After surgery
run 1	2 ± 2	2 ± 2	1 ± 1	1 ± 1
run 2	2 ± 2	1 ± 1	1 ± 1	1 ± 1

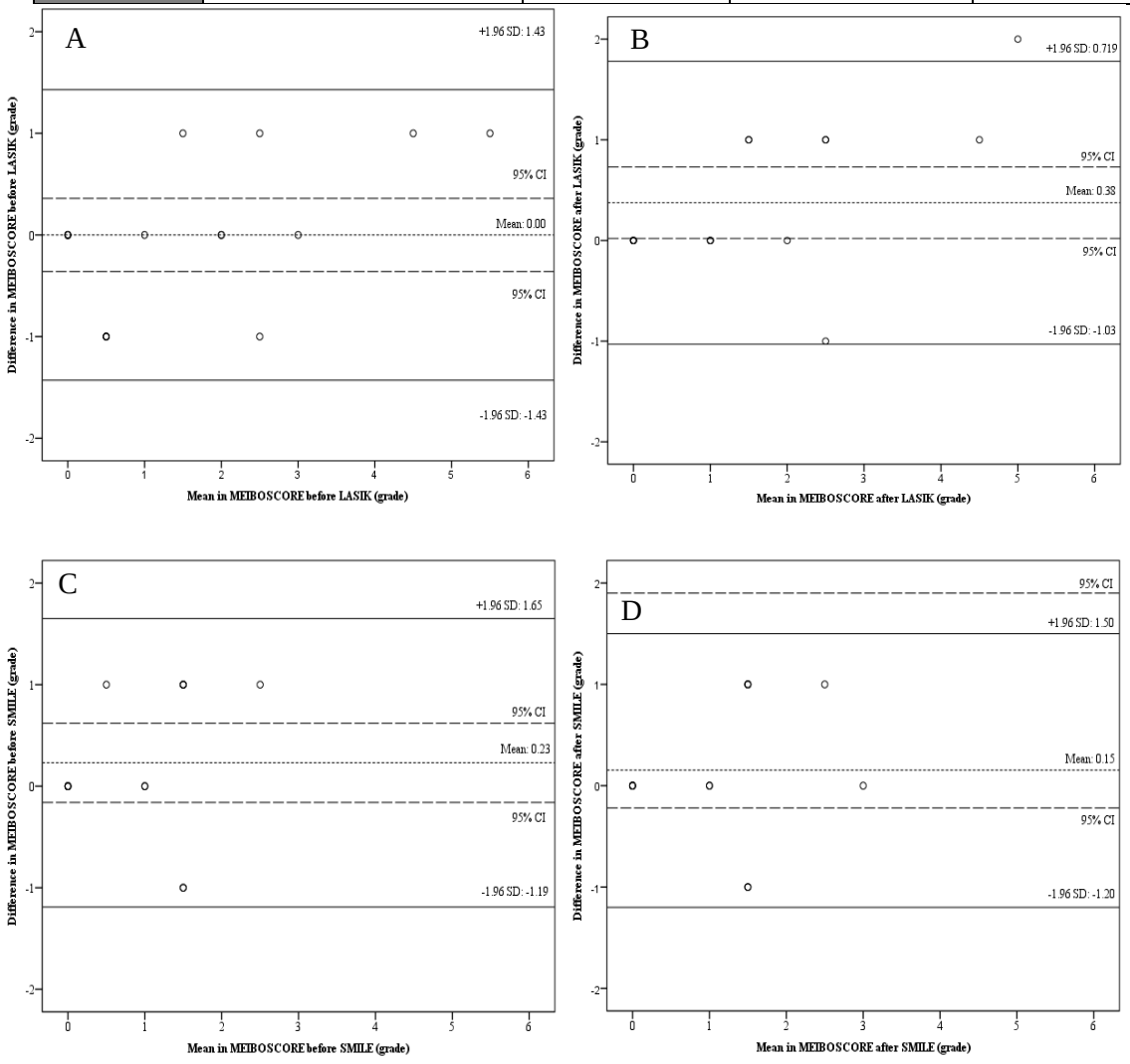

Figure 40 Meiboscore Bland–Altman plots (difference plot) (average of the two runs against the difference) comparing the run 1 and run 2. The mean difference is shown by the dotted line, the limits of agreement by the solid lines and the 95% CI by the dashed line. A) pre-surgery FS-LASIK B) post-surgery FS-LASIK C) pre-surgery SMILE D) post-surgery SMILE.

The intra-observer repeatability considering the Bland-Altman plots showed good results, indicating the consistency from the observer to assess each of the subjective metrics considered in DED in two different sessions (run 1 and run 2). Although, a potential error can be detected if the clinician is not trained using subjective DED metrics and, more important, if does not use the validated grading

scale available for clinicians and researchers (Arita et al., 2008; Bron et al., 2015; Celebi et al., 2016; García-Resúa et al., 2009; J. Guillon, 1998a; Santodomingo-Rubido et al., 2006).

However, despite the increasing interest in research and clinical setting in using IVCM in DED (Hong et al., 2010; Messmer et al., 2005; Randon et al., 2018), a lack of software which can automatically process scans from IVCM is evident. In fact, most of the scans acquired with IVCM are therefore processed using manual or semiautomatic programs (Ahmed et al., 2012; Hertz et al., 2011; Wu et al., 2012). Manual tracing of nerves, Matlab or Java algorithm (Meijering, 2010) have demonstrated several disadvantages such as time-consuming, observer-experience with bias in reproducibility and repeatability, etc. In a review by Alhatem et al. (2012), the researchers provided several possible applications of IVCM in DED like screening of the conjunctival epithelium and goblet cells alterations, corneal epithelium cell density, hyperreflectivity of the stromal keratocytes, corneal inflammatory cells, MG morphology and corneal nerves. However, in conclusion, they reported the need of an objective methodology which can help the clinicians to tailor a treatment based on the observed applications of IVCM in DED. The availability of automatic quantification of corneal nerves assessed by IVCM can also provide new insight in longitudinal studies or clinical trials because of the large numbers of participants. In a study by Dehghani et al. (2014), ACCMetrics showed excellent results from Bland-Altman plots and high intraclass correlation coefficient (ICC) with manual or semi-automated methods. Additionally, ACC metrics demonstrated to be 7x and 4x faster than both non-automated methods. In a study by Petropoulos et al. (2014), the automatic quantification of the subbasal corneal nerves required approximately 10 to 22 seconds against a manual analysis which can take from 2 to 7 minutes per image depending on the density of the nerves displayed. Recently, Giannaccare et al. (2019) presented the first study using ACCMetrics in IVCM scans to analyse the subbasal nerve plexus in healthy and DED patients. The researchers reported that DED patients had reduced density in main fibre nerves and branches with limitation on main nerves length compared to healthy subjects. Thus, ACCMetrics was able to discriminate DED patients from healthy subjects allowing new possible applications of this powerful analysis tool.

Chapter 3: Long-term patient-reported outcomes measures (PROMs) after refractive lens exchange (RLE) in a large population

3.1 Introduction

Wolffsohn and Davies (2018) have been recently suggested a definition of presbyopia as "… *when the physiologically normal age-related reduction in the eye's focusing range reaches a point, when optimally corrected for distance vision, that the clarity of vision at near is insufficient to satisfy an individual's requirements*". In a recent review by Fricke et al. (2018), the global prevalence of the condition is affecting approximately 1.8 billion of people in 2015. A large proportion of those patients, approximately 826 million, could experience a visual impairment due to poor or a lack of vision correction.

Among the different techniques to correct presbyopia and strategies to improve spectacle independence, the implantation of a MFIOL that allows patients clear vision at a range of distances, has attracted the attention of many ophthalmic professionals (surgeons) and presbyopic patients (Alio et al., 2017). Refractive lens exchange (RLE) also known as "clear lens exchange" is a type of lens surgery to correct refractive errors (e.g. myopia, hyperopia and astigmatism) together with presbyopia by replacing the crystalline lens with an artificial implant (e.g. MFIOL) in the presence or not of crystalline lens opacification (Rosen et al., 2016). Several recent studies have been performed (Alio et al., 2014c; Srinivasan et al., 2016; Yoon et al., 2018), confirming RLE as a safe and effective procedure. Rosen et al. (2016) reported meta-analysis data from 8,797 eyes where patients were able to reach postoperatively a mean monocular UDVA of 0.05 ± 0.006 logMAR. Additionally, 6,334 patients had a binocular UDVA of 0.04 ± 0.01 logMAR with a reported spectacle independence of 80.1% of the total where, in general, other studies reported a range between 30% to 90% with similar UDVA after surgery (R. Baig et al., 2016; Leyland et al., 2002). McNeely et al. (2017) also found excellent post-operative refractive outcomes (distance, intermediate, near) and patient 'satisfaction' (quality of vision questionnaire) at 3 and 12 months after surgery (n= 100 eyes).

The aging of the eye is a complex process: most of the structures of the ocular surface suffer from changes that can gradually affect their function and their morphology. In fact, age is one the most recognised risk factors in disturbing the homeostasis of the ocular surface (Lemp, 2008; Rico-Del-Viejo et al., 2018; Stapleton et al., 2017). As previously mentioned, RLE surgery is a refractive option for the patients over the age of 50 or so. Despite its safety and efficacy, RLE can potentially affect the status of the ocular surface contributing to the development of DED. Post-operative DED has been intensively investigated in the last years (Choi et al., 2018; Gomes et al., 2017; Iglesias et al., 2017; Ipek et al., 2018; Kato et al., 2017; Miyake et al., 2017; Park et al., 2016; Szakats et al., 2017; Trattler et al., 2017; Xue et al., 2018) and several factors have been reported as being responsible for DED after lens surgery: corneal epithelial and goblet cells loss, topical anaesthesia, lid speculum, etc. (Cochener et al., 2018; D. Goldberg, 2011; Gupta et al., 2018; Kasetsuwan et al., 2013). On the other hand, the pre-operative DED

screening in patients undergoing intraocular lens surgery is not always routinely carried out. Nevertheless, age at the time of surgery may play a role in changes such as hyposecretion of the lacrimal gland, increased tear film inflammatory cytokines, loss of sensory response, anterior blepharitis and MGD, etc. (Rico-Del-Viejo et al., 2018; Rocha et al., 2008; Yamaguchi, 2018).

The use of PROMs in healthcare is a relevant tool to report from a patient's perspective the health status before and after an intervention (e.g. surgery) (Gutacker et al., 2015). Additionally, it allows the practitioners and the health departments to understand what is deemed most important to patients and areas where improvement should be achieved. In lens surgery, and in particular with RLE surgery, PROMs questionnaires can be used to assess whether the patients are able to perform daily activities without any aid (e.g. if they are spectacle-independent) or which tasks/distances they need correction for (e.g. reading, working on a computer, etc.) or if they experience, in terms of frequency and intensity, any of the unplanned but possible photic phenomena or eye discomfort sometimes reported after RLE surgery (e.g. glare, halos, dryness, etc.) (Alio et al., 2014b).

One interesting approach has been conducted by Javitt et al. (2003), where the authors designed and performed a validated questionnaire (the Cataract TyPE Spec or TyPE) to assess the quality of life after MFIOL implantation pre- and 2 months post-operatively. TyPE questionnaire was tested in clinic and sent by mail revealing the correlation with the overall rating of vision and quality of life. In a study by Alio et al. (2004), PROMs questionnaires were considered to describe photic phenomena up to 1-year after different lens implantations (1 MFIOL, 1 bifocal diffractive and 1 pseudoaccommodating lens) in presbyopic patients (n= 80 eyes). Patients reported that the most common drawback with multifocal designs, as expected, were halos, glare and flashes. In another study patients reported the ability of MFIOLs to provide spectacle-independence with percentages up to 80% (Chiam et al., 2007), while another study pointed out the need for PROMs questionnaires to compare laser-assisted and traditional cataract surgery, rather than reporting on the clinical outcomes (e.g. VA, refractive error post-surgery, etc.) (A. C. Day et al., 2016).

In a comparative study considering 4 different questionnaires after lens surgery, Fung et al. (2016) reported the findings from the Cataract questionnaire (Catquest-9SF) (Sparrow et al., 2018), EQ-5D (Devlin et al., 2010), National Eye Institute Socioemotional Scale (NEI-SES) (McAlinden et al., 2011a), and the short-form Visual Function Index (VF-8R) (Gothwal et al., 2010): throughout the analysis, Catquest-9SF appeared to be the most effective PROMs questionnaire up to 3 months, despite a 30% non-respondent rate (total study cohort of 43 eyes).

However, PROMs questionnaires in lens surgery, especially in longer-term evaluation, may still not be as robust as desired due to their limited use and the lack of a standardised version and the range of questions asked. Michelotti et al. (2017) reported data from different countries such as Australia, India, Singapore, Sweden, UK and US: surprisingly, none of the hospital settings considered were using

any PROMs questionnaires for ophthalmic conditions like cataract or macular degeneration. In fact, DED is typically considered to be a short-term complication of lens surgery, but its prevalence in the longer post-operative period after surgery is unknown. Therefore, longer-term follow-up should allow the clinician to better understand how to deal with chronic DED symptoms and will help when counselling patients considering surgery.

In the present study, the aim was to assess how prevalent DED symptoms are, providing longer-term PROMs data (up to 7 years) in a large study population who had undergone MFIOL surgery, where vision fluctuations and DED were analysed to provide insights into their relationship with age.

3.2 Methods

3.2.1 Study design

This is a retrospective study based on the analysis of refractive outcomes and PROMs questionnaires of discharged patients that has received a favourable opinion from the Aston University Research Ethics Committee.

3.2.2 Subjects

All subjects considered in the study underwent refractive lensectomy with bilateral mutifocal IOL implantation in the presence or absence of cataract. They were identified on the EMR of the eye hospital group and were considered regardless of the lens type multifocal implantation (range included low/high add bifocals, trifocals and extended depth of field). Only patients who had been discharged from the hospitals for more than 18 months were included. Time of surgery ranged from January 1st, 2011 and June 30th, 2017. Each mailing consisted of a letter describing the purpose of the study (Research Participant Information Sheet - Version 01 - November 2017), a consent form (Consent Form Sheet - Version 01 - November 2017), a self-administered questionnaire (RLE Questionnaire - Version 01 - September 2017) and a postage-free return envelope (see Appendices 12).

3.2.3 Customised patients-reported outcomes measures

During the last years, different PROMs have been created to assess different clinical procedures in lens surgery (Correia et al., 2017). However, where some researchers found a weak correlation between the questionnaires considered (e.g. Catquest-9SF, EuroQol 5-dimensions questionnaire (EQ-5D), visual analog scale (EQ-VAS), etc.) and VA measured after surgery, other researchers presented the feasibility in evaluating the visual difficulty related to cataract surgery (Sparrow et al., 2018). There are several areas which are important to patients, not only the safety and efficacy of the procedures but also a range of other key parameters such as spectacle independence, quality of vision, patients' visual expectations, vision stability, photic phenomena, as well as more general areas including quality of care received, willingness to recommend, etc. Aspects such as photic phenomena and visual instability can lead to dissatisfaction with overall outcome irrespective of excellent objective clinical outcomes. One of the

most experienced drawback after lens surgery is discomfort that can be related to DED. In terms of DED and PROMs, Pan et al. (2017) reported the lack of any benefits in using autologous serum in their study from a patient perspective while Abetz et al. (2011) demonstrated the reliability of the IDEEL PROMs in Sjögren and non-Sjögren syndrome.

The aim of the present study was to better understand patient reported outcomes in the longer post-operative period and to ask a broad range of questions that, from previous feedback provided, are important to patients. Although, there are reports of studies in the literature that have assessed patients reported outcomes in the shorter terms, it was desirable to address a wider range of questions that could be used to develop appropriate questionnaire tools to be used to gather longer term patients feedback in future. However, we were unable to find a validated PROMs tool able to collect all of the desirable question items data in terms of patients' satisfaction, refractive, vision and comfort after MFIOL surgery. Therefore, a questionnaire was developed and customised based on questionnaires that have been used previously (e.g. Council for Refractive Surgery Quality Assurance, www. USAEyes.org, last accessed on 17 April 2019).

A customised questionnaire was designed by a number of refractive consultants, re3searchers and refractive optometrists. The questionnaire included general questions about spectacle independence, visual comfort in different light situations (day, dim light and night), quality of vision, complications rate, visual stability and reported fluctuations, photic phenomena, experience of having had the surgery, recommendation of the surgery to friends and relative, unaided vision satisfaction, dry eye complaints and quality of life. However, for the aim of this study, only questions related to visual fluctuations and dry eye were included in the analysis as the researchers involved in the current study were particularly interested to understand whether dry eye was a significant issue for patients in the longer post-operative period. The questions were:

- Question 9 (Q9) How stable is your vision throughout the day?
- Question 10 (Q 10): When do you experience the fluctuations in your vision?
- Question 20 (Q 20): To what extent do you experience dry eyes compared to prior surgery?
- Question 21(Q 21): During a typical day in the last month, how often did your eyes feel dry?
- Question 22 (Q 22): During a typical day in the last month, how often did your eyes look or feel excessively watery?

All the documents were mailed to the last known address. Of the 2,427 questionnaires mailed to patients previously operated, a total of 850 patients (35% of the total) returned the questionnaire. However, only 728 patients completed the questions related to DED and therefore only the correspondent refractive outcomes were included in the current analysis.

Firstly, the study cohort considered all patients together (All patients) and therefore dividing the participants in 3 different categories: Group 1 with patients up to 59 years, Group 2 with patients with ages between 60 to 69 and Group 3 with the rest of patients with age over 70 years (up to 86).

The demographic data are summarised in

Table 3:

Parameters	All patients	Group 1 (under 59)	Group 2 (60 to 69)	Group 3 (over 70)
Number of eyes	728	141	336	251
Mean age (y) ± SD	66.1 ± 7.1	55.7 ± 2.7	64.7 ± 2.9	73.7 ± 3.1
Range (y)	46-86	46 – 59	60 – 69	70 - 86
Male n (%), Female n (%)	217 (29.8) 511 (70.2)	42 (29.8), 99 (70.2)	87 (25.9), 249 (74.1)	88 (35.1), 163 (64.9)

Table 3 Demographics of the patients included in the study.

At the last follow-up appointment prior to discharge, monocular UDVA and CDVA were measured in logMAR at 6 meters and recorded onto the electronic medical record. The standard operating procedures for collecting logMAR acuity data was achieved using Topcon CC-100 computerized test charts (Topcon, Tokyo, Japan). SEQ was determined by the subjective refraction performed by a qualified optometrist. A standard operating procedure across the hospitals where maximum plus/minimum minus refraction for the maximum VA was applied. All the refractive outcomes considered in the study, were determined before surgery and at the discharge appointment (approximately 3 months postoperatively).

3.2.4 Surgery

All surgeries were performed by experienced consultant ophthalmic surgeons (n= 62) at seven different hospitals across the UK.

The RLE surgery procedures were performed through a 2.8 to 3.0 mm self-sealing corneal incisions. Thereafter, a continuous curvilinear capsulorhexis was performed to allow the breaking of the cortical portion of the lens via phacoemulsification. Finally, automated aspiration of the lens was undertaken to remove any remaining debris of the crystalline lens and a new artificial MFIOL was implanted. A series of multifocal intraocular designs were considered: e.g. low and high add bifocals, diffractive trifocals, EDOF. All the surgeries started with 1 drop of Phenylephrine 2.5%, 1 drop of Diclofenac Sodium 0.1% and 1 drop of Cyclopentolate Hydrochloride 1%. All the drops were instilled three times in a time interval of 10 minutes (e.g. first dose 8:00 AM, second dose 08:10 AM and so on). Thereafter, topical anaesthesia was instilled; 1 drop of Proxymetacaine 0.5% followed by 1 drop of Iodinated Povidone 5% for conjunctival antisepsis. The post-operative drop regime was the same for all patients; 1 drop of Dexamethasone 0.1% 6 times a day for 2 weeks, then 4 times a day for 2 weeks and finally 2 times a day for 2 weeks. Additionally, 1 antibiotic drop of Chloramphenicol 0.5% 4 times a day for 2 weeks.

3.2.5 Statistical Analysis

All data were analysed with SPSS 23.0 (SPSS Inc., Chicago, IL, USA). Data normality was tested using the Shapiro-Wilk test. Therefore, data non-normally distributed were analysed considering the Wilcoxon Signed-Rank test. Using age as a dependent factor, the three groups were compared using a non-parametric Kruskal-Wallis test by ranks and the related post-hoc analysis. Statistical significant difference was set to an alpha of 0.05.

3.3 Results

The VA and refractive outcomes data are summarized in Table 4 and Table 5, including all patients together and the groups divided considering the age. No significant differences were observed considering all patients together. In the age-group classification, the mean CDVA_PRE (before surgery) was slightly better but not significant (p= 0.134) in the older groups (Group 2 and Group 3, Table 4), while UDVA_POST (3 months after surgery) was similar in all the ages considered. Additionally, Table 4 shows the mean UDVA_POST in Group 1 with a significant improvement (p= 0.040), which was not observed in the older groups.

Visual acuity outcomes (mean ± SD, logMAR)				
Parameters	All patients	Group 1 (under 59)	Group 2 (60 to 69)	Group 3 (over 70)
CDVA_PRE (logMAR)	0.05 ± 0.16	0.08 ± 0.18	0.04 ± 0.14	0.04 ± 0.16
UDVA_POST (logMAR)	0.04 ± 0.13	0.03 ± 0.11	0.04 ± 0.13	0.05 ± 0.13
PRE *vs* POST (p-value)	0.713	0.040*	0.952	0.142

Table 4 Visual outcomes data summary before and after surgery. Asterisk denotes a significant difference.

No significant differences between pre-op CDVA and post-op UDVA were observed considering all eyes together. In the age-group classification, the mean SEQ after the surgery (SEQ_POST) was found to be reduced compared to pre-operatively (SEQ_PRE) in all the groups. However, only in Group 3, the reduction was found to be significantly different between the two visits (p= <0.001) (Table 5).

Refractive outcomes (mean ± SD, Diopters)				
Parameters	All patients	Group 1 (under 59)	Group 2 (60 to 69)	Group 3 (over 70)
SEQ_PRE (D)	-0.31 ± 4.00	-0.45 ± 4.34	-0.77 ± 4.12	-0.36 ± 3.54
SEQ_PRE range MIN – MAX (D)	-21.88, +10.63	-16.63, +10.63	-15.25, +9.37	-21.88, + 7.00
SEQ_POST (D)	-0.10 ± 0.40	-0.05 ± 0.37	-0.07 ± 0.39	-0.09 ± 0.44
SEQ_POST range MIN – MAX (D)	-1.88, +1.25	-1.38, +1.25	-1.88, +1.00	-1.75. +1.25
PRE *vs* POST (p-value)	0.132	0.880	0.289	<0.001*
DEV_PPOR (D)	0.02 ± 0.83	0.08 ± 1.69	0.03 ± 0.42	0.06 ± 0.41

Table 5 Refractive outcomes data summary before and after surgery. Asterisk denotes a significant difference.

As shown in the cumulative standardized Waring graphs for VA (2011), a post-operative monocular UDVA of 0 logMAR was achieved in 70%, 65% and 61% of Group 1, Group 2 and Group 3 eyes respectively (Figure 41). All the subjects enrolled in the study (100%) were able to reach 0.3 logMAR after surgery.

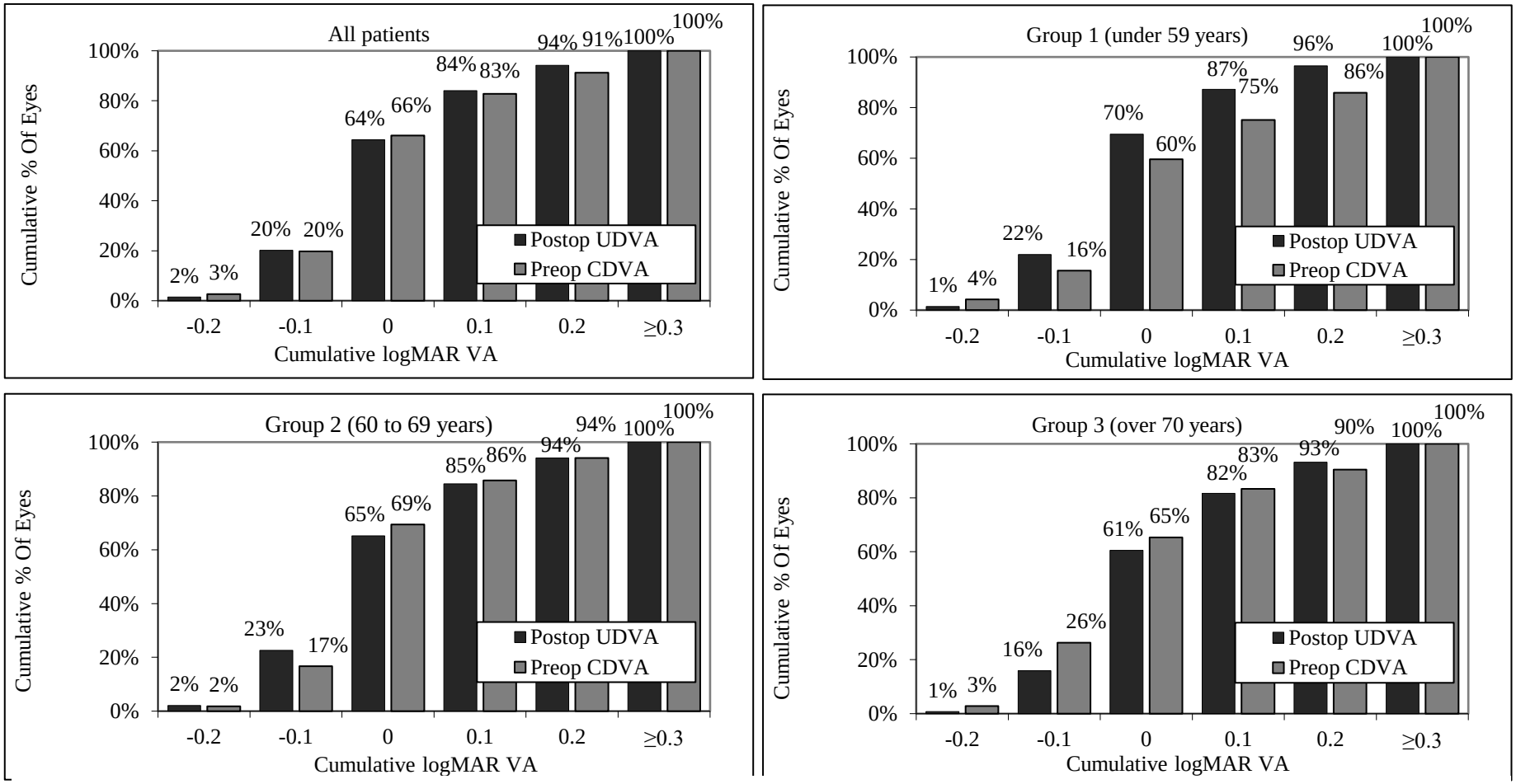

Figure 41 Cumulative pre- and post-operative unaided distance visual acuity (UDVA) and corrected distance visual acuity (CDVA) in all the groups: All patients, Group 1, Group 2, Group 3.

The residual post-operative refractive error represented by the means of the standardized Waring graphs (2011) was within ±0.50 D in 81%, 90%, 86% and 84% in All patients, Group 1, Group 2 and Group 3 respectively. Additionally, the refractive error was within ± 1.00 in 97%, 98%, 99% and 96% in All patients, Group 1, Group 2 and Group 3 respectively (Figure 42).

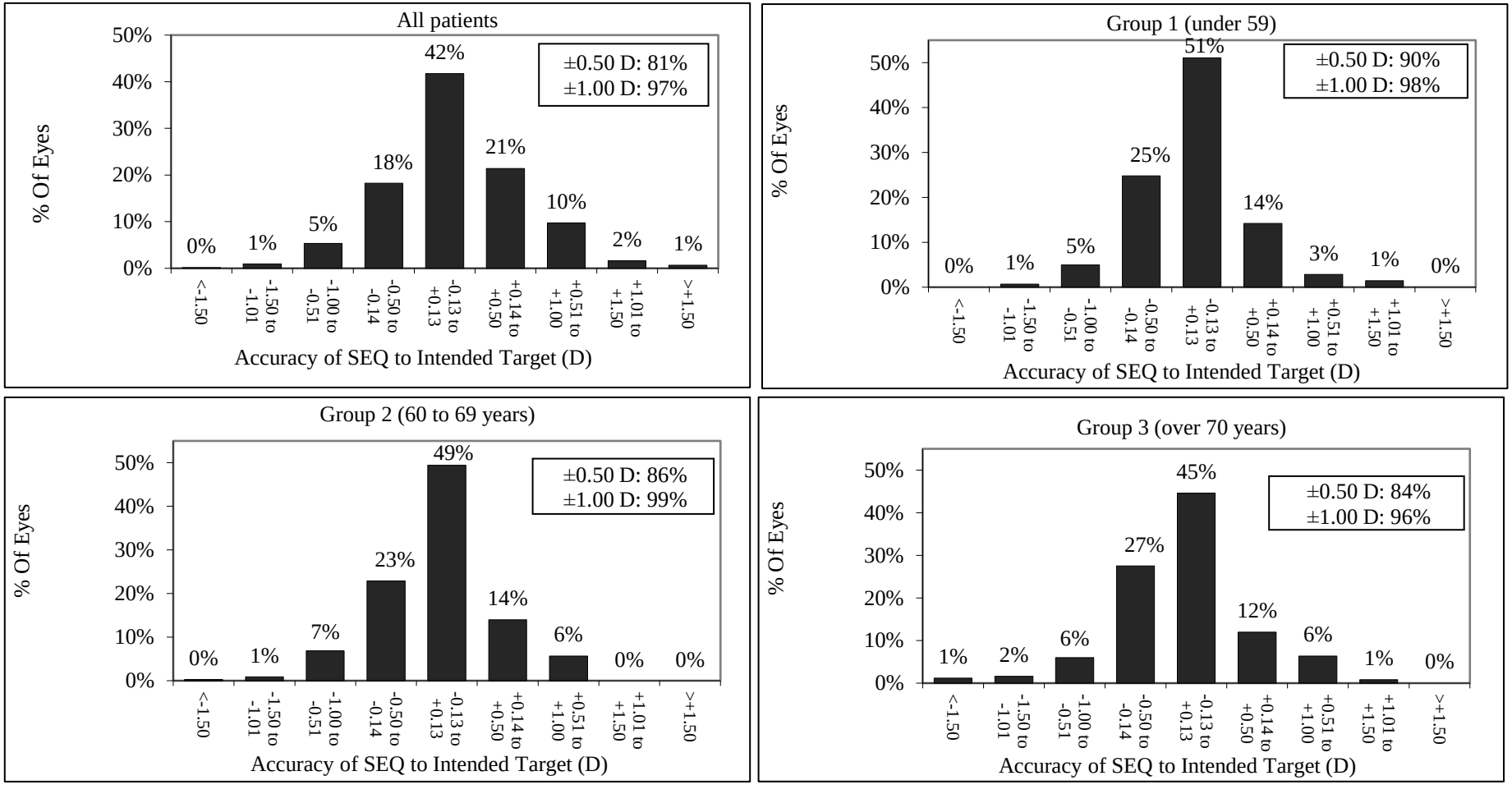

Figure 42 Accuracy of the surgical procedure in terms of residual refraction (SEQ) after surgery in acuity in all the groups: All patients, Group 1, Group 2, Group 3.

In terms of DED subjective assessment, five questions were selected considering vision fluctuations and symptoms based in dryness and watery eyes.

Figure 43 showed the stability of the vision throughout the day (Q 9). The reported trend was congruent across the groups where the younger Group 1 reported better outcomes. In fact, Group 1 had more than half of the patients with favourable findings (53%). In general, less than 10% of the study cohort reported unsatisfactory results for this aspect.

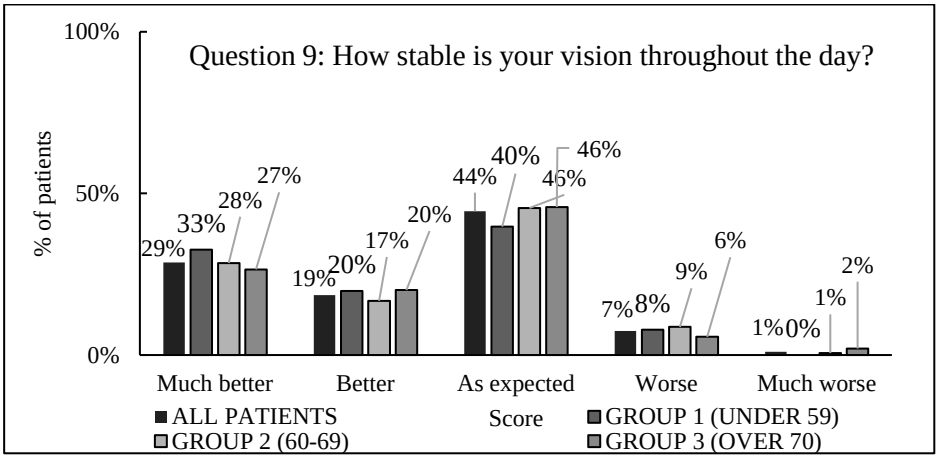

Figure 43 Percentage of scores from All patients, Group 1, Group 2 and Group 3 to the PROMs Question 9 based on vision stability.

In terms of visual fluctuations (Q 10), a large proportion of the patients considered (nearly 60%) did not report any disturbance. However, in most of the cases, if fluctuation was present, the "Evening" was the most common part of the day in which was observed (Figure 44).

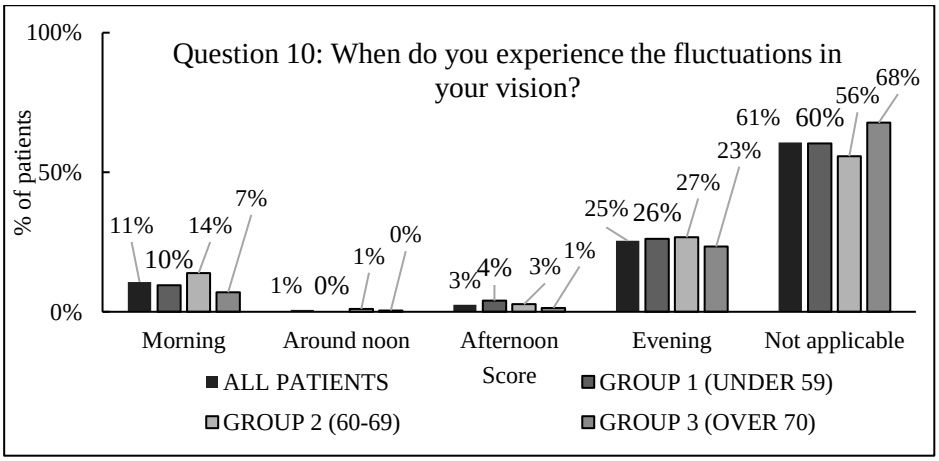

Figure 44 Percentage of scores from All patients, Group 1, Group 2 and Group 3 to the PROMs Question 10 based on the moment of the day where vision instability was experienced.

The issue of having experienced dry eye compared to prior to surgery (Q 20) was reported in half of the All patients, Group 1 and Group 2 while this was less in Group 3. However, the answers were worse in more than 20% of the entire study cohort (Figure 45).

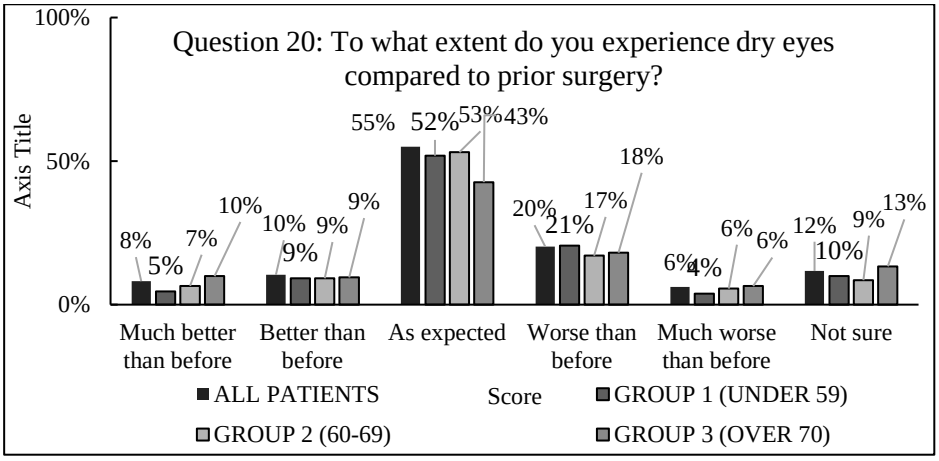

Figure 45 Percentage of scores from All patients, Group 1, Group 2 and Group 3 to the PROMs Question 20 based on the experience of dry eyes compared to before surgery.

The "dryness frequency" (Q 21) in all the groups revealed similar findings with half of the respondents with no dry eye issues experienced during the last month and less than 20% with frequent and constant dry eye (Figure 46).

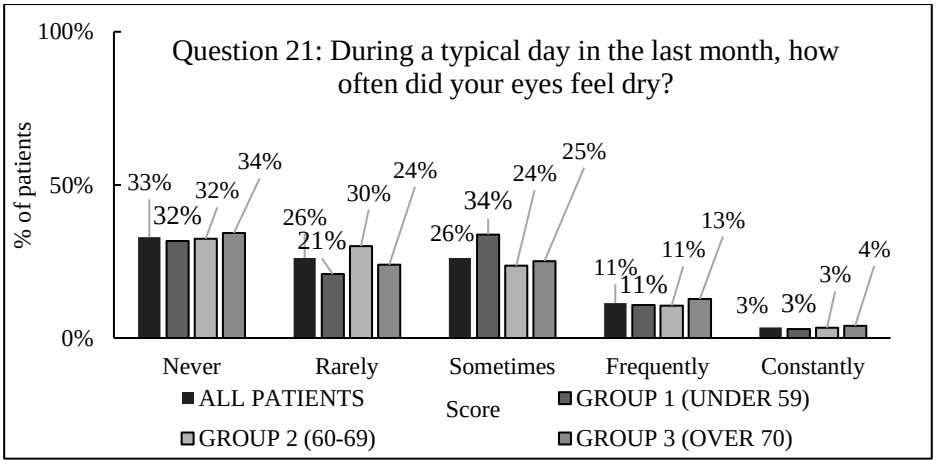

Figure 46 Percentage of scores from All patients, Group 1, Group 2 and Group 3 to the PROMs Question 21 based on the frequency of feeling the eyes dry.

Nearly half of the study groups did not report "watery eyes" (Q 22) whereas less than 30% of the respondents reported this issue from time to time (Figure 47). Using non-parametric analysis of variance, Q22 was the only question found to be statistically different across the groups. However, the percentages from Group 1 (under 59 years) were significantly ($p= 0.041$) reduced compared to Group 3 (over 70 years).

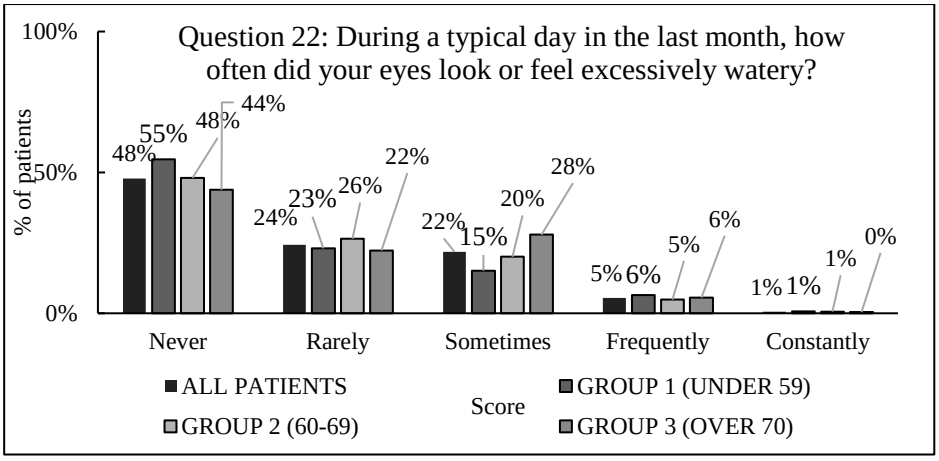

Figure 47 Percentage of scores from All patients, Group 1, Group 2 and Group 3 to the PROMs Question 22 based on the frequency of feeling the eyes "watery".

3.4 Discussion

RLE surgery is a form of elective IOL surgery that has become more popular during recent years (Alio et al., 2014b). Through the implantation of a MFIOL (trifocal, bifocal or EDoF or occasionally monofocal monovision IOLs), patients are able to achieve spectacle independence with excellent visual outcomes for distance, intermediate and near vision. However, newer metrics are needed to evaluate the patient responses after treatment to understand any improvements that can be made by the clinicians, suppliers and by the healthcare providers.

One of the many evaluation tools introduced in healthcare are PROMs that help to evaluate and improve a patient's response to a treatment (Gutacker et al., 2015). Correia et al. (2017) performed a systematic literature review to identify the topics covered by the PROMs questionnaires published up to 2016 in PubMed. Of the 130 ophthalmic PROMs questionnaires considered, only 6% of them were produced to investigate DED while nearly 18% were designed for lens surgery. The discrepancy between these results is remarkable as DED might be experienced after the procedure (Choi et al., 2018; Ipek et al., 2018; Trattler et al., 2017; Xue et al., 2018) but may also exist in those patients attending for lens surgery (Cochener et al., 2018; Gupta et al., 2018).

The TFOS DEWS II report stated that the prevalence in DED increase linearly with age (between 2% and 10.5% by decade) and after 50 years up to 30% worldwide are affected by the condition (Ezuddin et al., 2015). Additionally, as cataract usually develops after the age of 50 years, a link between DED, age and lens surgery could be predictable (Gomes et al., 2017). Most of the DED complications reported due to surgery are experienced in the immediate period after surgery (also known as post-operative DED). These are thought to be due to the effects of the lid speculum, microscope light, topical anaesthesia, drug regime, goblet cells loss, release of tear inflammatory markers, but also the transection of the subbasal corneal nerves due to corneal incision (Cetinkaya et al., 2015; Xue et al., 2018).

The results showed the RLE efficacy in providing an unaided VA equal or better than the corrected acuity prior to the surgery. In fact, as demonstrated by McNeely et al. (2017) and Rosen et al. (2016) through a meta-analysis of studies involving MFIOLs (n= 8,797 eyes), the mean UDVA after surgery was 0.05 ±0.01 logMAR as observed in the current results with 0.04 ± 0.13 logMAR, 0.03 ± 0.11 logMAR, 0.04 ± 0.13 logMAR and 0.05 ±0.13 logMAR in All patients, Group 1, Group 2 and Group 3 respectively. The improvement from CDVA_PRE to UDVA_POST was found to be statistically significant (p= 0.04), although the minimal difference (0.08 ± 0.18 logMAR vs 0.03 ± 0.11 logMAR) translates to less than 3 letters on a VA chart (Oduntan et al., 2009). In terms of residual refraction after surgery, the presented results demonstrated the refractive predictability of the procedures on providing more than 81% of the groups considered (Group 1 n= 141 eyes, Group 2 n= 336 eyes and Group 3 n=251 eyes) were within ±0.50 D of the predicted post-operative refraction as previously observed by Schallhorn et al. (2017b) in similar age-groups (50-54 years, 55-59 years and 60-65 years).

The use of PROMs in lens surgery is a recognized tool to observe and measure the outcomes in health care as perceived by patients (Sparrow et al., 2018). Abetz et al. (2011) set a validated PROMs questionnaire to consider incidence, treatment satisfaction and the burden in DED symptoms. However, despite having prepared the questionnaire to meet FDA requirements, the researchers did not consider DED after IOL surgery using PROMs metrics. In the present study, refractive data and completed PROMs questionnaires from 728 patients were included and then divided into three age-dependant groups previously operated with RLE surgery in a multi-centre setting in a time frame up to 7.5 years. However, for the purpose of this study, the focus of the analysis was on the 5 most relevant questions to determine the impact of DED in the population on an everyday life-basis since this data is currently not available from the published literature.

As recommended in the guidelines entitled "*Patient Information – Refractive Lens Exchange"* published on the official Royal College of Ophthalmologists (RCOphth) website (https://www.rcophth.ac.uk, last accessed on 25 April 2017), it is normal to experience a certain level of fluctuations of vision immediately after RLE procedure during the following weeks (up to 4-6 weeks). The main reason may be associated with the positioning of the MFIOLs in the capsular bag of the crystalline lens, post-operative drugs regime and post-operative DED potentially provoked by the corneal incisions that allow lens implantation (Alio et al., 2014c). In the current study analysis, considering the stability of the vision during the day (Q 9), 92%, 93%, 91% and 93% of All patients, Group 1, Group 2 and Group 3 respectively, answered "Much better than expected", "Better than expected" and "As expected". Consequently, visual performance was reported to be stable throughout the day in the majority of the patients. From the RCOphth guidelines and the current research, it seems reasonable to affirm that RLE surgery could provide stable vision after an initial period of adaptation which was also observed in long-term results.

The vision through a MFIOL could be potentially affected by photic phenomena such as glare and halos (Akella et al., 2018; Kelava et al., 2017; K. H. Kim et al., 2018; Maxwell et al., 2017; S. Y. Wang et al., 2017), influenced by the relationship between the lens geometry (multifocal diffractive or refractive), pupil diameter and consequently by the level of illumination. In all the study groups considered, the relevant fluctuations of vision (Q 10) were experienced in the evening (nearly 25 to 30% of the respondents). Thus, this might suggest that the visual tasks performed in lower levels of illumination (e.g. driving at night, watching television, etc.) have played a role in the answers and may have influenced the results in the study. Additionally, DED which is affected by diurnal variation could have been partly responsible for the negative responses regarding the visual fluctuations experienced in the evening (M. Guillon et al., 2018).

Q 20 examined the proportion of patients who have suffered from DED after the procedure compared with prior to surgery. Considering the sum of "As expected", "Worse than before" and "Much worse than before", DED prevalence was found in 73%, 77%, 76% and 67% in All patients, Group 1, Group 2 and Group 3 respectively. The results presented in the current study have revealed an interesting scenario: firstly, DED is a common condition as previously reported in lens surgery by different authors (Pedrotti et al., 2018; Qin et al., 2018; Xue et al., 2018) including after RLE procedures. Secondly, as one of the most common risk factors in DED development is age, the older group (Group 3) reported the lowest prevalence across the study cohorts; that probably means that Group 3 had already DED before attending the surgery.

Following the recent TFOS DEWS II, the prevalence of the disease was reported from 5 to 50% including symptoms with or without signs (Stapleton et al., 2017). In terms of frequency of feeling the eyes dry, the answers "Sometimes", "Frequently" and "Constantly" were reported in 40%, 48%, 38% and 42% in All patients, Group 1, Group 2 and Group 3 respectively. Thus, based on the epidemiologic studies summarised in TFOS DEWS II, it is not possible to affirm whether the DED prevalence in the current research population was influenced by surgery or by the "normal/expected" prevalence of the condition. However, at the current time, any other validated PROMs questionnaires were found to assess the incidence of DED in the longer term after lens surgery to compare with the results included in this study.

A depleted tear film could be potentially described by a patient as having "watery eyes": the reason behind this assertion is related to the compensatory effect that the ocular surface could demonstrate in the event of tear film instability, especially after lens surgery (Park et al., 2016). In fact, the response from the ocular surface to an unstable tear film is to induce more tear secretion engaging the reflex to the lacrimal gland (Bron et al., 2017). However, the impact of the procedure on corneal sensitivity that promotes tear film secretion, might have generated a reduction in the tear secretion with a potential limitation of the compensation process. In all the groups considered in the current study, the frequency of "watery eyes" (Q 22) has been reported in approximately half of the participants, however not as frequent as reports of dryness (Q 21).

Moreover, as demonstrated by Choi et al. (2018) and by Jung et al. (2016) lens surgery reduces MG expressibility affecting the tear film stability, but because of patients comfort and to keep the evaluation as less as possible invasive, the MG expressibility was not included making impossible further comparison.

3.4.1 Limitations of the Study

Due to the design of the current study, some limitations are acknowledged: firstly, the lack of pre-operative PROMs questionnaires to allow a comparison before and after surgery. Secondly, even if the questionnaire was designed to consider the most important metrics for patients based on the experience of the consultants and clinicians , the use of a validated quality of life instrument, such as the Catquest-9SF instrument or the recent UK developed Cat-PROM5 cataract surgery questionnaires in combination with validated DED questionnaires (e.g. OSDI or DEQ-5) could have added further value (Sparrow et al., 2018). Thirdly, as remarked in the TFOS DEWS II, DED symptomatology is important, but it is not sufficient to diagnose DED without signs (Wolffsohn et al., 2017). Finally, the lack of long terms PROMs questionnaires after RLE procedure makes the comparison between the presented research' results and the available literature difficult.

3.4.2 Conclusion

This is the first study to document the long-terms PROMs data (up to 7 years) in a large study population who had undergone RLE surgery with the implantation of a MFIOL. A significant percentage of the patients reported experiencing "dry eyes" (38%, n= 277) and "watery eyes" (52%, n= 379). RLE was shown to be efficacious in correcting refractive errors and overall satisfaction was very high (Alio et al., 2017; Rosen et al., 2016; Srinivasan et al., 2016). However, despite the link in the literature between age and DED, age was not identified as a relevant risk factor in visual fluctuations and DED in the cohort. Although the results might suggest that the questionnaire provided valuable insights into patients reported outcomes in the longer term after surgery, further research is required to validate the questionnaire tool so that it can be reliably used prospectively to provide a more comprehensive understanding of patients reported outcomes in the short, medium and longer term.

Chapter 4: Pre-operative dry eye signs and symptoms metrics in patients presenting for laser vision correction, cataract and refractive lens exchange (RLE) surgery and its effect on refractive outcomes.

4.1 Introduction

As detailed in section 1.5, different surgical options are nowadays available to safely correct the refractive error and, in case of presence of cataract, to restore the clarity of the crystalline lens due to ageing (Thompson et al., 2015). However, patients and clinicians should be aware of any ocular surface disturbances (e.g. DED) before attending a surgical procedure. In the development of DED, the most recognised risk factors are age, gender and race but also ocular surgeries such as corneal refractive and lens surgery were mentioned (Pult, 2018; Rico-Del-Viejo et al., 2018; Song et al., 2018; C. Sun et al., 2013; Sutu et al., 2016; Toda, 2018; Xue et al., 2018). The reasons for which ocular surgeries could potentially increase DED prevalence are related to intraoperative factors such as corneal incisions (Vestergaard, 2014), irrigation of the ocular surface (Sahu et al., 2015), microscope light (Y. Cho et al., 2009; Ipek et al., 2018), elevation of the inflammatory response in the tear film and also topical medications prescribed after surgery (Wilson et al., 2015). However, a consensus has not yet been reached on which type of traditional corneal refractive surgery has the greatest impact on the ocular surface (Bower et al., 2015; S. Lee et al., 2006; Rodriguez et al., 2007; Salomao et al., 2009; Z Shen et al., 2016b; Tanbakouee et al., 2016; Toda et al., 2002a; Yu et al., 2000) (Table 6). Recent technology advances in corneal refractive surgery have been implemented with a "flap-less" technique called small SMILE (see section 1.5.1.1.6) using a femtosecond laser. The results in terms of ocular surface and DED prevalence seem to be promising with better values in Schirmer test, TBUT, corneal sensitivity and corneal nerve regeneration but further research is needed to confirm the findings (Ganesh et al., 2018a; He et al., 2015; Recchioni et al., 2017; Sekundo et al., 2011). In terms of lens surgery, there is a significant proportion of the adult population aged 50 years or older who need to undergo cataract surgery or may want to be more spectacle-independent and are considering refractive lens exchange (RLE) surgery (Alio et al., 2017; Ezuddin et al., 2015). As previously mentioned, one of the risk factors in developing DED is age, thus in patients older than 50 years, a pre-operative examination can rule out the presence of DED and reduce the chance of errors in ocular biometry that will directly affect the refractive and visual outcomes (Cochener et al., 2018; Gupta et al., 2018; Olsen, 2007).

Authors, Year	Type of Surgery	Number of eyes	Age (mean ± SD)	Male (M)/ Female (F)	DED test	Results
Yu et al., 2000	LASIK	96 eyes	(31 ± NA)	21 M/38 F	Schirmer, basal tear value, TBUT	DED prevalence 1 day after 94.8%, 1 week after 85.4%, 1 month after 59.4%
Toda et al., 2002	LASIK	543 eyes	(33,1 ± NA)	223 F	Schirmer with anesthesia, TBUT, fluorescein and Rose Bengal staining, corneal sensitivity	Schirmer and TBUT decreased after surgery, ocular staining increased after surgery, corneal sensitivity recovered within 3 to 6 month after surgery
Lee et al., 2006	LASIK and LASEK	56 eyes LASIK, 52 eyes LASEK	(28.3 ± 4.2) LASIK (30.9 ± 4.5) LASEK	Not specified	Corneal sensitivity, TBUT, Schirmer, Confocal Microscopy	Corneal sensitivity: LASIK decreased at 6 months after surgery *vs* baseline, LASEK no differences. TBUT: LASIK decreased 3 and 6 months after surgery *vs* baseline. LASEK reduction over time. Schirmer: LASIK decrease at 3 months then recover to baseline at 6 months. Confocal microscopy: corneal nerve regeneration faster with LASEK
Rodriguez et al., 2007	FS-LASIK and manual microkeratome (MM)	34 eyes FS, 30 eyes MM	(38 ± 10) FS (33 ± 8) MM	20 M /14 F FS 12 M/18 F MM	Impression cytology	Goblet cell density: FS-LASIK higher decrease up to 6 months compared to MM-LASIK
Solomão et al., 2009	FS-LASIK and MM-LASIK	113 eyes FS, 70 eyes MM	(43 ± NA) FS (45 ± NA) MM	60 M/53 F FS 38 M/32 F MM	Punctate epithelial erosion scores and Dry Eye symptomatology	Lower punctate epithelial erosion scores in FS group than MM group 13% DED symptomatic FS group 41% DED symptomatic MM-LASIK group
Bower et al., 2015	LASIK and PRK	143 73 PRK, 70 LASIK	(29.9 ± 5.2) Total	39 M/34 F PRK 35 M/35 F LASIK	Schirmer test, TBUT, Rose Bengal staining	Symptoms higher on both PRK and LASIK up to 1 year; Schirmer test lower at 1 and 3 months after PRK; TBUT reduced a 1, 3 and 12 months after LASIK; Rose Bengal staining increased on both surgery but significant in PRK only after 3 months while LASIK in all post-op follow-up
Tanbakouee et al., 2016	PRK	76 eyes Low Schirmer value group (LSV): 36 eyes Normal Schirmer value group (NSV): 40 eyes	LSV 26.19 ± 3.79 NSV 27.82 ± 3.42	26 M/14 F LSV 20 M/16 F NSV	Schirmer test, TBUT, OSDI Score	3-months after surgery: significant Schirmer and TBUT test decreases in both groups. OSDI score no significant changes in both groups after surgery

Table 6 Summary of the studies about the impact of corneal refractive surgery over the ocular surface (data from 2000 up to 2016).

In recent years, clinicians and researchers have tried to improve DED diagnosis following the suggestions from the recent TFOS DEWS II report including subjective validated questionnaires and minimally invasive tests evidence-based (Wolffsohn et al., 2017). Different DED studies in prevalence and health-related QoL have remarked on the importance of assessing symptomatology using validated questionnaires such as the OSDI questionnaire (Hashemi et al., 2014; Malet et al., 2014). Pult et al. (2009; 2011) have previously shown in a healthy population and in contact lens wearers that OSDI moderately correlates with other DED signs (e.g. TMH, NIBUT, etc.) and other authors have remarked on its importance in screening the symptomatology before and after laser vision correction surgery (Beheshtnejad et al., 2015; Denoyer et al., 2015; Hays et al., 2017). OSDI is also a reliable way to assess DED symptomatology in lens surgery (Szakats et al., 2017; Xue et al., 2018).

As with symptomatology, DED signs assessment could play a crucial role in challenging the condition. Recently, tear film osmolarity has been recommended to be the *"single best metric to diagnose and classify"* DED (Wolffsohn et al., 2017). The introduction of the TearLab® Osmolarity System has improved the analysis of the tear film composition. Tomlinson et al. (2010) found the device clinically applicable to measure tear film osmolarity in DED and non-DED patients and in correlation with other similar devices. Although, as suggested in section 1.4.4.2.4.1, Szczesna-Iskander (2016) reported that clinical reliability with TearLab® is achievable with at least three consecutive measurements with a considerable waste of resources for a single test (e.g. high cost for each microchip). In terms of ocular surgery, tear film osmolarity was implemented in laser vision correction surgery and in cataract surgery. Sauvageot et al. (2017) have considered tear film osmolarity to compare the ocular surface in patients who underwent femtosecond laser-assisted LASIK or PRK where Gonzalez-Mesa et al. (2016) had considered it in cataract surgery reporting its clinical acceptance in the surgical field.

TMH can be assessed using an innovative source of illuminations (e.g. infrared) which can be assessed non-invasively by the means of a K5M. A study by Tian et al. (2016) reported its clinical repeatability and reproducibility, but the reliability of TMH measurements was lower in DED patients.

The stability of the tear film is considered a quality metric of the tear film as it is able to establish its resistance to evaporation (Craig et al., 2017b). One of the most performed tests is TBUT, but the preference would be without the use of any vital dyes (non-invasive BUT or NIBUT) (Bhandari et al., 2016). K5M can capture objective non-invasive ruptures of the tear film (NIKBUT) using infrared light with minimal impact on reflex tearing (Tian et al., 2016). However, different studies have shown that K5M does not compare favourably with other similar instruments (R. Lee et al., 2016a) or with other DED metrics (Abdelfattah et al., 2015).

Nonetheless, due to its ease of use, it is still considered one of the most powerful devices in DED assessment nowadays in the market (X. Wang et al., 2016).

The aim of the present work was to consider a pre-operative series of DED tests recommended by the recent TFOS DEWS II report such as OSDI, NIKBUT, TMH and tear film osmolarity to determine their correlation with the post-operative refractive and visual outcomes (UDVA, CDVA, SEQ and DEV_PPOR) after laser vision correction and lens surgery in a selected group of patients attending a real hospital settings. Additionally, to assess if those DED tests could be potentially considered as predicting factors with the post-operative refractive and visual outcomes.

4.2 Methods

4.2.1 Study design

The research is a prospective, longitudinal and observational study that has received a favourable opinion from the Aston University Research Ethics Committee.

4.2.2 Subjects

All subjects that were enrolled in the study were divided into groups considering the type of eye surgery that was performed: laser vision correction (LVC), cataract and RLE surgery. The LVC group was composed of 31 eyes of 31 subjects (15 males and 16 females) with the age ranged between 21 to 49 years (mean 31.4 ± 9.4 years). The cataract group was composed of 25 eyes of 25 subjects (8 males and 17 females) with the age ranged between 32 to 82 years (mean: 67.0 ± 12.2 years). The RLE group was composed of 44 eyes of 44 subjects (19 males and 25 females) with the age ranged between 47 and 71 years (mean: 58.6 ± 6.0 years). The eye with better visual VA or the dominant eye assessed considering motor dominance and sensory dominance tests in case of equal VA, was chosen for evaluation. in the study. The inclusion and exclusion criteria, ethics permissions, clinical and dry eye assessment for the study are detailed in Chapter 2. However, for the purpose of this study, the optometrist collected the outcomes measured including UDVA, CDVA and SEQ calculated considering the subjective refraction. DEV_PPOR was calculated considering the SEQ 1-month after surgery and the planned plano refraction (0 Diopters) for all patients. The dry eye assessment was performed by AR considering the following metrics: the subjective responses were considered with OSDI questionnaire and tear film osmolarity was collected using the TearLab® Osmolarity System. TMH and NIKBUT were measured using a K5M.

4.2.3 Surgery

All the surgeries were successfully performed by a team of experienced surgeons (I.M., M.W., N.G., S.K., S.M., S.S.). A pre-operative disinfection of the external part of the eye and anexa

using 5% povidone-iodine 1 hour prior to surgery was carried out in all the eye surgeries considered in the study.

4.2.3.1 LVC surgery

In the LVC surgery group, all the flaps were created using the VisuMax femtosecond laser (Carl Zeiss Meditec AG, Jena, Germany) platform set to a 500-kHz frequency. The diameter of the flaps was 8.5 mm with the hinge position and the side-cut angle at 90 degrees. The average flap thickness was approximately 90 to 100 microns. The stromal ablation was performed with the MEL 90 excimer laser platform (Carl Zeiss Meditec AG, Jena, Germany) using the Triple-A Advanced Ablation Algorithm to reach a high degree of precision and predictability with a 250-Hz pulse rate. The optical zone was 6.5 mm for all the candidates. All the surgeries started with topical anaesthesia with 2 drops of Proxymetacaine 0.5% followed by 1 drop of Diclofenac Sodium 0.1% to control ocular pain associated with epithelial defects. After surgery, patients were issued with Dexamethasone 0.1% and Ofloxacin 3mg/ml. Instructions for both sets of drops were 1 drop to be used 4 times per day for 7 days. If required, patients could make use of Paracetamol tablets: 2 every 4 to 6 hours for 2 days only.

4.2.3.2 Cataract and RLE surgeries

The cataract and RLE surgery procedures were performed with a 2.8 to 3.0 mm self-sealing corneal incision. Thereafter, a continuous curvilinear capsulorhexis was chosen to allow the breaking of the cortical portion of the lens via phacoemulsification. Finally, automated aspiration of the lens was undertaken to remove any remaining debris of the crystalline lens. The cataract group was implanted with the AMO Tecnis PCB00 (Abbott Medical Optics, Santa Ana, CA, USA) monofocal intra-ocular lens while the RLE group was implanted with the Zeiss AT Lisa tri839MP (Carl Zeiss Meditec, Jena, Germany) multifocal intra-ocular lens. All the cataract and RLE surgeries started with 1 drop of Phenylephrine 2.5%, 1 drop of Diclofenac Sodium 0.1% and 1 drop of Cyclopentolate Hydrochloride 1%. All the drops were instilled three times in a time interval of 10 minutes (e.g. first dose 8:00 AM, second dose 08:10 AM and so on). Thereafter, topical anaesthesia was instilled: 1 drop of Proxymetacaine 0.5% followed by 1 drop of Iodinated Povidone 5% for conjunctival antisepsis. The post-operative drop regime was the same for all patients: 1 drop of Dexamethasone 0.1% 6 times a day for 2 weeks, then 4 times a day for 2 weeks and finally 2 times a day for 2 weeks. Additionally, 1 antibiotic drop of Chloramphenicol 0.5% 4 times a day for 2 weeks.

4.2.4 Statistical Analysis

All statistical analysis was performed using SPSS 23.0 (SPSS Inc., Chicago, IL, USA). Data normality was tested using the Shapiro-Wilk test. The minimum sample size required for the study was 15 eyes of 15 patients in each type of surgery group (LVC, cataract and RLE) before

and 1month after surgery assuming a normal distribution with a level of statistical significance of 5% (α= 0.05) and a statistical power of 80% (1-β= 0.8). Nevertheless, a total of 100 eyes from 100 patients were recruited between the groups to allow for approx. a 30% drop-out rate.

To assess the changes in the refractive and visual outcomes, the normality was tested between pre- and post-operative UDVA, CDVA, SEQ and DEV_PPOR. If the data were normally distributed, a *t*-test was performed while if not a non-parametric test such the Wilcoxon Signed Rank Test was considered.

To perform the bivariate correlation analysis between the pre-operative DED metrics (OSDI, osmolarity, TMH and NIKBUT) and the post-operative refractive and visual outcomes metrics (UDVA, CDVA, SEQ and DEV_PPOR), data resulting as normally distributed (Shapiro-Wilk test >0.05) were analysed using the Pearson's test where data not normally distributed (Shapiro-Wilk test <0.05) were analysed using the Spearman's test.

4.3 Results

4.3.1 Refractive and visual outcomes

The changes in visual metrics such as UDVA, CDVA and SEQ before and after surgery are summarized in Table 7. A significant improvement was found when UDVA in the RLE group was compared before and 1 month after surgery (p-value = <0.001). CDVA in the cataract group showed a significant improvement between the follow-up (p-value = 0.003). The rest of the visual metrics considered were found not significant in comparison pre- *vs* post-surgery (p-value > 0.05).

UDVA (logMAR)	PRE	POST 1 month	p-value
LVC	0.73 ± 0.34	0.01 ± 0.18	0.068
RLE	0.41 ± 0.30	0.05 ± 0.11	<0.001*
CDVA (logMAR)	PRE	POST 1 month	p-value
Cataract	0.30 ± 0.29	0.05 ± 0.13	0.003*
SEQ (Diopters)	PRE	POST 1 month	p-value
LVC	-2.61 ± 3.27	-0.11 ± 0.45	0.051
Cataract	-0.45 ± 5.54	-0.19 ± 0.78	0.384
RLE	-0.57 ± 4.02	-0.15 ± 0.52	0.462

Table 7 Refractive and visual outcomes data summary before and after surgery. Unaided distance visual acuity (UDVA), pre-surgery (PRE), post-surgery (POST), laser vision correction (LVC, refractive lens exchange (RLE), corrected distance visual acuity (CDVA).

Only the significant correlations were summarized in Table 8, Table 9, Table 10. For the LVC and RLE groups, UDVA was considered as wherein the cataract group CDVA was taken into account.

4.3.2 Correlations in the LVC group

Pearson correlation analysis between UDVA after surgery and OSDI before surgery showed a strong positive association (r = 0.710, p= 0.021). Similar results were observed for Pearson correlation analysis between DEV_PPOR and OSDI before surgery with significant correlation observed (r = 0.700, p= 0.036). Osmolarity values before surgery showed a negative weak association with the tear meniscus height (r = -0.365, p= 0.043) (Table 8).

LVC GROUP								
Pearson's correlation coefficient		UDVA_1M_LVC	SEQ_1M_LVC	DEV_PPPOR_1M_LVC	OSDI_PRE_LVC	NIKBUT_PRE_LVC	TMH_PRE_LVC	OSMO_PRE_LVC
UDVA_1M_LVC	Correlation Coefficient	1	-0.853	0.909	0.710	-0.124	0.183	0.396
	Sig. (2-tailed)		0.003*	0.001*	0.021*	0.751	0.613	0.257
DEV_PPOR_1M_LVC	Correlation Coefficient	0.909	-0.826	1	0.700	-0.083	0.217	0.098
	Sig. (2-tailed)	0.001*	0.006*		0.036*	0.833	0.574	0.801
OSMO_PRE_LVC	Correlation Coefficient	0.396	-0.544	0.098	-0.183	-0.347	-0.365	1
	Sig. (2-tailed)	0.257	0.130	0.801	0.323	0.070	0.043*	

Table 8 Correlations observed in the LVC group: unaided distance visual acuity (UDVA), corrected distance visual acuity (CDVA), spherical equivalent refraction (SEQ), deviation from predicted post-operative refraction (DEV_PPOR), ocular surface disease index (OSDI), tear film osmolarity (OSMO), tear meniscus height (TMH), non-invasive Keratograph break-up time (NIKBUT). Asterisk denotes a significant correlation.

4.3.3 Correlations in the cataract group

Pearson correlation analysis performed between the variables considered showed a moderate positive relationship (r = 0.614, p= 0.009) only between CDVA after surgery and the pre-operative OSDI scores before (Table 9).

CATARACT GROUP								
Pearson's correlation coefficient		UDVA_1M_ Cataract	SEQ_1M_ Cataract	DEV_PPPOR_1M_ Cataract	OSDI_PRE_ Cataract	NIKBUT_PRE_ Cataract	TMH_PRE_ Cataract	OSMO_PRE_ Cataract
CDVA_1M_CAT	Correlation Coefficient	1	0.089	-0.080	0.614	-0.273	0.233	-0.219
	Sig. (2-tailed)		0.733	0.759	0.009*	0.306	0.368	0.433

Table 9 Correlations observed in the Cataract group: unaided distance visual acuity (UDVA), corrected distance visual acuity (CDVA), spherical equivalent refraction (SEQ), deviation from predicted post-operative refraction (DEV_PPOR), ocular surface disease index (OSDI), tear film osmolarity (OSMO), tear meniscus height (TMH), non-invasive Keratograph break-up time (NIKBUT). Asterisk denotes a significant correlation.

4.3.4 Correlations in the RLE group

Pearson correlation analysis between post-operative SEQ and pre-operative TMH showed a moderate negative association (r = -0.604, p= 0.003). Additionally, post-operative UDVA showed a significant correlation with TMH before surgery (r = 0.553, p= 0.008). Correlation analysis between UDVA after and OSDI before surgery showed a weak positive relationship (r = 0.447, p= 0.042) (Table 10).

RLE GROUP								
Pearson's correlation coefficient		SEQ_1M_RLE	NIKBUT_PRE_ RLE	UDVA_1M_ RLE	DEV_PPOR_1M_ RLE	OSDI_PRE_ _RLE	TMH_PRE_ RLE	OSMO_PRE_RLE
SEQ_1M_RLE	Correlation Coefficient	1	0.092	-0.567	-0.298	0.057	-0.604	-0.286
	Sig. (2-tailed)		0.693	0.006*	0.179	0.807	0.003*	0.322
UDVA_1M_RLE	Correlation Coefficient	-0.567	-0.202	1	0.536	0.447	0.553	0.161
	Sig. (2-tailed)	0.006*	0.381		0.010*	0.042*	0.008	0.582

Table 10 Correlations observed in the RLE group: unaided distance visual acuity (UDVA), corrected distance visual acuity (CDVA), spherical equivalent refraction (SEQ), deviation from predicted post-operative refraction (DEV_PPOR), ocular surface disease index (OSDI), tear film osmolarity (OSMO), tear meniscus height (TMH), non-invasive Keratograph break-up time (NIKBUT). Asterisk denotes a significant correlation

4.4 Discussion

During the management of different eye conditions such as age-related macular degeneration or diabetic retinopathy, it is common to predict visual outcomes considering other related metrics (e.g. retinal thickness acquired with OCT) (Keane et al., 2008). In lens surgery, the biomechanical properties of the cornea have been considered to predict the refractive outcomes: the corneal hysteresis (e.g. the ability of corneal tissue to absorb and dissipate energy during an applanation process) was found by Denoyer et al. (2013) as a predicting factor for inducing iatrogenic corneal astigmatism that could limit the expected visual outcomes. Before surgery, DED assessment can be performed and potentially considered to anticipate refractive and visual outcomes after treatment. Different studies have compared changes in DED and refractive metrics before and after surgery (Cetinkaya et al., 2015; Garcia-Zalisnak et al., 2014; Gibbons et al., 2016; Schallhorn et al., 2017b; Toda, 2018). Chuang et al. (2017) revised 16 papers, 6 of these were randomized controlled trials related to ocular surface and cataract surgery. The authors reported that a large proportion (approximately 60%) of those patients were asymptomatic before surgery but 87% of them started to suffer from DED after cataract surgery, with half of them showing ocular signs (e.g. corneal staining). Different studies have shown the impact of DED on vision considering tasks connected to the quality of life such as reading, driving, working and social activities (M. Li et al., 2012; Miljanović et al., 2007). As DED prevalence is increasing, with a peak in the aging population (>60 years) up to 73.5% (M. Uchino et al., 2006), it is important to understand each point of view in DED assessment and to establish a clinical validated routine, especially in potential candidates for eye surgery (Kanellopoulos et al., 2016). However, in the literature at the current date there are no studies which compare the relationship between the pre-operative DED assessment recommended by recent TFOS DEWS II report (symptoms plus signs) and the post-operative refractive and visual outcomes provided by laser vision correction, cataract and RLE surgery.

In terms of refractive and visual outcomes, all the surgeries considered in the study were found to be safe and effective in correcting the refractive errors in order to give patients a satisfactory level of VA after treatment (Table 7).

Despite the progress made in DED research in the last decades, patients symptomatology is not always in agreement with the signs in DED diagnosis (K. Nichols et al., 2004b). The lack of agreement could reduce the chance of a proper DED diagnosis and increase the difficulties in challenging the DED burden in our society in terms of economic and humanistic aspects (McDonald et al., 2016). In the current study, symptomatology was assessed using the OSDI questionnaire which is able to define vision-related function and discomfort in normal and DED patients as validated by Schiffman et al. (2000). In the study cohorts considered, the mean pre-operative OSDI scores were 10 ± 4, 37 ± 7 and 14 ± 4 in the LVC, Cataract and RLE groups

respectively. These values reflect the higher prevalence of DED symptomatology in the older population (e.g. younger group LVC; older groups cataract and RLE) as age is defined as a consistent and non-modifiable DED risk factor (Stapleton et al., 2017). However, it may be worth mentioning that results of the OSDI questionnaires administered to cataract patients may have skewed towards higher symptomatology values compared to the other groups because of the visual disturbance attributable to the lens opacification before the surgery. In fact, the OSDI questionnaire has half of the questions proposed (6 out of 12) which are based on vision-related functions, that cataracts can directly affect (Ni et al., 2015). In a study by Gupta et al. (2018), the researchers reported that 54% of the study cohort (69.5 ± 8.4 years) presenting for cataract surgery evaluation had abnormal symptoms (OSDI and Symptoms Assessment in Dry Eye (SANDE) questionnaire). Considering the presented results and assuming the proposed cut-off in discriminating patients with positive DED symptomatology (e.g. OSDI score ≥ 13, (Schiffman et al., 2000)), both lens surgery groups (cataract and RLE) reported positive DED symptoms. In the cataract group, the oldest cohort in the present study with a mean age of 67.0 ± 12.2 years, the pre-operative prevalence in symptoms was 84% (21 out of 25 subjects), where 68% (30 out of 44 subjects) in the RLE group with a mean age of 58.6 ± 6.0 years. Cochener et al. (2018) using the SPEED questionnaire score reported 45% of patients (69.0 ± 10.68 years) attending to cataract surgery had positive symptomatology findings where Murali (2017) reported abnormal McMonnies questionnaire scores (>10) in 37.8% of a rural cohort attending cataract surgery. However, the researcher did not include the age of the subjects enrolled. In terms of correlation, the current findings revealed that the overall DED symptomatology before surgery had a significant correlation with post-operative VA metrics in all the groups. Therefore, a postulation was done: the lower the pre-operative symptomatology scores, the higher the post-operative VA (skewed to more negative logMAR values). Thus, in the LVC group the positive correlation found between the post-operative UDVA and the pre-operative OSDI scores has supported this initial assumption. Additionally, it was expected that the higher the OSDI scores, the higher the deviation from the predicted post-operative refraction after surgery. In fact, in this cohort, the pre-operative OSDI scores were predictive of better refractive outcomes in terms of post-operative refractive errors and VA after LVC surgery. The current results are in agreement with Albietz et al. (2002) where the authors, considering LASIK for hyperopia, found a refractive regression of 1.00 D or more associated with DED symptomatology before surgery. However, Toda et al. (2002a) found no significant pre-operative differences in visual metrics in 543 patients with and without DED. The post-operative refractive outcomes after 3 months had more SEQ deviation (-0.25 ± 0.76 Diopters) in the DED group than the non-DED group (0.01 ± 0.55 Diopters) respectively. As previously mentioned, the visual disturbance produced by lens opacification can potentially affect VA, contrast sensitivity and can often generate glare (Shandiz et al., 2011). In addition, DED visual fluctuations may be added to lens opacification complaints

that vary during the day and negatively affect patients' quality of life (Carter, 1994; M. Li et al., 2012). As observed previously in the LVC group and also in the cataract group, the moderate but significant correlation between CDVA after surgery and the DED symptomatology before surgery, supported the current research hypothesis formulated for the LVC group: the lower the symptomatology scores before, the higher the logMAR VA after surgery (skewed to negative values). However, a comparison with other studies was not possible due to lack of similar research.

Tear film osmolarity has received a progressive interest in the last years (Sullivan et al., 2014; Sullivan et al., 2010). However, there is a limited number of research published in the pre-operative assessment of tear osmolarity: in a study cohort of Gupta et al. (2018) up to 57% had abnormal osmolarity findings, where 81% of the asymptomatic patients undergoing cataract surgery were found with hyperosmolarity (mOsm/L > 307) (Sullivan et al., 2010). In a study by Epitropoulos et al. (2015), the investigators suggested to include the measurement of tear film osmolarity before surgery to reduce the implication of DED in the refractive outcomes after surgery: in fact, the variability on the keratometric readings was affected in the hyperosmolar group with an unexpected refractive error up to 0.50 D in the calculation of the final IOL. In the study cohort of the present study, osmolarity has been found higher than the TFOS DEWS II recommended cut-off (e.g. ≥308 mOsm/L) in 3%, 28% and 14% in LVC, cataract and RLE groups respectively, suggesting that age (cataract group is the oldest group) could be responsible for the "saltiness" of the tear film. Correlating the results from osmolarity and TMH in the current study, the hypothesis was that in case of increased osmolarity values (indicating the presence of DED-related inflammation), the tear fluid secretion might be reduced. The findings presented in this research are in agreement with Garcia-Resua et al. (2014b) where the authors tested 177 patients using McMonnies questionnaire, OSDI score and tear osmolarity and slit-lamp for acquiring TMH. A similar correlation was found by Glasson et al. (2003) where the authors measured tear osmolality (milliosmoles per kilogram) instead of osmolarity (milliosmoles per litre) and then related the values with the tear meniscus acquired using the specular reflection performed by a slit lamp beam angled at 45°. However, in this clinical setting, TMH measurements were captured using the K5M infrared light that is non-invasive, reliable and correlates with other DED tests (e.g. TBUT, Schirmer test I) (K. Lee et al., 2017; Wei et al., 2016).

Tear film osmolarity may induce a depleted tear film with recurrent negative influence over the stability of the tear film (Baudouin et al., 2018; McMonnies, 2018; Tong et al., 2018b) (see section 1.4.4.2.4.1). Nowadays, new technologies allow measuring with more reliability and less variability the stability of the tear film avoiding the use of vital dyes or making contact with the eye (Tian et al., 2016). In the diagnostic test battery considered in the current thesis, due to

its validity, NIKBUT measured with the K5M was included because of its celerity in analysing the tear film stability (Abdelfattah et al., 2015). Following the PHACO Study (Trattler et al., 2017), one of the first multicenter studies based on ocular surface metrics before cataract surgery, DED prevalence in the older population (mean age 70.7 years) was detected in 60% of the total number of subjects enrolled (143 patients, 286 eyes). In fact, a considerable part of the patients (62.9%) had TBUT $\leq$ 5 s, 77% corneal staining and 18% had a Schirmer test with anaesthesia below 5 mm. The cataract group NIKBUT results (n=25 eyes) returned different findings compared to Trattler et al.: 26% of Cataract cohort had a tear film stability measured with K5M below 5 s, 52% of the total between 5 and 10 s and only 21% of the total above 10 s. However, considering the sum of all the percentages below 10 seconds, the results showed that 78% of the total eyes had one sign of DED. The cataract group could be potentially diagnosed as a DED group before the surgery, in fact, the findings revealed mean value below 10 s (NIKBUT_PRE_CAT mean 8.28 ± 1.18 s) (Wolffsohn et al., 2017). Nevertheless, even in these patients, cataract surgery has shown good visual results in the selected study population (CDVA before surgery 0.30 ± 0.29 logMAR *vs* CDVA after surgery 0.05 ± 0.13 logMAR).

K5M is able to produce reliable measurements of TMH in DED but not as reliable as in normal populations (Tian et al., 2016). Considering the suggested cut-off between healthy and DED patients (Wolffsohn et al., 2017), values below 0.20 mm in the height of the tear meniscus were calculated: 16%, 12% and 9% of LVC, cataract and RLE group respectively were found with values below 0.20 mm. However, as remarked by Doughty et al. (2002), there are several views in defining normal TMH values. The results of the current research showed an average TMH of 0.31 ± 0.15 mm, 0.27 ± 0.10 mm and 0.30 ± 0.10 mm in LVC, Cataract and RLE groups which are higher than the proposed healthy TMH value observed with a K5M by Tian et al. (2016). However, one potential limitation observed in the measurements was due to the shape of the inferior eyelid, especially in older subjects. In fact, the laxity of the eyelids tissue is a common finding that potentially can increase the variability in determining TMH (Salvi et al., 2006) (Figure 48). The RLE group showed a significant negative correlation between TMH and SEQ. Thus, it might be possible to consider TMH as a predicting factor in the post-operative refractive outcomes in the current study cohort but it should be taken into account the eyelid margin shape. In fact, one hypothesis was that the higher the tear film availability (in terms of quantity), the reduced refractive error after the surgery (Table 10). However, a comparison with other studies was not possible due to the limited availability of RLE surgery studies in the current literature where a TFOS DEWS II diagnostic test battery-like before the surgery was considered.

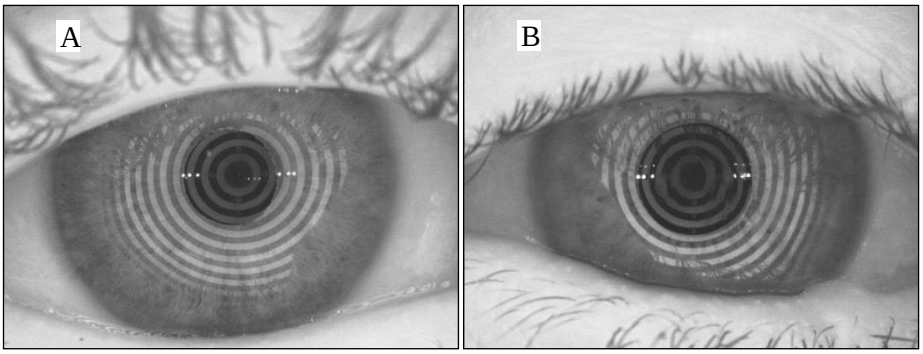

Figure 48 Inferior eyelid margin in a young subject (A) and in an elderly subject (B). Pictures assessed with infrared illumination by the means of Oculus K5M.

4.5 Limitations of the Study

One limitation of this study is the lack of age and gender-matched controls to avoid influence in DED prevalence as already observed in older and female participants (Stapleton et al., 2017). Additionally, the limited study follow-up (up to 1 month) did not allow to understand if the post-operative refractive outcomes and the DED metrics considered would improve over time.

4.6 Conclusion

To our knowledge, this was the first study to correlate pre-operative DED metrics with post-operative refractive results in a real hospital setting considering the recommended diagnostic battery from the TFOS DEWS II report. Despite the increasing importance for including tear osmolarity in research and in clinical settings, the current study revealed no correlation with the refractive outcomes. However, the observed reduction in the volume of the tear film (TMH) could have potentially led to hyperosmolarity (and vice versa). The current findings have suggested that a reduced pre-operative tear film volume and increased DED symptoms could potentially lead to less accurate refractive and visual outcomes. Therefore, it is recommended to test TMH and DED symptomatology and where needed to treat DED patients prior to laser vision correction or lens surgery to avoid any undesirable post-operative outcomes. Further studies, with longer post-operative follow-up and increased sample size are needed. However, the continued advancements in surgical techniques and in the DED treatments are also expected to improve the refractive and visual outcomes after both procedures.

Chapter 5: Determination of post-operative refractive predictability and visual and patients' outcomes in normal and hyperosmolar populations presenting for refractive lens exchange (RLE).

5.1 Introduction

Recent advances in IOL design have provided a vast range of options for patients interested of being spectacle-independent at all distance, considering MFIOL implantation after clear lens extraction (Alio et al., 2017). The surgery is a safe and effective procedure to correct far and near vision requirements with a high rate of the presbyopic patients able to be completely spectacle-independent after surgery (Rosen et al., 2016; Savini et al., 2018; Schallhorn et al., 2017b). However, as part of the pre-operative evaluation and the lens calculation is influenced by the tear film, it is crucial to optimise the ocular surface before the surgery. In fact, when the refractive outcomes after premium lens surgery are excellent, the patients are not experiencing any reduction in contrast sensitivity and VA (E. D. Donnenfeld et al., 2010; Gibbons et al., 2016; Llovet-Rausell et al., 2018).

Dry eye, presbyopia and lens surgery have in common one of the most recognized risk factor in ocular surface disease such as age (Stapleton et al., 2017). Following the results from the PHACO multi-centre study on the pre-operative ocular surface disturbance and lens surgery, less than 25% of the study cohort were previously diagnosed with DED, while the researchers found more than 80% of the participants with tear film instability and 47% with Schirmer test values reduced below 10 mm (Trattler et al., 2017). As demonstrated by Epitropoulos et al. (2015), DED had an impact in the lens calculation with a difference of approximately 1 Diopter (D) in the keratometry readings between two visits with a refractive influence in the final calculated IOL higher than 0.50 D in 10% of the patients considered. Additionally, the findings revealed that 17% of the eyes considered in the study cohort were found with increased tear film osmolarity values (hyperosmolarity) before lens surgery. In summary, previous studies have demonstrated the lack of a proper DED diagnosis and, simultaneously, the magnitude of error that DED could hypothetically imply during the pre-operative assessment.

Nowadays, it seems that tear film osmolarity has the potential to be considered as a gold standard metrics in DED (Willcox et al., 2017). The reason behind this assumption has been found in the number of publications regarding tear film osmolarity and dry eye tests during the last decade, and especially in its ability to distinguish between DED and non-DED patients. Considering Table 11, 6 studies out of 8 shown an overall agreement between tear film osmolarity and DED measurements (TBUT, Schirmer test, corneal and conjunctival staining and TMH) or suggest that tear film osmolarity can play a role itself on determinate the presence of ocular surface disturbance, anticipating additional DED findings.

Authors, Year	Number of subjects	DED tests considered	Results
Messmer et al., 2010	200 subjects (71 healthy, 129 DED)	Osmolarity, corneal & conjunctival staining, TBUT, Schirmer test with/without anaesthesia	Osmolarity cannot discriminate between healthy and DED subjects
Benelli et al., 2010	60 subjects	Osmolarity, Schirmer test, TBUT, fluorescein staining	Osmolarity is the only test able to track changes over the time of a treatment (e.g. artificial drops)
Sullivan et al., 2012	52 subjects	Osmolarity, Schirmer test, TBUT, staining, Meibomian grading, OSDI questionnaire	Osmolarity demonstrated the lowest variability among other tests over a 3-months period
Alves et al., 2014	125 subjects (27 SS, 28 GVHD,28 Graves orbitopathy, 8 facial palsies, 20 glaucomas treated with BKA topical drugs)	ODSI questionnaire, TBUT, fluorescein and lissamine green staining, Schirmer test and severity grading	Osmolarity test is not suggested in the best test combination to diagnose DED (e.g. OSDI/TBUT/Schirmer)
Schargus et al., 2015	20 subjects	Osmolarity, TBUT, OSDI questionnaire, fluorescein and lissamine green staining, Schirmer test	Osmolarity tends to indicate DED presence in mild subjects
Tukenmez-Dikmen et al., 2016	22 subjects	OSDI, osmolarity, tear meniscus with OCT, ocular staining, TBUT and Schirmer test with anaesthesia	Osmolarity and OSDI are not in correlation but osmolarity complies with TFOS DEWS grading system in detecting DED severity
Mathews et al., 2017	225 subjects (131 DED symptoms and signs, 52 only DED symptoms and 42 controls without DED)	Osmolarity, OSDI and ocular staining	Symptomatic DED patients expressed higher osmolarity values and higher variability than controls. Osmolarity can anticipate DED diagnosis
Garaszczuk et al., 2018	50 subjects	OSDI, osmolarity, tear clearance rate (TCR), TBUT, blinking frequency, corneal staining, TMH with OCT	Osmolarity has been found significantly correlated with TCR, corneal staining, blinking frequency

Table 11 Summary of the studies about the correlation between tear film osmolarity and other DED tests (data were considered starting from the introduction of the device TearLab® in the EU market, 2008, up to 2018). Tear break-up time (TBUT); ocular surface disease index (OSDI); tear meniscus height (TMH) optic coherence tomography (OCT); graft-versus-host disease (GVHD); benzalkonium chloride (BAK); TFOS Dry Eye WorkShop (TFOS DEWS); tear clearance rate (TCR).

TFOS DEWS II Diagnostic Methodology report suggested considering OSDI and DEQ-5 questionnaires in the DED diagnostic test battery as they are currently validated and reliable subjective tools (Wolffsohn et al., 2017). In a recent study by Ong et al. (2018), 326 patients were included to understand the discordance between signs and symptoms in DED evaluation. Both questionnaires, OSDI and DEQ, have revealed a similar contribution on assessing the influence of co-morbidities factors (arthritis, chronic pain outside the eye, anxiety and depression) in DED incidence. Considering the discrimination between normal, non-Sjögren and Sjögren subjects, again, both questionnaires have demonstrated to be correlated well to distinguish the proposed groups (Caffery et al., 2011).

In terms of objective measurements, TFOS DEWS II report presented the tear film stability as an important homeostasis marker together with ocular surface staining (e.g. fluorescein and lissamine green). Modern devices are now able to detect and map changes of the ocular surface less-invasively with infra-red illumination (Lan et al., 2014), and dynamically using high-speed videokeratoscopy (Llorens-Quintana et al., 2018) or interferometry (Arita et al., 2016). The instability of the tear film is a common finding in elderly population potentially interested by lens surgery, with a peak of prevalence around 80% of the subjects considered (Trattler et al., 2017; M. Uchino et al., 2006).

Despite the progress in DED evaluation, there is still a discrepancy between subjective and objective measurements but especially to diagnose specific subtypes of DED (e.g. aqueous-deficiency or evaporative). In a study by Hua et al. (2014), more than 900 subjects demonstrated discrepancy when a validated set of questions were compared with TBUT and tear film volume (Schirmer test). The same trend was observed by Sullivan et al. (2014), where no correlations were found between osmolarity, TBUT, Schirmer test, ocular staining, Meibomian glands and OSDI questionnaire. Additionally, even performing a correlation between objective measurements, a diagnosis mismatch can be found: in a study cohort of 561 subjects, Uchino et al. (2013) reported normal Schirmer test values in presence of reduced TBUT and increased corneal staining.

The aim of the present research was to determine the post-operative refractive predictability and visual and patient-reported outcomes in normal and hyperosmolar populations presenting for lens surgery. Additionally, to consider if the pre-operative tear film osmolarity correlates with DED diagnostic test battery recommended by the TFOS DEWS II report such as TBUT and ocular surface staining (Wolffsohn et al., 2017).

5.2 Methods

5.2.1 Study design

This was a prospective, longitudinal and observational study that received a favourable opinion from the Aston University Research Ethics Committee.

5.2.2 Subjects

The main parameters of the study population are summarized in Table 12**.**

Parameter	Normal (values ≤ 307 mOsm/L)	Hyperosmolar (values ≥ 308 mOsm/L)
Number of eyes	16	11
Mean age (y) ± SD	61.0 ± 6.8	56.6 ± 5.2
Male n (%), Female n (%)	7 (43.8%), 9 (56.3%)	5 (45.5%), 6 (54.5%)
Mean osmolarity (mOsm/L)	299 ± 8	314 ± 4

Table 12 Demographics of the patients included in the study.

The patients were divided into two groups considering the value of their tear film osmolarity assessed using a single measurement obtained with the TearLab® Osmolarity System: the Normal group was composed by patients with a value ≤ 307 mOsm/L while the Hyperosmolar group was composed by patients with a value ≥ 308 mOsm/L or an inter-eye variability of ≥ 8 mOsm/L. The inclusion and exclusion criteria, ethics permissions, clinical and dry eye assessment for the study are detailed in Chapter 2. However, for the purpose of this study, the optometrist collected the outcomes measured including UDVA, CDVA, SEQ calculated considering the subjective refraction and DEV_PPOR. The dry eye assessment was performed by AR considering the following metrics based on the recent TFOS DEWS II report: OSDI, DEQ-5, previous DED diagnosis, number of blinks and its completeness and tear film osmolarity. NIKBUT and ocular staining from cornea, conjunctiva and lid margin were acquired using a K5M. All the following examinations were performed before and 1 month after surgery.

5.2.3 Surgery

All the surgeries were successfully performed by a team of experienced surgeons (I.M., M.W., N.G., S.K., S.M., S.S.). A pre-operative disinfection of the external part of the eye and adnexa using 5% povidone-iodine 1 hour prior to surgery was carried out in all the eye surgeries considered in the study.

5.2.4 Refractive lens exchange surgery

The procedures were performed with a 2.8 to 3.0 mm self-sealing corneal incision. Thereafter, a continuous curvilinear capsulorhexis was conducted to allow the breaking of the cortical portion of the lens via phacoemulsification. Finally, automated aspiration of the lens was undertaken to remove any remaining debris of the crystalline lens. All the IOLs implanted were a diffractive trifocal and aspheric multifocal Zeiss AT Lisa tri839MP (Carl Zeiss Meditec, Jena, Germany) for patients with and without incipient cataract. The procedures started with 1 drop of Phenylephrine 2.5%, 1 drop of Diclofenac Sodium 0.1% and 1 drop of Cyclopentolate Hydrochloride 1%. All the drops were instilled three times in a time interval of 10 minutes (e.g. first dose 8:00 AM, second dose 08:10 AM and so on). Thereafter, topical anaesthesia was instilled: 1 drop of Proxymetacaine 0.5% followed by 1 drop of Iodinated Povidone 5% for conjunctival antisepsis. The post-operative drop regime was the same for all patients: 1 drop of Dexamethasone 0.1% 6 times a day for 2 weeks, then 4 times a day for 2 weeks and finally 2 times a day for 2 weeks. Additionally, 1 antibiotic drop of Chloramphenicol 0.5% 4 times a day for 2 weeks was prescribed.

5.2.5 Statistical Analysis

All statistical analysis was performed using SPSS v23.0 (SPSS Inc., Chicago, IL, USA). Data normality was tested using the Shapiro-Wilk test.

To assess the changes in the VA and refractive outcomes, the normality was assessed considering the Shapiro-Wilk test from UDVA, CDVA, SEQ and deviation from PPOR. If the data were normally distributed, a parametric *t*-test was performed while if not a non-parametric test such the Wilcoxon Signed Rank Test (in case of related samples) or Mann-Whitney U (in case of independent samples) was considered.

To perform the correlations between tear film osmolarity and TFOS DEWS II report diagnostic test battery, data resulting as normally distributed (Shapiro-Wilk test >0.05) were analysed using the Pearson's test where data not normally distributed (Shapiro-Wilk test <0.05) were analysed using the Spearman's test.

Multiple linear regressions were performed to assess the potential effect on the DEV_PPOR considering DED metrics that belong to the TFOS DEWS II report diagnostic test battery: tear film osmolarity, symptomatology assessed using OSDI and DEQ questionnaires, NIKBUT and ocular surface staining (e.g. corneal, conjunctival and lid margin length staining) compared in the study cohorts with sex and age-matched controls.

5.3 Results

5.3.1 Post-operative visual and refractive outcomes in normal and hyperosmolar groups

The VA and refractive outcomes data are summarized in Table 13.

Visual acuity outcomes (mean ± SD, logMAR)					
Group	Normal		Hyperosmolar		
CDVA_PRE	0.0 ± 0.1	p-value	0.0 ± 0.1	p-value	
UDVA_1M	0.0 ± 0.1	0.206	0.1 ± 0.1	0.105	
Refractive outcomes (mean ± SD, Diopters)					
Group	Normal		Hyperosmolar		
SEQ_PRE	-0.07 ± 2.79		0.68 ± 2.54		
(range MIN – MAX, D)	-7, + 3.50		-4, +5.13		
SEQ_1M	-0.09 ± 0.39		-0.10 ± 0.69	p-value	0.940
(range MIN – MAX, D)	-0.63, +0.63		-1.38, 0.75		
DEV_PPOR	0.34 ± 0.20		0.58 ± 0.37	p-value	0.036*

Table 13 Visual and refractive outcomes data summary before and after surgery. Standard deviation (SD); corrected-distance visual acuity (CDVA); pre-operative (PRE); unaided distance visual acuity (UDVA); spherical equivalent refraction (SEQ); minimum (MIN); maximum (MAX); deviation from predicted post-operative refraction (DEV_PPOR). Asterisk indicates statistical significance.

The mean CDVA_PRE before surgery was equal in both selected group, while the UDVA at 1 month was found slightly higher in the Normal group (Figure 49, A) than the Hyperosmolar group (Figure 49, B). However, when CDVA_PRE was tested to check difference with UDVA_1M, no significance was detected in both groups (Normal p= 0.206, Hyperosmolar p= 0.105). The cumulative logMAR VA was found reduced in the Hyperosmolar group.

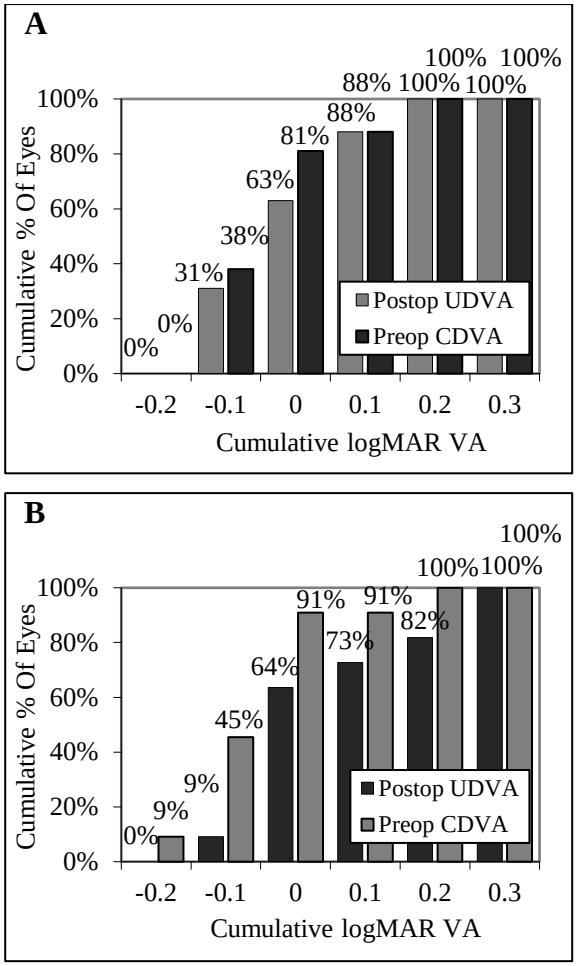

Figure 49 Cumulative pre- and post-operative un-aided distance visual acuity and corrected distance visual acuity in both groups: Normal (A) and Hyperosmolar (B).

The mean spherical equivalent refraction after the surgery (SEQ_1M) was found to be reduced compared to pre-operatively (SEQ_PRE) in both groups. The values after surgery were not significantly different between groups (p= 0.940).

The residual post-operative refractive error was within ± 0.50 D in 81% of the Normal group patients, while only slightly more than half of the patients (54%) belonging to the Hyperosmolar group have reached the same target after surgery. However, the refractive error was within ± 1.00 D in 100% and 90% in the Normal and Hyperosmolar group, respectively (Figure 50, C and D).

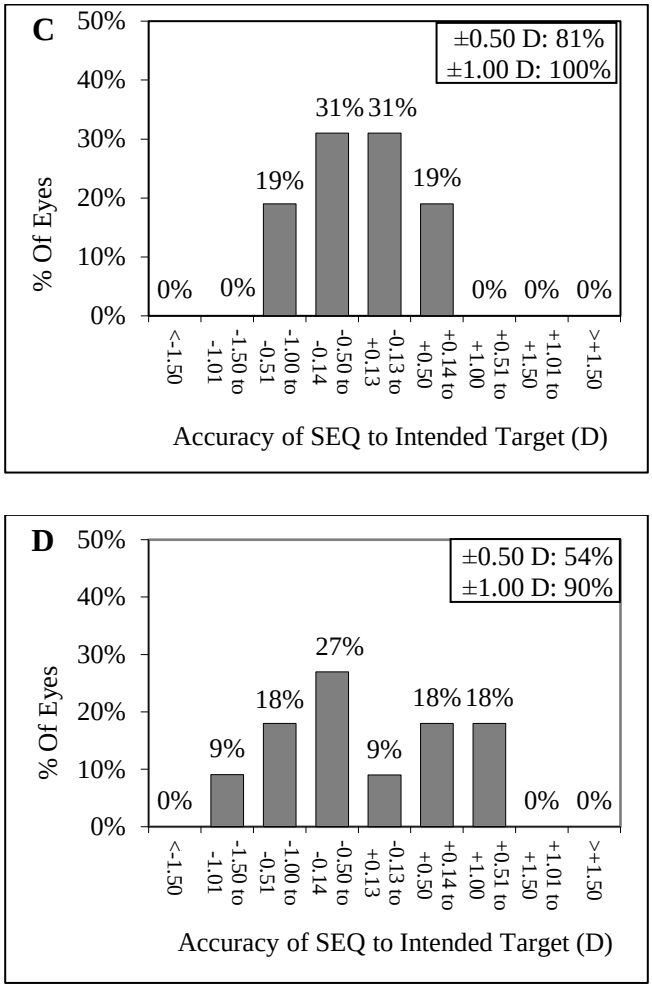

Figure 50 Accuracy of the surgical procedure in terms of residual refraction (SEQ) after surgery in Normal group (C) and Hyperosmolar group (D).

Finally, the difference between the two groups in terms of deviation from PPOR was found statistically significant as higher in the Hyperosmolar group (p= 0.036). Figure 51 shows the linear trend observed between tear film osmolarity and deviation from PPOR in both groups.

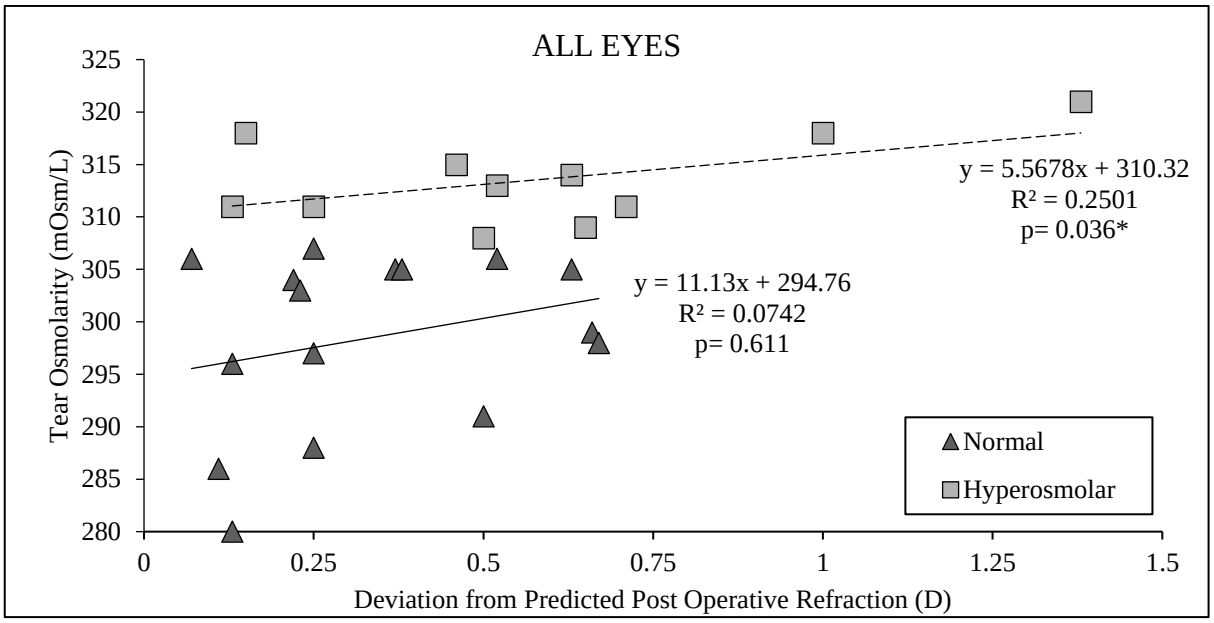

Figure 51 Correlation between tear film osmolarity with deviation from PPOR in normal (triangle) and hyperosmolar (square) groups. No-dashed line and dashed line represent a linear fit for the normal and hyperosmolar group, respectively. Asterisk denotes a significant difference.

5.3.2 Prevalence rate of ocular surface characteristics and DED

The presence of ocular surface staining using fluorescein and lissamine green revealed a positivity of 31% and 45% in the Normal and in the Hyperosmolar group, respectively (Figure 52, E and F).

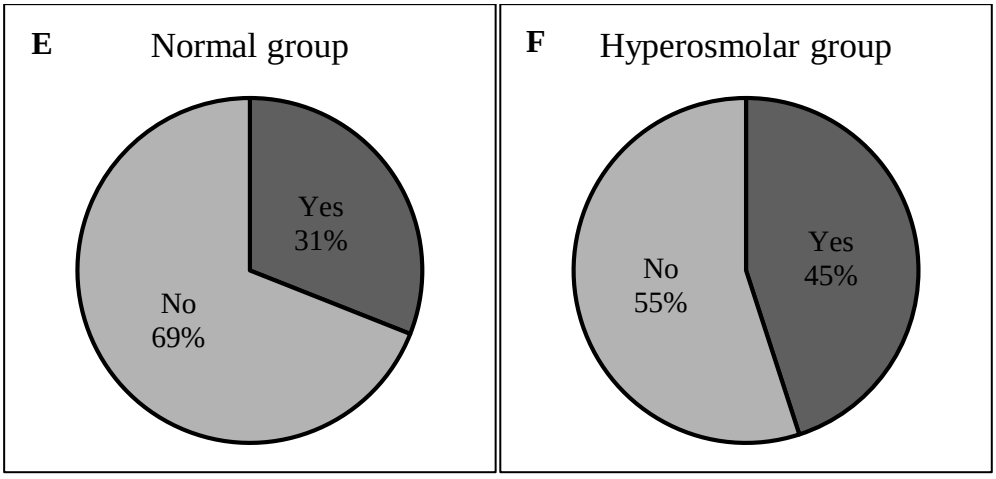

Figure 52 Percentage of presence of ocular surface staining: Normal group (E), Hyperosmolar group (F).

Similar trends were found in the patients 'answer related to a previous clinical diagnosis of DED where Normal group has answered with 19% of "Yes" while the Hyperosmolar group with 18% of "Yes". (Figure 53, G and H).

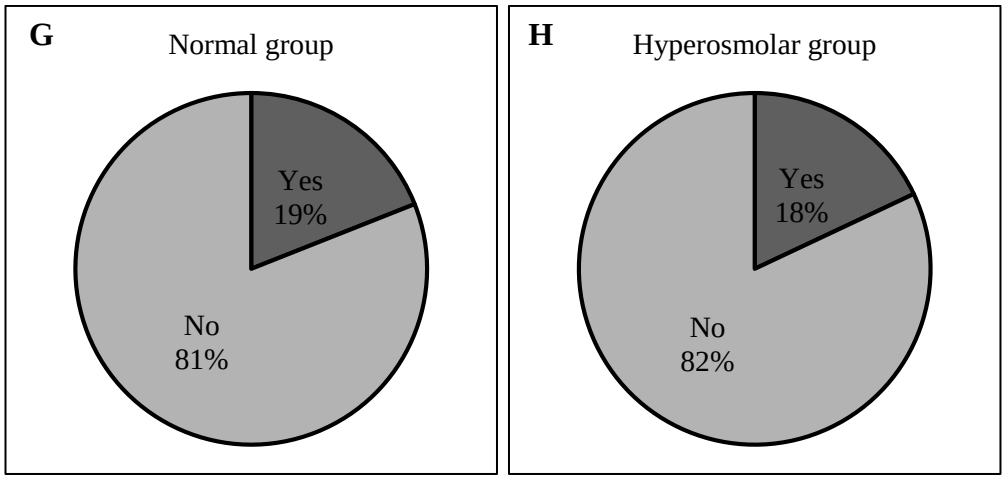

Figure 53 Percentage of patients with a previous clinical diagnosis of DED: Normal group (M), Hyperosmolar group (N).

The number of blinks was reduced in both groups; the Normal group had a percentage of patients under the cut-off of 10 per minute of 75% and the Hyperosmolar group of 45%. Incompleteness of the blinking process was recorded in 38% of the patients with the normal value of tear film osmolarity, while only in 18% of the ones with increased osmolarity values (Figure 54, I and J).

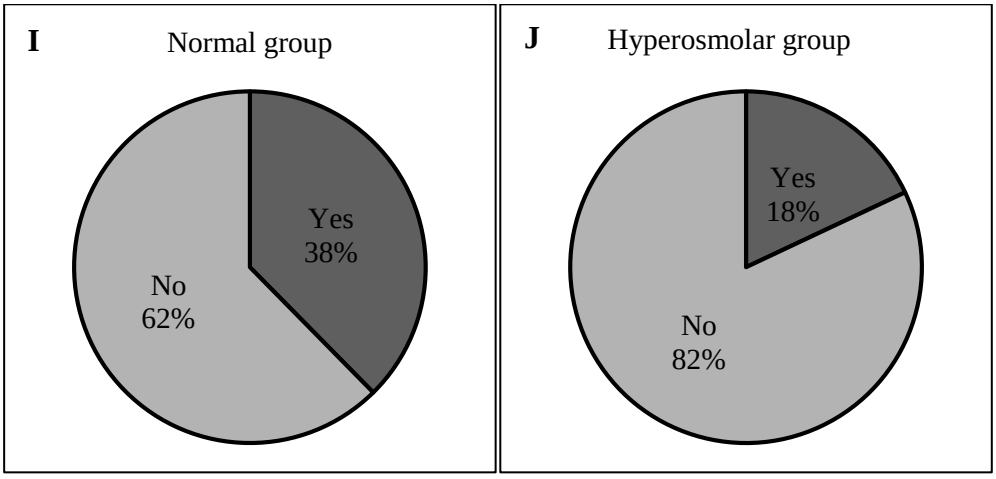

Figure 54 Percentage of patients with incomplete blinking observed: Normal group (I), Hyperosmolar group (J).

In a small percentage of eyes in both groups (6% and 9% in the Normal and Hyperosmolar group respectively) showed the presence of eyelids scurf (Figure 55, K and L).

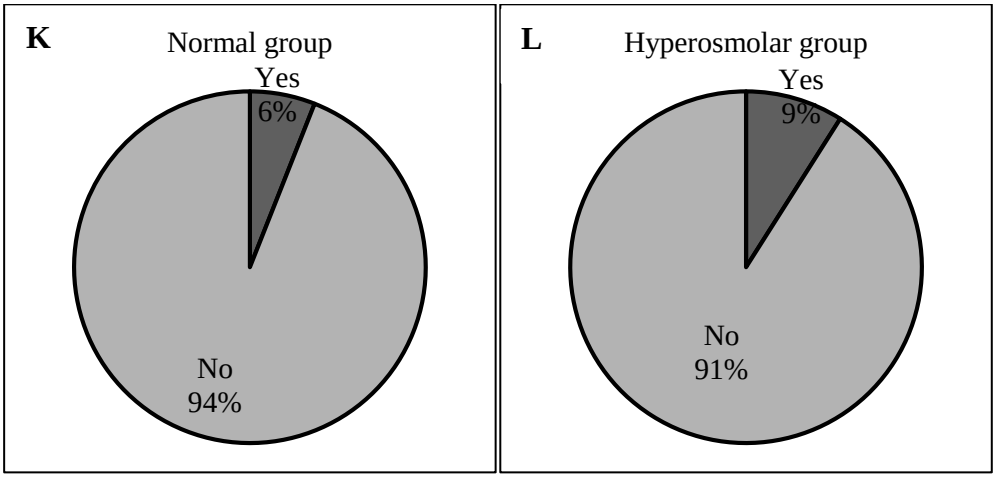

Figure 55 Percentage of patients with presence of eyelids scurf: Normal group (K), Hyperosmolar group (L).

5.3.3 Correlations between tear film osmolarity and TFOS DEWS II report diagnostic test battery

Tear film osmolarity (OSMO) has been considered to detect any correlation with the metrics proposed in the diagnostic TFOS DEWS II battery test in the groups considered before the surgery: Normal and Hyperosmolar (Table 14 and Table 15).

Normal Group		OSDI	DEQ (Spearman's rho)	NIKBUT	Corneal staining	Conjunctival staining	Lid margin staining
Tear film osmolarity (OSMO)	Pearson Correlation	-0.179	0.070	-0.261	0.239	0.100	0.245
	p-value	0.508	0.796	0.328	0.372	0.713	0.360

Table 14 Correlation in the Normal group between tear film osmolarity and other DED metrics proposed by TFOS DEWS II report diagnostic test battery.

Hyperosmolar Group		OSDI	DEQ	NIKBUT	Corneal staining	Conjunctival staining (Spearman's rho)	Lid margin staining
Tear film osmolarity (OSMO)	Pearson Correlation	-0.301	-0.008	0.192	-0.052	-0.144	0.513
	p-value	0.369	0.983	0.571	0.879	0.673	0.106

Table 15 Correlation in the Hyperosmolar group between tear film osmolarity and others DED metrics proposed by TFOS DEWS II report diagnostic test battery.

Despite the pre-operative detailed analysis, the tear film osmolarity was not significantly associated with the others DED metrics proposed by DEWS II report diagnostic test battery ($p > 0.05$).

5.3.4 Correlation between deviation from PPOR and DEWS II report diagnostic test battery

The correlations are summarized in Table 16. The power of the linear regression was considered with the *Adjusted R Square* which explains the percentage of variation produced by the independent variables such as all the diagnostic test battery proposed by the TFOS DEWS II report. The DED metrics considered showed no significance. Nevertheless, the power of the multiple linear regressions, following the *Adjusted R Square* was reduced to -0.011 in predicting deviation from PPOR.

TFOS DEWS II diagnostic battery test		DEV_PPOR	OSMO	OSDI	DEQ	NIKBUT	Corneal staining	Conjunctival staining	Lid margin staining
DEV_PPOR	Linear Regression	1.000	0.316	-0.021	-0.161	-0.172	-0.148	-0.128	-0.079
	p-value	0.105	0.055	0.766	0.249	0.119	0.463	0.976	0.438

Model	R	R Square	Adjusted R Square	St. Error of the Estimate
1	0.533	0.284	-0.011	0.240

Table 16 Correlation between deviation from predicted post-operative refraction (PPOR), tear film osmolarity (OSMO), Ocular Surface Disease Index (OSDI), Dry Eye Questionnaire (DEQ), non-invasive keratograph break-up time (NIKBUT) and ocular surface staining.

5.4 Discussion

The tear film osmolarity has raised importance in the clinical and research field during the last decade as it was considered one of the best single test to diagnose and classify DED (Potvin et al., 2015). The overall determination process of tear film osmolarity values has become more accessible with the introduction of a new device produced by TearLab®, able to detect and quantify mainly the active particles in the mucoacqueous layer of the tear film (Lemp et al., 2011). The tear film osmolarity detection is applied to classify DED severity: Willcox et al. (2017) have suggested classifying as normal patients with values included between 302.2 ± 8.3 mOsm/L, mild to moderate patients with 315.0 ± 11.4 mOsm/L and severe patients with 336.4 ± 22.3 mOsm/L. In terms of cut-off values widely accepted in DED diagnosis (Lemp et al., 2011), a sensitivity and specificity between 64-91% (Jacobi et al., 2011) and 78-96% (Khanal et al., 2008) have been observed with values ranging from 305 mOsm/L to 316 mOsm/L, respectively (Versura et al., 2010). However, in the current study, as any moderate to severe DED patients were included, the

cut-off accepted to create the groups has been set to 308 mOsm/L as previously reported by Jacobi et al. (2011).

Ocular surface disturbance in patients attending for lens surgery may increase variability in the average keratometry readings, with an influence of approximately 1 D in the measured corneal astigmatism that could potentially influence the calculation of the final IOL by more than 0.5 D (Epitropoulos et al., 2015). Moreover, the influence on the postoperative outcomes could be even higher if premium IOLs are considered for the implantation due to the type of geometry (e.g. splitting of the light rays for distance and near vision). In a retrospective review by Gibbons et al. (2016) 35% of patients (n= 26) were diagnosed with DED before surgery with post-operative complaints mainly related to residual refractive errors in combination with dry eyes (16% of the total). However, DED diagnosis is still confounded by the lack of association between signs and symptoms (K. Nichols et al., 2004b). In the present study, the presence of pre-operative DED symptoms was assessed in approximately 58% of the total, but only 19% of them have previously received a diagnosis of DED by their GP, ophthalmologist or optometrist. Following the study by Gupta et al (2018), tear film osmolarity has shown to be sensitive to detect DED in a population attending lens surgery (n= 120), especially because the prevalence of non-DED patients assessed using questionnaires was found in 83% of the total participants. Thus, in the current approach considering the tear film osmolarity cut-off of 308 mOsm/L was found in approximately 41% of the patients' total (n= 11), while the rest of the patients were found with values ≤ 307 mOsm/L and therefore considered as a Normal group (59% fo the total, n= 16) (Jacobi et al., 2011).

Patients who want to restore distance and near vision and being spectacle or contact lens independent may find RLE procedures useful with only potential photic visual phenomena and a reduction in contrast sensitivity as drawbacks of the surgery (e.g. halos and glares) (Alio et al., 2017). In order to improve the refractive outcomes after the surgery, the ocular surface should be in good status, as part of the preoperative measurements to calculate the IOL to implant, are based on the tear film (Olsen, 2007). In the current research, the Hyperosmolar group (41% of the total) was found with a deviation from the PPOR of more than 0.5 D following the assumption previously formulated by Epitropoulos et al. (2015) of a potential error in IOL calculation due to hyperosmolarity of the tear film. However, even without significance, the distance VA after surgery in the Hyperosmolar group (UDVA_1M) was slightly decreased compared to the Normal group. Hyperosmolarity has been linked with an increased tear instability (McMonnies, 2018): negative visual transitory effects brought by increased high order aberration (high instability of tear film/reduction of visual quality) could potentially limit the quality of vision in everyday tasks such as reading, driving or working with a computer (Montés-Micó et al., 2004). From Figure 49, it is interesting to discuss the cumulative VA observed 1month after surgery in both groups: in the Hyperosmolar group, before the surgery, patients were able to reach with spectacles the

logMAR VA for distance of -0,1 and -0,2 in approximately 9% and 45%, respectively. After surgery, as RLE surgery aims to leave the patients mostly spectacles-independent; the Hyperosmolar group was able to reach the logMAR VA for distance of -0,1 logMAR only in 9% while any of the subjects were able to reach -0.2 logMAR. In other words, while before the surgery the patients were able to reach good (-0.1 logMAR) to optimum (-0.2 logMAR) vision using their spectacles in a percentage of about 54%, after surgery the percentage has been resolutely reduced to 9% without any vision aid. It is true that a neuroadaptation period is often necessary for the patients after multifocal IOL implantation to improve VA (Rosen et al., 2016). However, considering the Normal group, the values of VA before and after surgery (CDVA_PRE vs UDVA_1M) were found similar, at least considering a VA of -0.1 logMAR. Thus, a potential leading cause of reduced VA after RLE seems to be related to the tear film osmolarity of the Hyperosmolar group. Gibbons et al. (2016) reported that the most common complaints after RLE surgery were associated with residual refractive error (57%) and dry eye (35%). In Figure 50, the current results confirm that DED is responsible in producing less accurate results in terms of SEQ after surgery with a limitation in reaching a residual error of ± 0.50 D in only 54% of the total hyperosmolar patients against 81% of the normal patients. Additionally, also the trends reported in the presented results based on the correlation between osmolarity and deviation from PPOR (Figure 51), described the increased skew line toward higher deviated results in the Hyperosmolar group. Nevertheless, at the current time is not possible to link the findings presented in terms of VA and SEQ accuracy before and after RLE surgery in normal and hyperosmolar patients for the lack of studies in the literature.

As symptomatology, tear film osmolarity and stability were not subjectively graded by the examiner. In order to test repeatability on the ocular surface staining metrics such as corneal, conjunctival and lid margin, a Bland-Altman (B-A) analysis was considered. Based on the B-A graphs (see 2.5.2), all the ocular surface staining were found not to vary consistently from the mean, thus, were considered repeatability between the two sessions. Prior study on repeatability of ocular surface staining has been done by Nichols et al. (2004a) with poor agreement, without considering the staining length of the lid margin. However, the ocular surface staining assessment considered in the present research had only the intention of quantifying the number of dots (punctuations) and the extension of the lid margin staining (length) from a single scan performed with the K5M without considering grading scales. Through this analysis, both groups were identified with signs of ocular surface disturbance. For example, considering Figure 52, 45% of the Hyperosmolar group were found with signs. In a previous study by Trattler et al. (2017), similar results were found in a larger population (n= 272 eyes) with peripheral corneal staining in 44.9% (NEI scale) and also central corneal staining (50% of the total). Comparing “the previous diagnosis of DED”, both groups reported percentages similar (19% and 18%) to the PHACO study population (25%) (Trattler et al., 2017) (Figure 53). In addition to the PHACO

study, the current research has implemented other DED metrics to consider which are blink rate, blink completeness and presence of eyelids scurf. The blink rate is reduced with age as confirmed by the current results (Lowgren et al., 2017). In fact, both the groups considered have a mean age of approximately 60 years and following the findings by Sun et al. (1997), persons with 50 years of age or older may have reduced blink rate due to eyelid kinematics (e.g. muscles action). The incompleteness of the blinking has been subjectively assessed during the evaluation with the lower values observed in the Hyperosmolar group. The reason behind this mechanism, also suggested by Ousler et al. (2014), could be potentially referred to the need of the hyperosmolar patients to renew completely the tear film with a full and complete blink compared to the Normal group. However, this hypothesis should be better assisted by the means of an objective evaluation (e.g. video monitoring or mobile app). The clinical examination of the eyelids is part of the comprehensive DED evaluation. In fact, it is really important to track changes over the eyelids that can potentially anticipate related conditions such as blepharitis and conjunctivitis that are common also in non-DED patients (D. Goldberg, 2011). In a multicenter and survey study performed by Lemp et al. (2009) in the US, the prevalence of blepharitis was estimated between 37% and 47% (n=5000) frequently associated with evaporative DED. Additionally, the rest of scurf/dandruff around eyelids may support the Demodex infestation (Gunnarsdottir et al., 2016) and degenerate in moderate to severe MGD (Nowinska et al., 2012). In the current study, even if the prevalence of eyelid scurf has been found reduced in both group, it may be useful to suggest a pre-operative screening and treatment (eyelid hygiene) before attending surgery to avoid any potential causes of infection and cancellation of the surgery (Stead et al., 2010).

At the present date, there is not a general DED diagnosis protocol to be conducted for patients attending RLE or in general prior lens surgery. However, a practical approach for a private clinical setting could be considered a fast and reliable tool in terms of DED screening detection such as tear film osmolarity evaluation and short-items questionnaires (e.g. DEQ-5) (Gupta et al., 2018). In fact, in case of positive findings during DED screening, the patient could be potentially referred for more detailed assessment to establish the subtype of the condition (e.g. ADDE or EDE, see sections 1.4.2.1 and 1.4.2.2) and plan a pre-operative treatment. Based on the findings by Sullivan (2010), the tear film osmolarity has the highest correlation value to disease severity and also Tomlison (2006) reported the importance of tear film osmolarity as a single parameter that could provide an insight of the status of the lacrimal system. Mathews et al. (2017), reported that the tear film osmolarity has been not well included in clinical practice because the results in the literature were disagreeing. From the works by Potvin et al. (2015), different cut-off values in tear osmolarity were considered with a potential limitation in reaching a general consensus to determinate patients with or without DED. However, the methodology considered in the current research adopted the cut-off value of $\geq$ 308 mOsml/L previously suggested by Potvin and later by the TFOS DEWS II report. In fact, 308 mOsml/L cut-off has reported the

ability to discriminate early stages of DED and normal patients in 90.7% and 81.3% of the time. In this research, several correlations were conducted to analyze the correspondence of the tear film osmolarity with the other DED metrics reported in the study (OSDI, DEQ, NIKBUT and ocular surface staining), without reaching statistical significance in either of the two groups. A hypothesis was made based on the fact that a possible contributing factor could have been the high variability in the current measurements: a single repeat, as reported by Szczesna-Iskander (2016) may be not sufficient to obtain reliable values. Nevertheless, from a cost point of view, in the current research was not possible to repeat the test three times. The mean tear film stability measured in the groups enrolled in the current study was 8.27 ± 5.40 s and 7.65 ± 3.54 s in Normal and Hyperosmolar patients respectively. Thus, based on the cut-off values of 10 s proposed in the literature (Tiffany, 2008), both groups failed to respect a normal tear film stability with potential variability over the tear film osmolarity measurements. The same variability observed in the tear film osmolarity assessment could have potentially influenced the correlations with ocular surface staining in both groups as conversely found before by other researchers (Fortes et al., 2011; Lemp et al., 2011; Versura et al., 2010).

To support the refractive outcomes analysis in the study, a linear regression was performed in order to understand if the deviation from PPOR (dependent variable) has been influenced or not by the DED metrics (independent variables). On this occasion, the analysis was performed considering all the eyes together to delineate a general trend in all the eyes (n= 27) and to increase the power of the analysis considering a larger sample size. In fact, for a level of confidence of 95% and a response distribution of 50%, the sample size suggested has been 26 with a marginal error of 5% (Hsieh et al., 1998). The only DED metrics close to reaching significance has been tear film osmolarity (p= 0.055), with an increasing deviation (higher residual errors after surgery) found linear with higher osmolarity values (Figure 51). The overall results reported in the current research reported a deviation from PPOR of 0.43 ± 0.30 D in the Normal group with increased values belongs to the Hyperosmolar group (0.58 ± 0.37 D) and were in agreement with Epitropoulos et al. (2015) that reported more than 0.5 D of deviation. The researchers suggested that hyperosmolarity is a contributing factor in the variability of the keratometry readings, as a precise estimation of corneal power is essential to obtain reliable biometry and lens calculations. In the current study, the keratometry readings were not collected but the deviation from PPOR could be addressed considering the hyperosmolarity. Any other remarkable DED tests are involved in the deviation from PPOR in the current study, as reported by the reduced value of *Adjusted R Square* (Table 16).

5.4.1 Limitations of the Study

One of the limitations in this study is the potential variability of the tear film osmolarity as only a single repeat was performed with potential bias in the final consideration (time of the day, visual

tasks before the tear collection, etc). Additionally, another limitation of the presented research is the fact that the dry eye assessment was performed before the surgery at one point in time that, due to the ocular surface fluctuations, might be different in another visit. Finally, the relatively small sample size has potentially biased the results increasing the standard error between the measurements.

5.4.2 Conclusion

The results of this study suggested that the increased osmolarity of the tear film could potentially lead to unwanted deviations (~0.60 D) from the predicted post-operative refraction in the populations presenting for lens surgery. The altered refractive outcomes had also effects on the visual function with important limitation in achieving good to optimum VA after surgery. As previously observed in the literature, there is a lack of correspondence between DED metrics such as tear film osmolarity, subjective questionnaires, tear film stability and ocular surface staining (K. Nichols et al., 2004b; Sullivan et al., 2014). However, the current research still advises to follow the DED diagnostic test battery recommended by the recent TFOS DEWS II report in order to improve the refractive predictability and visual and patient-reported outcomes in patients presenting for lens surgery.

Chapter 6 Dry eye and visual quality metrics before and after phacoemulsification surgery followed by intraocular implantation.

6.1 Introduction

Cataract is a progressive increase of opacification of the crystalline lens of the eye or its capsule (Kanski et al., 2011). The loss of transparency causes an overall reduction in VA and quality of life as patients affected may experience a reduction in their ability to perform everyday tasks (e.g. reading, driving, working, etc.) (Thompson et al., 2015). Additionally, patients may experience a deterioration in visual quality in terms of contrast sensitivity due to the opacification of the crystalline lens (Y. Liu et al., 2017). Due to its etiology, cataract is considered one of the most prevalent causes of reversible blindness in the world, together with uncorrected refractive error and glaucoma (Khairallah et al., 2015). The global population affected by visual impairment due to cataract is estimated to reach up to 57 million by 2020 due to population growth and augmented longevity (Flaxman et al., 2017). The causes of cataract are related to the oxidation of lens proteins, especially cysteine and methionine due to aging, exposure to ultraviolet light, diabetes, developmental abnormalities, smoking, trauma, metabolic disorders and changes due to drug intake (e.g. corticosteroids) (Asbell et al., 2005; Y. Liu et al., 2017; Modenese et al., 2018).

The only treatment for cataract is the surgical removal of the lens, typically followed by implantation of an artificial IOL. Moreover, cataract surgery has evolved to a procedure designed to simultaneously correct refractive errors (e.g. myopia, hyperopia, etc.) and lens opacification to allow relative spectacle-independent, at least for distance vision (Skiadaresi et al., 2012). Cataract surgery is one of the most commonly performed ophthalmic procedures worldwide and is known to be safe and efficacious (A C Day et al., 2015; Lundstrom et al., 2013). However, especially in the developing countries where cataract often remains untreated, 75% of patients with lens opacification are at risk of permanent blindness with potentially higher costs associated with the burden of the disease (Ramke et al., 2017; Tabin et al., 2008).

As previously reported by Stapleton et al. (2017), one of the risk factors observed for the development of DED is increasing age. As cataract is also related to ageing, a relationship between the two conditions is predictable. DED is not only responsible for postoperative complaints from patients following cataract surgery due to the impact of the procedure on the ocular surface (Y. Cho et al., 2009) but it could potentially affect preoperative measurements such as corneal topography and ocular biometry which are affected by a poor quality tear film. Schallhorn (2016) (data presented at the 2014 American Academy of Ophthalmology annual meeting) described post-operative refractive and patient-reported outcomes of more than 4970 lens surgery procedures. Of these procedures, 39% of the patients had a residual refractive error with a potential reduction on reported satisfaction with surgical outcomes due to ocular surface disturbances. The authors suggested carrying out a detailed ocular surface examination and

treatment for ocular surface issues in order to reduce the residual refractive error and improve patient satisfaction.

A pre-surgery manifestation of DED is MGD which has been observed to be one of the most common conditions that can potentially cancel or delay the date of surgery (Chuang et al., 2017). In a recent study by Cochener et al. (2018), 54% of the study population (n= 342 eyes) were found to have MGD and 46% of the total had DED symptomatology demonstrating that a consistently high number of patients attending for cataract surgery could manifest signs and symptoms of DED. However, as previously reported in another study by Nichols (2004b), a lack of a relationship has been established for different DED metrics, especially when symptoms are correlated with signs. Gupta et al. (2018) found a similar trend to Cochener as the prevalence of patients attending for cataract surgery with at least one tear film abnormality was detected in up to 81% of patients (n= 120). Nevertheless, no previous diagnosis was reported in more than half of the total (57%) addressing the importance of testing signs of DED before the procedure.

The tear film may alter after cataract surgery leading to the development of DED. This may be due to corneal incisions (Sutu et al., 2016), microscope light exposure (Ipek et al., 2018), speculum (Moon et al., 2014), use of peri-operative drugs (Kasetsuwan et al., 2013), goblet cells loss (Kato et al., 2017) and elevation of inflammatory cytokines in the tear film (X. J. Zhu et al., 2015). In a study by Park et al. (2016), DED symptomatology was higher at 1 and 2 months follow-up while a moderate return to the baseline values was observed at 1 month using objective DED metrics such as TBUT, corneal staining scores and corneal sensitivity measurements. Katesuwan et al. (2013) analysed data from patients after cataract surgery (n= 92) and found 9.8% of the patients had higher values for symptomatology (OSDI), 68.4% had tear film instability, 11.9% had reduced tear film volume and 58.7% had ocular surface staining assessed with the Oxford Schema grading scale (Bagbaba et al., 2018).

A plethora of different chemical agents used in cataract surgery can potentially lead to a disturbance of the tear film and temporary dryness (Oh et al., 2012). The agents used include topical anaesthetic and dilation drops followed by anti-inflammatory drugs (NSAIDs) and corticosteroids to manage pain and inflammation. Topical antibiotics are also used at the end of surgery and postoperatively to avoid infection.

A preoperative assessment of the tear film aims to prevent possible errors in IOL power calculation and keratometry due to sub-optimal tear film quality. Nowadays, thanks to the recent TFOS DEWS II report, a reliable diagnostic battery of test has been proposed: validated questionnaires together with non-invasive objective measurements have been suggested to screen for the presence of DED (Wolffsohn et al., 2017).

In summary, DED can potentially impact the quality of pre-operative measures used in IOL power calculations and also can impact on patient satisfaction with the outcomes of surgery. The aim of this study was to determine whether dryness symptoms and signs prior phacoemulsification followed by IOL implantation at a UK NHS hospital setting affected post-operative refractive targeting, dryness symptoms and light scatter assessed using an Aston Halometer which has shown to be a sensitive and repeatable hand-held device for the evaluation of glare (Buckhurst et al., 2015).

6.2 Methods

6.2.1 Study design

The research was a retrospective study which has received the favourable opinion from the University Hospitals Birmingham NHS Foundation Trust Ethics Committee, Birmingham, United Kingdom. The title of research "An observation study of dry eye management" with the South East Scotland REC 02 and project reference numbers REC 15/SS/0113 (see Appendices 12).

The clinical and dry eye assessments were performed by an experienced research optometrist at the Queen Elizabeth Hospital (Birmingham, UK). The author performed all analyses and interpretation of the study data.

6.2.2 Subjects

41 patients with cataract and no previous clinical diagnosis of DED participated. Patients attended for routine cataract surgery at a UK NHS hospital setting. One eye of each patient was included (n= 41), and in the case of bilateral cataract, only the eye with better VA or the dominant eye in the case of equal VA, was included. The inclusion and exclusion criteria, ethics permissions, clinical and dry eye assessment for the study are detailed in Chapter 2. However, for the purpose of this study, the research optometrist collected the outcomes measured including monocular CDVA, SEQ calculated considering the subjective refraction. The dry eye assessment included DEQ-5, NIKBUT with the Tearscope® while the halometry was performed using the Aston Halometer (AH). All the following examinations were performed before, 1 month and 6 months after surgery.

The main parameters of the study population are summarized in Table 17.

Parameter	Value
Mean age (years) ± SD	69.0 ± 9.0
Range (years)	47 - 85
Median (years)	69
Male n (%), Female n (%)	15 (37%), 26 (63%)

Table 17 Demographics of the patients included in the study.

All surgeries were successfully performed by a single expert ophthalmic consultant (S.K.) consisting of routine phacoemulsification and IOL implantation. All planned post-operative refractions were intended to reach within ± 0.50 D of emmetropia.

6.2.3 Phacoemulsification surgery followed by intraocular lens implantation

Pre-operative disinfection of the external eye and adnexa was carried out using 5% povidone-iodine 1 hour prior to surgery.

The surgical procedure began with topical anaesthesia followed by creating of a 3.0 mm self-sealing corneal incision. Thereafter, the surgeon proceeded with a continuous curvilinear capsulorhexis, breaking of the cortical portion of the lens, successively aspirating the remaining lens debris using a phacoemulsification probe. Finally, a Rayner 800s IOL was implanted (Rayner Intraocular Lenses Ltd, UK) within the intact capsular bag to restore the focusing power of the eye.

The post-operative drop regime was the same for all patients; with topical levofloxacin 1.5%, 4 times per day over 4 weeks together with topical nepafenac 0.1%, a non-steroidal anti-inflammatory drug (NSAID), for 1 week.

6.2.4 Aston Halometer

A custom halometer (AH), designed by Aston University (Buckhurst et al., 2015) was considered. The device simulates haloes by producing a source of glare from a bright white LED attached to the center of a tables screen iPad 4 (Apple, Cupertino, CA, USA). It is remotely controlled using a mobile device. The letters are moved in a circle in 8 different meridians, spaced at 45-degree intervals, and are presented to the patient in a clockwise direction at high contrast conditions set at 50%. The halo boundary was determined by considering the closest position to the LED where two out of three presentations of the target were correctly identified. The area of obscuration generated by the glare source, from the 8 different positions, was calculated and then summed to give the total area of dysphotopsia (Figure 56).

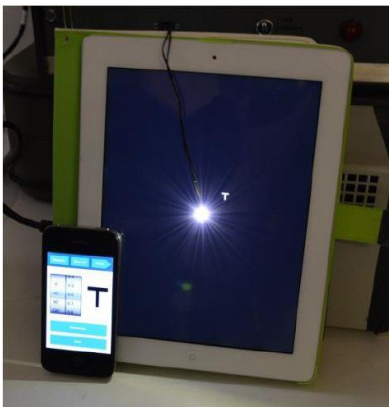

Figure 56 The Aston Halometer and the remote control used to present the targets.

6.2.5 Statistical Analysis

Statistical analysis was performed using SPSS 23.0 (SPSS Inc., Chicago, IL, USA). Data normality was tested using the Kolmogorov-Smirnov test for all the variables considered: CDVA, SEQ, DEQ-5, NITBUT and overall glare assessed with AH.

The refractive outcomes such as CDVA, SEQ and overall glare were assessed using a non-parametric Wilcoxon test before and after surgery together with three different characteristics using the DEQ-5 questionnaire: discomfort, dryness and watery eyes considering the frequency and intensity. Additionally, the Spearman's rank-order correlation analysis was performed between pre-operative dryness signs (PRE_OP_NITBUT) and symptoms (PRE_OP_DEQ-5) with the post-operative refractive outcomes (POST_OP_6M_SEQ), dryness symptoms (POST_OP_1M and 6M_DEQ) and light scatter (POST_OP_1M and 6M_GLARE).

6.2.6 Results

Post-operative SEQ at 6 months was found to be within ±0.50 D of the intended target refraction in 90% of the eyes and within ±1.00 D in 98% of eyes (Figure 57, A). In terms of vision, the average CDVA has improved from pre-operative values 0.5 ± 0.2 logMAR to 0.0 ± 0.1 logMAR after surgery, with 100% of the patients able to achieve 0 logMAR (p= 0.088) (Figure 57, B). Glare levels (overall area: 36.4 ± 9.6; range 15.3 – 56.1) before surgery were significantly reduced (p=0.0002) after surgery when tested at 1 month (overall area: 12.0 ± 4.7; range 5.8 – 26.3) and at 6 months (overall area: 7.8 ± 3.3; range 2.9 – 19.4), but there was no significant difference found between data at 1 and 6-months follow-up visits (Figure 58).

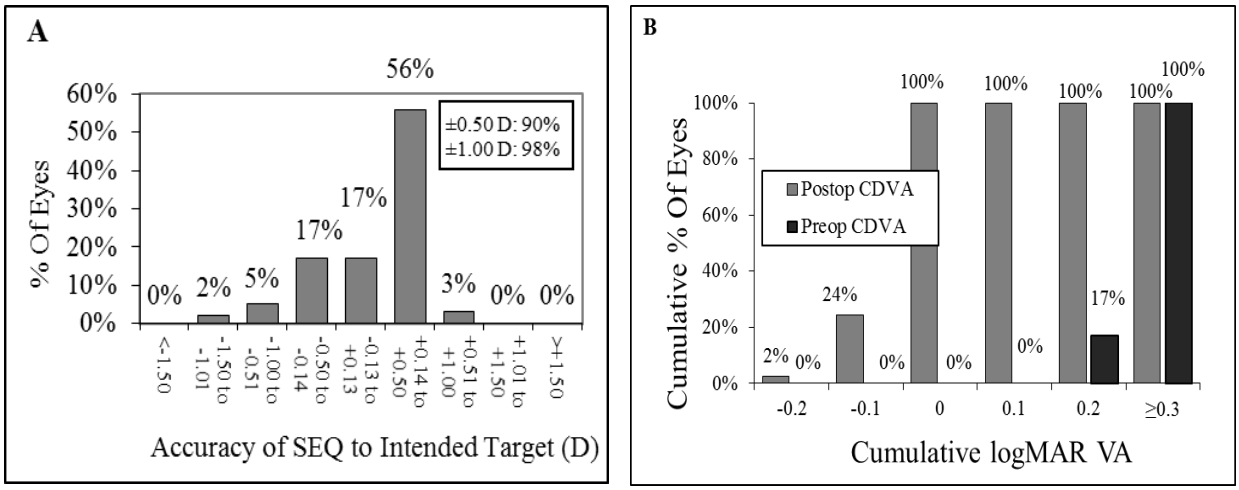

Figure 57 Refractive outcomes representing A) accuracy of the surgical procedure in terms of residual refraction after surgery B) the visual acuity before and after surgery (Preop CDVA vs Postop CDVA).

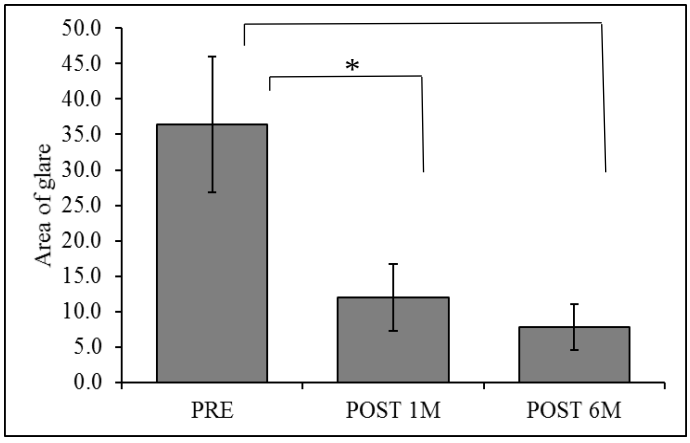

Figure 58 Glare levels (overall area) values pre-, 1 and 6 months after the surgery N = 41 eyes. Asterisk denotes a significant difference (p= 0.0002).

Discomfort frequency and intensity were found to be increased at the post-operative follow-up at 1 and 6 months compared with the pre-operative data, although differences were not statistically significant (p= 0.202 and p=0.977, respectively) (Figure 59).

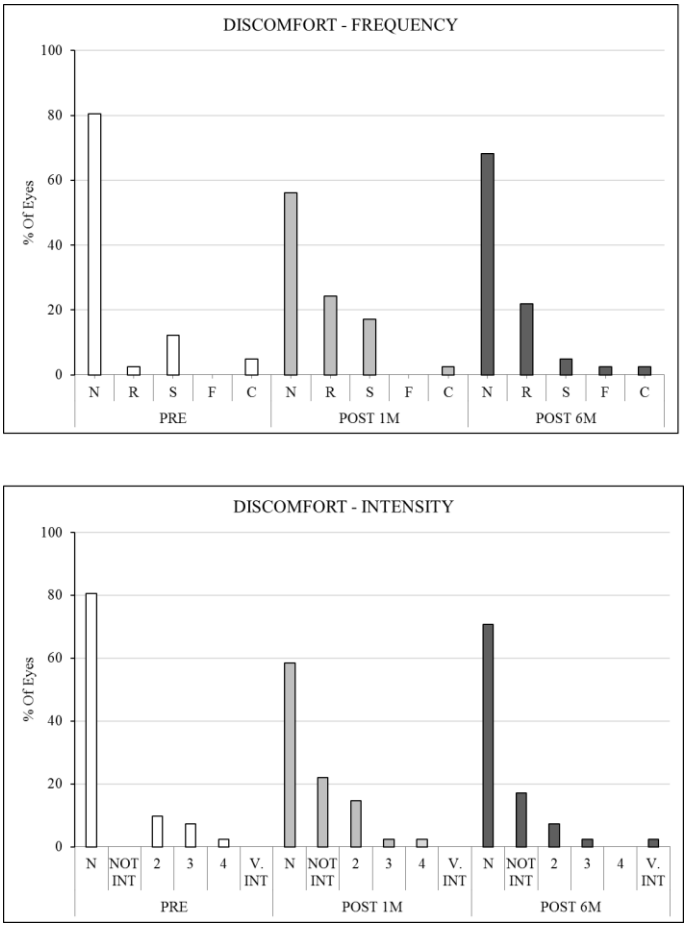

Figure 59 Discomfort items in DEQ-5 questionnaires score pre-, 1 and 6 months after the surgery N = 41 eyes (p> 0.05). Frequency options were: N= Never, R= Rarely, S= Sometimes, F= Frequently, C= Constantly. Intensity options were: N= Never have it, NOT INT= Not at All Intense, Score of 2, 3, 4, V.INT= Very Intense.

Pre-operative dryness in terms of frequency and intensity was found not statistically significant through the follow-ups despite a slight increase after surgery (p= 0.294 and p= 0.809 for frequency and intensity, respectively) (Figure 60).

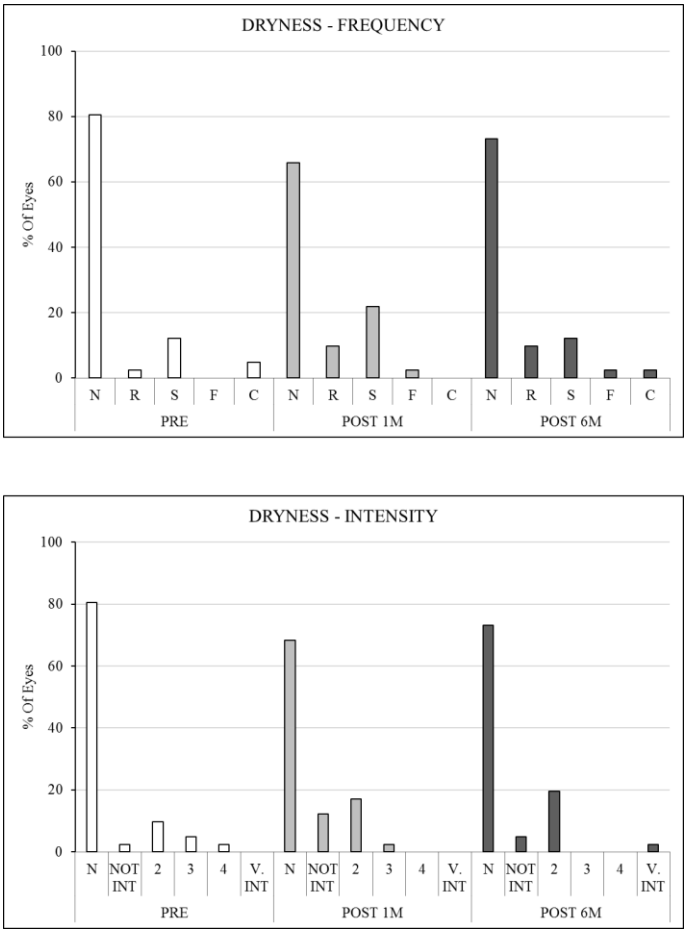

Figure 60 Dryness items in DEQ-5 questionnaires score pre-, 1 and 6 months after the surgery N = 41 eyes (p> 0.05). Please note Frequency options were: N= Never, R= Rarely, S= Sometimes, F= Frequently, C= Constantly. Intensity options were: N= Never have it, NOT INT= Not at All Intense, Score of 2, 3, 4, V.INT= Very Intense.

The frequency of watery eyes reported was found to be significantly increased at the post-operative follow-up at 1 (p= 0.013) and 6 months (p= 0.018) compared with the pre-operative data (Figure 61).

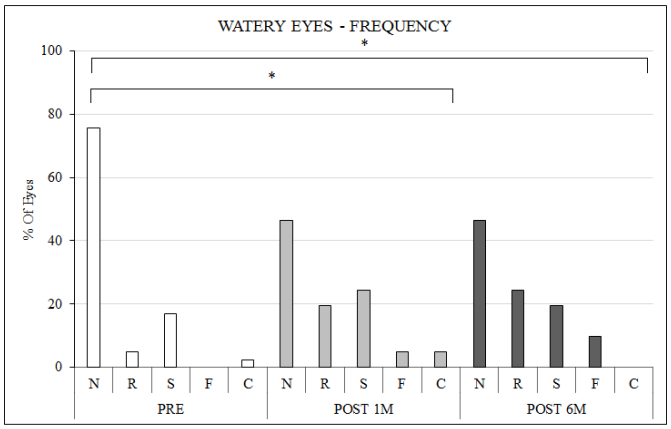

Figure 61 Watery eyes frequency items in DEQ-5 questionnaires score pre-, 1 and 6 months after the surgery N = 41 eyes. Frequency answers were: N= Never, R= Rarely, S= Sometimes, F= Frequently, C= Constantly. Asterisks denote a significant difference.

Table 18 reports the correlations considered in the study:

Spearman's rank-order correlation		POST_OP_6M_SEQ	PRE_OP_NITBUT	PRE_OP_DEQ	POST_OP_1M_DEQ	POST_OP_6M_DEQ	POST_OP_1M_GLARE_AREA_TOTAL	POST_OP_6M_GLARE_AREA_TOTAL
PRE_OP_NITBUT	Correlation Coefficient	0.138	1.000	-0.547	-0.344	-0.370	0.062	-0.046
	Sig. (2-tailed)	0.389		0.000	0.028	0.017	0.701	0.777
PRE_OP_DEQ	Correlation Coefficient	-0.043	-0.547	1.000	0.485**	0.538**	0.303	0.269
	Sig. (2-tailed)	0.789	0.000		0.001	0.0002	0.054	0.089

Table 18 Correlation between spherical equivalent refraction (SEQ), non-invasive tear break-up time (NITBUT), Dry Eye Questionnaire 5-items (DEQ) and glare before and after the surgery (*p-value < 0.05). N=41. Asterisks denote a significant difference.

Pre-operative NITBUT showed no correlation with the post-operative SEQ (r= 0.138; p= 0.39), but a significant correlation was found with the symptomatology assessed before (r= -0.547; p <0.001), 1 month (r= -0.344; p= 0.028) and 6- months after surgery (r= -0.370; p= 0.017) (Figure 62, A, B and C respectively). However, pre-operative NITBUT did not demonstrate any significant correlation with the post-operative level of dysphotopsia (GLARE_AREA_TOTAL) and at 1 month (r= 0.062; p= 0.701) and 6 months (r= -0.046; p= 0.777).

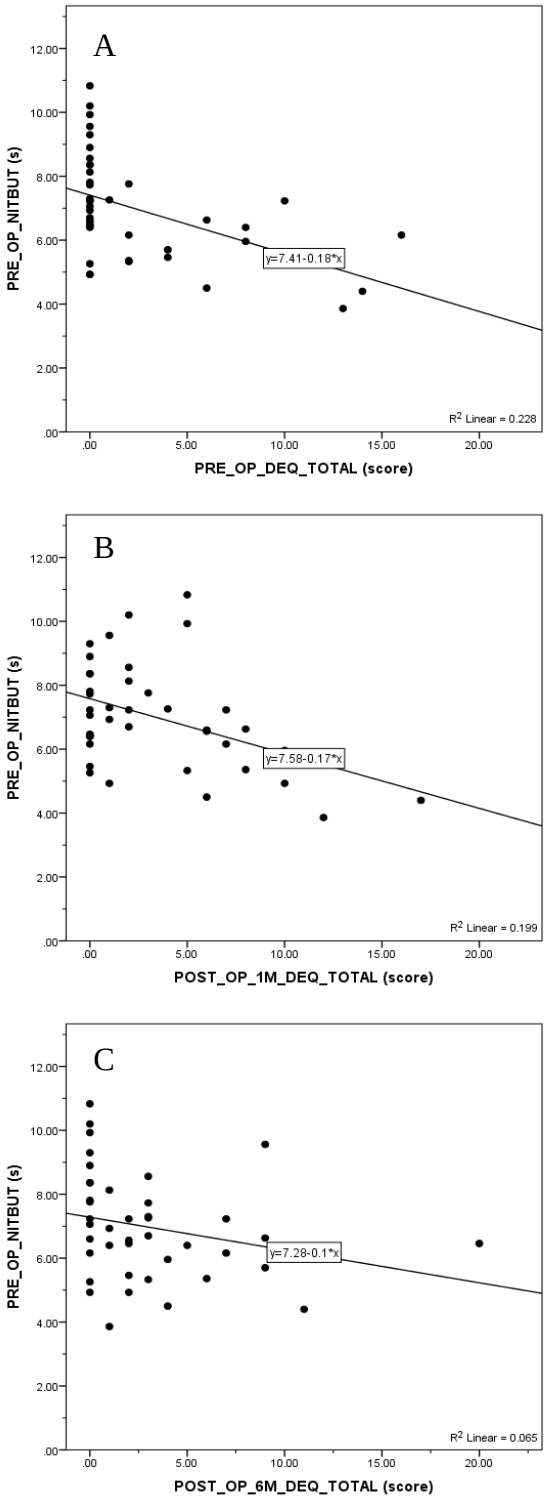

Figure 62 Pre-operative non-invasive tear break-up time values and the symptomatology assessed before (A), 1 month (B) and 6-months (C) after surgery. Dry eye questionnaire 5-items (DEQ), non-invasive break-up time (NITBUT).

Pre-operative DEQ-5 questionnaire scores did not correlate significantly with post-operative SEQ values (r= -0.043; p= 0.789). A statistically significant association was observed when pre-operative symptomatology was correlated with the scores at 1 month (r= 0.485; p= 0.01) and 6 months (r= 0.538; p= 0.0002) after surgery (Figure 63). DED symptomatology was not correlated with level of glare after surgery, neither at 1 month (r= 0.303; p= 0.054) or at 6 months after surgery (r= 0.269; p= 0.089).

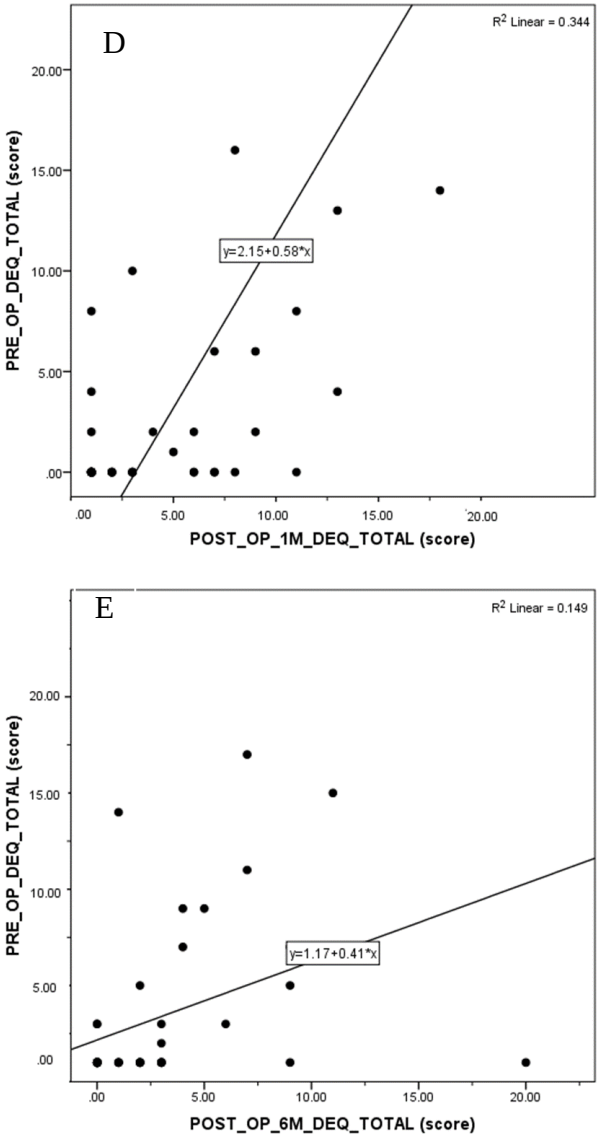

Figure 63 Pre-operative symptomatology assessed before *vs* 1 month (D) and before *vs* and 6-months (E) after surgery. Dry eye questionnaire 5-items (DEQ).

6.3 Discussion

Cataract is one of the most common causes of vision loss that affects more than 16 million people worldwide (Asbell et al., 2005; Y. Liu et al., 2017; Modenese et al., 2018). Together with vision, QoL and an individual's independence, especially in people older than 65 years, could be affected by the condition (Brian et al., 2001). Nowadays, cataract surgery followed by IOL implantation is able to restore vision with minimal risks (E. Chan et al., 2010; Y. Liu et al., 2017; Qin et al., 2018; S. Y. Wang et al., 2017). In the present study, the results showed good outcomes after surgery in terms of residual refractive error (SEQ) with 90% of the study populations (37 of 41 eyes) within ±0.50 D and all the patients with a CDVA of 0 logMAR. No operative complications were reported. These favourable results are consistent with those presented in previous studies (Aristodemou et al., 2019; Gogate et al., 2005; Lam et al., 2015; Lundstrom et al., 2013; Qin et al., 2018). Cataract-induced glare can lead to a reduction of visual quality and contrast sensitivity (Y. Liu et al., 2017; Williamson et al., 1992). By the means of a new hand-held device, the Aston Halometer, the changes before and after surgery in terms of glare were tracked reporting a substantial diminution of pre-operative glare: in fact, the surgery reduced light scattering from an average value (area) of 36.4 to 12.0 and 7.8, corresponding to a reduction of 67% and 79% at the post-op follow-up at 1 and 6 months, respectively.

In terms of DED assessment, some risks factors are related to cataract surgery which could potentially negatively impact the ocular surface and the tear film (Cetinkaya et al., 2015; Y. Cho et al., 2009; X. M. Li et al., 2007). Disruption of corneal nerves, corneal epithelial cells and goblet cells due to the surgical incisions are the factors likely to be most responsible for DED onset after surgery (Park et al., 2016; Trattler et al., 2017; Xue et al., 2018). Additionally, other factors such as the irrigation of the ocular surface (Kasetsuwan et al., 2013), the operating microscope light (Ipek et al., 2018), lack of lubrication, reduction of the intraoperative tear flow (Movahedan et al., 2012), and the use of the pre- and post-operative pharmaceutical agents (Mencucci et al., 2015) (e.g. anaesthetics, antibiotic and anti-inflammatory drops) can lead to similar problems. Ophthalmic professionals should consider taking measures to improve the ocular surface to reduce possible errors in the pre-operative IOL calculations and to avoid inducing postoperative symptoms that could adversely affect satisfaction with outcome (Afsharkhamseh et al., 2017). In fact, even when the surgery has been successfully performed, a considerable proportion of patients do report dissatisfaction due to postoperative residual refractive errors and discomfort (Kinard et al., 2013). In a recent study by Gibbons (2016), the most common complaints after cataract surgery were residual refractive errors (57%) and dry eye (35%). Alio et al. (2014a) reported that one limiting factor in achieving good visual outcomes after phacoemulsification surgery followed by IOL implantation is pre-existing corneal astigmatism. As keratometry and topography are devices typically based on the reflection from

the tear film, the measurements could potentially suffer from unexpected variability in dry eye patients. Epitropoulos et al. (2015) reported that patients with hyperosmolarity of the tear, one of the DED markers recommended in the TFOS DEWS II report (Willcox et al., 2017), showed approximately 1 D of variability in the readings with a potential influence over the final IOL calculation of more than 0.5 D. Specifically, ocular biometry prior to IOL surgery may demonstrate more variable measurements in dry eye patients. In a study by Bhatt et al. (2008), the patients whose SEQ deviated from the predicted value were measured with both biometry based on interferometry and that based on ultrasound. A difference of more than 1 D due to severe dry eye was found. The evidence-based methodology adopted in the current study has included dryness symptoms and signs prior surgery to determine how they affect the post-operative refractive outcomes, dryness symptoms and level of light scatter (e.g. glare). In order to do so, DED symptoms were assessed considering the DEQ-5 questionnaire while signs were measured non-invasively through the NITBUT test (Wolffsohn et al., 2017).

Since late 80s, subjective questionnaires have considered to monitor patients outcomes after cataract surgery: in a randomized controlled trial of 327 patients evaluated 1 year after lens surgery, Cheng (1987) compared the increase in patients rehabilitation time and cost-efficacy when surgery was compared with contact lens wear. More recently, a series of subjective questionnaires have been developed and used after intra-ocular lens implantation: for example, the Catquest-9SF or the CAT-PROMS5 (short questionnaire) that has demonstrated good performance and patient acceptability (Sparrow et al., 2018) or the quality of vision (QoV) questionnaire developed by Skiadaresi et al. (2012) to assess the patient-reported outcomes in terms of improvement in visual symptoms. DED questionnaires are able to detect the condition and its severity and monitor symptoms over time. DEQ-5 was selected due to its short length and the ability to discriminate in all the appointments scheduled. In the present study population, the prevalence of DED symptomatology increased from 20% pre-surgery to 41% at 1 month and then with a partial recovery to 34% at 6 months after surgery. These results were in agreement with Iglesias et al. (2017) where the authors reported DED-like symptoms up to 6 months in 32% of the patients. Additionally, the findings presented along this chapter were in agreement with Sahu et al. (2015) that have measured a peak scores of DEQ-5 questionnaire 2 months after surgery. However, despite the surgery has impacted all the questions increasing the scores in discomfort and dryness of the patients enrolled in the study, only the frequency of having “watery” eyes has found significant ($p< 0.05$). Gupta et al. (2018) reported that 54% of the patients ($n= 100$) presenting for cataract surgery had DED symptoms (OSDI or SANDE questionnaires) while X. M. Li et al. (2007) noted that preexisting DED was an important signal to develop symptomatology after the procedures. The current results showed a positive and significant correlation between pre-surgery DEQ-5 score and the following visits at 1 month ($r= 0.485$; $p=$

0.001) and 6 months (r= 0.538; p= 0.0002) indicating that an increased DED symptomatology before cataract surgery could potentially affect dryness symptoms and underrate the safety and efficacy of the uneventful procedures.

EDE is the most prevalent subtype of DED and is characterized by a reduced tear film stability (Bron et al., 2017; Chhadva et al., 2017). In this study, in order to be as less as possible invasive, the tear film stability was determined without the use of vital dyes (e.g. fluorescein) by the means of a Tearscope® with the intention of reducing the variability of the measurements (three repeats) (Elliott et al., 1998). Any significant correlations were reported with the refractive outcomes after surgery (SEQ at 6 months) but NITBUT before the surgery was significantly correlated with the symptomatology assessed in all the appointments. Despite different investigations have described the missing link between signs and symptoms (Bartlett et al., 2015; K. Nichols et al., 2004b), the results obtained from the current investigation are in agreement with Trattler et al. (2017) who have reported that most of the patients had reduced tear film stability before attending lens surgery, and potentially the instability before the surgery is more likely to have an increase in DED symptomatology after the procedure.

Visual quality could also be potentially affected by fluctuations produced by a depleted tear film and ocular discomfort (Huang et al., 2002). After correlating both pre-operative DED signs and symptoms (NITBUT and DEQ-5), with the hypothesis that both metrics were able to affect light scatter after surgery, an association was not found. In the case of NITBUT, a possible reason for the lack of correlation could be due to the nature of the two metrics. In fact, while the measurements of the glare using the AH was performed with the patients free to blink (dynamic conditions), NITBUT was measured with the patient forced to stare (static conditions) as long as the practitioner was able to detect a break in the tear film using the Tearscope® or as long as the patient was able to keep the eyes open. In other words, the patients were able to solve the potential visual fluctuations due to the tear film instability increasing the blink rate influencing the association of the visual metrics (glare) with DED signs. For the DED symptoms, the surgical procedure was able to reduce pre-operative glare due to lens opacification but the DEQ-5 questionnaire used was not able to provide detailed information about the visual improvement experienced by the patients. In fact, in the first post-operative follow-up (1 month), glare reduction was approximately 67% of the pre-operative value whereas the DEQ-5 increased to 41%. After 6 months, the same tendency was observed again: glare was decreased by 79% and the DEQ-5 was increased to 34% compared with the pre-operative values.

6.3.1 Limitations of the Study

Some limitations of this study are acknowledged. This study was an analysis of data (retrospective study) conducted on a modest number of subjects (n= 41) and there was no control group that did not undergo surgery included. Moreover, the inclusion of additional DED metrics (e.g. staining with vital dyes or Meibography) to correlate with the tear film stability measured over the time could have been useful to improve the understanding of the DED diagnosis in the current cohorts. In fact, due to the age of the study group (risk factor) and the multifactorial nature of the condition considering more signs is crucial to define DED subtypes (ADDE and EDE, see 1.4.2).

6.3.2 Conclusion

The study has demonstrated that DED symptomatology is increased after cataract surgery. In patients with previous DED symptoms correlated with the instability of the tear film, symptomatology is more likely to increase after surgery up to 6 months.

Additionally, for the first time, the current investigation was able to report the analysis of the pre-operative measurements of DEQ-5 and NITBUT that were not correlated with refractive outcome or objective assessment of glare using an Aston Halometer. However, DEQ-5 is a useful tool to evaluate ocular comfort but it is not designed to consider visual function that could potentially be affected by DED or by lens opacification and may not be a good sensitive indicator of post-operative vision or refractive outcome.

In summary, the inclusion of a pre-operative screening of dryness signs and symptoms prior to cataract surgery could potentially avoid the reduction in patients' comfort after the procedure. However, further researches are needed to establish the impact of phacoemulsification surgery on DED metrics could make DED variability-induced less substantial on lens surgery outcomes.

Chapter 7: Pilot study on clinical outcomes after small incision lenticule extraction (SMILE) surgery.

7.1 Introduction

Femtosecond laser technology has revolutionised laser refractive surgery since its implementation (Reinstein et al., 2014a) (see also 1.5.1.1.4). The first studies on understanding the safety and efficacy of the technique were performed over 15 years ago (Ratkay-Traub et al., 2003) while more relevant results were discovered in large cohort studies in 2010 (Blum et al.), 2013 (Vestergaard et al.), 2014 (J. R. Kim et al.) and 2017 (Reinstein et al., 2017b).

In the UK, more than 50,000 refractive surgery treatments have already been carried out (Barsam, 2017) and several ophthalmic surgeons have embraced the use of femtosecond lasers in their operating theatres. Initially, the femtosecond laser had been introduced to create a more precise flap in LASIK surgery compared with a microkeratome (stainless blade) (C. Sun et al., 2013) and since the advent of SMILE, it is now used as an "all-in-one" procedure, starting from the lenticule creation up to the side cut. However, as previously observed in a prospective evaluation by Titiyal et al. (2017), SMILE is not free from difficulties: the most common complications recorded in the surgeons learning curve analysis were lenticule dissection and lenticule extraction. In fact, from Titiyal et al. findings these complications in 16% of the study cohort during the first 50 procedures while a complication rate reduced to 2% in the following 50 operations.

The purpose of this study was to assess the clinical outcomes and tear film stability before and after the first cases of SMILE undertaken by surgeons in their early learning curve at a private eye hospital in the UK.

Methods

7.2 Study design

This is a retrospective study that has received a favourable opinion from the Optegra Eye Hospital London Medical Advisory Committee. The clinical records were entered the EMR system, from which the results were exported and provided to the author for analysis.

7.2.1 Subjects

The data considered are based on the early clinical outcomes of the first SMILE procedures performed in a single centre, private eye hospital in the UK (Optegra Eye Hospital London). All examinations included in the data analysis were performed pre-operatively and 3 months post-operatively.

The study cohort composed of 71 eyes of 37 patients (21 males and 16 females) with myopia associated with or without astigmatism: mean spherical equivalent refraction (SEQ_PRE) was -5.61 ± 2.25 Dioptres (D) with a range from -1.25 D to -10.00 D. The mean age was 33 ± 8 years. All surgeries were performed bilaterally, except in three patients that had surgery in one eye only because of the monocular refractive error. The target refraction was set to plano (0 D) to achieve emmetropia. No attempt was made to correct presbyopia in the study population (e.g. monovision treatment).

The inclusion and exclusion criteria, ethics permissions, clinical and dry eye assessment for the study are detailed in Chapter 2. However, an informed consent was obtained prior the study which has included the pre-operative measurement of UDVA (Snellen) and CDVA (Snellen and logMAR) at 6 meters using Topcon CC-100 computerized test charts, subjective manifest and cycloplegic refraction using an automatic phoropter head (Topcon, Tokyo, Japan), scotopic pupil size measurement with a handheld pupilometer Colvard (Oasis, Glendora, US), ocular motor balance and dominance testing. The post-operative spherical equivalent refraction (SEQ_3M) considered in the study, was determined by the post-operative subjective refraction measured at the 3 months' follow-up.

Additionally, simulated keratometry (SimK) was obtained using an Oculus Pentacam (Oculus, Wetzlar, Germany): whereby cross-sectional scans were captured using a "25-picture scan" mode in order to form a total keratometry map. Only the scans graded with acceptable quality by the instrument were referenced. All the keratometer measurements included were based on a 15° ring around the anterior corneal apex.

7.2.2 Dry eye assessment

The anterior segment assessment and TBUT by the means of a digital slit-lamp Topcon SL-D3013 (Topcon, Tokyo, Japan) were performed in all the subjects as described in section 2.4.

7.2.3 SMILE surgery

All the surgeries were performed by trained consultant ophthalmic surgeons (A.H., A.S. and R.M.). Pre-operative disinfection of the external part of the eye and anexa using 5% povidone-iodine 1 hour prior to surgery was carried out in all the cases.

The laser system used was the VisuMax femtosecond laser (Carl Zeiss Meditec AG, Jena, Germany). The device frequency was set to 500 kHz with a spot energy of 140 nJ. The spot distance was 4.3 μm and the tracking distance was 1.8 μm. The lenticule diameter was between 6.0 and 7 mm, depending on the pre-operative scotopic pupil size. Incision position was placed between 80-120° and a tunnel size 2 to 4 mm was used. The standard depth of the anterior lenticule was set to 135-140 μm. The same approach was used in all patients.

All surgeries started with topical anaesthesia using two drops of Proxymetacaine 0.5% applied 5 minutes and 1 minute before the procedure. At this stage, the ocular surface was irrigated and cleaned using preservative-free saline. Patients were instructed at each phase of the procedure, positioned under the laser and asked to fixate a green target to maintain fixation. The device was able to automatically control the pressure during the suction (approx. 20-25s duration) while a curved plano glass was placed in contact with the eye selected (Figure 64).

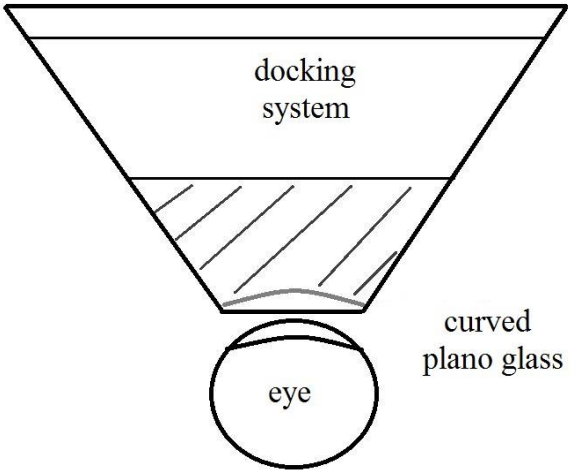

Figure 64 SMILE surgery docking system: the curved plano glass (pictured in grey line) is placed over the eye before starting the dissection procedure allowing through suction to create the lenticule.

Then the procedure was carried following four different steps:

1. cutting of the posterior surface of the lenticule
2. performing the vertical incision around lenticule perimeter
3. cutting of the anterior surface of the lenticule
4. creating the side cut entrance (corneal periphery) to allow the micromanipulator to dissect the lenticule and to the forceps to carefully extract the lenticule

After removal of the lenticule, the stromal tissue was rinsed with preservative-free saline. In the presence of epithelial abrasion, a bandage contact lens was applied. After surgery, patients were prescribed Dexamethasone 0.1% and Ofloxacin 3mg/ml. Instructions for both sets of drops were 1 drop to be used 4 times per day for 7 days.

7.2.4 Statistical analysis

All statistical analysis was performed using SPSS 23.0 (SPSS Inc., Chicago, IL, USA).

The main outcomes measures were: SEQ, UDVA, CDVA, TBUT and SimK before (_PRE) and 3 months after surgery (_3M). The Shapiro-Wilk test was used for testing data normality: Student's *t*-test was considered in normal data such as pre- and post-operative SEQ, while non-normally distributed data such as UDVA, CDVA, TBUT and SimK were tested using Wilcoxon signed ranks test. Spearman's correlation coefficient was used to assess the association between the individual clinical signs of TBUT and SimK after surgery. A p-value of less than 0.05 was studied to be statistically significant.

7.3 Results

Pre- and post-operative data are summarized in Table 19.

Stats	Baseline, mean ± SD (_PRE)	3-months, mean ± SD (_3M)	p-value
SEQ (D)	-5.61 ± 2.25	-0.13 ± 0.39	<0.01*
UDVA (logMAR)	1.44 ± 0.51	-0.07 ± 0.11	<0.01*
CDVA (logMAR)	-0.09 ± 0.09	-0.10 ± 0.09	0.927
TBUT (s)	6.2 ± 1.8	5.5 ± 1.7	0.116
CDVA_PRE *vs* UDVA_3M (logMAR)			0.153
SimK (D)	44.00 ± 0.79	39.78 ± 2.07	0.667
TBUT and SimK		Pearson correlation (r)	
		0.44	

Table 19 Clinical data: spherical equivalent refraction (SEQ); diopters (D), uncorrected distance visual acuity (UDVA); log of the minimum angle of resolution (logMAR); corrected distance visual acuity (CDVA); tear break-up time (TBUT); seconds (s); simulated keratometry readings (SimK); CDVA_PRE, corrected distance visual acuity before surgery (CDVA_PRE); uncorrected distance visual acuity 3 months after surgery (UDVA_3M). Asterisks denote a significant difference.

The mean SEQ 3-months after surgery (SEQ_3M) was found to be statistically reduced compared to pre-operative values (SEQ_PRE) ($p < 0.01$). The residual post-operative refraction was within ± 0.50 D of target in 82% of eyes and within ± 1.00 D of target in 94% of eyes (Figure 65).

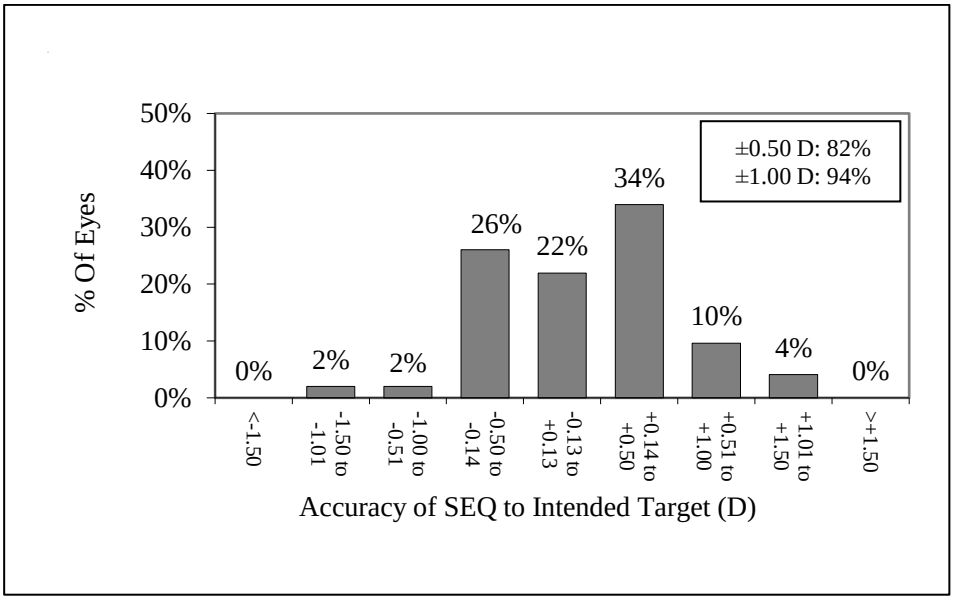

Figure 65 Accuracy of the surgical procedure inters of residual refraction after surgery. Spherical equivalent refraction (SEQ).

After surgery, UDVA improved significantly ($p < 0.01$), while there was no significant difference between pre-operative CDVA and post-operative UDVA at 3 months ($p = 0.153$) (Figure 66).

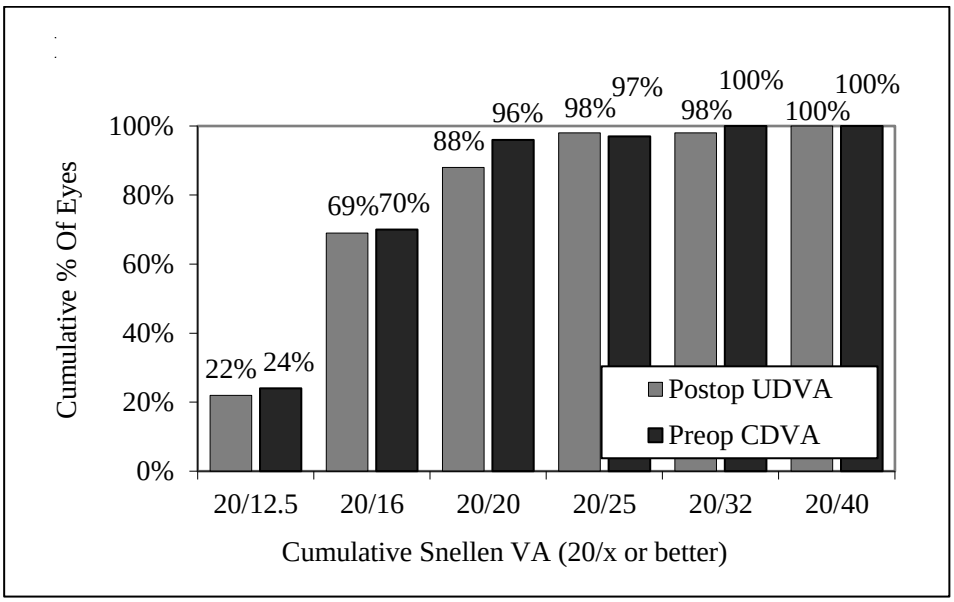

Figure 66 Visual acuity before and after surgery. Preop corrected distance visual acuity (CDVA) vs Postop unaided distance visual acuity (UDVA).

Three months after surgery, TBUT was not significantly different from that measured pre-operatively (Figure 67).

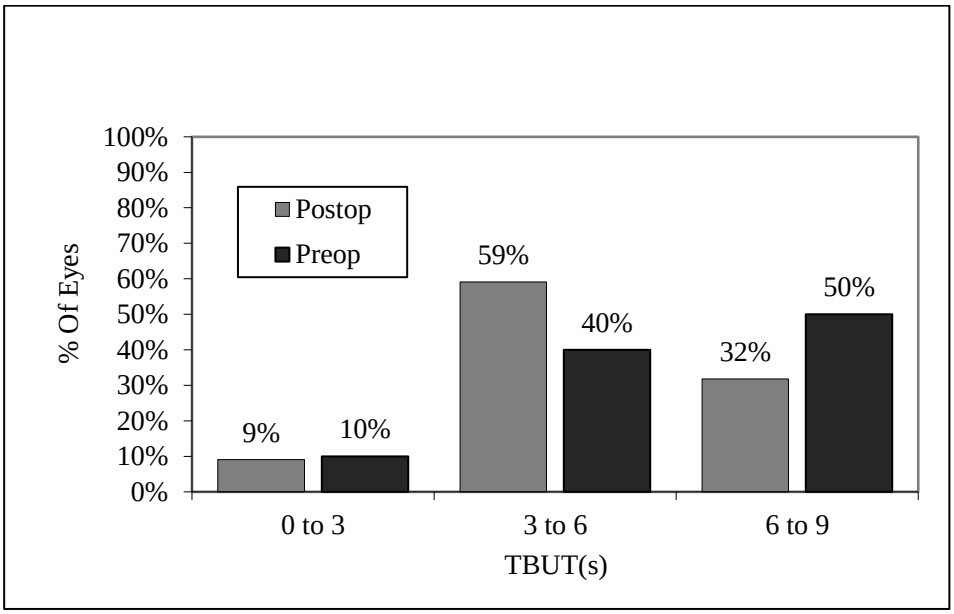

Figure 67 Pre- and post-operative measurements of the tear break-up time (TBUT) (s).

A moderate but positive trend (r= 0.44) was found between the changes in TBUT and SimK after surgery, however not significant (p= 0.651).

Complications were observed in 3 eyes, which included a minor epithelial abrasion in two eyes and some difficulty removing the lenticule in one eye. None of the complications have significantly affected the vision and the results highlighted the safety profile of SMILE by way of mitigating the flap complications that sometimes occur with LASIK (Melki et al., 2001).

7.4 Discussion

SMILE surgical technique has been approved by the FDA in 2016 after a series of pivotal studies that demonstrated its safety and minimally-invasive nature for vision correction (Reinstein et al., 2014b). The point of strength of this technique is related to the nature of the femtosecond laser that allows precise cutting and less post-operative dry eye complications compared to LASIK microkeratome (Aristeidou et al., 2015). In fact, the short laser pulses produced by the device, are focused in a diameter that is under 0.001 mm limiting the photo-disruptive process only to the target tissue (Chiche et al., 2018). Additionally, differently from LASIK surgery, the femtosecond laser is able to create a slice of stromal tissue called a lenticule without creating a flap that is known to reduce corneal sensitivity and lead to DED development (Qiu et al., 2016).

The results obtained by the first procedures in this private hospital settings are in agreement with other research: in fact, Vestergaard et al. (2012) reported in a study cohort of 144 patients that 77% and 95% of the patients were within ± 0.50 D and ± 1.00 D 3 months after surgery, respectively. Additionally, Lin et al. (2014) reported 98% of 31 patients with a SEQ at 3 months after surgery were within ± 1.00 D.

In terms of VA, the current results have showed excellent outcomes as the post-operative UDVA reached 20/20 in 88% of the study cohort, with a slight difference compared with other studies (Hansen et al., 2016; Kamiya et al., 2014). The reason behind these findings could be related to the different surgical settings considered across the research: in a previous study by Shat et al. (2011), the researchers found the relative importance of the scanning trajectory during the procedure. However, they did not report information about difference in energy and spot spacing but suggested that a delayed visual recovery could be provoked by a delayed time in cutting the lenticule. Thus, a speculation can be made as a slight difference observed in the presented results could be potentially accounted to the early phase of the learning curve from the surgeons involved or to the different pre-operative myopic defects to correct.

The tear film secretion and the blinking rate are characteristics related to the ocular surface through the corneal nerves architecture in the anterior surface of the cornea (e.g. epithelium and stroma). In fact, the cornea is one of the most innervated tissues of the human body and any type of influence brought by the refractive surgery may alter or suspend the nervous response leading to DED development (Situ et al., 2010). SMILE surgery is a flap-less procedure, thus is able to minimise the impact over the corneal nerve plexus (Cai et al., 2017; Shaaban et al., 2018; Z Shen et al., 2016b). Following the recent TFOS DEWS II report, Wolffsohn et colleagues (2017) confirmed the positive DED finding in terms of tear film stability (TBUT) under 10 s if measured with fluorescein dye. In the present study cohort, the reduced pre-operative tear TBUT encountered made it possible to address the patients to a type of surgery with a lower risk of

developing DED after the procedure (e.g. flapless SMILE surgery instead of flap creation with LASIK). In fact, before surgery all patients TBUT was below the proposed cut-off with 50%, 40% and 10% between 9 to 6 s, 6 to 3 s and 3 to 0 s, respectively. Additionally, the intended result should, therefore, be a preservation of the TBUT which is used to assess tear film stability. In a comparative study between LASIK and SMILE, Xu et al. (2014) found that dry eye metrics after the flap-less technique were better in the early post-operative evaluations than LASIK. Similar results were provided by Denoyer et al. (2015) where the post-operative TBUT measurements after LASIK were worse than SMILE surgery after 6 months. Although, Demirok et al. (2013), comparing the two laser refractive procedures at 3 months, did not find difference between pre- and post-operative data. A possible explanation of the different outcomes from different researchers could be potentially related to the variability of the TBUT measurements: on the one hand, fluorescein sodium might interfere with the structure of the tear film leading to more unstable results while on the other hand the ability of the practitioner (e.g. identifying correctly the appearance of a tear break) might influence the measurement as well. In a comparative study between invasive and non-invasive TBUT by the means of a K5M, the investigators reported superior TBUT using no staining (Lan et al., 2014).

As recommended by the TFOS DEWS II report, currently there is not a single recognized test for DED diagnosis and at least a symptomatology questionnaire and one homeostasis marker (such as TBUT or osmolarity or ocular surface staining) should be included to improve the diagnosis (Wolffsohn et al., 2017).

The Oculus Pentacam has been considered to evaluate patients' changes on the anterior curvature of the cornea before and after surgery and to relate them with the dry eye metric available, TBUT. The reason behind this correlation was to demonstrate if SMILE surgery, as it is not affecting directly the anterior surface except for the side cut to remove the lenticule, has or has no relationship with the ocular surface, in this case the stability of the tear film. Previously, Hong et al. (1997) reported reduced TBUT after the procedure indicating that the flattening of the corneal surface might be responsible of the changes observed up to 6 months. Additionally, as the Schirmer test findings (tear film volume) were not modified by the surgery, the authors reported that the modifications of the anterior surface by the means of the excimer laser has affected the prevalence of goblet cells that are fundamentals, together with the meibum lipid secreted by the Meibomian glands, to increase the stability of the tear film. However, the correlation presented in this research has failed to be significant, reporting that no difference was observed after SMILE surgery.

7.4.1 Limitation of the Study

This study has demonstrated two main limitations: the restricted number of cases in the retrospective design study and the reduced availability of tear film parameters, apart from TBUT. As mentioned before, the TFOS DEWS II report recommend to include the assessment of symptoms and signs to diagnose DED and exclude any other conditions that might be misdiagnosed (e.g. ocular allergy, SS, etc.) (Stapleton et al., 2017).

7.4.2 Conclusion

These preliminary results of three surgeons' first procedures in a private hospital setting advise that SMILE treatment is safe, effective and predictable as post-operative UDVA is equivalent to CDVA prior to the surgery and post-operative residual refraction is close to the predicted value (95% of the study cohort within ± 1.00 D). Nevertheless, there is a small reduction in measured tear break-up time, but this is not likely to represent a clinically significant reduction. On the contrary, it should be seen as a preservation in the early post-operative TBUT compared to more impacting surgery (e.g. LASIK and PRK).

Finally, the current results suggest that further research is required to better understand the impact of SMILE on the ocular surface in a "real world" settings.

Chapter 8: Early clinical changes in dry eye metrics and subbasal corneal nerve morphology before and after laser-assisted in situ keratomileusis (LASIK) and small incision lenticule extraction (SMILE) surgery.

8.1 Introduction

As detailed in Chapter 1, different surgical laser options for correcting myopia have been developed in the last decades with good results in terms of efficacy and safety of the procedures (Chansue et al., 2015a, 2015b; Chua et al., 2018; Farjo et al., 2013; Ganesh et al., 2018a; Moshirfar et al., 2018a; Shortt et al., 2006; Tomita et al., 2014). However, corneal laser vision correction is not without risk and these procedures can potentially impact on the ocular surface and lead to development of DED (Gao et al., 2014; J B Lee et al., 2000; Ni et al., 2015; O'Keefe, 1998; Z Shen et al., 2016b; Trokel et al., 1983). Researchers have shown a relationship between the physical, but temporary, effects of the surgical procedure (e.g. laser ablation) on the subbasal corneal nerves: in fact, the transections of the subbasal corneal nerves have been associated with a reduction in tear secretion due to diminution of corneal sensitivity (Beheshtnejad et al., 2015; De Paiva et al., 2006; Demirok et al., 2013; Denoyer et al., 2015; Labbe et al., 2013; J. K. Lee et al., 2015; Lui et al., 2003; Salomao et al., 2009; Sheludchenko et al., 2002; Shoja et al., 2007; C. Sun et al., 2013). Corneal nerve fibres damage may cause impaired corneal innervation resulting in decreased sensitivity and loss of homeostasis of the ocular surface where epithelial and endothelial cell functions are degraded (e.g. decreased cell migration and cell mitosis) (Lum et al., 2018). Additionally, the corneal epithelium and corneal nerves help each other in promoting growth factors: the epithelium is responsible for producing and secreting important growth factors to help corneal nerve trophism (neuropeptides, neurotrophins and nerve growth factor, etc.) whereas the nerves produce healing neuromediators for the regeneration of the epithelial cells (Lambiase et al., 2013; Mastropasqua et al., 2017). In different studies by Araki et al. (1993; 1994), the researchers showed results from denervated corneas which were more likely to suffer from corneal abnormalities, recurrent superficial erosion, impaired wound healing and infection.

Corneal sensitivity is assured by maintaining the homeostasis of the corneal nerves (stroma, subbasal nerve plexus and epithelial nerves of the cornea). In fact, a reduction in corneal sensitivity because of an injury (e.g. trauma or surgical procedure) will dramatically affect the correct functioning of the reflex loop formed by the ocular surface, trigeminal nerve, brain stem, facial nerve and lacrimal gland. The stimulation of the ocular surface nerves produces neural impulses transmitted via the trigeminal cranial nerve to the brain. Therefore, the brain transfers secretomotor nerve impulses via sympathetic nerves to the lacrimal gland which is responsible for tear secretion thus ensuring the homeostasis of the ocular surface (e.g. avoiding increased TF osmolarity) (Rolando et al., 2001) (Figure 68).

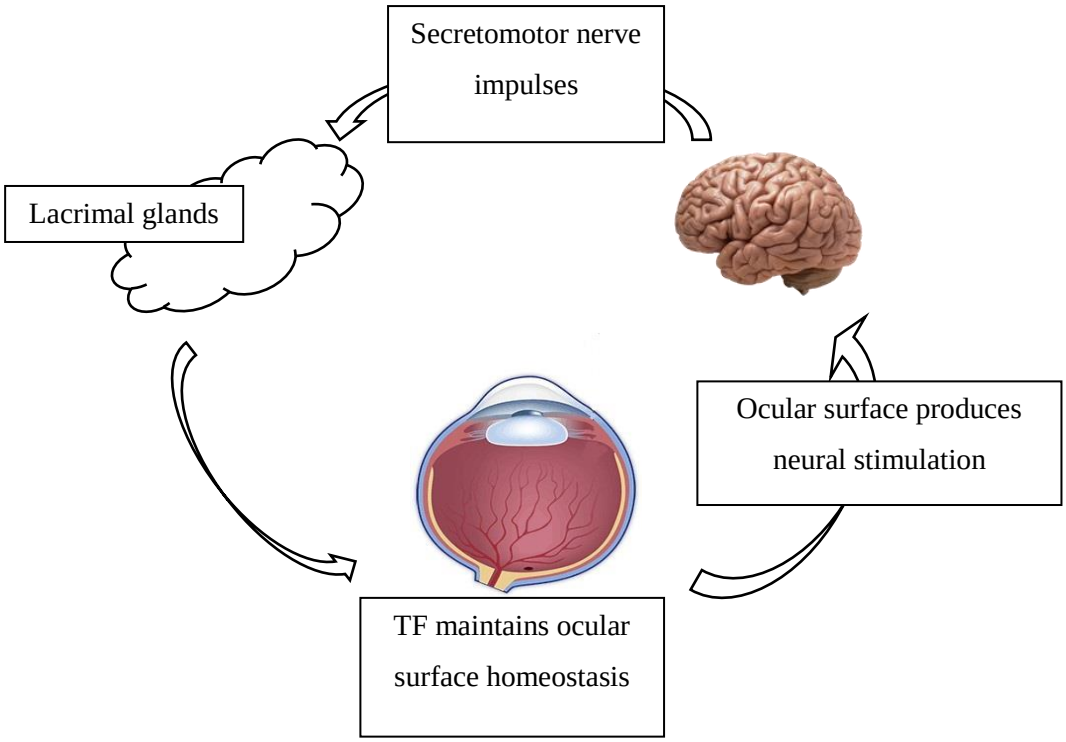

Figure 68 Schematic diagram of the reflex loop connection within the ocular surface and the lacrimal glands. Adapted from Rolando et al. 2001.

Corneal laser treatments can reduce the functionality of the neural circle which connects the ocular surface with the lacrimal gland resulting in a diminution in TF secretion together with diminished blink rates (Araki et al., 1993; Bragheeth et al., 2005; Calvillo et al., 2004; Frueh et al., 1998; Gonzalez-Perez et al., 2012; Muller et al., 2003).

LASIK surgery, one of the most common corneal refractive procedures to correct myopia, hyperopia and astigmatism (Duffey et al., 2005), is typically performed using a femtosecond laser (FS-LASIK), after receiving FDA approval in 2000 (Marino et al., 2017). The corneal flap created during FS-LASIK procedures has shown consistency and uniformity compared with the traditional microkeratome blade approach used previously (AlArfaj et al., 2014). FS-LASIK has been shown to have less complications such as irregular flap (post-operative astigmatism), corneal epithelial cell in-growth and diffuse lamellar keratitis and superior refractive outcomes than mechanical LASIK (Cosar et al., 2013; Hashmani et al., 2017; Romero-Diaz-de-Leon et al., 2016; Xia et al., 2015). However, patients with pre-operative DED may be considered unsuitable for laser vision correction surgery, if the condition is not amenable to treatment, as it is a cause of post-operative issues including visual discomfort, neuropathic pain and corneal infection (Ambrosio et al., 2003b).

SMILE surgery has received FDA approval in 2016 to correct myopia and astigmatism. One of the highlighted benefits of SMILE is the minimal disruption to the anterior corneal nerve plexus, through the use of a side cut tunnel (rather than a flap) and the removal

of mid-posterior stromal tissue (rather than more anterior tissue removal) (M. Li et al., 2013a). Additionally, the procedure aims to minimise the alteration of the corneal biomechanics, but more clinical studies are needed to confirm this (Chiche et al., 2018).

In a meta-analysis by Yan et al. (2017), 4223 eyes from 2 randomized clinical trials (RCTs) and 25 study cohorts were considered to assess the refractive outcomes between the FS-LASIK and SMILE surgery techniques and high order aberrations, ocular corneal biomechanics and contrast sensitivity. The researchers concluded that both procedures are a safe and effective for correcting myopia and astigmatism. In fact, they reported the advantages of SMILE vs. LASIK surgery in terms of reductions in post-operative aberrations (higher order aberrations and fourth order spherical aberration, $p< 0.001$). Additionally, SMILE surgery findings were more favourable in terms of preserving corneal biomechanics (corneal hysteresis $p= 0.0005$ and corneal resistance factor $p= 0.02$) compared to FS-LASIK.

Nowadays, there is a plethora of techniques available to assess and support the diagnosis of DED. Some of these rely on subjective responses from the patient (e.g. validated questionnaires), while others, especially with newer devices, can objectively analyse and estimate DED metrics such as tear film quantity, tear film stability and tear film composition. Previous research studies have considered tear film metrics before and after FS-LASIK and SMILE surgery. Xia et al. (2016) reported significant reductions in tear volume with FS-LASIK at 6-months' post-procedure, while SMILE patients had returned to baseline values by 3-months. In terms of DED symptoms, Li et al. (2013b) reported dry eye signs in both groups immediately after surgery with a significant reduction in TBUT up to 3 months in the SMILE group, and up to 6 months in the FS-LASIK group. These findings were supported by Gao et al. (2014), who found that TBUT was more reduced following FS-LASIK compared to SMILE. Following the recent TFOS DEWS II report (Wolffsohn et al., 2017), hyperosmolarity and instability of the tear film are considered as part of the "core mechanism" of DED. Denoyer et al. (2015) found high osmolarity values and reduced TBUT results in FS-LASIK group 6-months post-operatively with more than half of the cohort (57%) requiring the use of ocular lubricants post-procedure while this was the only case for 20% in the SMILE group.

The impact of corneal refractive procedures on the structure and function of the corneal nerve has been intensively investigated over the past decade or so using IVCM (X. Chen et al., 2018; Denoyer et al., 2015; Kheirkhah et al., 2017; M. Li et al., 2013a; M. Liu et al., 2015b; Riau et al., 2011; A. G. Smith et al., 2013; F. Zhang et al., 2012). IVCM can potentially help to disclose pathophysiology and help with the diagnosis of changes related to diabetes, keratitis and DED (Giannaccare et al., 2019; Matsumoto et al., 2018; McKelvie et al., 2018; Ostrovski et al., 2015). When applied to the ocular surface, IVCM can image epithelial cells, inflammatory cells, stromal cells (e.g. keratocytes) and MG. However, one of

the most important IVCM application is to evaluate with minimal invasiveness the overall structure of the corneal nerves, in particular, nerve fibre length and nerve fibre density. In fact, IVCM is able to provide scans of the living human cornea and the quality of the acquisitions can be comparable with histological samples without the need for fixing and processing samples, as with conventional light and electron microscopy (Pavan-Langston et al., 2010). For these reasons, IVCM has become an invaluable tool for diagnosing and monitoring corneal changes after ophthalmic treatments including laser vision correction due to the physical impact that the surgery could potentially generate over the ocular surface and in particular in the corneal nerve fibres. Bragheeth et al. (2005) considered the relationship between corneal sensitivity and corneal nerve fibres using IVCM. The researchers found a reduction, for more than 6 months, after LASIK surgery in corneal sensitivity assessed with a Cochet-Bonnet aesthesiometer (Luneau, France). Using IVCM, they observed the recovery of corneal innervation was not precisely correlated with the recovery of corneal sensitivity. Demirok et al. (2013) measured the corneal sensitivity using a Cochet-Bonnet aesthesiometer reporting a greater decrease after FS-LASIK than with SMILE for up to 3 months after surgery. Using IVCM, Denoyer et al. (2015) found the subbasal nerve structure was less affected by SMILE than with FS-LASIK at 1 and 6-months follow-up. The researchers suggested that the creation of the flap was responsible for the reduced nerve fibre density, nerve fibre length and nerve branchings. Also, Li et al. (2013b) in two different studies found that the corneal subbasal nerve morphology, corneal sensitivity and the tear film parameters (TBUT, OSDI, Schirmer test and corneal staining) after surgery were better with SMILE than LASIK. The impact of new surgical procedures on the ocular surface was analysed by Vestergaard et al. (2013a) who investigated the influence of FLEX through a LASIK-like flap and SMILE in high myopes using an IVCM device. They found the femtosecond laser flap-less surgery (SMILE) less likely to induce dry eye than the femtosecond laser flap surgery (FLEX) and that corneal nerve density did not correlate with DED metrics. However, despite the increasing interest in research and clinical settings in using IVCM in DED (Hong et al., 2010; Messmer et al., 2005; Randon et al., 2018), limitations in the software to process the scans from IVCM has been an issue. In fact, most of the scans acquired with IVCM are subsequently processed using manual or semiautomatic programs (Ahmed et al., 2012; Hertz et al., 2011; Wu et al., 2012). The manual tracing of nerves, using programmes such as Matlab or Java algorithms (Meijering, 2010) have demonstrated several disadvantages and are time-consuming, and subject to observer bias which can impact on reproducibility and repeatability, etc.

In a review by Alhatem et al. (2012), the researchers provided several possible applications of IVCM in DED such as examining the conjunctival epithelium and Goblet cells for alterations, corneal epithelial cell density, hyperreflectivity of the stromal keratocytes,

corneal inflammatory cells, MG morphology and corneal nerves. However, they reported the need for an objective methodology which can help the clinicians to tailor treatments based on the observations from IVCM in DED. The availability of more accurate objective quantification of corneal nerves assessed by IVCM could also provide new insight in longitudinal studies or clinical trials with large numbers of participants. In a study by Dehghani et al. (2014), ACCMetrics, a software for automatic quantification of the corneal nerve structure (see section 8.2.5), showed excellent results from Bland-Altman plots and high intraclass correlation coefficient (ICC) with manual or semi-automated methods of analysis. Additionally, ACCMetrics was shwon to be 7x and 4x faster than manual and semi-automated methods respectively. In a study by Petropoulos et al. (2014), the automatic quantification of the subbasal corneal nerves required approximately 10 to 22 seconds versus a manual analysis which can take from 2 to 7 minutes per image depending on the density of the nerves displayed. Recently, Giannaccare et al. (2019) presented the first study using ACCMetrics in IVCM scans to analyse the subbasal nerve plexus in healthy and DED patients. The researchers reported that DED patients had reduced density of the main fibre nerves and branches with limitations on main nerves length compared to healthy subjects. Thus, ACCMetrics was able to discriminate DED patients from healthy subjects allowing new possible applications of this powerful analysis tool.

In summary, a number of studies have been performed on the relationship between DED development with traditional and modern corneal laser vision correction procedures. However, there is heterogeneity in the protocols considered: some studies have included only objective DED metrics (TBUT, corneal staining, etc.), while others have included subjective tests with no validated questionnaires, with others only tracking changes related to post-operative DED using third party software for corneal nerve analysis. To address the gaps in the current knowledge, the aims of the present study were:

- to assess and compare the early clinical outcomes in patients undergoing FS-LASIK and SMILE surgery
- to determinate the impact of modern corneal laser procedures using the recommended protocol for DED assessment from the TFOS DEWS II report adopting the most advanced and least invasive devices available in the market at the current time of writing (Wolffsohn et al., 2017)
- to display and track changes in the corneal nerve fibres structure using IVCM and to apply a fully automated quantification of the corneal nerve fibre metrics with a validated software ACCMetrics which has been shown to be a rapid, objective and consistent alternative to manual or semi-automatic quantification (Dehghani et al., 2014; Giannaccare et al., 2019)

- to assess which, if any, DED metrics are correlated with the IVCM corneal nerve fibre metrics

8.2 Methods

8.2.1 Study design

This was a prospective, longitudinal and observational study that received a favourable opinion from the Aston University Research Ethics Committee.

8.2.2 Subjects

The patients enrolled in this study were divided into two groups considering two types of surgery: FS-LASIK and SMILE. All examinations were performed before and 1 month after surgery.

The FS-LASIK group was composed of 16 subjects (7 males; 9 females) with a mean ± SD age of 32.6 ± 9.1 years and mean pre-operative refraction of -3.48 ± 2.89 D (range from -7.50 to 2.38 D) while the SMILE group was composed of 13 subjects (5 males; 8 females) with a mean age of 32.2 ± 5.3 years and mean pre-operative refraction of -4.67 ± 2.12 D (range from -8.50 to -1.75 D). The eye with better VA or the dominant eye assessed considering motor dominance and sensory dominance tests in case of equal VA, was chosen for evaluation. in the study. The inclusion and exclusion criteria, ethics permissions, clinical and dry eye assessment for the study are detailed in Chapter 2. However, for the purpose of this study, the optometrist collected the outcomes measured including monocular UDVA, monocular CDVA, SEQ calculated from the subjective refraction. The dry eye assessment was performed by AR using the following metrics based on the latest TFOS DEWS II report: OSDI, DEQ-5, tear film osmolarity using the TearLab® Osmolarity System. TMH, NIKBUT and Meibography were measured using a K5M. At the end of the dry eye assessment, the patients'corneas were assessed using IVCM as detailed in section 8.2.4.

8.2.3 Surgery

All surgeries were performed by two experienced consultant ophthalmic surgeons (A.H. and A.S.). Pre-operative disinfection of the external part of the eye and anexa was performed using 5% povidone-iodine 1 hour prior to surgery in all cases.

8.2.3.1 FS-LASIK surgery

In the FS-LASIK surgery group, all the flaps were created using the VisuMax femtosecond laser (Carl Zeiss Meditec AG, Jena, Germany) platform set to a 500-kHz frequency. The diameter of the flaps was 8.5 mm with the hinge position and the side-cut angle at 90 degrees. The average flap thickness was approximately 90 to 100 microns. The stromal ablation was performed with the MEL 90 excimer laser platform (Carl Zeiss Meditec AG, Jena, Germany) using the Triple-A

Advanced Ablation Algorithm to reach a high degree of precision and predictability with a 250-Hz pulse rate. The optical zone was 6.5 mm for all cases. All surgeries were performed under topical anaesthesia with 2 drops of Proxymetacaine 0.5% (Bausch & Lomb, Bridgewater, US) followed by 1 drop of Diclofenac Sodium 0.1% (Bausch & Lomb, Bridgewater, US) to control ocular pain associated with epithelial defects. After surgery, patients were issued with topical drops with preservative based on Dexamethasone 0.1% and Ofloxacin 3mg/ml. Instructions for both sets of drops were 1 drop to be used 4 times per day for 7 days. If required, patients could make use of Paracetamol tablets: 2 every 4 to 6 hours for 2 days only.

8.2.3.2 SMILE surgery

In the SMILE surgery group, the laser system used was the VisuMax femtosecond laser (Carl Zeiss Meditec AG, Jena, Germany). The device frequency was set to 500 kHz with a spot energy of 140 nJ. The spot distance was 4.3 μm and the tracking distance was 1.8 μm. The lenticule diameter was between 6.5 and 7 mm, depending on the degree of astigmatism with a small incision position at 50/130° and a tunnel size from 2 to 4 mm. The standard depth of the anterior lenticule was set to 135-140 μm.

All surgeries started with topical anaesthesia using two drops of Proxymetacaine 0.5% applied 5 and 1 min before the procedure. At this stage, the ocular surface was irrigated and cleaned using preservative-free saline. Patients were instructed at each phase of the procedure, positioned under the laser and asked to fixate a green target to maintain fixation. The device was able to automatically control the pressure during the suction (approx. 20-25 s duration) while a curved plano glass was placed in contact with the eye selected. Then the procedure was carried following as detailed in section 7.2.3.

After removal of the lenticule, the stromal tissue was rinsed with preservative-free saline. In the case of epithelial erosion, a bandage contact lens was applied. After surgery, patients were prescribed with topical drops with preservative based on Dexamethasone 0.1% and Ofloxacin 3mg/ml. Instructions for both sets of drops were 1 drop to be used 4 times per day for 7 days.

8.2.4 In vivo confocal microscopy

As described above, IVCM is a minimally-invasive technique that can be used to detect changes in the corneal layers in different conditions such as diabetes (Petropoulos et al., 2015), fibre neuropathy (Tavakoli et al., 2010a), Parkinson's disease (Kass-Iliyya et al., 2015),in DED (Benitez-del-Castillo et al., 2007; Hosal et al., 2005; Tuominen et al., 2003) and in ophthalmic surgery such as laser vision correction (X. Chen et al., 2018; Denoyer et al., 2015; Kheirkhah et al., 2017; M. Li et al., 2013a; M. Liu et al., 2015b; Riau et al., 2011; A. G. Smith et al., 2013; F. Zhang et al., 2012).

The laser scanning confocal microscope used in this study was the Heidelberg Retinal Tomograph with Rostock Corneal Module (HRT-RCM) (Heidelberg Engineering GmbH, Dossenheim, Germany) (Figure 69, A). The device is able to scan the cornea with a 670 nm laser beam that achieves an axial resolution of approx. 7.6 μm. For the study, subbasal corneal nerve images were assessed in view of their relationship with the corneal sensitivity that influences the tear film secretion and the blink rate (Figure 69, D). In a study by Petropoulos et al. (2013), the device demonstrated good repeatability in the assessment of all the corneal nerve fibres metrics, except for the nerve branch density. However, the researchers suggested automated image analysis, as considered in this study with ACCMetrics software, could potentially increase repeatability. Reproducibility of IVCM with HRT-RCM was also confirmed by A. G. Smith et al. (2013).

After using non-preserved saline to rinse away any residual fluorescein or lissamine green dye from the previous dry eye assessment, a drop of topical anaesthetic (Minims Oxybuprocaine Hydrochloride 0.4%, Bausch & Lomb Ltd, UK) was instilled to temporarily suspend the blink reflex and make the IVCM procedure more comfortable for the patient.

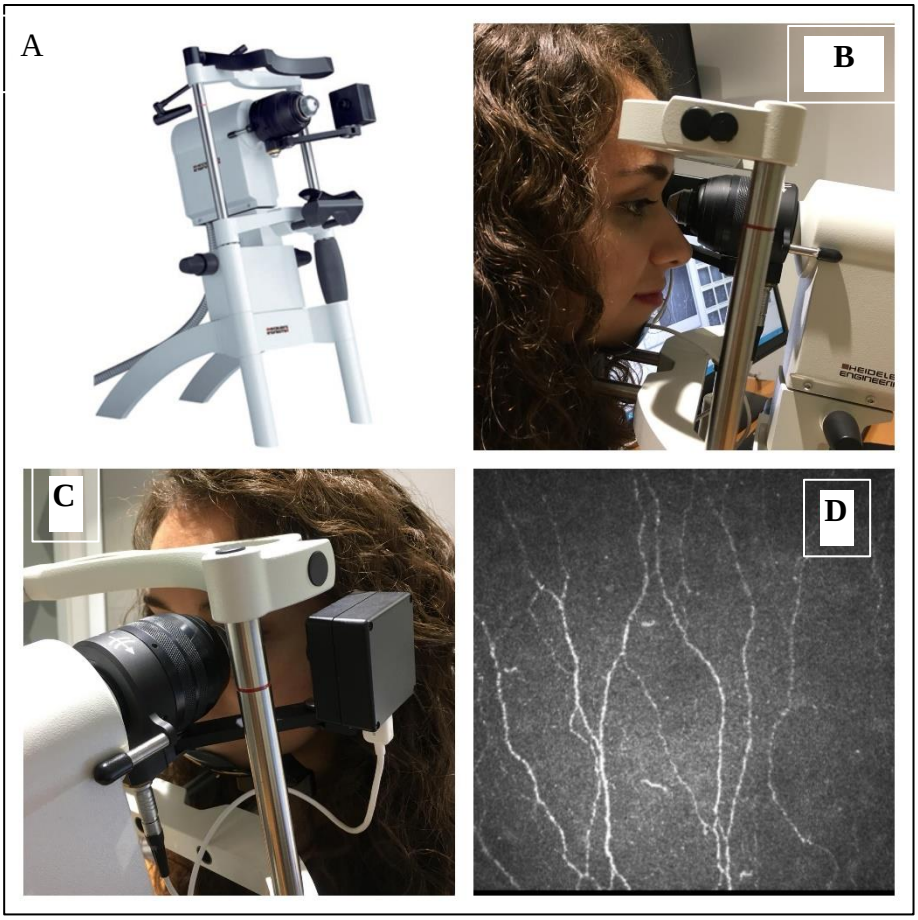

Figure 69 The Heidelberg Retinal Tomograph with Rostock Corneal Module (A) pictured with a patient (B and C) during the acquisition of images of the subbasal corneal nerves plexus (D).

After the topical anaesthetic was applied, a drop of a Viscotears ointment (Alcon

Laboratories, Fort Worth, US) was applied over the lens tip and a new sterile plastic cap TomoCap (Heidelberg Engineering GmbH, Dossenheim, Germany) was mounted in front of the microscope probe. The laser was focused and set for starting the measurements while a second drop of topical anaesthetic was instilled to prolong the anaesthesia, immediately before acquiring the scans. The patients were instructed to fixate on a small, bright white light (fixation target) with the non-examined eye during the scans to reduce blinking and possible eye movements (Figure 69, B). The side camera monitor was used to centre and position the IVCM over the cornea of the selected eye (Figure 69, C). Then, 5 to 10 images of the corneal subbasal nerve plexus were acquired at a depth range between 50 to 80 μm and exported as described in different studies (Dabbah et al., 2010; Ostrovski et al., 2015; Tavakoli et al., 2010b; Vestergaard et al., 2013a). The total acquisition time was between 15 to 25 seconds and the process was well tolerated by patients.

8.2.5 ACCMetrics

An automated corneal confocal software programme (formerly called ACCMetrics) is a biomedical software to obtain automated quantification of corneal nerve fibres was created by the University of Manchester Research Group (Manchester, UK). Essentially, the ACCMetrics analyses the images using two main processes: nerve-fibre detection and nerve-fibre quantification. The nerve-fibre detection works on methods based on machine learning to report the detection of curvilinear features. For example, the detection and classification of curvilinear features are important in the interpretation of different tasks such as road topography, defects in manufactured components or blood vessels and micro-structures observed in medical images. The methods considered in the software are the multi-scale “dual-model filter” (DMF) and the “dual-tree complex wavelet transform” (DCWT). DMF algorithm uses a dual-model property in a multi-scale framework which applies the vector analysis to detect the information from every pixel. Thereafter, the vector analysis uses a neural network as a classifier. In a comparative study of peripheral neuropathy in patients suffering from long term diabetes using DMF algorithm, Dabbah et al. (2011) showed that DMF algorithm in conjunction with neural networks as an automated analysis provided clinical performance as good as that with expert manual annotation. DWCT algorithm is used in image processing and analysis to describe the details of local structure. Additionally, as reported by Kushwaha et al. (2015) DCWT improves the image fusion producing images with higher quality and with better details in medical imaging. Thus, the combination of both algorithms allows the programme to distinguish and fuse the confocal scans.

Corneal confocal microscopy has a high level of background noise which makes it difficult to distinguish the main nerves from their branches (X. Chen et al., 2017c). The second process is nerve-fibre quantification which starts with the identification of the main nerve fibres (e.g. major length and width) considering length, orientation difference, intensity and width

parameters. All these parameters are then compared with subscales of images previously loaded in the software to obtain a matrix match. In the presented research study, the images were analyzed and those containing stromal or epithelium layers or artefacts (e.g. excessive compression of the layers/nerves) were not included in the analysis. The images with only subbasal corneal nerves were analyzed with a dimension measured 384 x 384 pixels with a pixel size of 1.00417 μm/pixel (Figure 70). The software is able to calculate the automated corneal nerve fibre density (ACNFD, number of main fibres per mm^2), the automated corneal nerve branch density (ACNBD, number of branches per mm^2), the automated corneal nerve fibre length (ACNFL, total length of main fibres and branches per mm^2). This approach has been validated previously (X. Chen et al., 2017c; Dabbah et al., 2011; Petropoulos et al., 2014). Additionally, the automated corneal nerve fibre fractal dimension (ACNFrD) was included which has been used to detect distorted nerve fibres linked to abnormality (e.g. changes in details perceived in a box image of 1x1, 2x2, 4x4, etc.) and is comparable with ACNF, ACNBD and ACNFL in diagnosing patients with irregularity of the nerve fibres (e.g. neuropathy). The software is able to calculate other metrics such as nerve fibre area, nerve fibre width, nerve fibre orientation histogram and nerve fibre width histogram but further studies are needed to validate these techniques considering repeatability studies.

The automatic quantification of the subbasal corneal nerves, specifically considering ACNF, ACNBD, ACNFL and ACNFrD took approximately 10 to 22 seconds (Petropoulos et al., 2014). Before discharging the patient, the eye was checked for signs of corneal staining due to contact with the probe (e.g. TomoCap).

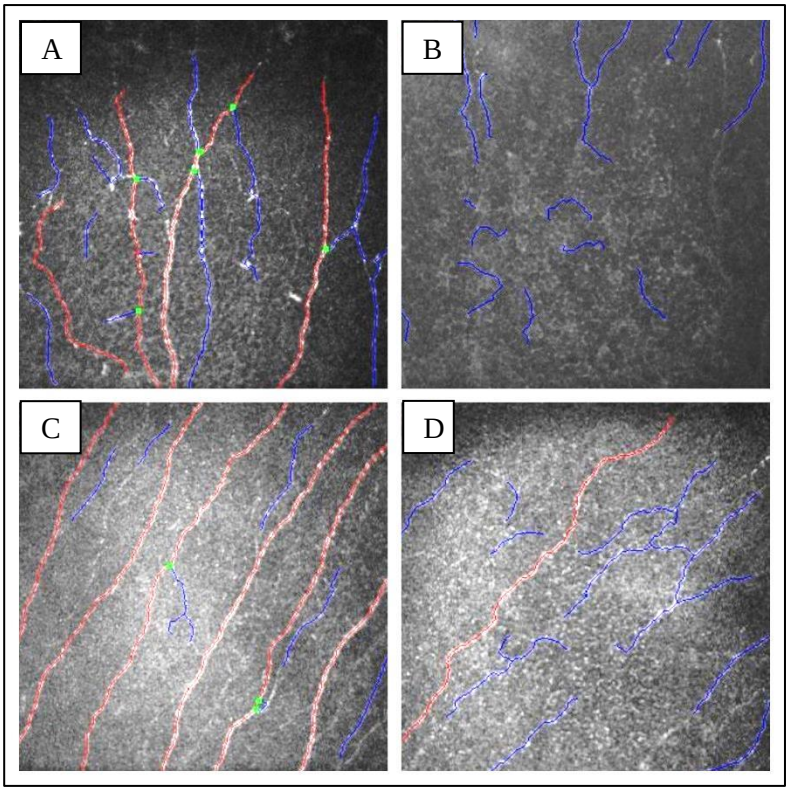

Figure 70 Sample of IVCM images of the subbasal corneal nerves fibre analysed with ACCMetrics: before LASIK surgery (A) and after (B), before SMILE surgery (C) and after (D). Main nerve fibres in red, nerve branches in blue and branch points in green.

8.2.6 Statistical Analysis

All statistical analysis was performed using SPSS 23.0 (SPSS Inc., Chicago, US). Data normality was tested using the Shapiro-Wilk test. The minimum sample size required for the study was 15 eyes of 15 patients in each surgery group (SMILE and LASIK) before and 1 month after the procedure. A total of 45 eyes from 45 patients were recruited to allow for a 30% drop-out rate (e.g. patients not attending the follow-up or patients not interested in having the surgery, etc.).

Group comparisons for normally distributed data were performed with Student's *t*-test, and paired variables were compared before and after the treatment. However, in the case of non-normally distributed variables, Wilcoxon signed rank test was applied with 2 related samples while using Mann-Whitney U test with 2 independent samples.

To perform the bivariate correlation analysis, normally distributed data (Shapiro-Wilk test >0.05) were analysed using the Pearson's test whereas data not normally distributed (Shapiro-Wilk test <0.05) were analysed using the Spearman's test.

8.3 Results

8.3.1 Clinical outcomes before and after surgery in FS-LASIK and SMILE surgery

6% of the patients belonging to the FS-LASIK group were able to reach a VA of -0.2 logMAR at the pre-operative (CDVA) and post-operative (UDVA) appointments. 63% of the patients achieved a post-operative UDVA of -0.1 logMAR at 1 month compared to 81% of the eyes pre-operatively (p= 0.473). Moreover, all eyes achieved 0 logMAR before and one month after surgery (Figure 71, A). In terms of accuracy of the procedure, 87% of the eyes in the FS-LASIK group were found to be within ± 0.50 D of the intended target refraction and 100% of the eyes were within ± 1.00 D (Figure 71, B).

There was no difference in terms of sex (p= 0.709) and age (p= 0.918) between the two groups.

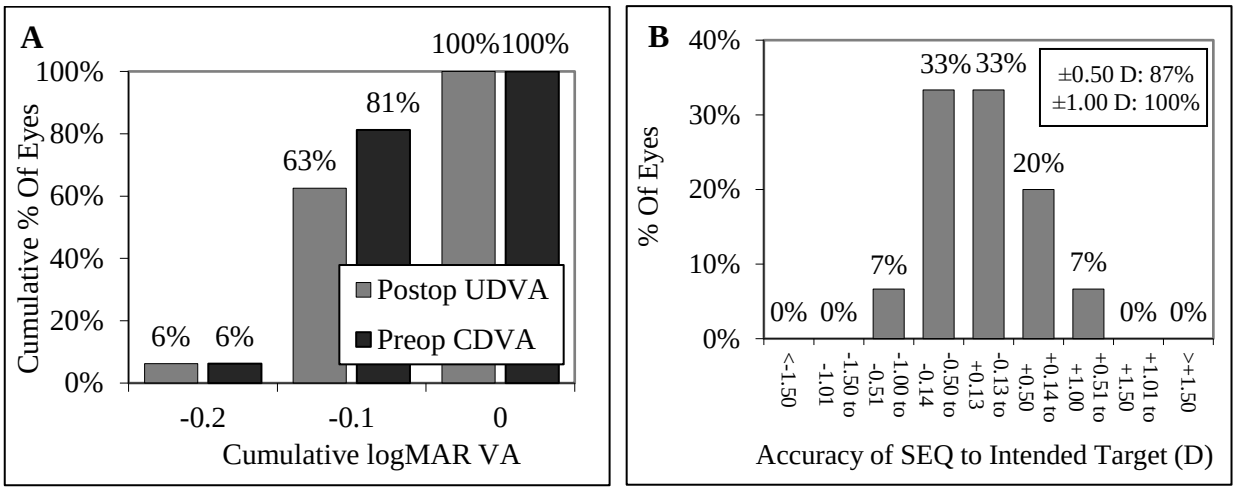

Figure 71 Refractive outcomes in the FS-LASIK group (n= 16): representing A) the visual acuity before and after surgery (Preop CDVA vs Postop UDVA) and B) the accuracy of the surgical procedure in terms of residual refraction after surgery.

15% of eyes in the SMILE group achieved a VA of -0.2 logMAR at both the pre-operative (CDVA) and post-operative (UDVA) appointments. 46% of eyes achieved a post-operative UDVA of -0.1 logMAR or better *vs* 92% of eyes pre-operatively (p= 0.694), 92% of the eyes achieved VA of 0.1 and 0.2 logMAR or better respectively (Figure 72, C). However, 100% of the patients achieved a VA of 0.3 logMAR at 1 month. In terms of accuracy of the procedure, SMILE group was found to be within ± 0.50 D of the intended target refraction in 77% of eyes and within ± 1.00 D in 100% of eyes at 1 month (Figure 72, D). When compared, the techniques showed no significant difference in terms of post-operative UDVA (p= 0.721) and post-operative SEQ (p= 0.769) at 1 month.

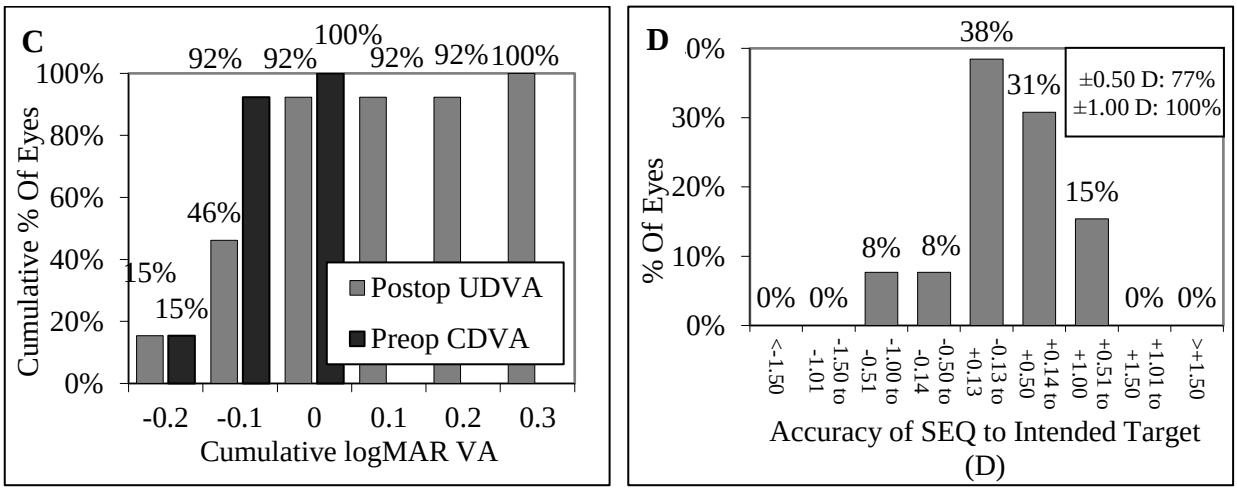

Figure 72 Refractive outcomes in the SMILE subgroup (n= 13): representing C) the visual acuity before and after surgery (Preop corrected distance visual acuity (CDVA) vs Postop unaided distance visual acuity (UDVA) and D) accuracy of the surgical procedure in terms of residual refraction after surgery.

In terms of symptoms, FS-LASIK group patients showed a significant increase on both questionnaires at the 1-month appointment (OSDI pre-scores *vs.* post-scores: 8 ± 12 *vs*. 34 ± 23, DEQ-5 pre-scores *vs* post-scores: 5 ± 3 vs 12 ± 5) (p= 0.001). No significant increase in questionnaire scores was detected within the SMILE group (p= 0.374). FS-LASIK surgery had a significant impact after surgery on the symptomatology compared with SMILE surgery assessed with the OSDI questionnaire (p= 0.039) and with DEQ-5 questionnaire (p= 0.006) (Figure 73).

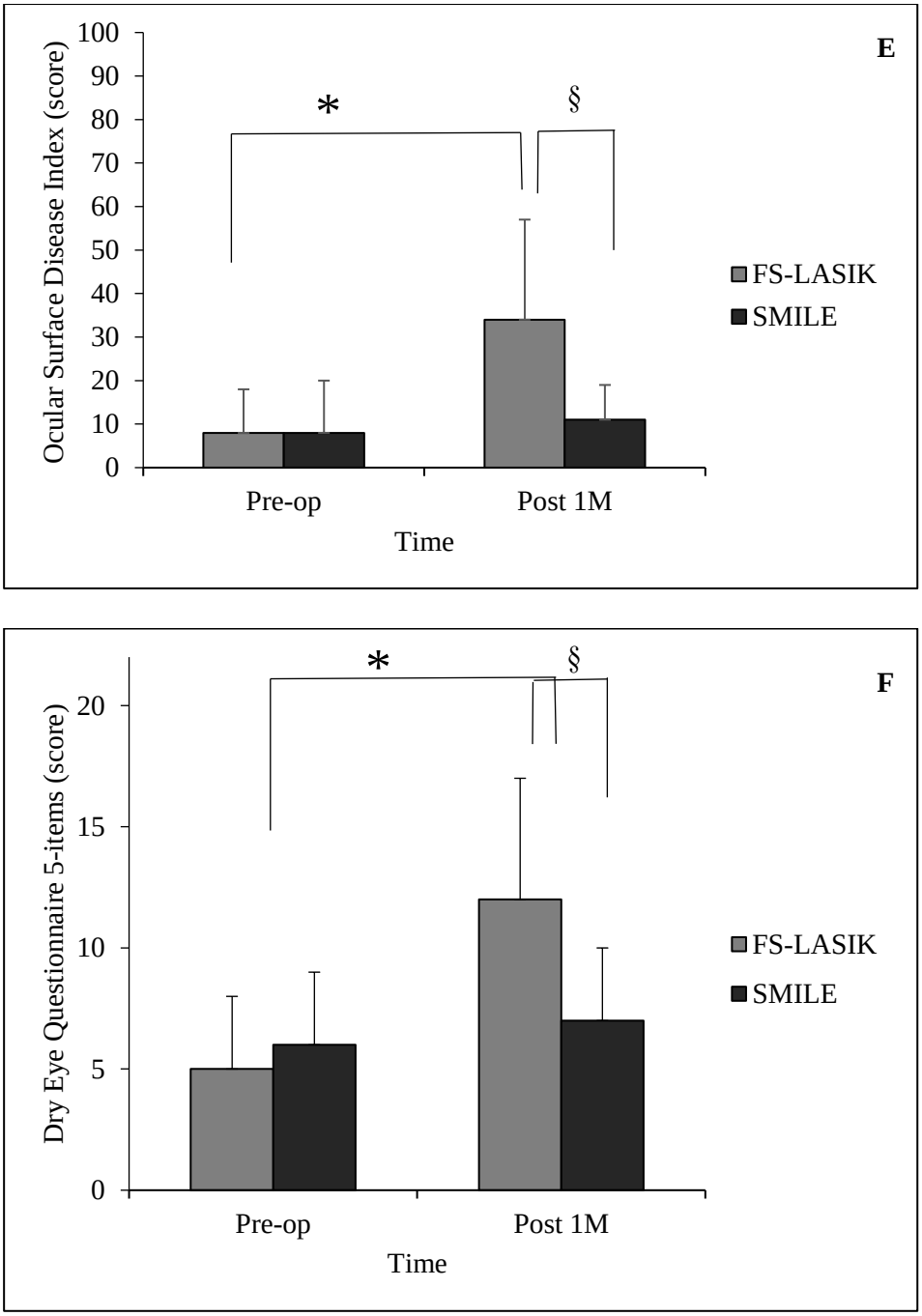

Figure 73 Ocular surface disease index (OSDI) (pictured in E) and dry eye questionnaire 5-items (DEQ-5) (pictured in F) scores before (Pre-op) and after (Post 1M) surgery with error bars indicating standard deviation. *denotes a significant difference compared with pre-operative level (p= 0.001) and § denotes a significant difference between the techniques (OSDI p= 0.039, DEQ-5 p= 0.006) FS-LASIK n= 16 and SMILE n= 13.

Tear osmolarity values were not significantly changed after the surgeries (FS-LASIK p= 0.629 and SMILE p= 0.975) for both groups: FS-LASIK pre-op 295 ± 12 mOsm/L and post-op 300 ± 14 mOsm/L p=0.629 and SMILE pre-op 291 ± 10 mOsm/L and post-op 289 ± 9 mOsm/L) (p= 0.975). Additionally, between the techniques, tear osmolarity was not significantly different (p= 0.054) (Figure 74).

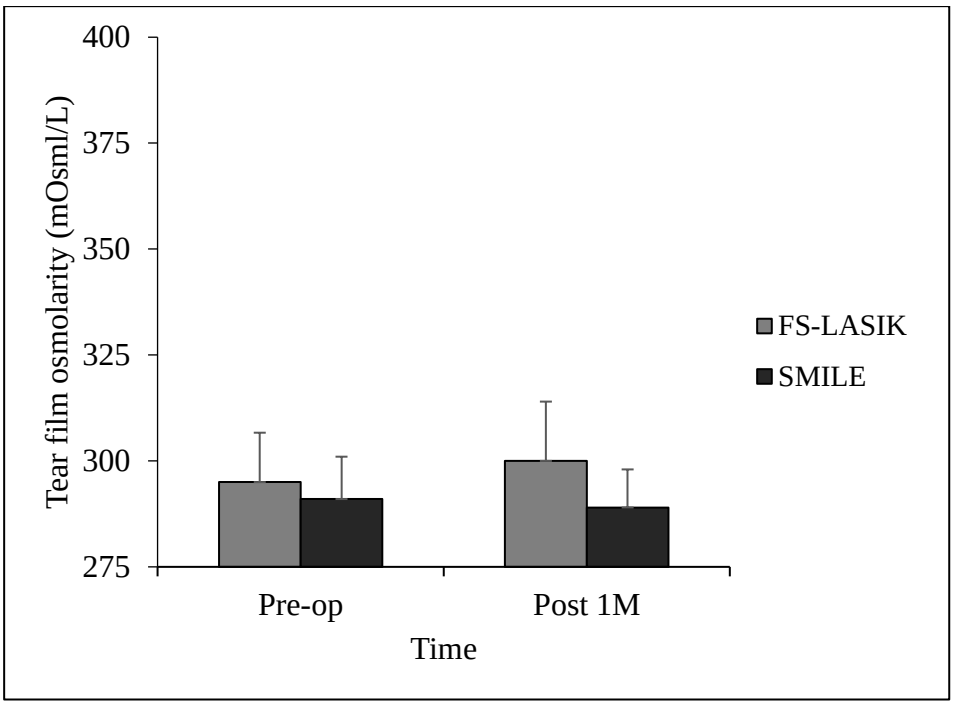

Figure 74 Tear film osmolarity values obtained pre and post operatively with error bars indicating standard deviation (Pre-op= pre-operative, Post 1M= post-operative at 1 month). FS-LASIK n= 16 and SMILE n= 13.

The tear film volume as estimated from the height of the tear meniscus in millimetres (TMH) was significantly reduced after surgery (0.22 ± 0.09 mm) in the FS-LASIK group compared to before the surgery (0.32 ± 0.13 mm) (p=0.005). No significant changes were noted in the SMILE group (TMH before 0.30 ± 0.07 mm *vs*. after 0.33 ± 0.08 mm (p=0.248). No significant differences were found when the procedures were compared postoperatively (p= 0.253) (Figure 75).

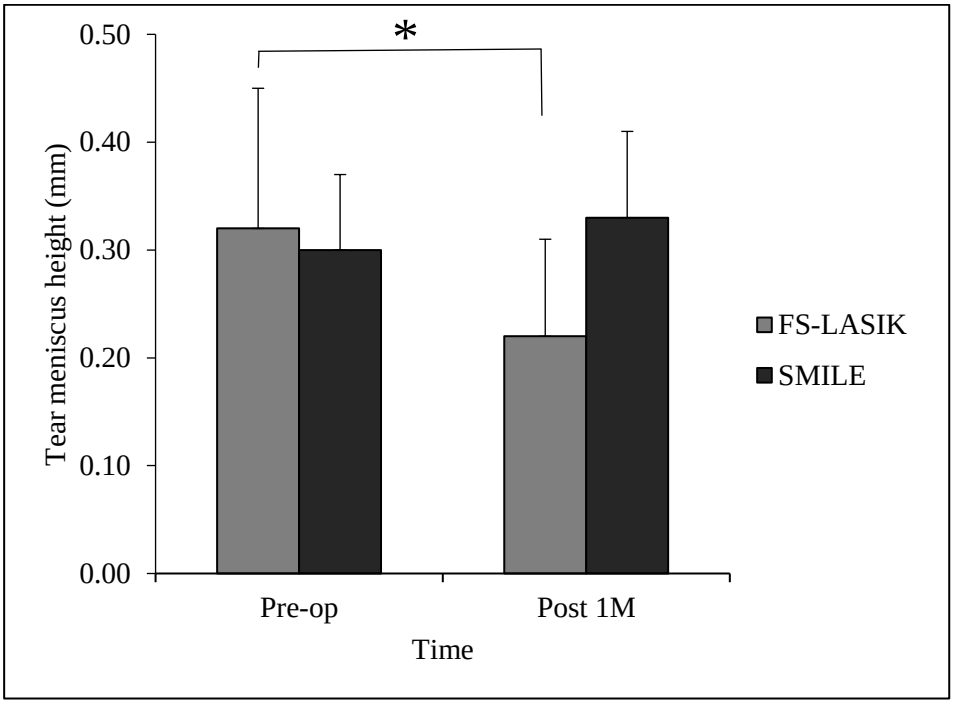

Figure 75 Tear meniscus height (TMH) before and after surgery with error bars indicating standard deviation (Pre-op= pre-operative, Post 1M= post-operative at 1 month). Asterisk denotes a significant difference compared with the pre-operative level (p= 0.05). FS-LASIK n= 16 and SMILE n= 13.

NIKBUT was found to be significantly decreased at one month after surgery in the FS-LASIK group only (p= 0.001) but was not different between the techniques (p= 0.114) (Figure 76).

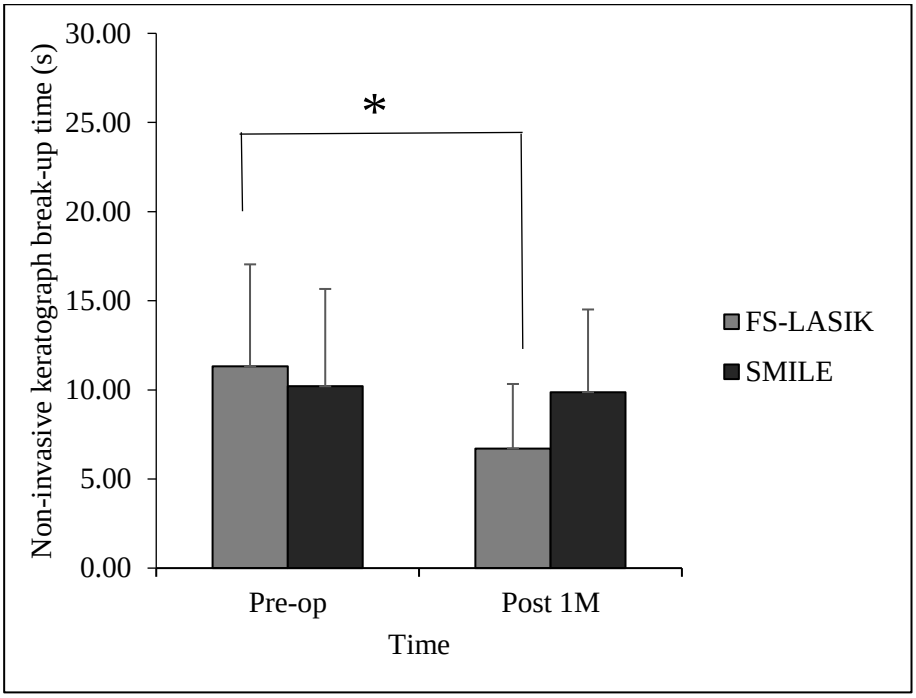

Figure 76 Non-invasive keratograph break-up time (NIKBUT) in seconds between the surgery follow-up with error bars indicating standard deviation (Pre-op= pre-operative, Post 1M= post-operative at 1 month). Asterisk denotes a significant difference compared with the pre-operative value (p= 0.01). FS-LASIK n= 16 and SMILE n= 13.

No significant changes were observed within either of the groups for corneal and conjunctival staining at the follow-up appointments (Oxford score before FS-LASIK 0 ± 1 score *vs* after 0 ± 1 score) (p= 0.609) (Oxford score before SMILE 0 ± 1 score *vs* after 0 ± 1 score) (p= 0.742) and either between the techniques (p= 0.938).

The MG assessment score at 1 month after surgery was not significantly different from the before surgery value in both groups (FS-LASIK p= 0.164, SMILE p= 0.137) and there was no difference between the two techniques (p= 0.587) (Figure 77).

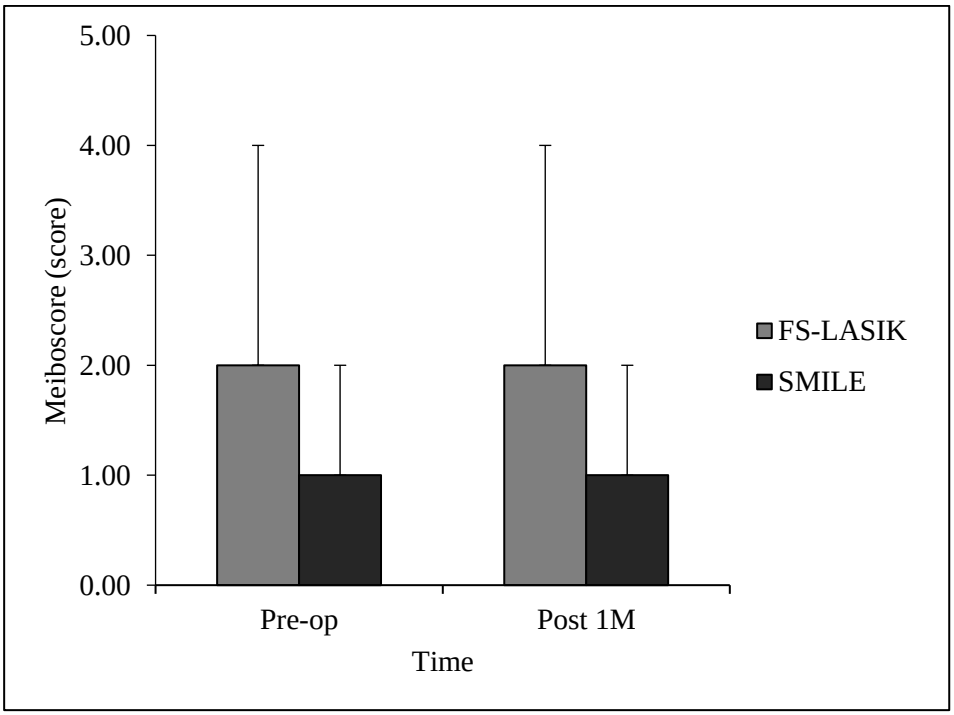

Figure 77 Meiboscore grading scale values obtained before (Pre-op) and 1 month after surgery (Post-1M) with error bars indicating standard deviation. FS-LASIK n= 16 and SMILE n= 13.

The subbasal corneal nerve metrics assessed in the FS-LASIK group are shown in Table 20 and in Figure 78: a significant reduction was observed after surgery for all the subbasal corneal nerve metrics considered in the study.

FS-LASIK group			
Stats	PRE	POST 1M	p-value
ACNFD (nr. main fibres per mm^2)	17.6 ± 4.3	4.9 ± 1.1	0.001*
ACNBD (nr. branches per mm^2)	12.8 ± 7.5	3.2 ± 0.7	0.001*
ACNFL (length fibres and branches per mm^2)	12.4 ± 2.3	3.3 ± 1.3	0.001*
ACNFrD (changes in details)	1.47 ± 0.04	1.38 ± 0.12	0.001*

Table 20 Subbasal corneal nerve structure in FS-LASIK group: automated corneal nerve fibre density (ACNFD), automated corneal nerve branch density (ACNBD), automated corneal nerve fibre length (ACNFL) and automated corneal nerve fibre fractal dimension (ACNFrD) obtained before (Pre-op) and 1 month after surgery (Post-1M). Asterisks denote significant differences compared with pre-operative level. FS-LASIK n= 16.

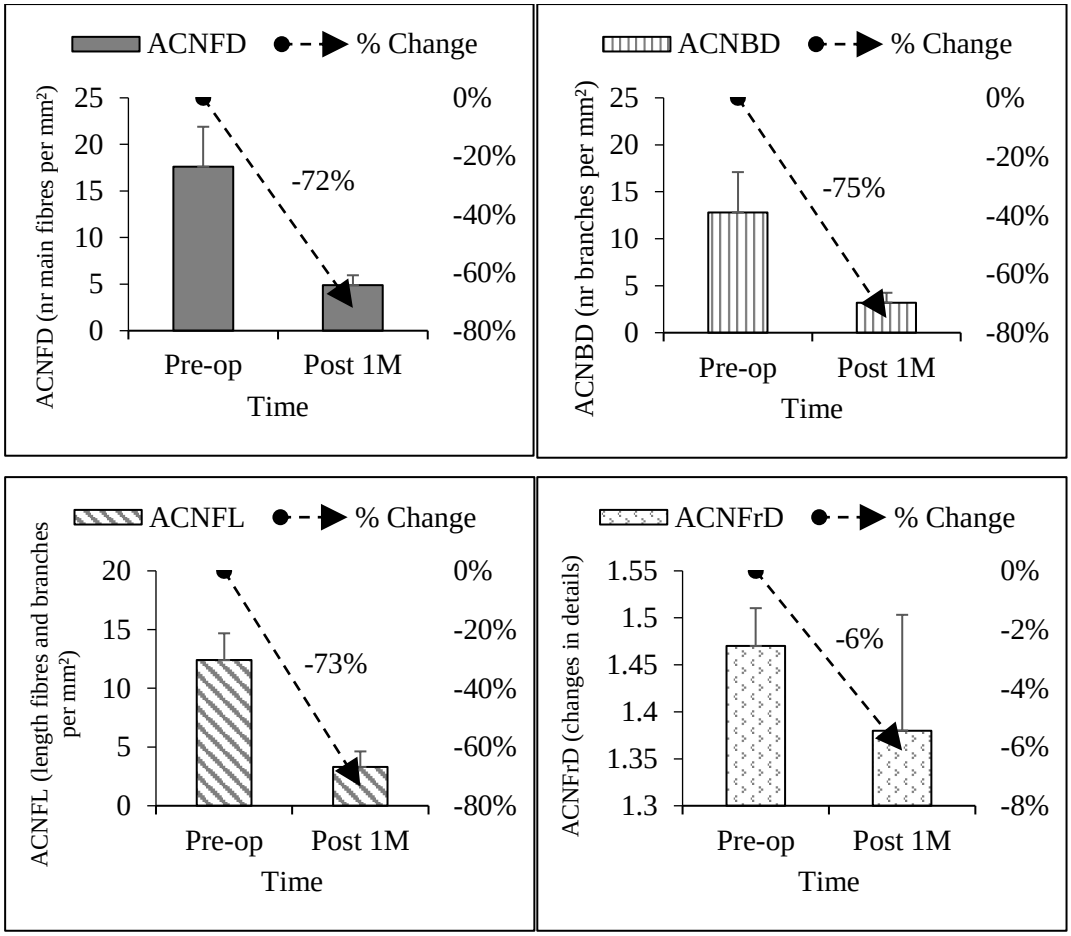

Figure 78 Subbasal corneal nerve structure changes in FS-LASIK group: automated corneal nerve fibre density (ACNFD), automated corneal nerve branch density (ACNBD), automated corneal nerve fibre length (ACNFL) and automated corneal nerve fibre fractal dimension (ACNFrD) obtained before (Pre-op) and 1 month after surgery (Post-1M). FS-LASIK n= 16.

The changes of the subbasal corneal nerve structure in SMILE group are added in Table 21 and in Figure 79: a significant reduction was observed after surgery for all the subbasal corneal nerve metrics considered in the study, except for the ACNFD.

SMILE group			
Stats	PRE	POST 1M	p-value
ACNFD (nr. main fibres per mm^2)	18.0 ± 7.1	15.6 ± 3.9	0.071
ACNBD (nr. branches per mm^2)	15.5 ± 8.3	12.0 ± 5.4	0.003*
ACNFL (length fibres and branches per mm^2)	11.3 ± 3.1	10.4 ± 2.4	0.035*
ACNFrD (changes in details)	1.47 ± 0.04	1.40 ± 0.14	0.022*

Table 21 Subbasal corneal nerve structure in SMILE group: automated corneal nerve fibre density (ACNFD), automated corneal nerve branch density (ACNBD), automated corneal nerve fibre length (ACNFL) and automated corneal nerve fibre fractal dimension (ACNFrD) obtained before (Pre-op) and 1 month after surgery (Post-1M). Asterisks denote significant differences compared with pre-operative level. SMILE n= 13.

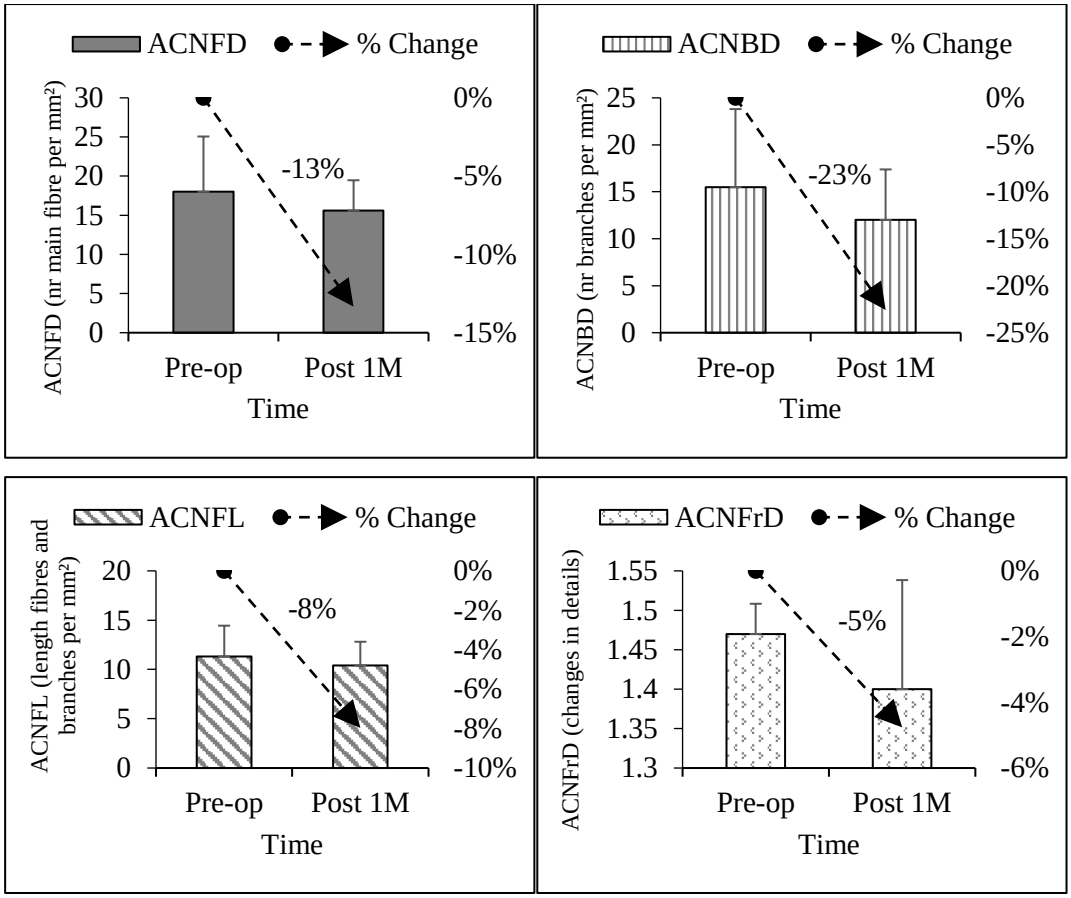

Figure 79 Subbasal corneal nerve structure changes in SMILE group: automated corneal nerve fibre density (ACNFD), automated corneal nerve branch density (ACNBD), automated corneal nerve fibre length (ACNFL) and automated corneal nerve fibre fractal dimension (ACNFrD) obtained before (Pre-op) and 1 month after surgery (Post-1M). SMILE n= 13.

The reduction observed after FS-LASIK in the subbasal corneal nerve parameters such as ACNFD, ACNBD, ACNFL was statistically significant compared with those observed after SMILE surgery (p= 0.001 for all), except for ACNFrD which was not significantly different between the surgery (p= 0.124).

8.3.2 Correlation within DED metrics and between subbasal corneal nerve metrics structure

A Spearman's Rank analysis was performed between DED metrics such as OSDI, DEQ-5, tear film osmolarity, TMH, NIKBUT and Meibography and the subbasal cornea nerve metrics such as ACNFD, ACNBD, ACNFL and ACNFrD. The significant correlations are presented in the matrix tables below ($p < 0.05$) (Table 22 and Table 23):

FS-LASIK GROUP (n=16)								
Spearman's rank-order correlation		OSDI_PRE _FS-LASIK	OSDI_POST1M _FS-LASIK	NIKBUT_PRE_ FS-LASIK	NIKBUT_POST1M _FS-LASIK	DEQ5_POST1M_ FS-LASIK	TMH_POST1M _FS-LASIK	ACNFL_PRE _FS-LASIK
OSDI_PRE_FS-LASIK	Correlation Coefficient	1.000	0.652	-0.065	-0.180	0.133	-0.053	-0.132
	Sig. (2-tailed)		0.006*	0.810	0.505	0.623	0.846	0.625
OSDI_POST1M_FS-LASIK	Correlation Coefficient	0.652	1.000	0.049	-0.364	0.105	-0.374	0.097
	Sig. (2-tailed)	0.006*		0.858	0.166	0.698	0.153	0.720
NIKBUT_PRE_FS-LASIK	Correlation Coefficient	-0.065	0.049	1.000	0.701	-0.742	0.189	0.345
	Sig. (2-tailed)	0.810	0.858		0.02*	0.001*	0.469	0.176
NIKBUT_POST1M_FS-LASIK	Correlation Coefficient	-0.180	-0.364	0.701	1.000	-0.456	0.650	0.072
	Sig. (2-tailed)	0.505	0.166	0.02*		0.076	0.005*	0.783
DEQ5_POST1M_FS-LASIK	Correlation Coefficient	0.133	0.105	-0.742	-0.456	1.000	0.020	-0.545

	Sig. (2-tailed)	0.623	0.698	0.001*	0.076		0.941	0.029*
TMH_POST1M_FS-LASIK	Correlation Coefficient	-0.053	-0.374	0.189	0.650	0.020	1.000	-0.022
	Sig. (2-tailed)	0.846	0.153	0.469	0.005*	0.941		0.933
ACNFL_PRE_FS-LASIK	Correlation Coefficient	-0.132	0.097	0.345	0.072	-0.545	-0.022	1.000
	Sig. (2-tailed)	0.625	0.720	0.176	0.783	0.029*	0.933	

Table 22 Correlation between DED metrics considered. Asterisks denote significant differences compared with pre-operative level. FS-LASIK group n= 16.

SMILE GROUP (n=13)				
Spearman's rank-order correlation		DEQ_PRE_SMILE	NIKBUT_POST1M_SMILE	NIKBUT_PRE_SMILE
DEQ5_PRE_SMILE	Correlation Coefficient	1.000	-0.566	-0.046
	Sig. (2-tailed)		0.044*	0.882
NIKBUT_POST1M_SMILE	Correlation Coefficient	-0.566	1.000	0.877
	Sig. (2-tailed)	0.044*		0.001*
NIKBUT_PRE_SMILE	Correlation Coefficient	-0.046	0.877	1.000
	Sig. (2-tailed)	0.882	0.001*	

Table 23 Correlation between DED metrics considered. Asterisks denote significant differences compared with the pre-operative level. SMILE group n= 13.

8.4 Discussion

Nowadays, different refractive laser treatments such as PRK, LASIK, epi-LASIK, LASEK, FS-LASIK and SMILE are options to correct refractive error by changing the topography of the cornea (Chansue et al., 2015a; Dong et al., 2014; McAlinden, 2012; Pinero et al., 2016; Schallhorn et al., 2003; Shortt et al., 2006). All these procedures are considered safe and effective for correcting myopia, hyperopia and astigmatism where most of the possible complications can be prevented or will resolve (Alio et al., 2008; Chua et al., 2018; Moshirfar et al., 2018b; Reinstein et al., 2018). The most common postoperative complications are related to disturbances of visual quality such as glare and halos that potentially can reduce vision when the level of light is reduced or when the pupils enlarge (e.g. driving at night, cinema or visual display terminal tasks) (Courtin et al., 2016; Fan-Paul et al., 2002; Moshirfar et al., 2017; Tomita et al., 2014). However, one of the most common complaints after corneal laser vision correction in terms of discomfort and visual fluctuation is DED (Bower et al., 2015; Cai et al., 2017; Garcia-Zalisnak et al., 2014; Xie, 2016). In a review by Quinto et al. (2008), both PRK and LASIK were shown to be responsible for patients developing DED, typically temporary, after the procedures. Tear secretion and the blinking rate are stimulated by the nervous response of the subbasal corneal nerve fibres distributed inside the corneal stroma penetrating through Bowman's membrane. These fibres pass from the peripheral cornea and then toward the corneal centre in a radial manner creating the subbasal corneal nerve loop. Any damage or insult to this structure, for example in case of corneal refractive surgery, may impact the ocular surface sensitivity, decreasing the aqueous tear secretion, inducing dryness (Bron et al., 2017). To help preserve the subbasal nerve plexus, SMILE has been introduced in 2016 (FDA approval) to treat myopia and astigmatism only, without the need of a corneal flap. In a retrospective study by Reinstein et al. (2014b), 110 eyes were evaluated up to 12 months after SMILE surgery for low myopia: the results showed good safety and efficacy of SMILE with similar refractive outcomes (mean refraction -0.05 D at 1 year) to LASIK. Additionally, Ağca et colleagues (2018) presented refractive outcome data from 37 eyes with high myopia (over 6 D) up to 5 years after SMILE, revealing 59% and 92% of the participants were within ± 0.50 D and ± 1.00 D of the planned refractive target. The same trend was reported by Burazovitch et al. (2018) where 88% of 616 eyes with SEQ between 1 to 11 D were able to reach 0.1 logMAR 5 years after surgery. The current refractive results after 1 month were in agreement with previous studies, where no complications were reported, showing good safety and efficacy (Ganesh et al., 2018a; F. Lin et al., 2014; Yan et al., 2017). However, a slight reduction in eyes achieving 0.1 logMAR in the SMILE group at one month compared to the FS-LASIK group was found (92% vs 100%) that can be compared with the refractive outcomes from another study by Pietilä et al. (2018). In Pietilä et al. findings, 80% and 83% of a total of 300 eyes achieved 0 logMAR with SMILE and FS-LASIK procedures respectively with no significant difference, as reported by the results presented in the current research (p= 0.271). The minor

difference between the procedures observed in terms of visual recovery after SMILE has been recently been investigated by Ganesh et al. (2018b): the researchers analysed the stromal interface after surgery through to 3 months, finding that the roughness of the interface was negatively correlated with CDVA, corneal MTF and corneal Strehl ratio (e.g. reduction of visual quality). Thus, it would seem that the healing recovery of the stromal tissue in SMILE surgery is dependent on keratocyte activation that increases the light backscatter (diffuse reflection from the tissue) as shown by the IVCM scans from Ağca et colleagues (2018). However, a further consideration is that both SMILE and FS-LASIK, were performed with the femtosecond laser. The energy used in the SMILE procedure was set to 140 nJ for both lenticule creation and side cut opening while the energy used in FS-LASIK is an unknown variable (proprietary to the manufacturer). However, as reported by Ganesh et al. (2018b), even with low energy, the keratocyte activity may be a variable in visual recovery, especially in the first weeks/months. In terms of accuracy of the refractive procedures from the current research, 87% of the FS-LASIK patients (n= 14) versus 77% (n= 10) of the SMILE patients had a refraction within ± 0.50 D after 1 month. Both procedures gave a post-operative target refraction within ± 1.00 D in 100% of the patients as previously reported by different studies (F. Lin et al., 2014; M. Liu et al., 2016; Zeren Shen et al., 2016a) and when compared, FS-LASIK and SMILE did not show a significant difference (p= 0.769).

In the present study, both OSDI and DEQ-5 questionnaires showed a significant worsening in DED symptoms in patients that had undergone FS-LASIK but this was not significant in the SMILE group. DEQ-5 questionnaire had worse results in the FS-LASIK group reaching a two folds' increase compared to the pre-operative values (5 ± 3 vs 12 ± 5). The reason behind these differences has been reported in two different comparison studies by Denoyer et al. (2015) and Li et al. (2013b). Both authors hypothesized that the cutting of the subbasal corneal nerve fibres due to the flap creation (LASIK) is more impacting compared with the cutting created to extract the stromal lenticule in SMILE surgery, leading to increased OSDI scores up to 6 months after surgery. In support of these findings, when both surgeries were compared, the OSDI and DEQ-5 scores were significantly higher in the FS-LASIK patients compared to the SMILE group (p= 0.039 and p= 0.006).

Different studies have reported the importance of quantifying the osmolarity of the tear film (Garcia-Resua et al., 2014b; Mathews et al., 2017; Potvin et al., 2015). However, it is not yet clear how robust the osmolarity measurement of the tear film is and whether it can be considered as "*the single best metric to diagnose and classify DED"* (Lemp et al., 2011; Potvin et al., 2015). Szczesna-Iskander (2016) reported that three consecutive measurements should be taken into account to increase the clinical reliability, whereas Bunya et al. (2015) describe high variability in the measurement when associated with patients diagnosed with DED. In the current

study, tear film osmolarity showed no significant changes before and after both types of surgery in agreement with previous studies (Demirok et al., 2013; Denoyer et al., 2015) while Kacerovska et al. (2018) found that FS-LASIK impacted more on the ocular surface than SMILE. When the techniques were compared, no significant changes were reported but following the publication of Szczesna-Iskander (2016), tear osmolarity should be assessed three times (using three different chips) to reduce its variability while in all the research studies included in this thesis only one measurement was performed.

TMH has been assessed non-invasively with infra-red light by means a K5M which has been reported to have high repeatability and reproducibility of TMH measurements in both DED and non-DED patients (K. Lee et al., 2017; Tian et al., 2016), but not in agreement with traditional measurement with a vital dye (e.g. fluorescein). TMH assessed non-invasively by the means of an anterior segment OCT, was found to be reduced in the earliest follow-up (1 week and 1 month) in patients operated with mechanical LASIKor FS-LASIK than with SMILE procedures. However, in the SMILE group of Denoyer and Less's research, patients were able to return to 95% of TMH pre-operative level after 1 month, where both LASIK procedures (microkeratome and FS laser) needed up to 6 months to reach pre-operative TMH levels (Shaaban et al., 2018). The current results showed a significant TMH reduction ($p= 0.005$) in the FS-LASIK group after surgery as previously reported by Jung et al. (2017). Despite the fact that approx. 2 to 5 mm corneal incision is performed in SMILE *versus.* 7 to 8 mm in FS-LASIK for flap creation, no significant changes were observed when the procedures were compared in terms of TMH measurements. As most of the tear film volume is produced by the lacrimal gland that is innervated by parasympathetic and sympathetic nerves, any damage to the corneal trigeminal branch or to the lacrimal gland reflex arc may reduce the secretion of tears reducing not only the TMH, but also other tear film characteristics (Hosal et al., 2005).

In a meta-analysis by Shen et colleagues (2016b), six different studies were included (5 cohorts and 1 RCT) with 291eyes in the SMILE group and 277 eyes in the FS-LASIK group. The analysis showed that SMILE surgery performed better in terms of tear film stability. However, most of these studies have measured TBUT with fluorescein with potentially higher variability due to the interference of the vital dye with the tear film structure (Huntjens et al., 2018). The TBUT results collected in this study using NIKBUT technique (Figure 76) confirmed that FS-LASIK 1-month after surgery had more impact over the ocular surface, shortening the stability of the tear film by 40% while SMILE surgery gave values similar to before the surgery with a change of approximately 3%. However, both techniques reduced the tear film stability (at 1 month) under the suggested 10 s cut-off reported in the recent TFOS DEWS II but without remarkable difference between the techniques.

Corneal and conjunctival staining using two of the most common vital dyes, fluorescein and lissamine green, were used in the current study (Bron et al., 2003). As reported by Korb et al. (2008) the use of fluorescein 2% and lissamine green 1% is able to detect both corneal and conjunctival staining without any adverse reaction or discomfort. In a review by Moshirfar et al. (2015), SMILE surgery could potentially induce epithelial abrasions due to the suction ring applied during the procedure while FS-LASIK showed the presence of staining in the ocular surface immediately after surgery (Azuma et al., 2014; Denoyer et al., 2015; Salomao et al., 2009). However, despite the physical impact of the procedures, both corneal and conjunctival staining in both groups were found to be similar to the pre-operative values. In a previous comparative study between FS-LASIK and SMILE by Zhang et al. (2016) the presence of staining was detected only 1 week after surgery and then this recovered at 1-month follow-up, supporting the presented results. A comparison was not possible at 1 week due to the post-operative drugs regime based on Dexamethasone 0.1% and Ofloxacin 3mg/ml with preservatives that could have an impact on the repeatability and reliability of the measurements and therefore the follow-up was performed at 1 month. However, other researchers reported significant staining with FS-LASIK compared to SMILE, attributing the cause as a disturbed interaction between the corneal nerves and the epithelial cells (lack of promoting epithelial grow factors) (M. Li et al., 2013b). Although in the present research FS-LASIK had more impact in severing the corneal nerves, the staining was not significantly different between the techniques.

Chen et al. (2017b) suggested considering TBUT and LLT together with the upper and lower MG as they are involved in protecting the ocular surface (McMonnies, 2018). However, as LLT recordings were not available in this study, MG atrophy was measured using the K5M (Figure 80) as MG are the site of production of the meibum lipids which directly affect the LLT status (Arita et al., 2016). To classify MG atrophy, the Meiboscore from Arita et al. (2008) was utilised, which is a validated grading score to consider the loss of MG from the upper and the lower eyelids. Jung et colleagues (2017) suggested a possible connection between the development of MGD and the reduction of corneal sensitivity after LASIK. The reduction of the tear film volume and blinking rate due to the impact of the procedure on the subbasal corneal nerve loop may increase tear film osmolarity leading to a cascade of inflammatory processes which can induce MGD (Toda, 2018). In the present study, no significant changes were reported in osmolarity or MG structure after FS-LASIK and SMILE procedures. However, it might be worth including the measurements of the osmolarity to clinically classify DED subtypes such as ADDE or EDE as suggested by Bron et al. (2017) despite its variability (Bunya et al., 2015; Szczesna-Iskander, 2016). Furthermore, as pictured in Figure 77, the SMILE group showed a pre-operative Meiboscore lower than FS-LASIK and for this reason and due to the importance of the MG in tear film stability pre-surgery, the patients received detailed information on how SMILE

could have less impact on the ocular surface. However, in the results showed in this research study both techniques were not different in the atrophy of the tarsal glands as the duration of the procedures is similar (less than 15 min per eyes) as the intraoperative factors adopted (e.g. microscope light, eye speculum, etc.) (Hamed et al., 2018).

SMILE surgery is also defined as an "all-in-one" procedure. In fact, all the steps of the procedure are performed with the same laser, apart from the lenticule extraction. This could potentially reduce the operating time compared to the FS-LASIK surgery where the flap creation is performed with the femtosecond laser, but the corneal ablation is performed using an excimer laser (Reinstein et al., 2014a). In fact, after topical anaesthesia, a sterile eye speculum is applied to help keep the eye open during the procedure. Thus, because the total suction in SMILE surgery is approximately 25 to 35 seconds (Gab-Alla, 2017) followed by the time to extract the lenticule, FS-LASIK surgery could be longer and increase the residence time of the speculum over the eye potentially leading to changes to the MG (Jung et al., 2017). However, there is no evidence as to whether SMILE surgery could be a better choice to avoid exacerbating or inducing MGD as most of the publications are focused on the fact that the flapless procedure has less impact on the subbasal corneal nerve plexus. Finally, the current research showed that none of the surgical procedures considered had an effect on increasing the MG area of loss (e.g. unchanged Meiboscore before vs after surgery). However, to diagnose MGD, other MG functions should be evaluated such as quantity and quality of meibum lipid secreted after and further studies are needed to clarify the impact of both procedures on MGD development (Figure 80).

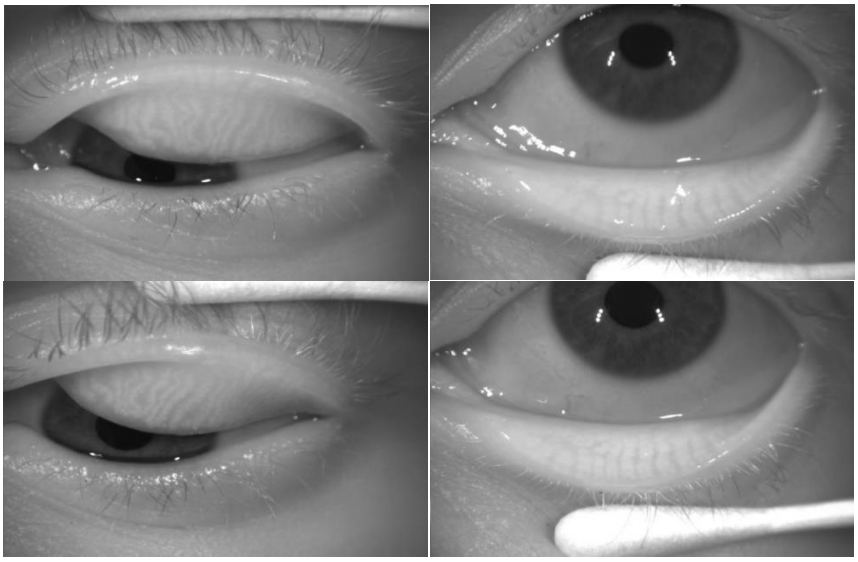

Figure 80 Infrared light scans of the upper and lower Meibomian glands before (A and B) and after FS-LASIK procedure (C and D).

As mentioned in the introduction, SMILE surgery is recognized to have less impact on the subbasal corneal nerve structure compared to FS-LASIK (Cai et al., 2017; Denoyer et al., 2015; Ni et al., 2015; Xia et al., 2016). In order to track corneal structure changes (e.g. nerve fibres or keratocytes), a minimally-invasive technique, called IVCM, has been used to investigate this during the last decade. As previously published by Smith et al. (2013), IVCM has been shown to be a powerful, reliable and no-invasive technique to study changes in corneal nerve fibres, that potentially could anticipate early stage neuropathy associated with Fabry's disease, diabetes and *Acanthamoeba* keratitis (De Craene et al., 2018; Tavakoli et al., 2011). In this research, 4 different parameters of the subbasal corneal nerve structure were assessed such as corneal nerve fibres density, corneal nerve branch density, corneal nerve fibre length and corneal nerve fractal dimension calculated using a software developed by a research group from the University of Manchester: the ACCMetrics. The automatic quantification of corneal nerves assessed by IVCM is helpful in reducing the bias from manual tracing of nerves or using external software where accessibility may be limited to only a few clinicians or researchers (Meijering, 2010). ACCMetrics has been tested in term of reproducibility for early detection of diabetic neuropathy by Ostrovsky et colleagues (2015) resulting in reduced bias when compared with manual analysis. Dehghani et al. (2014) reported excellent correlations with manual or semi-automated methods, promoting also the ACCMetrics ability in reducing time required to undertake the analysis (7x and 4x faster than non-automated methods respectively). Petropoulos et al. (2014) reported the time needed to automatically quantify the subbasal cornea nerves was 10 to 22 seconds per scan against 2 to 7 minutes needed in the manual quantification, depending on the density of the nerves. However, this is the first study where the automated analysis of the subbasal corneal nerve structure (ACCMetrics) is considered before and after FS-LASIK and SMILE procedures. One of the first studies considering IVCM after corneal refractive surgery (e.g. PRK), was conducted by Cavanagh et al. (1993). The researchers were able to observe, without quantifying the activation, keratocytes 6 weeks after surgery (e.g. irregular distribution and abnormal keratocytes nuclei shape) and also the subbasal nerve plexus under regeneration with no signs of corneal nerve fibres. Successively, Frueh et al. (1998) reported the reduced presence of the basal epithelial nerve plexus 4 months after PRK surgery observed only in 7 eyes (60% of the study cohort). The reason behind the difficulty in observing the nerve fibres under the sub-epithelial layer was due to the hyperreflectivity of this layer, in fact, after 12 months it was possible to observe the nerve fibres in all the eyes considered (n = 12). Since 2000, researchers have started to relate IVCM scans with corneal sensitivity measures after corneal refractive procedures. In a study by Linna et al. (2000) central corneal nerve fibre bundles recovered to before surgery levels only 12 to 24 months after the surgery, whereas the temporal fibres recovered from 3 months onward. Additionally, the authors found that the areas without nerve fibres or with shortened nerve fibres were the ones with lower sensitivity measured with the Cochet-Bonnet esthesiometer. IVCM has

been used after laser refractive procedures (LASIK and PRK) to track the regeneration of the subbasal corneal nerve fibres (Erie et al., 2005). Firstly, the subbasal nerve density recovered to near pre-operative values only at 2 and 5 years after PRK and LASIK, respectively. Secondly, as the corneal sensitivity recovered before complete nerve fibre regeneration, it should be useful to associate the aesthesiometry assessment together with the IVCM after surgery to obtain a more complete diagnosis. However, as reported by Benítez-del-Castillo (2007), the non-contact aesthesiometer, rather than the Cochet-Bonnet, may be a better device to assess corneal sensitivity in patients with or without DED (Versura et al., 2010). In terms of SMILE surgery and subbasal corneal nerve fibre structure, Vestergaard and colleagues (2013a) conducted a study where modern corneal refractive procedures performed using the femtosecond laser were compared. The authors reported that even if the corneal nerve density and number of long nerve fibres were significantly decreased after femtosecond lenticule extraction (FLEX) and SMILE up to 6 months, the second technique did not affect the corneal sensitivity at all. Moreover, when patients reported discomfort after surgery, 74% of the study cohort operated with FLEX surgery manifested dryness while only 9% did with SMILE surgery up to 7 days. The study also included the correlation of the corneal nerve density with some of the most important DED metrics such as NIBUT and fluorescein TBUT without reporting significant results. Denoyer et al. (2015) compared FS-LASIK and SMILE surgery using DED metrics and IVCM analysis. The results of this study suggested that SMILE had less impact on the subbasal corneal nerve fibres and therefore less impact over the ocular surface compared to FS-LASIK surgery. In the current study, in contrast to Denoyer's study, ACCMetrics was implemented for tracing and determining the corneal nerves instead of a manual or semi-automated procedure that potentially could have induced bias from the operator during the analysis. Using the ACCMetrics analysis, a significant reduction in a FS-LASIK group in terms of subbasal corneal nerves (up to 75%) after surgery was observed while in SMILE group the impact was less important (up to 23%), as previously observed by Denoyer. Additionally, the presented results showed a significant reduction on all the subbasal corneal parameters in the FS-LASIK group compared to the SMILE group, confirming that the flap-less procedure was less impacting. Additionally, the reduction observed in the current study in terms of corneal nerve fibre density had similar findings to those of Calvillo et al. (2004) where LASIK performed with a microkeratome induced subbasal nerve reduction >90%. Furthermore, in the same study cohort, the subbasal corneal nerve fibre recovery evaluated at 3 years was <60% of the pre-operative level in LASIK and therefore surgery that impacts less on nerve structure, may reduce also post-operative DED. Finally, ACCMetrics software was also able to provide a newer corneal nerve metric called corneal nerves fractal dimension. As reported by Chen et al. (2018), the use of fractal dimension analysis could improve differential diagnosis in conditions such as diabetic sensorimotor polyneuropathy. In reality, the reduced values observed in terms of ACNFrD may indicate an abnormality of the corneal nerve fibres

anticipating an early stage of neuropathy or the worsening of a previously diagnosed condition. Giannaccare et al. (2019) reported ACNFrD as a measure of structural complexity of the corneal nerves. However, following their results, ACNFrD parameter did not show significant variation in discriminating DED patients from healthy subjects with limited diagnostic power. The presented ACNFrD results measured were significantly reduced after surgery in both procedures but significant changes appeared when the procedures were compared. It might worth considering ACNFrD with a longer post-operative follow-up to track the structural complexity of the corneal nerves during the healing process.

In terms of correlations, both symptomatology questionnaires such as OSDI and DEQ-5 were compared. The reason of having both questionnaires in the current study was, as recommended by TFOS DEWS II (2017), to "*use the OSDI due to its strong establishment in the field or the DEQ-5 due to its short length and discriminative ability"*. However, any significant correlations between the questionnaires were found, but a significant correlation was found for the OSDI questionnaire pre- and post-operatively in the FS-LASIK group. In fact, as previously reported by Cohen and Spierer (2018) pre-operative symptoms (high OSDI scores) may improve the chance of having post-operative DED, therefore careful pre-operative screening is advisable.

In the current study, NIKTBUT assessed using non-invasive infra-red light has shown interesting results in terms of correlation with other DED metrics: in fact, as previously reported by Begley et al. (2013) the thinning of the tear film was related with reduced stability of the tear film and increased DED symptoms. In the FS-LASIK group presented, a reduced NIKTBUT before the surgery was associated with reduced NIKTBUT values after surgery and with a depleted volume of the tear film (TMH). In the SMILE group presented, a negative correlation between TBUT and symptoms was determined as the pre-operative increased symptoms were observed with reduced stability of the tear film after surgery supporting the need for testing DED symptomatology before undergoing ocular surgery, irrespective of which surgical technique is being considered (Ni et al., 2015).

As previously reported by Denoyer et colleagues (2015), who have studied corneal nerve morphology and DED functions, the current DED symptomatology was correlated with the corneal nerve fibre length. However, as reported by Vestergaard et al. (2013a) comparing FLEX and SMILE techniques, none of the other DED metrics considered in both groups (TBUT and TMH) were correlated with the corneal nerve fibre structure.

8.4.1 Limitations of the Study

Some limitations are acknowledged to the present study. For example, the study did not employ randomised design (e.g. double-masked study). Patients in both groups were matched in terms of age, sex and refractive state but without randomisation, some limitation compared with studies

with the paired-eye approach. Also, patients and author were not masked as the patients' enrolment and follow-up has been performed by the same author (AR).

In terms of DED metrics considered, a list of limitations is detailed below:

- the corneal sensitivity by the means of a Cochet-Bonnet esthesiometer was not included in the study, although it is unclear on the usefulness of this device in DED diagnosis due to its weak correlation with other DED metrics (Versura et al., 2010).
- the MG evaluation was limited to the structure, evaluating only the amount of loss/atrophy of the upper and lower eyelids. Thus, quantity or quality assessments of the meibum lipids were not performed, to reduce the invasiveness of the dry eye assessment, limiting the ability of diagnosing MG dysfunction in both groups.
- ACCMetrics was not able to provide any information about tortuosity, which has been demonstrated to have a role in DED. Nevertheless, the software might have included artefacts in the quantification (e.g. dendritic cells) leading to false-negative and false-positive results.

Finally, a larger sample size for the cohorts with longer follow-up schedules would have been preferred.

8.4.2 Conclusion

In conclusion, FS-LASIK and SMILE safely corrected the refractive errors providing favourable visual outcomes in all the study cohorts. However, FS-LASIK surgery had more impact on DED symptomatology than SMILE surgery. Considering the TFOS DEWS II diagnostic test battery and by the means of some of the most advanced devices currently available, the changes due to the flap surgery on the tear film volume (TMH) and tear film stability (NIKBUT) were observed comparing the pre-operative values within the post-operative values.

Automated quantification of the subbasal corneal nerve fibres obtained from IVCM scans is a rapid alternative technique. In the current research using IVCM, SMILE surgery led to significantly less change to the corneal nerve fibres metrics considered compared to FS-LASIK. This could suggest that SMILE surgery had less impacting on the sensory nerve loop of the cornea leading to less post-operative DED. However, the changes in the corneal nerve fibres observed with IVCM in both surgeries, were not correlated within DED metrics with a lack of association observed between those factors. Further studies are needed to explore the relationship between subbasal corneal nerve fibres assessed using IVCM with post-operative ocular dryness in modern corneal laser procedures.

Chapter 9: Short term changes in ocular surface disease in patients after minimally invasive glaucoma surgery with iStent Inject®. A pilot investigation.

9.1 Introduction

The burden of glaucoma disease, the second leading cause of blindness in the world, affects 64.3 million people in 2013 with the current estimation in increasing to 76.0 million people in 2020 and a potential growth up to 111.8 million people in 2040 (Tham et al., 2014). Among all the management options (Lusthaus et al., 2019), one of the most common is using topical eyedrops which have the aim to control the intraocular pressure (IOP) to maintain optic nerve integrity avoiding neuropathy and preserve the overall level of vision (Marshall et al., 2018). However, despite their efficacy in controlling IOP (Dikopf et al., 2017), many topical drugs are currently prescribed with preservatives (e.g. benzalkonium chloride, stabilized oxychloro complex, polyquaternium-1, etc.) which have several side-effects including conjunctival inflammation (Furtado et al., 2012), ocular hyperemia, periorbital chemosis (Pisella et al., 2004), foreign body sensation, stinging or burning, dry eye sensation (Jaenen et al., 2007), decreased TBUT, diminution of TMH, increased eyelid margin abnormality, conjunctival hyperemia (Wong et al., 2018), LLT thinning (S. Lee et al., 2016b), ocular surface staining (Yamazaki et al., 2010) (Figure 81), Meibomian glands dysfunction (Arita et al., 2012a, 2012b), etc. Facing the problem of DED in glaucoma patients managed with topical drops, clinicians can reduce complication observed with BAK by minimising exposure (see section 1.6.2 for more details), changing the type of preservative (e.g. to sodium perborate) or prescribe a DED treatment together with the anti-glaucoma topical drops (X. Zhang et al., 2019).

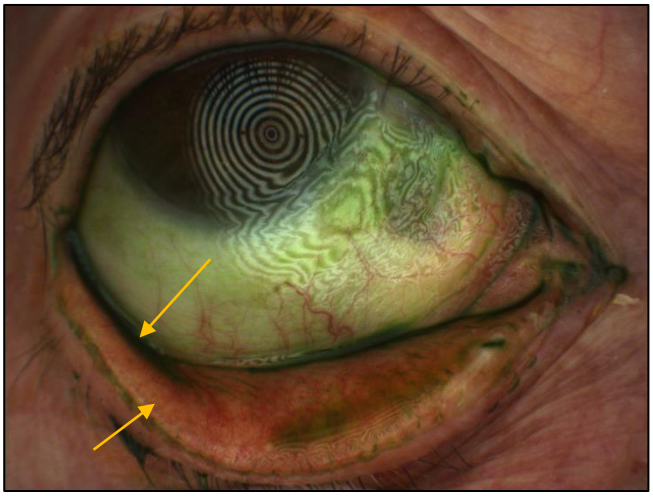

Figure 81 Ocular surface of a patient exposed to long-term use of anti-glaucoma topical drugs (yellow arrows indicate staining of the inferior eyelid assessed via lissamine green).

As reported in the literature (Baudouin, 2008; Jaenen et al., 2007; Pisella et al., 2002), one of the suggested approaches is to switch to non-preserved anti-glaucoma topical drops with the main aim to keep the IOP under control. In a study by Tokuda et al. (2017), the researchers by switching from BAK-preserved Latanoprost to preservative-free Tafluprost while controlling

IOP, observed a recovery in the corneal epithelial cell barrier in 4 weeks with less corneal staining and improved TBUT. Nevertheless, additional studies are required with longer follow-up periods to confirm these findings. More recently, in a publication from Economou et al. (2018) ocular signs and symptoms improved after switching from preserved Latanoprost to its non-preserved version. In fact, in the group treated without preservatives, TBUT was higher, ocular symptoms were absent and a lower incidence of clinical conjunctival hyperemia was noted. However, one limitation in the strategy to change to non-preserved antiglaucoma topical drops is their availability because of their increased cost (Thygesen, 2018).

Among the options to control IOP while improving the status of the ocular surface, glaucoma surgery is also a viable alternative (see section 1.6) (Gracner, 2018; Raj et al., 2018; Russo et al., 2009). Nowadays, MIGS has been shown to be efficacious and safe in IOP regulation (D. Chen et al., 2017a). MIGS improves the aqueous outflow by targeting the Schlemm's canal, the inner space between the conjunctiva or the suprachoroidal space (Schehlein et al., 2017). MIGS can involve implantation of a small device called iStent Inject® (less than 0.5 mm), made of a single-piece of heparin-coated titanium body indicated for open-angle glaucoma. A prospective multi-centre study of iStent Inject® was published by Voskanyan et al. (2014): all the patients with open-angle glaucoma enrolled (n= 99) were implanted with 2 devices. 66% of the total at 12 months (n= 92) reached an IOP ≤ 18 mmHg in whereas 81% of the subjects with one medication only or no medication, in addition, reached an IOP equal or lower than 18 mmHg. However, the greater reduction in IOP (approx. 30%), without medication, was achieved in more than 77% of the subjects. Therefore, the researchers were able to demonstrate for the first time that the implantation of 2 devices was an effective and safe procedure to solely control IOP without the use of medication, or at least with only one topical drop. Positive findings were also revealed by Fea et al. (2014) who enrolled patients (n= 94) from 7 countries (US, West and East EU) and implanted 2 iStent Inject® devices. IOP ≤ 18 mmHg was achieved in 92.6% of the eyes without any reported complications at the 12-months appointment (e.g. corneal oedema, epithelial defect, capsular opacification, etc.). Additionally, the study demonstrated that the implantation of 2 devices was able to obtain the same results as the use of 2 medications (e.g. topical drops) which could potentially lead to improvement in the ocular surface. Unfortunately, the ocular surface was not assessed before or after surgery, limiting the understanding of the discontinuance of the topical drops and the possible improvements from DED due to MIGS.

In a meta-analysis made of 5 studies (n= 248 subjects) by Malvankar-Mehta et al. (2015) demonstrated that the implantation of 2 iStent Inject® devices lead to a reduction in using topical drops of about 1.45 bottle per patient (e.g. topical drugs with preservative) in 6 months, maintaining IOP controlled.

Leung et al. (2008) reported DED symptoms in 59% of patients using anti-glaucoma topical drops with signs of reduced tear volume (61%), ocular surface staining (22%), abnormal tear film stability (78%). Additionally, the researched reported that BAK-preservatives topical drops were responsible for developing approximately 2 times odds the presence of lissamine green staining. Ghosh et al. (2012) observed 70.3% of glaucomatous patients managed with drops having signs of DED (n= 300) without finding any correlations with symptoms. However, as the patients enrolled were treated for 6 months or more using topical medication, the cytotoxicity of BAK-preserved formulation to control IOP could have potentially reduced the corneal sensitivity while inducing inflammation of the ocular surface (Bron et al., 2017; Furtado et al., 2012; Rhee et al., 2017).

In summary, the higher prevalence of DED in glaucomatous patients using topical medication (mostly with preservatives), the lack of compliance of the patients in following the prescribed regime, the discomfort in using drops (e.g. red eye or difficulty in instillation), etc., has resulted in interest in less invasive treatment in order to control IOP that could avoid an increase in chronic DED. However, the potentially beneficial effects the procedure with the implantation of iStent Inject® on the ocular surface have not been investigated to date. The aim of the current study was to apply a battery of DED diagnostic tests in glaucoma patients listed for MIGS with iStent (proposed by latest TFOS DEWS II report (Wolffsohn et al., 2017)), to understand the short-term changes in ocular surface disease in patients after minimally invasive glaucoma surgery.

9.2 Methods

9.2.1 Study design

This was a prospective, longitudinal and observational pilot study that received a favourable opinion from the Aston University Research Ethics Committee.

9.2.2 Subjects

Five glaucoma subjects, who were attending for MIGS consultation at a private eye hospital in the UK (Optegra Eye Hospital, Birmingham) were invited to take part. All examinations were performed before and 1 month after surgery. Inclusion criteria were: pseudophakic subjects with open-angle glaucoma, current treatment with one to three medications for at least 1 year, C:D ratio of 0.9 or less. Exclusion criteria: previous glaucoma surgery (e.g. selective laser trabeculoplasty), abnormal angle anatomy, corneal dystrophy or opacity, drug-controlled IOP ≥ 45 mmHg. Additional inclusion and exclusion criteria are listed in Chapter 2.

Demographics for the study population are presented in Table 24. The mean cup-to-disc ratio (C:D ratio) was 0.7 ± 0.2 where a higher ratio suggests more glaucomatous damage. Subjects were taking prostaglandin analogues (1 drop in the evening) and had a mean medicated IOP before surgery of 23.8 ± 1.8 mmHg.

Parameter	Values
Number of eyes	5
Mean age (y) ± SD	71.4 ± 8.4
Range (y)	60 – 83
Male n (%),	3 (60),
Female n (%)	2 (40)

Table 24 Demographics of the patients included in the study.

For study purposes, the consultant ophthalmic surgeon measured IOP using a Goldmann applanation tonometer, assessed C:D ratio using the Spectralis OCT (Heidelberg Engineering GmbH, Dossenheim, Germany) and performed a full eye examination to detect any abnormality of the eye which could potentially exclude the subject from taking part in the study. The staff health care technician measured the CDVA following a standard operating procedure that describes visual acuity assessment using a Topcon CC-100 computerized test chart (Topcon, Tokyo, Japan). The dry eye assessment was performed by AR considering the following metrics: OSDI, DEQ-5, tear film osmolarity by the means of the TearLab® Osmolarity System. NIKBUT, TMH, ocular surface staining, Meibography, ocular redness, LLT were assessed using a K5M.

9.2.3 Surgery

All surgeries were performed by an experienced consultant ophthalmic surgeon (I.M.) in a single centre hospital in the UK and not in association with cataract surgery. Pre-operative disinfection of the external part of the eye and anexa was performed using 5% povidone-iodine 1 hour prior to surgery in all cases. MIGS was performed with a standard clear corneal incision (approx. 2.85 mm) under topical anaesthesia with 2 drops of Proxymetacaine 0.5% (Bausch & Lomb, Bridgewater, US). The implantation of 2 iStent Inject® devices started with the injection of acetylcholine 1% (acetylcholine, 1%, Alcon Cusi) into the anterior chamber to induce the closing of the pupil (Figure 82).

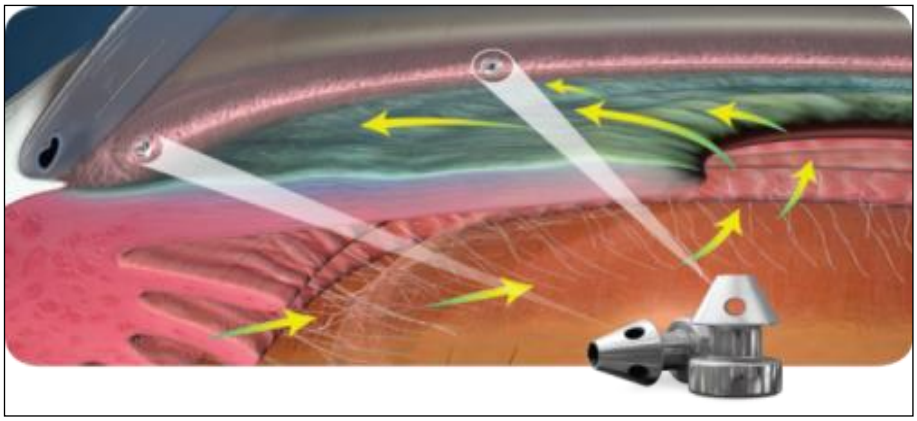

Figure 82 Anatomical site of the angle of the eyes where the two iStent Inject® were implanted (Courtesy of Glaukos Corporation, Laguna Hills, US).

To improve the visualization of the angle, the Healon viscoelastic agent (Abbott Medical Optics, Santa Ana, US) was injected in the anterior chamber. All the implantations were located in the nasal side where the iStent Inject® was introduced via the anterior chamber, through the trabecular meshwork and then into the Schlemm's canal (3 to 4 o'clock right eye, 9 to 8 o'clock left eye as suggested by the manufacturer). Once in position, the stent was released from its applicator and the procedure was repeated for the second device. Finally, the anterior chamber was flushed to eliminate any rest of debris or blood and to ensure the right position of the stents and the viscoelastic gel was removed and replaced with saline solution to restore physiologic pressure. After surgery, patients were prescribed with non-preserved topical drops (Dexamethasone 0.1% and Ofloxacin 3mg/ml). Instructions for both sets of drops were 1 drop to be used 4 times per day for 7 days. Anti-glaucoma topical drops were prescribed after surgery only in the event of increased pressure (compared to before surgery). At the 1-month follow-up, the consultant performed a slit lamp evaluation followed by applanation tonometry for IOP assessment and the nurse staff checked CDVA. All implantations were verified using gonioscopy.

9.2.4 Statistical Analysis

All data were analysed with SPSS 23.0 (SPSS Inc., Chicago, IL, USA). Data normality was confirmed using the Shapiro-Wilk test and therefore a paired sample *t*-test was used to compare outcomes before and after the implantations. Statistical significant difference was set to an alpha of 0.05.

9.3 Results

The pre-operative CDVA was not significantly different before and after the surgery (0.49 ± 0.31 logMAR *vs* 0.47 ± 0.27 logMAR, p= 0.119).

A 26% reduction in IOP at the 1-month appointment was observed although it did not reach statistical signification (pre 23.8 ± 1.8 mmHg *vs* post 17.7 ± 1.2 mmHg) (p= 0.084).

In terms of symptoms, OSDI questionnaires revealed a significant reduction in DED score after surgery (p= 0.022) that was not significant with DEQ-5 questionnaire (p= 0.554) (Figure 83).

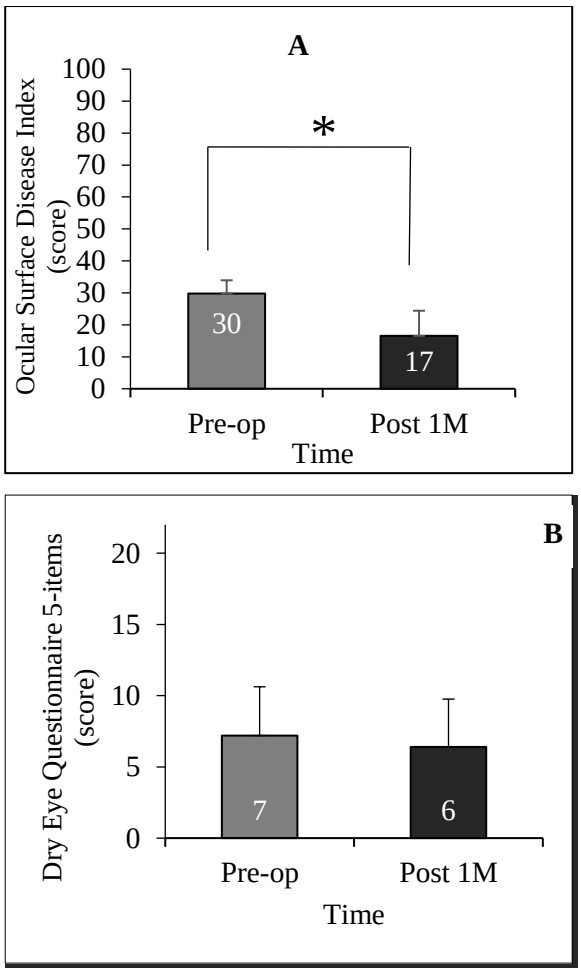

Figure 83 Ocular surface disease index (OSDI) (A) and dry eye questionnaire 5-items (DEQ-5) (B) scores before (Pre-op) and after (Post 1M) surgery with error bars indicating standard deviation. Asterisk denotes a significant difference compared with the pre-operative level (p= 0.022).

Tear film osmolarity values were not significantly different after the surgery (p= 0.06) (Figure 84) while tear film stability showed a significant improvement (p= 0.005) (Figure 85).

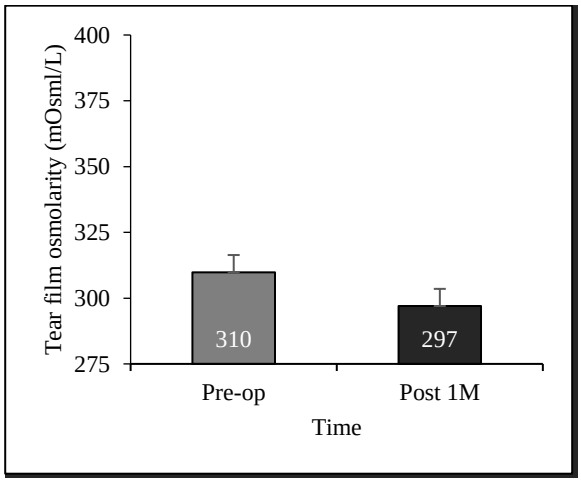

Figure 84 Tear film osmolarity values obtained pre and postoperatively with error bars indicating standard deviation (Pre-op= pre-operative, Post 1M= post-operative at 1 month).

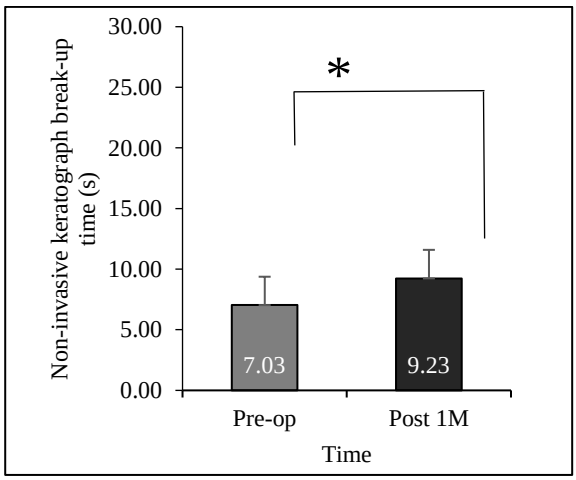

Figure 85 Non-invasive keratograph break-up time (NIKBUT) in seconds between the surgery follow-up with error bars indicating standard deviation (Pre-op= pre-operative, Post 1M= post-operative at 1 month). Asterisk denotes a significant difference compared with the pre-operative value (p= 0.005).

The variation in TMH before and after surgery was minimal and not significant (p= 0.468) while a significant change compared to baseline was observed for corneal and conjunctival staining at the follow-up appointment (Oxford score before 3.60 ± 0.55 score *vs* after 2.40 ± 0.55 score) (p= 0.033) (Figure 86).

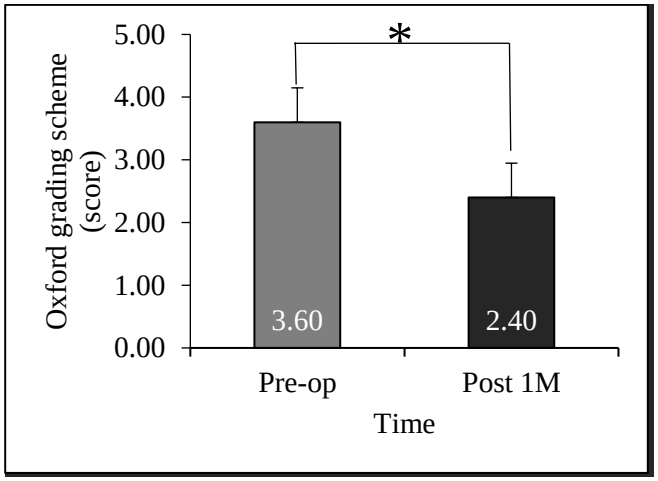

Figure 86 Ocular surface staining assessed with Oxford grading scheme score between the surgery follow-up with error bars indicating standard deviation (Pre-op= pre-operative, Post 1M= post-operative at 1 month). Asterisk denotes a significant difference compared with the pre-operative value (p= 0.033*)

No significant changes were assessed before *vs* after surgery for MG Meiboscore (MG means Meibomian glands) (p= 0.374), ocular redness (bulbar p= 0.896 and limbar p= 0.116) and lipid layer thickness (LLT) (p= 0.669).

9.4 Discussion

The leading cause of DED in glaucoma patients is the interaction between the ocular surface and the preserved drugs to control IOP (Leung et al., 2008; Perez Bartolome et al., 2018; Thygesen, 2018; Wong et al., 2018; X. Zhang et al., 2019). During the last years, several publications revealed how the preservatives included in anti-glaucoma formulations influence DED metrics: symptomatology (Jaenen et al., 2007), ocular surface staining, ocular redness (Baudouin et al., 2010), reduced TBUT (Ramli et al., 2015), etc. However, despite several publications evaluating safety and efficacy of MIGS iStent Inject® for controlling control (Arriola-Villalobos et al., 2013; Fea et al., 2014; Voskanyan et al., 2014), at the current date there are no publications regarding how this type of surgical management of glaucoma can potentially improve the status of the ocular surface in patients previously using preserved eyedrops.

In the current study, CDVA and IOP after MIGS were not significantly changed after surgery. Patients could avoid using anti-glaucoma topical drugs in the first month, which was inside the follow-up period considered in the study. In view of the IOP reduction obtained from baseline (approximately 26%), the presented results were in agreement with the 1-month data from Shiba et al. (2017).

Studies of symptomatology in glaucoma patients revealed a high prevalence of DED up to 70-80% of the study cohorts considered (Jaenen et al., 2007; Pisella et al., 2002). In a study by van Went et al. (2011) 82% reported an OSDI score > 22 which indicated positive DED symptomatology (OSDI cut-off ≥ 13, Wolffsohn et al. (2017)) in patients with glaucoma on eyedrops. Went's findings suggested to change the topical drops treatment in 36% of them might avoid the aggravation of the ocular surface disease. Based on the findings of the current study with patients treated for more than 1 year, the pre-operative prevalence of positive DED assessed using OSDI questionnaire with a cut-off value >13 score was of 100% while it was significantly reduced (p= 0.022) to 40% (2 out of 5) after MIGS. A non-significant diminution using DEQ-5 comparing before *vs* after surgery was found. A hypothesis was done for this result: as the recall time of the questionnaires is different (e.g. DEQ-5 1 month before *vs* OSDI 1 week before), the reduction perceived with DEQ-5 was modest as closer to the day of the surgery and therefore no significant changes affected the study population enrolled. However, further studies are needed to compare the obtained results with other as DEQ-5 is not the most commonly adopted in the literature within glaucoma cohorts.

In the absence of a direct comparison between DED metrics and MIGS in the literature, the current research considered the findings from published articles of trabeculectomy and DED. In fact, trabeculectomy is one of the most performed glaucoma surgeries to control IOP and reduce dependency on topical eyedrops (Koike et al., 2018; Lusthaus et al., 2019; Marshall et al., 2018). In a study by Tong et al. (2018a), patients were screened using DED tests such SANDE questionnaire, Schirmer's test, tear osmolarity revealing an improvement of the ocular surface homeostasis after ceasing to use anti-glaucoma eyedrops. As remarked by S. Lee et al. (2013), tear osmolarity in patients using anti-glaucoma topical drops increases because preservatives weaken the lipid barrier of the tear film leading to increased evaporation. In the explanation of the "*Vicious Circle of Dry Eye Disease"*, Bron et al. (2017) stated that evaporation and increased tear film osmolarity can start the inflammatory process over the ocular surface. Any significant changes were found in tear film osmolarity (before 310 ± 7 mOsm/L *vs* after 297 ± 7 mOsm/L, p= 0.163) but MIGS reduced the mean osmolarity under the cut-off (e.g. ≥ 308 mOsm/L) for having hyperosmolarity suggested by recent TFOS DEWS II report and other published studies (Jacobi et al., 2011; Lemp et al., 2011; Wolffsohn et al., 2017).

Neves Mendes et al. (2012) detected a reduction in tear film stability due to the filtering bleb produced in trabeculectomy. Moreover, as published in a study from Ji et al. (2016) patients with DED and filtering blebs reported more dryness, gritty or sandy sensation, reduced fluorescein TBUT, increased corneal staining. The difference in procedures could explain the improvement in the presented results as MIGS does not require the creation of a bleb to control IOP.

NIKBUT demonstrated a significant improvement after MIGS (p= 0.005). This result is supported by the fact that anti-glaucoma drops directly affect the composition of the tear film, as mentioned before, leading to a depleted stability. Tong et al. (2018a) found reduced tear film stability using a K5M in a group of patients using prostaglandin analogues, as with the study cohort enrolled in this research. However, despite the significant improvement (before 7.03 ± 2.34 s *vs* after 9.23 ± 2.36 s p= 0.011), the patients considered in the current research were not able to reach the published cut-off of 10 s after MIGS and further follow-up is required to understand the changes over longer time periods. Considering Zhong and colleagues' study in trabeculectomy surgery (2018), a significant reduction was observed at the 1-month appointment in the stability of the tear film (before 13.82 ± 1.11 s *vs* after surgery 11.05 ± 1.51 s, p<0.001).

TMH was subjectively detected by the means of a built-in calliper which accuracy relies on the experience of the observer to place correctly the calliper. Zhong et al. (2018) reported a 0.01 mm difference (plus 0.02 mm SD) of change at 1-month after trabeculectomy. Notwithstanding, citing a previous article from Tian et al. (2016), TMH acquired by a K5M device showed good repeatability and reproducibility only in healthy subjects while its reliability in glaucoma patients has not been established yet. Moreover, patients exposed to long-term use of topical eyedrops treatments (e.g. more than 1 year) may develop irregularity in the eyelids margins increasing the variability of TMH measurements (T. Lee et al., 2018; Wong et al., 2018) (Figure 87).

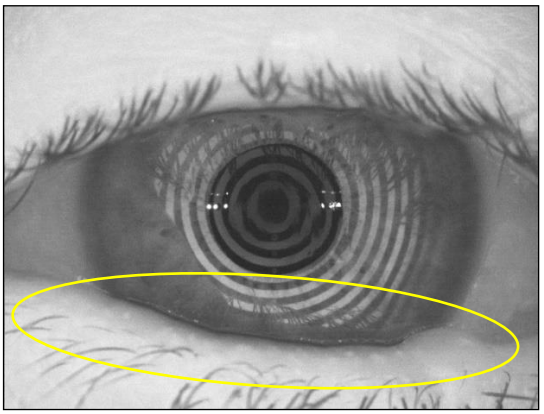

Figure 87 Irregular lower eyelid margin in a patient exposed to long-term use of anti-glaucoma topical drugs.

A significant impact from trabeculectomy surgery was recorded in Zhong's year study in corneal staining score (p< 0.001) although the scoring system considered was not specified. However, a comparison between MIGS and trabeculectomy was not the aim of the current study but a less degradation in DED metrics with MIGS compared to trabeculectomy could potentially be expected due to the lack of the filtering bleb in MIGS. In contrast with the findings from Wong et al. (2018) where corneal staining was found not to differ in patients using anti-glaucoma drops

in one eye and in the fellow eye non-treated, the presented results comparing staining data before and after MIGS, reported a significant improvement (p= 0.033) in the status of the ocular surface (cornea and conjunctiva).

Mocan et al. (2016) discovered that 92% of patients (n= 25) with long-term use of prostaglandin analogue drops (more than 12 months) for treating glaucoma had MGD. Topical drops appear to affect the terminal ducts of the MG leading to abnormalities in the blood vessel around the eyelids (e.g. vascular engorgements). Prolonged MG duct blockage leads to atrophy of the glands resulting in increased gland drop-out. Further evidence was also provided by Arita et al. (2012a) who have identified in glaucoma patients treated with prostaglandin β-blockers significant MGD in terms of meiboscore (gland atrophy). The following results based only on the Meibomian gland loss (e.g. Meiboscore), were unable to present significant changes between the two appointments (before and at 1 month). A possible reason is based on the fact that MGs are not able to recover from drop-out even if an eyelid hygiene treatment is performed. In a study by Yin et al. (2017), despite the lack of compliance in using eyelid hygiene in 33% of the study group, the other patients were able to reduce drop-out of MG of about 5% in 1 month of treatment. However, there is some controversy in recovering from MG drop-out as both studies from Aronowicz et al. (2006) and Finis et al. (2014) did not find improvements. In the current study, any eyelid hygiene treatment was prescribed to the study cohort after surgery and therefore future studies may include this as an additional variable.

Ocular redness is a common sign observed in patients using topical drops for glaucoma (Feldman, 2003). In a review of medical and pharmacy surveys in the US health network, more than 13.997 patients which started hypotensive treatment were considered (65% of the total were receiving prostaglandins). Amongst these, approximately 70% of them experienced conjunctival hyperemia (Zimmerman et al., 2007). The automatic assessment of ocular redness using a K5M was found useful in patients with glaucoma by Perez Bartolome et al. (2018) who identified prostaglandins as a risk factor in conjunctival hyperemia. However, the automatic grading provided by the device was reported by the same investigators to be not comparable with subjective grading (Perez-Bartolome et al., 2018). The presented results showed that the bulbar conjunctiva was more affected by preserved topical drugs than the limbal area but any comparison with other studies was possible as many of them reported the findings considering both locations (bulbar and limbar together). In addition, El Ameen et al. (2018) confirmed the use of non-preserved prostaglandins drops improved ocular redness reducing the ocular toxicity induced by BAK.

Preservatives in the topical formulation affect the tear film due to their property to destabilise LLT and the cytotoxicity of the corneal epithelial cells (Georgiev et al., 2017). From

the results published by S. Lee et al. (2016b), LLT, measured with interferometry, the clinicians demonstrated a significant reduction in patients with glaucoma and ocular surface disease treated with preserved topical drops than patients with DED without glaucoma. Additionally, the duration of the treatment was negatively correlated with LLT (the longer the treatment, the thinner the lipid layer) exposing patients with chronic disease to a more pronounced decay of the lipids in the tear film, generating evaporative DED. The findings from the current research revealed no significant changes in LLT (p= 0.669) that could potentially be limited by the short term evaluation (1 month). 60% of the patients attending MIGS were found with a reduced LTT graded as "*open meshwork*" which is the thinnest grade following (J. Guillon (1998b). However, after the surgery the percentage of "*open meshwork"* passed from 60 to 40%.

9.5 Limitations of the Study

The current pilot investigation suffered from several limitations including a small sample size. Firstly, a wash-out period was not possible as the patients did not stop their anti-glaucoma drops before attending the surgery. Secondly, the patients considered had a wide spread in terms of duration of exposure to preserved eyedrops. In fact, patients with 5 years of treatment could have been included together with patients with only 12 months of treatment. Finally, the MG analysis was restricted to the area of loss only to reduce the invasiveness of the dry eye assessment. Other parameters to more fully quantify MGD such as meibum expressibility and lid margin regularity were not included in the analysis to reduce patients' discomfort and the invasiveness of the dry eye assessment.

9.6 Conclusion

Despite the limitations, the results of this pilot study are very encouraging and short-term improvement and positive changes in patients changing from anti-glaucoma topical drops to MIGS (in this case, two iStent Inject®devices). Reduction in IOP was achieved by the procedure and some DED metrics such as symptomatology, stability of the tear film and ocular surface staining improved. Further studies are needed to understand the longer-term results in DED metrics provided by MIGS surgery.

Chapter 10: Summary & Conclusions

In the present thesis, a series of experimental studies was carried out to identify the impact of DED in ophthalmic surgery and, in particular, in those procedures involving the cornea and the crystalline lens for refractive and cataract indications. Additionally, a pilot study was designed around a minimally-invasive glaucoma surgery procedure to explore the impact of this on the ocular surface, as opposed to traditional anti-glaucoma medication therapy.

Newer intraocular lenses for presbyopic patients have been introduced to correct refractive error while restoring the ability of the eye to see clearly at different distances (e.g. far, intermediate and near) by the implantation of a multifocal IOL (Alio et al., 2014c; Alio et al., 2017; Alio et al., 2004; Stapleton et al., 2017). Despite the emerging data from patients in reporting their perceived outcomes of treatments in several eye conditions (e.g. glaucoma, age-related macular degeneration, etc.) (Braithwaite et al., 2019; Denniston et al., 2014; Hee et al., 2018; Taylor et al., 2016), very little has been documented on patient reported outcomes measures (PROMs) after multifocal intraocular lens surgery in the longer-term. This is important not least for counselling those patients interested in having surgery. To address this gap, a study of PROMs in a large cohort of patients (n= 728) up to 7 years after MFIOL surgery was undertaken. Particular attention was paid to those metrics more linked to DED. A significant percentage of patients reported “dry eyes” (38%, n= 277) and “watery eyes” (52%, n= 379). A surprising finding from the study was that age was not found to be a relevant risk factor in DED issues after RLE surgery (Chapter 3).

In the light of treatment of an eye condition, clinicians often predict visual outcomes considering other related metrics such as retinal parameters assessed with OCT or biomechanical properties of the cornea (Keane et al., 2008; Koc et al., 2016). As DED is often only reported after corneal refractive and lens procedures (e.g. due to the impact of laser ablation and corneal incisions) (Cochener et al., 2018; Gupta et al., 2018), a minimally to non-invasive DED pre-operative measurements could help clinicians to identify those patients at risk of post-operative DED issues and treat them accordingly before undergoing surgery. Evidence-based DED screening protocols should not only be capable of identifying those DED patients particularly at risk of unsatisfactory outcomes, but also to optimise the refractive and visual outcomes after surgery. Using a range of DED measurements (described in Chapter 4), reduced tear meniscus height (TMH) and increased symptomatology through a validated questionnaire (OSDI) were identified as measures that can potentially reduce the chance of having less accurate refractive and poorer visual outcomes. Chapter 4 also revealed no correlation between tear osmolarity with the refractive outcomes.

Although generally RLE surgery with implantation of a multifocal IOL has been shown to be safe and efficacious across age groups, there are factors that could affect the predictability of the procedure. As stated in the first reported in DED (Lemp, 1995) and in the following TFOS DEWS I (Lemp et al., 2007) and TFOS DEWS II reports (Bron et al., 2017), hyperosmolarity of the tear film is the core factor in triggering the inflammatory response over the ocular surface leading to DED. The analysis of the refractive outcomes in normal and hyperosmolar populations undergoing modern intraocular lens surgery (Chapter 5) revealed suboptimal refractive outcomes (up to 0.60 D of deviation from the predicted post-operative refraction) in hyperosmolar patients, which may impact on visual outcomes after the procedure. After considering a range of measurements used in DED diagnosis, due to the nature of the condition, a lack of association between symptoms and signs was noted as previously reported in the literature (K. Nichols et al., 2004b). Considering the findings from Chapter 4, tear film osmolarity may be not helpful in predicting post-operative refractive outcomes. In contrast, findings from Chapter 5 reported that the pre-operative assessment can possibly help the clinicians in identifying those patients who may benefit from pre-operative treatment in order to improve the refractive predictability and visual and patient-reported outcomes.

Cataract surgery may result in increased DED symptomatology in elderly populations, in part due to the increased tear film instability (e.g. age-related Meibomian gland dysfunction). Despite this, cataract surgery was able to improve the visual quality assessed by the means of a novel device (Aston Halometer). The results showed a reduction in the photic phenomena (e.g. light scatter) which were not associated with DED symptoms. Possibly, DEQ-5 questionnaire considered in the study (Chapter 6) may not be a good alternative in indicating the post-operative vision after cataract surgery.

The relatively recent introduction of femtosecond-laser technology has marked a new era in corneal refractive surgery with the advent of new procedures such as SMILE (Friedman et al., 2017; Hashmani et al., 2017; Manche et al., 2018; Marino et al., 2017; Miruna et al., 2016; Reinstein et al., 2014a). Together with providing excellent refractive outcomes (Chansue et al., 2015a), SMILE surgery has been shown to have less impact over the ocular surface with the potential to reduce post-operative DED (Cai et al., 2017; Z Shen et al., 2016b). Despite the surgical steps are substantially different from traditional corneal refractive surgery (e.g. LASIK flap and excimer ablation), the first cases of SMILE undertaken by ophthalmic surgeons in their early learning curve reported any complications and considerable refractive outcomes with limited influence on tear film stability (Chapter 7). As expected traditional and modern laser vision correction procedures were able to correct myopia and astigmatism, but due to the "flap-less" feature of SMILE, better preservation of the ocular surface was demonstrated avoiding the significant increase in DED symptomatology, decrease in tear film volume and stability observed

with femtosecond laser-assisted LASIK. Additionally, using in-vivo confocal microscopy (IVCM), the results showed how the structure of the subbasal corneal nerves was maintained better with SMILE (Chapter 8).

The introduction of newer treatments for glaucoma aims to improve patients' ocular health status (control IOP, maintaining the integrity of the retinal nerve fibres and visual field), their compliance with respect to use of the prescribed drug regime and quality of life (reducing discomfort). As reported in the literature, a majority of glaucoma patients, due to their ongoing treatment with preserved topical eyedrops (often containing BAK) may experience one or more DED characteristics (signs or symptoms) (Lusthaus et al., 2019; Thygesen, 2018; X. Zhang et al., 2019; Zhong et al., 2018). Among the recent innovations, minimally-invasive glaucoma surgery (MIGS) aims to reduce the dependence on topical eyedrops whilst maintaining control of IOP which, if formulated with preservatives, may increase the chance of DED development. The results of a pilot study in which a series of DED measures was analysed in glaucoma patients, demonstrated that MIGS had great potential for improving patients' DED symptomatology and tear stability while reducing the damage of the ocular surface (e.g. corneal staining) compared to before the surgery.

10.1 Future work

10.2 PROMs

In the last years, different PROMs tools have been validated for health care treatments (Braithwaite et al., 2019). In Chapter 3, a PROMs tool was used to explore the longer-term feedback from patients after RLE surgery and to assess, in particular, the frequency and impact of DED symptoms experienced. A validated PROMs tool would be useful to analyse the short, medium and longer-term response from patients after refractive lensectomy surgery, and longer term PROMs data will be valuable with newer procedures such as SMILE (Chapter 7 & Chapter 8) where only shorter term PROMs data are presently available.

10.3 Pre-operative DED screening

Detecting pre-operative DED can provide an opportunity for timely treatment to improve the post-operative refractive and visual outcomes after corneal refractive and lens surgery (Chapter 4 and Chapter 5). Consequently, it would be important to screen patients before the surgery, to identify those with positive biomarkers (as recommended by the TFOS DEWS II report) and implement a pre-operative treatment strategy with the aim of improving the results after surgery. It might be interesting to define different groups based on the DED subtypes encountered (aqueous-deficient or evaporative), applying a customised treatment and to observe the results of the surgery comparing with non-treated groups with similar DED subtypes.

10.4 Halometry with multifocal IOL

In Chapter 6, the Aston Halometer was used to measure photic phenomena before and after surgery in patients undergoing cataract surgery with implantation of a monofocal IOL. As reported by Alio et al. (2017), the typical period of adaptation in lens surgery with implantation of a multifocal IOL is between 3-months and 1 year. However, it is not always possible clinically, firstly to objectively measure the level of dysphotopsia with multifocal IOLs and, secondly to track the changes over time. It might be interesting to assess patients with multifocal IOLs over longer-term period using a device such as the Aston Halometer which has been shown to be sensitive and repeatable in quantifying objectively the dysphotopsia.

10.5 IVCM and corneal refractive procedures

With the advent of newer corneal refractive procedures such as SMILE, the interest in understanding the impact over the ocular surface has required advanced methods to investigate and track the possible changes. IVCM is a useful research technique although refinements in the data capture methods and the analysis of the scans are needed to make this technique more feasible to perform in routine practice.

The number of SMILE procedures is likely to increase as more clinicians adopt the procedure and it is extended to treat hyperopia and presbyopia (Y. Liu et al., 2018; Luft et al., 2018). To improve the current knowledge about the relationship between DED and age it would be interesting to apply a modern DED tests as recommended by TFOS DEWS (Chapter 8) in presbyopic patients undergoing (modified) monovision treatments with flap-less surgery.

10.6 Minimally-invasive glaucoma surgery and DED

A link between the use of preserved topical eyedrops for controlling IOP and DED has been observed in the literature (Thygesen, 2018; X. Zhang et al., 2019; Zhong et al., 2018). The short-term results after MIGS reported in Chapter 9 were promising and an improvement in the homeostasis of the ocular surface was observed. It would be useful to include longer follow-up periods (e.g. 3, 6 and 12 months) and other glaucoma surgery procedures such as selective laser trabeculoplasty.

10.7 Concluding statement

The research studies described in the thesis have examined the role of DED in cataract and refractive surgery. Despite the safety and efficacy of corneal and lens treatments to restore optimal levels of vision (Agca et al., 2018; Chua et al., 2018; Rosen et al., 2016; Zhuang et al., 2019), a significant part of the population undergoing those surgeries may develop surgical-induced dry eye which could affect quality of life, work productivity and social relationships. Additionally, based on the link between age and DED (Stapleton et al., 2017), patients presenting for ophthalmic surgery are at risk of sub-optimal post-operative refractive and visual outcomes

due to DED, which could potentially impact on satisfaction with outcomes and reduce quality of life (e.g. eye discomfort, lack of independence, depression, etc.). The inclusion of an evidence-based diagnostic test battery, such as that proposed in the recent TFOS DEWS II (Wolffsohn et al., 2017), was found useful in determining not only the impact of the ophthalmic procedures over the ocular surface but also to appreciate which are the most interesting measures to include in a "real-world" clinical setting such as an eye hospital.

The development of less-invasive surgical procedures to correct refractive error such as myopia, hyperopia, astigmatism (e.g. FS-LASIK and SMILE) and presbyopia (RLE and cataract surgery with MFIOL) or to reduce the dependence on drugs for controlling IOP in glaucoma patients (e.g MIGS) should begin with an assessment for the ocular surface. While the research in the field of DED has evolved rapidly in the last years, the inclusion of those techniques in routine clinical practice have not proceeded as rapidly. The research studies carried out in this thesis could provide useful insights to help clinicians (e.g. consultants, optometrists, GPs, etc.) to improve refractive, visual and patient-reported outcomes.

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Appendices

12.1 Aston University Life and Health Sciences Ethics Committee acceptance of amendment to project REC REF: 1050.

Aston University

Aston University
Aston Triangle
Birmingham
B4 7ET
0121 204 3000

Date: 10/03/2018

Life and Health Sciences

Dear **Clare O' Donnell & Alberto Recchioni**

Study title:	**Dry eye: pre- and post-operatively signs and symptoms with cataract and refractive surgeries.**
REC REF:	Ethics application 1050

Confirmation of Ethical Opinion

On behalf of the Committee, I am pleased to confirm a favourable opinion for the above research based on the basis described in the application form, protocol and supporting documentation listed below.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
PhD Ethics Application 1050	-	
Research_Participant_Information_Sheet_alb_revised_Alberto Recchioni	1	Feb 2017
Questionnaire – OSDI	-	Feb 2017
RiskAssessmentForm 1 of 2_Revised_Alberto_Recchioni	-	Feb 2017
RiskAssessmentForm 2 of 2_Revised_Alberto_Recchioni	-	Feb 2017
Dry_Eye_Research_Flyer_9		Feb 2018

With the Committee's best wishes for the success of this project.
Yours sincerely

Dr Nichola Seare
Chair of the University Research Ethics Committee

12.2 Aston University Life and Health Sciences Ethics Committee Decision letter for project REC REF: 1050.

Aston University

Aston University
Aston Triangle
Birmingham
B4 7ET
0121 204 3000

Date: 01/06/17

Life and Health Sciences

Dear **Clare O' Donnell & Alberto Recchioni**

Study title:	**Dry eye: pre- and post-operatively signs and symptoms with cataract and refractive surgeries.**
REC REF:	Ethics application 1050

Confirmation of Ethical Opinion

On behalf of the Committee, I am pleased to confirm a favourable opinion for the above research based on the basis described in the application form, protocol and supporting documentation listed below.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
PhD Ethics Application 1050	-	
Research_Participant_Information_Sheet_alb_revised_Alberto Recchioni	1	Feb 2017
Questionnaire – OSDI	-	Feb 2017
RiskAssessmentForm 1 of 2_Revised_Alberto_Recchioni	-	Feb 2017
RiskAssessmentForm 2 of 2_Revised_Alberto_Recchioni	-	Feb 2017

With the Committee's best wishes for the success of this project.
Yours sincerely

Dr Nichola Seare
Chair of the University Research Ethics Committee

12.3 South East Scotland REC 02 Ethics Committee Decision letter for project REC REF: 15/SS/0113.

Lothian NHS Board

South East Scotland Research Ethics Committee 02

Waverley Gate
2-4 Waterloo Place
Edinburgh
EH1 3EG
Telephone 0131 536 9000

www.nhslothian.scot.nhs.uk

Date 16 June 2015
Your Ref
Our Ref

Enquiries to: Joyce Clearie
Extension: 35674
Direct Line: 0131 465 5674
Email: Joyce.Clearie@nhslothian.scot.nhs.uk

16 June 2015

Prof James Wolffsohn
Deputy Dean Life and Health Sciences
Aston University
Life and Health Sciences
Aston Triangle
Birmingham
B4 7ET

Dear Prof Wolffsohn

Study title: **An observational study of dry eye management**
REC reference: **15/SS/0113**
Protocol number: **JWDE001**
IRAS project ID: **173203**

Thank you for your letter of 16th June 2015. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 15 June 2015

Documents received

The documents received were as follows:

Document	*Version*	*Date*
Covering letter on headed paper [Cover Letter response to ethics re FOwAC]	NA	16 June 2015
GP/consultant information sheets or letters [GP Letter]	1	16 June 2015
Participant consent form [Consent Form]	2	16 June 2015
Participant information sheet (PIS) [Patient information sheet]	2	16 June 2015

Approved documents

The final list of approved documentation for the study is therefore as follows:

Document	*Version*	*Date*
Covering letter on headed paper [Cover Letter response to ethics re FOwAC]	NA	16 June 2015
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [UMAL Insurance]	01/08/2014	01 August 2014
GP/consultant information sheets or letters [GP Letter]	1	16 June 2015

NHS
Lothian

Letter from sponsor [113S/JW]	08/06/2015	08 June 2015
Participant consent form [Consent Form]	2	16 June 2015
Participant information sheet (PIS) [Patient information sheet]	2	16 June 2015
REC Application Form [REC_Form_09062015]		09 June 2015
Research protocol or project proposal [Protocol]	1	16 April 2015
Summary CV for Chief Investigator (CI) [CI CV]	9th June 2016	09 June 2015
Validated questionnaire [OSDI]	NA	

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

15/SS/0113 **Please quote this number on all correspondence**

Yours sincerely

Joyce Clearie
SESREC 2 Manager

E-mail: joyce.clearie@nhslothian.scot.nhs.uk

Copy to: *Mrs Alpa Patel*
Dr Chris Counsell, Queen Elizabeth Hospital Birmingham

12.4 Aston University Life and Health Sciences Ethics Committee Decision letter for project REC REF: 1185.

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Memo

Life and Health Sciences Ethics Committee's Decision Letter

To: Andreas Hartwig

Cc: Kara Hanaphy

Administrator, Life and Health Sciences Ethics Committee

From: Dr Rebecca Knibb

Chair, Life and Health Sciences Ethics Committee

Date: 23/11/2017

Subject: **Project #1185** Long term evaluation of patients satisfaction and clinical outcomes after multifocal intraocular lens implantation

Thank you for your submission. The additional information for the above proposal has been considered by the Chair of the LHS Ethics Committee.

Please see below for details of the decision and the approved documents.

Reviewer's recommendation: Favourable opinion

Please see the tabled list below of approved documents:

Documentation	Version/s	Date	Approved
Response to reviewers' comments 1	1	N/A	✓
Response to reviewers' comments 2	1	N/A	✓
Consent form	1	3/11/17	✓
Participant Information Sheet	2	3/11/17	✓
Rle audit questionnaire	N/A	N/A	✓

After starting your research please notify the LHS Research Ethics Committee of any of the following:

Substantial amendments. Any amendment should be sent as a Word document, with the amendment highlighted. The amendment request must be accompanied by all amended documents, e.g. protocols, participant information sheets, consent forms etc. Please include a version number and amended date to the file name of any amended documentation (e.g. "Ethics Application #100 Protocol v2 amended 17/02/12.doc").

New Investigators

The end of the study

Please email all notifications and reports to lhs_ethics@aston.ac.uk and quote the original project reference number with all correspondence.

Ethics documents can be downloaded from: http://www.ethics.aston.ac.uk/documents-all. Please note that these documents can ONLY be opened using Mozilla Firefox or the latest Internet Explorer version (IE9).

Statement of Compliance

The Committee is constituted in accordance with the Government Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK. In accord with University Regulation REG/11/203(2), this application was considered to have low potential risk and was reviewed by three appropriately qualified members, including the Chair of the Life and Health Sciences Ethics Committee.

Yours sincerely,

Dr Rebecca Knibb
Chair, LHS Ethics Committee

12.5 Patient Information sheet and consent form for experimental participants at Aston University for project REC REF: 1050.

Aston University
Life & Health Sciences

Optegra
EYE HEALTH CARE

RESEARCH PARTICIPANT INFORMATION SHEET
– Version 01 – February 2017

Title of the study: Dry eye, pre- and post-operative signs and symptoms after cataract or refractive surgery

You are being invited to take part in a research project that will be conducted at Aston University and Optegra Eye Hospitals. Before you decide it is important for you to understand why the research is being done and what is involved. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this information sheet.

What is the purpose of the project?

The purpose of the study is to evaluate signs and symptoms of dry eye in patients undergoing eye surgery. By studying the results of different diagnostic tests over a period of time we will be able to investigate potential factors that affect dry eye development to help develop new strategies to identify and treat dry eyes.

Why have I been chosen?

You have been chosen because you and your surgeon have decided that you will be having eye surgery.

What will happen to me if I decide to take part?

If you agree to take part in the study, your surgery and pre- and post-operative care will be carried out as usual and we will collaborate with your surgeon to exchange data.

In addition to the tests that are performed to measure your vision and the shape of your eye, we will ask you to undergo a series of safe and painless clinical tests in order to assess the status of your ocular surface, your tear film and your subjective comfort before and after surgery. Your subjective comfort will be assessed using a questionnaire.

All assessments will be performed during your hospital visits and the total number of visits will be up to three visits: pre-operative consultation, first post-operative follow-up and second post-operative follow-up. The total visit time will be no more than 30 minutes (Figure 1). The first post-operative follow-up will take place up to 3 months after surgery and the second post-operative follow-up will take place up to 9 months after surgery.

Figure 1 Diagram procedure of the study "Dry eye, pre- and post-operative signs and symptoms after cataract or refractive surgery"

Are there any potential risks in taking part in the study?

There is a moderate risk associated with taking part in the study as it only involves routine clinical procedures which are known to be safe and painless.

Do I have to take part?

No. It is entirely up to you whether you take part and you are free to withdraw at any time during the study without giving any reason. Your decision about participating in the research will not affect your medical care in any way.

Expenses and payments

There will be no payment for attending in this study.

Will my taking part in this project be kept confidential?

You will be given a unique identification code and any information from your clinical notes, examinations and questionnaires will be kept anonymous. The data will be stored in a secure environment and is only accessible to researchers involved in the study.

What will happen to the results of the research study?

The results of the study may be published in scientific journals and presented at congresses, but your identity will not be revealed in publications or lectures. If you would like to be updated about the results of the study you should ask one of the research team members to add your details to the mailing list for updates.

Who is organising and funding the research?

Aston University is the organiser and sponsor of the study.

Who has reviewed the project?

The project has been reviewed and received the favourable opinion by Aston University's Ethics Committee, Birmingham, UK.

Who do I contact if something goes wrong or I need further information?

If you require more information about this study, please contact:

Research Lead:

Dr Clare O´Donnell: Clare.ODonnell@optegra.com +44 161 240 0724

Research Assistant:

Alberto Recchioni: alberto.recchioni@optegra.com +44 074 740 739 14

Who do I contact if I wish to make a complaint about the way in which the research is conducted?

If you are concerned about your participation in the research study, please contact the main investigators, details above. If your concerns are not being solved by them, you can contact with the Director of Governance – Mr John Walter – by email j.g.walter@aston.ac.uk or by telephone 0121 204 4869.

Thank you for taking the time to read this information and for considering to take part in this study.

Aston University
Life & Health Sciences

Optegra
EYE HEALTH CARE

CONSENT FORM for PARTICIPANTS – Version 01 – February 2017

NAME OF PARTICIPANT _____DATE OF BIRTH: DD / MM / YY

Patient Identification Number for this trial:

Title of Project: Dry eye, pre- and post-operatively signs and symptoms after cataract and refractive surgery.

Project investigators: Alberto Recchioni, Clare O´Donnell, James Wolffsohn, Andreas Hartwig

Please complete the boxes with your initials:

1. I confirm that I have read and understood the information sheet Version 01 for this study and I have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that the researchers may need to review certain sections of my medical records and I therefore give my permission to do so. ☐

4. I agree to take part in the above study. ☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Person taking consent (If different from Investigator)	Date	Signature
ALBERTO RECCHIONI	_____	_____
Investigator	Date	Signature

12.6 Patient Information sheet and consent form for experimental participants at Aston University for project REC REF: 15/SS/0113.

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PARTICIPANT INFORMATION SHEET v2, 16th June 2015

Project Title

An Observational Study of Dry Eye Treatment

Invitation

We like to invite you to take part in a study to help us understand how well dry eye treatments work for individual patients and to develop new and improved treatments.

Before you decide if you would like to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. If you have any questions or require any further information please ask a member of the research team whose details are at the end of this information sheet.

What is the purpose of the study?

Dry eye is an irritating chronic condition that affects many people. Although newer treatments differ from each other in what elements of the tear film (fluid covering the front of the eye) they aim to replace, there is currently limited knowledge of which signs and symptoms are best treated by which treatment. Therefore, this study will assess your dry eye in detail and will assess the effectiveness of the treatment you have been prescribed. Over time this will aid us in personalising the treatments prescribed to patients.

Why have I been chosen?

You have been chosen because you have reported having dry eye.

What will happen to me if I take part?

If you agree to take part, in addition to the tests and treatment that are provided as routine care for patients with dry eye you will be asked to complete a questionnaire about your dry eye symptoms at each clinic visit. You will also be asked to keep a brief diary between visits to record your eye comfort and the number of drops used each day.

We will ask you to give us permission to use the data that is collected as part of your routine care for research. The data will be anonymised before it is used for research.

There are no extra visits as all the data will be collected at your routine appointments. You will be followed up until you are discharged from the clinic.

Will I benefit from taking part in the study?

Whilst the study is not designed to give direct benefit to participants, we hope the research will improve the care of dry eye in the future.

Do I have to take part?

No. It is entirely up to you whether you take part and you are free to withdraw at any time during the research without giving any reason. Your decision about participating in the study will not affect your medical care in any way.

Expenses and payments

There is no payment for participating in the study as it is an observation of routine clinical care.

Will my taking part in this study be kept confidential?

You will be given a unique identification code and any information from your clinical notes, examinations and questionnaires will be stored using this code to ensure that the information is anonymous. The data will be stored in a secure environment and only accessible to researchers involved in the study.

What happens if I am harmed by the study?

It is unlikely that you will be harmed by the study, but medical research is covered for mishaps in the same way as for patients undergoing treatment in the NHS i.e. compensation is only available if negligence occurs.

What will happen to the results of the research study?

The results of the study may be published in medical journals and presented at conferences, but you will not be identified in publications or lectures.

If you would like to be updated about the results of the study you should ask one of the research team to add your details to the mailing list for updates.

Who is organising and funding the research?

Aston University is organising the study.

Who has reviewed the study?

The study has been reviewed and given a favourable opinion by the South East Scotland Research Ethics Committee 02.

Who do I contact if I have any concerns about the way in which the research is conducted?

If you have any concerns about the way in which the study is conducted you should in the first instance contact the researchers named at the end of this information sheet. They will do their best to address your concerns; but if they are unable to resolve the concerns you raise you can contact the Secretary to the Aston University Ethics Committee – Mr John Walter – on j.g.walter@aston.ac.uk or telephone 0121 204 4869.

Who do I contact for further information?

If you require more information about this study please contact:

Research Lead: Prof James Wolffsohn: j.s.w.wolffsohn@aston.ac.uk 01212044140

Independent Contact: If you would like independent advice on any aspect of this study, please contact the PALS (Patient Advice and Liaison Service) at the New Queen Hospital Elizabeth Hospital (part of the University Hospitals NHS Foundation Trust) on 0121 371 3280

Thank you for taking the time to read this information and for considering taking part in this study.

JWDE001 - Participant Information Sheet, Version 2, 16th June 2015

Aston University
Life & Health Sciences

Participant Identification Number for this study:

CONSENT FORM

Title of Project: **An Observational Study of Dry Eye Treatment**

Please initial box

1. I confirm that I have read the information sheet dated … 2015 (Version ….) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from Aston University and/or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I consent to be contacted in future regarding other ethically approved research. ☐

5. I agree to take part in the above study. ☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

One copy for the Participant, one copy to be filed in the Participants Hospital Notes, one copy to be filed in the Site File

12.7 Patient Information sheet and consent form for experimental participants at Aston University for project REC REF: 1185.

Optegra
EYE HEALTH CARE

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«Title» «First_name» «Surname»
«Address_line_1»
«Address_line_2»
«Address_line_3»
«Address_line_4»
«Post_code»

March 2018

Dear «Title» «Surname»,

As a previous patient at Optegra Eye Health Care, you are being invited to take part in a research project that will be conducted at Aston University and Optegra Eye Hospitals. Before you decide it is important for you to understand why the research is being done and what is involved. Please take time to read the attached information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

If you wish to take part in our study, please initial and sign the attached consent form and please fill out the attached questionnaire. Be aware that most documents are double-sided. We are interested in your visual performance with both eyes together. If you would like to provide additional details for each eye individually, please use the comments fields. Please return both documents (consent form and questionnaire) in the attached pre-paid envelope.

Thank you very much for choosing Optegra for your surgery and for taking time to read the information sheet.

Kind regards,

Clare O'Donnell
PhD MBA MCOptom FAAO FBCLA
Head Eye Sciences

Aston University
Life & Health Sciences

Optegra
EYE HEALTH CARE

RESEARCH PARTICIPANT INFORMATION SHEET

Version 02 – November 2017

Title of the study: Long term evaluation of patient satisfaction and clinical outcomes after multifocal intraocular lens implantation

You are being invited to take part in a research project that will be conducted at Aston University and Optegra Eye Hospitals. Before you decide it is important for you to understand why the research is being done and what is involved. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this information sheet.

What is the purpose of the project?

The purpose of the study is to evaluate feedback results of lens surgery over time.

Why have I been chosen?

You have been chosen because you have undergone intraocular lens surgery at Optegra.

What will happen to me if I decide to take part?

If you agree to take part in the study, you are asked to fill out the attached survey questionnaire and return it with the signed consent form to us.

Are there any potential risks in taking part in the study?

There are no risks associated with taking part in the study as it only involves filling out a questionnaire.

Do I have to take part?

No. It is entirely up to you whether you take part and you are free to withdraw at any time without giving any reason. Your decision about participating in the research will not affect your medical care at Optegra in any way.

Expenses and payments

There will be no payment for filling out the questionnaire.

Will my taking part in this project be kept confidential?

You will be given a unique identification code and any information from your clinical notes, examinations and questionnaires will be kept anonymous. The data will be stored in a secure environment and is only accessible to researchers involved in the study.

What will happen to the results of the research study?

The returned questionnaires will be stored in secure and dedicated areas at Optegra for at least 10 years. The results of the study may be published in scientific journals and presented at congresses, but your identity will not be revealed in publications or lectures.

Who is organising and funding the research?

Aston University is the organiser of the study and Optegra is the sponsor of the study.

Who has reviewed the project?

The project has been reviewed and received a favourable opinion by Aston University's Ethics Committee, Birmingham, UK.

Who do I contact if something goes wrong or I need further information?

If you require more information about this study, please contact:

Dr Clare O'Donnell: Clare.ODonnell@optegra.com 0161 240 0700

Who do I contact if I wish to make a complaint about the way in which the research is conducted?

If you are concerned about your participation in the research study, please contact the main investigators, details above. If your concerns are not being solved by them, you can contact the Director of Governance – Mr John Walter – by email j.g.walter@aston.ac.uk or by telephone 0121 204 4869.

Thank you for taking the time to read this information and for considering taking part in this study.

Aston University
Life & Health Sciences

Optegra
EYE HEALTH CARE

CONSENT FORM for PARTICIPANTS Version 01 – November 2017

NAME OF PARTICIPANT: «First_name» «Surname»

DATE OF BIRTH: «Date_of_birth»

Patient Identification Number for this trial: «Hospital_numbers»

Title of Project: Long term evaluation of patient satisfaction and clinical outcomes after multifocal intraocular lens implantation

Project investigators: Andreas Hartwig, Clare O'Donnell, Jay Dermott, Sundeep Vaswani and Irmina Gabryl

Please complete the boxes with your INITIALS:

1. I confirm that I have read and understood the information sheet Version 02 for this study and I have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that the researchers may need to review certain sections of my medical records and I therefore give my permission to do so. ☐
4. I agree to take part in the above study. ☐

Name of **Patient**	Date	Signature

Name of **Person taking consent**	Date	Signature

12.8 Sample of the Ocular Surface Disease Index and Dry Eye 5-items questionnaires.

Subject n°:

QUESTIONNAIRES

Instructions: Circle the number in the box that best represents each answer.

Have you experienced any of the following *during the last week*:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	
1. Eyes that are sensitive to light?	4	3	2	1	0	N/A
2. Eye 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

Have problems with your eyes limited you in performing any of the following *during the last week*:

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 a bank machine (ATM)	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A

Have your eyes felt uncomfortable in any of the following situations *during the last week*:

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

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 (0) — Not at All Intense (1) — 2 — 3 — 4 — Very Intense (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 discomfort, **how intense was this feeling of dryness** at the end of the day, within two hours of going to bed

Never have it (0) — Not at All Intense (1) — 2 — 3 — 4 — Very Intense (5)

3 Questions about WATERY EYES:

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

0 Never **1** Rarely **2** Sometimes **3** Frequently **4** Constantly

4 Questions about IRRITATED EYES:

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

0 Never **1** Rarely **2** Sometimes **3** Frequently **4** Constantly

Have you had a previous clinical diagnosis of dry eye? Yes ☐ No ☐

12.9 Supporting publications

12.9.1 Chapter 1

Recchioni, A., Ipek, T., Hartwig, A., O'Donnell, C. (2017). Dry eye, cataract and refractive surgery. *Optician* (C55675): 18-26.

12.9.2 Chapter 7

Recchioni, A., Hartwig, A., Dermott, J., Vaswani, S., Bhatt, J., Morris, R., O'Donnell, C. (2017). Early clinical outcomes after small incision lenticule extraction surgery (SMILE). *Contact Lens Anterior Eye* 41(1): 132-135.