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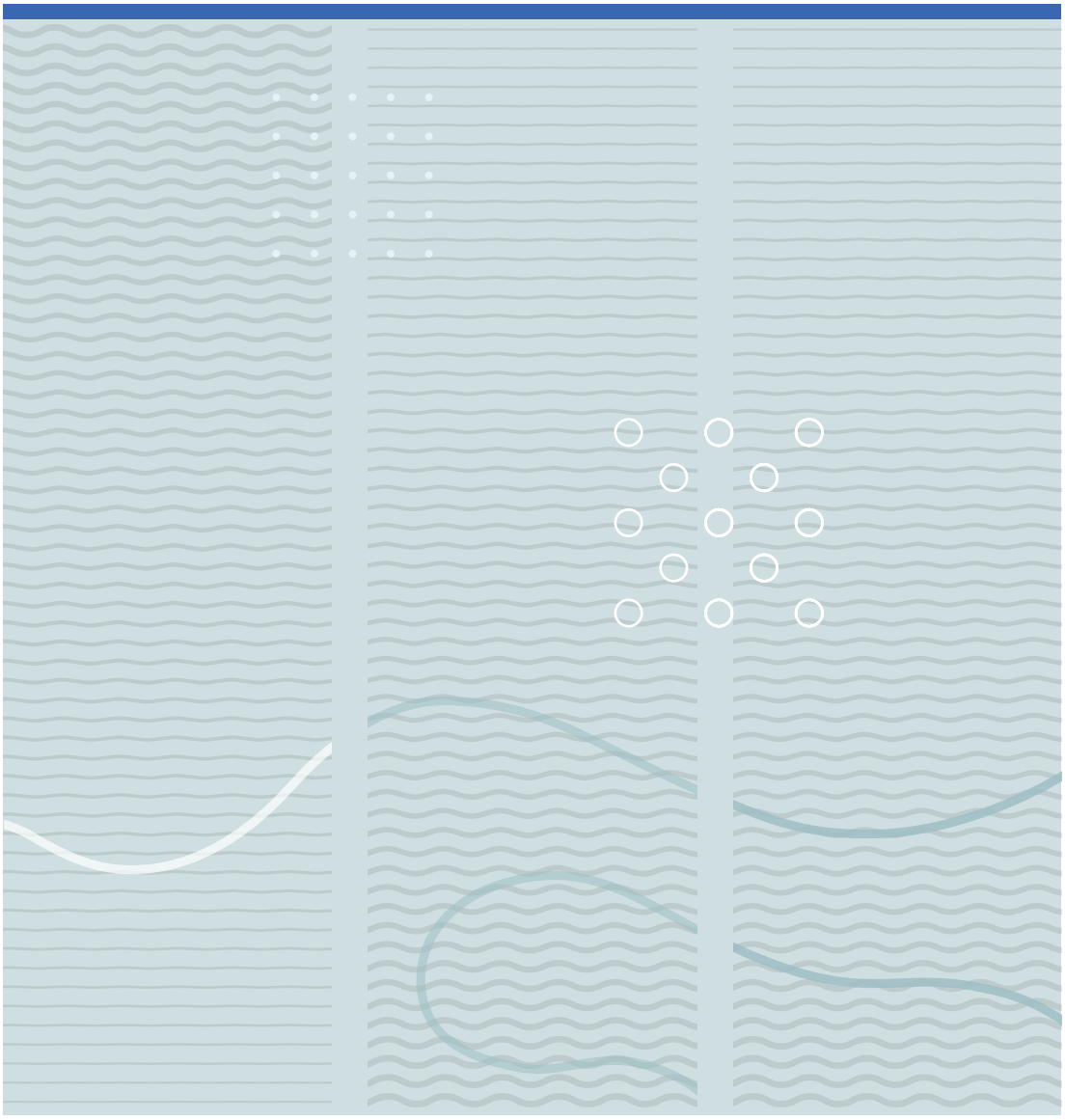
Bjørn Gjerdrum

Improvement in refractive precision for intraocular lens power calculations in patients with a history of laser vision correction for myopia



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List of papers

Published:

Paper 1: Brenner LF, Gjerdrum B, Aakre BM, Lundmark PO, Nistad K. **Presbyopic refractive lens exchange with trifocal intraocular lens implantation after corneal laser vision correction**: Refractive results and biometry analysis. *J Cataract Refract Surg.* 2019;45(10):1404-1415.

Paper 2: Gjerdrum B, Gundersen KG, Lundmark PO, Potvin R, Aakre BM. **Prevalence of Signs and Symptoms of Dry Eye Disease 5 to 15 Years After Refractive Surgery**. *Clin Ophthalmol.* 2020;14:269-279.

Paper 3:

Gjerdrum B, Gundersen KG, Lundmark PO, Aakre BM. **Repeatability of OCT-based versus Scheimpflug- and reflection-based keratometry in patients with hyperosmolar and normal tear film.** *Clin Ophthalmol.* 2020;14:3991-4003

Paper 4

Gjerdrum B, Gundersen KG, Lundmark PO, Aakre BM. **Refractive Precision of Ray Tracing IOL Calculations Based on OCT Data versus Traditional IOL Calculation Formulas Based on Reflectometry in Patients with a History of Laser Vision Correction for Myopia.** *Clin. Ophthalmology.* 2021;Volume 15:845-857.

Research presentations

Some results presented in this thesis has been presented at international conferences:

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Gjerdrum B, Gundersen K G, Aakre B (2019) Comparing the prevalence of ocular surface disorder in patients who underwent refractive surgery (laser vision correction or implantable collamer lens) 5–15 years ago to a similar population with no history of surgery. Free paper presentation 37tht Congress of the ESCRS Paris France

Abstract

In Cataract surgery and refractive lens exchange (RLE) planning, calculations of intraocular lens (IOL) power depend on, at a minimum, the measurement of corneal curvature and the axial length of the eye. In patients without prior refractive surgery, the accuracy of the procedure is high. However, for patients who have previously undergone laser vision correction (LVC) the precision is much lower because calculations based on empiric formulas does not account for the individual altered shape in these patients' corneas. Erroneous keratometric measurement due to unstable tear film may be an additional confounding factor. The aim of this thesis was to improve refractive precision for cataract or RLE in patients with previous LVC for myopia by applying exact calculations based true individual measurements of the patient's eyes, and thus reduce the risk of ecological fallacy.

A retrospective analysis of postoperative refractive results and recalculated IOL power with optimized lens constants and target nomograms was conducted to assess possible improvement in traditional formula-based calculations. Thereafter, a cross-sectional case-control study was performed comparing signs and symptoms of dry eye disease in patients with a history of LVC to a control group. In the next study, repeatability of different keratometers was compared in patients with hyperosmolar and normal tears. Finally, a prospective interventional single-arm study was conducted to compare traditional IOL calculations with individual ray tracing calculations in cataract and RLE patients who had previously undergone myopic LVC.

Results from the retrospective study indicated that a refined protocol could improve traditional formula based IOL calculations in patients with previous myopic LVC. However, using ray-tracing calculation based on OCT measurements of the anterior segment of the eye could yield similar or even better results. Ray tracing methods does not require analysis of previous results, and thus, is more applicable in any clinic. Furthermore the method does not require knowledge of a patients previous LVC treatment and can yield accurate results also for patients without previous refractive surgery. In the prevalence study, osmolarity results indicated higher risk of DED in previous LVC patients compared to a control group. However, there was no evidence that repeatability of keratometry was influenced by osmolarity.

Keywords: Cataract, Refractive lens exchange, post LVC IOL-calculation, ray tracing IOL calculation, dry eye disease, reflectometry, Scheimpflug, OCT, repeatability, hyperosmolarity, person-centred eye-care

Abbreviations

ACD -Anterior Chamber depth
AI -Artificial intelligence
AL -Axial length
AP -Anterior /posterior (ratio of corneal curvature)
AQD -Aqueous depth
CCT -Central corneal thickness
CDVA -Corrected distance visual acuity
CR -Coefficient of repeatability
D -Diopters
DED -Dry eye disease
EDOF -Extended depth of focus
ELP -Effective lens position
IOL -Intraocular lens
K -Keratometry
LASIK -Laser in situ keratomileusis
LT -Lens thickness
LVC -Laser vision correction
MF -Multifocal
NIKBUT -Non-invasive keratograph break-up time
OCT - Optical coherence tomography
OLCR -Optical low coherence reflectometry
OQAS -Optical quality analysis system
OSDI -Ocular surface disease index
OSI -Ocular scatter index
OSI -Optical scatter index
PCI -Partial coherence interferometry
PCP -Posterior corneal power
pIOL -Phakic intraocular lens
PRK -Photorefractive keratectomy
Q-value -corneal asphericity
RLE -Refractive lens exchange
RPE -Refractive precision error
SD -Standard deviation
SimK -Simulated keratometry(topography equivalent to keratometry)
SS -Swept source
TBUT -Tear Break up time
TCP -Total corneal power
UDVA -Uncorrected distance visual acuity

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1 Introduction

1.1 Background

Cataract is clouding of the crystalline lens that leads to reduced vision and ultimately blindness if not treated. Cataract surgery is a commonly performed procedure with about 4,5 million surgeries conducted in the EU in 2016.[1] It is in general a safe and highly accurate procedure, in which a cloudy crystalline lens is replaced by a new artificial intraocular lens (IOL) which also allows for correcting almost any refractive error. Refractive lens exchange (RLE) is basically the same procedure, but the main target for surgery is reduced or eliminated dependency of spectacles or contact lenses even if the crystalline lens is clear. For patients who have previously undergone laser vision correction (LVC), the accuracy of the surgery is much lower due to several sources of error.[2] These errors result from the altered corneal shape produced by the LVC, which makes the corneal properties deviate from those of the untreated population.[3] Most IOL power calculation formulas are based on simplified theoretic eye models containing several assumed physical and optical properties or regression formulas derived from a study population. In addition, constants specific to each IOL are used to account for different IOL properties that influence the final IOL position in the eye; these can also be optimized to account for different surgical techniques and instrumentation.[4-6] Specific formulas for patients with previous LVC have also been developed mainly by further modification of existing formulas. Still, IOL calculations in post LVC patients are considered a challenge.[7-10]

Laser vision correction for refractive errors have been commercially available since the early 1990´s.[11] Laser in situ keratomileusis (LASIK) is the most common LVC procedure with more than 16 million procedures globally to 2015.[12,13] The volumes in the US and Europe have been about 1.5 million surgeries per year since 2010.[12,14] Assuming that most LVC patients were between 25 to 35 years of age at the time of surgery, it is likely that the number of patients with previous LVC needing cataract or seeking RLE will increase in the future. Furthermore, patients who have had previous LVC are likely to be more interested in cataract or RLE surgery because they have a demonstrated interest in low dependence on spectacles or contact lenses. These patients have high expectations, and often prefer multifocal IOLs, which are more sensitive to residual refractive errors.[10] This creates a challenge, as LVC is associated with more variability in refractive outcomes after cataract surgery. Previous LVC may even increase the risk and reduce the options and for a second

corneal refractive surgery ("touch-up") to correct residual error. These factors increase the chair time required for each patient, which has a cost for both the patient and clinic.

1.2 Vision and refractive errors

Vision is one of our most important senses and is important for placing ourselves and navigating in our physical surroundings, as well as helping us communicating with other people. A clear vision from infancy is important, as development of our visual system rely on a focused retinal image that is transferred to the visual cortex in the brain. A lack of a focused retinal image due to refractive errors or other reasons, during infancy and early childhood leads to amblyopia and possibly vision impairment.[15] This means that the vision later cannot be fully restored even if the refractive error is corrected. Impaired or uncorrected poor vision will create challenges through life, as it can affect learning, social development, and daily tasks.

1.2.1 Refractive errors

Emmetropia is the refractive state of the eye in which parallel light (from distant objects) is focused clearly on the retina. In contrast, ametropia refers a refractive state where the retinal image is blurred. In myopia, light from distance is refracted too much so that the focal point falls in front of the retina. Hyperopia is the opposite, where light rays from a distant object have a virtual focal point behind the retina. An unfocused retinal image creates a blur circle which increase in diameter with increasing refractive error. Astigmatism refers to the state where the eye demonstrates a difference in refractive state in two meridians, so that the retinal image may be more blurred in one meridian. In this case the retinal image will be a blurred ellipse. Astigmatism may appear in addition to myopia or hyperopia or alone as mixed astigmatism where one meridian is myopic and one is hyperopic. Higher order aberrations appear as a result of asymmetries or irregularities in the optical system, that cannot be defined as myopia, hyperopia or astigmatism.[16,17]

Presbyopia is the normal age-related condition where the crystalline lens lose its ability to change the focal distance to near objects. In principle, this will affect all humans after 40-50 yeas of age, but the presence of refractive errors may affect the actual effect of presbyopia so that it appears to be better or worse.[18]

1.2.2 Correction of refractive errors

The Romans were possibly the first to use glass spheres for magnifying to see small text, and the first wearable glasses with convex lenses dates back to the 13th century in Italy.[19] The first mention of concave lenses for myopia is from around 1450.[20]

The correction of refractive error with spectacles will in many cases be unproblematic. However, for some people eyeglasses might be challenging; they may restrain physical activities, cause discomfort due heavy weight or anatomical reasons, or they may in some cases affect social life. Presbyopia correction is more challenging than correcting just ametropia because the needed correction depends on the focal distance. This can be solved with multiple spectacles, or with multifocal spectacle lenses are designed to provide a smooth, seamless progression of power for good vision at all distances. Nevertheless, progressive lenses produce some side effects and users may experience moderate to severe visual symptoms such as blurred vision, headaches, perceived movement of the peripheral visual field, balance issues, and nausea.[21]

Contact lenses may offer an alternative to spectacles, and the high comfort of modern contact lenses makes it suitable for many people. However, contact lenses might not be suitable for all refractive errors; Contact lenses for high hyperopia or high astigmatism may be unstable on the cornea, as could be the case with very flat or steep corneas, or eyelid deformities. However, dry eyes are probably the most common problem in contact lens wear, and different studies have shown that contact lens wearers could have from 2 to 5 times higher risk of experiencing dry eyes symptoms compared to non-wearers.[22,23] Monovision is the term when one eye is corrected for distance and one for near to provide presbyopic correction. This solution can work out surprisingly well but reduces stereopsis and contrast sensitivity. Different designs of progressive or multifocal contact lenses exist, and may also be used in different combination, including modified monovision. However, research has shown a lack of predictability of preference for different designs.[21] This indicates that it may be challenging to find the best solution for a given patient. The main reasons for discontinuation of contact lenses in a presbyopic population is both discomfort and blurred vision.[24]

Refractive surgery is another solution that can help if the refractive error is stable. The reasons for selecting refractive surgery can be many; problems with spectacles or contacts, not wanting to wear eyeglasses for vanity reasons, or a personal preference of not

being dependent of vision aids. Some studies have shown an increase in quality of life after refractive surgery, although the effect may be transient.[25,26]

Presbyopia correction with refractive surgery is more challenging than ametropia due to side effects and limitations but may be outweighed by the benefits of being less dependent on spectacles or contact lenses (which have their own side effects and limitations) for many people. A common solution for presbyopic refractive surgery is refractive lens exchange. This is the same treatment as in cataract surgery, where a cloudy crystalline lens is replaced with an artificial intra ocular lens (IOL), but the main target is to reduce or eliminate spectacle dependence. Presbyopic RLE with multifocal or extended depth of focus (EDOF) IOLs is particularly dependent on an accurate refractive outcome, as even small residual refractive errors may reduce the effect of the treatment. In cataract surgery the main target is to treat cataract, but today, preexisting ametropia is often corrected as a routine, and patients may opt for correction of astigmatism or presbyopia as well, in which case the refractive precision is a significant factor.

1.3 The eye and ocular dimensions

The eye is the sensory organ that makes it possible for our brain to sense our surroundings by the means of light. Reflected light from our surroundings is refracted through the cornea, passes through the aqueous humour of the anterior chamber. The iris blocks the most peripheral rays, while the central and paracentral rays is refracted through the crystalline lens, passes through the vitreous humour and is focused on the retina to form an optical image of the surroundings. The retinal nerve fibers respond to stimulation from different wavelengths and intensity of the light and carries the signals to the visual cortex of the brain where it is perceived as a visual image. The human eye can vary significantly in size and refractive power. Sikorsky et al found the following mean and range of ocular dimensions in 167 healthy eyes: Central corneal thickness, 0.55 mm (0.48 - 0.68 mm); anterior chamber depth (ACD), 3.4 mm (1.6 – 4.3 mm), lens thickness (LT) 4.1 mm (3.3 -5.4 mm); axial length (AL), 23.6 mm (19.1- 34.5 mm).[27] The total refractive power is about 60 D, of which the corneal and lens contributes to approximately 2/3, and 1/3, respectively (Figure 1).[18],

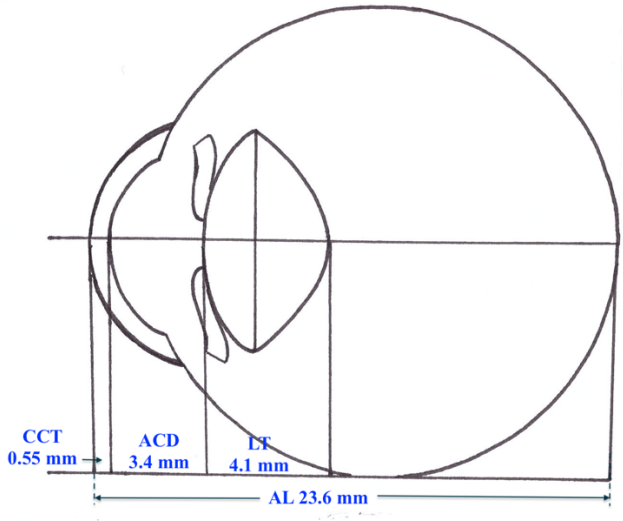

Figure 1: Dimensions of the Eye

CCT: Central corneal thickness; ACD: Anterior Chamber Depth; LT: Lens Thickness; AL: Axial Length. Values from Sikorski et al.[27] Figure adapted from Donaldson et al.[18]

1.4 The pre-ocular tear film

The tear film is overlaying the epithelium of the whole ocular surface. The tear film is the initial refracting surface for light entering the visual system and it protects and moisten the cornea and the conjunctiva. The tear film act as a single dynamic functional unit. It is extremely thin, 2-5µm, it follows the corneal and conjunctival contours, and is usually highly stable. For many decades, the tear film layer has been described as a three-layer model: a mucin layer covering the ocular surface and lowering the hydrophobicity; an aqueous layer to nurse the epithelium and a lipid layer to prevent evaporation. It is now commonly considered that the mucin and aqueous layers are a single layer of mucoaquesous gel, with a decreasing concentration of mucins outwards from the epithelium. The mucoaquesous layer provides lubrication and hydration, and nurse the epithelial cells with oxygen, metabolites and antimicrobial proteins. Mucins provide lubrication, barrier formation, hydration and increase the adhesion of water and facilitates the spreading of tears. Mucins may prevent debris and pathogens from binding to the ocular surface through entrapment in the mucus layer and blinking.

The bulk of the tear volume and flow is via secretion from the lacrimal gland, with a smaller portion from the conjunctiva. Afferent sensory nerves of the cornea and conjunctiva are activated by stimulation of the ocular surface. Efferent parasympathetic and sympathetic nerves stimulate the secretion from the lacrimal gland. Tears have been classified into four

types: Basal, reflex, emotional and closed eye. Basal, reflex and emotional tears are mainly produced from the lacrimal gland.

The lipid layer is derived from meibomian gland secretions and is about 40 nm thick although the thickness varies across the ocular surface. It appears to be continuous over the menisci and continues to move upwards over the ocular surface after blink. There is evidence that the lipid film spread over the mucoaqueous subphase prevents it from collapsing as it thins, but whether it suppress evaporation is poorly understood.

The distribution of tears happens through blinking, as the upper lid pulls a layer of tears over the cornea by capillary action, then the lipid layer drifts upwards, possibly dragging aqueous tears along with it. After the blink, tears redistribute and causes the precorneal tear film to separate from the tear menisci such that the diffusion between these compartments does not occur. The tear flows from the region of supply towards the puncta facilitating turnover and removal of tears. Between blinking, thinning of the tear film occurs, mainly due to evaporation rather than due to fluid flow. Possibly, the whole tear film structure with its key components and spreading contribute to increased evaporative resistance.

Tear film osmolarity has been described as a single measurement that gives insight into the balance between tear production, evaporation, drainage and absorption. The osmolarity of the normal tear film is mainly determined by the concentration of electrolytes. A hyperosmotic shift appears during the blink interval as the tear film thins due to evaporation. The level of hyperosmotic shift is driven by the thinning rate. With a low thinning rate the osmolarity increase from about 300 mOsm/L to about 330 mOsm/L in 25 seconds. In the case of a high thinning rate the osmolarity can reach up to 1900 mOsm/L. Those rates are significantly higher than rates found in the tear meniscus due to mixing of the fluid from the ocular surface and the secretion of new tears. However, the difference is predicted to be relatively small in none-dry eye but to increase with increased evaporation rate. Mean tear film osmolarity values of samples from the tear menisci range from 270 mOsm/L to 315 mOsm/L. An osmolarity 302.2 ± 8.3 mOsm/L and a variation between right and left eye of 6.9 ± 5.9 mOsm/L is classified as normal. There seems to be no statistical of clinically relevant effect of age or race, but the effect of sex on osmolarity is uncertain.

A stable precorneal tear film is viewed as a hallmark of ocular health because it is the primary refracting surface and it creates a protective and lubricated environment for the ocular and palpebral tissue. The human tear film will normally collapse or “break-up” in about 25 seconds without blinking. A much shorter break-up time is viewed as evidence of

tear film instability which is a sign if dry eyes. It has been shown an association between dry eye and compromised visual acuity. In dry eye subjects, delayed blinking give rise to higher order aberrations, and visual acuity measured after suspension of blinking have been shown to be worse than in normals. [28,29]

1.5 Optical properties of the cornea

The most important refractive part of the eye is the cornea (Figure 2). It is responsible for approximately 2/3 of the total refractive power of the eye.[18] The front surface of the cornea is the first and most powerful refractive surface, and its refracting power is depending on the radius of curvature and the change in refractive index between the air and the corneal surface.[30] The total refractive power of the cornea also depends on power of the posterior surface; its radius of curvature and the change in refractive index between the cornea and the aqueous humour. Traditionally, the power of the cornea has been estimated from measurement of anterior curvature (keratometry) at diameter of about 2,5 mm, taking the posterior surface into account by using an artificial refractive index (keratometric index) in a thin lens formula. This approach assumes that the central cornea is spherical, that paraxial optics apply and that the cornea has a fixed anterior to posterior curve ratio (AP ratio).[31,32]

Around 1850, Herman von Helmholtz developed the first keratometer that could accurately measure the corneal curvature, using two adjustable glass plates tilted in the opposite direction to create double image reflected on the cornea. By adjusting the displacement of the double image until the edges of the two images touched, the size of the image could be determined, and the corneal curvature could be calculated. He concluded that measurements of the posterior cornea were not reliable and used a keratometric index of 1.3365 to estimate the corneal power. Later Jawal and Schiøtz used the value of 1.3375, partly because it gave an easy conversion of 7.5mm to 45 D. Different keratometric indicis have later been used by different keratometer manufacturers, for instance 1.336 and 1.332.[33] In 1986 Olsen proposed a keratometric index of 1.315 based on calculations using Gullstrand´s eye model (where the anterior and posterior corneal radius is 7.7 and 6.8 mm respectively giving an AP ratio of 1.13).[32] Later studies using instruments that measures the posterior curvature has later shown mean keratometric indices of 1.327 to 1.330.[34] It has also been shown that the AP ratio is not constant: Fam et al examined almost 2500 eyes and found a mean AP ratio of 1.22 , ranging from 1.1 to 1.35.[35]

The true refractive index of the cornea is often quoted as 1.376.[31] However, studies have shown that the refractive index of the cornea is probably higher than previously envisioned, that it varies with the different structures in the eye and that significant inter-subject variations can occur.[30]

In a study from 2016 Næser et al used a Scheimpflug device, which also measures the posterior cornea, to calculate and compare various expressions for total corneal power. In a sample of 951 eyes, using a 3mm zone centered on the cornea apex, they found a mean anterior radius of curvature of 7.8 mm (ranging from 6.9 to 8.8 mm) and mean posterior radius of 6.4 mm (5.8 - 7.4 mm)(Figure 2: Radii and refractive indices of the anterior segment). They compared the corneal power derived in the 3mm zone with different calculation methods: a) simulated keratometry (SimK), which was calculated from the anterior radius and a keratometric index of 1.3375, b) the "equivalent power", calculated using thick lens formula with cornea refractive index of 1.376 and the refractive index of the aqueous humour of 1.336, and c) the "total cornea refractive power", using ray tracing with Snell´s law of refraction and thus taking spherical aberrations into account. The highest mean value was found with SimK (43.4 D), followed by the "total cornea refractive power" (42.8 D), and the lowest mean value was found with the "equivalent power"(42.3 D). They also compared the total cornea refractive power in different zone diameters and found significantly increasing values with increasing diameters above 2mm; for the 8 mm zone the mean refractive power was about 1 D higher compared to the 2mm zone.[34]

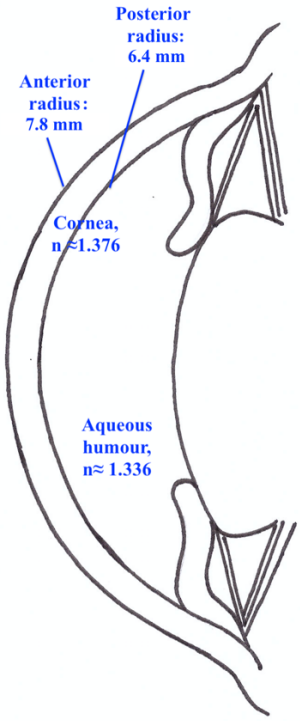

Figure 2: Radii and refractive indices of the anterior segment

Values from Næser et al.[34]

1.5.1 Corneal asphericity

Traditional calculations of refractive power of the cornea often based on the assumption that the cornea is spherical, although this is not the case. The normal corneal is prolate, i.e. flattening from the apex toward the periphery.[36] The contour of the cornea is commonly represented as a conic section described by the apical radius of curvature and the corneal asphericity. The corneal asphericity (Q) describes the rate of curvature change from the apex to the periphery and different Q values represents different conic sections: Q >0 describes an oblate ellipse, Q = 0 a sphere, Q between 0 and -1 a prolate ellipse, Q = -1 a parabola and Q < -1 describes a hyperbola. Although most human corneas have prolate shape, a small percentage of normal adults are oblate, steepening from the corneal apex toward the periphery.[37] A mean Q value of -0.24 ± 0.12 in a 7mm zone was found in a study of 1484 eyes.[38] It has also been shown that the Q value varies with the diameter it is measured and the degree of astigmatism, but also with the meridional regions.[36,39] A Q value of -0.53 eliminates spherical aberrations so that the corneal refractive power is constant in the entire optical zone. An average cornea with a apical radius of 7.7 and a Q value of -0.26 will have around +1 D of spherical aberration for a 6 mm zone.[40] This means that for the average cornea, the refractive

power increase with increasing pupil diameter, which gives a relative myopia low in low light conditions.

1.6 The crystalline lens

Together with the cornea, the crystalline lens helps to refract the light to focus on the retina, and by changing the shape (accommodation) it adjusts the focal distance. It is located behind the iris and attached by a ring of fibrous tissue (zonules) at the equator and connected to the ciliary body. About 90% of the dry weigh of the lens consist of structural proteins in addition to, sugar, lipids, water and antioxidants.[41] In addition to focusing light, the crystalline lens also helps protect the visual system from damage from UV rays. While wavelengths below 295 nm is absorbed by the cornea, the lens absorbs wavelengths between 295 and 400 mm.[41] An important function of the lens is the accommodation. When the ciliary body is relaxed it creates a tension on the zonules, which stretches the lens in the equatorial direction and induces a flattening of the curvature of the lens. In this state, light from far distance is focused on the retina. When the ciliary body contracts, the tension on the lens is loosened and it will take on a more curved shape, which leads to the focusing of light from near objects on the retina.

1.6.1 Ageing and presbyopia

Presbyopia is the gradual loss of the crystalline lens' ability to focus on nearby objects as the result of a physiologic degenerative process.[42] Age dependent changes in the lens gradually occurs over several decades but will often not manifest itself until after the age of 40 years. The lens continues to grow through life as new fiber cells are produced while old cells are deposited on preexisting layers. The increased lens size is associated with changes in the optical power, the ability to accommodate, and ultimately the transparency.[18] In addition, reduction in water transportation leads to change in nutrients, metabolic substances and antioxidants which possibly damage lenticular proteins, increase nucleus water content, and thereby reduce the refractive index.[18,41] The exact cause of presbyopia is still unknown, but a gradual increase in hydrostatic pressure and water content may explain increased stiffness. Furthermore, decreased elasticity of the capsule may fail to reshape the stiffened lens.[18]

The loss of accommodation is usually the first perceived changes of the lens. For most people, an increasing awareness of difficulties with focusing at near, in particular in poor light condition, will start between the age of 40 to 45 years. Presbyopia affects all individuals at some point, and the global prevalence of presbyopia is predicted to increase to 1.8 billion by 2050.[43] By the age of 50, most people will be dependent reading glasses to read small print. Exceptions may be patients with a moderate myopia, who may demonstrate good reading vision when removing their distance correction, or persons who are myopic in one eye. High astigmatism and irregular cornea may also in some cases lead to an increased depth focus and reduce the need for reading aids.

There is a range of different definitions for presbyopia, but Wolffsohn and Davies proposed a new definition: “Presbyopia occurs when the physiologically normal age-related reduction in the eyes 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”.[21]

1.6.2 Cataract

Cataract is a partial or total opacification of the crystalline lens. The most common type of cataract is age related, but it may be iatrogenic, associated with other ocular or systemic disease, or induced by ocular trauma. Common symptoms are loss of visual acuity and contrast sensitivity, but may also include photophobia, monocular diplopia, refractive change and change in color vision.[44] Several of the same mechanisms that leads to presbyopia also leads to a loss of transparency of the lens and ultimately cataract. It is thought that the failure of the lens microcirculation system to regulate cell volume in the lens cortex, or to deliver antioxidants to the lens nucleus, is a common underlying mechanism responsible for the light scattering in cataract.[18] Photooxidative stress induced by UV radiation is enhanced by increased levels of oxygen around the lens, possibly due to age related changes in the vitreous humour.[41] There are three main types of cataract, although the majority of cataracts are of mixed types (Figure 3).[45] Cortical and nuclear cataract is the two most common types of age related cataract, while posterior subcapsular cataract is most often associated with the use of systemic or topical steroids.[18,46]

Cortical cataract is prevalent in the elderly and in diabetes patients and is often seen clinically as wedge- or spoke-like opacities in the lens cortex. It can induce significant shift in astigmatism, due to asymmetric change in the refractive index caused by localized zones of

liquification. These liquified zones surrounded by cells with normal morphological structure causes the light scattering.

Age related nuclear cataract appear clinically as a browning of the lens nucleus. The morphology of the nucleus remains unchanged, but it is generally agreed that oxidative stress leads to formation of protein disulfides and other cross-linkages that again lead to protein aggregation and light scattering.[18] This will often lead to symmetrical increase in refractive index within the nucleus, causing spherical aberration and a myopic shift.[45,47]

The prevalence of cataract increases with age. The national eye institute in the U.S. have reported a prevalence in 2010 of about 9 % in the age group of 50-55 years, 36 % for 70-74 years, and 68% above the age above 80 years. The prevalence was sex dependent with 39% of cases being males and 61% females.[48] In a review by Hashemi et al they found the global age-standardized pooled prevalence estimate of 17% for any cataract, 8% both for cortical and nuclear cataract and 2% for posterior subcapsular cataract. However, the prevalence varied with region and age group.[49]

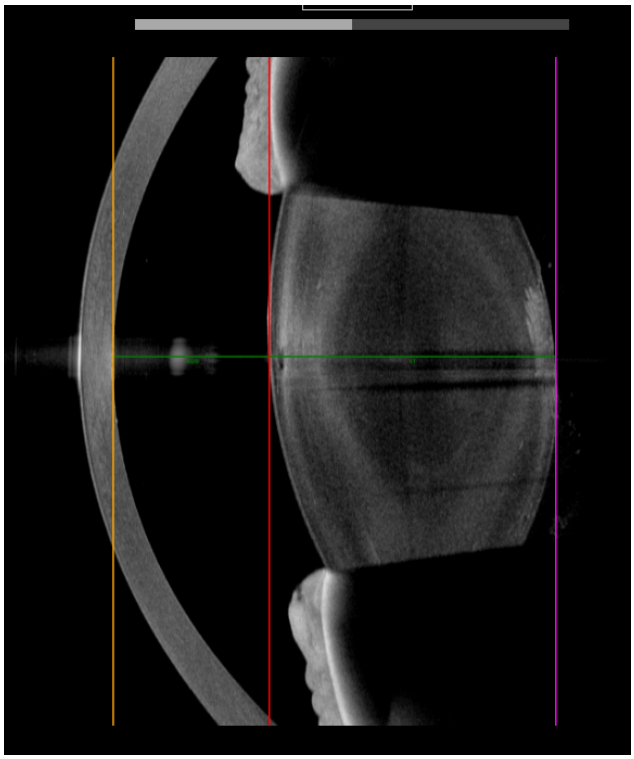

Figure 3: Anterior Segment OCT image of cortical and subcapsular cataract

1.7 Cataract and refractive surgery

1.7.1 Cataract surgery

Cataract surgery is a common surgical procedure, where a clouded crystalline lens is being replaced with an artificial intraocular lens (IOL). It is one of the most commonly performed surgeries today with more than 20 million procedures estimated annually.[50] In 2017 41 000 surgeries were performed in Norway.[51]

The history of cataract possibly dates back to the fifth century BCE. Both Indian and Egyptian origin of the couching procedure have been suggested, but similarities also suggest a previous common origin.[52] The couching procedure initially consisted of striking the eye with a blunt object, which forced the weekend zonules of a mature cataract to break, so that the lens dislocated into the vitreous cavity. Later, couching needles were inserted into the eye to break the zonules to cause the dislocation. The first report of cataract extraction occurred in Paris in 1748.[53] Topical cocaine anesthesia and surgical antisepsis was adopted around 1880. The early extraction techniques involved removing the entire lens in one piece using an incision that went halfway around the cornea. This limited the procedure to mature cataract so that the lens would not break and lens material fall into the vitreous cavity causing inflammation. A major advance was the introduction of the extracapsular technique where the intact lens capsule is left behind and act as a barrier to the vitreous cavity.[53] Phacoemulsification was introduced in 1967; ultrasonography is used to break the lens into small fragments which is aspirated. Development of combined ultrasonographic irrigation and aspiration handpieces have led to wounds as small as than 2 mm.

Originally, with the lens removed, patients would have to depend on high-power hyperopic lenses to restore vision.[53] The firs intraocular lens was implanted by Harold Ridley in 1949, but a widespread use of IOLs didn't occur until around 1980.[52] Development of IOL materials led to foldable lenses which today can be inserted in 2 mm incisions, minimizing wound healing and surgically induced astigmatism.[53]

1.7.2 Cataract surgery as a refractive procedure

The original IOL implanted by Ridley was designed based on curvatures of the crystalline lens described by Gullstrand. However, the high refractive index of the material was not accounted for, leading to a myopic result of -20D. The Russian ophthalmologist Svyatoslav Fyodorov described the first theoretical IOL calculation formula in 1967.[54]

Despite this, and despite that it was known that the biological lens power had a significant distribution, fixed IOL power (or sometimes adjusted for preoperative ametropia) was frequently used through the 1970s.[54,55] Later studies showed that fixed a fixed lens power would leave about 5% of the patients with a refractive power >5D, which could lead to significant aniseikonia an problems with binocular vision.[4] In 1983 Percival reported that choosing optical power (2 D step) based on "clinical judgement" yielded 77% of eyes with refraction between -1.75 D and +0.75 D, while the use of ultrasound a-scan biometry and IOL calculations yielded 90% within the same range.[56] In 1998, Drexler et al showed that with the use of an optical biometer (partial coherence interferometry - PCI) accuracy of IOL calculations could be expected to be within ±0.5 D in 60% and within ± 1 D in 85% of patients, with a range of ± 1.5 D.[57] A clinical applicable PCI biometry system became commercially available in 1999.[58] With the prospect of having a majority of patients with refractive result of less than 0.5 D, cataract surgery had also become a refractive procedure.

1.7.3 Refractive lens exchange

RLE is basically the same the procedure as for cataract surgery but the reason and the main target is to reduce or eliminate need for spectacles or contact lenses. As yet, there is no IOL that can fully mimic the accommodative function of the crystalline lens of a younger individual (below 40 years of age). Therefore, RLE is usually only performed after the onset of presbyopia, but may be considered earlier, for instance in cases with high ametropia (hyperopia). If standard monofocal IOLs is used, often the patients will be corrected for distance vision while dependent on reading glasses, although the opposite or monovision may be an option. However, many patients wish to correct both distance and reading vision (presbyopic RLE) by having a multifocal (MF) IOLs. Trifocal and extended depth of focus is the most common types of MF IOLs used today. RLE is the most common procedure correction of presbyopia, although LVC and ICL procedures are available. The reason for this is that almost any refractive errors can be corrected, the result is likely to be stable and the procedure will prevent cataract later in life.[59]

MF can eliminate or reduce the need for reading glasses but are also known to produce side effects (loss of contrast, halo or glare, and limited range of focus). Due to neural adaption, the perceived side effects usually decrease over time to an acceptable level where the benefits of reduced spectacle dependency are greater than the costs of visual side effects.

[60]MF IOLs are reliant on a minimal residual refractive error, preferably within ± 0.25 D, although some patients may tolerate a refractive error of ±0.5 D. Higher residual errors will in most cases require a second surgery to achieve the intended visual outcome.

1.7.4 Corneal refractive surgery

The ideas of correcting refractive errors with surgery at least dates back to the late 18th century when both the Dutch ophthalmologist, Lans and the American ophthalmologist Bates described corrections for corneal astigmatism with non-penetrating corneal incisions. A method for correcting myopia with radial incisions was described in 1953 by the Japanese ophthalmologist Sato, and later refined by Fyodorov in 1972 to become a popular technique up till around 1985. Other early techniques include; resecting of a corneal disk which was frozen, placed in a lathe, milled to change the corneal curvature and sutured back in place (keratomileusis), in epikeratoplasty a lenticule cut from a donor cornea is placed on the de-epithelialized cornea of the recipient, intra corneal lenses and intra corneal rings.[61]
Except for intracorneal rings, these methods were gradually replaced after the introduction of excimer laser.
The most common refractive surgery procedure for patients under the age of 40-45 is LVC. Photorefractive keratectomy (PRK) was the earlies technique for LVC, first performed in 1985. In this technique the corneal epithelium is mechanically removed, and the corneal surface is reshaped with an excimer laser. This approach is associated with significant postoperative pain and slow vision recovery.[62] Laser situ keratomileusis (LASIK) was introduced around 1990, with the major advantages of less pain, rapid vision recovery and low risk of scarring or haze.[11,62] LASIK is a two-step procedure, where first a hinged flap is created with a microkeratome or a femtosecond laser, and then the stromal bed is reshaped with an excimer laser before the flap is repositioned. It has become the most common LVC procedures with more than 16 million procedures globally to 2015 and more than three million procedures is estimated in Europe since 2016.[12,13] LVC procedures is mostly performed to correct myopia, astigmatism, and to some extent hyperopia[63]. An excimer laser is used to alter the corneal curve and hence the refractive state of the eye by removing stromal tissue from the cornea through a process known as photoablative decomposition (often termed photoablation or just ablation).[64] In myopic treatment, central tissue is removed to flatten the central corneal curve (Figure 4), and in hyperopic treatment peripheral tissue is removed to steepen the corneal curve.

Another technique, small incision lenticular extraction (SMILE) became available in 2011. In this technique, a femtosecond laser is used to dissect an intrastromal lenticule, which is extracted through a small pocket. This can alter the cornea to correct myopia or astigmatism. SMILE is considered to offer greater biomechanical stability, without the risks associated with flap creation.[62]

Laser treatments can also be used for treating presbyopia, either with one eye corrected for distance and the other for near (monovision), or by modifying the asphericity (Q-value) to create an extended depth of focus.[21] However, presbyopic laser may not be a permanent solution because of continued age-related change in the crystalline lens.

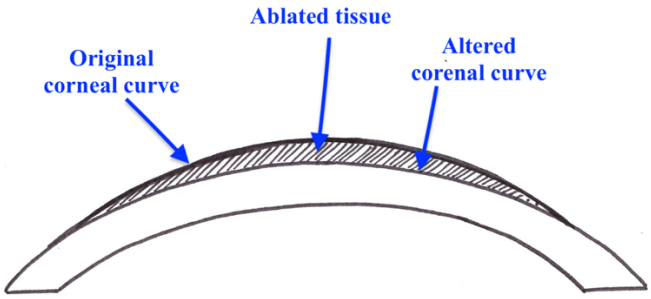

Figure 4 Illustration of altered corneal curve in myopic LCV treatment (exaggerated dimensions)

1.7.5 Phakic intraocular lens

Phakic intraocular lens (pIOL) that can be used for correcting also larger refractive errors, both myopia and hyperopia. Some patients may be better candidates for pIOL implantation due to pupil size, dry eyes, inadequate tissue volume for LASIK, abnormal topographic shape or personal preferences for a reversible procedure.[65] pIOL is known to increase the risk for developing cataract and it has been suggested that a pIOL may influence the ACD and AL measurements used in IOL calculation. However, studies have shown equivocal effect of pIOL on AL measurements and IOL calculations.[66,67]

1.8 Dry Eye disease

Dry eye disease (DED) is a common disease which affects hundreds of millions of people, and clinical awareness has risen considerably around the world through the last decades.[68,69]

The TFOS DEWS II (Tear Film and Ocular Surface Society International Dry Eye Workshop II) report has defined dry eye as:

> "…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."

However, there remains a lack of standardized testing methods and criteria for categorizing dry eye; reported prevalence ranges from 5 to 50% when based on signs and symptoms, and up to 75% based on signs only.[70] Classification of dry eyes is usually based subjective symptoms combined with several diagnostic tests, like tear break-up time (TBUT), tear osmolarity, and ocular staining. Tear volume and lipid dynamics and meibomian gland dysfunction allow subclassification, which informs management of DED.

Tear osmolarity has been shown to be the best single metric both to diagnose and classify DED and evidence indicates that tear hyperosmolarity contributes to, and is representative of, the mechanisms involved in the development and progression of DED.[71,72] In a review report by Potvin et al. they found that a majority of the studies reviewed supported the use of tear osmolarity as a tool for diagnosis and severity grading.[73] Sullivan et al found tear film osmolarity to be the single best marker of disease severity across normal, mild/moderate, and severe DED categories.[74] A cut-off of 316 mOsm/L is considered best for diagnosing moderate to severe DED diagnosis, while a cut-off of 308 mOsm/L is a sensitive threshold for diagnosing mild to moderate DED[29,75].

1.8.1 Dry eye after laser in situ keratomileusis

Dry eye is the most commonly reported problem following laser in situ keratomileusis. (LASIK) surgery.[76,77] Corneal afferent nerve fibers are cut during flap creation and stromal ablation. The nerve damage interrupts the cornea to lacrimal gland reflex arc, which in turn impairs tear secretion and reduces blink rate.[78] Tear osmolarity may increase as a result of decreased secretion of lacrimal gland protein and water, or as a result of a reduced blink rate, with a corresponding increase in the evaporation of the tears.[79] LASIK induced dry eye is believed to resolve in most cases within the first postoperative year, but studies have shown reduced corneal nerve density two years after surgery, and altered nerve morphology as long as 15 years after surgery.[77,79-84]

1.9 Ocular Biometry

Ocular biometry is the measurements of the various dimensions of the eye, in particular measurements needed for calculating the IOL power used in cataract or RLE surgery. Ocular biometry usually includes keratometry, AL, ACD and often LT and central corneal thickness (CCT). For many years, ultrasound biometry was the only way to measure the AL. This was measured as the distance from the surface of the cornea to the inner limiting membrane. The greatest limitation was the dependency on good patient cooperation and examiner technique for proper alignment and to avoid indentation of the cornea. Immersion ultrasound later improved accuracy by using a saline filled shell between the probe and the eye.[85]

Optical biometry was introduced in 1999 and has since replaced ultrasound biometry. In addition to increase accuracy, it is faster, non-invasive and nearly user independent. Biometry for IOL calculation is often performed with a optical low coherence reflectometry (OLCR) device or a partial coherence interferometry (PCI) device, both of which use reflections from the corneal surface to calculate the corneal power and laser interferometry for AL measurements. The PCI device uses slit illumination to assess the ACD as the distance between the anterior corneal apex and the anterior surface of the crystalline lens. One advantage with the OLCR device is that it can also detect the signal maxima from both surfaces of the cornea and the crystalline lens to produce an a-scan of both cornea thickness, ACD, LT and AL, and also measures the corneal diameter.[86] Anatomically, the ACD is the distance from the posterior cornea to the anterior surface of the crystalline lens, but as often measured from the anterior surface of the cornea which is the value that is used in IOL calculation formulas.

PCI and OLCR biometers rely on good reflections of mires from the pre-corneal tear film to measure corneal curvature (Figure 5). Studies have shown that an uneven or unstable tear film produces optical aberrations and may directly reduce the accuracy and repeatability of these measurements(Figure 6Figure 5).[87,88] Thus erroneous keratometric measurement due to unstable tear film may be an additional confounding factor in post-LVC IOL power calculations. In the following, the term “reflectometry” and “reflection based keratometry” will be used interchangeably to refer to keratometry obtained by reflections from the pre corneal tear film.

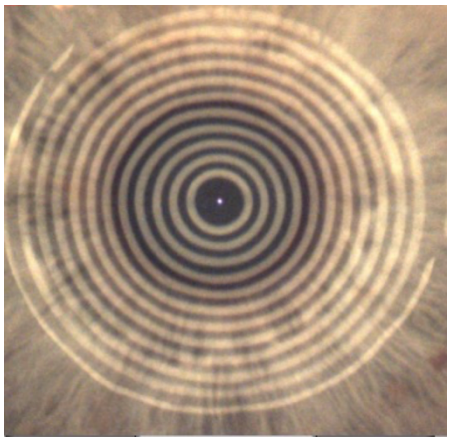

Figure 5 Regular mires from stable tear film

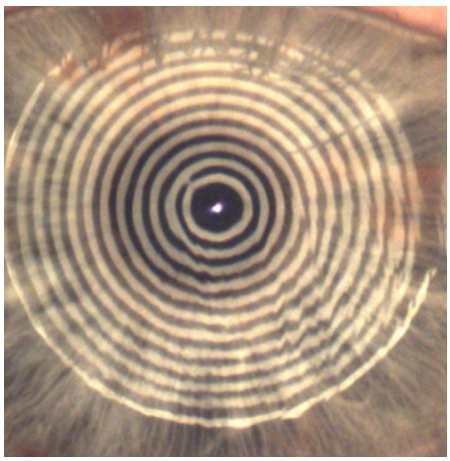

Figure 6 Irregular mires from unstable tear film

Other devices, like those based on Scheimpflug imaging or Optical Coherence Tomography (OCT) do not use reflections, but tomographic images, and may be less dependent on tear film quality (Figure 7). A Scheimpflug device can provide a tomographic image of the anterior and the posterior corneal surfaces, as well as the anterior chamber and lens.[89] One limitation of Scheimpflug imaging is the low resolution and poor quality of the anterior segment scans.[90] OCT is a high speed, high resolution, noncontact optical imaging technique for noninvasive cross-sectional imaging of biologic systems.[91] Swept-source (SS) OCT has several advantages over other technologies used in ocular biometry, such as deeper light penetration or long-range OCT imaging of posterior segment structure.[92] Backscatter from the SS laser beam creates multiple intensity-based cross-sectional images which are used to create three-dimensional surfaces from which parameters can be derived (Figure 8).[93] One advantage with the OCT-based biometers is that all measurements are based on infrared light, not visible to the patient´s eye, making the measurement more comfortable and facilitating target

fixation. The long wavelength also improves penetration of cataract for devices that measure the AL.

An instrument that does not rely on individual tear film quality may be a better choice for IOL calculations, particularly in post-LVC patients where erroneous keratometry will come in addition to other known sources of error.

Figure 7 OCT image of the anterior segment

1.9.1 Anterior, posterior and total keratometry

Conventional reflection-based keratometry measures only the front surface of the cornea. The corneal power is then calculated using an assumed keratometric index to include the contribution of the back surface and yield total corneal refractive power.[32] Scheimpflug and OCT devices can measure both corneal surface, cornel thickness and also provide total corneal power based on true measurements. Measurements of the posterior cornea a useful tool for detection and follow-up of cornea ectasia. It has been widely used in evaluating safety of LVC. The true corneal power may not differ significantly from keratometric power in normal, or “average” eyes (depending on which keratometric index is used). Yet, for irregular corneas or after LVC, true corneal power can be useful, for instance in IOL calculations. Even though posterior corneal measurements have been available for some years, it has not been widely used in IOL calculation , mainly because most formulas have been developed for anterior keratometry.

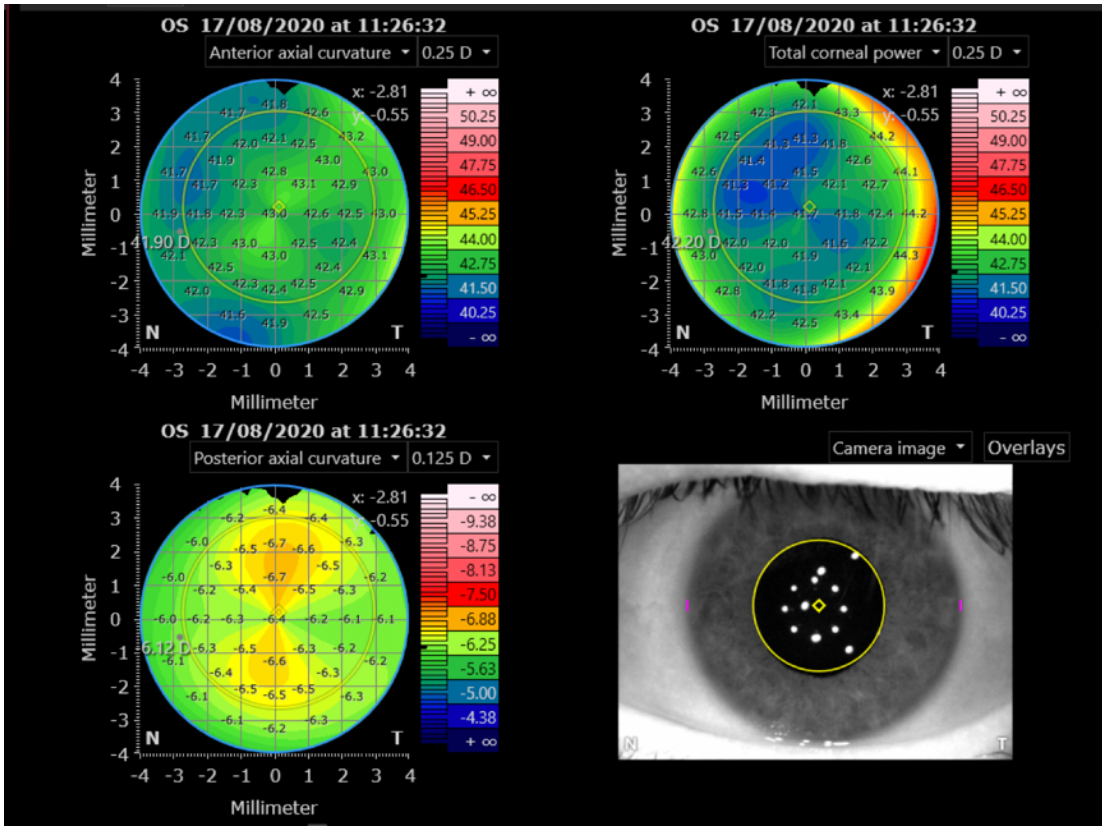

Figure 8 Anterior, posterior and total corneal power

Different values for corneal power values for anterior axial curvature (upper left) and total corneal power (upper right). Notably is the difference in astigmatism due to the contribution of the posterior astigmatism (lower left.

1.10 IOL calculations

> "The very best intraocular lens power selection methods, however, still depend on the very best preoperative measurements, which are unique and individual to each patient."
> -Warren Hill et al, 2017.[94]

In cataract or RLE surgery planning, calculations of IOL power depend on biometry: the measurement of the corneal curvature, the axial length of the eye, and often the anterior chamber depth and lens thickness. Traditionally only the anterior surface of the cornea is measured, and a total corneal refractive power is calculated based on an assumed ratio of the front and back surface. This value can be used in various IOL-power formulas which contains some element of empirical adjustments to achieve the best results on an average

population. Methods of IOL calculation have been proposed. Koch et al have proposed to classify different IOL calculation methods in the following way:[54]

1) Historic refraction based (obsolete): Average or fixed IOL power adjusted for refractive error
2) Regression: Derived from analysis of previous data, without the use of theoretical optics
3) Vergence: Based on Gaussian (paraxial) optics and Fyodorov´s original paper describing the first theoretical IOL calculation formula. Most formulas are based on this method. The primary concern with these formulas is the estimation of the effective lens position (ELP). The earlier formulas used two variables (corneal power and axial length) to estimate IOL power and ELP. Three-variable formulas include also anterior chamber depth, while five-variable formulas also include lens thickness and corneal diameter. One formula also includes age and pre-cataract refraction, in total 7 variables.
4) Artificial intelligence (AI): This is a form of regression but uses huge databases and neural network or pattern recognition with sophisticated data interpolation.[95,96] They allow predictions based on clinical data to find relationships not otherwise evident in theoretical approaches.
5) Ray tracing: Based on exact calculation of single rays using Snell´s law of refraction. (see next section)

Method 2, 3 and 4 rely on constants that are specific for each type of IOL and are meant to compensate for each lens´ intraocular performance, for instance, post-operative lens position, lens material or method for biometric measurements. Further constant optimization can be performed to refine the refractive results for a variety of practice-specific variables, such as keratometers, biometers, and surgical technique.[5,54]

In patients with “normal” corneas without prior refractive surgery, the accuracy of the cataract or RLE procedure is high with refractive prediction within ±0.50 for 75% to 84% and within ±1.0 for 97% to 99% (Figure 9).[97]

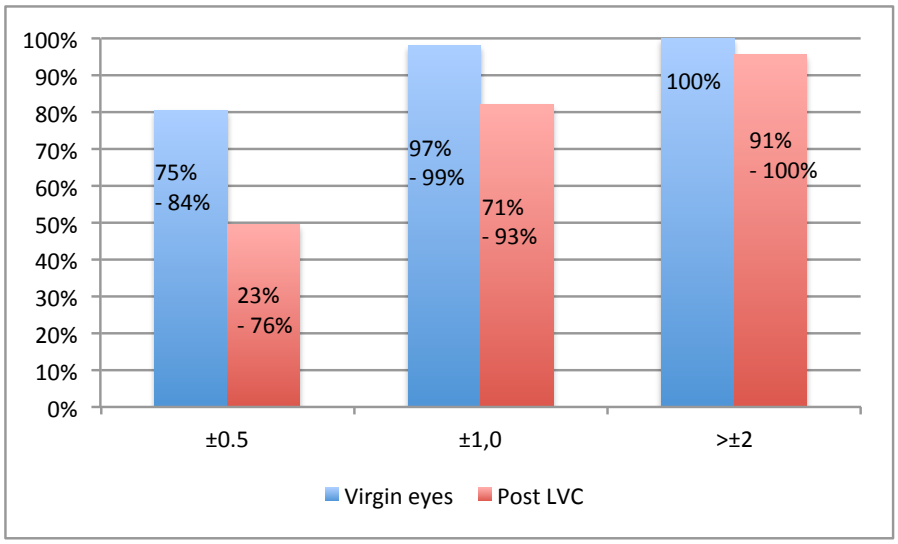

Figure 9: Refractive prediction of IOL calculations in patients without previously untreated eyes(virgin eyes) and with previous myopic LCV.[10,96,97]

1.10.1 Ray tracing IOL calculations

Arguably, if one could measure all optical properties of the eye accurately, any calculations should be equally accurate, regardless of previous refractive surgery or not. Ray tracing IOL calculations do not use approximations but are exact calculations of refraction based on Snell´s Law. Available data is used to calculate the best focus for single rays at varying radial distances from the optical axis through all surfaces of the cornea and the IOL.[98] Such software was described as early as 2002 by Preußner et al but the utility has been limited by the amount of and the accuracy of the input data. Recent development in technology have improved the possibility to measure the physical and optical properties of the human eyes. Several types of instruments using different technologies are available, and OCT based technology being one of the most promising, due to the high resolution, high speed, and the capability to measure structures deeper in the eye. Thus, the potential of ray-tracing calculations has increased significantly. There is however a limitation in predicting effective postoperative refractive results, namely the individual postoperative shrinkage of the capsular bag. This shrinkage is natural and inevitable and has the potential to displace the implanted IOL and influence the effective power of the lens. This is found to be the largest source of error in IOL-calculations for untreated, “normal” eyes.[99] The OKULIX ray tracing IOL calculation software do not use optimizable constants, but a predicted ACD, representing the geometric position of the IOL and defined as the distance from the posterior cornea to the anterior surface of the IOL.[100]

This distance is often termed aqueous depth (AQD), which we will use here to avoid confusion with the ACD measured from the anterior cornea in conventional biometry. Since IOL position depends on individual capsular bag shrinkage after surgery, it cannot be calculated exactly. Instead, a model calculation is used to predict the most probable IOL position based on AL, position and thickness of the crystalline lens (when measured). It is specific for each IOL type and have been adjusted to match the geometrically measured IOL positions during the software development.[101] Further adjustment by the user is not recommended since complication-free state-of-the-art cataract surgery should give no significant impact of the surgical procedure on RPE.(Paul Rolf Preußner, PhD, e-mail communication, January 2020).

1.10.2 IOL-calculations after refractive surgery

For patients who have previously had laser vision correction (LVC), the precision of IOL calculations remains a challenge due to several sources of error. The reason for this is that in LVC the front surface of the cornea is altered to change the corneal power, and thus, the patient's refraction. This results in inaccurate IOL calculations primarily due to 3 factors:

1) Inaccurate determination of the true total corneal refractive power: Corneal power is a critical variable for IOL power calculation. As previously discussed, the corneal power is traditionally determined by measuring the anterior surface by means of reflectometry and converting the curvature with the use of a fictitious keratometric index to account for the contribution of posterior cornea.[102] While this approximation may be sufficiently accurate for the average population it does not hold true for patients with previous LVC because only the anterior corneal surface is altered. This is known as the keratometric index error.[103] In myopic LVC the anterior corneal surface is flattened, but the posterior curve remains relatively unchanged. Corneal refractive power based on anterior curvature will be overestimated (Figure 10) due to the reduced posterior to anterior surface ratio and IOL power will underestimated (Figure 11).[102,104]

2) Estimation of the post-operative ELP is important in the IOL power calculation in general. The ELP is a virtual variable, often the lens plane of a thin lens, that does not necessary reflect the anatomical IOL position after surgery.[4] Nevertheless, it is a considerable source of error if it incorrectly estimated. Some formulas rely on corneal power to estimate the ELP, resulting in an underestimation after myopic LVC and overestimation after hyperopic LVC.[105] Other formulas uses the ACD or AL to predict the ELP.

3) The radius error, or instrument error, occurs because the central corneal curvature is extrapolated from paracentral measurements with most biometers. After myopic LVC the central cornea may be flatter than suggested by this extrapolated value.[2,102]
Other factors such as reduced corneal thickness and altered corneal asphericity or higher order aberrations may also contribute.[103,106] In addition, tear film instability may influence the keratometry measurement and individual shrinkage of the postoperative capsular bag may influence the actual postoperative IOL position and hence the refraction.

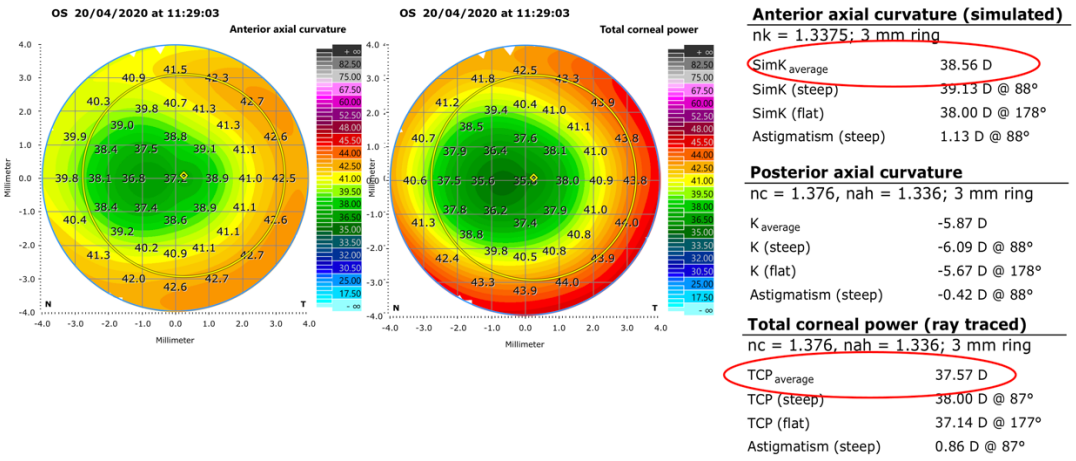

Figure 10 Keratometric power (anterior axial curvature) and total corneal power.
Example of corneal power over-estimated from anterior surface only (anterior axial curvature) and total corneal power calculated from of anterior and posterior surface of a cornea with previous -6 D of LVC treatment. Total corneal power is about 1 D lower than estimated from anterior curve. Total corneal astigmatism is 0.4D lower.

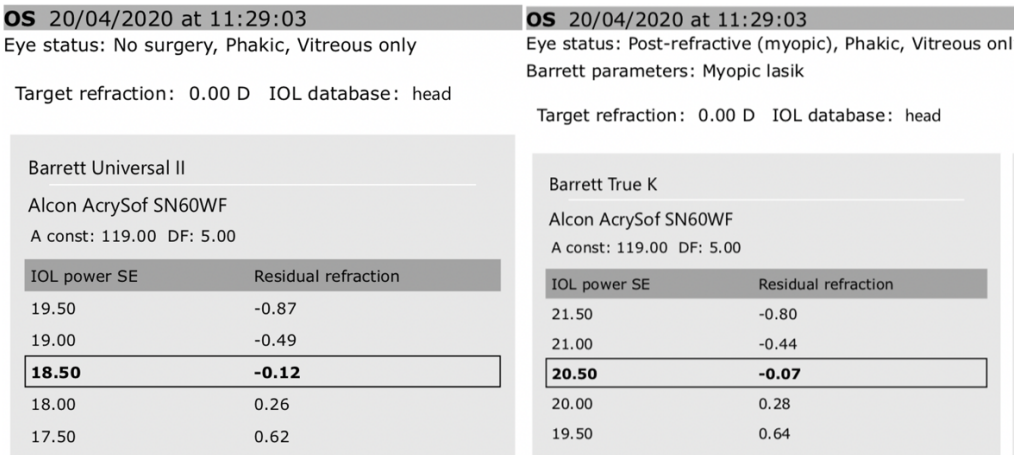

Figure 11 Normal eye IOL formula (left) and Post LVC IOL formula (right)

IOL power calculated with a formula for normal eyes (left) and a post LVC formula (right) for the same post-LVC eye as in figure 10. Predicted IOL power is underestimated with about 2 D, equivalent to about 1.5 D of refractive difference.

More than 30 post LVC IOL calculation formulas or methods have been proposed to compensate for these known sources of error. Several formulas depend on historic data, i.e. historic refraction and/or historic keratometry to calculate the true corneal power or to use separate historic keratometry for determination of ELP.[96] The corneal bypass method uses the preoperative corneal curvature together with a target refraction set for the preoperative refraction to avoid the keratometric index error and the radius error.[7] The contact lens over refraction method was developed to avoid the use of historic data altogether. In this method the patient was fitted with a rigid contact lens and the corneal power is calculated as the sum of the contact lens base curve, power, and over-refraction minus the manifest refraction. However, this method has later proven unreliable.[3,107] Other no-history methods do not rely on exact preoperative data but need only to know if the treatment was myopic or hyperopic. For instance, the Haigis-L formula is an adaption of the Haigis formula (which uses ACD to predict ELP). Here the effective corneal power is estimated from the measured anterior corneal curvature in combination with a linear regression derived from a study population and a fixed correction for the underestimated ACD due to the laser ablation.[58,103] The Shammas no-history method uses a similar approach, with a regression equation to correct the postoperative measured k-value to be used in a previously described formula, where AL is used for ELP prediction.[108,109] Another no-history formula is Barret True K No History. The details of this formula are not published, but it uses an internal regression formula to calculate an estimated change in manifest refraction.[110] The Wang-Koch-Maloney formula for myopic LVC uses keratometry obtained from topography converted with a different keratometric index, and subtracts an assumed posterior corneal power.[3,95] Other formulas, like the Potvin-Shammas-Hill formula, the Galilei-formula and the OCT-formula are based on theoretical formulas, but instead of keratometry, uses total corneal power from instruments that provide actual measurements of the posterior cornea.[95,111,112]

The most commonly used post LVC formulas are available with an on-line calculator from the ASCRS website.[95] Depending on the amount of available data, predicted IOL power is presented for different formulas, including the maximum, minimum and average of the different formulas. It has been proposed to look at several formulas to assess the IOL power most likely to give the intended refractive result.[113] All these formulas are modifications of either a) theoretic IOL formulas based on a theoretical eye model which relies on Gaussian optics where light rays are assumed to refract as paraxial rays, or b) regression formulas based

on clinical studies. Despite advances in these methods, studies have shown that prediction errors are not as good as for IOL- calculations in untreated eyes (Figure 9).[10,96] Mean prediction errors have in some studies been close to the results for untreated eyes, but with a much wider range.[114]

LVC has been commercially available for about 30 years. Assuming that most of the patients were between 25 and 35 years at the time of treatment the number of patients presenting for cataract RLE surgery will likely increase in the future. For cataract and RLE patients who have had previous LVC, the predictability may improve if more and sufficiently accurate data can be retrieved to account for individual characteristics in each patient's eyes.

2 Motivation and aim of research

2.1 Motivation

Through the last decades the refractive results of cataract and RLE surgery have improved greatly, with most patients (about 80%) ending with a refractive error of less than 0.5 D (some studies have reported up to 91% within 0.5D), and only a few percent with more than 0.75 or 1 D. However, for patients with a history of LVC the accuracy of IOL calculations is much lower. Altered corneal curvature makes some of the assumptions used in IOL calculations for normal eyes (without previous LVC) erroneous. Accordingly, different formulas have been refined or developed to adjust for this, mostly by applying new assumptions or new regression equations to account for the laser treated cornea. Yet the variability is much higher compared to untreated patients. Tomographic instruments that can map the full cornea and the anterior segment have existed for a while but have not been widely used for IOL calculations, mainly because conventional formulas are developed for conventional biometry and besides, results from studies of such methods have failed to demonstrate improved results compared to other post-LVC formulas. Likewise, ray tracing calculation have also been used with different assumptions and thus, not shown significant improvement in accuracy.

For some patients, a residual refractive error may not be a problem: Some might gradually have become used to uncorrected refractive errors. Others are accustomed to wearing glasses, and do not expect or wish to be independent of them. However, patients who have a history of previous LVC have once made a choice for refractive surgery to be

independent from glasses or contact lenses. They usually have high expectations and often opt for toric and or multifocal IOLs. For these patients, a significant residual refractive error will often present a problem. The ideal situation is postoperative refraction within ±0.25 D, but often 0.5D and sometimes 0.75 is accepted with monofocal IOLs. Multifocal IOLs, however, are more sensitive to residual refractive errors, and with an error of 0.50 D they have lost a significant part of the intended effect, and a refractive error of 0.75 D or more will almost certainly create a need for additional surgery or dependency of glasses.

During more than 10 years doing pre-exams and follow up for refractive lens exchange, I have experienced that more accurate measurements, safer, less invasive and more predictable surgery together with technological progress in IOL technology have created possibilities for patient to opt for independence or reduced dependence of glasses or contact lenses. At the same time, I have also seen an increase in post-LVC patients needing cataract or wanting RLE surgery. These patients have already demonstrated a great interest in freedom form glasses or contact. In contrast, the probability of achieving this is much lower. This increases the risk for needing a second refractive surgery (touch-up) to correct residual. These factors increase the chair time required for each patient, which has a cost for both the patient ant the clinic.

My personal motivation for doing research in this field is due to a natural curiosity combined with a wish to offer equal possibilities for each single patient, also if the patient has previously had laser surgery. To be more specific, I have been curious about possibilities to take advantage of existing technology, like corneal tomography and ray-tracing calculation, to improve predictability and hence increase the chance of meeting patient expectations.

2.2 Aims and objectives

The aim of this thesis was to assess if accuracy of IOL calculations could be improved by comparing individual calculation based on actual individual measurements with empirically adjusted formulas based conventional biometry.

The primary objective for each paper were:

1. To evaluate the refractive outcome of previous RLE surgery in post LVC patients and analyze the IOL power predictions to develop a protocol to minimize refractive deviations based on conventional post-LVC calculation formulas.
2. To compare the prevalence of DED as determined by different signs and symptoms in patients with previous refractive surgery to a control group to assess if post LVC patients is at higher risk of tear film instability which may affect keratometry measurements and therefore IOL calculation at the time of cataract surgery.
3. To compare the repeatability of different keratometers in patients with normal and hyperosmolar tears to assess if some instruments is less likely produce erroneous keratometry which will affect IOL calculations.
4. To compare the refractive precision of ray tracing IOL calculations based on OCT data with traditional IOL calculation formulas based on reflectometry in patients with previous myopic LVC to assess if individual calculations can improve predictions compared to empirically based or refined methods.

3 Methods

This section contains an overview of design and methods of the four studies. Further details are described in each paper.

3.1 Study overview

All studies followed the tenets of the Declaration of Helsinki. All studies, except for the first (paper I) was approved by the Regional Committee for Medical and Health Research Ethics in Norway (appendix 1), and written informed consents was obtained. The committee considered the first study to be not a medical study but a quality control, and thus did not require approval.

In a retrospective study (paper 1) refractive results from previous presbyopic RLE in LVC-patients were evaluated and IOL predictions recalculated with different formulas (based on conventional reflection-based biometry) with newly optimized IOL constants. Results were analyzed and a nomogram target for the best formulas were developed. In a cross-sectional study (paper 2), the prevalence of dry eye 5 to 15 years after refractive surgery was compared to a control group. In another (paper 3), differences in repeatability of keratometry between different instruments were compared between a group with hyperosmolar tears and a group with normal tears. In a treatment study (paper 4), refractive predictions were compared between ray tracing IOL calculations based on OCT biometry and post LVC formulas based on conventional reflection-based biometry. (Figure 12: Overview of study design)

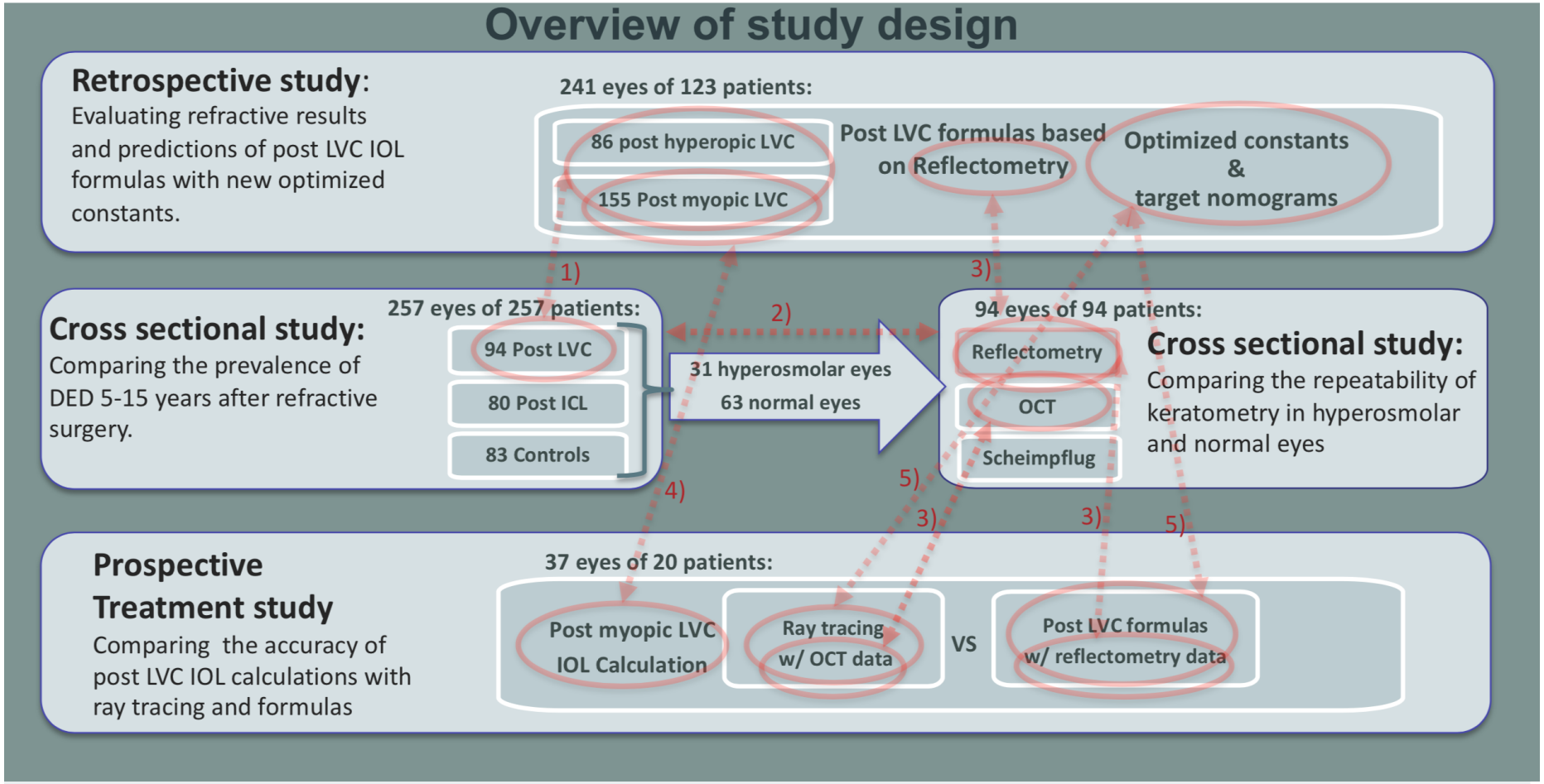

Figure 12: Overview of study design

Red lines demonstrating connections between studies: 1) Are post LVC patients more likely to have DED? 2) Does DED affect keratometry measurements? 3) Does DED affect measurements of reflection-based keratometry more than OCT and Scheimpflug keratometry? 4) Can IOL-calculations be improved in Post myopic LVC patients? 5)Ray tracing IOL calculations based on OCT data VS formulas with optimized constants and nomograms.

3.2 Study designs and participants

The first study was retrospective study where pre- and postoperative data from a group of patients with a history of previous laser vision correction, who had already had RLE-treatment. It was a multi-center, single IOL-platforms study of consecutive patients with a history of previous LVC patients who had trifocal IOLs implanted at Memira clinics in Norway, Sweden and Denmark from 2015 to 2017. The study included patients with previous hyperopic or myopic LVC, but main focus in this thesis is the results from the myopic ablation group. Refractive results were presented and recalculation of IOL power and predicted results was done with newly developed IOL constants based on 1400 normal eyes that had uneventful presbyopic RLE and implantation at Memira clinics. Original pre-RLE biometry data from a PCI device with reflection-based keratometry (Zeiss IOLMaster) was used. Different IOL calculation formulas were compared, the two best formulas were selected, and a target nomogram was developed to achieve the lowest difference between the predicted and achieved refractive result (refractive prediction error - RPE) .

In a cross-sectional prevalence study (paper 2) participants were recruited from patients who had undergone LVC or ICL at Ifocus Eye clinic in Haugesund 5–15 years ago. Patients from a population who were pre-examined or screened and found eligible for refractive surgery but who had elected not to proceed were age matched and recruited as controls. Eligible participants were identified from clinical patient records. Recruitment and data collection were performed from March 2018 to January 2019. Dry eye was evaluated using categorical cut-off criteria for tear film osmolarity, dynamic ocular scatter index (OSI), non-invasive break-up time, tear production (Schirmer 1), meibography and a subjective questionnaire, and compared between groups. One eye was randomly selected as the test eye, but osmolarity was tested in both eyes as established cut-off criteria includes both eyes.

In a cross-sectional repeatability study (paper 3) patients were recruited from the prevalence study. Inclusion criteria were tear-film osmolarity of 316 mOsm/L or higher in either eye (hyperosmolar group) or 308 mOsm/L or lower in both eyes (control group). In the hyperosmolar group the eye with the higher osmolarity was chosen as a test eye. In the control group a test eye was randomly chosen. Four instruments were used to measure the keratometry in all patients: a low- coherence reflectometry (OLCR) biometer (Haag Streit Lenstar 900), a rotating Scheimpflug camera tomographer (Oculus Pentacam HR), a SS OCT tomographer (Casia SS-1000) and a new SS OCT combined tomographer/biometer

(Heidelberg Anterion). Keratometry was measured twice in each eye with a timespan minimum of 1 minute between each measurement with the same instrument and 5 minutes between different instruments.

In the final treatment study, patients who presented at Ifocus eye clinic for cataract or RLE surgery from May 2019 to June 2020 and had a history of myopic LVC treatment were recruited. Patients with ICL-implant or a history of complicated LVC surgery were excluded. Biometry was measured with the same reflectometry device and the two OCT devices used in the repeatability study. IOL calculations were performed with ray tracing calculations with data from two OCT devices and with two post LVC formulas based on reflectometry and IOL constants optimized for normal eyes. Visual and refractive outcome was recorded on follow-up examination 2-4 months after surgery and the RPE was compared for all calculation methods.

For all studies (including the original surgeries for the retrospective study), inclusion criteria were bilaterally good ocular health, with no pathology or systemic disease involving the eye (except dry eye in the prevalence study and cataract in the retrospective and the treatment study). Exclusion criteria included ectatic disease, manifest corneal scarring, lid deformities, and any acute or chronic disease or illness that would confound the results of the studies or compromise the visual outcome of surgery.

3.3 Clinical evaluation

Before cataract or RLE surgery it is standard procedure for all patients to have preoperatively had a full optometric and ophthalmic examination, including uncorrected and corrected distance visual acuity (UDVA and CDVA), manifest refraction (sphere and cylinder), slit-lamp biomicroscopy, and fundoscopy or wide-field retinal imaging. This had been performed before initial surgery for all patients reported in the retrospective study and was also performed for all patient participating in the treatment study. Also, for patients in both these studies, a preoperative counseling during which needs, preferences, and expectations were evaluated.

In the cross-sectional prevalence study all patients had a full optometric assessment, and if indicated, further ophthalmic assessments were performed. Participants in the cross-sectional repeatability study was recruited form the prevalence study, so no further assessment except the study tests was performed for these patients.

3.4 Study tests and outcome variables

Both the retrospective study (paper 1) and the treatment study (paper 4) share several similarities regarding outcome variables: For retrospective study refractive and visual outcome was collected from the patient records while for the treatment study (paper 4) this was collected during the study follow up examination. These data included uncorrected and corrected distance visual acuity (UDVA and CDVA), and distance refraction (sphere and cylinder). In both studies IOL calculations were performed with conventional post-LVC data based on reflection biometry and optimized IOL constants. The optimizations for retrospective study were performed based on data from *several surgeons* in *several clinics* (following the same surgical protocol) and collected after the initial surgery but before the study recalculation. The optimizations for the treatment study were done based on data for *one surgeon* in *one clinic* before the surgery/study.

For the treatment study, IOL calculations were also performed with the Okulix ray tracing IOL-calculation software based on OCT data. This calculation does not require optimization of lens constants but calculates the predicted AQD based on a built-in database on the most commonly used IOLs. For the calculation with the Casia data, the AL value from the Lenstar was manually entered. For each OCT device, two separate measurements were used to perform two different ray tracing IOL-calculation, and the average IOL power for each device was used for analysis. All IOL calculations were assessed to choose the power of the implanted IOL. Toric IOLs were used to correct corneal astigmatism, but only the spherical equivalent of the IOL power and the postoperative refraction were analyzed in this study. The primary outcome variable for both IOL calculation studies was refractive prediction error (RPE), which was calculated as the achieved spherical equivalent (SE) refraction minus the predicted SE refraction.

For the prevalence study, tear film osmolarity was selected as the primary outcome variable because it is documented to have an effect on repeatability of keratometry. The cut-off criteria for categorizing hyperosmolarity was the worse eye having an osmolarity of ≥316 mOsm/L or a between-eye difference ≥8 mOsm/L. The cut-off for categorizing dry eye for the other tests were: Visual Break Up Time (based on ocular scatter index) ≤ 10 seconds; Non-Invasive Keratograph Break Up Time ≤ 10 seconds; Schirmer 1 test, wetting ≤10 mm after 5 minutes; lower eyelid meibography, meiboscore of ≥ 1.5; Subjective ocular surface disease questionnaire, *OSDI ≥ 13.*

In the repeatability study, the difference in K-value between two repeated measurements was calculated. All instruments provided anterior keratometry (SimK) based on a fictious refractive index of 1.3375, while the Scheimpflug and the two OCT devices also provided posterior corneal power (PCP) and total total corneal power (TCP) readings based on the refractive indices of 1.376 for the cornea and 1.336 for the aqueous humour. The differences in SimK were defined as the primary outcome, as this was the only keratometry provided by the reflectometry device. However, comparison of PK and TK differences between the Scheimpflug and the two OCT devices in the two groups were of interest as total keratometry can be useful in IOL power calculations. The coefficient of repeatability (CR) is the value below which the absolute differences between two measurements would lie with 95% probability.[115] The CR was calculated as the within-subject standard deviation multiplied by 2.77.[115,116]

3.5 Sample size

The sample in the retrospective study was limited by the available patient records for the patients that met the inclusion criteria. For the other studies sample size was determined using an alpha of 0.05 and a power of 0.8.

In the prevalence study normative data from another study was used to calculate an expected difference in mean osmolarity between group. The power analysis revealed that 79 subjects in each group was needed.

For the repeatability study we expected a SD of 0.1 D and wanted to reliably detect a difference of at least 0.1 D between two measurements. The power analysis revealed that we needed at least 17 eyes in each group.

In the treatment study, the sample size calculation was based on a mean difference in prediction error between the two calculation methods with an expected standard deviation (SD) of 0.4 D. A sample of 22 eyes was determined to be sufficient to reliably detect a difference in RPE of at least 0.25D

3.6 Analysis

For all the studies descriptive statistics included the minimum, maximum, mean and standard deviation. Statistical analysis was performed using t-test, ANOVA or nonparametric tests as appropriate and Pearson´s x^2 -test or Fisher exact test was used for comparing frequencies. A p-value ≤0.05 (two-sided) was considered statistically significant. P-values for comparisons

of primary outcome variables were adjusted with the Holm-Bonferroni method for multiple comparisons (paper 3 and 4).

In both the repeatability study and the treatment study, mixed effects models were used to account for relations between subjects (repeated measurement) and between two eyes of one subjected, and to control for other effects, like instrument order or the previous LVC treatments. Such models are designed for modeling continuous correlated hierarchical/multilevel data, and one of the main strengths is the ability to handle unbalanced data. They offer maximal use of available data and are efficient also with a substantial amount of nonrandom missingness. The models were designed with "subject" and, for the treatment study, "eye (nested) within subject". P-values were obtained by likelihood ratio tests of a) the full model with the effect in question against b) the model without the effect in question. "Subject" (and "eye within subject") were kept as a random effect in all models. In the treatment study, parameter specific p-values were obtained with Satterthwaite's method. Statistical analyses were performed using SPSS for Mac statistical software package (version 20.0, IBM Corp.), the R Commander (version 2.6-0) (R Core Team, Vienna, Austria), or the RStudio data-analysis software (version 1.2.1335, RStudio Inc, Boston, MA, USA) with the lme4 and the ggplot2 packages. A p-value ≤ 0.05 (two-sided) was considered statistically significant.

3.7 Post hoc analysis

In the prevalence study correlations between osmolarity and other factors known to affect dry eye (like age, sex, preoperative refraction, time of day, and season) were tested with Pearson´s correlation coefficient of determination or Spearman's rank correlation.

In the repeatability study differences in repeatability between instruments for all subjects were analyzed using the t-test or nonparametric tests as appropriate. *p*-Values for the comparison of SimK differences (primary outcome) were adjusted with the Holm–Bonferroni method for multiple comparisons. CR was compared between instruments.

In the treatment study, the ray tracing calculations were based on an average of two calculations from two measurements with each OCT device. To determine if repeatability of measurement was a significant source of error, the coefficient of repeatability was calculated for both OCT devices. The ray tracing IOL calculation software calculates a predicted

postoperative AQD. The AQD prediction error (AQD PE) was calculated as the actual postoperative AQD measured by the newest OCT device minus the predicted AQD. The correlation between the RPE and AQD PE was tested with Pearson´s correlation coefficient.

4 Results

This section contains the main result that support the final conclusions. Further details are described in each paper.

4.1 Main Results Paper 1

In our retrospective study (paper I) we analyzed 241 eyes from 143 patients who had a history of previous LVC and had trifocal IOL implantation from 2015 to 2017. Only the results from the myopic group are presented here. There were 155 eyes analyzed in the myopic ablation group. We found a mean uncorrected Snellen visual acuity of 0.9 ± 0.2 and corrected visual acuity of 1.1 ±0.1. Postoperative SE was -0.25 ± 0.38 D ranging from -1,25 D to +0.75 D, 80% of the eyes had a refractive error of ±0.5 D or less and 97% had ±1 D or less.

IOL power was recalculated with new optimized constants. Figure 13 shows a box plot of the arithmetic refractive prediction error for the previous history formulas (A) and the no history formulas (B). In cases with previous history data, the Masket formula, ASCRS minimum formula, Barrett true-K nomogram with a target of 0.15 D, and Haigis-L nomogram with a target of 0.45 D yielded the lowest RPE, with the results not statistically different from zero. The no-history group included subjects also from the previous history group, but calculations were performed with no-history formulas. The Haigis-L formula with a nomogram target of 0.45 D yielded the lowest mean RPE and median absolute error (MedAE) and was the only formula that was not statistically significantly different from zero ($P > 0.25$, one-sample t-test). Figure 14 shows percentage of eyes within certain range of absolute RPE for the previous history formulas (A) and the no history formulas (B). In the previous history group the absolute prediction error was within ± 0.5 D, ± 0.75 D and ± 1.0 D in 72%, 98% and 100%, respectively for Barret True K nomogram with target +0.15 D, and 81%, 94% and 100%, respectively for Haigis-L nomogram with target +0.45 D. In the no history group the

Haigis-L nomogram yielded significantly more eyes within ±0.5 D (83%) when comparing pairs of formulas.

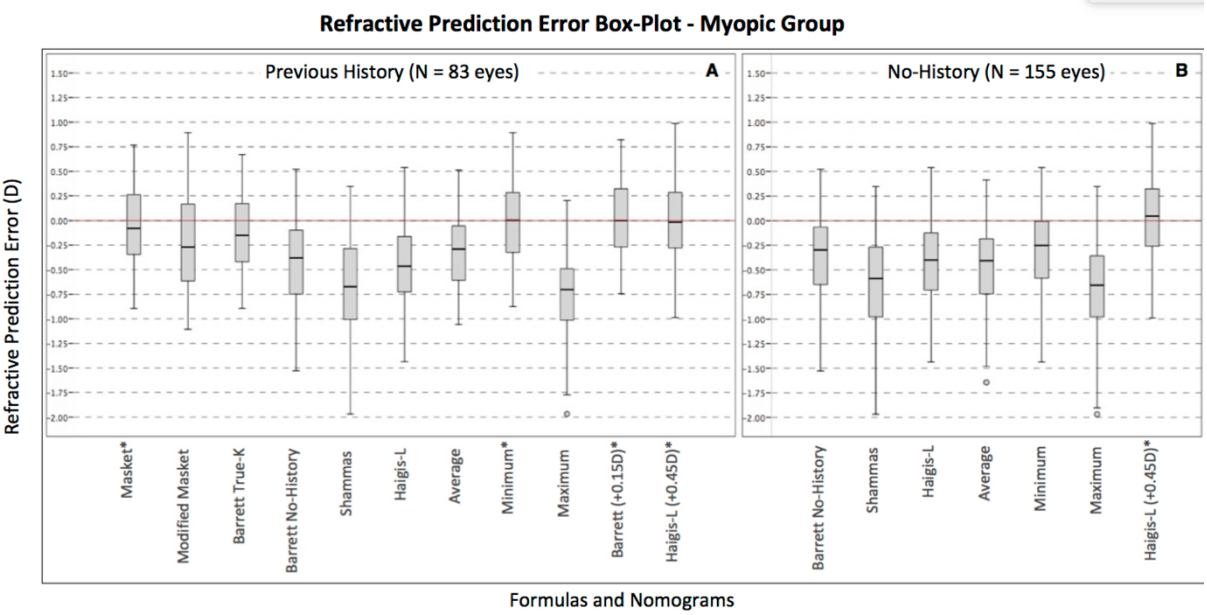

Figure 13 Box plot of arithmetic refractive prediction error

Different previous History formulas (A) and No-history formulas (B) are shown together with the average, minimum and maximum and the best performing nomogram

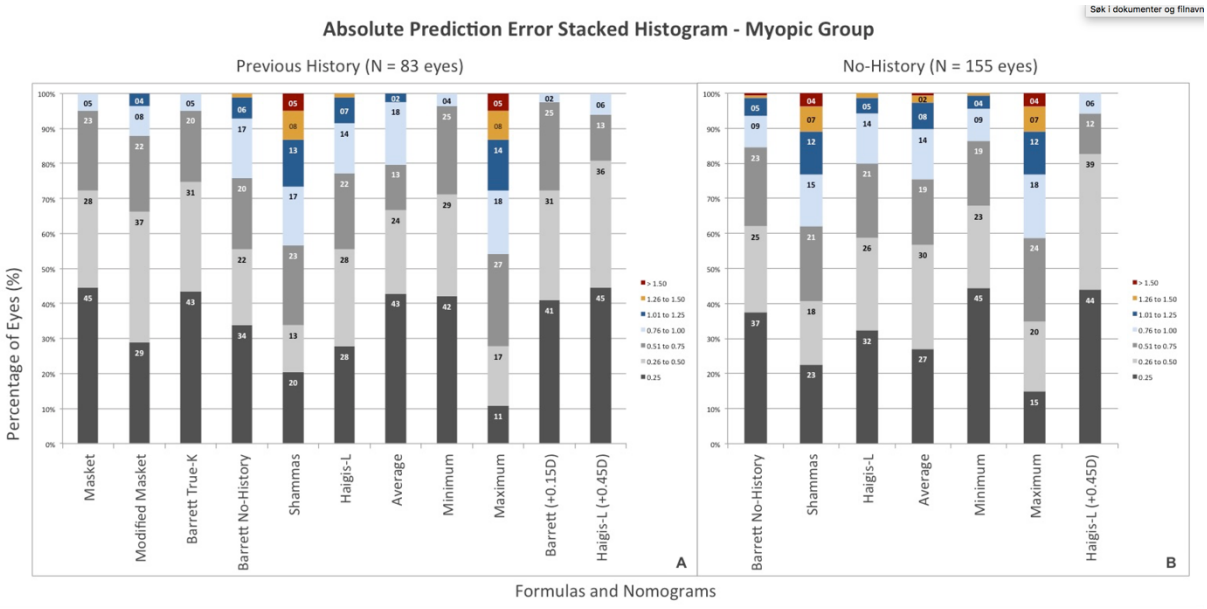

Figure 14 Percentages of eyes within certain range of absolute prediction error

4.2 Main Results Paper 2

The study included 94 patients with LVC, 80 patients with ICL and 83 patients in the control group. When results where categorized according to cut-off criteria, the frequency of hyperosmolarity was statistically significantly higher in the LVC group vs. the control group (73% vs. 50%), but not significantly different between the ICL and control group (Figure 15). The frequency of VBUT≤10 seconds was significantly higher in the ICL group vs. the control group (33% vs 17%). No other single objective tests or combination of criteria showed any significant difference between LVC or ICL and the control group. The frequency of OSDI ≥13 tended to be lower in the LVC group relative to the control (19% vs 31%), but this was not statistically significant (p = 0.06). The frequency of OSDI ≥13 in the ICL group was the same as the control (31%). We could not establish any significant correlation between osmolarity and any of the other single DED tests. However, the frequency of hyperosmolarity was significantly higher in patients with two or more other indicators of DED (66% vs 52%, p=0.03).

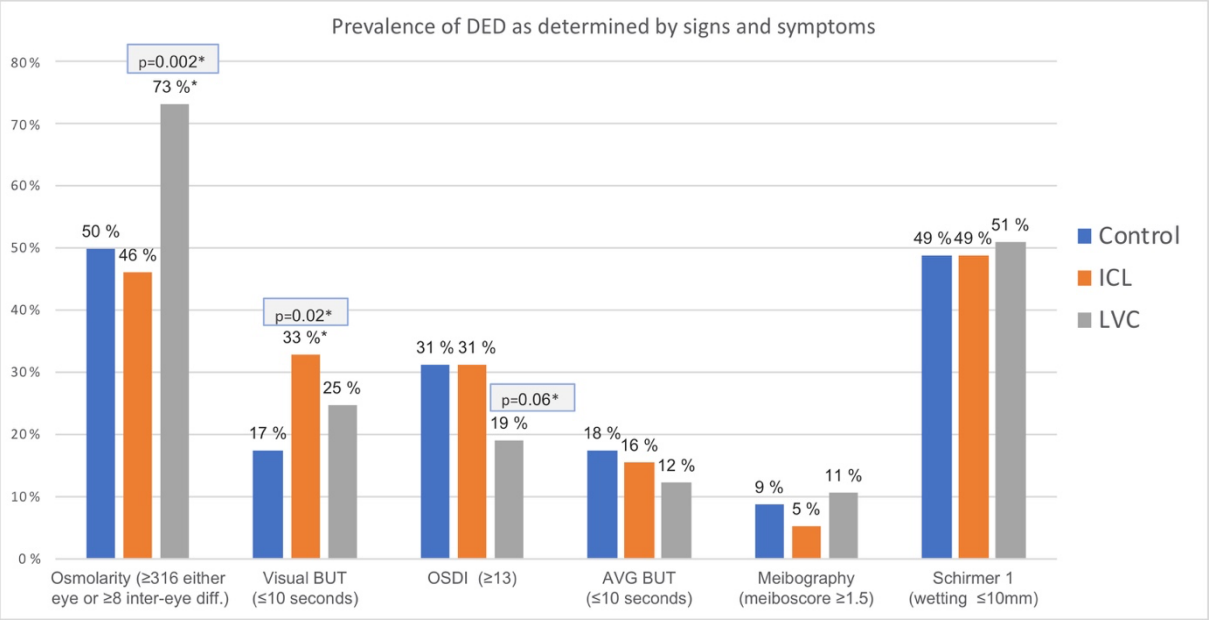

Figure 15 Prevalence of signs and symptoms of DED
Prevalence of DED as determined by different tests between LVC or ICL and control group
***Notes:** *Pearson´s χ^2: difference from control group.*
***Abbreviations:** BUT= Break-up time, OSDI = Ocular surface disease index, AVG = average, ICL = Implantable collamer lens, LVC = laser vision correction*

4.3 Main Results Paper 3

The study included 94 subjects, 31 in the hyperosmolar group and 63 in the control group. The main outcome variables were anterior keratometry (SimK) differences but also posterior corneal power (PCP) and total corneal power (TCP) were considered as these are of interest in IOL-calculations

A linear mixed effects model was designed with “osmolarity group”, “instrument” and “previous LVC” as fixed effects and “subject” and “instrument order” as random effect. For all keratometry variables the models suggested that “instrument” was a statistically significant effect but “osmolarity group” was not ($p<0.01$ and $p>0.05$, respectively).

Analysis including all subjects showed statistically significant differences in means of the instruments (Figure 16): Both the Casia and the Anterion had significantly higher mean difference of average SimK compared to the Lenstar (0.1 D and 0.1 D vs 0.05 D, respectively, adjusted $p <0.03$), and average TK compared to the Pentacam (0.10 D and 0.12 D vs 0.06 D), $p <0.01$). The Casia had statistically significantly higher mean magnitude of SimK vector differences compared to the Lenstar (0.27 D vs 0.18 D, adj. $p<0.01$) and of TK vector differences compared to the Pentacam (0.27 D vs 0.18 D, $p< 0.01$).

The CR for each instrument with all subjects is shown in (Figure 17). The Casia and Anterion devices had higher CR for average SimK and TK compared to the Lenstar and the Pentacam respectively, while the Casia had higher CR of SimK and TK vector differences of astigmatism compared to the Lenstar and the Pentacam, respectively.

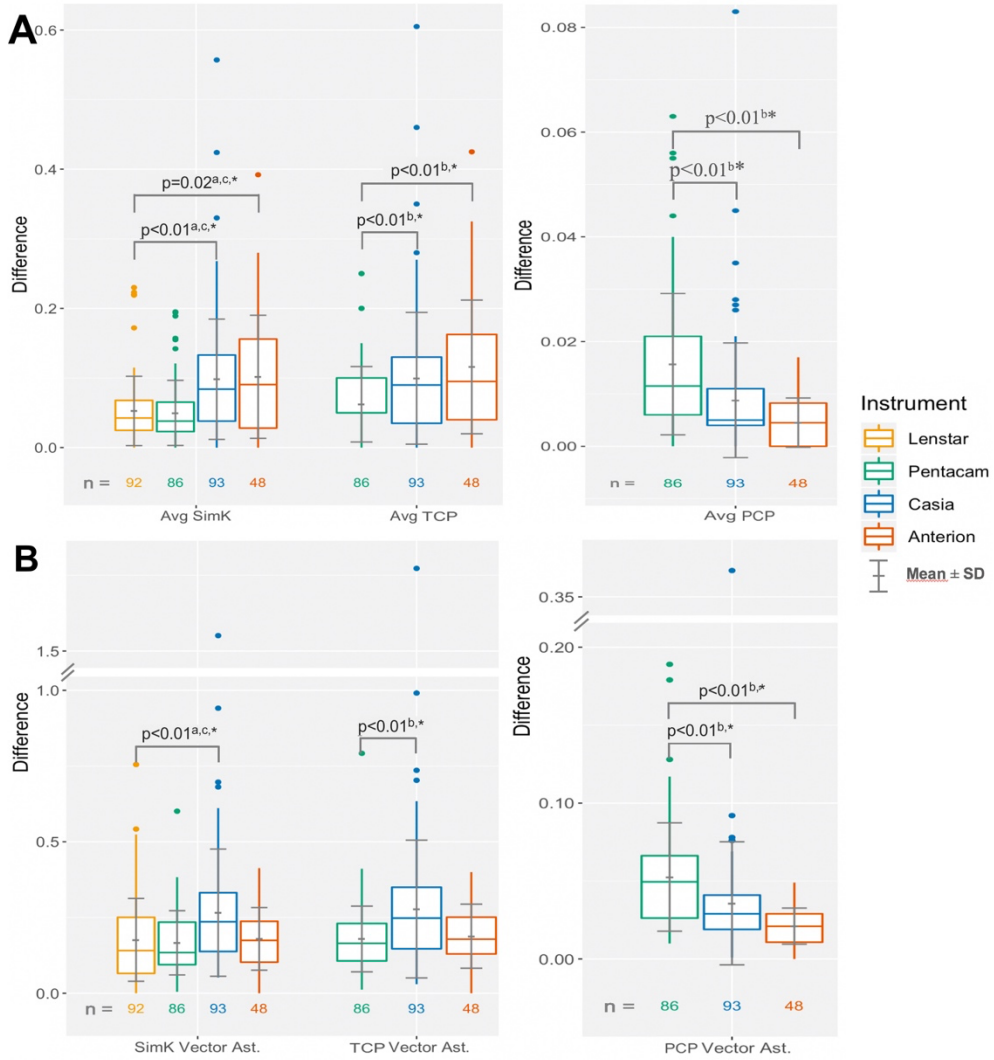

Figure 16 Mean difference of repeated measurements of average keratometry (A) and vector difference of astigmatism (B) with all subjects.
***Notes**: [a]Wilcoxon signed-rank test comparison with the Lenstar; [b]Wilcoxon signed-rank test comparison with the Pentacam; [c]Holm–Bonferroni adjusted p (six comparisons). *Statistically significant.*
***Abbreviations:** Difference, absolute difference of repeated measurements; SimK, simulated keratometry; TCP, total corneal power; PCP, posterior corneal power; Avg, average; Vector Ast, magnitude of vector difference of astigmatism; SD, standard deviation.*

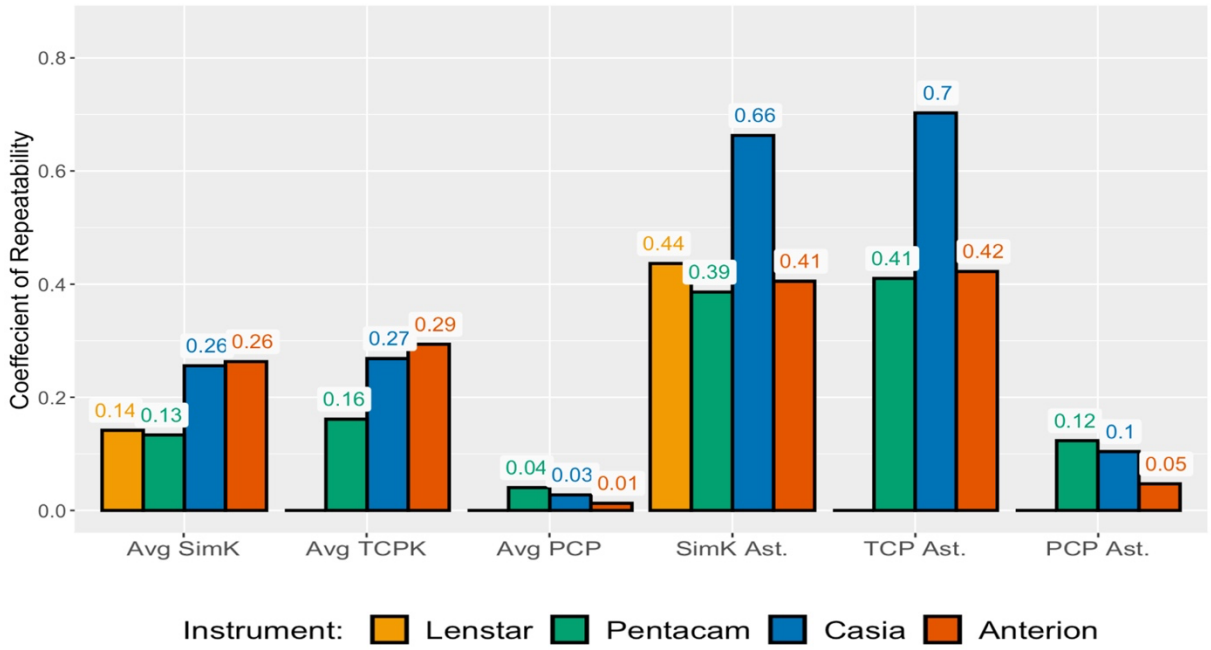

Figure 17 Coefficient of repeatability for each instrument with all subjects.
***Abbreviations**: SimK, simulated keratometry; TCP, total corneal power; PCP, posterior corneal power; Avg, average; Ast., magnitude of vector difference of astigmatism.*

4.4 Results Paper 4

4.4.1 Main results

The treatment study included 37 eyes from 20 patients with a history of previous myopic LVC. The mean age was 57 years, and 42% had cataract, while 58% came for refractive lens exchange. The lowest arithmetic RPE was found with the ray tracing (OKULIX) calculation based on biometry from the Anterion OCT device. This was statistically significantly better than the Barret True K No History formula (-0.13 D and -0.32 D, respectively), which had the best prediction error of the formula-based calculations (Figure 18 A). The Anterion-OKULIX calculation had the lowest absolute prediction error. However, the difference was statistically significantly versus the Haigis-L formula only (Figure 18 B). The Anterion-OKULIX had the lowest magnitude of range of both arithmetic (1.11 D) and absolute RPE (0.64 D) and the lowest standard deviation of absolute RPE (0.19 D), while the Barret TK NH had the lowest SD (0.27 D) of arithmetic RPE. The Anterion-OKULIX calculation yielded statistically significantly higher percentage of eyes within ±0.25 (60%) and also highest percentage within ±0.50 and ±0.75 (88% and 100%, respectively), but this was statistically significant compared to Haigis-L only (Figure 19).

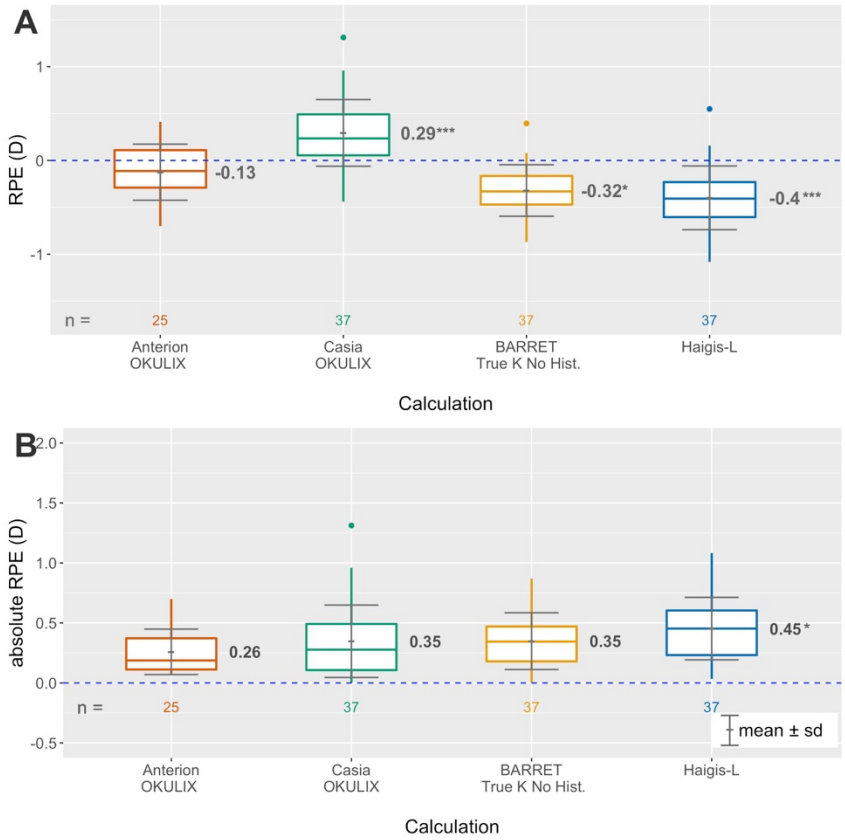

Figure 18 Boxplot of (A) arithmetic and (B) absolute prediction error.

*Notes: *Adjusted p ≤0.05; ***adjusted p <0.001 (mixed models estimates different from Anterion OKULIX). Abbreviation: RPE, refractive prediction error.*

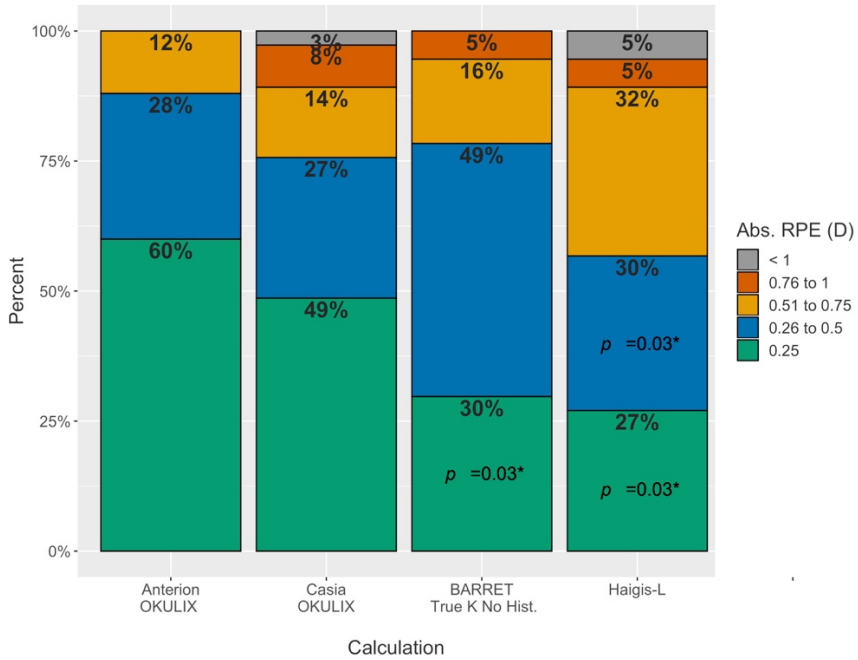

Figure 19 Percentages of eyes within certain range of absolute RPE

*Notes *Mixed models estimates statistically significantly different from Anterion-OKULIX (Holm-Bonferroni adjusted p-values)*
Abbreviations Abs, Absolute; RPE, refractive prediction error; p, adjusted p-value

4.4.2 Repeatability of OCT Ray Tracing

The ray tracing calculations were repeated with two measurements from both OCT devices. The coefficient of repeatability for the OKULIX IOL calculations with each OCT device was calculated. The CR was 0.23 and 0.41 with the Anterion and the Casia data, respectively. This equals the 95% limits of agreement in a Bland-Altman plot (Figure 20)

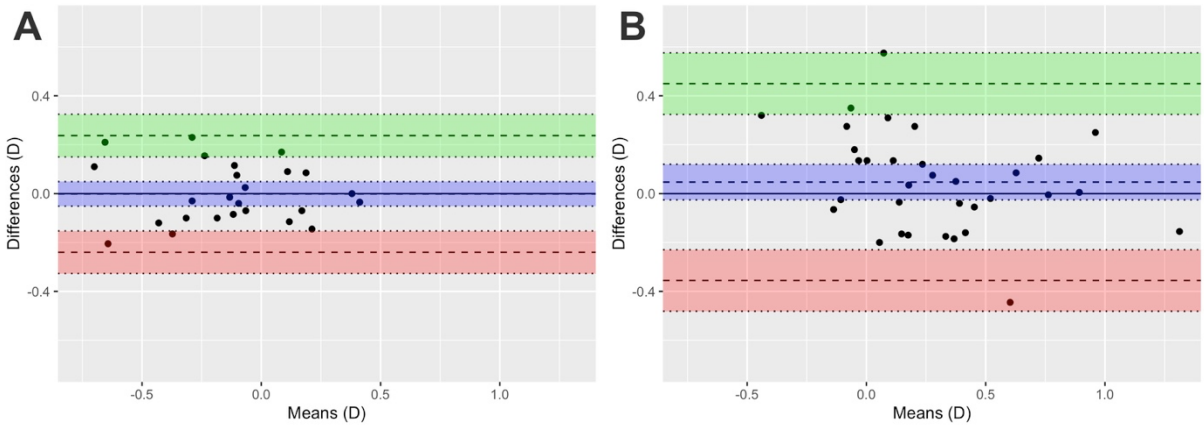

Figure 20 Bland-Altman plot of differences between repeated IOL calculations of A)Anterion-Okulix and B) Casia-Okulix

4.4.3 Aqueous Depth Prediction Error

The mean AQD PE for the ray tracing calculation was −0.11 ± 0.13 mm and −0.14 ± 0.22 mm for the Anterion and Casia data, respectively. This was statistically significantly different from zero for both devices, but not between the devices. A linear model with RPE as the dependent variable and AQD PE as the independent variable showed an intercept and slope of −0.01 and 1.00 for the Anterion and 0.41 and 1.00 for the Casia. This was statistically significant for the slope for both devices and for the intercept for the Casia. The adjusted R2 was 0.39 and 0.17 for the Casia and the Anterion, respectively (Figure 21).

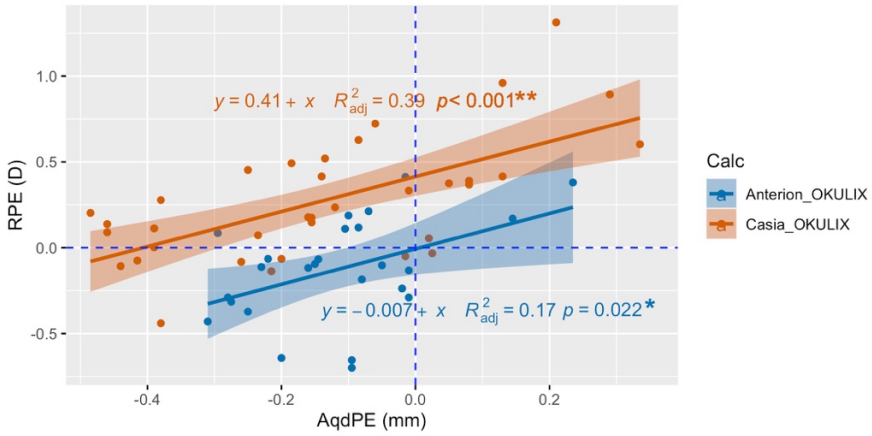

Figure 21 Correlation between RPE and AQD *PE of the ray tracing calculation for the OCT devices.*

*Notes: *Slope statistically significant; **intercept and slope statistically significant.*
Abbreviations: RPE, refractive prediction error (D); AqdPE, aqueous depth prediction error (mm); Calc, IOL-calculation.

5 Discussion

5.1 Thesis main results

Previous studies have shown that refractive prediction of IOL calculations after refractive surgery have improved but still remains a challenge. This thesis has investigated the possible improvement in refractive predictions for IOL power calculations for patients with a history of myopic LVC. Compared to previous studies, the results showed some improvement is possible by analyzing previous results and applying new lens constants and target nomograms. However, the most accurate refractive prediction was found using ray tracing IOL calculation software with data from an OCT biometer. Our study showed that predictability for patients with previous myopic LVC was comparable to results seen in studies of IOL calculation for normal eyes without previous surgery.[117]

5.2 Lens constant optimization

The retrospective study assessed if it was possible to improve results based on a multi-center single protocol (the same IOL, biometry device and surgical procedure, but with different surgeons and clinicians) in a large volume practice. In this study the initial refractive results were better than seen in several other post LVC studies, but the actual choice of IOL power

was based on different formula calculation and the arbitrary choice from clinical experience rather than a strict protocol.

The study showed that recalculating IOL power for post LVC patients with new constants based on normal eyes together with a target nomogram could improve refractive results. This improved the SD and the range of RPE but with a systematic offset for the mean. This offset shows that the constants developed for normal eyes was not optimal for the post LVC population. Ideally if a large enough cohort of LVC patients were available, constants should be optimized for this population. However, optimizing constants for post-LVC patients represents a problem (and studies where this is done are few, if any): The greater variability seen in post LVC patients means that it would require more data to get reliable constants. At the same time there is a relative low percentage of these patients (possibly less than 5%). So, in this study the RPE was adjusted by applying a target nomogram to achieve the highest number eyes with a RPE within ±0.5 D, ±0.75 D and ± 1.00 D (81%, 94% and 100%, respectively) which was higher than seen in previous studies of IOL calculation after LVC.[10,96]

However, even with the best formula in this study, a range of prediction errors of 2 D indicated that refractive surprises could still be a clinical challenge for the individual patient. Furthermore, these results may not be achievable for smaller clinics that do not have access to a high number of previous surgeries. The results presented were based on optimized lens constants from more than 1000 previous surgeries of normal eyes with the same specific IOL and surgical protocol, and the proposed nomograms were based on the 155 eyes analyzed in the study. The constants and nomograms presented in our study can only be adopted by clinics using the same IOL, biometer and surgical technique. Individual variations in surgical technique, different instrumentation, and even different populations may yield different results.

5.3 Post-LVC IOL-calculation errors.

The three main source of error in post LVC IOL calculations (the keratometric error, the ELP error and the radius error) are well documented, but even though specific formulas that address this problem have been developed through the years, these calculations remain challenging. Other possible errors include reduce corneal thickness, altered corneal asphericity or higher order aberrations may also contribute.[103,106] For IOL calculation in any patient, individual shrinkage of the postoperative capsular which can influence the actual

postoperative IOL position may be an additional error source, and tear film instability may be another: When using reflection based keratometry poor tear film quality may affect keratometry, which is a critical value for the IOL calculation at the time of cataract surgery. Epitropoulos et al studied the effect of osmolarity on repeatability of a reflectometry device om a cataract population and found that in a hyperosmolar group 8% had a difference of more than 0.5 D and 5% mor than 1 D between repeated measurement, while all subjects had differences <0.5 in the normal group.[87] In patients with previous LVC 1.0 D of difference in keratometry would give approximately 0.8 to 1.2 D of difference in refractive outcome.[118] While several post LVC formulas result in mean RPE around ±0.5, the range could be from -2 to +1 D. In the cases with the highest errors this is likely the result of several errors, and erroneous keratometry due to tear film instability may be one.

5.4 Prevalence of hyperosmolarity after refractive surgery

Dry eye is the most commonly reported complication after LASIK surgery, and studies have shown incomplete nerve regeneration several years after surgery.[77,83,84] Therefore, a study to investigate if dry eyes could affect LASIK patients in the longer term was conducted. The prevalence of hyperosmolarity was found to statistically significantly higher in patients with a history of LVC 5 to 15 year earlier than in a matched control group. Even though tear film osmolarity is not a direct measurement of tear film stability, it is one of the key signs of dry eye. So, arguably, patient with a history of LVC as long as 5 to 15 year ago suffer from increased risk for tear film instability which could affect keratometry at the time of cataract surgery.

The study did show a relatively high prevalence of hyperosmolarity in all groups. This could possibly be related to the fact that many patients who experience problems with contact lenses due to dry eyes consider refractive surgery as a solution, and up to 73% of LVC patients have been reported to seek surgery because of difficulties with contact lens wear.[119] Furthermore, studies have also shown that preexisting dry eye is the most significant risk factor for developing dry eyes after LASIK surgery.

There was a tendency of fewer subjective symptoms in the LVC group compared to the control group, which may seem contradictory. However, studies have shown that subjective and objective symptoms may not agree due to differences in age, tolerance, environment and even long-standing dry eye which can reduce sensitivity.[119] Considering the results in the

present study, LASIK may induce or mask dry eye permanently due to reduced sensitivity from incomplete nerve regeneration. In consequence, when evaluating these patients, for instance before cataract or refractive surgery, objective dry eye tests, including tear film osmolarity if possible, should be considered even without subjective symptoms.

5.5 Effect of tear osmolarity on repeatability of keratometry

A study was conducted to test the hypothesis that keratometry measurements from instruments that do not rely on reflections from the tear film would be less dependent on tear film quality. The repeatability of OCT-based keratometry versus Scheimpflug- and reflection-based keratometry was compared in a group with hyperosmolar tears and a control group with normal tears.

Using hyperosmolarity as a proxy for tear film quality, we could not find evidence that repeatability was influenced by osmolarity with any of the instruments studied. In Contrast, Epitropoulos et al found significantly higher variability of keratometry with an IOLMaster in the hyperosmolar group. There may be several reasons for the different results in this study: Reflectometry does depend on good reflections from the tear film, but the differences in design and working mode between these two reflectometry devices may affect the repeatability: The IOLMaster uses 6 light spots and averages 3 measurements in 3 seconds, while the Lenstar uses 32 light spot and averages 5 measurements in about 3 minutes. As such the Lenstar may be more effective in averaging the random variability and hence give more repeatable results. Furthermore, in the present study the measurements were repeated within 1-2 minutes, while Epitropoulos et al performed their repeated measurements on different visits, which may give rise to a variability in osmolarity between visits (the mean osmolarity was 8.4 mOsm/L lower on the second visit in their study). Other differences include differences in mean age, which was 71 in the Epitropoulos study and 43 in the present study. Estimates of prevalence of DED based on tear film break up time (TBUT) increase with 10% for each decade after 40- 49 years of age.[119] So, there could have been fewer subjects with unstable tear film and consequently less variability in keratometry in the present study. Finally, even though both hyperosmolarity and instability of the tear film are considered hallmarks of DED, osmolarity is not a measure of tear stability itself, and there is a lack of evidence that the osmolarity of a tear sample from the tear meniscus is representative of the osmolarity of the ocular surface. [28,71,120] Therefore it may be questioned if osmolarity is a good indicator for tear film stability.

5.6 Effect of variability of keratometry on IOL calculations

Our results for all subjects showed that the mean differences in repeated measurements of the different devices were relatively low (< 0.1 D for average keratometry and <0.3 D for vector difference of astigmatism). Even so, a coefficient of repeatability of 0.3 D shows that both OCT devices have greater chance of errors in average K (maximum difference was 0.4 D and 0.6 D for the Anterion and the Casia, respectively), which could be clinically relevant in some cases. The Casia had a CR of about 0.7 D (maximum >1.5 D) for astigmatism which was higher than with the other instruments. These findings have been supported by some other studies of OCT devices[121,122]. A such, when using the OCT devices investigated in this study for IOL calculations, the results should be based on an average of at least two separate measurements.

5.7 Effect of total corneal power on IOL calculations

The two OCT devices showed similar CR for TCP as for SimK. TCP is calculated from the curvature of both the anterior and the posterior surface of the cornea. Arguably, for eyes with a healthy, regular and untreated cornea, measurements of the posterior cornea to provide total corneal power may not be necessary. The contribution from the posterior cornea is less than 1/5 of the total corneal power. However, in patients with irregular corneas or a history of refractive surgery, a corresponding erroneous ratio of the front and back surface of the cornea could be clinically significant. For instance, a cornea treated for −3 D of myopia could give 0.8–1.5 D of measurement error (depending on the assumed refractive index) when using SimK only. This would in most cases with moderate or high myopia outweigh variability of the average TCP measurements seen in this study.

5.8 Ray tracing IOL calculations

The purpose of the final study was to assess the accuracy of ray tracing IOL calculations based on OCT data in patients with a history of previous myopic LVC. The hypothesis was that such exact calculations based on actual individual measurements, could improve accuracy

for these patients compared to modified theoretic or empiric formulas based on conventional reflection-based biometry.

The ray tracing calculations based on the newest OCT devices (Anterion) yielded better results compared to the Casia OCT device and the best formula-based calculation (Barret TK NH). The Anterion-OKULIX calculation had the lowest mean and range of arithmetic RPE and the lowest standard deviation and range of absolute RPE. However, the Barret TK NH showed the lowest SD of arithmetic RPE. The Anterion-OKULIX calculation also demonstrated the highest percentage of eyes within ±0.25, ±0.50, and±0.75.

There seem to be a lack of other studies assessing ray tracing IOL calculations based on complete OCT data, but some studies have used ray tracing as a part of the calculation.[123,124] However, these studies used several empirically drawn assumptions of corneal properties, so a direct comparison may not be valid. Several studies have investigated the use of total corneal power instead of keratometry in combination with theoretical post-LVC IOL calculations.[10,111,125,126] Some of these studies showed that the use of TCP is likely to improve IOL- calculations in post-LVC patients. However, they used corneal power from a limited area or ring in paraxial vergence formulas. In present study, results appeared even better, which was likely to result from the ray tracing calculations using OCT tomography data for a full optic zone of 5 mm and that the software takes spherical aberrations of both the IOL and the cornea into account.

Some studies have compared formula calculations with ray tracing calculations (based on OCT, Scheimpflug or reflectometry) in unoperated eyes, all of which found similar or better results with ray tracing compared to formula calculations.[127-129] In a recent study of 10.000 normal eyes Darcy et al compared several newer formulas incorporating artificial intelligence. They found that a theoretic formula combined with artificial intelligence yielded 43%, 72% and 95% of eyes within ± 0.25, ±0.50 and ±1.00. The best ray tracing calculation in our study appear to give even better results than seen in any of these studies, indicating that this method is suitable also for eyes with no prior history of refractive surgery.

5.8.1 Precision and repeatability of OCT data for ray tracing IOL calculations.

The mean arithmetic RPE for the Casia-OKULIX calculation was statistically significantly worse than for the Anterion-OKULIX. This could indicate a difference in precision or repeatability of the measurements between the two instruments. One difference between the

devices is that the Casia does not include AL measurement, so for the Okulix calculation, the AL was taken from the OLCR- device. The Anterion measures the AL using a longer wavelength. This offers better tissue penetration, which improves the likelihood of accurate AL measurements in a higher percentage of eyes compared to OLCR device.[130]

The ray tracing calculations were based on an average of two separate measurements and calculations with each device. The calculations based on data from the Casia device had almost twice as high coefficient of repeatability compared to the Anterion. Variance in measurements may be partially explained by slightly different positions of the eye's surfaces at each measurement. A longer acquisition time for the Casia versus the Anterion (2.4 and 1 second, respectively) may increase risk of significant eye movement that could affect the measurements.

5.8.2 Prediction of AQD with Ray tracing IOL calculation

The predictability of the lens position influences the refractive predictability. Unlike IOL calculation formulas, prediction of the lens position from the OKULIX calculation relates to the physical IOL position that can be measured postoperatively as AQD. The mean AQD PE was not statistically significantly different between the two OCT devices, so this could not explain the higher RPE seen in the Casia-Okulix calculation. However, the Casia showed greater variance, and the correlation between AQD PE and RPE was stronger with the Casia. The AQD PE explained 39% of the total variance in RPE for the Casia, but only 17% for the Anterion. The lower predictability of AQD for the Casia-OKULIX calculation could be related to the fact that the Casia does not provide a measurement of the crystalline lens position or thickness.

5.8.3 Ray tracing IOL calculation and person-centred eye-care.

The accuracy of IOL calculations have improved greatly the last decades. In a much-sited editorial by Koch et al from 2017 they argued that the best formulas used with the best instrument in patients that have "normal" eyes, and with skilled clinicians and surgeons and careful evaluation of raw data could yield prediction error within ±0.5 D as high as 90 % of

the eyes, but that majority of surgeons yielded around 78% within ±0.50 D. They also pointed out that patients with complex eyes like very long or short eyes, irregular corneas, or previous surgery required new formulas or modifications of existing ones.[54] This assertions were more or less supported in a recent review by Savini et.al of studies that included several newer formulas (including AI). However they found variability between studies and the best study was limited to 88% within ±0.5 D. This variability indicates that empirical assumptions is a limitation also in normal eyes. AI methods are considered promising as they can continue to evolve and improve the accuracy, but this depends on the continued collections of data from surgeries.

Arguably, if all properties of the patient's eyes could be measured exactly there would be no need for assumptions, and calculations could reveal the true refractive result for a certain IOL power. The ray tracing calculations are exact calculations that do not use approximations. Individual rays are calculated using Snell´s law, as they undergo refraction at all surfaces of the cornea an IOL.[98] The results (paper 4) show that when used with a new OCT based biometer the accuracy is close to 90% within ±0.5 for eyes with previous myopic LVC. Patients with a history of LVC treatments are considered to have more complex eyes which deviates from the eyes of the normal population. Yet, the results in the present study were comparable with the best formula calculations for normal eyes found in the literature.

In addition to showing accurate results in the present study, ray tracing IOL calculation can provide several advantages over conventional formulas:

1) The calculation can be used for any patients: Patients with untreated, normal eyes, patients with irregular corneas due to trauma or ectasia as well as patients that have had different types of corneal refractive surgery.

2) There is no need for knowledge of prior surgical treatments. Some patients may not know exactly the power of the LVC treatment or even if it was hyperopic or myopic. For instance, our first study we found one eye with LVC treatment for mixed astigmatism (with zero spherical equivalent), where the calculation for this eye was based on hyperopic LVC when it should have been calculated as an unoperated eye.

3) There is no need for optimizing lens constants or adjusting targets based on empiric data for different clinics, surgeons.

4) There is no need for time-consuming evaluation of several formulas (some of which also need different optimized constants)

5) The software takes corneal aberrations into account by calculation the smallest blur circle on the retina.

6) The software uses radii, refractive index, and asphericity for available IOL types and calculates the IOL power which gives the best focus. This means that the effect of asphericity in different IOLs on corneal aberrations also can be considered.

The main limitation for the ray-tracing method is accuracy of input data, as demonstrated by the repeatability of keratometry (paper 3), and the also when comparing the repeatability of the ray tracing calculation and the AQD PE between the two OCT devices (paper 4). Until such time as software updates allow for averaging several measurements to reduce variability, it is recommended that IOL power selection with the OCT devices studied here should be based on two or more measurements.

5.9 Methodological considerations and study limitations

5.9.1 Study design and sample

In the repeatability study, the participants were recruited from the prevalence study based on osmolarity. However several subjects were excluded because the osmolarity measured on the study examination were outside the inclusion criteria. Also the newest OCT device was included late in the study, so the final sample size for the Anterion device was limited, with relatively few participants in the hyperosmolar group.

The treatment study had a limited number of eyes. It is well documented that different IOL calculation formulas are less accurate for more complex eyes. This is, however, less likely for the ray tracing calculation based on OCT data which are based on actual measurements instead of assumptions. As such a larger sample, including more extreme values of K, ACD or AL may show greater difference between the Ray tracing calculations and the formulas

5.9.2 Measurements and procedures

In the prevalence study humidity was not controlled, which could have affected the results. Only previous LASIK patients, so no conclusion about LASEK, PRK or SMILE could be drawn.

In the repeatability study the participants were relatively young (43 years). The purpose of the study was to compare the repeatability of different instruments in patients with hyperosmolar and normal tears, using osmolarity as a proxy for tear film quality(short break up time. An older study population may have given different results, as prevalence of DED based on TBUT increase with age.[119]

In the treatment study, the ray tracing IOL calculation were performed for a pupil size of 2.5 mm which is the standard value recommended in software the user manual. The patient's pupil size was not measured or considered. Adjusting the pupil size for the calculation in accordance with the patient pupil size might have given different the results. Correction astigmatism with toric IOLs is important to achieve a good refractive result. However, accuracy of astigmatism correction was not analyzed, so no conclusion about the toric calculation of the ray tracing software can be drawn.

5.10 Future perspectives

5.10.1 Warranted studies

The results of this thesis give rise to other interesting questions to be studied in the future Theoretically, ray tracing IOL calculations should yield equally accurate results for any patients, also without previous refractive surgery. Studies of populations with virgin eyes, advocated. Also studies of patients with previous hyperopic ablation, other types of corneal surgery or even irregular corneas is of interest. Studies including adjustment of the ray tracing calculation for individual pupil size is interesting, as this may be useful in predicting not only IOL power, but also which type of IOL design (asphericity) that gives the best focus. AI - artificial intelligence methods are showing promising results. Studies comparing AI and ray tracing would be of interest.

5.10.2 Future advances

The results seen in the treatment study, with almost 90% of patients within 0.5D of predicted refraction, may be close to the limit of what can achieve today because of other limitations in the data:[54]

-True IOL power: IOLs are produced with a certain tolerance. Future IOLs should be labelled with the actual power measured on quality control

-Refraction: Subjective refraction may vary in the same individual due to visual acuity, tear film quality, pupil size, or random choice when the true refraction is between two incremental steps of power. Optometrists and ophthalmologist may have preferences for performing the subjective refraction that could affect the result. Advances in instruments may provide more accurate objective refraction that can support or even replace than subjective refraction. The effect of pupil size on refraction is of particular interest.

-Individual postoperative shrinkage of the capsular bag affects the refractive effect of the IOL and limits the predictability of IOL calculations. Future research may find ways to predict or limit this effect.

Technology will continue to improve. This will likely lead to development of new instruments capable of even more accurate measurements of the human eye, and hence mor accurate IOL calculations. In the future, IOLs could be custom made to fit the eye perfectly, including power, asphericity, or even correction of higher order aberrations. This will be the ultimate situation for person-centred eye care

6 Conclusion

Our results have shown that IOL-calculations in post myopic LVC patients with optimize lens constants and the use of nomograms could yield mean prediction errors that are close to those found in studies of patients without prior refractive surgery. However the range of error is greater than for normal eyes; from -1 D to +1 D and 6% of eyes with a prediction error greater than 0.75 D. As such, further improvement is desirable. Furthermore, this approach requires knowledge of the type of LVC treatment (hyperopic or myopic) and that a surgeon or clinic has access to enough previous data from normal eyes to optimize the constants and enough data on post LVC patients to adjust the mean prediction error with a nomogram target.

Osmolarity differences suggested that patients with previous LVC up to 15 years ago have increased risk of tear film instability. This could affect keratometry readings, which is a critical value in IOL-calculations. However, differences in repeated measurement between instruments in patients with hyperosmolar tear film and a control group suggested that the repeatability of keratometry was not affected by hyperosmolar tear film. Regardless of tear film osmolarity, the results indicated that clinically relevant errors were more likely to appear with OCT devices compared to anterior surface reflectometry. Yet, using OCT based total corneal power in special cases, like post-LVC patients, may outweigh the random errors related to measurements.

Ray tracing IOL calculations are exact and individual calculations based on accurate measurements that does not rely on a patient's history and is less dependent of empiric data. Ray tracing IOL-calculation based on data from a new OCT device yielded similar or better prediction errors compared to traditional post LVC formulas based on reflectometry data. Furthermore this method can be used an all patients. However, repeatability of both keratometry and RPE for the OCT devices suggested that the ray tracing IOL calculation should be based on an average of at least two calculations from different measurements.

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Paper 1

Brenner LF, Gjerdrum B, Aakre BM, Lundmark PO, Nistad K. **Presbyopic refractive lens exchange with trifocal intraocular lens implantation after corneal laser vision correction**: Refractive results and biometry analysis. *J Cataract Refract Surg.* 2019;45(10):1404-1415.

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Paper 2

Gjerdrum B, Gundersen KG, Lundmark PO, Potvin R, Aakre BM. **Prevalence of Signs and Symptoms of Dry Eye Disease 5 to 15 Years After Refractive Surgery**. *Clin Ophthalmol.* 2020;14:269-279.

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ORIGINAL RESEARCH

Prevalence of Signs and Symptoms of Dry Eye Disease 5 to 15 After Refractive Surgery

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Purpose: To compare the prevalence of dry eye disease (DED) as determined by signs and symptoms in patients with a history of laser vision correction (LVC) or implantable collamer lens (ICL) implantation 5–15 years ago with a matched control group with no history of refractive surgery.

Patient and Methods: This was a cross-sectional case-control study. The subject population included patients who had LVC or ICL 5 to 15 years ago. The control group was age matched. A test eye was randomly chosen. Subjects were required to have good ocular health. DED was evaluated using categorical cut-off criteria for tear film osmolarity (measured in both eyes), the subjective Ocular Surface Disease Index (OSDI), the dynamic Objective Scatter Index (OSI), non-invasive keratography tear break-up time (NIKBUT), meibography, and the Schirmer 1 test.

Results: The study included 257 subjects (94 LVC, 80 ICL, 83 control). The frequency of hyperosmolarity was significantly higher in the LVC group vs the control (73% vs 50%, p = 0.002), In contrast, the frequency of subjective symptoms tended to be lower in the LVC group than in the control group (19% vs 31%; p = 0.06). These differences were not seen between the ICL and control group.

Conclusion: The results suggest that LVC may cause tear film instability as indicated by hyperosmolar tears up to 15 years after surgery, with few subjective symptoms of dry eye. This may have implications for IOL calculations for cataract or refractive lens exchange later in life.

Keywords: tear film, hyperosmolarity, OSDI, post LVC

Introduction

Cataract surgery and RLE are common surgical procedures where the natural crystalline lens of the eye is being replaced with an artificial intraocular lens (IOL). Calculations of IOL power depend on measurements (biometry) of (at a minimum) corneal curvature and axial length of the eye, but often include anterior chamber depth and lens thickness as well. In general, the accuracy of the procedure is high in patients without prior refractive surgery. However, for patients who have previously undergone laser treatment for myopia the precision is much lower, primarily due to 2 factors: inaccurate determination of the true total corneal refractive power and incorrect estimation of the effective lens position.[1,2] Traditional optical biometers use reflections from the pre-corneal tear film to measure curvature as a part of the IOL power calculation. An uneven or unstable tear film due to dry eye may directly reduce the accuracy and repeatability of these measurements.[3]

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Dry eye disease (DED) is a common disease and clinical awareness has risen considerably around the world through the last three decades.[4] The TFOS DEWS II (Tear Film and Ocular Surface Society International Dry Eye Workshop II) report has defined dry eye as

> . . . 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.[5]

While this definition is helpful, there is a lack of standardized testing methods and criteria for categorizing dry eye. As such, reported prevalence ranges from 5% to 50% when based on signs and symptoms, and up to 75% based on signs only.[5]

Traditionally, classification has been based on consideration of the source – evaporative or aqueous deficient. The DEWS II revised classification indicates that these etiologies are overlapping.[4] In a sense, all forms of DED are evaporative, because they are all associated with tear hyperosmolarity.[6] The new DED definition emphasizes the role of homeostasis of the tear film, and diagnostic homeostasis marker tests are the minimum data set to be collected.[7] A recommended diagnostic test battery includes screening with a questionnaire, and homeostasis markers (non-invasive tear break-up time, osmolarity and staining). DED is diagnosed if the patient has symptoms and one of the homeostasis markers is positive, even without the full battery of recommended tests.[7] Further testing of tear volume and lipids/meibomian glands is recommended for subtype classification before initiating appropriate treatment.[7]

Dry eye can be caused by different iatrogenic interventions including systemic or local drugs, contact lenses, eye surgery such as corneal refractive surgery and cataract surgery.[8] Laser in situ keratomileusis (LASIK) surgery is among the most common operations performed worldwide, with more than 16 million procedures globally to 2015 and more than three million procedures in the US since 2015.[9,10] Dry eye is the most commonly reported problem following LASIK surgery.[11,12] Corneal afferent nerve fibers are severed during flap creation and stromal ablation. The nerve damage interrupts the cornea to lacrimal gland reflex arc that impairs both basal and reflex tear secretion, reduces blink rate, and causes a disruption of the neurotrophic factors released from the corneal nerves.[13] Tear osmolarity may increase as a result of decreased secretion of lacrimal gland protein, electrolyte and water secretion, and in addition a drop in the blink rate, with an increase in the evaporation of the tears.[14] Increased tear osmolarity induces ocular surface inflammation by activating stress kinases which alter the ocular surface.[14] Another mechanism associated with refractive surgery is LASIK-induced neurotrophic epitheliopathy (LINE), in which corneal staining is secondary to a reduction of blinking and a decreased release of neurotrophic factors.[14,15] Other potential contributing factors include an inflammatory response to surgery and frequent use of eyedrops with preservatives, damage to the goblet cells by suction ring induced pressure, altered tear-film stability caused by changes in corneal curvature, medication-induced effects, and even discontinued wear of eyeglasses.[14,16,17] For some patients, the sensations of dry eye could arise from spontaneous firing by the damaged or regenerating corneal peripheral nerves causing pain of neuropathic origin, or "phantom cornea".[18] Almost all patients will have transient dry eye in the postoperative period but the estimates of prevalence vary widely with 40–59% at 1 month and 10–40% at 6 months.[14,16,19,20] It is believed to resolve in most cases within the first postoperative year, but other studies have shown higher osmolarity 12 months after LASIK and that nerve regeneration may not be complete at 18 months.[14,16,18,21] The majority of articles documenting dry eye after laser vision correction (LVC) surgery include only a limited time of observation after surgery. To the best of our knowledge, there are no studies evaluating dry eye as long as 5 years or more after refractive surgery.

The implantable collamer lens (ICL; STAAR Surgical, Monrovia, CA), a posterior chamber phakic IOL (pIOL), has a history of 30 years in refractive surgery around the world.[22] The procedure can be used to correct a higher range of ametropia than LVC. Some patients may be better candidates for ICL implantation due to pupil size, dry eyes, inadequate tissue volume for LASIK, abnormal topographic shape or personal preferences for a reversible procedure.[23] While no studies specifically addressing dry eye after ICL implantation are evident in the literature, it is occasionally reported in general studies of the lens. In a study of 56 patients having ICL, two patients reported mild, and one reported moderate symptoms of dry eyes.[23] Naj et al, in a meta-analysis of 7 studies (511 eyes) comparing iris fixated pIOL and ICL, reported 1 incident of clinical significant dry eye.[24] Given the similarities of the ICL procedure to cataract or Refractive Lens Exchange

(RLE) surgery, some of the same risk factors for dry eye should exist. Cataract surgery has been shown to independently transiently induce or exacerbate dry eye; studies have shown that dry eye symptoms increase after uncomplicated phacoemulsification but generally resolve after about 3 months.[8] The signs associated with post-cataract dry eye include decrease in tear break up time, increased ocular surface staining and changes in tear volume. The presumed pathophysiological mechanisms underlying cataract surgery induced dry eye include use of topical anesthetics, exposure desiccation, possible light toxicity from the operating microscope, nerve transection, elevation of inflammatory factors, goblet cell loss, and meibomian gland dysfunction (MGD).[8] The surgical trauma may also affect corneal sensitivity, increase inflammation and contribute to tear film instability.[8]

Since data were available for the ICL patients and limited information exists in the literature on the frequency of DED in this group, we chose to include these patients in our study. ICL implantations are not associated with dry eyes or reduced precision in IOL calculations so the ICL group serves as an extra control group. The aim of this study was to compare the prevalence of DED as determined by different signs and symptoms in patients undergoing LVC or ICL 5 to 15 years ago to a similar population with no history of refractive surgery, as unstable tear film may be a confounding source of error in calculating IOL-power in post-LVC patients. Long-term observation data can add to our understanding of these sources of error in IOL calculation for post-LVC patients in particular, to determine if it needs to be given extra consideration in this population.

Patients and Methods

The study was a cross-sectional case-control study involving data from the Ifocus private eye clinic in Haugesund, Norway. Participants were recruited from patients who had undergone LVC (LASIK or Femto-LASIK) or ICL 5–15 years ago. All surgeries were performed by the same surgeon. LASIK surgeries were performed with Amadeus II microkeratome with superior hinge and 130-micron flap thickness. Femto-LASIK (1 subject) were performed with Wavelight FS 200 with superior hinge and 110-micron flap thickness. ICL surgery was performed with a temporal 2,75 mm main incision and two side ports at 60 degrees from the main incision. The anterior chamber was filled with viscoelastic, and the ICL (STAAR Surgical Company, Lake Forest, CA, USA) was implanted into the anterior chamber. The haptics were positioned behind the iris into the sulcus. Toric lenses were rotated to the planned axis. Surgical iridectomy was performed near 12 o'clock position. Viscoelastic was removed and pupil contracted using Miochol-E (Bausch &Lomb Bridgewater, NJ 08807 USA)

Patients from a population who were pre-examined or screened and found eligible for refractive surgery but who had elected not to proceed were age matched and recruited as controls. Eligible participants were identified from clinical patient records, randomly selected and consecutively recruited (by telephone, e-mail, or text message). Recruitment and data collection were performed from March 2018 to January 2019. The study followed the tenets of the Declaration of Helsinki and was approved by the Regional Committee for Medical and Health Research Ethics in Norway (Ref no 2018/75). A written informed consent was obtained.

Inclusion criteria were age over 20 years at the time of original surgery, bilaterally good ocular health, with no pathology or systemic disease involving the corneal surface, and corrected visual acuity ≥0.1 logMAR at the time of recruitment. Exclusion criteria were manifest corneal scarring, lid deformities, any acute or chronic disease or illness that would confound the results of the study, pregnancy or lactation, recent intra- or extra-ocular surgery, ICL patients who have had a subsequent corneal refractive surgery (laser touch-up), previous radial keratotomy, or other corneal surgery besides LASIK (e.g. photorefractive keratectomy (PRK), Laser-assisted subepithelial keratectomy (LASEK), transplant, lamellar keratoplasty). Patients were instructed to not wear contact lenses on the examination day and/or not to use any eyedrops for at least 2 h before the examination.

One eye was randomly selected as the test eye. Uncorrected distance visual acuity (UDVA), refraction and corrected distance visual acuity (CDVA) were tested after osmolarity and the other tests in the order described below. A timespan of at least 5 mins was given between the HD-analyzer and the Keratograph, to allow for stabilization of the tear film. If some measurements were not possible to obtain because of eye-movements, blinking or other reasons, these patients were rescheduled (if possible), and a complete new set of measurements was taken. Otherwise, the test was recorded as n/a. Visual acuity was recorded on a Snellen chart and converted to logMAR. All testing was done by one clinician (B.G.).

Tear Film Osmolarity

Tear film osmolarity was measured with the Tearlab Osmolarity System (Tearlab Corp., Escondido, California, USA) Tear film osmolarity was selected as the primary outcome measure for the study, as it is documented to have an effect on repeatability of keratometry.[3] Osmolarity was always the first test on all patients, and both eyes were measured as recommended by the manufacturer and because commonly used criteria for DED involve the osmolarity in both eyes. Testing was performed as described by the manufacturer.[25] It is suggested that a cut-off of 316 mOsm/L is best for diagnosing moderate to severe DED. Furthermore, a between-eye difference ≥8 mOsm/L is a sign of loss of tear film homeostasis.[7] As such, the cut-off criteria for categorizing hyperosmolarity in this study were the worse eye having an osmolarity of ≥316 mOsm/L or a between-eye difference ≥8 mOsm/L.

Dynamic Ocular Scatter Index (OSI)

The optical quality of the tear film was assessed with the HD Analyzer quality analysis system (OQAS) (HD analyzer, Visiometrics S.L., Terrassa, Spain). Details of the system and testing procedure are described elsewhere.[26] The dynamic Ocular Scatter Index (OSI) is recorded for a total of 20 s. For each patient measurement, the device calculates the mean OSI, the standard deviation (OSI St.d) and the difference (OSI difference) between maximum (OSI max) and minimum OSI (OSI min). The Vision Break-Up Time (VBUT) is the time in seconds (maximum 10 s) before the subject's OSI increases one unit from the minimum observed value. The changes in OSI (OSI std, OSI difference, and VBUT) are a result of tear film dynamics as other opacities in the cornea, lens or vitreous body do not change during the interblink interval.[27,28] The summary statistics for the OSI mean, OSI Standard Deviation, OSI Difference and VBUT for all patients were reported. The cut-off criteria for categorizing DED were a VBUT< 10 s.

Subjective OSDI Questionnaire

The OSDI questionnaire is a validated and widely used questionnaire for clinical trials related to the eye.[7,29] Using a total of 12 questions with a score from 0 to 4, the OSDI score is obtained by multiplying the sum by 25 and dividing by the number of questions answered. This yields a score from 0 to 100, with higher scores representing greater disability.[29] For this study, only the total score was recorded. The cut-off criteria for categorizing DED were an OSDI score ≥13.[7]

Non-Invasive Keratograph Break Up Time (NIKBUT)

NIKBUT was assessed using the Oculus Keratograph 5M (Oculus, Wetzlar, Germany). Placido rings are reflected on the corneal surface. The system detects distortion in the reflected mires which is recorded as a break in the tear film. Details of the system and testing procedure are described in the instruction manual and user guide.[30,31] The system detects the 1st break-up time and average break-up time (NIKBUT average) but only the latter was reported in this study. Based on studies of fluorescein break-up time (FBUT) and comparison between FBUT and NIKBUT, our cut-off criteria for categorizing DED were NIKBUT average ≤10 seconds.[7,32–35]

Meibography

Meibography was assessed using the meiboscan function of the Oculus Keratograph 5M (Oculus, Wetzlar, Germany). Meibography allows observation of the silhouette of the meibomian gland morphological structure.[7] Details of the system, testing procedure and grading are described in the instruction manual and user guide.[30,31] Results were recorded on a 0–3 (0.5 step) continuous scale: Grade 0 (no loss of meibomian glands), Grade 1 (0-1/3 loss), Grade 2 (1/3−2/3 loss) and grade 3 (loss >2/3). A study by Arita et al considered a summed meiboscore of upper and lower eyelid ≥3 as abnormal.[36] For this study assessment of the lower eye lid was considered sufficient.[37] Based on this our criteria for categorizing DED was a lower eyelid meiboscore of ≥1.5.

Schirmer 1

The Schirmer test was performed without anaesthesia (Schirmer 1) using a Schirmer paper strip (HUB Pharmaceuticals, Rancho Cucamonga, CA). It is a standardized test, providing an estimation of stimulated reflex tear flow.[7] Details of the testing procedure are described elsewhere.[7] The cut-off criteria for categorizing DED was ≤10 mm after 5 mins, a threshold that is commonly accepted in clinical trials.[38]

Analysis

Data were recorded on an Excel spreadsheet (Microsoft Corp., Redmond, WA, USA). The data file from the HD

Analyzer and the exported NIKBUT data from the Keratograph were transferred to the data in the spreadsheet, and cross checked. Descriptive statistics included the minimum, maximum, mean, standard deviation and the interquartile range (IQR). Statistical analysis was performed using *t*-test, ANOVA or nonparametric tests as appropriate and Pearson χ^2 test was used for comparing frequencies. Missing data were not included in the analysis. A p-value0.05 (two-sided) was considered statistically significant. Statistical analyses were performed using the RStudio data-analysis software (version 1.2.1335) RStudio Inc (Boston, MA, USA) and R Commander (version 2.60) (R Core Team, Vienna, Austria).

Post Hoc Analysis

Correlations between osmolarity and other factors known to affect dry eye (like age, sex, preoperative refraction, time of day, and season), and between minimum OSI and dynamic OSI were tested with Pearson´s correlation coefficient of determination or Spearman's rank correlation for nonparametric variables.

Results

Subject demographics and refractive error are shown in Table 1. A total of 893 patients were examined for eligibility, 661 were found eligible, but 242 could not be reached or lived too far away. Of the remaining 419 patients, 96(74%), 80(85%) and 85(67%) were recruited in the LVC, ICL and control group, respectively. One patient was excluded because of possible systemic disease, two were excluded because of LVC surgery less than five years ago, and one was excluded because of lactation. A total of 257 patients were included in the study: 94 (45 females, 49 males) in the LVC group, 80 (57 females, 23 males) in the ICL group and 83 (41 females, 42 males)

Table 1 Demographics, Pre- and Postoperative Refraction and Visual Acuity

		LVC, n=94	ICL, n=80	CTRL, n=83	p
		Mean ± SD (Range)	**Mean ± SD (Range)**	**Mean ± SD (Range)**	
Sex: f %		47.9%	71.2%	49,4%	0.003 [a]*
Age, years		41.3 ± 6.3 (29 to 57)	40.8 ± 8.8 (25 to 64)	41.2 ± 8.1 (23 to 56)	0.905[b]
Years since treatment		7.7 ± 1.3 (5.2 to 12.8)	10.2 ± 3.1 (5.0 to 14.7)		<0.001[c]
Pre-Tx	MRSE, DS	−2.76 ± 1.75 (−8.00 to +2.37)	−6.10 ± 5.16 (−17.12 to +8.00)	−1.38 ± 3.45 (−9.37 to +6.87)	<0.001[d]*
	CYL, DC	−0.94 ± 0.88 (−3.50 to 0)	−1.40 ± 1.43 (−8.75 to 0)	−0.87 ± 1.20 (−7.00–0)	0.001[e]*
	BCVA, (logMAR)	−0.05 ± 0.04 (−0.18 to 0.05)	0.00 ± 0.07 (−0.18 to 0.3)	−0.06 ± 0.07 (−0.18 to 0.10)	<0.001[e]*
Post-Tx	MRSE	−0.07 ± 0.38 (−2.37 to +0.75)	−0.19+0.59 (−2.25 to +1.50)		0.017[f]*
	CYL	−0.19 ± 0.25 (−1.0 to 0)	−0.38 ± 0.38 (−1.50 to 0)		<0.001[f]*
	UCVA (logMAR)	−0.03 ± 0.12 (−0.18 to 0.70)	0.06 ± 0.16 (−0.18 to 0.7)		<0.001[f]*
	BCVA (logMAR)	−0.07 ± 0.05 (−0.18 to 0.02)	−0.03 ± 0.06 (−0.18 to 0.10)		<0.001[f]*

Notes: [a]Pearson´s χ^2 test ICL difference from CTRL, [b]Anova (unequal variance), [c]Wilcoxon rank-sum test between ICL/LVC, [d]Kruskal–Wallis rank-sum test, [e]Wilcoxon rank-sum test difference between ICL and CTRL, [f]Wilcoxon rank-sum test, *Statistically significant.

Abbreviations: LVC, Laser Vision Correction; ICL, Implantable Collamer Lens; CTRL, Control group; MRSE, mean spherical equivalent refraction; CYL, refractive cylinder; BCVA, best-corrected visual acuity (logMAR); UCVA, uncorrected visual acuity (logMAR); Pre-Tx, historic data before surgery; Post-Tx, post-treatment data (study examination).

in the control group. The ICL group had significantly more females vs the control group and significantly longer time since surgery vs the LVC group. There were significant differences in preoperative refraction between groups.

Table 2 summarizes the mean values of the various testing results. None of the tests showed significant differences in mean values except for the OSI measures. The OSI measures were significantly higher in the ICL group compared to the control group. However, the minimum OSI was significantly correlated to OSI Standard Deviation, OSI Difference, and VBUT (Spearman´s Rho: 0.43, 0.45 and −0,33, respectively, $p<0.01$) for all subjects.

When results were categorized according to the cut-off criteria described in the methods (Table 3), the frequency of hyperosmolarity was significantly higher in the LVC group vs the control group (73% vs 50%), but not significantly different between the ICL and control group (Figure 1). The frequency of VBUT≤10 s was significantly higher in the ICL group vs the control group (33% vs 17%). No other single objective tests or combination of criteria showed any significant difference between LVC or ICL and the control group. The frequency of OSDI ≥13 tended to be lower in the LVC group relative to the control (19% vs 31%); this was not statistically significant ($p = 0.06$). The frequency of OSDI ≥13 in the ICL group was the same as the control (31%).

We could not establish any significant correlation between osmolarity and any of the other single DED tests. However, the frequency of hyperosmolarity was significantly higher in patients with two or more other indicators of DED (66% vs 52% mOsm/L, $p=0.03$).

There was no significant correlation between osmolarity and pre-operative mean spherical equivalent refraction (pre-MRSE) for the LVC group alone. Stepwise multivariate analysis including all patients tended towards a positive correlation between osmolarity and age and pre-MRSE (Pearson´s R^2 =0.08, $p < 0.01$ and 0.03, respectively). While significant, these correlations are weak. An example of this is shown in Figure 2; it can be seen that several outliers are influencing the fit. The single eye osmolarity cut-off value of 316 mOsm/L is shown for reference.

Discussion

The main objective was to compare the prevalence of DED as determined by different signs and symptoms in patients with previous refractive surgery to a control group, because this may affect keratometry measurement and therefore IOL calculation at the time of cataract surgery. Epitropoulos et al compared repeatability of keratometry in a hyperosmolar and a normal group. In the hyperosmolar group, 8% had a difference of more than 0.50 D, and 5% had a difference of more than 1 D while all subjects had less than 0.5 D in the normal group.[3] For a patient with previous myopic LVC, a difference in keratometry of 1D could give approximately 0.8 D to 1.2 D difference in refractive outcome when using post-LVC IOL calculation formulas.[39] The contribution of errors from tear-film instability could be relatively small when compared to sources of error like keratometric index error and incorrect estimate of the effective lens position. However, these errors are attempted solved in the post-LVC IOL formulas. While average prediction error for several Post-LVC formulas are within ± 0.5, it could range from +1D to −2D.[40,41] Arguably, in the cases with highest prediction errors, several factors probably contribute, like diameter error, actual IOL position, and erroneous keratometric measurement due to unstable tear film may be another. Therefore, it is interesting to know if previous LVC patients have higher risk of unstable tear film than patients without prior refractive surgery.

Although not shown in mean osmolarity of the test eye, when using cut-off values as described, we found that the prevalence hyperosmolarity was significantly higher in the LVC group vs the control group and the ICL group. This is likely a consequence of the fact that both intra- and inter-eye variability of osmolarity is a hallmark of DED.[42] The prevalence of DED in both the LVC group and the control group was relatively high compared to some other studies. One study reported osmolarity greater than 308mOsm/L in 30% at 12 months after LASIK.[21]

De Paiva et al found that dry eye was associated with preoperative myopia and ablation depth at 6 months after surgery, possibly because of nerves needing to regenerate a longer distance in the case of deeper ablation depth.[20] We did not find correlation between pre-MRSE and Osmolarity in the LVC group. This difference may be explained in that our subjects had 5 years or more since surgery and differences in regeneration due to ablation depth have been leveled out. A meta-analysis by Feng et al found significantly higher tear-BUT, less loss of sensation and less corneal staining in patients with horizontal hinge flap compared to superior hinge flaps, but all our patient had nasal hinge except for one Femto-LASIK patient.[16]

A meta-analysis in the DEWS II epidemiology report found prevalence of DED in the general population varying from 14% to 39% based on symptoms, and 16% to 86% based

Table 2 Mean Values and Standard Deviation of Different DED Tests (Test Eye)

	LVC		ICL		CTRL		p
	Mean ± SD (Range, IQR)	**n**	**Mean ± SD (Range, IQR)**	**n**	**Mean ± SD (Range, IQR)**	**n**	
Osmolarity test eye (mOsm/L)	311 ± 17 (281 to 383, 16)	92	305.9 ± 11 (282 to 330, 12)	80	309.7 ± 14 (290 to 370, 14)	82	0.183[a]
OSI Minimum OSI St.d OSI Difference VBUT	1.1 ± 0.6 (0.2 to 3.8, 0.7) 0.4 ± 0.4 (0.0 to 1.8, 0.4) 1.4 ± 1.3 (0.1 to 5.5, 1.5) 9.1 ± 2.5 (0.5 to 10.0, 0)	93	1.6 ± 1.1 (0.4 to 7.6,1.1) 0.4 ± 0.5 (0.0 to 2.2, 0.5) 1.8 ± 1.8 (0.2 to 9.0, 2.0) 8.4 ± 3.2 (0.5 to 10.0, 1.75)	79	1.2 ± 0.6 (0.3 to 3.2, 0.7) 0.2 ± 0.3 (0.0 to 2.0, 0.2) 1.1 ± 1.1 (0.1 to 6.9, 1.0) 9.1 ± 2.2 (1.0 to 10.0, 0)	81	<0.001[b]* 0.002[b]* 0.003[b]* 0.054[a]
OSDI	10 ± 13 (0 to 67, 8)	94	11 ± 12 (0 to 65, 15)	80	10.9 ± 10.5 (0 to 50, 14)	83	0.438
NIKBUT avg. (seconds)	17.1 ± 5.6 (4.9 to 25.0, 9.0)	91	16.8 ± 5.6 (4.5 to 25, 9.2)	77	16.8 ± 6.0 (4.7 to 25.0, 9.8)	80	0.921
Meibography (Meiboscore)	0.5 ± 0.7 (0.0 to 3.0, 0.7)	94	0.3 ± 0.5 (0.0 to 2.2, 0.4)	78	0.4 ± 0.7 (0.0 to 3.0, 0.5)	80	0.300
Schirmer 1 (mm)	13 ± 9 0 to 35, 12	94	14 ± 11 0 to 35, 15.0	76	15 ± 11 (0 to 35, 20)	82	0.968

Notes: [a]Kruskal–Wallis rank-sum test. [b]Wilcoxon rank-sum between ICL and CTR, *Statistically significant.

Abbreviations: SD, standard deviation; IQR, Interquartile range; LVC, Laser Vision Correction; ICL, Implantable Collamer Lens; CTRL, Control group; OSDI, Ocular Surface Disease Index; NIKBUT, non-invasive keratograph break-up time; OSI, Ocular scatter index; OSI mean, mean OSI for each patient; OSI St.d =standard deviation of OSI for each patient; VBUT (Vision break-up time), the time before an increase in OSI of 1 unit due to tear break-up.

Table 3 Prevalence of DED as Determined by Signs and Symptoms

Treatment group	LVC			ICL			CTRL	
Test variable (Cut-off values)	**%**	**n**	**p[a]**	**%**	**n**	**p[a]**	**%**	**n**
Osmolarity (≥316 either eye or ≥8 inter-eye diff.)	73.3%	90	0.002*	46.2%	80	0.63	50%	82
VBUT (≤10 seconds)	24.7%	93	0.23	32,9%	79	0.02*	17,3%	81
OSDI (≥13)	19.1%	94	0.06	31.2%	80	.99	31.3%	83
NIKBUT avg (≤10 seconds)	12.1%	91	0.32	15.6%	77	0.75	17.5%	80
Meibography (meiboscore ≥1.5)	10.6%	94	0.68	5.1%	78	0.37	8.8%	80
Schirmer (mm wetting ≤10mm)	51.1%	94	0.76	48.7%	76	0.99	48.8%	82
OSDI and one other indicator	18.1%	94	0.55	27,5%	80	0.39	21.7%	83

Notes: [a]Pearson's χ^2: difference from control. *Statistically significant.
Abbreviations: LVC, Laser Vision Correction; ICL, Implantable Collamer Lens; CTRL, Control group; OSDI, Ocular Surface Disease Index; NIKBUT avg, average non-invasive keratograph break-up time; VBUT, HD analyzer Vision break up time.

on signs.[43] Gupta et al found abnormal osmolarity (>307mOsm/L in either eye or an inter-eye difference >7mOsm/L) in 57% of 120 patients (including 25 patients with previous refractive surgery) presenting for cataract surgery.[44]

The relative high prevalence of DED in all groups could possibly be related to the fact that many patients who have problems with contact lenses due to dry eyes consider refractive surgery as a solution, and up to 73% of LVC patients have been reported to seek surgery because of difficulties with contact lens wear.[14,45] There are several risk factors for developing dry eye after LASIK, with pre-existing dry eye being the most significant.[14,46] Konomi et al suggested that lower preoperative tear volume may increase the risk of chronic dry eye.[47] In addition, age is a risk factor for DED and the LVC and ICL groups in this study were on average 8 and 10 years older, respectively, than at time of their surgery.[6]

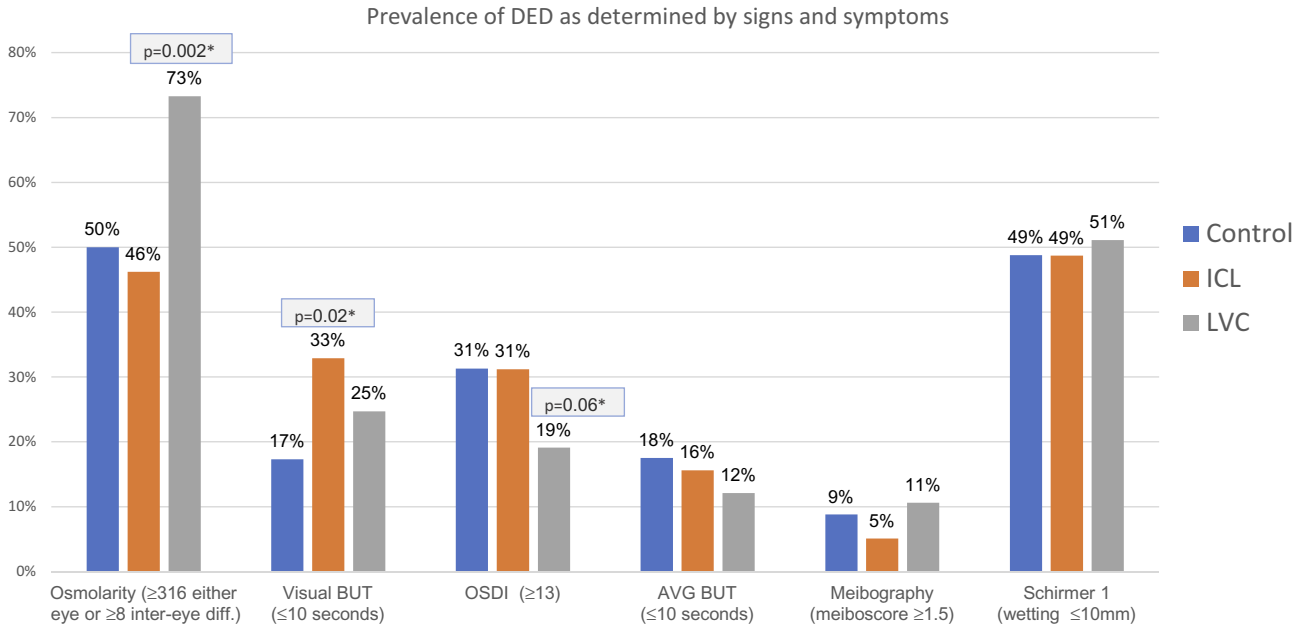

Figure 1 Comparing the prevalence of DED as determined by different tests between LVC or ICL and control group.
Notes: *Pearson's χ^2: difference from control group.
Abbreviations: BUT, Break-up time; OSDI, ocular surface disease index; AVG, average; ICL, Implantable collamer lens; LVC, laser vision correction.

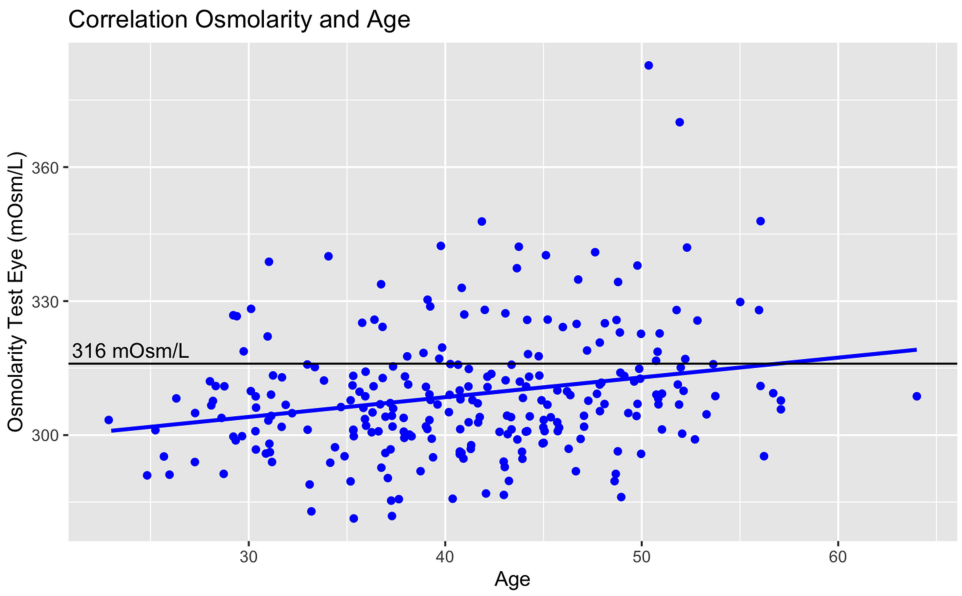

Figure 2 Example of weak correlations, here between osmolarity and age. Several outliers are influencing the fit. The single eye osmolarity cut-off value of 316 mOsm/L is shown for reference.

The mean of the dynamic OSI measures was significantly higher in the ICL group, but these measures were correlated to the minimum OSI (before tear film changes). The introduction of a pIOL into an optical system could reduce the optical quality of the system significantly,[48] so the increased OSI values in the ICL group may be a result of reduced optical quality. The device software normalizes measurement to compensate for different levels of scatter, but this might not be sufficient in the case of a pIOL.

There was a tendency for fewer subjective symptoms in the LVC group. Studies have shown that subjective and objective symptoms may not agree due to differences in age, tolerance, environment and even long-standing dry eye which can reduce sensitivity.[3,43] In post-LASIK patients, it may be that reduced symptoms are due to reduced sensitivity. A review report by Shtein found that studies of nerve morphology have shown reduced density 3–5 year after surgery.[49] This strengthens the hypothesis that LASIK surgery can induce and even mask dry eye permanently due to incomplete nerve regeneration. In consequence, the recommendation in the DEWS II report on diagnosing DED by subjective symptoms and one homeostasis marker may not be optimal for post-LVC patients.[7]

We could not establish a significant correlation between osmolarity and other single dry eye tests. The lack of correlation between different diagnostic tests is likely a consequence of the multi-factorial nature of DED and the fact that different diagnostic tests reveal different aspects of the disease.[50,51] However, we did find that patients with two or more other indicators of DED showed a significant higher frequency of hyperosmolarity. Classification of dry eyes is usually based on several tests, but tear osmolarity has been shown to be the best single metric both to diagnose and classify DED and evidence indicates that tear hyperosmolarity contributes to, and is representative of, the mechanisms involved in the development and progression of DED.[42,51] In a review report by Potvin et al they found that a majority of the studies reviewed supported the use of tear osmolarity as a tool of diagnosis and severity grading.[50]

There are some limitations to the study. There was a risk of selection bias as patients were informed about the study on recruitment and patients with symptoms may have been more interested in participating, but the proportion of patients who agreed to participate was high and the subjective symptom score was low. Factors such as systemic or topical drugs and occupation should be the same across groups, but where not controlled and might have influenced our findings. There were significantly more females in the ICL group, though there was no correlation between sex and osmolarity. Also, there were significant differences in pre-MRSE, but only weak correlation between pre-MRSE and osmolarity. The study included patients with a large span of years since surgery and there were significant differences in this time span between groups, but there was no correlation between years since surgery and osmolarity. In addition, the first

surgeries were as long as 15 years ago and surgical techniques may have changed, which might have influenced our findings relative to those that are more recent. Our study included only LASIK and Femto-LASIK surgeries, so we did not address whether LASEK or PRK affects dry eye.

Conclusion

Osmolarity differences suggested a significantly higher prevalence of DED in patients who underwent LVC 5 to 15 years ago than in a matched control group, though the LVC group had fewer subjective symptoms. The recommendation in the DEWS II report on diagnosing DED by subjective symptoms and one homeostasis marker may not be optimal for post-LVC patients. Hyperosmolarity increases the risk for tear film instability which is likely to be a confounding source of error for post-LVC IOL calculations. Further studies of post-LVC tear film quality are advocated. For instance, of interest is the potential effect of reduced tear quality on repeatability of measurements with different types of keratometers.

Disclosure

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Paper 3

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ORIGINAL RESEARCH

Repeatability of OCT-Based versus Scheimpflug- and Reflection-Based Keratometry in Patients with Hyperosmolar and Normal Tear Film

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Purpose: To compare the repeatability of keratometry between different instruments in patients with hyperosmolar tear film and a control group.

Patients and Methods: Subjects with tear-film osmolarity of 316 mOsm/L or more in either eye or 308 m/Osm/L or lower in both eyes were assigned to the hyperosmolar and the control group, respectively. The test eye was the eye with higher osmolarity in the hyperosmolar group and randomly chosen in the control group. The repeatability of keratometry was compared between a reflectometry device (Haag-Streit Lenstar 900), a Scheimpflug device (Oculus Pentacam HR) and two optical coherence tomography (OCT) devices (Tomey Casia SS-1000 and Heidelberg Anterion), based on two measurements from each device.

Results: The study included 94 subjects (31 hyperosmolar and 63 controls). Both OCT devices had higher mean differences of average simulated keratometry (SimK) vs the Lenstar in both groups, though all differences in means were <0.07 D. The Casia had the highest mean vector difference of SimK astigmatism in the control group (differences in means <0.11 D). These differences of the instruments were statistically significant ($p < 0.02$), except for the Anterion in the control group. With all subjects, the coefficient of repeatability varied from 0.1 to 0.3 for average SimK (highest for both OCT devices) and from 0.4 to 0.7 for SimK astigmatism (highest for the Casia). Similar results were found for total corneal power (OCT devices compared to the Pentacam).

Conclusion: Both OCT devices show more variability in average SimK and the Casia more variability in SimK astigmatism compared to the Lenstar and the Pentacam. However, the results suggested that repeatability was not influenced by osmolarity.

Keywords: reflectometry, Scheimpflug, OCT, repeatability, hyperosmolarity, Placido rings

Introduction

In cataract surgery and refractive lens exchange planning, calculations of intraocular lens (IOL) power depend on biometry: the measurement of corneal curvature, the axial length of the eye, and often the anterior chamber depth and lens thickness. In patients without prior refractive surgery the accuracy of the procedure is high. However, for patients who have previously undergone laser vision correction (LVC) the precision is much lower, primarily due to three factors: inaccurate determination of the true total corneal refractive power, incorrect estimation of the effective lens position, and incorrectly estimated central corneal power from paracentral measurements.[1–4] Other factors such as corneal thickness and actual postoperative IOL position could also contribute. Traditional optical biometers rely

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on good reflections of mires from the precorneal tear film to measure the corneal curvature. Studies have shown that an uneven or unstable tear film can produce optical aberrations, which may directly reduce the accuracy and repeatability of these measurements.[5,6] Therefore, erroneous keratometric measurement due to unstable tear film may be an additional confounding factor in post-LVC IOL power calculations. Observation data can help us understand these sources of error and determine if it needs to be given extra consideration in IOL calculation for post-LVC patients in particular.

Dry eye disease (DED) is a common disease which affects hundreds of millions of people. The classification of dry eye is usually based on several diagnostic tests, but tear osmolarity has been suggested to be the best single metric both to diagnose and classify DED and evidence indicates that tear hyperosmolarity both contributes to, and is representative of, the mechanisms involved in the development and progression of DED.[7,8] A majority of the studies in a review report supported the use of tear osmolarity as a tool for diagnosis and severity grading, and Sullivan et al found tear-film osmolarity to be the single best marker of disease severity across normal, mild/moderate, and severe DED categories.[9,10] A cutoff of 316 mOsm/L is considered best for diagnosing moderate to severe DED, while a cutoff of 308 mOsm/L is a sensitive threshold for diagnosing mild to moderate DED.[11,12]

Dry eye is the most commonly reported problem following laser in-situ keratomileusis (LASIK) surgery.[13,14] Corneal afferent nerve fibers are severed, and tear osmolarity may increase as a result of decreased secretion of lacrimal gland protein and water, or as a result of a reduced blink rate, with a corresponding increase in the evaporation of the tears.[15] In a recent study, the prevalence of hyperosmolarity in a group of patients with a history of LASIK 5– 15 years earlier was found to be statistically significantly higher than in a matched control group.[16]

Traditional reflection-based keratometry measures the corneal front surface only. The corneal power is then calculated using an assumed refractive index to include the contribution of the back surface.[17] Other devices, like those based on Scheimpflug imaging or optical coherence tomography (OCT), do not use reflections but tomographic images, and may be less dependent on tear-film quality.

A Scheimpflug device can provide a tomographic image of the anterior and the posterior corneal surfaces, as well as the anterior chamber and lens.[18] One limitation of Scheimpflug imaging is the low resolution and poor quality of the anterior segment scans.[19] OCT is a high-speed, high-resolution, noncontact optical imaging technique for noninvasive cross-sectional imaging of biologic systems.[20] Recent OCT systems have been designed to capture the anterior segment or even the full eye.[21,22] Spectral-domain and swept-source (SS) OCT are variations of Fourier-domain OCT, with the latter offering better visualization of structures and increased scanning speed.[23] Both combined anterior/posterior and dedicated anterior segment (AS) systems are available for anterior segment assessment. While combined systems offer lower price and higher resolution due to shorter wavelength of light, the lack of collimated light at the cornea makes the measurements distance-dependent.[24] Dedicated AS systems offers better tissue penetration and imaging depth due to of higher wavelength of light, and also larger measurement diameter.[24,25]

The aim of this study was to compare the repeatability of keratometry between different instruments in patients with a hyperosmolar tear film and a control group of patients with a normal tear film. Our hypothesis was that keratometers that do not rely on reflections from the precorneal tear film would be less dependent on tear-film quality than traditional reflection-based keratometers.

Patients and Methods

This study was a cross-sectional case-control study involving data from a private eye clinic in Haugesund, Norway. Participants were primarily recruited from a population of participants in another clinical study which included measurement of tear-film osmolarity. Patients who had tear-film osmolarity measured during an eye examination were also considered. Recruitment and data collection were performed from May 2019 to March 2020. The study followed the tenets of the Declaration of Helsinki and was approved by the Regional Committee for Medical and Health Research Ethics in Norway (Ref no. 2018/1526). A written informed consent was obtained.

Inclusion criteria were tear-film osmolarity of 316 mOsm/L or higher in either eye (hyperosmolar group) or 308 mOsm/L or lower in both eyes (control group), bilaterally good ocular health, with no pathology or systemic disease involving the corneal surface. Exclusion criteria included ectatic disease, manifest corneal scarring, lid deformities, and any acute or chronic disease or illness that would confound the results of the study. Patients were instructed to not wear contact lenses on the

examination day and not to use any eye drops for at least two hours before examination. Tear-film osmolarity was measured with the Tearlab® Osmolarity System (Tearlab Corp., Escondido, CA, USA). This was always the first test on all patients, and both eyes were measured as recommended by the manufacturer. One eye of each subject was included in the analysis. In the hyperosmolar group, the eye with the higher osmolarity was chosen as a test eye and in the control group the test eye was randomly chosen. Three instruments were used to measure the biometry of all subjects: a low-coherence reflectometry biometer (Lenstar 900®, Haag-Streit AG, Koeniz, Switzerland), a rotating Scheimpflug camera tomographer (Pentacam® HR, Oculus, Wetzlar, Germany), and an AS SS OCT (Casia SS-1000, Tomey Corporation, Nagoya, Japan). A new AS SS OCT (Anterion®, Heidelberg Engineering GmbH, Heidelberg, Germany) was available for 48 subjects (from December 2019), and analyzed with corresponding data for the other instruments.

The instrument order was randomly chosen. Keratometry was measured twice in both eyes with each instrument. To allow for stabilization of the tear film, a timespan minimum of 1 minute was taken between each measurement with the same instrument and a minimum of 5 minutes was taken between different instruments. Patients were instructed to blink normally between measurements, and to keep both eyes open during the measurement. With all instruments except the Lenstar, the measurement was done in a single pass acquisition. With the Lenstar each measurement was a composite of five separate acquisitions. All instruments except the Casia provided a quality check of the acquisition. If indicated, the acquisition was repeated once or twice as necessary, and the better one used for the calculations. All measurements were done by one clinician (B.G.).

The data from the measurements were extracted from instrument-generated tables or pdf files to an Excel spreadsheet (Microsoft Corp., Redmond, WA, USA), and then imported to a Filemaker Pro database (Claris International Inc., Santa Clara, CA, USA) for data checking, collation, and preliminary analysis. For each measurement in each eye, the mean K reading and the keratometric astigmatism were calculated.

Keratometry and Corneal Power (K)

To compare the repeatability of each instrument, the difference in the average K value (average of keratometry or corneal power in two meridians) between two measurements was calculated, as was the magnitude of the vector difference between the two astigmatism values. Vector differences include differences in both the magnitude and axis of corneal astigmatism. All instruments provided simulated keratometry (SimK) based on the anterior curvature and a fictitious refractive index of 1.3375. The Pentacam, Casia, and Anterion devices also provided posterior corneal power (PCP) and total corneal power (TCP) readings based on the refractive indices of 1.376 for the cornea and 1.336 for the aqueous humour. The value for TCP was calculated differently for the three instruments: the Pentacam True Net Power is the sum of the anterior and posterior surface, the Casia Real K is the sum of the anterior and posterior surface with cornea thickness correction, and the Anterion Total Corneal Power is calculated using ray-tracing.[26–28] The differences in SimK were defined as the primary outcome, as this is the only K value provided by the reflectometry device. However, comparison of PCP and TCP differences between the Scheimpflug and the two OCT devices in the two groups is of interest as TCP can be useful in IOL power calculations. The study did not assess the agreement between instruments, so no conclusion about interchangeability of K-values could be drawn.

Sample Size

The sample size calculation was based on the mean differences in the SimK readings between two measurements. With an expected SD of 0.1 D for average K and 0.2 D for astigmatism we wanted to be able to reliably detect if the mean difference between two measurements of each instrument was of at least 0.1 D for the average K and 0.2 D for the vector difference. Using an alpha of 0.05 and a power of 0.8 the power analyses revealed that we would need 17 subjects in each group.

Analysis

Descriptive statistics included the minimum, maximum, mean, and standard deviation of all measurements and calculated values. Statistical analysis was performed using the *t*-test, analysis of variance (ANOVA) or non-parametric tests as appropriate. *p*-Values for the comparison of SimK differences (primary outcome) were adjusted with the Holm–Bonferroni method for multiple comparisons.[29,30] Pearson's X^2 test and Fisher exact test were used for comparing frequencies. The coefficient of repeatability (CR) is the value below which the absolute differences between two measurements would lie with

Table 1 Demographics, Osmolarity and Keratometry by Osmolarity Group

	Hyperosmolar, *n* = 31	**Control, *n* = 63**	***p***
	Mean ± SD (Range)	**Mean ± SD (Range)**	
Sex, f	48.4%	54.0%	0.77[a]
Age	44.7 ± 8.4 (30 to 68)	42.4 ± 8.3 (27–62)	0.04[b,*]
Previous LVC	38.7%	31.7%	0.66[a]
Osmolarity	326 ± 12 (316 to 365)	298 ± 7 (281–308)	<0.01[b,*]
Average SimK[c] (D)	42.39 ± 2.14 (36.24 to 46.53)	43.01 ± 1.93 (38.25–47.49)	0.02[b,*]
SimK Astigmatism[c,d] (D)	1.06 ± 0.65 (0.12 to 3.35)	1.3 ± 1.1 (0.02–6.38)	0.23[b]

Notes: [a]Pearson's χ^2 test. [b]Wilcoxon rank-sum test. [c]Mean of all instruments. [d]Magnitude of astigmatism. *Statistically significant.
Abbreviations: LVC, laser vision correction; SimK, simulated keratometry.

95% probability.[31] The CR was calculated as the within-subject standard deviation multiplied by 2.77.[31,32] The within-subject standard deviation was calculated as the square root of half the mean of the squared differences between two measurements.[31]

Subject variances and instrument test order could possibly influence the results, as could the altered central corneal curvature of patients with previous LVC. To control for this, linear mixed-effects analyses with "osmolarity group," "instrument," and "previous LVC" as fixed effects and "subject" and "instrument order" as random effects were performed for each outcome variable. *p*-Values were obtained by likelihood ratio tests of (a) the full model with the effect in question against (b) the model without the effect in question. "Subject" was kept as a random effect in all models.

Statistical analyses were performed using the RStudio data-analysis software (version 1.2.1335, RStudio Inc, Boston, MA, USA) and the lme4 and the ggplot2 packages.[33,34] A p-value ≤ 0.05 (two-sided) was considered statistically significant.

Post-Hoc Testing

Differences in repeatability between instruments for all subjects were analyzed using the *t*-test or nonparametric tests as appropriate. *p*-Values for the comparison of SimK differences (primary outcome) were adjusted with the Holm–Bonferroni method for multiple comparisons. CR was compared between instruments.

Results

Of 104 subjects who agreed to participate, 10 subjects were excluded because of tear-film osmolarity outside the inclusion criteria. The study included 94 subjects: 31 (15 females, 16 males) in the hyperosmolar group and 63 (34 females, 29 males) in the control group (Table 1). Some measurements were missing due to technical problems (seven and two subjects with the Pentacam and the Lenstar, respectively) and two were missed because the wrong eye was measured (one subject with the Pentacam and one with the Casia).

Keratometry and Corneal Power Differences

Average K

Both the Casia and the Anterion devices had statistically significantly higher mean differences of average SimK compared to the Lenstar in the hyperosmolar group (0.08 D and 0.11 D vs 0.04 D, respectively). Also, in the control group the Casia and the Anterion had higher means relative to the Lenstar (0.10 D and 0.10 D vs 0.06 D, respectively), but this was statistically significant only for the Casia (Table 2A and Figure 1A).

Both the Casia and the Anterion had a statistically significantly higher mean difference of average TCP versus the Pentacam in the hyperosmolar group (0.09 D and 0.12 D vs 0.06 D, respectively). In the control group, the Casia and the Anterion had higher mean difference of average TCP versus the Pentacam (0.10 D and 0.12 D vs 0.07 D, respectively), but again the mean difference was statistically significant only for the Casia (Table 2A and Figure 1A).

Both OCT devices had statistically significantly lower mean differences of average PCP compared to the Pentacam in both groups but all the differences in means were <0.02D (Table 2A and Figure 1B).

In the control group, the Anterion had significantly more subjects with average TCP difference greater than 0.25 D compared to the Lenstar [4 of 32 (12%) vs 0 of 58] (Figure 2A).

Table 2 Mean Absolute Difference and Standard Deviation Between Repeated Measurements of (A) Average K and (B) Astigmatism

	Hyperosmolar Group				**Control Group**			
A Average K absolute difference (D)	Lenstar *n* = 31	Pentacam *n* = 28	Casia *n* = 31	Anterion *n* = 16	Lenstar *n* = 61	Pentacam *n* = 58	Casia *n* = 62	Anterion *n* = 32
	Mean ± SD (Range) *p* (p_{adj})	Mean ± SD (Range) *p* (p_{adj})	Mean ± SD (Range) *p* (p_{adj})	Mean ± SD (Range) *p* (p_{adj})	Mean ± SD (Range)	Mean ± SD (Range) *p* (p_{adj})	Mean ± SD (Range) *p* (p_{adj})	Mean ± SD (Range) *p* (p_{adj})
Average SimK	0.04 ± 0.03 (0–0.11)	0.04 ± 0.04 (0–0.11) 0.89[a] (1[a])	0.08 ± 0.06 (0–0.14) 0.001[a] (0.011[a,*])	0.11 ± 0.08 (0– 0.28) 0.004[a] (0.032[a,*])	0.06 ± 0.06 (0–0.23)	0.05 ± 0.06 (0– 0.20) 0.85[a] (1[a])	0.10 ± 0.10 (0– 0.56) 0.002[a] (0.020[a,*])	0.10 ± 0.09 (0– 0.39) 0.026[a] (0.210[a])
Average PCP		0.022 ± 0.016 (0.001–0.063)	0.008 ± 0.009 (0– 0.045) 0.002[b,*]	0.006 ± 0.004 (0– 0.011) 0.001[b,*]		0.013 ± 0.011 (0 – 0.056)	0.009 ± 0.011 (0– 0.083) 0.006[b,*]	0.004 ± 0.005 (0– 0.017) <0.001[b,*]
Average TCP		0.06 ± 0.04 (0–0.15)	0.09 ± 0.07 (0– 0.28) 0.03[b,*]	0.12 ± 0.09 (0– 0.32) 0.04[b,*]		0.07 ± 0.06 (0– 0.25)	0.10 ± 0.11 (0– 0.60) 0.015[b,*]	0.12 ± 0.10 (0– 0.42) 0.08[b]
B Astigmatism vector difference (D)								
SimK Astigmatism	0.16 ± 0.12 (0.01–0.52)	0.14 ± 0.08 (0.01– 0.34) 0.52[a] (1[a])	0.21 ± 0.14 (0.01– 0.61) 0.12[a] (0.84[a])	0.17 ± 0.10 (0.05– 0.38) 0.46[a] (1[a])	0.19 ± 0.15 (0–0.76)	0.18 ± 0.11 (0– 0.60) 0.674[a] (1[a])	0.29 ± 0.23 (0–1.55) <0.001[a] (0.006[a,*])	0.18 ± 0.11 (0–0.41) 0.442[a] (1[a])
PCP Astigmatism		0.060 ± 0.04 (0.011– 0.189)	0.033 ± 0.019 (0.007– 0.076) 0.03[b,*]	0.021 ± 0.009 (0.009– 0.037) 0.006[b,*]		0.049 ± 0.028 (0.01- 0.117)	0.037 ± 0.047 (0.01– 0.367) <0.001[b,*]	0.021 ± 0.013 (0– 0.049) <0.001[b,*]
TCP Astigmatism		0.17 ± 0.08 (0.04– 0.36)	0.22 ± 0.15 (0.03– 0.63) 0.45[b]	0.18 ± 0.11 (0.06– 0.38) 0.78[b]		0.18 ± 0.12 (0.01– 0.79)	0.31 ± 0.25 (0.06– 1.77) 0.007[b,*]	0.19 ± 0.11 (0– 0.40) 0.769

Notes: [a]Wilcoxon signed-rank test comparison with the Lenstar; [b]Wilcoxon signed-rank test comparison with the Pentacam. *Statistically significant.
Abbreviations: K, keratometry or corneal power; SD, standard deviation; SimK, simulated keratometry; PCP, posterior corneal power; TCP, total corneal power; Average, difference in average K; Astigmatism, magnitude of vector difference of astigmatism; p_{adj}, Holm–Bonferroni adjusted *p*-value for 12 comparisons (Sim K average and astigmatism).

Vector Astigmatism

The only statistically significant difference in SimK and TCP vector differences was found in the control group; the Casia had a significantly higher vector difference for SimK compared to the Lenstar (0.29 D vs 0.19 D, respectively) and for TCP compared to the Pentacam (0.31 D vs 0.18 D, respectively) (Table 2B and Figure 3A). The Casia and the Anterion had a statistically significantly lower PCP vector difference compared to the Pentacam in both groups, but all differences in means between instrument were less than 0.04 D (Table 2B and Figure 3B).

Figure 2B shows the percentage of subjects with vector differences of SimK or TCP greater than 0.5 D and vector differences in PCP greater than 0.1 D. In the hyperosmolar group, both the Casia and the Anterion had fewer subjects (0 of 31 and 0 of 16) with a PCP vector astigmatism difference greater than 0.1 D compared to the Pentacam [5 of 28 (18%)], but this was statistically significant only for the Casia.

Linear Mixed-Effect Models

The model was designed with "Osmolarity group," "instrument," and "previous LVC" as fixed effects and "subject" and "instrument order" as random effects. Likelihood ratio tests were used to compare the full model to a model with one effect removed. If not significantly different, the simpler model was kept and compared to a new model without another effect.

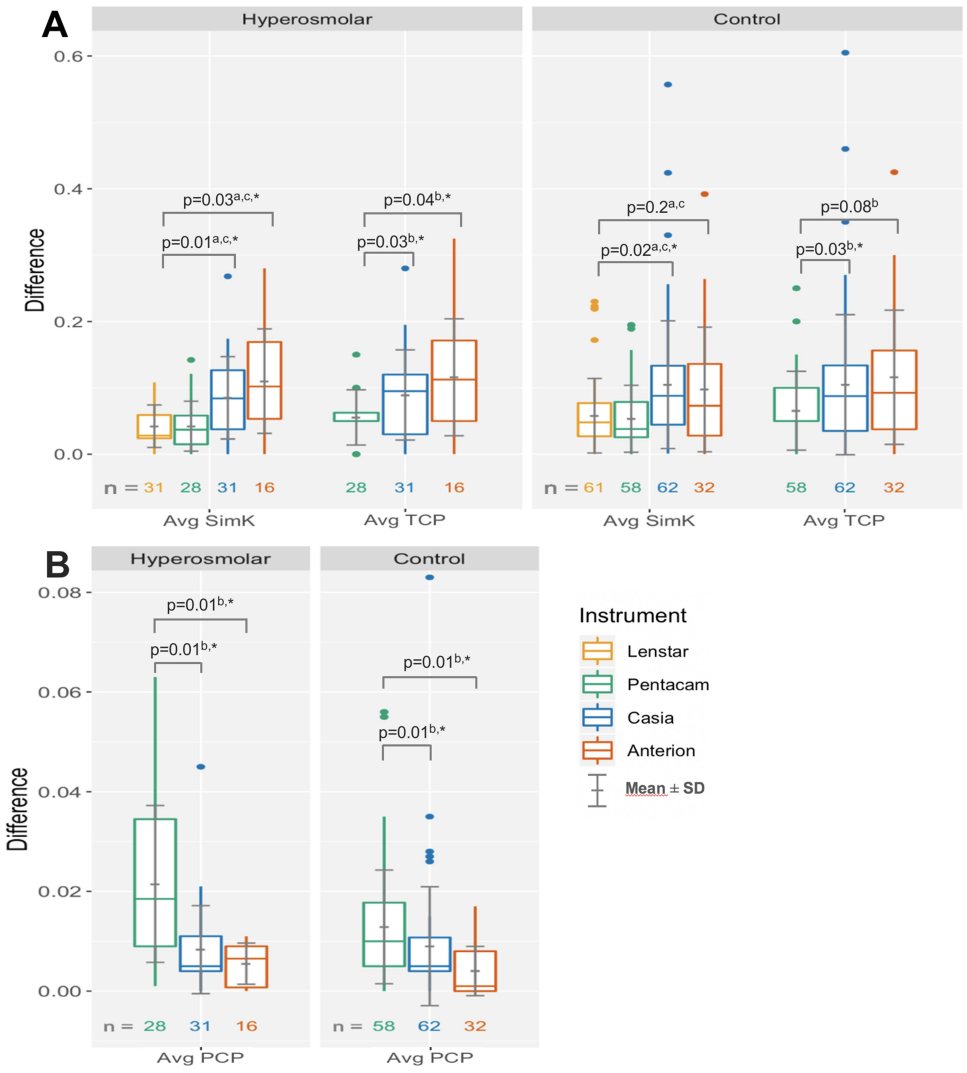

Figure 1 Absolute difference of repeated measurements of (**A**) average SimK and TCP and (**B**) average PCP.
Notes: [a]Wilcoxon signed-rank test comparison with the Lenstar; [b]Wilcoxon signed-rank test comparison with the Pentacam; [c]Holm–Bonferroni adjusted *p* (12 comparisons). *Statistically significant.
Abbreviations: Difference, absolute difference of repeated measurements; Avg, average; SimK, simulated keratometry; TCP, total corneal power; PCP, posterior corneal power; SD, standard deviation.

"Subject" was kept as a random effect for all models. For all outcome variables the models suggested that "instrument" was a statistically significant effect ($p < 0.01$) but "osmolarity group," "previous LVC," and "instrument order" was not ($p > 0.05$, $p > 0.1$, and $p > 0.3$, respectively). One subject in the control group had a SimK and TCP magnitude of vector difference of >1.5 D with the Casia. When the linear mixed-effects models were run without this outlier, the significance level was $p > 0.2$ for the "osmolarity group" term.

Coefficient of Repeatability

The OCT devices had the highest CR for average SimK and average TCP in both groups. The Casia had the highest CR for SimK and TCP vector astigmatism in both groups (Table 3).

Post-Hoc Analysis

Analysis with all subjects showed statistically significant differences in means of the instruments (Figure 4A and B): both the Casia and the Anterion had significantly higher mean difference of average SimK compared to the Lenstar (0.1 and 0.1 vs 0.05, respectively, adjusted $p < 0.03$), and average TCP compared to the Pentacam (0.10 and 0.12 vs 0.06, $p < 0.01$). The Casia had statistically significantly higher mean magnitude of SimK vector differences compared to the Lenstar (0.27 vs 0.18, adjusted $p < 0.01$) and of TCP vector differences compared to the Pentacam (0.27

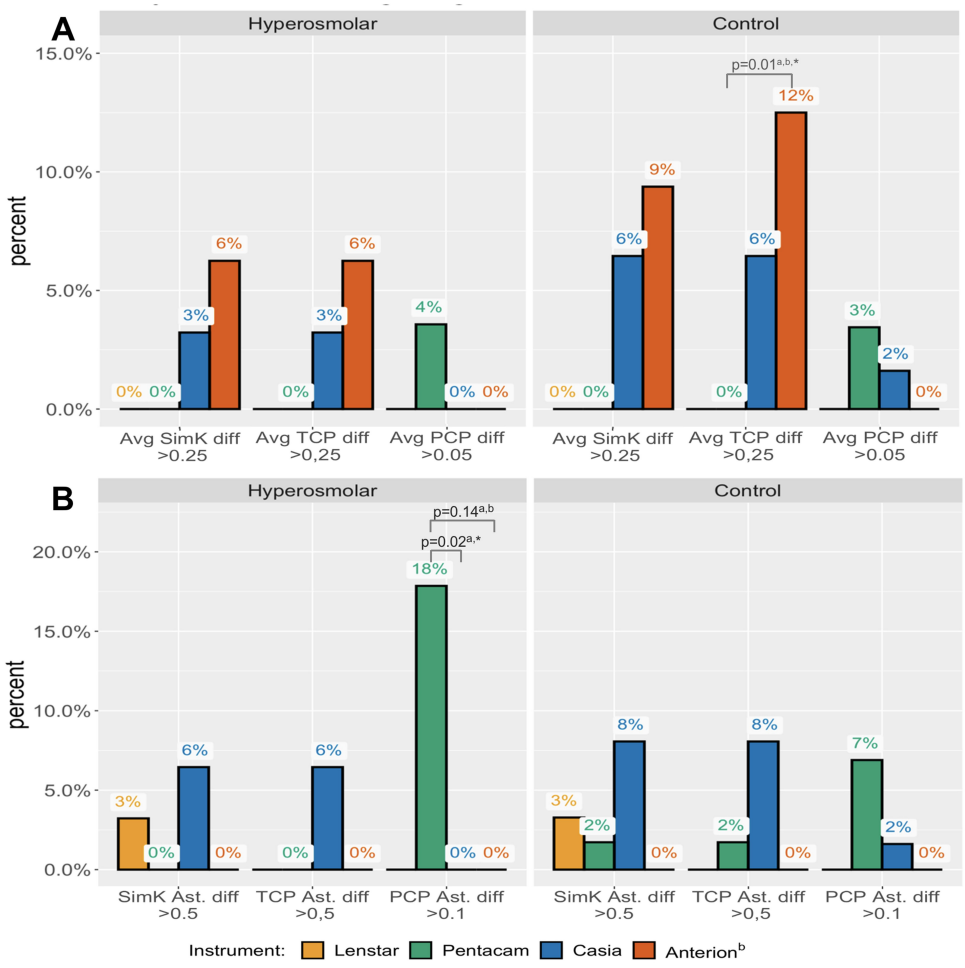

Figure 2 Percentage of subjects with (**A**) average K differences and (**B**) vector differences greater than certain values.
Notes: [a]Fisher exact test comparison with the Pentacam; [b]the Anterion compared with corresponding data from the Pentacam. *Statistically significant.
Abbreviations: Avg, average; SimK, simulated keratometry; PCP, posterior corneal power; TCP, total corneal power; diff, absolute difference in average K; Ast. diff, magnitude of vector difference of astigmatism.

vs 0.18, $p < 0.01$). Both OCT devices had significantly lower mean difference of average PCP and PCP vector difference compared to the Pentacam($p < 0.01$).

The Casia and Anterion devices had higher CR for average SimK and TCP compared to the Lenstar and Penetacam, respectively, while the Casia had higher CR of SimK and TCP vector differences of astigmatism compared to the Lenstar and Pentacam, respectively. Both OCT devices had lower CR of PCP differences compared to the Pentacam (Figure 5).

Discussion

The main objective in this study was to compare the repeatability of different keratometers in patients with normal and hyperosmolar tears because tear-film instability may affect keratometry, which is a critical variable in the IOL power calculation at the time of cataract surgery. We hypothesized that keratometers which do not rely on reflections from the precorneal tear film would be less dependent on tear-film quality than traditional reflection-based keratometers. However, using tear-film osmolarity as a proxy for tear-film quality, we did not find statistically significantly higher differences in repeatability of simulated keratometry with the reflectometry device compared to the Scheimpflug or the OCT devices in the hyperosmolar or the normal subject groups.

In the hyperosmolar group, both OCT devices had statistically significantly higher mean differences of average SimK compared to the reflectometry device. Also, in the control group both OCT devices had higher mean differences, but this was only statistically significant for the Anterion. The Casia had a significantly higher mean difference in SimK vector magnitude compared to the Lenstar in the control group but not in the hyperosmolar

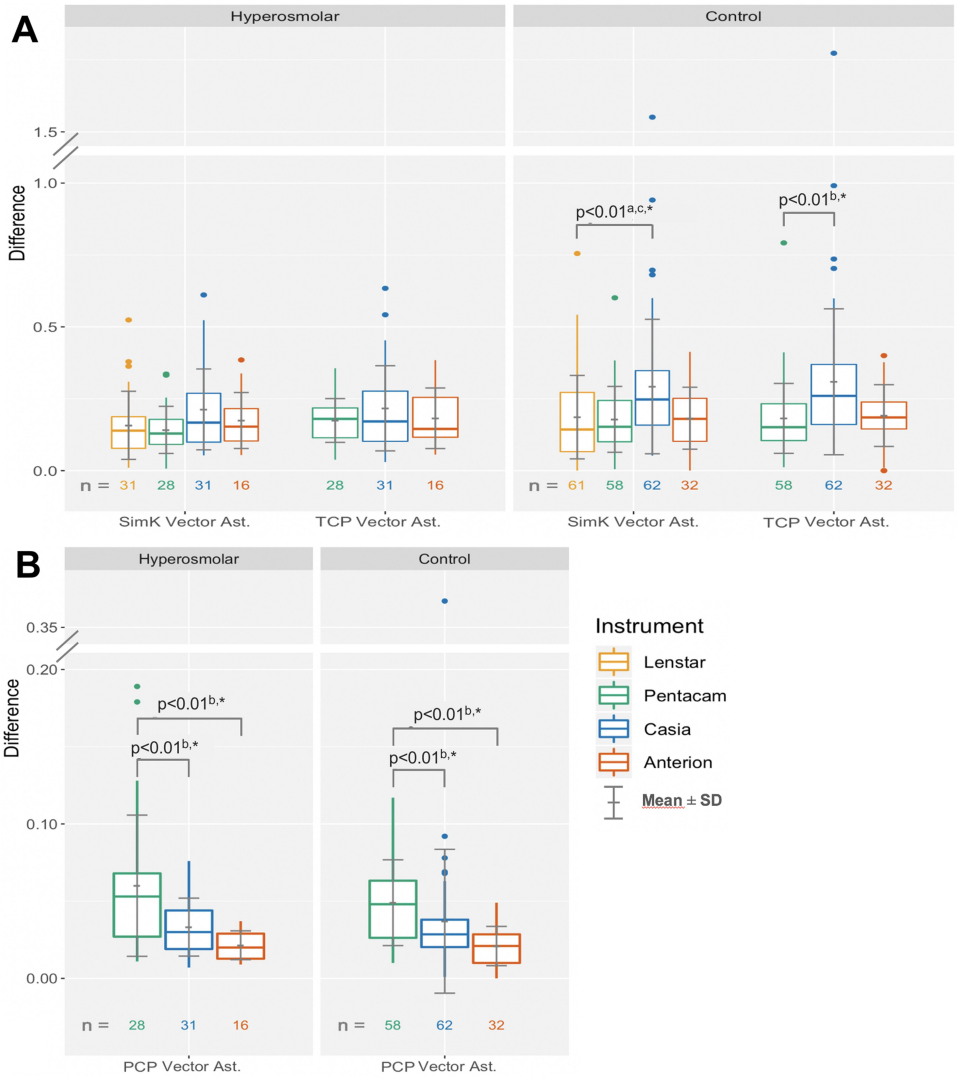

Figure 3 Difference of repeated measurements of (**A**) SimK and TCP vector astigmatism and (**B**) PCP vector astigmatism.
Notes: [a]Wilcoxon signed-rank test comparison with the Lenstar; [b]Wilcoxon signed-rank test comparison with the Pentacam; [c]Holm–Bonferroni adjusted *p* (12 comparisons). *Statistically significant.
Abbreviations: Difference, absolute difference of repeated measurements; SimK, simulated keratometry; TCP, total corneal power; PCP, posterior corneal power; Vector Ast., magnitude of vector difference of astigmatism; SD, standard deviation.

group. Because both the Casia and the Anterion rely on the same type of technology, the results appear contradictory. Furthermore, the mixed-effects model, which controlled for the random effects of "subject" and "instrument order," suggested that "osmolarity group" was not a significant factor.

Epitropoulos et al compared the repeatability of simulated keratometry in a hyperosmolar and a normal group and found that in the hyperosmolar group 8% had a difference of more than 0.50 D and 5% had a difference of more than 1 D, while all subjects had less than 0.5 D in the normal group.[5] There are some differences between these two studies that could contribute to the different results with reflection-based keratometry. In the study of Epitropoulos et al they used an IOLMaster in which keratometry relies on reflections of six light spots at 2.5 mm diameter. Keratometry is measured automatically three times during approximately 3 seconds to produce a composite value. They also used a manual keratometer for some measurements. The relatively short measurement time for both these instruments may not have been sufficient to average the random variability created by an unstable tear film. With the Lenstar, reflection keratometry is based on 32 measurement points located on

Table 3 Coefficient of Repeatability

	Hyperosmolar				Control			
K (D)	**Lenstar *n* = 31**	**Pentacam *n* = 28**	**Casia *n* = 31**	**Anterion *n* = 16**	**Lenstar *n* = 61**	**Pentacam *n* = 58**	**Casia *n* = 62**	**Anterion *n* = 32**
	CR	**CR**	**CR**	**CR**	**CR**	**CR**	**CR**	**CR**
Average SimK	0.10	0.11	0.20	0.26	0.16	0.14	0.28	0.26
Average PCP		0.05	0.02	0.01		0.03	0.03	0.01
Average TCP		0.13	0.22	0.28		0.17	0.29	0.30
SimK Astigmatism	0.38	0.32	0.50	0.39	0.46	0.41	0.73	0.41
PCP Astigmatism		0.15	0.07	0.05		0.11	0.12	0.05
TCP Astigmatism		0.37	0.51	0.41		0.43	0.78	0.43

Abbreviations: K, keratometry or corneal power; CR, coefficient of repeatability; SimK, anterior keratometry; PCP, posterior corneal power; TCP, total corneal power; Average, difference in average K; Astigmatism, magnitude of vector difference of astigmatism; CR, coefficient of repeatability.

two concentric rings of 16 points each at 1.65 mm and 2.3 mm diameter, and the final K-value is a composite of five separate measurements taking about 2–4 minutes. This procedure may average the random variability produced by an unstable tear film and consequently give more repeatable measurements. In addition, in the study of Epitropoulos et al the subject had their two exams taken on separate visits, which could also give rise to higher variability in osmolarity between visits (mean osmolarity was 8.4 mOsm/L lower on second visit), while in the present study all the measurements were made during the same visit. A further possible confounding factor is that the average age in the Epitropoulos et al study was 71 years and in the present study 43 years; the prevalence of signs of DED increase with age.[35] For instance, estimates of prevalence based on tear break up time (TBUT) increase with 10% for each decade after 40–49 years of age.[36] As such, there could have been fewer subjects with unstable tear film and thus less variability in keratometry in the present study. Even though both hyperosmolarity and instability of the tear film are considered hallmarks of DED, osmolarity is not a measure of tear stability itself.[8,37,38] Furthermore, there is lack of evidence that osmolarity of a tear sample from the tear meniscus is representative of the osmolarity of the ocular surface.[38] Therefore, the question could arise whether hyperosmolarity is a good indicator of short TBUT.

Our findings are supported by some other studies: Dogan et al compared the repeatability for a Sirius Scheimpflug device in patients with dry eyes to healthy patients and found excellent agreement of repeated SimK average measurements in both groups.[39] Jensen et al found no statistically significant differences in the K-values of the IOLMaster 700 when comparing repeated measurements with and without different artificial tear drops, although no evaluation of dry eyes was reported.[40]

For PCP, both OCT devices had statistically significantly lower means of both average K and astigmatism differences compared to the Scheimpflug device in both groups. The Pentacam had significantly more subjects with a PCP astigmatism difference more than 0.1 compared to the Casia in the hyperosmolar group but not in the control group. This could indicate that tear-film stability affects posterior corneal power measurements with a Scheimpflug device, but we have found no support in the literature for this. Furthermore, the mixed-effects model was not statistically significant for the "osmolarity group."

The total corneal power, which is of interest in IOL power calculations, was calculated from both anterior and posterior measurements. However, the differences in posterior corneal power did not appear to affect the differences of the total corneal power because of the small difference in refractive index between the posterior cornea and the aqueous humour. The results for total corneal power were similar to those for the simulated keratometry.

When comparing different instruments with all subjects, we found statistically significant differences in means of both the average K and the magnitude of vector difference of astigmatism: Both OCT devices had higher differences in average SimK compared to the Lenstar and average TCP differences compared to the Pentacam. The Casia had the highest mean magnitude of SimK and TCP

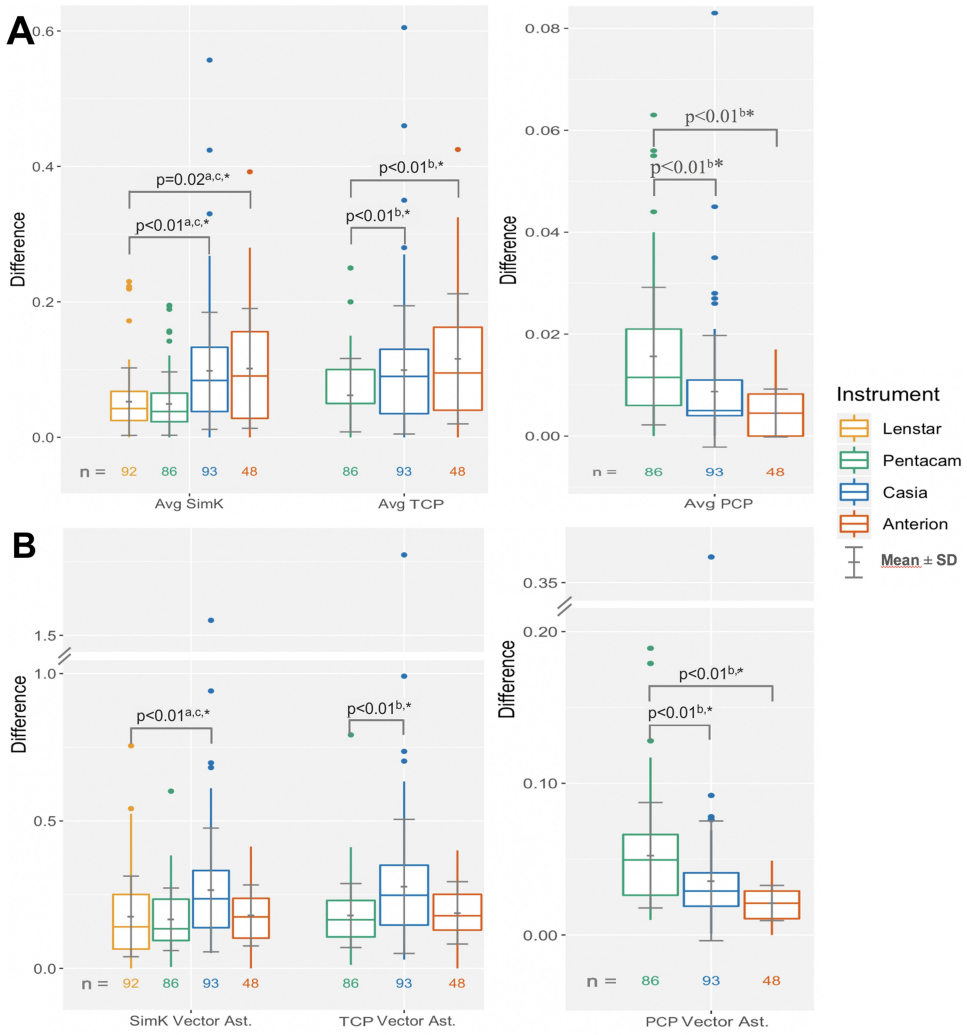

Figure 4 Difference of repeated measurements of (**A**) average keratometry and (**B**) vector difference of astigmatism with all subjects.
Notes: [a]Wilcoxon signed-rank test comparison with the Lenstar; [b]Wilcoxon signed-rank test comparison with the Pentacam; [c]Holm–Bonferroni adjusted *p* (six comparisons). *Statistically significant.
Abbreviations: Difference, absolute difference of repeated measurements; SimK, simulated keratometry; TCP, total corneal power; PCP, posterior corneal power; Avg, average; Vector Ast, magnitude of vector difference of astigmatism; SD, standard deviation.

vector differences, while both of the OCT devices had lower mean difference of average PCP and PCP vector difference. Even though the mean differences in average K were small (<0.1 D), a CR of 0.3 shows that both OCT devices have greater chance of errors in average K, which could be clinically relevant in some cases. The newest OCT device, the Anterion, had similar CR for keratometric astigmatism compared to the Lenstar and the Pentacam (0.4), but the Casia had a CR of about 0.7 for both SimK and TCP astigmatism. This shows that variability in measurements should be considered a relevant source of error when assessing corneal astigmatism with all devices in this study, but for the Casia in particular.

Our results for repeatability were comparable to some other studies. Two studies reported CR for average SimK from 0.28 to 0.35 for reflection keratometry.[41,42] Wylegala et al reported a CR of anterior and posterior corneal power (in two meridians) with a spectral domain OCT (Revo NX) to be 0.33–0.46 and 0.10–0.11, respectively.[24] One study reported a CR with the Pentacam for K1/K2 and astigmatism to be 0.07 and 0.39–0.44, respectively, for both SimK and TCP, and 0.11 and 0.12, respectively, for PCP.[43] Another study found that repeatability was worse for anterior elevation but better for posterior elevation with the Casia compared to the Pentacam.[44]

The Casia had the highest differences of SimK and TCP astigmatism and the two largest outliers. This could be related to the fact that the Casia was the only instrument with fully automated alignment and the only instrument that did not provide a quality check of the acquisition.

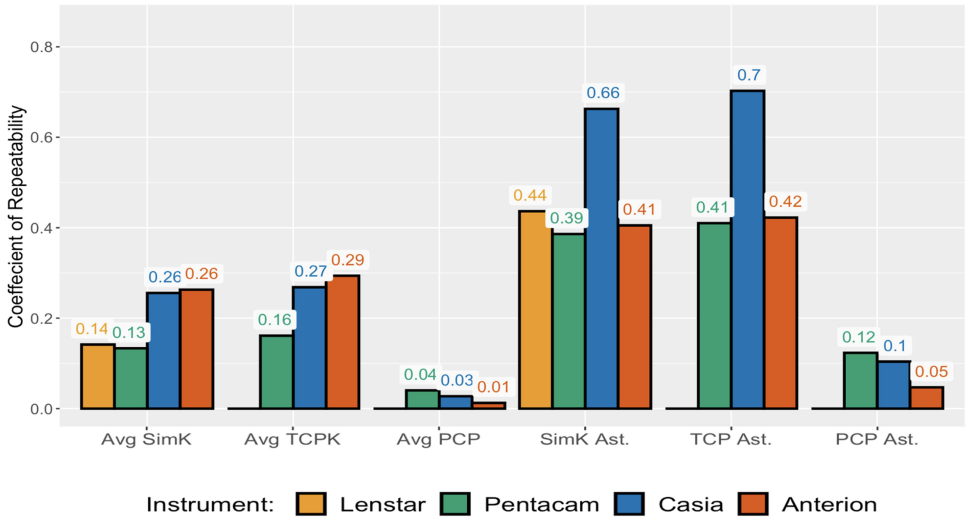

Figure 5 Coefficient of repeatability for each instrument with all subjects.
Abbreviations: SimK, simulated keratometry; TCP, total corneal power; PCP, posterior corneal power; Avg, average; Ast., magnitude of vector difference of astigmatism.

The Pentacam had the lowest difference of average TCP, and together with the Anterion the lowest magnitude of vector difference of TCP astigmatism. TCP is calculated from the curvature of both the anterior and the posterior surface of the cornea. Arguably, for eyes with a healthy, regular and untreated cornea, measurements of the posterior cornea to yield average total corneal power may not be necessary. The contribution from the posterior cornea is less than 1/5 of the total corneal power. However, in patients with irregular corneas or a history of refractive surgery, a corresponding erroneous ratio of the front and back surface of the cornea could be clinically significant. For instance, a cornea treated for −3 D of myopia could give 0.8–1.5 D of measurement error (depending on the assumed refractive index) when using SimK only. This would in most cases with moderate or high myopia outweigh variability of the average TCP measurements seen in this study.

Keratometric astigmatism based on simulated keratometry has been shown to be overestimated for with-the-rule, and underestimated for against-the-rule astigmatism.[45] In one study, different nomograms and online calculators designed to compensate for the contribution of posterior cornea yielded average prediction errors for astigmatism around 0.5 D with two different reflectometry devices. However, the maximum prediction errors for these methods ranged from 0.9 D to more than 2 D.[46] Using total corneal power could improve the prediction errors for astigmatism. Averaging two or more measurements would likely give more repeatable results and hence improve the clinical benefit of including measurements of the posterior cornea in calculation of IOL power or IOL cylinder.

There are some limitations to the study. The full study procedure took about 40 minutes to complete. We tried to control the influence of the measurement procedure by waiting at least 5 minutes between different instruments, but it may have influenced the tear-film quality. The reflectometry device used an average of several measurements, but a comparison of the repeatability between single measurements may have been better to detect the possible influence of the tear-film quality. Finally, the cohorts were smaller when the Anterion device was compared to the other devices (n = 48) and this could have affected the results.

Conclusion

Differences in repeated measurement between instruments in patients with hyperosmolar tear film and a control group suggested that the repeatability of keratometry was not affected by hyperosmolar tear film. We did find statistically significant differences of instruments for all subjects, with the lowest differences of SimK for the reflectometry and the Scheimpflug devices. While the mean differences between measurements were low, the coefficient of repeatability showed that clinically relevant errors were more likely to appear with both OCT devices for average keratometry and with the Casia for keratometric astigmatism, compared to the reflectometry and the Scheimpflug devices. Using total corneal power in special cases, like

post-LVC patients, may outweigh random errors related to measurement. However, when using the OCT or Scheimpflug devices for IOL calculations we suggest taking two measurements and averaging the results. Further studies of the clinical implications of using total corneal power is advocated. For instance, of interest is the potential effect of using total corneal power on the predictability of IOL calculation in post-LVC patients.

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Disclosure

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Paper 4

Gjerdrum B, Gundersen KG, Lundmark PO, Aakre BM. **Refractive Precision of Ray Tracing IOL Calculations Based on OCT Data versus Traditional IOL Calculation Formulas Based on Reflectometry in Patients with a History of Laser Vision Correction for Myopia.** *Clin. Ophthalmology.* 2021;Volume 15:845-857.

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ORIGINAL RESEARCH

Refractive Precision of Ray Tracing IOL Calculations Based on OCT Data versus Traditional IOL Calculation Formulas Based on Reflectometry in Patients with a History of Laser Vision Correction for Myopia

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Purpose: To compare the refractive predictability of ray tracing IOL calculations based on OCT data versus traditional IOL calculation formulas based on reflectometry in patients with a history of previous myopic laser vision correction (LVC).

Patients and Methods: This was a prospective interventional single-arm study of IOL calculations for cataract and refractive lens exchange (RLE) patients with a history of myopic LVC. Preoperative biometric data were collected using an optical low coherence reflectometry (OLCR) device (Haag-Streit Lenstar 900) and two optical coherence tomography (OCT) devices (Tomey Casia SS-1000 and Heidelberg Engineering Anterion). Traditional post LVC formulas (Barret True-K no-history and Haigis-L) with reflectometry data, and ray tracing IOL calculation software (OKULIX, Panopsis GmbH, Mainz, Germany) with OCT data were used to calculate IOL power. Follow-up examination was 2 to 3 months after surgery. The main outcome measure, refractive prediction error (RPE), was calculated as the achieved postoperative refraction minus the predicted refraction.

Results: We found that the best ray tracing combination (Anterion-OKULIX) resulted in an arithmetic prediction error statistically significantly lower than that achieved with the best formula calculation (Barret True-K no-history) (−0.13 D and −0.32 D, respectively, adjusted $p = 0.01$), while the Barret TK NH had the lowest SD. The absolute prediction error was 0.26 D and 0.35 D for Anterion-OKULIX and Barret TK NH, respectively, but this was not statistically significantly different. The Anterion-OKULIX calculation also had the highest percentage of eyes within ± 0.25, compared to both formulas and within ±0.50 and ±0.75 compared to the Haigis-L ($p = 0.03$).

Conclusion: Ray tracing calculation based on OCT data from the Anterion device can yield similar or better results than traditional post LVC formulas. Ray tracing calculations are based on individual measurements and do not rely on the ocular history of the patient and are therefore applicable for any patient, also without previous refractive surgery.

Keywords: post-LVC, OCT, ray tracing, IOL calculation, biometry, individual calculation, prediction error

Introduction

Cataract surgery and refractive lens exchange (RLE) today are safe and highly accurate procedures and almost any type of refractive errors can be corrected. RLE differs from cataract surgery only in the sense that the primary aim of the surgery is

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to reduce spectacle dependence. Intraocular lens (IOL) power calculations rely on accurate measurements of the corneal curvature and the axial length (AL), but often also anterior chamber depth (ACD) and lens thickness (LT). In addition, constants specific to each IOL are used to account for different IOL properties that influence the final IOL position in the eye; these can also be optimized to account for different surgical techniques and instrumentation.[1–3]

For patients who have previously had laser vision correction (LVC), the precision of IOL calculations remains a challenge due to several sources of error. Inaccurate determination of the corneal refractive power is perhaps the most important, along with an incorrect estimation of the effective lens position (ELP) from corneal power and incorrect estimation of the central corneal curvature from paracentral measurements.[1,4–6] Reduced corneal thickness, altered corneal asphericity or higher order aberrations may also contribute.[4,7] In addition, for IOL calculation in any patient, tear film instability may influence the keratometry measurement and individual shrinkage of the postoperative capsular bag may influence the actual postoperative IOL position and hence the refraction.

Corneal power is a critical variable for IOL power calculation. Traditionally, the corneal power is determined by measuring the anterior surface by means of reflectometry. This curvature is converted to corneal power with the use of a fictitious refractive index (the keratometric index) to account for the contribution of posterior corneal curvature.[6] While this approximation may be sufficiently accurate for the average population, it does not hold true for patients with previous LVC because the anterior corneal surface is altered. This is known as the keratometric index error.[4] In myopic LVC the anterior corneal surface is flattened, but the posterior curve remains relatively unchanged. Corneal refractive power based on anterior curvature will be underestimated due to the reduced posterior to anterior surface ratio.[6,8]

Estimation of the post-operative ELP is important in the IOL power calculation in general. The ELP is a virtual variable, often the lens plane of a thin lens, that does not necessarily reflect the anatomical IOL position after surgery.[1] Nevertheless, it is a considerable source of error if it is incorrectly estimated. Some formulas rely on corneal power to estimate the ELP, resulting in an underestimation after myopic LVC and overestimation after hyperopic LVC.[9] Other formulas use the ACD or AL to predict the ELP. Anatomically, the ACD is the distance from the posterior cornea to the anterior surface of the crystalline lens, but it is often measured from the anterior surface of the cornea.

The radius error (or instrument error) occurs because the central corneal curvature is extrapolated from paracentral measurements with most biometers. After myopic LVC, the central cornea may be flatter than suggested by this extrapolated value.[6]

More than 30 post-LVC IOL calculation formulas or methods have been proposed to compensate for these known sources of error. Several formulas depend on historic data, ie historic refraction and/or historic keratometry to calculate the true corneal power or to use separate historic keratometry for the determination of ELP.[10] The corneal bypass method uses the preoperative corneal curvature together with a target refraction set for the preoperative refraction to avoid the keratometric index error and the radius error.[11]

Other methods, so-called non-history methods, do not rely on exact preoperative data but need only to know if the treatment was myopic or hyperopic. For instance, the Haigis-L formula is an adaption of the Haigis formula (which uses ACD to predict ELP). Here the effective corneal power is estimated from the measured anterior corneal curvature in combination with a linear regression derived from a study population and a fixed correction for the underestimated ACD due to the laser ablation.[4,12] The Shammas no-history method uses a similar approach, with a regression equation to correct the postoperative measured k-value to be used in a previously described formula, where AL is used for ELP prediction.[13,14] The Wang-Koch -Maloney formula for myopic LVC uses keratometry obtained from topography converted with a different keratometric index and subtracts an assumed posterior power.[15,16] Another no-history formula is the Barret True K No History (Barret TK NH). The details of this formula are not published, but it uses an internal regression formula to calculate an estimated change in manifest refraction.[17] Other formulas, like the Potvin-Shammas-Hill formula, the Galilei-formula and the OCT-formula are based on theoretical formulas, but instead of keratometry, uses total corneal power from instruments that provide actual measurements of the posterior cornea.[15,18,19]

The most commonly used post-LVC formulas are available with an online calculator from the ASCRS website.[15] Depending on the amount of available data,

predicted IOL power is presented for different formulas, including the maximum, minimum and average of the different formulas. It has been proposed to look at several formulas to assess the IOL power most likely to give the intended refractive result.[20] All these formulas are modifications of either a) theoretic IOL formulas based on a theoretical eye model which relies on Gaussian optics where light rays are assumed to refract as paraxial rays, or b) regression formulas based on clinical studies.

A different approach to IOL calculations is the use of ray tracing calculations. These are exact calculations based on Snell´s Law, using available data to calculate the best focus for single rays at varying radial distances from the optical axis through the different refractive media of the eye. One such software is the OKULIX Ray-Tracing-Calculation for the Pseudophakic Eye (Panopsis GmbH, Mainz, Germany). The OKULIX software does not use IOL power, but manufacture provided radii, refractive index, asphericity, and thickness for available IOL types and calculates the IOL power which gives the best focus, ie the smallest simulated image of a Landolt C on the fovea. Since IOL position depends on individual capsular bag shrinkage after surgery, it cannot be calculated exactly. Instead, a model calculation is used to predict the most probable IOL position based on AL, position and thickness of the crystalline lens (when measured).[21] Adjustments in this predicted IOL position are already done by the manufacturer and any further adjustment by the user is not recommended (Paul Rolf Preußner, PhD, e-mail communication, January 2020).

Conventional biometry for IOL calculation is often performed with an optical low coherence reflectometry (OLCR) device or a partial coherence interferometry (PCI) device, both of which use reflections from the corneal surface to calculate the corneal power and laser interferometry for AL measurements. One advantage with the OLCR device is that it can also detect the signal maxima from both surfaces of the cornea and the crystalline lens to produce an a-scan of cornea thickness, ACD and LT.

OCT is a high speed, high resolution, noncontact optical imaging technique for noninvasive cross-sectional imaging of biologic systems.[22] Recent anterior segment (AS) OCT systems have been designed to produce tomographic images and provide accurate measurements of the AS.[23,24] Spectral-domain and swept-source (SS) OCT are variations of Fourier-domain OCT, with the latter offering better visualization of structures and increased scanning speed.[23] Backscatter from a SS laser beam creates multiple intensity-based cross-sectional images which are used to create three-dimensional surfaces from which parameters can be derived.[25] One advantage with the OCT-based biometers is that all measurements are based on infrared light, not visible to the patient´s eye, making the measurement more comfortable and facilitating target fixation. Another advantage is that they do not depend on reflection from the pre-corneal tear film. However, some studies have shown lower repeatability of OCT-based keratometry compared to reflectometry or Scheimpflug-based keratometry.[26–29]

Laser in situ keratomileusis (LASIK) is the most common LVC procedure, with more than 16 million procedures globally to 2015.[30] The volumes in the US and Europe have been about 1.5 million surgeries per year since 2010.[31,32] Assuming that the bulk of LVC patients are between 25 and 35 years old at the time of surgery, the number of LVC patients with cataract or seeking presbyopic RLE is likely to increase in future.

The aim of this study was to assess the accuracy of ray tracing IOL-calculations based on OCT data in patients with a history of myopic laser vision correction and to compare refractive prediction error with some well-established no-history post LVC formulas based on OLCR biometry. Our hypothesis was that ray tracing based on OCT data could improve refractive predictability for post-LVC IOL calculations.

Patients and Methods

This was a prospective one-arm treatment study of patients presenting for cataract or RLE surgery who had previously had myopic LASIK or photorefractive keratectomy (PRK). The study was conducted in a private eye clinic in Haugesund, Norway. Recruitment and data collection were performed from May 2019 to August 2020. The study followed the tenets of the Declaration of Helsinki and was approved by the Regional Committee for Medical and Health Research Ethics in Norway (Ref. no 2019/768). A written informed consent was obtained. Inclusion criteria were bilaterally good ocular health, with no pathology or systemic disease involving the corneal surface. Exclusion criteria were complicated LVC surgery, ectatic disease, lid deformities, or any acute or chronic disease or illness that could confound the results of the study.

Examination

All patients had a full optometric and ophthalmic examination, including uncorrected and corrected distance

visual acuity (UDVA and CDVA), manifest refraction (sphere and cylinder), slit-lamp biomicroscopy, and fundoscopy or wide-field retinal imaging. The macula, fovea, and vitreomacular interface were evaluated using fundoscopy, OCT, or both. All patients had comprehensive preoperative counseling during which their needs, wishes, preferences, and expectations were evaluated. Patients requesting multifocal IOLs were informed about increased sensitivity to residual refractive errors and that the normal optical side effects could possibly increase due to optical aberrations caused by the LVC treatment. If the patient was motivated and given that the likely results could meet the expectations, a primary implantation with monofocal IOLs and a secondary implantation of multifocal supplementary IOLs 3 months later were offered. Only the results from the primary surgery were included in the study.

Biometry

Two instruments were used to measure the biometry of all subjects: a low-coherence reflectometry (OLCR) biometer (Lenstar 900®, Haag-Streit AG, Koeniz, Switzerland), and an SS OCT (Casia SS-1000, Tomey Corporation, Nagoya, Japan). A new SS OCT (Anterion®, Heidelberg Engineering GmbH, Heidelberg, Germany) was included in the study from December 2019, and results were analyzed with corresponding data from the other instruments. All measurements were performed by one clinician (BG).

The Lenstar 900 uses reflection keratometry based on 32 measurement points located on two concentric rings of 16 points each at 1.65 mm and 2.3 mm diameter. The keratometry index used was 1.3375. The Lenstar also provides an a-scan of corneal thickness, ACD, LT and AL. The final values are composites of five separate measurements.

With the Anterion, the "Cataract" examination consists of four steps of image acquisition; cornea data, anterior segment data, and two acquisitions of axial length, each started manually. The Anterion provides cornea tomography, ACD, LT and AL. Both the Lenstar and the Anterion provided a quality check of the acquisitions. Only acquisitions of acceptable quality were used for the calculations.

The Casia provides tomography of the cornea but not ACD, LT or AL. Each measurement is done in a single pass acquisition with fully automated alignment. No automatic quality check was provided, but a manual check was performed. If data were missing from the maps, the measurement was repeated. With both OCT devices, two separate measurements were performed for each eye.

IOL Calculations

IOL Calculations with two post-LVC formulas were performed with data from the Lenstar: the Barret TK NH formula, which was included in the device software, and the Haigis-L formula. The ASCRS online calculator (version 4.8) was initially used for the Haigis-L calculation. However, this calculator only provides a predicted IOL power for a given target refraction but not the predicted refraction for a given IOL power. Therefore, for the RPE analysis, the Haigis-L formula was entered in an excel spreadsheet together with the constants and biometry data exported from the Lenstar and used to calculate the predicted refraction for the implanted IOL power.

All patients received one of the two IOL models: Acrysof® IQ or Acrysof® IQ toric (Alcon Laboratories, Inc., Fort Worth, TX, USA). The following constants were used for the calculations:

Acrysof IQ: Haigis (a0, a1 and a2) 1.309, 0.4, 0.1, respectively; Barret LF, 1.88.

Acrysof IQ toric: Haigis (a0, a1 and a2) 1.441, 0.4, 0.1, respectively; Barret LF, 1.99.

The Lens factor (LF) for the Barret formula and the Haigis a0 were optimized for the surgeon based on results from normal eyes.

Ray tracing IOL calculations were performed with OKULIX Ray-Tracing-Calculation for the Pseudophakic Eye version 9.16 using data from the OCT devices. The software calculates the predicted ACD based on a built-in database on the most commonly used IOLs, which is regularly updated. For the calculation with the Casia data, the AL value from the Lenstar was manually entered. For each OCT device, two separate OKULIX calculations were performed, once for each measurement, and the average predicted refraction from each instrument was used in the analysis. The IOL power that was implanted was based on the average predicted IOL power from Barret TK NH formula and the ray tracing calculations.

Toric IOL cylinder power and axis were calculated using the Barret toric IOL calculator included in the Verion™ Image-guided System (Alcon Laboratories, Inc., Fort Worth, TX, USA). Toric power was chosen so that the targeted residual cylinder was between 0.25 undercorrection and 0.1 overcorrection.

Surgery

All surgeries were performed by one surgeon (KG), using a superior 2.2 mm primary incision and two side ports 60

degrees from the primary incision. The Verion system was used for orienting incisions, the capsulorhexis and the final orientation of the IOL in the eye. Bilateral surgeries were performed on the same day.

Outcome Variables

Postoperative data were collected 2–4 months after surgery, including UDVA, CDVA and distance refraction (sphere and cylinder). Distance subjective refraction was performed in 0.25 D steps with a lane length of 6 m. The aqueous depth (AQD) was measured with the Anterion as the distance from the posterior cornea to the anterior IOL. The primary outcome variable was arithmetic and absolute refractive prediction error (RPE), which was calculated as the achieved minus the predicted spherical equivalent refraction with each formula or calculation. A negative prediction error indicates a more myopic result than the predicted refraction. Absolute error (AE) was calculated by adjusting the mean arithmetic error to zero for each formula and taking the absolute value. This represents the ideal situation where lens constants are perfectly adjusted for the sample.[3,33] Median absolute error (MedAE) and range of AE were reported.

Sample Size

The sample size calculation was based on a mean difference in prediction error between the two calculation methods with an expected standard deviation (SD) of 0.4 D. Using an alpha of 0.05 and a power of 0.8, a sample of 22 eyes was determined to be sufficient to reliably detect a difference in RPE of at least 0.25D.

Analysis

Descriptive statistics included the minimum, maximum, mean, standard deviation and achieved refractive outcome. Statistical analysis was performed using the *t*-test, analysis of variance (ANOVA) or nonparametric tests as appropriate. P-values were adjusted with the Holm–Bonferroni method for multiple comparisons.[29,30] Since two eyes from one subject are related, linear and logistic mixed-effects models were used to analyze data from both eyes of each subject. Such models are designed for modeling continuous correlated hierarchical/multilevel data, and one of the main strengths is the ability to handle unbalanced data.[34] They offer maximal use of available data and are efficient also with a substantial amount of nonrandom missingness.[35,36] The models were designed with "subject" and "eye (nested) within subject" as random effects, which causes the comparisons to be done in a paired manner. The Anterion-OKULIX calculation was used as a contrast. P-values were obtained by likelihood ratio tests of a) the full model with the effect in question against b) the model without the effect in question. "Subject" and "eye within subject" were kept as random effects in all models. Parameter specific p-values from the final models were obtained with Satterthwaite's method.[34]

Statistical analyses were performed using the RStudio data-analysis software (version 1.2.1335, RStudio Inc, Boston, MA, USA) and the lme4, lmerTest and ggplot2 packages.[34,37,38] A p-value ≤0.05 (two-sided) was considered statistically significant.

Post Hoc Analysis

Ray tracing calculation could only be performed with data from a single measurement of the OCT device. The IOL predictions were based on the average of two separate measurements and calculations with each device. To assess if the repeatability of the measurement with the OCT devices was a relevant source of error, the coefficient of repeatability (CR) was calculated as 2.77 times the within-subjects standard deviation. The within-subjects standard deviation was calculated as the square root of half the mean of the squared differences between the two calculations.

The actual postoperative lens position affects the final refractive result. The OKULIX software predicts the ACD as the distance from the posterior cornea to the anterior surface of the IOL.[39] This distance is often termed aqueous depth (AQD), which we will use here to avoid confusion with the ACD measured from the anterior cornea in conventional biometry. The AQD prediction error (AQD PE) was calculated as the actual postoperative AQD measured by the Anterion minus the predicted AQD. The correlation between the RPE and AQD PE was tested with Pearson´s correlation coefficient.

Results

The study included 37 eyes of 20 subjects. Data collected with the Anterion included 25 eyes of 13 subjects. Mean age was 60 years and 45% were cataract patients. Toric IOLs weree implanted in 65% (24 of 37 eyes) (Table 1). All subjects who were asked agreed to participate, but one patient was excluded because of presbyopic LVC. One eye from one patient was excluded because the LASIK flap had been removed after complicated LASIK surgery.

Table 1 Demographics

Eyes		37	
Subjects		20	
Sex, F		30%	
		Mean ± SD	Range
Age (years)		56,9 ± 4.9	49 to 66
K (D)[a]		40.5 ± 1.9	36.5 to 44.4
Corneal astigmatism[a]		0.86 ± 0.40	0.20 to 1.74
ACD (mm)[a]		3.35 ± 0.33	2.8 to 4.0
AL (mm)[a]		25.3 ±1.2	22.6 to 28.06
Previous LVC (D)	SE (n=31)[b] Cyl (n=18)[b]	−3,7 ± 2.6 −1.6 ±1.8	−10 to −1.6 −5,3 to 0
IOL power implanted		20.3 ± 2.3	15 to 24.5
Toric IOLs (IOL cyl 1.0/1.5)		65% (35%/30%)	

Notes: [a]Lenstar measurement; [b]subjects with reliable information on the previous LVC treatment.
Abbreviations: F, female; D, diopters; SD, standard deviation; RLE, refractive lens exchange; SE, spherical equivalent refraction; Cyl, cylinder refraction; LVC, laser vision correction; IOL, intraocular lens; IOL cyl, IOL cylindrical power.

Mean follow-up time was 2.8 (1.5 to 4.1) months. UDVA was 0.0 logMAR and mean spherical equivalent was +0.05 D, which was not statistically significantly different from zero (Table 2).

Refractive Prediction Error

Mean RPE and Median Absolute Error

The Anterion-OKULIX calculation had the best arithmetic RPE of all calculation methods. The mean RPE was −0.13 D, 0.29 D, −0.32 D and −0.40 D for the Anterion-OKULIX, Casia-OKULIX, Barret TK NH, and Haigis-L, respectively (Table 3, Figure 1A). The Anterion-OKULIX also had the lowest absolute RPE. The mean absolute RPE was (0.26 D, 0.35 D, 0.35 D and 0.45 D) (Table 3, Figure 1B). The Anterion-OKULIX had the lowest range of both arithmetic (1.11 D) and absolute RPE (0.64 D) and the lowest standard deviation of absolute RPE (0.19 D), while the Barret TK NH had the lowest SD (0.27 D) of arithmetic RPE. The Barret TK NH had the lowest MedAE (0.16 D), while the Anterion-OKULIX had the lowest range of AE (0.57) (Table 3).

Table 2 Refractive Results

	Mean ± SD	Range	p[a]
Months postop	2.8 ± 0.8	1.5 to 4.1	
UDVA (logMAR)	0.00 ± 0.09	−0.17 to 0.22	0.8
CDVA (logMAR)	−0.06 ± 0.07	−0.18 to 0.07	<0.01*
SE (D)	0.05 ± 0.31	−0.88 to 0.75	0.23
Cyl (D)	−0.26 ± 0.30	−1.00 to 0	<0.01*
SE ≤ ±0.25	68%		
Cyl ≤ 0.5	86%		

Notes: [a]Wilcoxon sign-rank test difference from zero; *statistically significant.
Abbreviations: SD, standard deviation; UDVA, uncorrected distance visual acuity, CDVA, corrected distance visual acuity; SE, spherical equivalent refraction; Cyl, cylinder refraction.

Linear mixed-effects models were used to include both eyes of each subject in the analysis. The Anterion-OKULIX calculation was used as a contrast, causing paired comparisons with the other calculation methods. For both the arithmetic and absolute RPE models, "calculation method" was a statistically significant effect (p <0.001) but "LVC spherical equivalent treatment" was not (p >0.59). The arithmetic RPE model suggested an estimate of −0.16 D for the Anterion-OKULIX (intercept) and a difference of +0.45 D (= +0.29 D), −0.17 D (= −0.32 D) and −0.24 (= −0.40 D), for Casia-OKULIX, Barret TK NH and Haigis-L, respectively, adjusted p <0.02. For the absolute RPE model, the Anterion-OKULIX (intercept) had the lowest estimate (0.26 D), but this was statistically significantly different only from the Haigis-L (+0.19 D = 0.45 D), adj. p =0.03.

Percentages Within Certain Range of RPE

The Anterion-OKULIX calculations showed the highest percentages of eyes with prediction errors within ±0.25, ±0.5 and ±0.75 (60%, 88%, and 100%, respectively) (Figure 2). Logistic mixed-effects models with "RPE within ±0.25" or "RPE within ±0.50" as categorical outcomes showed that "calculation method" was a statistically significant effect (p <0.01) but "LVC spherical equivalent treatment" was not (p >0.8). The Anterion-OKULIX calculation had a statistically significantly higher percentage of eyes within ±0.25 compared to the Barret TK NH and Haigis-L formulas (adj. p =0.03), and within ±0.50 compared to the Haigis-L formula (adj. p =0.03).

Repeatability of OCT Ray Tracing

The ray tracing calculations were repeated with two measurements from both OCT devices.

The coefficient of repeatability for the OKULIX IOL calculations with each OCT device was calculated. The CR was 0.23 and 0.41 with the Anterion and the Casia data, respectively. This equals the 95% limits of agreement

Table 3 Arithmetic RPE, Absolute RPE and Median Absolute Error

Calculation/formula	Eyes	Arithmetic RPE		Absolute RPE	
	n	Mean ± SD	Min to max (range)	Mean ± SD (range)	MedAE** (range)
Anterion-OKULIX	25	−0.13 ± 0.30	−0.7 to 0.41 (1.11)	0.26 ± 0.19 (0.64)	0.21 (0.57)
Casia-OKULIX	37	0.29 ± 0.36*	−0.44 to1.31 (1.75)	0.35 ± 0.30 (1.31)	0.23 (1.00)
Barret TK NH	37	−0.32 ± 0.27*	−0.87 to 0.40 (1.27)	0.35 ± 0.24 (0.87)	0.16 (0.72)
Haigis-L	37	−0.40 ± 0.34*	−1.08 to 0.55 (1.63)	0.45 ± 0.26* (1.05)	0.18 (0.95)

Notes: *Mixed models estimates statistically significantly different from Anterion-OKULIX (Holm-Bonferroni adjusted p-values); **arithmetic mean error reduced to zero.
Abbreviations: MedAE, median absolute error; Barret TK NH, Barret true K no history.

in a Bland–Altman plot (Figure 3). The predicted AQD did not differ by more than 0.01 mm between two repeated calculations.

Aqueous Depth Prediction Error

The mean AQD PE for the ray tracing calculation was −0.11 ± 0.13 mm and −0.14 ± 0.22 mm for the Anterion and Casia data, respectively. This was statistically significantly different from zero for both devices, but not between the devices. A linear model with RPE as the dependent variable and AQD PE as the independent variable showed an intercept and slope of −0.01 and 1.00 for the Anterion and 0.41 and 1.00 for the Casia. This was statistically significant for the slope for both devices and for the intercept for the Casia.

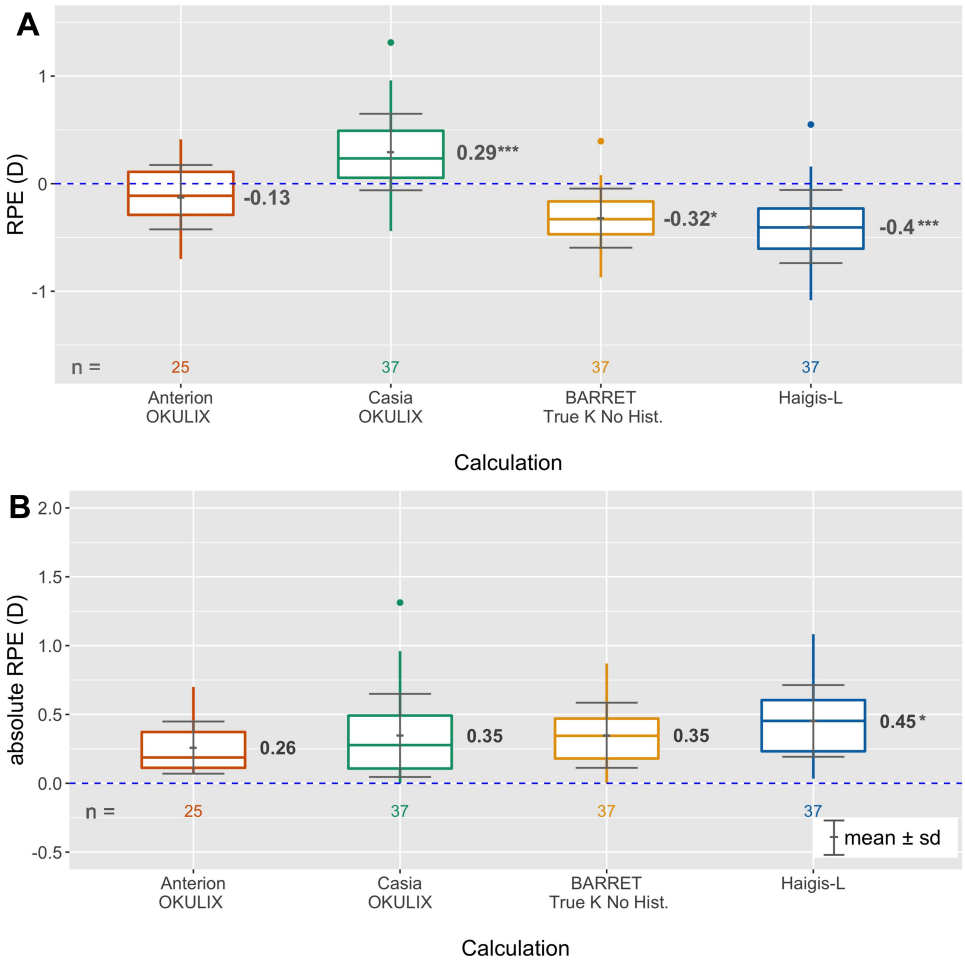

Figure 1 Boxplot of (**A**) arithmetic and (**B**) absolute prediction error.
Notes: *Adjusted $p \leq 0.05$; ***adjusted $p < 0.001$ (mixed models estimates different from Anterion OKULIX).
Abbreviation: RPE, refractive prediction error.

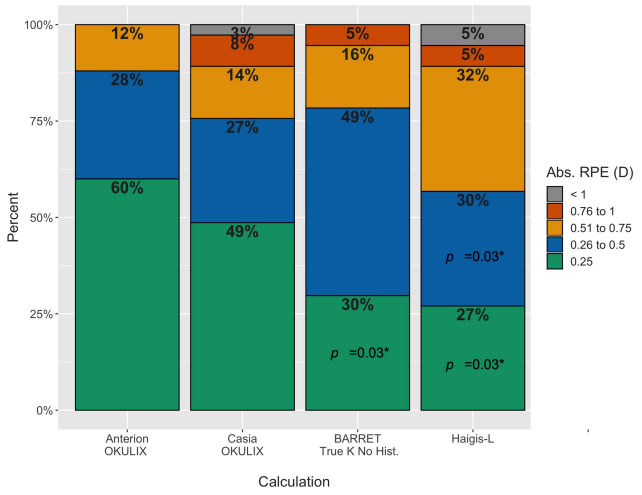

Figure 2 Percentages of eyes within certain range of RPE.
Notes: *Logistic mixed models estimates statistically significantly different from Anterion-OKULIX (Holm-Bonferroni adjusted p-values).
Abbreviations: Abs, absolute; RPE, refractive prediction error; *p*, adjusted *p*-value.

The adjusted R^2 was 0.39 and 0.17 for the Casia and the Anterion, respectively (Figure 4).

Discussion

The main objective of this study was to assess the accuracy of ray tracing IOL calculations based on OCT data in patients with a history of myopic LVC. We hypothesized that such IOL calculations could improve refractive predictability in these patients. We found that the arithmetic RPE of ray tracing calculations with data from the newest OCT device (Anterion) was statistically significantly better than the calculations with data from the Casia SS-1000 and traditional post-LVC formulas with constants optimized for normal eyes. The Anterion-OKULIX calculation had the lowest range for arithmetic RPE and the lowest SD and range of absolute RPE. However, the Barret TK NH had the lowest SD for the arithmetic RPE. The SD is considered important in formula comparison because it reflects the variability, while the mean, if not zero, means that the constants are not optimized for the study sample. The arithmetic mean was zeroed out for the comparison of AE, representing the ideal situation where the lens constants are perfectly optimized for the study sample. The Barret TK NH had the lowest MedAE, while the Anterion-OKULIX had the lowest range of AE. However, this comparison of AE between formulas and ray tracing calculation may not be valid for two reasons: 1) For the OKULIX, adjusting an offset for the predicted AQD would have to be based on measured AQD, not RPE, and besides the manufacturer does not recommend it. 2) Optimizing constants for post-LVC patients represents a problem (and we have not seen any studies where this is done): The greater variability seen in post-LVC patients means that it would require more data to get reliable constants. At the same time, there is a relatively low percentage of these patients (less than 3% in our clinic). So, for a post-LVC formula study, comparing RPE and SD with lens constants for normal eyes may be more representative for predicting future results. This has also been pointed out by Wang et al:

> . . . these data represent the normal clinical scenario in which surgeons routinely use their lens constants in normal cataract patients and do not have specific optimized lens constants for post-LASIK/PRK eyes.[40]

The Anterion-OKULIX calculation gave a statistically significantly higher percentage of eyes with RPE within ±0.25 compared to both formulas and also the highest

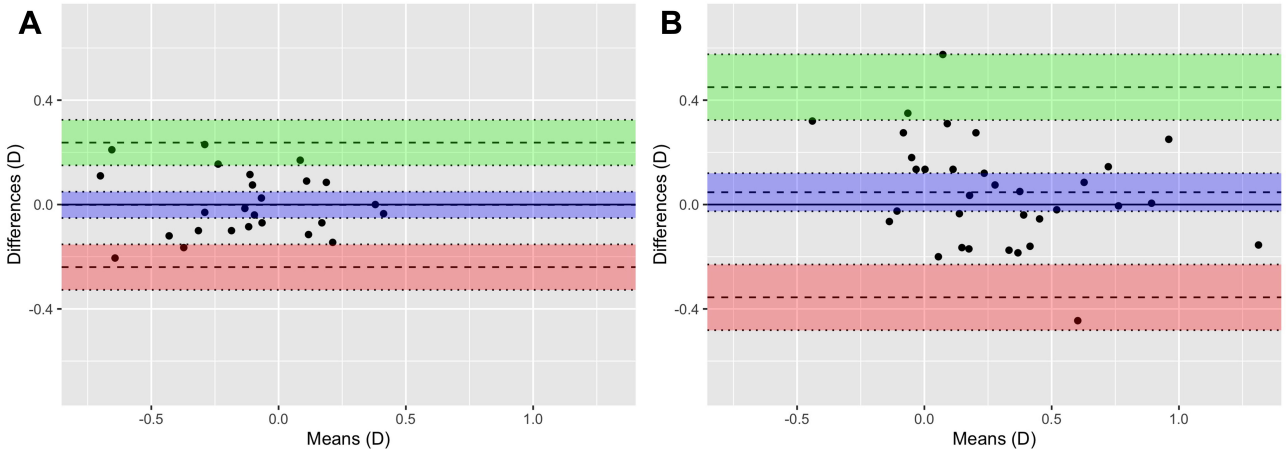

Figure 3 Bland–Altman plot with 95% limits of agreement between two repeated measurements/calculations of RPE with (**A**) Anterion-OKULIX, and (**B**) Casia-OKULIX.

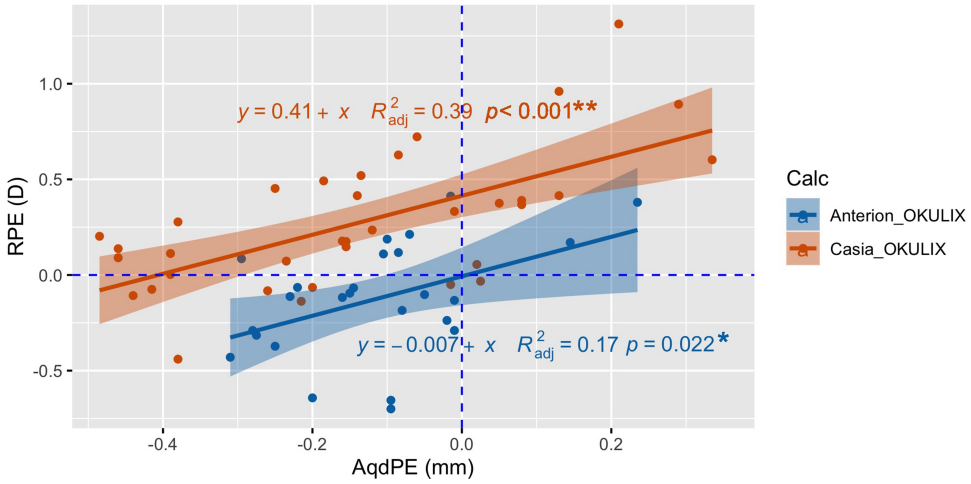

Figure 4 Correlation between RPE and aqueous depth prediction error for the OCT devices.
Notes: *Slope statistically significant; **intercept and slope statistically significant.
Abbreviations: RPE, refractive prediction error (D); AqdPE, aqueous depth prediction error (mm); Calc, IOL-calculation.

percentage within ±0.50, but this was only statistically significant compared to the Haigis-L formula.

To the best of our knowledge, there have not been any other studies analyzing the predictability of completely OCT-based ray tracing IOL calculations in post-LVC patients. However, some studies have investigated ray tracing calculations as a part of the post-LVC IOL-calculations: In a study of 24 eyes of 17 patients with previous myopic LVC, OKULIX IOL calculation based on anterior surface topography (with a fixed corneal thickness and a fixed ratio of anterior to posterior corneal radius) resulted in 42% and 75% of eyes with RPE within ±0.50 D and ±1.00 D, respectively.[41] Another study including 25 eyes of 25 patients with previous LVC found that ray tracing IOL calculation based on anterior corneal curvatures, but with different modified equivalent refractive indices, yielded an IOL-power prediction error within ±0.5 D (equivalent to about 0.35 D RPE) and ±1 D (0.7 D RPE) in 84% of eyes for both criteria. However, in this study, the individual calculation included several assumed pre or post LVC corneal properties, and the best equivalent refractive index was the mean of the study population.[42] So, both of these studies included several empirically drawn assumptions of corneal properties. As such, direct comparisons may not be valid.

Other studies have assessed the use of total corneal power in post-LVC IOL calculations: In a study by Savini et al they found that total corneal power (TCP) by ray tracing based on Scheimpflug corneal tomography gave corneal powers that differed from SimK by from 0.1 to 2.0 D. However, the use of TCP in traditional IOL formulas did not improve results as these formulas were developed for SimK.[43] Potvin and Hill analyzed different total corneal power values from a Scheimpflug device (Pentacam) combined with different IOL formulas. They developed a formula (Potvin-Shammas-Hill) based on the true net power in the 4 mm zone combined with the Shammas no-history formula and found an expected distribution RPE of 34%, 66% and 91% within ±0.25 D, ±0.50 D and ±1.00 D, respectively.[18] Helaly et al used a Scheimpflug equivalent K reading (anterior surface measurement adjusted to account for the back-surface) but combined two formulas to improve accuracy. Their best combination gave RPE within ±0.50 D and ±1.00 D for 67% and 93%, respectively.[44] Two recent studies compared no-history formulas with conventional formulas using TCP from an IOLMaster 700: Yeo et al found the best prediction errors using TCP with the EVO (a new unpublished formula), Barret TK NH, and Haigis formulas with 69%, 64% and 64%, respectively, within ±0.5 D and 83% within ±0.75 D for all three formulas, which was better than both the Barret TK NH and the Haigis-L.[45] Lawless et al found the best results with the Barret TK (TCP), followed by Barret TK NH and Haigis TCP with; 35%, 38% and 40%, respectively, within ±0.25 D; 75%, 63% and 60%, respectively, within ±0.50 D; 90%, 83% and 80%, respectively, within ±0.75 D.[46] Both these studies show that the use of TCP is likely to improve IOL-calculations in post-LVC patients. This could be expected as and both the Haigis-L and Barret TK NH uses

a regression equation, with its inherent variance, to account for the altered corneal power in post LVC corneas. In the present study, the percentage of eyes within certain ranges of RPE for the Anterion-OKULIX calculation appear even better, which is likely to result from the ray tracing calculations using OCT tomography data for a full optic zone of 5 mm and also that the software takes spherical aberrations of both the IOL and the cornea into account.

Several authors have investigated Ray tracing IOL calculations in unoperated eyes. One study compared different ray tracing IOL calculations and found with Placido topography data, 72% and 98%, and with AS OCT data (Casia SS 1000) 77% and 97% within ± 0.50 D and ± 1.00 D, respectively.[47] The latter compares well with the Casia-OKULIX results in the present study (76% and 97%), which indicates that the predictability of ray tracing IOL calculations with OCT data is not limited to eyes with previous LVC. Hoffman and Lindemann (2013) used OKULIX with Lenstar data in a series of normal eyes and found 53%, 81% and 100% within ±0.25, ± 0.50 D and ± 1.00 D, respectively.[48] A recent study by Hirnschall et al investigated a new method for ray tracing–based IOL power calculation using individualized eye model data with a new OCT biometer (IOLMaster 700). In this eye model, the cornea front surface topography was reconstructed from reflection keratometry with 18 measurement spots. They found a mean absolute RPE of 0.33 ± 0.29 D, range 0.00 to 1.13 D, and 48%, 80% and 85% with RPE <0.25, <0.50 and <0.75, respectively.[49] All these studies found that ray tracing calculations yielded similar or better results than formula calculations. A recent study by Darcy et al compared newer formulas incorporating artificial intelligence (AI) with established formulas in more than 10.000 normal eyes. They found that the best AI-formula yielded 43%, 72% and 95% within ± 0.25, ±0.50 and ±1.00.[50] In the present study, results from the Anterion-OKULIX calculation appear even better than these studies indicating that this method is suitable also for eyes with no prior history of refractive surgery.

The mean arithmetic RPE for the Casia-OKULIX calculation was statistically significantly worse than for the Anterion-OKULIX. This could indicate a difference in accuracy (precision, repeatability or reproducibility) of the measurements between the two instruments. When comparing the repeatability of the two calculations for each device we found that the coefficient of repeatability was almost twice as high for the Casia as for the Anterion (0.41 versus 0.23). This shows that variability of measurements is a relevant source of error for both OCT devices, but for the Casia in particular.

Variance in measurements may be partially explained by slightly different positions of the eye's surfaces at each measurement as repeated measurements are unlikely to be taken from precisely the same angle and position.[28,51] The differences in variability for the OCT devices may be related to the difference in acquisition time (2.4 seconds for the Casia and less than one second each for cornea and AS data for the Anterion). So the risk for significant eye movement may be higher for the Casia. Furthermore, the Anterion includes AL measurement, while for the Casia-OKULIX calculation, the AL was taken from the OLCR-device. An SS-OCT with a longer wavelength offers better tissue penetration compared to OLCR, improving the likelihood of accurate AL measurements in a higher percentage of eyes.[52]

The postoperative refraction also depends on the actual postoperative lens position. Although this is influenced by the individual postoperative shrinkage of the capsular bag, the predictability of the lens position influences the refractive predictability. All IOL calculations use some prediction of the lens position which often is virtual, but the AQD from the OKULIX calculation relates to the physical IOL position that can be measured postoperatively. The mean AQD PE was not statistically significantly different between the two OCT devices, so this could not explain the higher RPE seen in the Casia-Okulix calculation. However, the Casia showed greater variance, and the correlation between AQD PE and RPE was stronger with the Casia. The AQD PE explained 39% of the total variance in RPE for the Casia, but only 17% for the Anterion. The lower predictability of AQD for the Casia-OKULIX calculation could be related to the fact that the Casia does not provide a measurement of the crystalline lens position or thickness.

The results for the post LVC formulas in this study are comparable to other studies. In a study from 2019 by Vrijman et al, they found the best RPE with the Barret TK NH formula, with 70% and 89% within ±0.5 D and ±1.00 D, respectively, while the Haigis-L showed 56% and 86% within ±0.5 D and ±1.00 D, respectively.[53] This was comparable with the formula results in the present study. Wang et al found similar results with the Haigis-L with 60% and 94% within ±0.50 D and ±1.00 D, respectively.[11] Brenner et al

found the prediction errors within ±0.25 D, ±0.5 D and ±1.0 D for 37%, 62% and 94% with Barret TK NH which is comparable with the present study. By applying a nomogram target of +0.45 D to the Haigis-L, they found 44%, 83% and 100% within ±0.25 D, ±0.5 D and ±1.0, respectively, which was better than both formulas in the present study.[54]

In our clinic, ray tracing based on data from the Anterion OCT biometer is now our preferred method for IOL power calculation for post-LVC patients. In addition to showing similar or better results compared with the best formula calculation in this study, some of the apparent advantages for such a method is that it does not require knowledge about previous surgery and no need for choosing from several formulas. Furthermore, adjustments of the predicted AQD are not necessary or recommended since complication-free state-of-the-art cataract surgery should give no significant impact of the surgical procedure on RPE and thus, no good reason for an "individualization" (Paul Rolf Preußner, PhD, e-mail communication, January 2020).

We have also seen promising results for IOL calculations in single cases with corneal graft, removed LASIK flap and extreme hyperopia. In theory, with sufficient and accurate data from the anterior segment, the ray tracing IOL calculation should be accurate for any patient, whether they have virgin eyes, have had any type of cornea surgery or have irregular corneas.

A limitation of the study is the low sample size. Even though we achieved a power of 0.8 for the 0.05 significance level, our sample includes a limited number of different combinations of biometric properties of the eye. More extreme values of AL, K or ACD and LT could give different results. However, this is less likely with the ray tracing calculations as these are exact calculations based on the true individual measurements of the subject's eye. Further studies including larger cohorts and different IOLs are advocated. Additional studies including eyes with previous hyperopic LVC or radial keratotomy would also be of interest.

Conclusion

We found that Ray tracing calculation based on data from a new OCT-based biometer achieved better arithmetic RPE and similar absolute RPE compared to formula-based calculations. Variability in OCT-based biometry measurement is a primary concern. Until such time as software updates allow for averaging several measurements to reduce variability, it is recommended that IOL power selection with the OCT devices studied here be based on two or more measurements.

Data Availability

The data that support the findings of this study are openly available at http://usn.figshare.com/.

Disclosure

Mr Bjørn Gjerdrum reports grants from The Research Council of Norway, grants from SkatteFUNN R&D tax incentive scheme, grants from Memira AS, during the conduct of the study. The authors report no other conflicts of interest related to this work.

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Appendix 1

Approvals from the Regional Committee for Medical and Health Research Ethics

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Claus Henning Thorsen	22845515	18.10.2018	2018/1569/REK sør-øst C
			Deres dato:	Deres referanse:
			14.08.2018	

Vår referanse må oppgis ved alle henvendelser

Luis Felipe Brenner
Memira ASi

2018/1569 Linseskifte med trifokale linser etter tidligere corneal laserkirurgi

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst) i møtet 20.09.2018. Vurderingen er gjort med hjemmel i helseforskningsloven § 10.

Forskningsansvarlig: Memira AS
Prosjektleder: Luis Felipe Brenner

Prosjektomtale (original):
Studien er en retrospektiv analyse av 241 etterfølgende RLE operasjoner der trifokale intraokulære linser er implantert i øyne som tidligere har fått korrigert en synsfeil med laserkirurgi. Det er kjent at de tradisjonelle formlene for beregning av linsestyrke til intraokulære linser ikke er valide på øyne som tidligere har gjennomgått laserkirurgi. Det er derfor utviklet flere formler til dette formål og det er ikke konsensus om én formel som gir det beste resultatet. Målet med studien er å evaluere de refraktive resultatene (sikkerhet, effektivitet og presisjon) og å definere en protokoll som gir best treffsikkerhet ved beregning av linser til denne pasientgruppen. For å vurdere presisjonen vil vi retrospektiv beregne anbefalt styrke med de ulike biometriske formlene og sammenligne med implantert linsestyrke og refraktiv resultat. Hypotesen er at denne kunnskapen kan benyttes til å utvikle en protokoll som øker presisjonen av linsestyrke til øyne som har gjennomgått laserkirurgi.

Vurdering
I dette prosjektet ønsker man ved retrospektiv gjennomgang av pasientjournaler å avdekke hvilken metode for beregning av linsestyrke som egner seg best for gruppen pasienter som har gjennomgått en RLE operasjon (inngrep hvor øyets linse erstattes med en kunstig flerstyrkelinse) etter forutgående korrigering av synsfeil ved laserkirurgi.

Det skal gjøres en retrospektiv analyse av refraktive data etter en veletablert prosedyre (phacoemulsifikasjon) med spesifikke inklusjonskriterier for tidligere laseropererte pasienter. De resultatene som skal sammenstilles er de samme målingene som alltid samles etter RLE.

Komiteen oppfatter dette som kvalitetssikring av behandling og prosjektet har dermed ikke som formål å generere ny kunnskap om helse og sykdom, slik dette forstås i helseforskningsloven §§ 2 og 4.

Komiteen viser for øvrig til hvordan kvalitetssikring forstås i Helse- og omsorgsdepartementets veileder til helseforskningsloven:

«Kvalitetssikring kan defineres som prosjekter, undersøkelser, evalueringer o.l. som har som formål å kontrollere at diagnostikk og behandlings faktisk gir de intenderte resultater. Nasjonale tiltak for å sikre og

forbedre kvaliteten i tjenestene inkluderer utvikling av nasjonale kvalitetsindikatorer, samordning og styrking av medisinske kvalitetsregistre og utarbeide gode faglige retningslinjer. Kvalitetsarbeidet må baseres på systematisk dokumentasjon.»

Etter komiteens vurdering faller prosjektet utenfor helseforskningslovens virkeområde, jf. helseforskningsloven § 2, jf. § 4 første ledd bokstav a.

Prosjektet kan gjennomføres uten godkjenning av REK innenfor de ordinære ordninger for helsetjenesten med hensyn til for eksempel regler for taushetsplikt og personvern. Søker bør derfor ta kontakt med enten forskerstøtteavdeling eller personvernombud for å avklare hvilke retningslinjer som er gjeldende.

Vedtak
Etter søknaden fremstår prosjektet ikke som medisinsk og helsefaglig forskning, og det faller derfor utenfor helseforskningslovens virkeområde, jf. helseforskningsloven § 2.

Komiteens avgjørelse var enstemmig.

Komiteens vedtak kan påklages til Den nasjonale forskningsetiske komite for medisin og helsefag, jfr. helseforskningsloven § 10, tredje ledd og forvaltningsloven § 28. En eventuell klage sendes til REK sør-øst C. Klagefristen er tre uker fra mottak av dette brevet, jfr. forvaltningsloven § 29.

Med vennlig hilsen

Britt Ingjerd Nesheim
professor dr. med.
leder REK sør-øst C

Claus Henning Thorsen
Rådgiver

Kopi til:luis.brenner@memira.no

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK vest	Jessica Svärd	55978497	12.03.2018	2018/75/REK vest
			Deres dato:	Deres referanse:
			26.02.2018	

Vår referanse må oppgis ved alle henvendelser

Bjørn Gjerdrum
Sørhauggaten 111

2018/75 Forekomst av avvikende tårefilm hos pasienter som har gjennomtått refraktiv kirurgi for 5-15 år siden

Forskningsansvarlig: IFocus Øyeklinikk AS
Ny Prosjektleder: Kjell Gunnar Gundersen

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK vest) i møtet 12.04.2018. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10. Tilbakemeldingen ble vurdert av leder for REK vest med hjemmel i helseforskningsloven (hfl.) § 11.

Prosjektomtale
Refraktiv laserbehandling (LASIK) kan gi forstyrrelser i øyets tårefilm i en periode etter operasjon. Studier har vist at regenerasjon av hornhinnens nerver kan være ufullstendig og dermed er det mulig at tårefilmen kan være påvirket i lang tid eller permanent. Vi er ikke kjent med studier av tårefilm så lenge som 5 år etter laseroperasjon, eller om ICL (linseimplantat) -behandling påvirker tårefilmen. Kunnskapen vil ha verdi for både klinikere og fremtidige pasienter som ønsker å gjennomgå refraktiv laserbehandling eller ICL-behandling. Avvikende tårekvalitet vil også være en betydelig forsterkende feilkilde når denne gruppen skal gjøre grå stær eller RLE-operasjon. Vil avdekke om pasienter som har gjennomgått a) refraktiv laserbehandling, eller b) ICL-behandling, for 5-15 år siden, har økt forekomst av avvikende tårefilm sammenlignet med en kontrollgruppe uten tidligere refraktiv behandling. Det er en kasus-kontrollstudie med en enkeltstående undersøkelse (tversnittsdesign).

Komiteens vurdering

Prosjektleders kompetanse
Prosjektleder skal ha de nødvendige forskningskvalifikasjonene og erfaringer for å kunne oppfylle prosjektleders plikter, jf. helseforskningsloven § 4 f. Bjørn Gjerdrum, er PhD-student og komiteen mener at han ikke har nødvendige forskningskvalifikasjoner for å være prosjektleder i dette prosjektet. Komiteen foreslår at Kjell Gunnar Gundersen tar rollen som prosjektleder.

Informasjonsskriv
Det bør stå i informasjonsskrivet hvordan kontrollgruppen blir plukket ut, slik at disse forstår hvorfor de blir kontaktet. Det må gå frem at deltakelse innebærer å stille til konsultasjon, 1 time. Informasjonen om at prøvene av tårefilmen skal lagres i en forskningsbiobank knyttet til Biologisk Fakultet ved Universitetet i Oslo må tas vekk siden det ikke er søkt om opprettelse av forskningsbiobank. I søknadsskjema står at prøvene skal destrueres innen 2 måneder, det er da ikke nødvendig å opprette biobank.

Komiteen ber prosjektleder vurdere å dekke reisekostnader for forskningsdeltakerne.

Komiteen ba om tilbakemelding med:
hvem som skal være prosjektleder,
ved hvilken utdanningsinstitusjon Bjørn Gjerdrum er registrert som PhD-student
og et informasjonsskriv som er revidert etter komiteens merknader

Tilbakemelding til komiteen

Prosjektleder endres til Kjell Gunnar Gundersen.

Bjørn Gjerdrum er registrert som PhD student ved Høgskolen i Sørøst-norge, Fakultet for helse- og sosialvitenskap. Opptaksbrev vedlagt.

Vedr prøver av tårefilm og lagring i biobank: Vi beklager at det er diskrepans mellom søknad og informasjonsskriv. Bakgrunnen for dette er at samarbeidet med Biokjemisk Institutt, Universitetet i Oslo og professor Tor Paaske Utheim kom i stand sent i prosjektet og at dette ikke ble ajourført i alle dokument. Viser derfor videre til vedlagt tilsvar til professor Tor Paaske Utheim vedrørende hans biobank. Kapillærprøvene vil bli tatt fortløpende av alle studiedeltagere og oppbevart i ultrafryser ved iFocus Øyeklinikk. Når rekrutteringen til studien er fullført og alle prøver tatt, vil kapillærprøvene sendes nedfryst til Biokjemisk institutt for Multiplex analyse. Etter endt analyse vil prøvene bli oppbevart i denne biobanken til prosjektet er fullført og resultatene publisert. Dette kan ta inntil 3 år. Skulle REK Vest ha nye spørsmål knyttet til dette aspektet eller andre deler av prosjektet kan prosjektleder nås direkte på telefon 91648707 eller via mail.

Informasjonsskriv er endret i følgende:
-Beskrivelse av hvordan kontrollgruppe er plukket ut
-At deltakelse innebærer å stille til konsultasjon 1 time
-At prøver av tårefilm oppbevares i en forskningsbiobank knyttet til Biokjemisk Institutt, Universitetet i Oslo og opphører etter at prosjektet er fullført og resultatene publisert. Dette kan ta inntil 3 år.

Vi vil vurdere om det finnes rom for å dekke reisekostnader for forskningsdeltakerne.

REK vest ved leder har vurdert tilbakemeldingen.

Vurdering

REK vest godkjenner Kjell Gunnar Gundersen som prosjektleder og tar informasjon om at Bjørn Gjerdrum er registrert som PhD-student ved Høgskolen i Sørøst-norge til orientering.

Vedrørende biobank så er forskningsbiobanken "Vevskultur" med godkjenningsnummer 2013/1924 og Tor Paaske Utheim som ansvarshavende en generell forskningsbiobank. En generell forskningsbiobank har evig levetid og prøver kan ikke lagres i denne en kort tid for å så destrueres. REK vest godkjenner opprettelse av en prosjektspesifikk forskningsbiobank med navn "Forekomst av avvikende tårefilm hos pasienter som har gjennomgått refraktiv kirurgi for 5-15 år siden" ved iFocus Øyeklinikk med Kjell Gunnar Gundersen som ansvarshavende. Denne biobanken opphører ved prosjektslutt og prøvene må da destrueres. Kapillærprøvene kan likevel sendes til Biokjemisk Institutt, Universitetet i Oslo for Multiplex analyse.

REK vest sender melding til biobankregisteret om opprettelse av biobanken.

Informasjonen om biobank i informasjonsskrivet må revideres i forhold til hvilken biobank prøvene lagres i. Øvrige endringer i informasjonsskrivet godkjennes.

REK vest vurderer prosjektet som forsvarlig å gjennomføre.

Vilkår

Informasjonen om biobank i informasjonsskrivet må revideres i forhold til hvilken biobank prøvene lagres i og sendes til REK vest på post@helseforskning.etikkom.no.

Vedtak
REK vest godkjenner prosjektet på betingelse av at ovenevnte vilkår tas til følge.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK vest på eget skjema senest 01.09.2019, jf. hfl. § 12. Prosjektleder skal sende søknad om prosjektendring til REK vest dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK vest. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK vest, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

Marit Grønning
Prof. Dr.med.
Komitéleder

Jessica Svärd
rådgiver

Kopi til:kg@ifocus.no

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK vest	Jessica Svärd	55978497	25.09.2018	2018/1526/REK vest
			Deres dato:	**Deres referanse:**
			14.08.2018	

Vår referanse må oppgis ved alle henvendelser

Kjell Gunnar Gundersen
Sørhauggaten 111

2018/1526 Instrumentavhengig variabilitet av keratometriske målinger hos normale og hos pasienter med hyperosmolar tårefilm

Forskningsansvarlig: IFocus Øyeklinikk AS
Prosjektleder: Kjell Gunnar Gundersen

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK vest) i møtet 05.09.2018. Vurderingen er gjort med hjemmel i helseforskningsloven (hforsknl) § 10.

Prosjektomtale
Grå stær (katarakt) operasjon og refraktiv linsebytte (RLE) er vanlige operasjoner med generell høy refraktiv treffsikkerhet. Styrken på linseimplantatet beregnes fra bl.a. målinger av hornhinnens kurve og øyets akselengde (biometri). Tidligere refraktiv laserbehandling påvirker nøyaktigheten av slik biometri dels pga. avvikende hornhinnekurve men muligens også pga. økt forekomst av avvikende tårekvalitet. Avvikende tårekvalitet kan gi betydelig usikkerhet ved tradisjonell refleksjonsbasert måling av hornhinnens kurve(keratometri). Optical coherence tomography (OCT) er teknologi som kan gi tomografiske bilder av strukturer i øyet. Vi ønsker å avdekke om keratometri med et nyere OCT basert biometer er mindre sensitiv for tårekvalitet enn et tradisjonelt biometer med refleksjonbasert keratometri ved å sammenligne instrumentenes repeterbarhet i en gruppe med avvikende tårekvalitet (i form av forhøyet saltinnhold (osmolaritet)), og i en kontrollgruppe

Vurdering

Forsvarlighet
Prosjektet ønsker å avdekke om keratometri med et nyere OCT basert biometer er mindre sensitiv for tårekvalitet enn et tradisjonelt biometer i en gruppe med avvikende tårekvalitet og i en kontrollgruppe. Prosjektet innebærer at deltakerne må komme til én times konsultasjon hvor keratometrisk måling blir gjort. I tillegg registreres relevante helseopplysninger. REK vest vurderer studien som forsvarlig å gjennomføre.

Prosjekttittel
REK vest vurdere det slik at prosjekttittelen bør omformuleres til forslagsvis «Instrumentavhengig variabilitet av keratometriske målinger hos pasienter med normal tårefilm og hos pasienter med hyperosmolar tårefilm».

Rekruttering
Opptil 40 pasienter med avvikende tårekvalitet i form av forhøyet osmolaritet og opptil 40 kontroller med normal tårekvalitet skal primært rekrutteres fra studie 2018/75 hvor osmolaritet blir målt eller i følge med

annen undersøkelse ved klinikken hvor slike målinger blir gjort. REK vest har ingen innvendinger til hvordan rekrutteringen skjer.

Målinger i regi av studien
Tårefilmens osmolaritet, biometri for beregning av intraokulær linsestyrke (hornhinnekrumning, aksellengde, forkammerdybde, linsetykkelse, irisdiameter).

Helseopplysninger
Kjønn, alder, øyestatus (dvs. visus, refraksjon, øyetrykk, billeddiagnostikk), annen systemisk sykdom. Relevante opplysninger knyttet til pasientenes generelle sykehistorie, spesielt vektet mot tidligere øyesykdommer.

Lagring av data og koblingsnøkkel
Koblingsnøkkel vil kun være kjent av forskningsleder og tre prosjektmedarbeidere. Nøkkelen vil bli oppbevart i låst skap i avlåst kontor (utenfor arbeidstid). Forskningsdata vil lagres i pasientjournal, dette må informeres om i informasjonsskrivet.

Reiseutgifter
Proskjektleder angir at studiedeltagere ikke vil få dekket noen utgifter, men dersom det er avgjørende (ved for eksempel lang reisevei) vil vi vurdere å dekke reiseutgifter.

Deltakelse i studier skal ikke innebære tilleggsutgifter for deltakerne. Deltakere som kommer til klinikken for å gjøre målingene utenom ordinær behandling må få dekket reiseutgifter.

Informasjons- og samtykkeskriv
REK vest syns at informasjonsskrivet er godt formulert. Det mangler dog informasjon om at data blir lagret i pasientjournal.

Vilkår

Informasjonsskriv knyttet til studien revideres i tråd med ovennevnte merknad og ny mal på REKs nettsider, slik at informasjonen som gis til deltakerne er forenlig med ny personopplysningslov. Komiteen ber om at revidert informasjonsskriv ettersendes REK vest på post@helseforskning.etikkom.no.

Vi gjør oppmerksom på at det kreves et juridisk grunnlag for å behandle personopplysninger. Nytt av 20. juli 2018 er at REKs godkjenning ikke lenger gir et juridisk grunnlag for å behandle personopplysninger. Nå må denne behandlingen også oppfylle krav i personvernforordningen. Fortsatt skal alle forskningsprosjekter som omfattes av helseforskningsloven forhåndgodkjennes av REK, men egen institusjon har ansvar for at behandlingen av personopplysninger er i henhold til personvernforordningen.

Vedtak
REK har gjort en helhetlig forskningsetisk vurdering av alle prosjektets sider. Prosjektet godkjennes med hjemmel i helseforskningsloven §§ 10 og 33 på betingelse av at ovennevnte vilkår tas til følge.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK vest på eget skjema senest 31.03.2020, jf. hfl. § 12. Prosjektleder skal sende søknad om prosjektendring til REK vest dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK vest. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK vest, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

Marit Grønning
prof. dr.med.
Komitéleder

Jessica Svärd
rådgiver

Kopi til:kg@ifocus.no

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK vest	Anna Stephansen	55978496	21.06.2019	2019/768/REK vest
			Deres dato:	
			30.04.2019	

Vår referanse må oppgis ved alle henvendelser

Kjell Gunnar Gundersen
Sørhauggaten 111

2019/768 Forbedring av refraktivt resultat av grå stær- eller linsebytteoperasjon for pasienter med tidligere synskorrigerende laserbehandling for nærsynthet

Forskningsansvarlig: IFocus Øyeklinikk AS
Prosjektleder: Kjell Gunnar Gundersen

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK vest) i møtet 05.06.2019. Vurderingen er gjort med hjemmel i helseforskningsloven (hforsknl) § 10.

Prosjektomtale
Det er veldokumentert at pasienter som gjennomgår katarakt-(grå stær) eller RLE- (refraktivt linsebytte) operasjon og tidligere har hatt synskorrigerende laseroperasjon har betydelig redusert treffsikkerhet. Ved tradisjonell optisk biometri måles hornhinnens fremre kurve, og sammen med akselengde beregnes IOL-styrke med erfaringsbaserte (empiriske) formler. Ved OCT-basert biometri kan man måle både fremre og bakre kurve på hornhinnen og andre avstander i øyet. Dette kan benyttes med individuell beregning av øyets lysbrytning (ray-tracing) for å beregne IOL-styrke. Denne beregningen sammen med tradsjonell beregning vil vi benytte til å velge IOL-styrke som mest sannsynlig gir optimalt resultat. Refraktiv treffsikkerhet for forskjellige metoder beregnes så i etterkant ved å sammenligne beregnet refraktiv styrke med faktisk oppnådd refraktiv styrke for hver pasient.

Vurdering

Formålet med studien er å forbedre presisjon ved katarakt- (grå stær) eller RLE- (refraktivt linsebytte) operasjon for pasienter med tidligere synskorrigerende laser operasjon.

Det er en prospektiv studie der man vil beregne styrken ved kunstig linse (IOL) ved å måle hornhinnens og øyet dimensjoner (biometri) hos pasienter som tidligere har gjennomgått laserbehandling av hornhinnen. I prosjektet vil man benytte instrumenter med nyere teknologi (OCT) til å gjøre individuell beregning av lysbrytningen i øyet. Disse målingene vil inngå i en vanlig forundersøkelse til operasjon. I prosjektet vil man innhente en del opplysninger fra journal samt registrere mål som er relevante for beregning av ny øyelinse.

Forsvarlighet
Pasienter skal gjennom tradisjonell optisk biometri og ny OCT-basert biometri. Dette kan benyttes med individuell beregning av øyets lysbrytning (ray-tracing) for å beregne IOL-styrke som mest sannsynlig gir optimalt resultat. Ved bruk av denne fremgangsmåten vil pasienter få større nøyaktighet for synsresultatet, og ingen ytterligere risiko utover det som må beregnes i operasjonsøyemed. Målet er at pasienter som har hatt synskorrigerende laseroperasjon skal oppnå minst like høy individuell treffsikkerhet som pasienter med

tidligere uoperert øyne. REK vest vurderer studien som forsvarlig å gjennomføre slik den er lagt opp.

Merknader til informasjonsskriv

Det er ingen prøver i prosjektet og derfor må setningen om at ' Dersom du trekker deg fra prosjektet, kan du kreve å få slettet innsamlede prøver og opplysninger..' slettes.

Ved trekking skal det oppgis kontaktopplysninger til prosjektleder, ikke til PhD-studenten.

Rekruttering

Man satser på rekruttering av 60 pasienter ved IFocus Øyeklinikk AS K. Aktuelle deltakere blir identifisert i forbindelse med henvisning eller forundersøkelse til katarakt eller RLE-operasjon. REK vest har ingen innvendinger mot dette.

Prosjektsluttdato
Prosjektleder skriver at ' Materialet vil bli arkivert i avidentiserbart form i låst skap.' REK vest gjør oppmerksom på at ved prosjektslutt skal alle data enten slettes eller anonymiseres (det vil si at koblingsnøkkel skal slettes). Alle data i prosjektperioden skal oppbevares i tråd med forskningsansvarlig sine rutiner.

Vilkår: oppdatert informasjonsskriv sendes REK vest for vurdering til rek-vest@uib.no.

Vedtak

REK vest har gjort en helhetlig forskningsetisk vurdering av alle prosjektets sider. Prosjektet godkjennes med hjemmel i helseforskningsloven § 10 på betingelse av at det ovennevnte vilkåret tas til følge.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK vest på eget skjema senest 01.12.2021, jf. hfl. § 12. Prosjektleder skal sende søknad om prosjektendring til REK vest dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK vest. Klagefristen er 31.08.19. Dersom vedtaket opprettholdes av REK vest, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

Marit Grønning
dr.med.
Avdelingsdirektør, professor

Anna Stephansen
sekretariatsleder

Kopi til:kg@ifocus.no

Doctoral dissertation no. 99
2021

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Improvement in refractive precision for intraocular lens power calculations in patients with a history of laser vision correction for myopia

Dissertation for the degree of Ph.D

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Bjørn Gjerdrum

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