Impact of Wavefront-Guided Laser *in situ* Keratomileusis on Monochromatic Higher Order Aberrations and Vision

By

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Author’s Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

Wavefront-guided (WFG) laser *in situ* keratomileusis (LASIK) differs from conventional surgery by applying a refined algorithm for tissue removal, based on information from preoperative wavefront aberration data. Since the introduction of this technology, there have been few investigations comprehensively reporting outcomes, particularly for hyperopic treatments. This thesis aimed to determine the impact of myopic and hyperopic WFG LASIK on visual acuity, contrast sensitivity, higher order aberrations and subjective ratings, as well as determine the relationship between these outcome measures.

Bilateral WFG LASIK was performed on 324 myopic eyes (162 subjects) and 62 hyperopic eyes (31 subjects). High contrast (HC) and low contrast (LC) best-corrected visual acuity (BCVA) and contrast sensitivity were assessed using ETDRS charts and vertical sinusoidal gratings, respectively. Higher order ocular aberrations were measured using a Shack-Hartmann wavefront sensor and analyzed across a 5.0 mm pupil. Subjective ratings were assessed using a closed-ended categorical questionnaire. Assessments were conducted prior to surgery and at three and six months postoperatively.

WFG LASIK had minimal impact on BCVA and contrast sensitivity; however there was an impact on the magnitude and profile of higher order aberrations, which differed between the myopic and hyperopic groups. There was a greater increase in higher order aberrations for the hyperopic group, who also had a tendency to have lower visual outcomes and worse subjective ratings. Despite these results, there were no associations between subjective ratings and higher order aberrations, LC BCVA or contrast sensitivity for both groups and a clear understanding of the relationship between these outcome measures was not apparent. Factor analysis revealed a variety of factors that contributed to the outcome measures for this data set, with the three main factors being: *subjective ratings, vision* and *optical quality*.

In conclusion, WFG LASIK had excellent outcomes in terms of visual acuity, contrast sensitivity, and subjective ratings, despite an increase in higher order aberrations compared with those found prior to surgery. Hyperopic outcomes were slightly worse than myopic outcomes. Further investigation is required to determine the impact of higher order aberrations on visual acuity, contrast sensitivity and subjective ratings, as well as the relationship between these measures.

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Chapter 1

Background and literature review

Preface

Laser *in situ* keratomileusis (LASIK) can be defined as the permanent correction of refractive error by the programmed ablation of corneal tissue using an excimer laser. Wavefront-guided (WFG) LASIK is a technique used to apply a refined algorithm for tissue removal based on information from preoperative wavefront aberration data. The ultimate goal of this procedure is to reduce the amount of postoperative lower and higher order aberrations in order to improve visual quality and subjective results following surgery. As a result of wavefront aberrometry being used as an objective measure of preoperative and postoperative visual quality, there is a better understanding of the impact of LASIK on the optics of the eye. This thesis aims to investigate the impact of WFG LASIK on the monochromatic higher order aberrations of the eye for myopes and hyperopes and to determine how these relate to standard measures of surgical outcomes, such as visual acuity, contrast sensitivity and subjective complaints. A greater understanding of these areas can lead to enhanced information which will help to further refine this procedure, in an attempt to improve clinical outcomes. Additionally, determining how well current visual performance measures reflect these optical changes will aid in the future development of an improved vision testing strategy to clinically measure postoperative results.

Background

Basic structure of the eye

As light enters the eye it first passes through the tears and the cornea, followed by the aqueous humour and the crystalline lens. The tear film covered corneal interface provides approximately two thirds of the refractive power of the eye and the crystalline lens provides approximately one third.[1] After passing through the lens, light travels through the vitreous humour before reaching the retina. Both the aqueous humour and vitreous humour have little influence on the refractive power of the eye. Once light reaches the retina, it is absorbed by photoreceptor cells, which transduce the light energy into electrical impulses, which are carried to the brain by the optic nerve, for final visual processing. As this thesis is related to refractive surgery, which alters the shape of the cornea, the focus will be on the optical and physical properties of the cornea. However, a more detailed description of the other refractive components of the eye can be found in the textbook “Optics of the Human Eye” by W.N. Charman.[1]

The cornea is a highly specialized tissue enabling it to optimally refract and transmit light. It has a diameter of approximately 11.5 mm and a thickness of 500 µm to 600 µm in the center and 600 µm to 800 µm at the periphery. In humans, the refractive power of the cornea is approximately 43 dioptres.[1] The average cornea has a prolate elliptical shape (i.e. steeper centrally and flatter in the periphery). The peripheral cornea also exhibits less toricity than the central cornea.[2] Work has suggested that there is significant meridional variation in corneal asphericity, and that the steeper principal corneal meridian flattens at a slightly faster rate than the flattest meridian.[2] The corneal collagen orientation has been found to become circumferentially oriented in the peripheral cornea, which could be an anatomic reason for the reduction in toricity found in this area.[3, 4] Most individuals exhibit a small degree of with-the-rule astigmatism (i.e. the steepest corneal meridian is oriented near vertical).[2, 5] The back surface of the cornea has been shown to have a toric surface,[6] however due to the small refractive index change from the cornea to the aqueous the back surface plays only a small role in the total power of the eye (approximately -6D).[1]

Structurally, the cornea consists of five main layers (refer to Figure 1). From front to back, they are: (1) the epithelium, (2) Bowmans layer, (3) stroma, (4) Descemets membrane and (5) the endothelium.

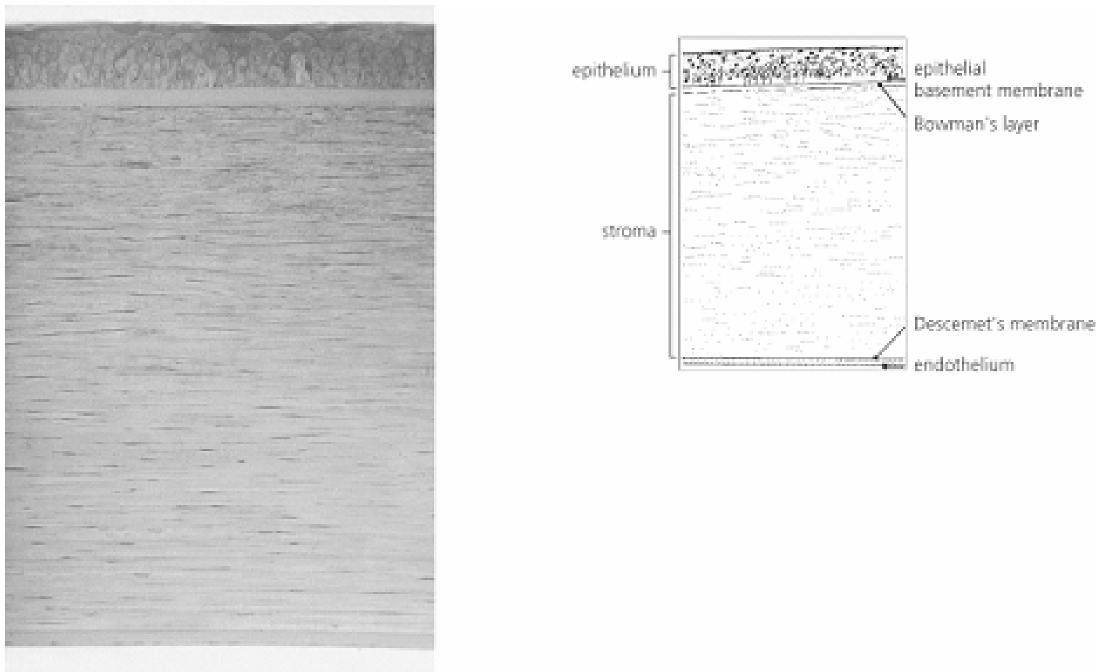

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Figure 1: Layers of the human cornea.[7]

The corneal epithelium is a multicellular structure and has an average thickness of nearly 50 µm and is five to seven layers thick.[8] The lateral borders of the cells are attached by desmosomes and the basal plasma membrane is attached to the basement membrane by hemidesmosomes. Running between epithelial cells is an extensive network of sensory nerve fibre endings. Removal of the epithelium causes little or no change in the anterior corneal curvature, suggesting that it has a minimal role in corneal strength.[9] It does play a major role in wound healing and can quickly regenerate in approximately seven days.[8]

Bowmans layer is immediately beneath the basement membrane of the epithelium and is an 8 µm to 12 µm thick, acellular condensation of stroma made up of collagen fibres.[10] In relation to the stroma, individual collagen fibrils are two-thirds smaller (20-25 nm in diameter) and more randomly oriented.[10] The function of this membrane is not entirely clear, however it has been hypothesized that it helps to maintain epithelial regularity and/or serves to prevent close contact between epithelial and stromal cells.[8] Wilson et al.[11] postulate that Bowmans layer may be actively maintained throughout adult life by regulatory systems mediated by the epithelium.

The corneal stroma lies beneath Bowmans layer and comprises nearly 90% of the total corneal thickness.[12] It is unique among connective tissues, in that it is extremely organized and transparent. On a weight basis, the stroma is approximately 78% water, 15% collagen and 7% non collagenous proteins, proteoglycans and salts.[12] Three hundred to five hundred lamellae, 0.2 mm broad and approximately 2 µm thick run from limbus to limbus and are stacked with angular offsets.[4] This orientation becomes increasingly random in the anterior stroma where significantly more oblique branching and interweaving are noted.[10] Interlamellar branching is also more extensive in the corneal periphery than in its centre.[13] The collagen fibers are enmeshed in a ground matrix of glycosaminoglycans such as keratin sulfate and chondroitin sulfates.[14] Both substances, particularly chondroitin sulfate, are markedly hydrophilic and contribute to a negative intrastromal fluid pressure under which the entire stroma is heavily compressed.[12] The stroma is further compressed at the posterior surface by intraocular pressure.[15] In the normal physiologic state this compression is maintained by a combination of lamellar tension, anterior evaporation of the tear film,[16] low permeability of the epithelial and endothelial layers to water,[17] and active endothelial transport of bicarbonate. Structurally, a proportion of the anterior lamellae insert into Bowmans layer to contribute to the stability of the corneal shape.[4] According to swelling experiments, the most anterior aspect of the stroma swells less than the posterior aspect. This has been attributed to the higher degree of interweaving of the anterior lamellae, which protects against changes in corneal curvature.[18] A greater degree of swelling in the posterior cornea has also been attributed to water-retention differences between proteoglycans distributed in the anterior and posterior aspects of the cornea.[19, 20]

Posterior to the stroma lays Descemets membrane. This is a thin acellular layer that serves as the modified basement membrane of the endothelium. This layer can be as thick as 10 µm and is regenerated by the endothelium if damaged.[8] It has been postulated that tension exerted on Descemets membrane may help to maintain corneal curvature.[8]

The most posterior layer of the cornea is the endothelium, which consists of a single layer of flattened, polygonal cells, 4-6 µm thick, whose plasma membranes interdigitate with one another. Endothelial cells are connected by tight junctions and they play a major role in controlling the normal hydration of the cornea, both by a barrier function limiting access of water from the aqueous humour to the corneal stroma, and by an active transport mechanism. The endothelium is characterized by a low regenerative capacity.[21] The overall lack of proliferation in the endothelium results in age-related decrease in cell density, with an average cell loss of 0.3% to 0.6% per year.[22]

Refractive error and ocular aberrations

Ideally, if the eye were a perfect optical system it would focus all rays of light from a distant point source into a singe image point on the retina. However, the eye suffers from various optical irregularities including aberrations and scatter. An optical aberration in an imaging system is any ray of light that is misdirected from its desired image point. The two largest aberrations affecting vision in healthy, non-surgically treated eyes are the second-order aberrations defocus and astigmatism. Defocus refers to a translation along the optical axis away from the plane of best focus. Myopia is the condition where light rays from a distant object converge to a point in front of the retinal image plane and hyperopia is the condition where light rays from a distant object converge to a point behind the retinal image plane. In astigmatism, light rays from a distant object converge to form two perpendicular principal meridians. These principal meridians can occur (one or both) in front, behind, or on either side of the retinal image plane. Examples of these conditions are shown in Figure 2.

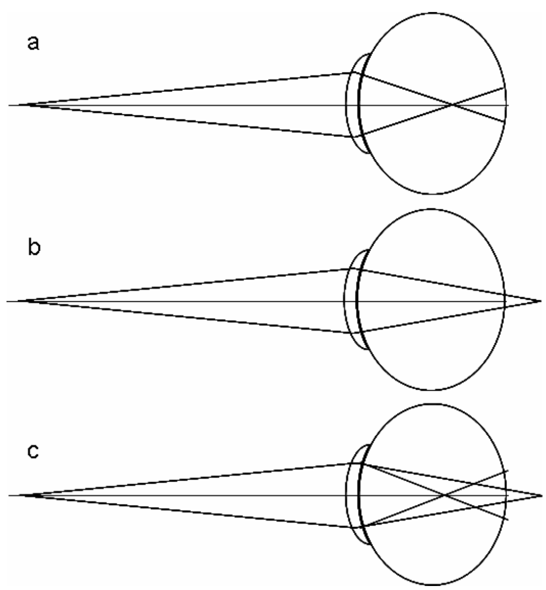


Figure 2: Simplified schematic of an eye with a) myopia b) hyperopia and c) astigmatism

At birth, the eye is too short for the optical power of the cornea and lens and is therefore hyperopic.[23] During development, the process of emmetropization occurs, whereby the axial length of the eye increases to match the optical power of the eye. There has been a great deal of work aimed at understanding this process, which is outside the scope of this thesis. Ultimately, the refractive error of the eye is strongly related to its axial length, with myopes having longer axial lengths and hyperopes having shorter axial lengths, particularly for high refractive errors.[24, 25] Some studies also report a low, but statistically significant association, between corneal curvature and refractive error, with myopic eyes being steeper centrally[24] and more oblate peripherally[26] than hyperopic eyes. However, other authors have not reported a significant correlation between corneal curvature and refractive error.[27, 28] It has been suggested that the ratio between axial length and corneal radius of curvature may have a stronger relationship with refractive error than corneal curvature alone.[29, 30]

Ocular astigmatism is a combination of corneal astigmatism, which occurs as a result of unequal curvature along the two principal meridians of the anterior cornea, and internal astigmatism, which may be due to the posterior cornea and/or the crystalline lens. It has been suggested that internal astigmatism is approximately 0.5D and is relatively constant with different amounts of corneal astigmatism occurring across subjects.[31] A recent comprehensive literature review of astigmatism is provided by Read et al.[32]

According to a recent overview of myopic and hyperopic refractive error in adults,[33] the prevalence of adult myopia ranges from 12.6% to 18%, except for populations of Chinese and European decent, which had rates of 28% and 26.5%, respectively. For children, the prevalence of myopia is greater for populations of Asian decent.[33] The prevalence of hyperopia is greater than myopia, with a prevalence rate between 36%[34] and 57%.[35] With age, there is a trend for a hyperopic shift in adults around 45 years, which continues until 60 to 80 years, when a shift towards myopia occurs.[33] A higher prevalence of hyperopia in woman and less refractive error in Hispanic and black ethnic groups has been reported.[36] Low amounts of astigmatism occurs commonly, but higher amounts occur less frequently.[32] One study on 1112 military patients reported 0.25D or more astigmatism in 63% of the eyes, with 70% being less than or equal to 1.00D.[37]

In addition to the second-order aberrations defocus and astigmatism, ocular higher order aberrations (third-order and above) exist, but normally to a lesser degree. Ophthalmic prescriptions have typically excluded these ocular higher order aberrations because they could not easily be measured or corrected by traditional means, such as spectacles or contact lenses. Wavefront aberrometers are now commonly being used to characterize these higher order aberrations in order to provide additional information relating to the optical quality of the eye.

Introduction to wavefront sensing

Methods of measurement

Techniques to measure ocular aberrations have been around for many decades. A wavefront sensor quantifies the wavefront error of the eye, which is defined as the difference between an unaberrated reference wavefront and the actual wavefront formed by the eye's optics. Applegate et al.[38] provide a review of the methods of measuring aberrations of the eye. As described in this review article, some of the current wavefront sensors are based on the simple device known as Scheiner's disk, which was described nearly 400 years ago.[38] The theory behind Scheiner's disk is that two retinal images are formed from a distant point source of light when viewed through a disk with two holes.[39] A lens of the correct power could then be used to bring the two points of light together on the retina, providing information relating to the eye's optics. Smirnov later expanded this method by using a moveable light source for the outer pinhole and a fixed light source for the central pinhole as a reference. The isolated ray of light could then be redirected by adjusting the moveable light source along an x (horizontal) or y (vertical) direction until it intersected the fixed light on the retina. The movement along x and y provided the measurements of the ray aberration for the eye at that given pupil position. This could be repeated for many different positions in order to determine the wavefront aberration for the entire pupil. Currently, the subjective spatially resolved refractometer[40] and objective ray-tracing refractometer[41, 42] are based on the same principle. The advantage of a ray-tracing system is that it measures each point separately, as opposed to all data points passing through the pupil at once, so it avoids the criss-crossing of light rays, which can lead to errors in calculating the wavefront error in a highly aberrated eye.

In 1846, Tscherning demonstrated that deviations of light can be quantified subjectively by viewing a point source through a grid superimposed on a blurring lens.[43] In the 1970s Howland and Howland used the design of Tscherning's aberroscope, combined with a crossed-cylinder lens, to project a grid pattern of light onto the retina that subjectively assessed the monochromatic aberrations of the eye.[44] The main limitation of this method was that it was time-consuming and imprecise due to its subjective nature. This method was later modified to eliminate the uncertainty of the subjective sketches by photographing the grid on the subject's retina.[45]

Concurrent with these developments, Hartmann used the principle of Scheiner's disk and perforated an opaque screen with multiple, tiny holes. The deviation of each narrow bundle of light rays as they passed through these holes provided the error in the wavefront slope.[38] Following this, Shack and Platt used tiny lenses instead of apertures to focus light into an array of spots, which is known as the Shack-Hartmann technique.[46] The Shack-Hartmann aberrometer utilizes a bundle of light that enters the eye and is reflected off the retina. As the light is reflected through the eye, it is subject to the eye's aberrations and projects out through the exit pupil, striking a grid of tiny lenses, called a micro-lenslet array. Each of the tiny lenses focuses a small part of the wavefront onto a charge-coupled device (CCD). The spatial displacement of each spot relative to the optical axis of the corresponding lenslet is a direct measure of the local slope of the incident wavefront as it passes through the entrance aperture of the lenslet. Integration of these individual slope measurements provides the shape of the aberrated wavefront exiting the eye.

Comparisons have been made between methods of wavefront sensing.[47-49] Moreno-Barriuso et al.[47] compared laser ray tracing, the Shack-Hartmann wavefront sensor (both objective methods) and the spatially resolved refractometer (a subjective method) and found that all three techniques provide similar information for wavefront aberrations in normal eyes. Figure 3 provides a summary of the methods for the main types of wavefront sensors used to measure ocular aberrations and each has its own set of advantages and disadvantages. Shack-Hartmann wavefront sensors are fast and easy to use and have become a popular choice (a more detailed description can be found in Chapter 2).

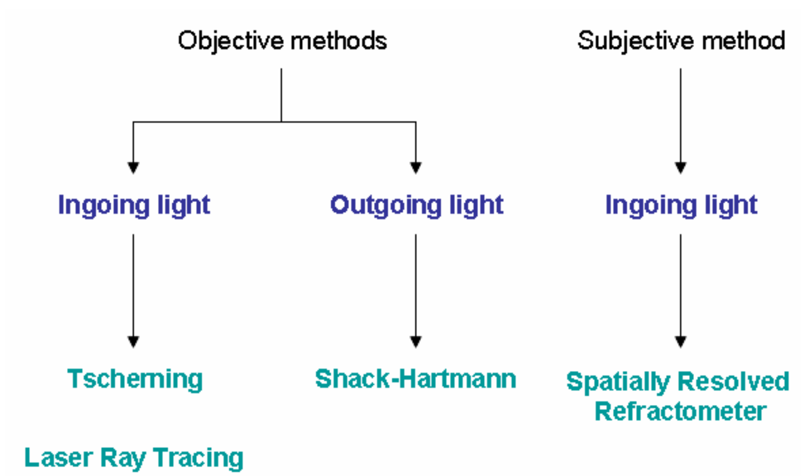


Figure 3: Summary of the general methods for various wavefront sensors

Zernike expansion of wavefront aberrations

Regardless of the technique, the purpose of a wavefront sensor is to measure the optical quality of the eye. This is done by measuring the wavefront error, which describes the deviation of the point-by-point values of an actual wavefront over a given aperture from an ideal shape (see Figure 4 below).

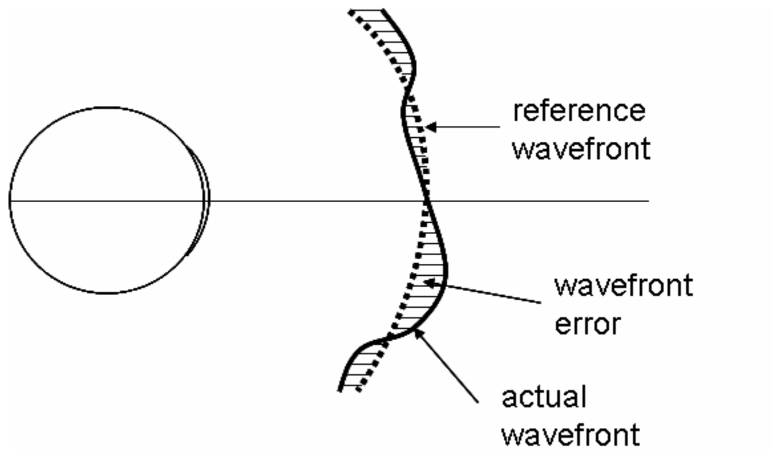


Figure 4: Wavefront error is the difference between the reference wavefront and the actual wavefront

The wavefront error can be broken down into its constituent aberrations and mathematically represented using a method called Zernike decomposition. The Zernike polynomial is the current American National Standards Institute (ANSI) standard (ANSI Z80.28) fitting function for description of ocular aberration in the eye.[50] Essentially, Zernike polynomials are mathematical descriptions of different, individual shapes or modes and describe wave aberration functions over circular pupils with unit radius. These individual modes add together in order to depict the final wavefront representing the optics of the eye. The wave aberration function, $W(x,y)$, is represented by a weighted sum of the series of Zernike modes:

$$W(x,y) = \sum_{n,m} C^{m}_{n} Z^{m}_{n}\,(x,y) \qquad (1)$$

where $W(x,y)$ is defined over the x,y coordinates of the pupil, C is the Zernike coefficient corresponding to a particular Zernike mode, Z, and n and m refer to the different radial order and meridional frequency, respectively. The Zernike polynomials become more complex as the order increases, which is important when describing a highly aberrated eye. A two-dimensional representation of the individual Zernike terms can be found in Figure 5.

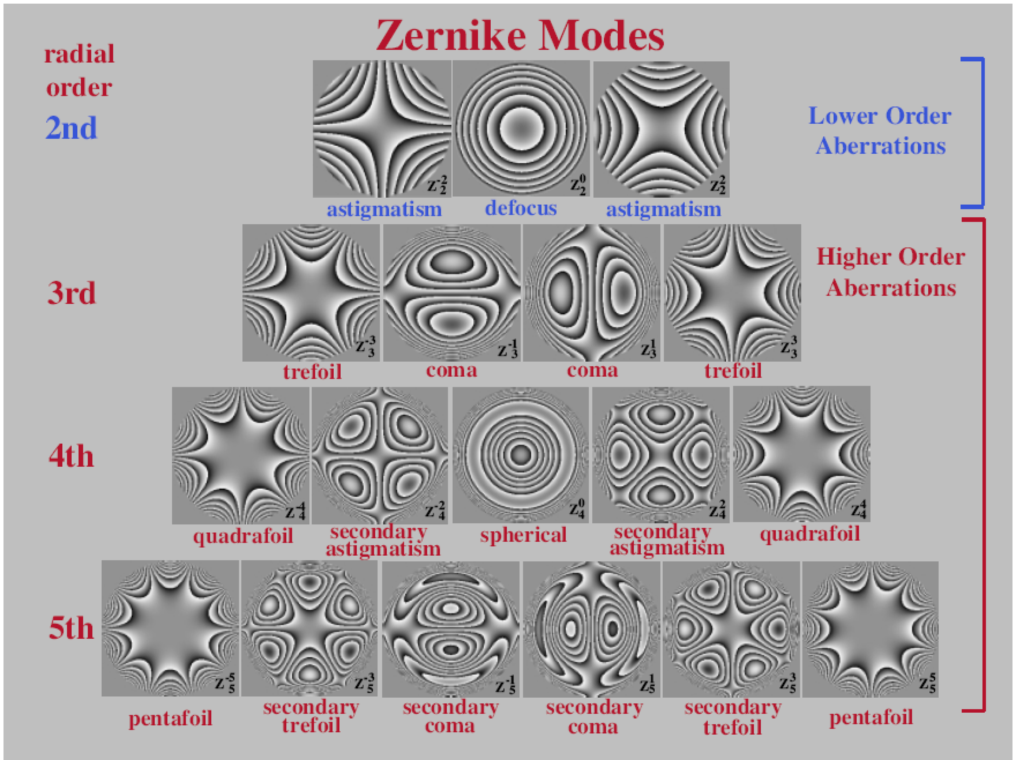


Figure 5: Individual Zernike polynomial modes. Courtesy David Williams' Laboratory, University of Rochester

In 1994, Liang and associates used a Shack–Hartmann wavefront sensor to describe higher order aberrations in the human eye[51] and in 1997 combined this with adaptive optics to correct the eye's lower and higher order aberrations.[52] This group and others have shown the potential visual benefit of correcting these higher order aberrations by measuring an improvement in contrast sensitivity.[52, 53] As a result, there have been more clinical use of wavefront aberrometry and a greater number of studies on the impact of higher order aberrations on vision.[54, 55] In general, higher order aberrations are correlated with a reduction in visual acuity and contrast sensitivity, particularly when tested in dim lighting conditions, when the pupil is large. Applegate et al[56] report that certain higher order aberrations are more detrimental to vision than others and that certain combinations of higher order aberrations can result in improved visual performance, despite an overall increase in magnitude of aberrations. This has led to a lot of recent and ongoing work investigating vision metrics to better understand the impact of higher order aberrations on vision.

Aberrations generated by individual components of the eye interact to reduce the total amount of ocular higher order aberrations. For instance, the cornea is prolate in shape (flattens towards the periphery) and usually exhibits positive spherical aberration.[57] In young individuals the crystalline lens exhibits negative spherical aberration.[58] Studies in young adults have found that the total ocular spherical aberration is less than corneal spherical aberration, suggesting partial compensation of corneal aberrations by the crystalline lens.[59] As the eye ages, however, the optics of the crystalline lens changes (three-fold between the ages of 20-70 years) [57] and results in a change from negative spherical aberration to positive spherical aberration.[58] These results imply that the degradation of the ocular optics with age can be explained largely by the loss of the balance between the aberrations of the cornea and the lens.[57, 60-63] In addition to changes in spherical aberration, increases in coma with age have been reported to result from the cornea becoming more asymmetric.[60, 64] One study reported that the shape of the cornea changes over time from with-the-rule to against-the-rule astigmatism.[64] It should be noted, however, that the decreasing diameter of the pupil with age limits the influence that changes in aberration structure has on image optical quality.[64, 65] In addition, a small amount of aberrations can be beneficial, with a small amount of aberrations resulting in a larger depth-of field.[66]

Temporal changes in higher-order aberrations have been measured following the blink. The tear film is the most anterior refractive surface of the eye and plays a very important role in maintaining a smooth optical surface for light transmission through the cornea. Local variations in the tear film can result in changes in the anterior radius, resulting in higher order aberrations[67] and subsequent reductions in image quality.[68] It has been reported that the irregularities in the tear-film surface immediately after a blink are often not smoothed in time before the next blink.[53] In addition, the inter-blink interval can vary with task.[69]

Diurnal changes in corneal thickness, corneal sensitivity and intraocular pressure have been reported and all have been found to be highest upon awakening.[70, 71] Srivannaboon et al[72] investigated the diurnal variation of higher-order aberrations and found no statistically significant change in aberrations up to the fourth order across an eight hour time period.

Systematic changes in aberrations depend on the accommodative state. Atchison and colleagues[73] found small decreases in spherical aberration as subjects accommodated up to 3.00 D, but He and colleagues[40] found small increases in fifth and higher order terms if subjects accommodated more than 4.00 D. Small differences in vertical and horizontal coma have been found between higher-order aberrations measured with the use of cyclopentolate compared to phenylephrine.[74] The authors hypothesized that these changes are due to a shift or tilt of the lens during accommodation, asymmetric surface changes on the lens during accommodation, or that the dilation effects of phenylephrine and cyclopentolate result in slightly different positions for the pupil center with respect to the eye's optics.[74] Aside from accommodation, variability of wave aberrations is also influenced by the Zernike order, measurement error, tear film stability and pupil size.[75, 76] Repeatability of measuring wave aberrations has been performed over time. Fluctuations have been reported to be 0.009 µm within a second, 0.018 µm within an hour, 0.021 µm within a week and 0.031 µm within a year.[77]

Minimizing higher order aberrations of the eye has not traditionally been a goal with conventional refractive error correction, however new methods to correct them are now being investigated. A large area of this research has been in the field of refractive surgery, which has come a long way over the past few decades.

Introduction to refractive surgery

Evolution of photorefractive surgery

Trial and error is often necessary in order to understand and demonstrate the benefit of new technology. This is particularly true in the field of refractive surgery, where surgical techniques have changed dramatically over the past 25 years, as a result of knowledge acquired with clinical practice. A greater understanding has been gained of the effect of refractive surgery on the eye and how the eye responds to surgery. Ultimately, this has led to more information that is being used to better predict outcomes and further improve results.

Incisional surgery is one of the earliest categories of refractive surgery and includes both astigmatic keratotomy (AK) and radial keratotomy (RK). For these procedures, incisions are strategically placed in the cornea in order to relax stromal lamellar tension and alter the anterior curvature of the cornea. The first human procedure was performed by Tutomu Sato in 1943 and resulted in damage to the endothelium due to a posterior keratotomy approach, where the incision was made too deep within the cornea.[78] Fyodorov and Durnev pioneered modern RK, with an anterior keratotomy approach in 1960,[79], where incisions were made more anterior in the cornea and resulted in less corneal damage.

Anterior RK was first performed in humans by Fyodorov in 1974 and then introduced to the United States by Leo Bores in 1978.[80] Many technological advancements followed and in 1981 a large, nine centre, 10-year Prospective Evaluation of Radial Keratotomy (PERK) study[81] was funded by the U.S. National Eye Institute to determine the outcome of a single radial keratotomy technique. This study demonstrated relatively good safety and efficacy, however a hyperopic shift of +1.00D or more in 43% of eyes between 6 months and 10 years following surgery was discovered.[82] The lack of stability and predictability of RK was further documented by a diurnal change in refraction, corneal curvature and visual acuity following surgery.[83-85] McDonnell *et al.*[85] reported a change of -0.50 to -1.62 D in 51% of 71 patients from morning to evening at the 11-year follow-up from the PERK study. Despite the unpredictable effects, incisional techniques have provided a great deal of information about how the cornea responds to weakening of the corneal lamellae following multiple radial incisions. While these techniques and are much less common today, they are still being used in some cases to reduce corneal astigmatism.

Concurrent with the development of RK, the fundamentals of lamellar corneal refractive surgery were pioneered by Prof. Jose I. Barraquer, beginning in 1949.[86] Barraquer developed the lamellar techniques of keratophakia and microkeratome freeze keratomileusis. The essence of the lamellar technique was to remove, add, or modify the corneal stroma so that the anterior corneal curvature is altered. Keratophakia involved the addition of a disc of donor corneal stroma under a lamellar flap to increase the corneal curvature. For microkeratome freeze keratomileusis, a thin, free cap of corneal tissue was removed, frozen and reshaped using a cryolathe and then replaced onto the stromal bed to alter corneal curvature.[86] Both of these techniques were difficult to perform and lead to unpredictable results. Several years of refinement and experimentation lead to automated lamellar keratoplasty (ALK) in the early 1960s. ALK implemented similar principles to microkeratome freeze keratomileusis, however instead of removing, reshaping and replacing a segment of anterior corneal tissue, a microkeratome was used to cut a small flap in the anterior cornea under which a thin disc of tissue was removed from the central stroma. The thickness and diameter of the disc was related to the patient's refractive error and resulted in a change in anterior corneal curvature. Despite the improvement over previous methods to correct myopia, ALK was largely abandoned for RK, which was less invasive and easier to perform.[86]

In 1973 ophthalmologist Stephen Trokel began testing excimer laser technology and its potential use in conjunction with, or as a replacement for, the microkeratome. The excimer laser uses a combination of argon (Ar) and fluride (F) gases to create an unstable, high-energy ArF molecule that, when excited, releases UV radiation with a wavelength of 193 μm. Two of the fundamental elements of laser tissue ablation are fluence and beam homogeneity. Fluence is defined as the amount of energy applied to the ablative zone, whereas homogeneity is defined as the pattern of energy distribution within the exposed area. Removal or ablation of tissue through chemical decompensation requires that a sufficient amount of laser energy is absorbed per tissue volume in order to break the molecular bonds of the material.[87] The excimer laser with 193 µm laser energy has been found to be optimal for precise ablation of corneal tissue, with minimal risk to the surrounding tissue.[88, 89]

The use of the excimer laser for stromal ablation was a major breakthrough in technology for refractive surgery. In 1983, Trokel and Srinivasan first described the removal of corneal tissue with an excimer laser for refractive surgery[88] and the first human application was by Theo Seiler in 1987, on an eye with melanoma.[90] Photorefractive keratotomy (PRK) thus evolved, which involves the mechanical debridement of the epithelium and subsequent laser ablation of the anterior stroma. The Food and Drug Administration (FDA) in the United States gave pre-market approval to use the excimer laser for PRK in the treatment of myopia in 1995.[90]

For modern PRK, following the removal of the epithelium and laser ablation of the anterior stroma, a bandage lens is placed on the eye, under which the epithelium is allowed to proliferate and migrate to cover the anterior corneal surface, which usually takes 3 to 4 days. Further epithelial and stromal healing follows and can continue for months afterwards. Compared to RK, PRK eliminated the unpredictability related to the use of incisions in the cornea, as well as the loss of corneal integrity that produced the marked diurnal variations in refractive error. PRK proved to provide more predictable results for low to moderate myopes,[91] however PRK has its own list of disadvantages. Intraoperative complications include loose epithelium during epithelial debridement or poor fixation by the patient resulting in decentration of the ablation.[90] Postoperative complications related to healing can result in poor predictability, central haze formation, and regression for moderate myopia (-6 to -10D) and even more so for high myopia (>-10D).[92-104] This postoperative regression has been attributed mainly to epithelial hyperplasia[100, 105, 106] and also to stromal regrowth.[107] The main risk factor for regression is the magnitude of the correction undertaken.[104, 108, 109] Postoperative pain is also a disadvantage of PRK.

In 1990 a different laser refractive procedure was described by IG Pallikaris. Pallikaris performed stromal ablation under a flap of corneal tissue and coined the term “LASIK” (laser *in situ* keratomileusis).[110] This novel concept of a corneal flap was created in order to preserve the epithelium and Bowmans layer and provide a natural bandage over the area of stromal ablation. There were three major developments which paved the way for wider acceptance of this technique. The first was the invention of the automated microkeratome in the 1990s, which provided more precise incisions and a thinner, more uniform flap than earlier models. The second was the origination of a “hinged flap”, which improved safety due to the elimination of the loss of “free caps”. The third major advancement in LASIK was the development of the sutureless technique, as surgeons recognized that adequate corneal flap adhesion was possible without the use of sutures.[86] One of main advantages was that LASIK minimized the epithelial-stromal interactions, which reduced the effects of wound healing and haze formation.[111-115] Post-operative recovery was also faster, with less discomfort compared to PRK. Additionally, higher refractive errors were able to be corrected due to reduced haze formation and less refractive regression.[114-116] Subsequently, LASIK has rapidly grown to become the most common refractive procedure performed today.

Conventional (non wavefront-guided) LASIK

Prior to discussing the results of LASIK surgery, it is first necessary to understand the procedure in detail in order to identify the various factors which might contribute to the final outcome. For conventional LASIK, the information used to derive the treatment of refractive error is based on the individual’s lower order aberrations, defocus and astigmatism. This information is manually entered into the laser and converted by the laser algorithm into an ablation profile for treatment. Once the patient has been prepared for surgery, which includes cleaning the eye area and the use of topical anaesthetic drops to numb the eye, they are positioned on the laser bed. An adhesive drape is placed superiorly and inferiorly on the eye to prevent the patient’s eyelashes from interfering with the laser. An eyelid speculum is then inserted to retract the eyelids and prevent blinking during surgery and circular positioning marks are placed on the cornea using gention violet dye, to help with flap repositioning once the procedure is complete. The cornea is then irrigated to maintain hydration and remove any excess debris. Next, a suction ring is place on the eye, typically with an inner diameter of 8.5 or 9.5 mm. The function of the suction ring is to stabilize the eye, to elevate intraocular pressure to create an even thickness keratectomy, and to provide a geared track for advancement of the microkeratome. Once adequate suction has been achieved (typically enough to increase the intraocular pressure to 65 mmHg),[86] a mechanical microkeratome is locked in place on the suction ring. The microkeratome rotates on a pivot and sweeps across the cornea, using a sideways oscillating blade to cut a flap of corneal tissue to a predetermined depth (either 160 or 180 µm).

After the flap has been cut, the surgeon gently lifts the flap back over the hinge and out of the way of the ablation area. Ultrasonic pachymetry is then used to measure the thickness of the residual cornea. Following this, the surgeon engages the eye-tracker (now present on most lasers) and instructs the patient to observe a fixation light. Stromal ablation then follows, with the number of laser pulses and time of surgery determined by the amount of correction. The area of stromal ablation is typically divided into two zones: an optic zone where the treatment is placed, and a transition zone where the edge of the optic zone is blended into the surrounding tissue. Both the optical zone and transition zone can vary in size and together define what is called the treatment zone. On average, optical zones are between 5.5 to 7.0 mm and transition zones between 1.0 to 1.5 mm. Various factors are involved in determining the optimal size of the optic zone. Smaller optic zones require less tissue removal, but if they are too small they can interfere with light entering the pupil and lead to glare and halos.[117] Early procedures were performed over a small optic zone and in some cases did not have a blended transition to non-treated cornea, which resulted in poor optical quality.[118-120] Although larger optical zones can minimize this effect,[118] the down sides include a greater amount of tissue removal and less predictability.[121, 122] When possible, the size of the optic zone is generally chosen to be slightly larger than the patient's mesopic pupil size.

Once the laser ablation is complete, the flap is repositioned over the cornea and smoothed with a wet sponge to prevent wrinkles. The surgeon checks for alignment of the flap by using the gentian violet markings and monitors adherence by watching for shifting while the patient blinks. The corneal flap immediately adheres to the stromal surface because of capillary action of the glycoproteins in the stromal ground substance and due to the endothelial pump.[123] After 24 to 48 hours an epithelial scar begins to form at the flap edge as a result of wound healing. A stromal seal and scar within Bowmans layer forms weeks to months following surgery, which is the strongest mechanism for flap adherence.[124]

Over the years LASIK has been refined so that the correction of defocus and astigmatism is quite successful, with the majority of patients achieving uncorrected visual acuity $\geq$ 6/6 and spherical equivalent refractive error of $\leq$ 0.50D (specific outcomes are presented in Chapter 3). Regardless of the advantages of LASIK, there have been reports of reduced visual quality after surgery, despite acceptable visual acuity and minimal refractive error.[125-127]

Investigations of postoperative subjective visual complaints have found a correlation with the ablation zone size,[117] mesopic pupil size,[128] and the amount of attempted correction. [129, 130] Starburst, haloes around lights and increased light sensitivity are just a few of the symptoms that have been reported following surgery.[131-134] The main difficulty, however, has been that these subjective complaints do not always match the level of postoperative best-corrected visual acuity (BCVA).[134, 135] As mentioned previously, aberrometry provides objective information on how light entering the eye deviates from a point focus. Ultimately, research investigating aberrations following surgery has indicated that even though only lower order aberrations (defocus and astigmatism) were actively being corrected, unwanted higher order aberrations were being surgically-induced.[126, 127, 134] These increases in higher order aberrations have been found to correlate with a decrease in visual quality.[54, 125, 136] More information on the subjective impact of higher order aberrations is presented in Chapter 5.

These findings have guided the development of wavefront-guided (WFG) refractive surgery, which uses preoperative aberration data to customize ablation patterns and refine treatments. WFG LASIK is the main topic of this thesis.

Wavefront-guided LASIK

WFG LASIK differs from conventional LASIK with respect to the information that is provided to the laser to program the laser ablation. The surgery itself (as described previously) is the same. For WFG LASIK, a wavefront aberrometer is used to measure the optics of the eye prior to surgery, which includes both lower order aberrations (defocus and astigmatism) and higher order aberrations. This information is provided to the laser in order to calculate the exact laser ablation required for treatment. Due to the more optically rigorous demands of the treatment, proper alignment and registration are necessary in order to place the treatment correctly on the eye. This has resulted in a number of minimum requirements that are necessary for both the laser and the registration system, which will be explained in more detail in Chapter 2.

Many of the initial studies on WFG LASIK were contralateral studies comparing WFG treatments in one eye with non-WFG treatments in the other eye. Many of these studies have revealed improved outcomes with WFG-LASIK, measuring reduced higher order aberrations in the WFG treated eye.[137-139] Regardless of the improvement of WFG-LASIK over non-WFG LASIK, however, surgically induced higher order aberrations still occur. Kohnen et al[140] reported the one year results for WFG-LASIK in 51 eyes and found a significant increase in spherical aberration, despite excellent defocus and astigmatism correction. Probably the greatest difficulty in achieving an aberration-free correction is due the ocular response to surgery.

Ocular response to surgery

Despite improvements in measuring and delivering accurate and precise refractive treatments to the eye, additional challenging factors still exist and are related to the ocular response to surgery. Two of these factors are intrinsic to the LASIK procedure, namely the creation of the flap and stromal ablation. Two additional factors are the corneal biomechanical and wound healing changes, which can mask precise ablation attempts, as well as lead to unpredictable results. These areas have attracted a large amount of interest over the past few years and will be discussed in more detail in the sections to follow.

Creation of the flap

Creation of the flap in LASIK is thought to be a possible source of inconsistency. Flap thickness - measured using optical coherence tomography (OCT),[141-144] confocal microscopy[145] and very high frequency ultrasound[146] - has a large amount of variability.[142, 147-157] In addition, temporal portions of the flap may be thinner than nasal portions.[158] The theory behind this difference is that it is due to a slower speed of blade advancement nasally with the microkeratome. Flanagan et al[159] examined the accuracy of 4428 flaps and found that thicker corneas and younger age resulted in thicker flaps and that flap thickness differed between microkeratomes.

In addition to inconsistent flap thickness, the microkeratome cut may result in a small hyperopic shift in refraction[160] and an increase in higher order aberrations.[161-164] Using a two-step procedure with two different microkeratomes, Waheed et al[164] found a small increase in all higher order aberrations except coma, with no predictable trends. Porter et al.[162] also investigated surgically induced aberrations following flap creation and found no observable trends over two months; however the flap was not lifted in this study. They suggest that manipulation and misalignment of the flap may be more responsible for an increase in higher order aberrations than the creation of the flap itself.[162]

A new procedure for flap creation uses a femtosecond laser. Early results using this technology have revealed highly accurate and reproducible flaps.[165] A study comparing outcomes with femtosecond laser and two other mechanical microkeratomes found fewer total higher order aberrations, including spherical aberration, with the femtosecond laser.[166] Surgically-induced coma, however, was similar between the three methods. A mechanical microkeratome was used in this study and is described in Chapter 2.

Stromal ablation

The relationship between the refractive effect produced and the depth of ablation is depicted by an algorithm developed by Munnerlyn et al.[167] The Munnerlyn formula:

$$\text{depth of ablation} = (\text{dioptres of correction x ablation diameter}^2) \div 3$$

essentially states that the depth of ablation increases exponentially with the square of the optical zone size. A greater amount of tissue ablation is required for larger refractive corrections.

The majority of surgically-induced higher order aberrations result from stromal ablation.[162] Many factors influence stromal ablation, including the attempted correction,[121, 122] optic zone size, laser characteristics and environmental factors.[168] The ablation rate, or depth per laser pulse, varies from 0.2 to 0.5 µm.[169] The ablation rate and quality of laser ablation depends on the radiant exposure produced by the laser. There are two basic laser delivery systems of laser energy: broad and scanning beam. Broad beam delivery systems utilize a computer-controlled variable iris diaphragm or variable-sized apertures for myopic correction. High speed photography has been used to observe the event of tissue ejection with laser ablation.[170, 171] Most of the ejected material dissipates with air flow, while part of it falls back onto the tissue surface. Both airborne and re-deposited material can block subsequent laser pulses. This has been implicated as a mechanism that contributes to the formation of localized steep central areas of corneal curvature, also known as “central islands”, with broad beam lasers.[171, 172] In order to reduce the formation of steep central islands, current laser systems utilize scanning beams of either fixed or variable size. The advantage of scanning systems is that they manipulate a small beam, which is highly homogenous.[172] The trade-offs include increased treatment time, corneal dehydration and a greater susceptibility to small amounts of decentration. WFG treatments require precision. Guirao et al.[173] determined that beam sizes ≤ 1.0 mm were adequate for correcting up to fourth order Zernike terms, with sixth order terms requiring beams ≤ 0.6 mm in diameter. A review of non-WFG LASIK across different types of lasers has shown a significant trend toward improved outcomes with improved laser technology.[174]

Mrochen et al.[175] investigated the relationship between corneal curvature and ablation efficiency and found that effective ablation decreases with increasing radius at the corneal surface. Yoon et al.[176] have suggested that a variable ablation depth per pulse caused by non-normal incidence of the laser spot on the cornea is partially responsible for the induction of positive spherical aberration in myopic treatments and negative spherical aberration in hyperopic treatments. Dougherty et al[168] found that corneal hydration affects stromal ablation depth, with excessive dehydration of the stromal bed leading to increased ablation.

Essentially, the greater the amount of attempted correction, the greater the amount of laser ablation required. This leads to less predictable results, in part due to the technical causes described above, as well as additional factors such as wound healing and biomechanical changes.

Wound healing

Wound repair involves both epithelial and stromal involvement. Epithelial hyperplasia and stromal remodelling are thought to be the two most important wound healing factors affecting the precise ablation attempts for WFG-LASIK,[177] both of which can be associated with refractive regression and haze. Keratocyte apoptosis is the first detectable event following epithelial injury, serving as a trigger for an exceedingly complex cascade of events to follow.[178] General epithelial wound healing includes the epithelial cells flattening, elongating and migrating as a sheet to first cover the wound. Following this, cells distal to the original wound undergo cell proliferation, stratification and differentiation. Lastly, the basement membrane is reformed and extracellular matrix is resynthesized and reassembled.[179] Stromal wound healing starts with apoptosis of the stromal keratocytes adjacent to the area of epithelial damage. Keratocytes adjacent to the apoptotic cells then proliferate and become fibroblasts and migrate to the wound area. This is followed by the fibroblasts transforming into myofibroblasts, which express actin and are involved with contracting the wound.[179]

As mentioned earlier, epithelial hyperplasia can occur after both LASIK[180-182] and PRK.[100, 106] The exact mechanism of epithelial hyperplasia remains unknown, however it may be a part of the wound-healing process or a response to the biomechanical changes of the cornea, such as tissue loss, redistribution of corneal tension,[183] and/or innervation changes.[184, 185] It has been suggested that epithelial hyperplasia is responsible for early reduction of postoperative over-correction, with later changes attributable to stromal remodeling.[186] Gauthier et al[100] suggest that for each 18 µm of epithelial hyperplasia, an additional 1.0 D of regression occurs. Factors associated with epithelial hyperplasia include small ablation zones, greater attempted corrections, and deep, irregular ablations.[106]

Changes within the stroma also occur following LASIK surgery. Regenerative remodeling of corneal repair tissue was first defined by Cintron and Kublin[187] almost 30 years ago. They documented the changes that occurred following deposition of opaque fibrotic wound tissue after penetrating injuries in young rabbit corneas and found that remodeling results in the re-establishment of parallel layers of collagen lamellae across the injured region. Small changes in flap thickness up to 1 week[144, 158] and in stromal bed thickness and overall stromal thickness up to 3 months after LASIK have been reported.[158] This could be due to several processes that occur during the early postoperative period: re-absorption of fluid introduced by intraoperative irrigation, biomechanical hydration shift, epithelial thickness modulation in response to laser ablation[144], and interface reflectivity change. After one week these systematic changes are small (<6μm).[144]

The formation of corneal haze has proven to be a considerable problem for PRK surgery. With LASIK, it is thought that the flap maintains a zone of normal cornea between the epithelium and stroma, which diminishes the interactions between cells that lead to the generation of myofibroblasts.[188] More healing occurs at the flap margins, however, where there is direct contact between the epithelium and stroma. Scar tissue is formed as a result of the fibrotic wound healing response at the flap margin. Haze can occur at the interface after LASIK and has been found to be related to the volume of stromal tissue removal,[104] diffuse lamellar keratitis and the retention of epithelial debris.

Modulating the wound healing response following surgery is an attempt to control biological variability and improve outcomes. Pharmacologic and gene therapy, most of which are aimed at inhibiting keratocyte apoptosis, continue to be explored.[115, 178]

Corneal biomechanical changes

There are a number of factors related to the biomechanical response of the cornea to surgery that are difficult to predict and can contribute to discrepancies between attempted and achieved visual outcomes. Current methods of assessing candidacy includes a review of systemic and ocular health history and medications, manifest and cycloplegic refraction, careful ocular health evaluation, corneal topography, ultrasound pachymetry and more recently wavefront aberrometry. Pre-operatively, two individuals can have very similar measurements, but end up with different post-operative outcomes.

The shape-subtraction model forming the basis for LASIK ablation profiles assumes a biologically and biomechanically inert cornea.[189] In reality, however, biological changes in the cornea result from stromal ablation and flap creation. Before the biomechanical response of the cornea to surgery can be understood, underlying corneal properties need to be examined. This is complicated due to the fact that corneal properties are not rotationally or axially uniform between the centre to the periphery or the anterior to the posterior cornea, respectively.[190]

Bowmans layer and the stroma provide the majority of corneal tensile strength, due to the fact they contain collagen fibrils.[190] Extensiometry studies, however, suggest that removal of Bowmans layer does not measurably alter the mechanical properties of the cornea.[191] Interweaving of collagen bundles between neighboring lamellae in the stroma provide an important structural foundation for transfer of tensile loads between lamellae.[189, 192] Cohesive tensile strength is greater in the anterior 40% of the corneal stroma and tensile strength increases with age.[193]

The stiffness, or elastic modulus, of the cornea is non-linear, with an initial slow uptake of load, followed by strain when maximal fibril recruitment is approached. There is a wide range of elastic modulus values reported in the literature, which is due in large part to variability in tissue hydration, loading conditions and experimental techniques using ex vivo tissue.[194]

Cohesive strength is a measure of interlamellar resistance to separation in the transverse direction and is expressed as a function of distance from the corneal center.[87] Interlamellar cohesive strength is important, since these connections provide a mechanical link between peripheral stromal expansion and central flattening with photoablation. Cohesive strength is greater in the peripheral compared to the central cornea[13] and in the superior compared to the inferior region.[195] This asymmetric distribution of cohesive strengths could be an important source of induced corneal astigmatism following keratorefractive surgery and for the predilection of infero-central corneal steepening with keratoconus.[195] Greater cohesive strength has also been reported in the posterior stroma compared to the anterior stroma, [196] which is relevant in regard to changes resulting from various ablation depths.

Shear strength describes the resistance to shearing and sliding of one lamella over another in the plane parallel to the lamellar axes (the longitudinal direction).[13, 195] The interweaving of collagen bundles provides shear strength, and is more extensive in the periphery than the center.[192] Although low compared to its tensile strength, shear strength provides a mechanism for tensile load transfer between lamellae that may affect corneal shape after photoablation.[192] Abnormalities in shear strength have been suggested in the pathogenesis of corneal ectasia,[197, 198] which is a progressive steepening and thinning of the cornea.[199]

In general, postoperative biomechanical changes have been attributed to changes in peripheral corneal curvature, which has a secondary effect on central corneal shape.[192] Dupps and Roberts[192] propose that laser ablation of the central corneal collagen lamellae reduces tension in peripheral layers, which results in central corneal flattening for both myopic and hyperopic procedures. Yoon et al.[176] used clinical data for corneal asphericity and spherical aberration changes following myopic and hyperopic treatments. They report that these data were best fit by combining variable ablation depth with treatment, as well as the biomechanical response of the cornea. They suggest a similar biomechanical change as Roberts[200] for myopes, however their hyperopic biomechanical model suggests central corneal steepening with peripheral corneal flattening. Further testing is still required to determine the exact biomechanical response of the cornea to treatment. Factors such as age, corneal thickness, corneal hydration and collagen properties may also play important roles.[201]

The LASIK flap itself may induce hyperopia, astigmatism and higher order aberrations that depend upon hinge position.[161, 202, 203] An increase in with-the-rule astigmatism has been attributed to flap creation with a superior hinge.[203-205] The hyperopic shift that occurs following flap creation supports the corneal biomechanical theory proposed by Roberts,[200] which indicates central corneal flattening and peripheral corneal steepening with the severing of corneal collagen lamellae. Astigmatism and higher-order aberrations could result from a non-uniform flap thickness or the asymmetry in corneal cohesive strength.[203] Potgieter et al.[203] suggest that a superiorly placed hinge and the motion of the microkeratome results in surgically-induced higher order aberrations, specifically vertical coma.

The creation of the flap unavoidably results in the severing of corneal nerves. Mixed reports exist regarding the placement of the hinge, with some authors reporting greater sensitivity loss with superior placed hinges[206] and others finding no difference in corneal sensitivity[207] or dry eye signs and/or symptoms[208] with flap hinge location. The width of the hinge could also be a factor, as narrower hinges have been attributed to greater loss of corneal sensitivity following LASIK.[209] Ultimately, confocal microscopy and other techniques show recovery of corneal sensitivity even without full regeneration of nerve bundle diameter, length or density,[210, 211] however the effect this has on corneal healing is not fully understood. Newer techniques using femtosecond lasers create thin and precise flaps.[212] An advantage is that these thin flaps are more anterior within the stroma compared to flaps created with mechanical microkeratomes and will hopefully result in slightly greater corneal stability following surgery. Potential disadvantages are that the flap is more fragile and that the distance between the stroma and epithelium is closer, which could result in an increased wound healing response.

Stromal ablation during LASIK decreases the tensile strength of the cornea by reducing the load-bearing portion of the cornea. Central ablation of stromal tissue relaxes lamellar tension in residual peripheral lamellar segments, which decreases local resistance to swelling and results in peripheral stromal thickening.[190] Most numerical models of refractive surgery state that the tensile load previously borne by the full complement of lamellae is shifted to the remaining posterior fibers, which now strain (stretch) slightly under the concentrated stress.[213] Since the limbal circumference is fixed, this would imply that this stretch occurs as central corneal bulging and anterior steepening. More recently, the proposed peripheral response has been considered, suggesting a peripheral thickening and peripheral steepening, with coincident central flattening.[200]

An increase in the forward shift of the posterior cornea has been reported following myopic LASIK.[214-216] Lee et al[214] have found that this forward shift is correlated with the residual corneal bed thickness and the ablation ratio per total corneal thickness. They report that no statistically significant changes in the post-surgical forward shift of the posterior corneal surface occurs if the residual corneal thickness remained greater than 350 µm or the ablation percentage was less than 10% of the total cornea thickness. The consequence of this forward shift is not entirely clear and requires further investigation.

The interaction of biomechanical effects and the depth of the ablation is an important consideration with respect to refractive outcomes. Litwin et al[9] demonstrated a depth-dependant response of the cornea using successive 50µm PTK ablations in four pressurized donor globes. The stroma's nonlinear response to ablation depth has further been explained in terms of the biomechanical response of the cornea.[200] Flattening may increase with ablation depth due to exaggeration of peripheral thickening and its secondary effects on central curvature in the anterior and mid stroma. When the ablation extends into the deep stroma is has been postulated that peripheral thickening may become decoupled from central curvature changes, due to the decrease in interlamellar connections in the posterior stroma. At this point, the flattening response due to peripheral thickening reaches a maximum and changes to central steepening as a result of central corneal weakening.[200]

Secondary procedures may respond differently than primary procedures, since the corneas are structurally and biomechanically different before and after surgery. Clinically, according to the biomechanical theory proposed by Roberts, an intrinsic flattening response augments the effects of a myopic procedure and impedes efforts to correct hyperopia.[200] This is supported by the observation that large over-corrections must be applied to treat high levels of primary hyperopia.[217] If an identical algorithm is used to treat secondary hyperopia of the same magnitude (i.e., after previous myopic LASIK), a significant overcorrection results and is attributed to the difference between the biomechanical status of the cornea before and after surgery.[217]

Ultimately, how much of the final corneal shape following LASIK is due to the biomechanical response, healing, or the ablation profile requires a great deal of additional attention. Future improvements and better predictability in refractive surgery will need to include an enhanced understanding of the wound healing and biomechanical changes following surgery. Recent work has investigated the effect of biomodulators in order to achieve more predictable outcomes. Currently, Mitomycin C is being used following surface ablation (PRK) for high myopia in order to reduce the risk for haze and regression.[115] The long term effects of biomodulators such as Mitomycin C and transforming growth factor (TGF)-β, for example, are currently unknown. Mitomycin C has been implicated with stem cell loss and the loss of keratocytes.[115] Computational models of corneal biomechanics are now beginning to incorporate fibril orientation data,[218] with the purpose of simulating more effectively the tissue's response to surgery. Symmetry in collagen organization between left and right eyes are also being investigated.[219]

Adverse events

The main safety concern for LASIK is weakening of the cornea, leading to corneal ectasia. It has been suggested that a minimum residual stromal thickness of 250 μm should be achieved to avoid complications such as iatrogenic keratectasia.[220-224] Despite the fact that nearly 17 million LASIK procedures have been performed since the early 1990s,[225] there has been few reports of long-term safety data. There are four papers published in the literature, reporting five to six year outcomes for 303 eyes.[226-229] Three recent studies on LASIK have reported the prevalence of corneal ectasia to be between 0.2% and 0.66%.[230-232] It can be postulated that current knowledge and screening techniques, including corneal topography to screen for keratoconus and thinner corneal flaps, has reduced the risk for ectasia. A review of corneal ectasia is provided by Randleman et al.[199]

Additional postoperative complications can occur, such as infection, diffuse lamellar keratitis, epithelial ingrowth, ocular surface dryness and clinically significant striae, to name a few. A comprehensive review of these complications can be found in the literature[233] and will not be discussed here.

Measures of visual quality

When attempting to correct the optics of the eye in order to optimize vision, it is first important to understand the limits of vision. Sampling of the retinal photoreceptors imposes a limit to the resolution of the eye.[234] This upper limit of resolution is called the "Nyquist sampling limit", which states that the maximum spatial frequency which can be resolved is equal to one half of the sampling frequency. In the human eye the highest density of cone photoreceptors is in the fovea.[234] Photorecepters in the foveola are approximately 2 μm in diameter.[38] Foveal cone spacing is approximately 120 samples/degree, therefore the maximum spatial frequency that can be properly detected according to this theory is 60 cycles/degree (equivalent to 6/3 acuity).[234] When a frequency greater than the Nyquist sampling limit lands on the retina, the image is under sampled. This means that aliasing (or distortion) can occur and the image could be misinterpreted.[38] In addition to the sampling limit, in order for the eye to resolve two objects as being two discrete images, the distance between these two objects must fulfill the criteria for the minimum angle of resolution. This minimum angle is defined by the Rayleigh criterion, which states the following:

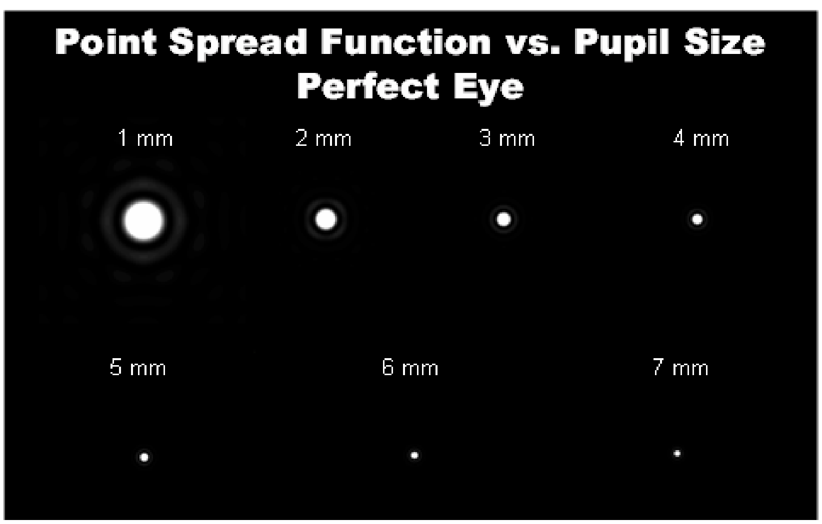
$$\theta_{\min} \quad =(1.22x\lambda) \;/\; a$$

where $\theta_{\min}$ = the angle subtended at the nodal point of the eye, λ = the wavelength of the light and a = the pupil diameter.[235]

Another retinal factor affecting perceived image quality is the Stiles-Crawford effect. The Stiles-Crawford effect states that light entering retinal cones at an oblique angle is perceived as being less bright than light entering along the axis.[1] Optically, the benefit of this is that light from the margins of the pupil, where aberrations are worse, will not contribute as much to image quality as light entering from the center of the pupil.[236]

Chromatic aberration describes the effect of wavelength on image formation in the eye. As the wavelength of light decreases, the amount of refraction increases. This means that shorter wavelengths will be refracted more than longer wavelengths and there will be a dispersion effect when various wavelengths of light are refracted simultaneously. Longitudinal chromatic aberration is when different wavelengths are focused at different distances along the optical axis, whereas transverse chromatic aberration is when different wavelengths are focused at different positions in the focal plane (due to differences in magnification). Chromatic aberration in a typical eye results in a chromatic difference in refraction of approximately 2.0D between 400 and 700 nm.[237] Fortunately, the impact of chromatic defocus depends on luminance. Most of the brightness in a broad spectral target comes from wavelengths near the peak of the spectral luminosity function (555nm), over which the chromatic difference is reduced to within ±0.25D.[238] Wavefront sensing only measures monochromatic light and does not provide information regarding the effect of chromatic aberrations.

Optical quality can be described using wavefront aberrations and also by other methods, such as the point spread function (PSF). The point spread function (PSF) is the image of an infinite point of light. Figure 6 shows monochromatic point spread functions for an aberrated and non-aberrated optical system with various pupil sizes.



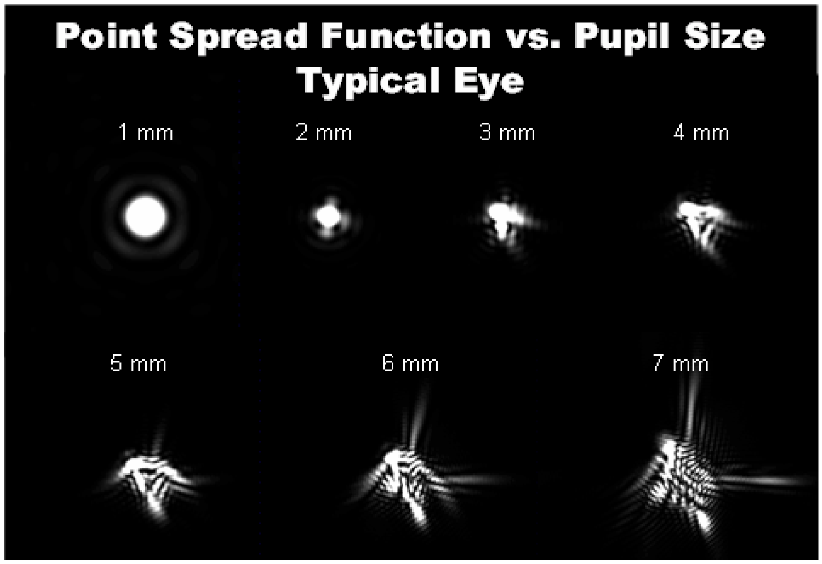


Figure 6: Monochromatic PSFs for various pupil sizes in a diffraction-limited eye (top) and a normal eye with higher order aberrations present (bottom). Courtesy of Austin Roorda (vision.berkeley.edu/roordalab).

As Figure 6 illustrates, the PSFs for the diffraction-limited system begin to differ from the aberrated system at around 2mm. Other studies have also demonstrated that the normal aberrated eye is diffraction-limited for a pupil size between 1 mm and 3 mm in monochromatic light.[44, 45] As the pupil becomes large (>3 mm), aberrations begin to degrade the retinal image. These relationships highlight the importance between pupil size and optical quality, making it an important factor to consider when assessing visual performance. The PSF can be assessed in terms of brightness, where maximal brightness is divided by the actual brightness, known as the "strehl ratio". The PSF can also be assessed in terms of the spread or width of the function. This is known as the "blur circle diameter".

In brief, the modulation transfer function (MTF) indicates the ability of an optical system to reproduce (transfer) different modulation (contrast) for different spatial frequencies from an object to the image. The MTF is the ratio of image contrast over the object contrast as a function of spatial frequency. As such, the MTF is the optical contribution to the contrast sensitivity function (CSF). The difference between spatial phase of the object and the spatial phase of the image as a function of spatial frequency and orientation of the grating object is called the phase transfer function (PTF). Together, the MTF and PTF define the optical transfer function (OTF) of an imaging system. All of these measures can be derived from wavefront aberrations and are linked together using a mathematical operation called the

Fourier transform.[239] A more detailed description of these optical quality measures is outside the scope of this thesis and can be found elsewhere.[239]

Visual acuity

Visual acuity is defined as the finest spatial detail that the visual system can resolve. One of the most widely used visual acuity charts is the Snellen chart. Visual acuity is typically expressed as the Snellen fraction, V, such that V=d/D, where d is the distance at which the letter can first be identified, and D is the distance at which the same letter subtends a visual angle of 5 minutes of arc. The benefits of this chart are that it is easy to use and provides information regarding uncorrected refractive error, cataract and significant macular disease. It has been found, however, that the repeatability of visual acuity made with the Snellen chart is poor and discrepancies of two lines or more can occur with repeat testing.[240] Some of this variability is due to testing at the incorrect distance and not using the recommended level of illumination.[241] Although this would be less likely to occur in a research setting, there are design issues inherent with the Snellen chart that need to be considered. These issues include: variation in the number of letters on each line, variable contour interaction (i.e. crowding), variable letter legibility, variation in the ratio of the sizes of the letters between successive lines and lack of a standardized scoring system which can reduce the sensitivity to detect changes over time.[242]

The ETDRS (Early Treatment of Diabetic Retinopathy Study) visual acuity chart was used in this study and is a logarithm of the minimum angle of recognition (logMAR) chart. It is expressed as the logarithm of the angular width (in arc minutes) of a limb of the smallest letter that can be correctly identified by a patient at a testing distance of 6 metres. A letter that has 1 arc minute detail at 6 metres (a 6/6 Snellen letter) has a logMAR value of 0. LogMAR charts have several advantages over the conventional Snellen chart. They use a set of letters that are equally legible and the same numbers of letters are presented on each line of the chart. They also incorporate equal spacing between lines. Scoring for these charts is also more precise, as equal weighting is given to every letter on the chart, and the score for each letter is incorporated in the overall acuity score.[243] The precision of the by-letter visual acuity measurements for the ETDRS chart has been reported as 0.051 logMAR.[244]

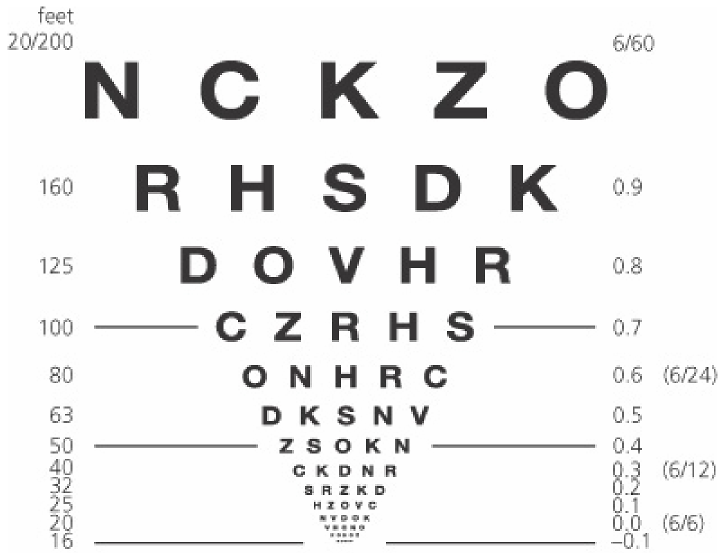


Figure 7: Early Treatment of Diabetic Retinopathy (ETDRS) logMAR high contrast visual acuity chart.[245]

Besides the use of an appropriate visual acuity chart, another way to capture additional information is to measure different aspects of vision quality. A recent study found that mesopic low contrast acuity testing was the best indicator of visual performance following refractive surgery.[246] Low contrast acuity is a more difficult task than high contrast acuity and can therefore capture more subtle changes in vision.[247, 248] Unfortunately, low contrast acuity is still a high spatial frequency resolution task and does not provide information about vision for mid to low spatial frequencies.

Contrast sensitivity

Images in the everyday world vary in size, shape and contrast. Spatial processing of these images requires decomposing the image into its basic components and then reassembling these to produce filtered representations of the image. Any complex image can be decomposed into a set of sine-waves of the appropriate frequency, amplitude, orientation and phase. Sine-wave gratings are an alternating pattern of light and dark bars of a particular orientation and phase and are characterized in terms of three variables: spatial frequency, contrast and orientation. The number of cycles per degree of visual angle is referred to as spatial frequency. Contrast sensitivity is defined as the ability to detect the presence of minimal luminance differences between objects or areas.[249] In addition to gratings, contrast sensitivity can also be measured using letter optotypes. In brief, contrast sensitivity is the inverse of contrast at threshold. According to Michelson, contrast is described as:

$$\text{Contrast} = (L_{max} - L_{min}) / (L_{max} + L_{min})$$

where L_{max} represents the maximum and L_{min} the minimum luminance of a sine wave pattern.[250] The contrast sensitivity function (CSF) is a plot of contrast sensitivity as a function of spatial frequency. The typical appearance of the CSF for a normal observer can be seen in Figure 8, which also shows the relationship between contrast sensitivity and high and low contrast visual acuity.

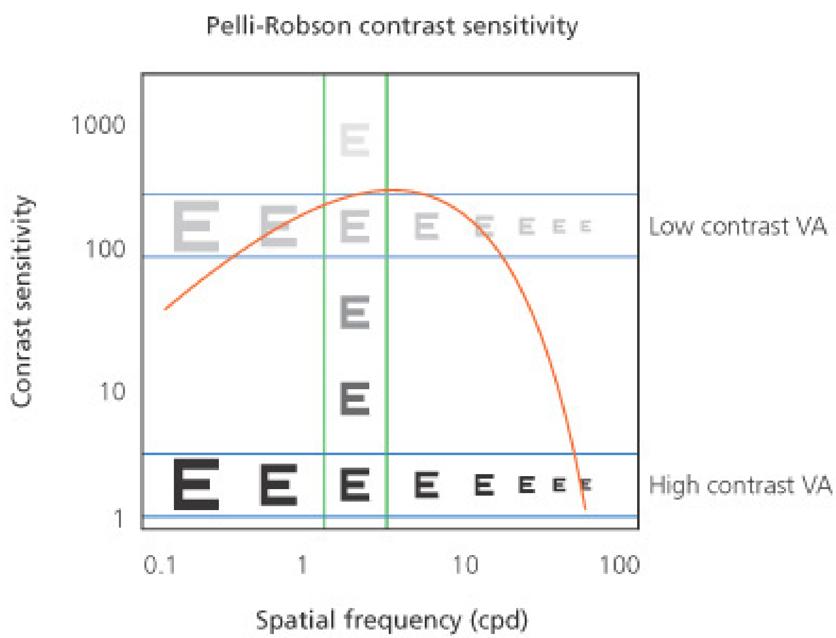


Figure 8: Contrast sensitivity as a function of spatial frequency.[245]

Spatial contrast sensitivity has been found to be more useful than visual acuity for the detection and discrimination of larger objects in the environment[251] Furthermore, lower spatial frequencies are crucial for face detection, while higher spatial frequencies are important for face identification.[251, 252] In light of this, contrast sensitivity is often measured in order to provide additional information about how well a patient sees and is often used in clinical trials assessing vision loss from glaucoma and cataract. Decreasing the luminance to mesopic levels also allows the pupil to dilate, which typically decreases retinal image quality and visual performance, increasing the predictive power of the test.[253]

Measuring optical quality is an extremely important aspect of assessing changes in vision. Clinically, it is important to use the appropriate test under the appropriate conditions and be able to interpret the results accurately. Clinical testing strategies can be targeted to the specific outcome that is expected. Following WFG LASIK, detecting subtle changes in optical quality as a result of changes in monochromatic higher order aberrations is important to determine the visual impact of the procedure.

Research aims

The goal of this thesis is to provide insight into WFG LASIK, in an attempt to further understand clinical outcomes for both myopic and hyperopic treatments. This thesis is organized into eight chapters. Chapter 2 describes the instruments, methods and study population. Chapter 3 reports general outcomes and investigates visual acuity and contrast sensitivity following WFG LASIK. Chapter 4 examines the characteristics of monochromatic aberrations before and after WFG LASIK while Chapter 5 further explores the impact of WFG LASIK on higher order aberrations of the eye. Chapter 6 examines the effect of surgery on subjective visual complaints and the remaining two chapters, Chapter 7 and Chapter 8, will summarize the results, provide conclusions and discuss future work in this area. The specific aims for this thesis are as follows:

1. To determine the impact of WFG LASIK on visual acuity and contrast sensitivity and to determine the ability of these tests to reflect post-surgical changes in higher order aberrations.
2. To describe and explore the monochromatic higher order aberrations before and after WFG LASIK for myopia and hyperopia.
3. To assess the visual impact of WFG LASIK on qualitative vision following surgery.

Chapter 2

Methods

Study description

This was a prospective, bilateral eye clinical trial conducted at the University of Waterloo, Waterloo, Ontario as a joint collaboration between The Laser Center (TLC) Waterloo and the Centre for Contact Lens Research (CCLR). This clinical trial was part of a larger pre-market approval submission to the Food and Drug Association (FDA) investigating the safety and efficacy of wavefront-guided (WFG) LASIK to treat myopia with and without astigmatism and hyperopia with and without astigmatism. The sponsor of the study was the surgical division of Alcon, Laboratories Inc. (Orlando, FL). The FDA submission was for the approval of CustomCornea® LASIK, which consisted of the measurement of refractive error with the LADARWave® aberrometer combined with treatment using the LADARVision® 4000 laser. This thesis examines the impact of WFG-LASIK on higher order aberrations and vision using the data collected from the clinical trial conducted at this site.

The examination schedule included a preoperative examination to determine eligibility and to record preoperative findings. Surgery was booked within 60 days of this exam and was followed by a one day, one week, one month, three month, four month and six month visit. For the purpose of this thesis, attention was paid to the preoperative and six month visits. In some cases the results for the three month visit were reported, in order to explore changes over time.

Treatments were based on diagnostic refractive data directly obtained from the wavefront measurement device (no nomogram adjustments were permitted) and surgery was performed by a single surgeon, Dr. Omar J. Hakim, at TLC Waterloo. The primary outcome goal was emmetropia for all eyes (monovision was not an option in this trial).

Preoperative preparation included a centration measurement on the LADARWave® system using the subject's undilated pupil. Following this, one drop of Phenylephrine 2.5% (Mydfrin, Alcon Laboratories, Fort Worth, TX) and one drop of Tropicamide 1% (Mydriacyl, Alcon Laboratories, Fort

Worth, TX) were administered for the myopic group. For the hyperopic group, one drop of Phenylephrine 2.5% (Mydfrin, Alcon Laboratories, Fort Worth, TX) and one drop of cyclopentolate hydrochloride 1.0% (Cyclogyl, Alcon Laboratories, Fort Worth, TX) were administered. It has been reported that pharmacologically dilating the eye can result in a small hyperopic shift in the defocus term (more common with hyperopic corrections), but that the higher order aberrations are unaffected.[254] After the diameter of the pupil reached ≥7.0 mm (approximately 30 minutes after instillation of the dilating drops) the subject's bulbar conjunctiva was marked just outside the limbus using gentian violet dye at the 3 and 9 o'clock positions. This was performed while the subject was sitting upright with his/her head vertical. These markings were then used for alignment of the centration reticules on the LADARWave® System in order to compensate for cyclotorsional rotation when the subject was in the horizontal position on the laser bed. Five minutes after the marks were made, in order to allow for tear film stabilization, aberrations were measured with the LADARWave® System, which is described in more detail below. Once the aberration measurements were obtained, this information was exported to a diskette, transported to the LADARVision®4000 System and the subject was prepared for surgery. The subject was properly oriented on the laser bed by realigning the limbus and the reference marks previously applied. This was done by using identical software on the graphical user interface of the LADARVision®4000 System.

Postoperative treatment consisted of instillation of topical 0.3% ofloxacin (Ocuflox; Allergan, Toronto, Canada) and topical 0.1% dexamethasone (Maxidex; Alcon, Toronto, Canada) every hour for the first day and then four times a day for the next four days. Bion® Tears (Alcon, Toronto, Canada) were instilled hourly for the first day and then as needed thereafter for dryness.

Wavefront measurements

In this study wavefront measurements were taken using a Shack-Hartmann aberrometer (LADARWave; Alcon Laboratories, Inc., Fort Worth, TX). Calibration was completed using a mounted physical model eye with known aberrations and was completed each time the instrument was turned on. The instrument projects an infrared beam of wavelength 820nm through the pupil, with a pulse duration of approximately 0.1 seconds and a beam power between 15 μW and 30 μW. The light is reflected off the retina and is relayed by an optical system onto a micro-lenslet array within a receiving/analyzing box. This system then processes the data and calculates the ocular aberrations. The software scales the wavefront data to account for the differences resulting from the use of near-infrared radiation, as opposed to clinically relevant visible light. A simple description of the set-up of a Shack-Hartmann wavefront sensor can be found in Figure 9.

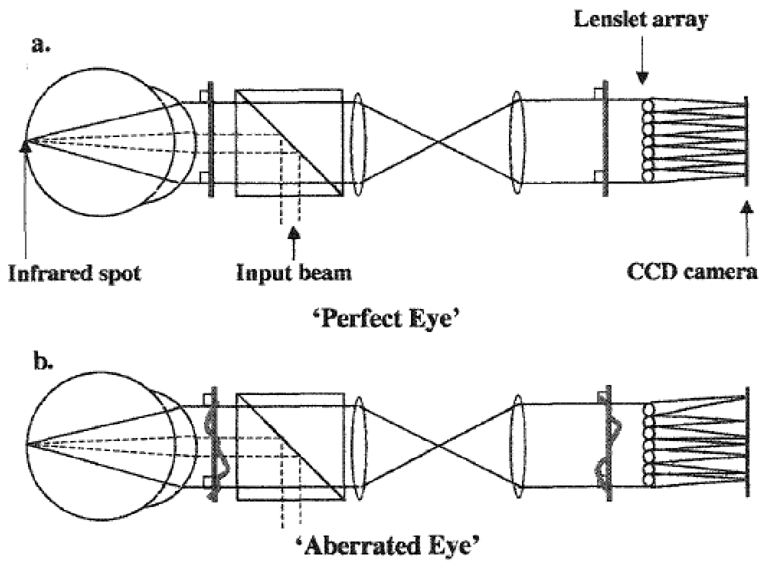


Figure 9: Simplified schematic of a Shack-Hartmann wavefront sensor for a) an eye with perfect optics and b) and eye with monochromatic aberrations. Courtesy of Jason Porter, University of Houston and David Williams' Laboratory, University of Rochester.

The ocular aberrations are represented in this thesis by means of Zernike polynomials. The units are micrometres (μm) and positive values indicate that the reflected wavefront emerging from the eye is phase-advanced relative to the wavefront at the center of the pupil. Negative values indicate that the reflected wavefront emerging from the eye is phase-retarded relative to the wavefront at the center of the pupil. As recommended by the Vision Science and its Applications (VSIA) taskforce,[50] a right-hand coordinate system and the double-index naming convention was used. This states that each mode of the Zernike expansion is identified by a subscript radial order (*n*, the degree of the polynomial) and a superscript meridional frequency (± *m*, the number of cycles of sinusoidal variation across 360 degrees). There are n+1 modes in each order and each mode is normalized to have unit variance.

The line of sight is used as the reference axis for wavefront aberration measurements. The line of sight in the normal eye is the path of the chief ray from the fixation point to the retinal fovea. Therefore, aberrations measured with respect to this axis will have the pupil center as the origin of a Cartesian reference frame.[255] The aberrometer was objectively co-axially aligned with the line of sight and calculations for specifying the optical aberration of the eye are referenced to the plane of the entrance pupil. The reference is a perfect spot pattern created by a plane wave of light focused at the focal point of each lens in the lenslet array. An aberrated eye will result in a deformed wavefront which will shift the image spot formed by each lens by a factor proportional to the local tilt of the wavefront at each lens surface (see Figure 10). The local slopes or partial derivatives are measured by quantifying the displacement of the image spot from the reference spot. The partial derivatives of the wavefront W(x,y) at the spot positions (x,y) are determined using the formulae:

$$\frac{\partial W(x,y)}{\partial x} = \frac{\Delta x}{f}$$

$$\frac{\partial W(x,y)}{\partial y} = \frac{\Delta y}{f}$$

where f represents the focal length of the lenslets and Δx and Δy represent the shift of the image spots in the x and y directions, respectively.[51]

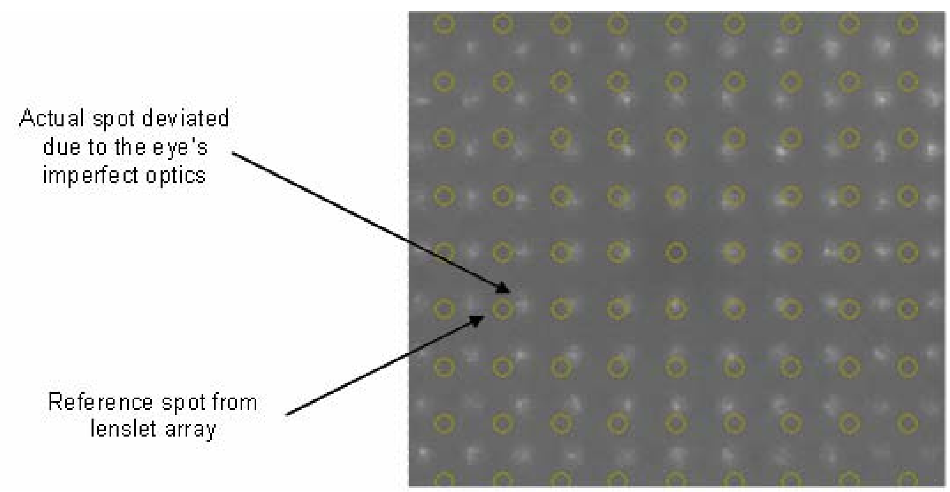


Figure 10: Example of the reference centroids and the Shack-Hartman spot pattern with the LADARWave device.

The number of lenslets in the array determines the spatial resolution of the system, and the sensitivity is limited to the focal length of each lens. Consequently, there is a trade-off between the greater number of lenses and the greater light-gathering power, or aperture, of each lens. The underlying assumption of this wavefront sensing technique is that the lenslets are small in diameter compared to the distortions present in the optical wavefront. In other words, we assume that the wavefront is locally flat over the finite diameter of the lenslet.[38] This assumption begins to break down even for coarse, lower-order, aberrations when the magnitude of those aberrations is large. In this case, the wavefront is significantly curved over the lenslet aperture and the result is a blurry spot which is difficult to localize.[38]

The second limitation concerns aberrations which are not necessarily large in magnitude, but are on a very fine spatial scale. These "micro-aberratons" scatter light and blur the spots formed by the optometer.[38] Although these blurry spots are problematic, they nevertheless contain useful information about the degree and location of scattering sources inside the eye.

An assumption in this study was that tear film break-up did not influence higher order aberration structure. It has been found that tear break-up can increase the higher order aberrations measured by a Shack-Hartmann aberrometer.[256] This effect was minimized by having the subject blink prior to each measurement and by carefully assessing the wavefront image quality prior to saving the data. If the lenslet pattern was blurred in any way (see Figure 11), the measurement was rejected and then repeated.

Subjects were aligned using a forehead and chin rest and asked to fixate on a target. The fixation optical subsystem provided the subject with an unambiguous fixation point and included adjustable optics to compensate for inherent refractive error. The optics of the instrument was adjusted to "fog" the eye, first clarifying the fixation target and then optically adjusting it beyond the subject's far point to minimize accommodation. After the subject was aligned, they were asked to complete three full blinks and then hold their eye open, while keeping their eye still, for the duration of the measurement. Following each measurement, the system operator determined the acceptability of the measurement by studying the spot diagram over the entire dilated pupil area. Blurring of the data image or absence of data over part of this region were criteria for rejection and the image was recaptured. If the spot diagram was acceptable, the image was saved. Examples of an unacceptable spot diagram is presented in Figure 11. A total of five acceptable measurements were taken per eye and the best three were identified and averaged by the software. Measurements were completed for the right eye, followed by the left eye for all subjects. Each measurement was performed in 60 milliseconds and the whole procedure took roughly 10 minutes.

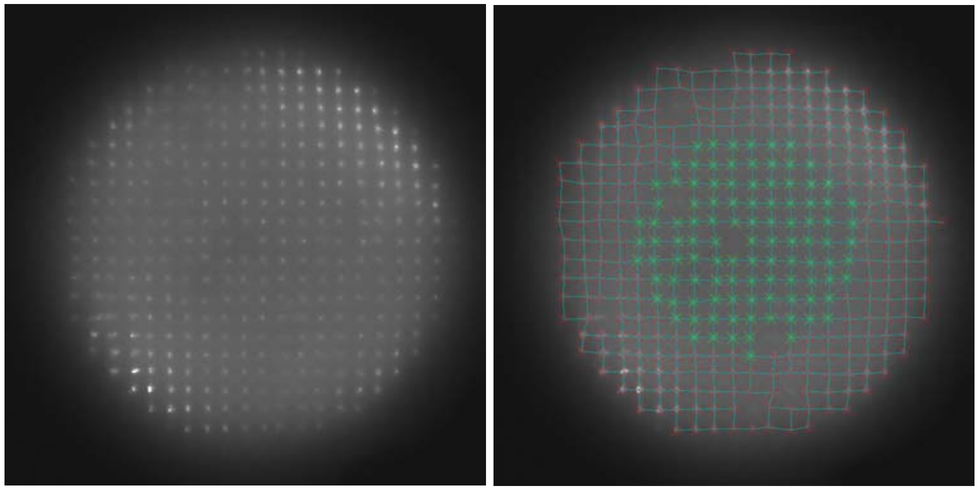


Figure 11: Example of an unacceptable spot pattern due to break-up of the tear film from the LADARWave device on the left. The software indicates areas where the data could not be used, which is shown as a distorted grid pattern with missing points on the right.

The 3rd and 4th-order aberrations were used to report the higher order aberrations in this study. Comprehensive clinical testing was conducted at the preoperative, three month and six month visits.

Excimer laser characteristics

The Alcon Summit Autonomous LADARVision® 4000 system uses an argon fluoride (ArF) excimer laser beam of Gaussian profile with a wavelength of 193 nm and diameter of <0.90mm. It produces 10 nanosecond pulses with a repetition rate between 50 to 60 pulses per second. The laser beam at the corneal plane has pulse energy of 2.4 to 3.0 mJ and an average radiant exposure of 180 to 240 mJ/cm^2. Less than a micron of tissue is removed with each pulse due to the fact that the photon energy of the short wavelength, ultraviolet radiation, is sufficiently high to break the molecular bonds at the surface of the cornea.

This laser combines eye tracking with the scanning of the small excimer beam. The LADARTracker® system uses a patented laser radar eye tracker and actively tracks the position of the eye by irradiating it with pulses of 905 nm infrared energy and analyzing characteristics of the returning laser radiation. This eye tracker is based on closed-loop technology, which compensates for eye movements using continuous, constant feedback on the location of the eye and has a sampling frequency of 4000 Hz. Porter et al.[257] discuss the types of eye movements that can occur during refractive surgery, which include fixational movements such as tremor and microsaccades and larger, slow drift movements in eye position. They found that the most problematic eye movements during surgery were due to relatively slow drifts in eye position during surgery and suggest that an eye tracker would have to track frequencies of between 15 Hz and 30 Hz to correct for these movements.[257] The LADARTracker® system requires a pupil diameter of 7.0 mm and locks onto the edge of the pupil. Studies on eye tracking systems have shown that eye tracking does not necessarily improve centration, with a mean (± standard deviation) decentration of 0.43 ± 0.21 mm reported.[258] Further studies have indicated that even an ablation decentration less than 1.0 mm may result in increased ocular aberrations.[259]

Flap creation

Flaps were created using a mechanical microkeratome (Hansatome®, Bausch & Lomb, Rochester, NY). A minimum flap thickness of 160 μm with a minimum diameter of 9.5 mm was attempted for all eyes. This microkeratome has an automated pivoting motion and creates a superior-positioned hinge.

Ablation profiles

In order to effectively decrease the optical power for a myopic eye, more laser pulses are applied to the central stroma, in order to reduce the corneal radius of curvature across the treatment zone. In order to increase the effective power for a hyperopic eye, more pulses are applied to the mid-peripheral cornea. The removal of stroma in a zone in the mid-periphery results in an increase in corneal radius of curvature across the treatment zone. It has been stated that transition zones are used for hyperopic treatments in order to minimize epithelial hyperplasia and surface remodeling that may lead to significant regression.[177] Astigmatism is treated by differential removal of tissue in one of the principal meridians, either by flattening the steep axis (minus cylinder format) or steepening the flat axis (plus cylinder format). Myopic astigmatism is usually treated with the minus cylinder format and hyperopic astigmatism is usually treated with the plus cylinder format.[86] In this study the LADARVision® 4000 system provided a customized treatment, with an optical zone of 6.5 mm and a blend zone of 1.25 mm, producing a total optical zone of 9.0 mm. Figure 12 displays examples of laser ablation spot patterns for spherical myopia and hyperopia.

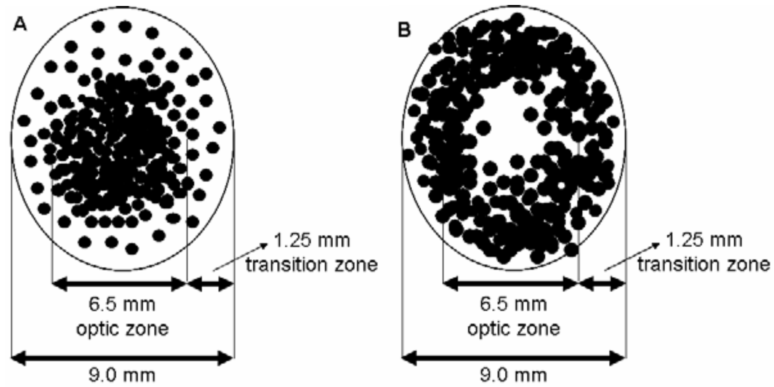


Figure 12: Simplified schematic showing the laser ablation spot pattern for a) spherical myopia b) spherical hyperopia.

Visual acuity measurements

At the preoperative and three and six month postoperative visits, high contrast (HC) and 10% low contrast (LC) best-corrected visual acuities (BCVA) were measured undilated and monocularly using ETDRS logMAR charts (VectorVision™, Dayton, OH) at 4 metres (m). Testing was done under low level, ambient, indirect room illuminance of 10-12 candelas per square metre (cd/m^2) or less, measured with a luminance meter (Minolta CS-100) at the patient's eye. Two different letter charts were switched between eyes at each visit.

Contrast sensitivity measurements

Contrast sensitivity was also measured at the preoperative, three month and six month visits using the CSV-1000E Contrast Testing Instrument (VectorVision™, Dayton, OH) under both photopic and mesopic conditions. The device uses vertical sine-wave gratings and incorporates a self-calibrating, retroilluminated test face. Testing was performed undilated and monocularly at 2.5m with best spectacle correction in place for four spatial frequencies: 3 cycles per degree (cpd), 6 cpd, 12 cpd and 18 cpd, each with eight different levels of contrast. The last correct answer at each spatial frequency was recorded as the contrast threshold in logarithmic (log) units. For the photopic condition, luminance at the patient's eye was between 50-75 cd/m^2. For the mesopic condition, all room lighting was off yielding a luminance between 0.1 to 0.3 cd/m^2 at the subject's eye. For mesopic measurements, neutral density filters were placed in front of the subject's eye creating a chart luminance as seen by the subject of 1.0 to 3.0 cd/m^2. As with HC and LC BCVA, different grating charts were switched between eyes.

Qualitative vision measurements

Qualitative vision was assessed using a questionnaire with closed-ended categorical questions prior to surgery and at each follow-up visit. Four-point scales were used at the preoperative visit and five-point scales at the follow-up visits. The questionnaire was administered by the investigator and the subjects were reminded of the instructions prior to filling in their responses. Preoperative questionnaires were completed while wearing spectacles; postoperative questionnaires were completed without correction (unless reading glasses were required) and subjects did not see their previous responses.

Subjects

The study received ethics clearance through the Office of Research Ethics, University of Waterloo and informed consent was obtained from each subject prior to study entry. All procedures followed the principles expressed in the Declaration of Helsinki. Subjects were screened and were enrolled only if they satisfied many inclusion criteria, including no history of ocular disease, prior surgery, corneal abnormalities or any systemic disease or medication which could potentially affect vision. Soft contact lenses and rigid gas permeable lenses were removed for a minimum of two and three weeks, respectively, prior to the preoperative examination.

Following a successful screening appointment, subjects were enrolled into the study and surgery was performed within 60 days. Wavefront guided LASIK was performed on 324 myopic eyes (164 subjects) with and without astigmatism and 64 hyperopic eyes (33 subjects) with and without astigmatism. Four subjects required treatment on one eye only. In addition, one subject moved out of town after one month and one subject was lost to follow-up. Data for these six subjects were not used for subsequent analysis; otherwise there were no missing data. Despite being a bilateral clinical trial, most of the data reported in this thesis is for the right eye only, unless otherwise indicated.

Results have been reported separately for the myopic group and the hyperopic group. The myopic data is from 162 subjects, each having a spherical manifest refraction between -0.25 D and -6.25 D (mean -2.84 D, standard deviation ± 1.35 D) and refractive astigmatism between 0 D and -4.00 D (-0.81 D ± 0.74 D). The age ranged between 20 and 60 years (37.7 ± 9.27 years) and there were 97 males and 65 females. Habitual correction included soft contact lenses (n=124), RGP lenses (n=7), PMMA lenses (n=2) and spectacles (n=29). A summary of the preoperative information for the myopic group is provided in Table 1. The age and mean refractive spherical equivalent (MRSE) distributions can be seen in Figure 13 and Figure 14, respectively.

Table 1: Preoperative information for the myopic group (n=162).

	Mean ± standard deviation (range)
Age (years)	37.7 ± 9.3 (20 to 60)
Gender	97 males; 65 females
Manifest sphere (D)	-2.84 ± 1.35 (-0.25 to -6.50)
Manifest cylinder (D)	-0.81 ± 0.74 (0 to -4.00)
Keratometry readings	
Flattest meridian (D)	43.24 ± 1.45 (38.25 to 47.75)
Steepest meridian (D)	44.20 ± 1.52 (40.50 to 48.50)

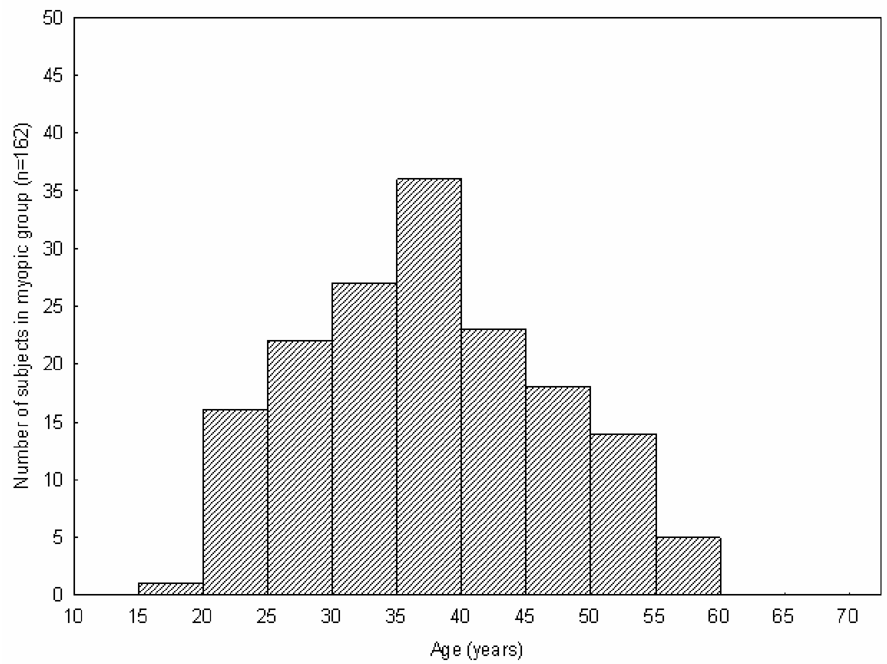


Figure 13: Age distribution for the myopic group.

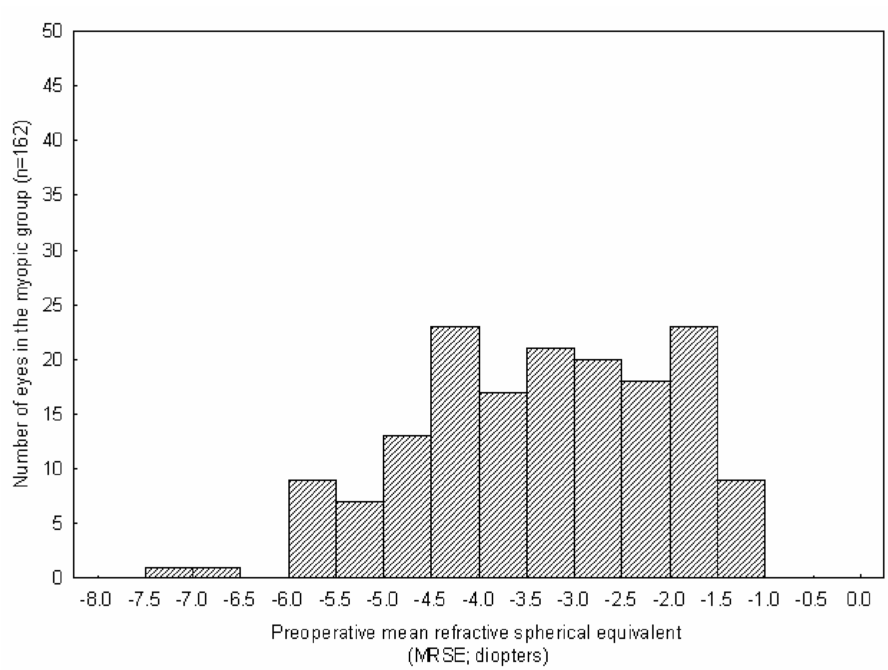


Figure 14: Distribution of the preoperative mean refractive spherical equivalent for the myopic group.

The hyperopic data are from 31 subjects, each having a preoperative manifest refraction between +1.00 D and +5.00 D (mean +2.60 D, standard deviation ± 1.15 D) and refractive astigmatism between 0 D and -3.75 D (-0.87 D ± 0.87 D). The age ranged between 23 and 65 years (45.4 ± 11.3 years) and there were 20 males and 11 females. Habitual correction included soft contact lenses (n=16) and spectacles (n=15). A summary of the characteristics of the hyperopic group is provided in Table 2. The age distribution can be seen in Figure 15.

Table 2: Preoperative information for the hyperopic group (n=31)

	Mean ± standard deviation (range)
Age (years)	45.4 ± 11.3 (23 to 65)
Gender	20 males; 11 females
Manifest sphere (D)	+2.60 ± 1.15 (+1.00 to +5.00)
Manifest cylinder (D)	-0.87 ± 0.87 (0 to -3.75)
Keratometry readings	
Flattest meridian (D)	42.28 ± 1.16 (39.00 to 42.25)
Steepest meridian (D)	43.35 ± 1.15 (41.25 to 45.50)

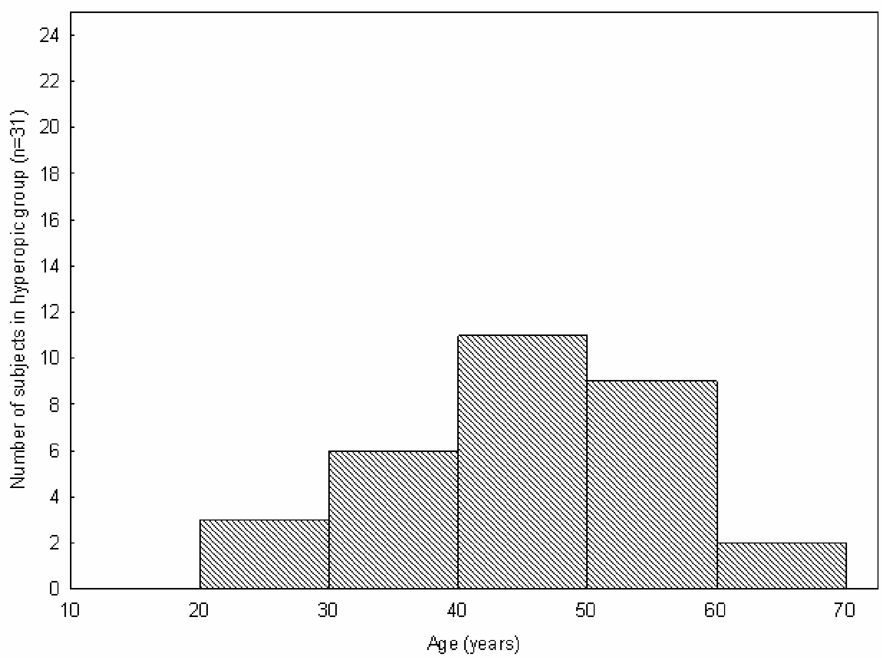


Figure 15: Age distribution in hyperopic group.

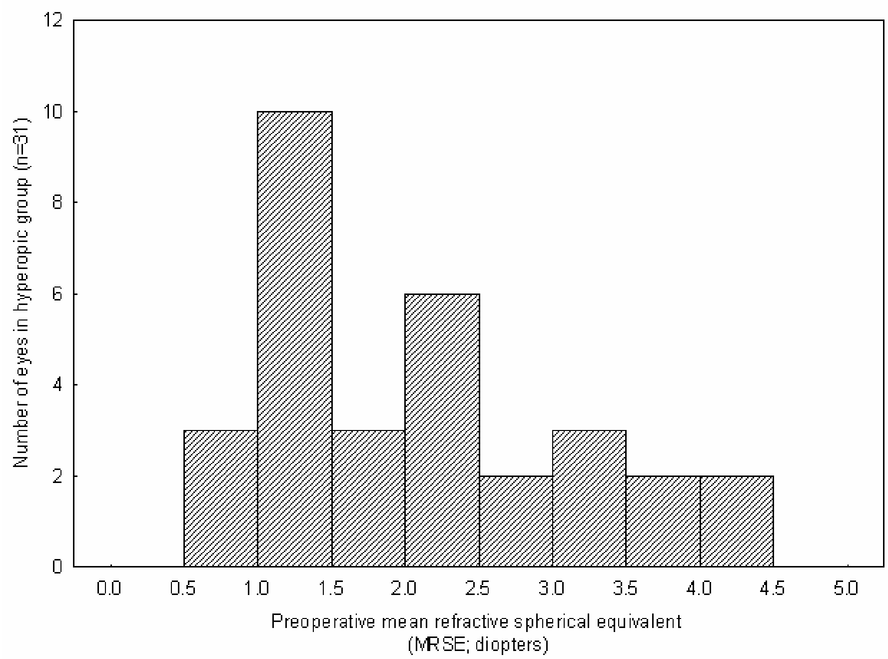


Figure 16: Distribution of the preoperative mean refractive spherical equivalent in the hyperopic group.

In general, our study sample contained more males than females and the age was slightly higher in the hyperopic group compared to the myopic group. Recruitment for the subjects was completed by TLC Waterloo. Information gathered during a typical surgical consultation was used to assess whether an individual passed general inclusion criteria for the study (i.e. met refractive error criteria and had good ocular health). If these criteria were met, a brief description of the study was presented to the individual. If they were interested in participating, they were then scheduled for a full preoperative assessment at the Centre for Contact Lens Research where baseline and preoperative information were collected. If all of the study inclusion criteria were met, the subject was enrolled into the study and scheduled for surgery. There is no plausible explanation as to why more males were enrolled into the study than females. The demographic at TLC Waterloo is relatively equal between males and females (personal communication). The mean age for both the myopic and hyperopic groups reflect the typical age for general refractive surgery, which might signify the financial capability for surgery as well as refractive stability. Hyperopia can become more of an issue for individuals as their amplitude of accommodation decreases with age. It is expected that this is the likely reason for the slightly older population in the hyperopic group, compared to the myopic group.

The following chapter investigates the general outcomes following WFG LASIK for both the myopic and the hyperopic groups. Safety and efficacy results are presented and then more detail regarding the visual outcomes is described.

Chapter 3

Visual acuity and contrast sensitivity following wavefront-guided LASIK

Introduction

Refractive surgery outcomes are routinely reported in terms of postoperative manifest refractive spherical equivalent (MRSE), uncorrected visual acuity (UCVA) and best corrected visual acuity (BCVA). High contrast (HC) BCVA, while providing useful information regarding high spatial frequency vision, can be unaffected by variations in optical quality, such as higher order aberrations.[134, 246] In addition, subjective complaints of poor optical quality, such as glare and halos at night, have been reported despite acceptable HC BCVA, MRSE and UCVA.[174, 260]

As described in Chapter 1, a variety of clinical tests are available that provide different information about visual quality. Unfortunately, it is not entirely clear which tests are affected by subtle changes in optical quality, such as those changes that may occur following wavefront-guided (WFG) LASIK. In addition, there are no reports in the literature of low contrast (LC) BCVA following hyperopic LASIK. The primary objective of this investigation was to determine the effect of WFG LASIK on high contrast (HC) and LC visual acuity and photopic and mesopic contrast sensitivity. A secondary objective was to explore the relationship between these tests and ocular higher order aberrations following WFG LASIK (higher order aberrations before and after WFG LASIK will be described in Chapter 4 and Chapter 5).

Methods

Repeated Measures analyses and post-hoc tests were used to determine significance, which was set at $p<0.05$. A Bonferroni correction was applied to the vision testing and higher order aberration analyses, resulting in an adjusted level of significance of 0.05/25. Calculations were undertaken using Statistica 7 software (StatSoft Inc, Tulsa, OK). Snellen acuities were used to report visual acuity results, in order to compare these results to previous FDA outcomes. However, logMAR values were used when looking at changes over time. Standard deviation (SD) has been reported for preoperative information to illustrate the spread in the data in the population, while standard error of the mean (SEM) has been reported postoperatively to represent the precision of the sample mean.[261] Information regarding the various testing devices used to measure visual acuity and contrast sensitivity can be found in Chapter 2.

Results

Safety criteria

With respect to the safety criteria used by the FDA,[262] no eye lost ≥ 2 lines of HC BCVA, no eye had HC BCVA worse than 6/12 and no eye had an increase of more than 2.00 D of cylinder magnitude for either the myopic or hyperopic group, following WFG LASIK in this study.

Efficacy: correction of refractive error

For the myopic group, the percentage of eyes at six months with a MRSE within ± 1.00 D and ± 0.50 D was 98.1% and 80.9%, respectively. For the hyperopic group, the percentage of eyes at six months with a MRSE within ± 1.00 D and ± 0.50 D was 96.8% and 71.0%, respectively. The percentage of eyes with UCVA ≥ 6/6 and ≥ 6/12 at six months was 84.0% and 99.5%, respectively for the myopic group and 87.2% and 96.9%, respectively for the hyperopic group as shown in Figure 17 and Figure 18. The results for the myopic and hyperopic groups were similar; however the distributions of Figure 17 and Figure 18 indicate that a greater number of eyes in the myopic group had better than 6/4.5 UCVA compared to the hyperopic group. Overall, success in terms of postoperative MRSE and UCVA was excellent for both groups following WFG LASIK.

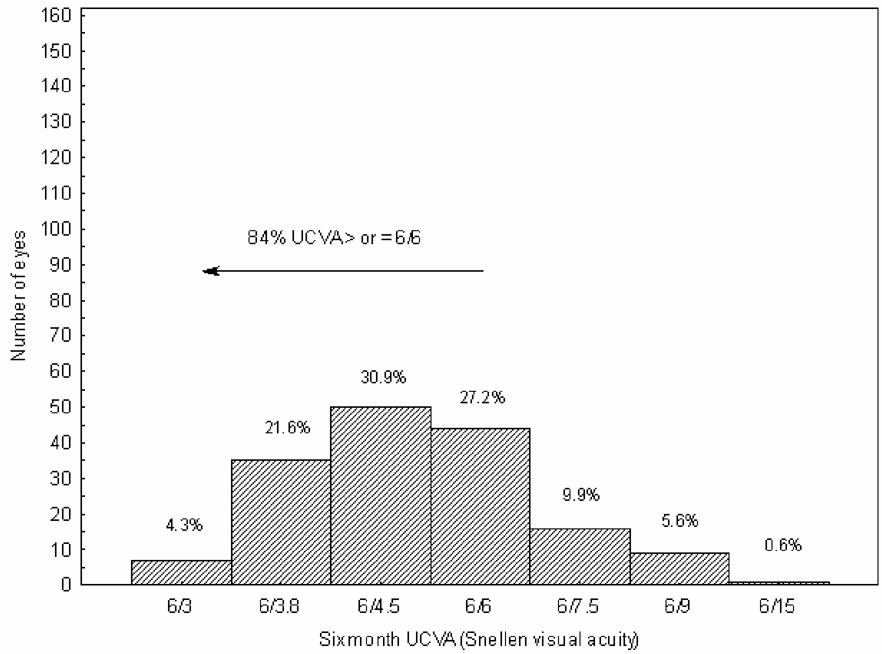


Figure 17: High contrast uncorrected Snellen visual acuity for the myopic group (n=162 eyes) six months following WFG LASIK.

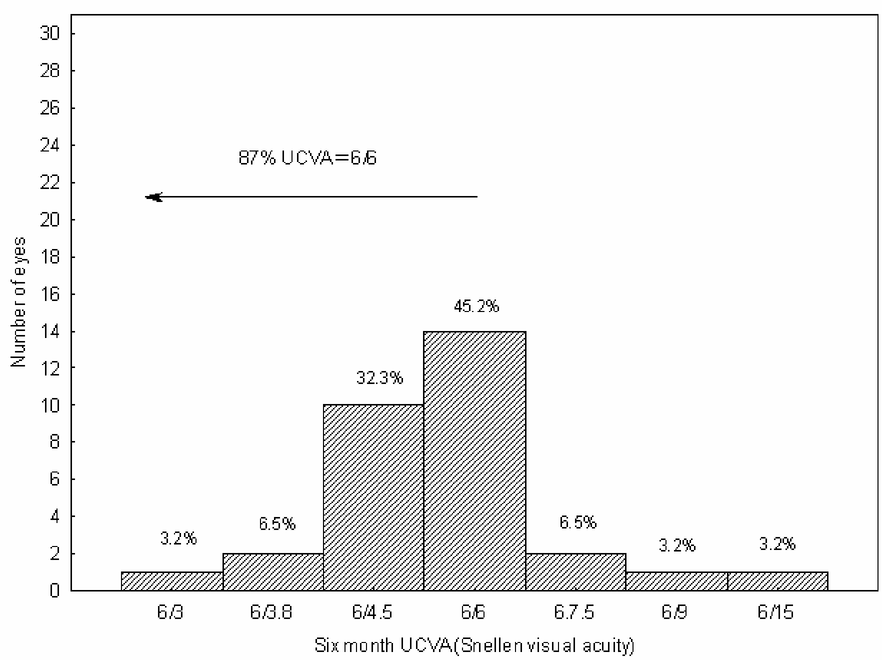


Figure 18: High contrast uncorrected Snellen visual acuity for the hyperopic group (n=31 eyes) six months following WFG LASIK.

Effect of WFG LASIK on visual acuity

The change in HC and LC BCVA can be observed in Figure 19 and Figure 20 for the myopic and hyperopic group, respectively. The majority of eyes had no change; however a large percentage in both groups gained one line of HC and LC BCVA. Comparing the distributions of Figure 19 and Figure 20, a greater percentage of eyes in the hyperopic group exhibited a loss in HC or LC BCVA compared to the myopic group.

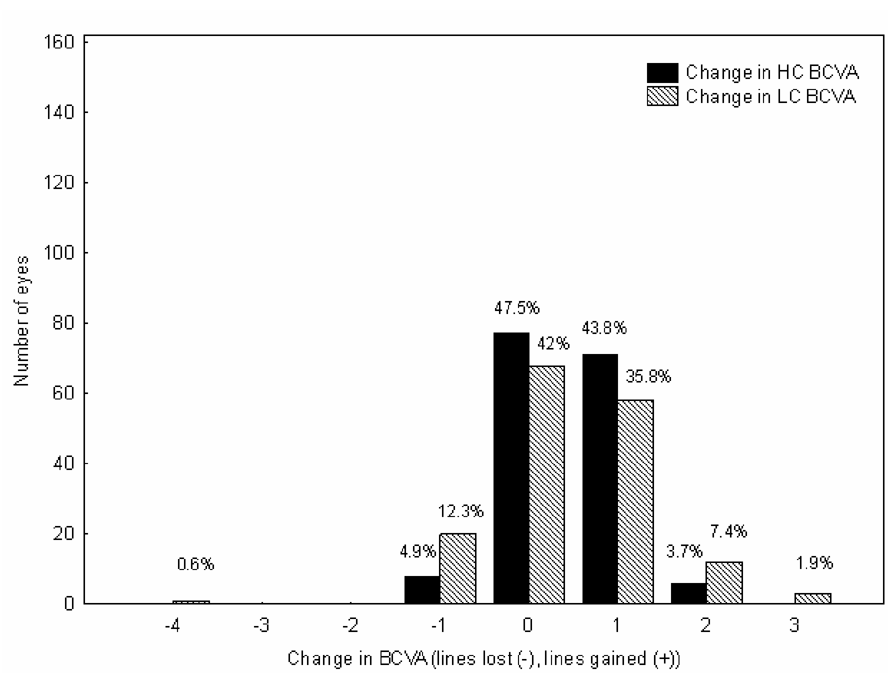


Figure 19: Change in HC and LC BCVA for the myopic group six months following WFG LASIK

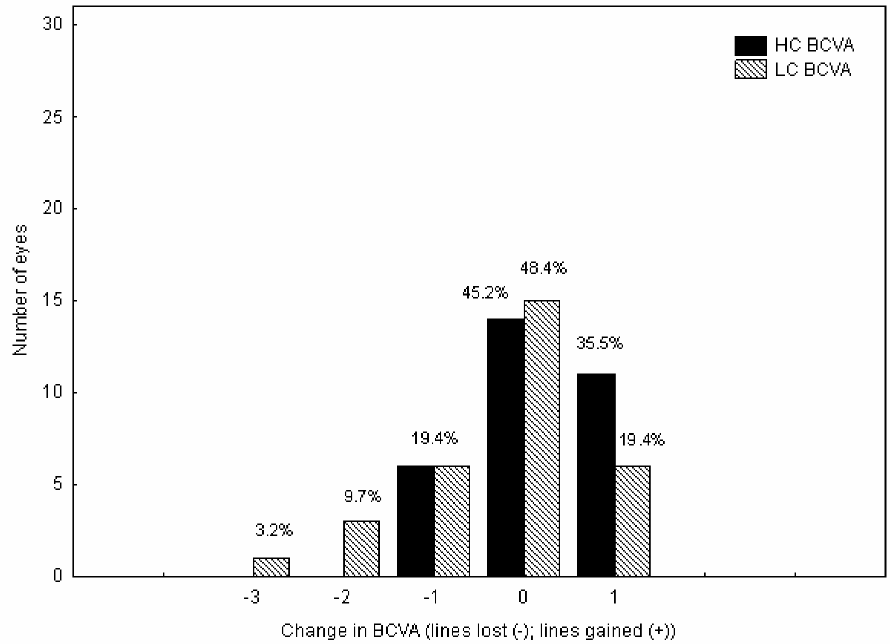


Figure 20: Change in HC and LC BCVA for the hyperopic group six months following WFG LASIK

Repeated measures showed a statistically significant increase in HC BCVA at three and six months compared to the preoperative visit for the myopic group (p<0.001). There was also a small, statistically significant increase in HC BCVA from three to six months (p<0.001). LC BCVA was also greater at three months and six months compared to the preoperative visit (both p<0.001), however there was no significant change between three and six months (p>0.05). Results for HC and LC BCVA at each of the visits for the myopic group are displayed in Figure 21 and Table 3.

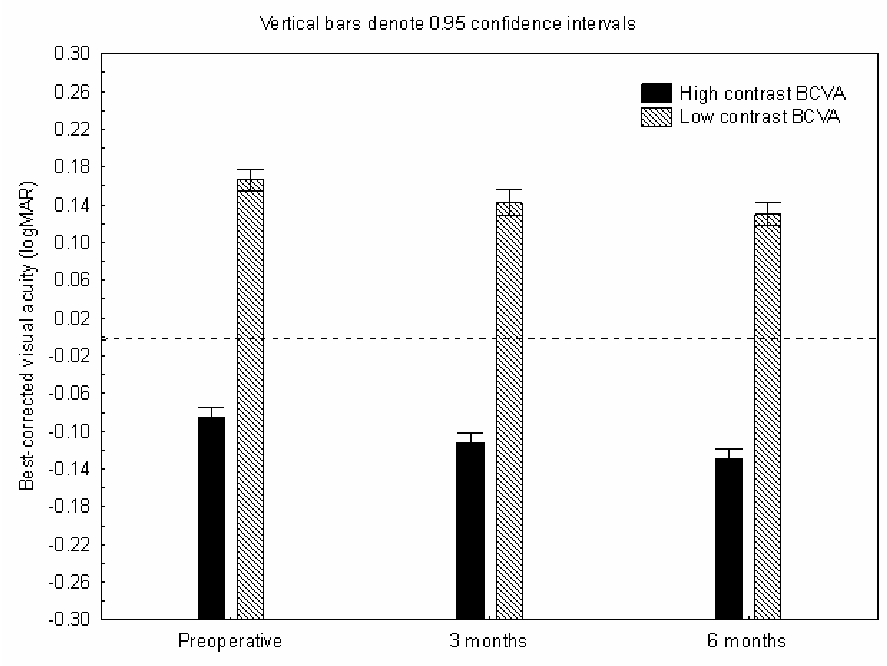


Figure 21: HC and LC BCVA for the myopic group following WFG LASIK.

Table 3: HC and LC BCVA (logMAR) for the myopic group following WFG LASIK. Statistically significant (p<0.005) differences between the preoperative and six month visit are shown in bold.

	BCVA myopic group (mean ± SEM)			
	Preoperative visit	3 months	6 months	p value
HC BCVA	-0.085 ± 0.005	-0.112 ± 0.005	-0.130 ± 0.005	**<0.001**
LC BCVA	0.167 ± 0.006	0.142 ± 0.007	0.130 ± 0.006	**<0.001**

For the hyperopic group, repeated measures analyses revealed no significant change in HC or LC BCVA following surgery (all p>0.05) (see Figure 22). There was a slight trend of LC BCVA worsening at three months, which showed some recovery by six months. Data can be found in Table 4.

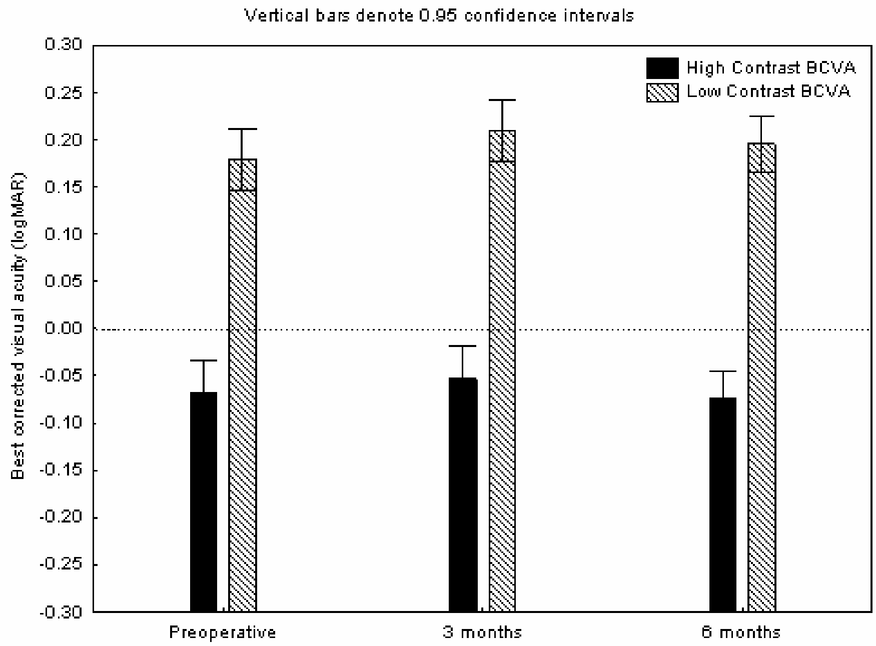


Figure 22: HC and LC BCVA for the hyperopic group following WFG LASIK

Table 4: HC and LC BCVA (logMAR) for the hyperopic group following WFG LASIK. No statistically significant differences were found (all p>0.05).

	BCVA hyperopic group (mean ± SEM)			
	Preoperative visit	3 months	6 months	p value
HC BCVA	-0.069 ± 0.017	-0.054 ± 0.017	-0.074 ± 0.014	>0.05
LC BCVA	0.179 ± 0.016	0.209 ± 0.016	0.196 ± 0.015	>0.05

Correlation between visual acuity and higher order aberrations

As mentioned previously, the higher order aberration results following WFG LASIK are described in detail in Chapter 4 and Chapter 5. The relationship between BCVA and six month higher order aberrations was investigated, in an attempt to determine whether a larger magnitude or a greater change in higher order aberrations resulted in a worsening of BCVA.

After correcting for multiple comparisons, statistically significant correlations were found between HC and LC BCVA and the magnitude of higher order aberrations at six months for the myopic group (see Table 5). The correlation results between the change in HC and LC BCVA and the change in higher order aberrations are presented in Table 6. These associations suggest that increases in certain higher order aberrations are associated with a decrease in visual acuity. As an example, the correlation plot for the absolute change in Z^3_3 and the change in LC BCVA is shown in Figure 23. The result was still significant when the two outliers were removed (r=-0.251, p<0.001). In general, statistically significant correlations were stronger and slightly more numerous for LC BCVA compared to HC BCVA, and for the absolute magnitude compared to the absolute change following surgery.

Table 5: Correlation between six month HC and LC BCVA and the absolute magnitude of higher order Zernike coefficients for the myopic group. Statistically significant (p<0.005) correlations are shown in bold.

Visual acuity (logMAR)	Higher order Zernike coefficient terms (correlation coefficient, p-value)								
	6M Z^{-1}_3	6M Z^1_3	6M Z^{-3}_3	6M Z^3_3	6M Z^0_4	6M Z^{-2}_4	6M Z^2_4	6M Z^{-4}_4	6M Z^4_4
HC BCVA	0.045 p=0.574	**0.255 p=0.001**	0.208 p=0.008	**0.258 p=0.001**	0.065 p=0.414	**0.324 p<0.001**	0.207 p=0.008	0.142 p=0.071	**0.232 p=0.003**
LC BCVA	0.144 p=0.067	**0.286 p<0.001**	**0.292 p<0.001**	**0.319 p<0.001**	0.195 p=0.013	**0.347 p<0.001**	0.211 p=0.007	0.192 p=0.014	**0.367 p<0.001**

Table 6: Correlation between the change in HC and LC BCVA and the absolute magnitude of change in higher order Zernike coefficient values following WFG LASIK for the myopic group. Statistically significant (p<0.005) correlations are shown in bold.

Visual acuity change (logMAR)	Higher order Zernike coefficient terms (correlation coefficient, p-value)								
	6M Z^{-1}_3	6M Z^1_3	6M Z^{-3}_3	6M Z^3_3	6M Z^0_4	6M Z^{-2}_4	6M Z^2_4	6M Z^{-4}_4	6M Z^4_4
HC BCVA	-0.049 p=0.534	0.096 p=0.223	-0.090 p=0.256	**-0.230 p=0.003**	-0.041 p=0.609	-0.052 p=0.514	-0.111 p=0.162	0.009 p=0.914	-0.084 p=0.286
LC BCVA	-0.163 p=0.039	0.056 p=0.481	-0.137 p=0.082	**-0.259 p=0.001**	-0.057 p=0.475	**-0.228 p=0.003**	-0.092 p=0.246	-0.009 p=0.908	-0.132 p=0.094

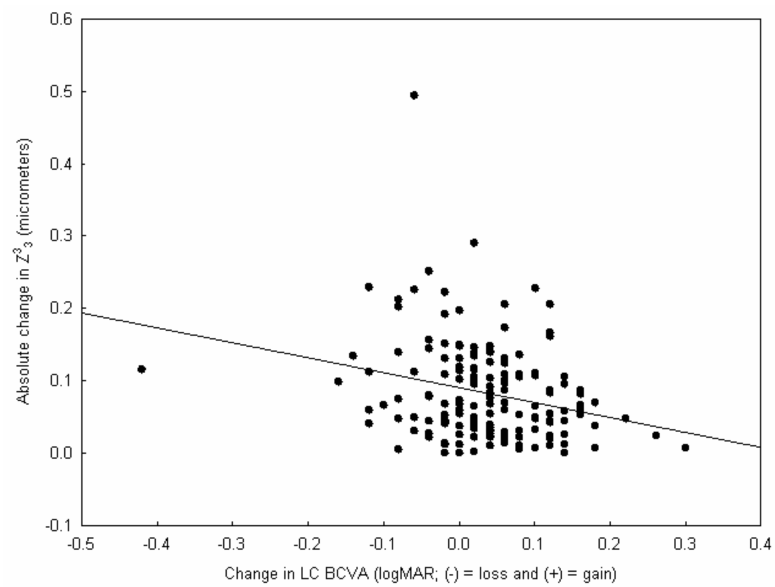


Figure 23: Correlation between the change in LC BCVA and the absolute change in Z^3_3 for the myopic group (r=-0.259, p=0.001). Univariate regression is shown.

Correlation results for the hyperopic group are shown in Table 7 and Table 8. After correcting for multiple comparisons, the only statistically significant correlation was between LC BCVA and the magnitude of the fourth order aberration, Z^0_4 (spherical aberration; $p<0.005$). The correlation plot for LC BCVA and the absolute magnitude of Z^0_4 is shown in Figure 24. No significant correlations were found between the change in BCVA and the change in higher order aberrations (all $p>0.005$).

Table 7: Correlation between six month HC and LC BCVA and the absolute magnitude of higher order Zernike coefficients for the hyperopic group. Statistically significant (p<0.005) correlations are shown in bold.

Visual acuity (logMAR)	Higher order Zernike coefficient terms (correlation coefficient, p-value)								
	6M Z^{-1}_3	6M Z^1_3	6M Z^{-3}_3	6M Z^3_3	6M Z^0_4	6M Z^{-2}_4	6M Z^2_4	6M Z^{-4}_4	6M Z^4_4
HC BCVA	-0.046 p=0.805	0.056 p=0.766	0.376 p=0.037	-0.142 p=0.448	0.359 p=0.047	0.076 p=0.685	-0.234 p=0.204	0.053 p=0.779	-0.012 p=0.949
LC BCVA	0.123 p=0.511	0.339 p=0.062	0.465 p=0.008	-0.143 p=0.939	**0.617 p<0.001**	0.081 p=0.666	-0.126 p=0.500	-0.059 p=0.753	-0.032 p=0.866

Table 8: Correlation between the change in HC and LC BCVA and the absolute magnitude of change in higher order Zernike coefficient values following WFG LASIK for the hyperopic group. No statistically significant correlations were found (all p>0.005).

Visual acuity change (logMAR)	Higher order Zernike coefficient terms (correlation coefficient, p-value)								
	6M Z^{-1}_{3}	6M Z^{1}_{3}	6M Z^{-3}_{3}	6M Z^{3}_{3}	6M Z^{0}_{4}	6M Z^{-2}_{4}	6M Z^{2}_{4}	6M Z^{-4}_{4}	6M Z^{4}_{4}
HC BCVA	-0.170 p=0.359	-0.379 p=0.036	-0.271 p=0.141	0.232 p=0.210	-0.400 p=0.026	0.098 p=0.600	0.169 p=0.363	-0.315 p=0.084	0.054 p=0.774
LC BCVA	-0.323 p=0.076	-0.216 p=0.244	-0.429 p=0.016	-0.334 p=0.066	-0.421 p=0.018	-0.195 p=0.294	-0.226 p=0.222	-0.244 p=0.186	-0.129 p=0.489

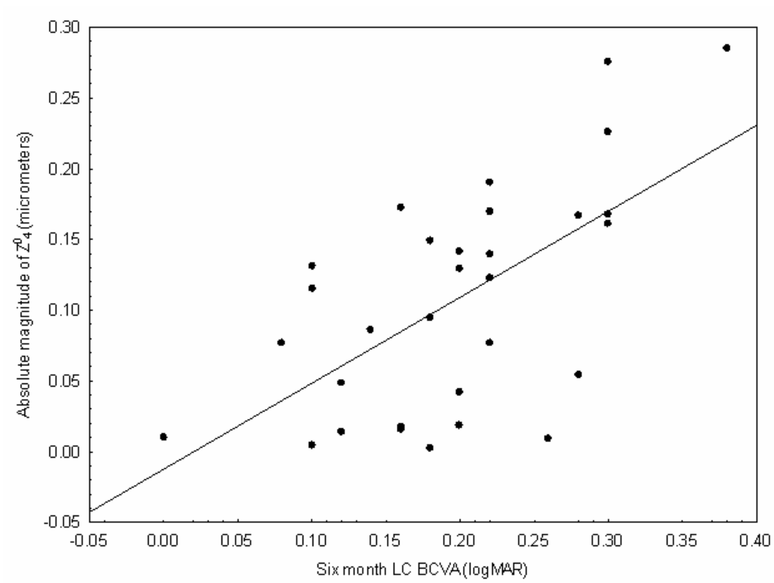


Figure 24: Correlation between LC BCVA and the absolute change in Z^0_4 for the hyperopic group (r=0.617, p<0.001). Univariate regression is shown.

Contrast sensitivity

<u>Photopic contrast sensitivity</u>

Figure 25 displays the best-corrected photopic contrast sensitivity results for the myopic group. There was a statistically significant increase in photopic contrast sensitivity at spatial frequencies 3, 6 and 12 cpd (all $p<0.001$). No change was found at spatial frequency 18 cpd ($p=0.97$). There was little effect of WFG LASIK on photopic contrast sensitivity for the hyperopic group, as shown in Figure 26. No statistically significant changes were noted between the preoperative, three or six month visits (all $p>0.91$). Data for photopic contrast sensitivity for both groups can be found in Table 9.

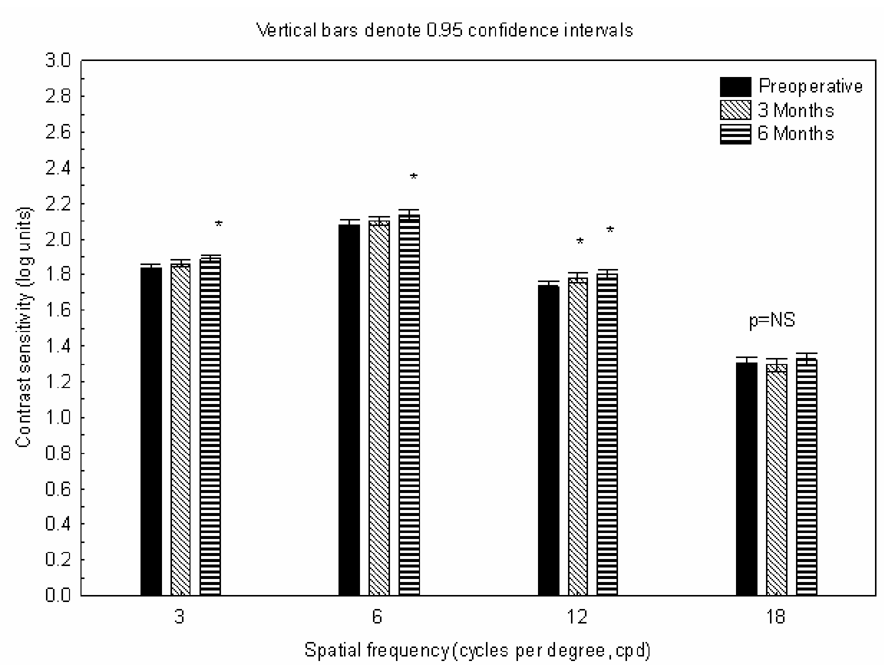


Figure 25: Photopic contrast sensitivity for the myopic group. Statistically significant changes (p<0.005) from the preoperative visit are marked *.

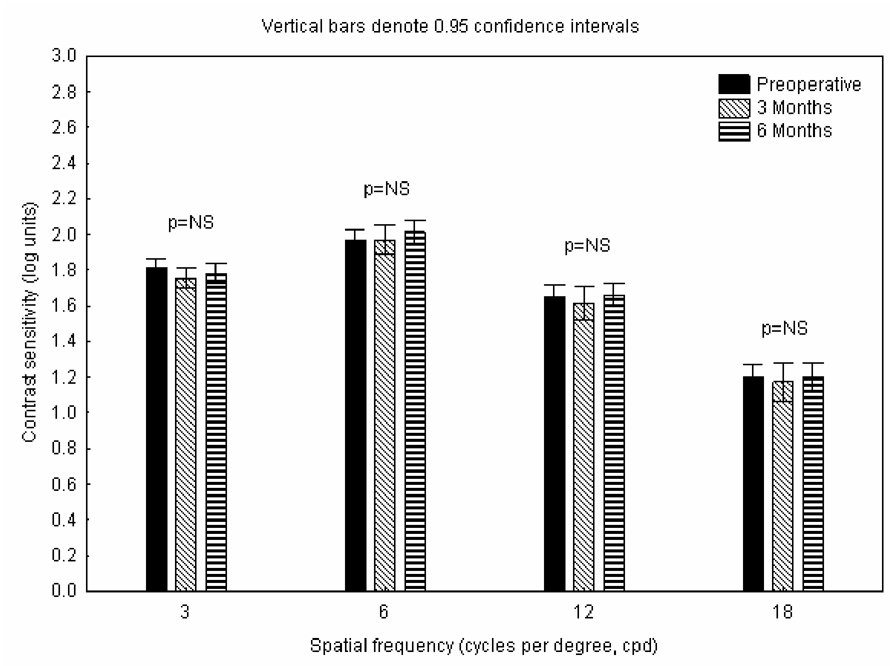


Figure 26: Photopic contrast sensitivity for the hyperopic group. There were no statistically significant changes (all p>0.005).

Table 9: Photopic contrast sensitivity results at the preoperative and six month visit for the myopic and hyperopic groups. Statistically significant differences (p<0.005) are shown in bold.

	Photopic contrast sensitivity for the myopic group (mean ± SEM)			
Visit	3 cpd	6 cpd	12 cpd	18 cpd
Preoperative	1.835 ± 0.011	2.080 ± 0.013	1.737 ± 0.014	1.308 ± 0.015
Six month	1.888 ± 0.011	2.137 ± 0.012	1.803 ± 0014	1.326 ± 0.018
	p<0.001	**p<0.001**	**p<0.001**	p=0.97
	Photopic contrast sensitivity for the hyperopic group (mean ± SEM)			
Visit	3 cpd	6 cpd	12 cpd	18 cpd
Preoperative	1.810 ± 0.028	1.966 ± 0.032	1.647 ± 0.035	1.202 ± 0.035
Six month	1.781 ± 0.028	2.015 ± 0.032	1.661 ± 0.031	1.201 ± 0.039
	p>0.99	p=0.92	p>0.99	p>0.99

The percentage of subjects in the myopic and hyperopic group that achieved the maximum score for the CSV-1000E contrast sensitivity test under photopic conditions is recorded in Table 10. In the myopic group a large percentage of eyes achieved the maximum score, suggesting that photopic contrast sensitivity testing in this study suffered from a ceiling effect, particularly at the six month visit. Such a large ceiling effect was not observed for the hyperopic group at baseline or six months.

Table 10: The percentage of subjects in the myopic and hyperopic groups who achieved the maximum contrast sensitivity score under photopic conditions.

Spatial Frequency (cpd)	% (# eyes) Myopic group			% (# eyes) Hyperopic group	
	Maximum Log CS	maximum at baseline	maximum at six months	maximum at baseline	maximum at six months
3	2.08	9.9% (16)	22.8% (37)	9.7% (3)	3.2% (1)
6	2.29	24.7% (40)	37.0% (60)	6.5% (2)	16.1% (5)
12	1.99	16.7% (27)	29.0% (47)	6.5% (2)	3.2% (1)
18	1.55	22.8% (37)	34.0% (55)	6.5% (2)	9.7% (3)

Mesopic contrast sensitivity

Best-corrected mesopic contrast sensitivity for the myopic group is shown in Figure 27. There was a statistically significant improvement in contrast sensitivity from the preoperative visit to the six month visit at spatial frequencies 12 cpd and 18 cpd ($p<0.001$). There was no significant change in contrast sensitivity between three and six months (both $p>0.05$). Figure 28 displays the mesopic contrast sensitivity for the hyperopic group. There was no significant change in contrast sensitivity over time at any of the spatial frequencies (all $p>0.05$). Data for mesopic contrast sensitivity for both groups can be found in Table 11.

The percentage of subjects in the myopic and hyperopic group that achieved the maximum score for the CSV-1000E CS test under mesopic conditions is recorded in Table 12. Very few eyes in either group achieved the maximum score.

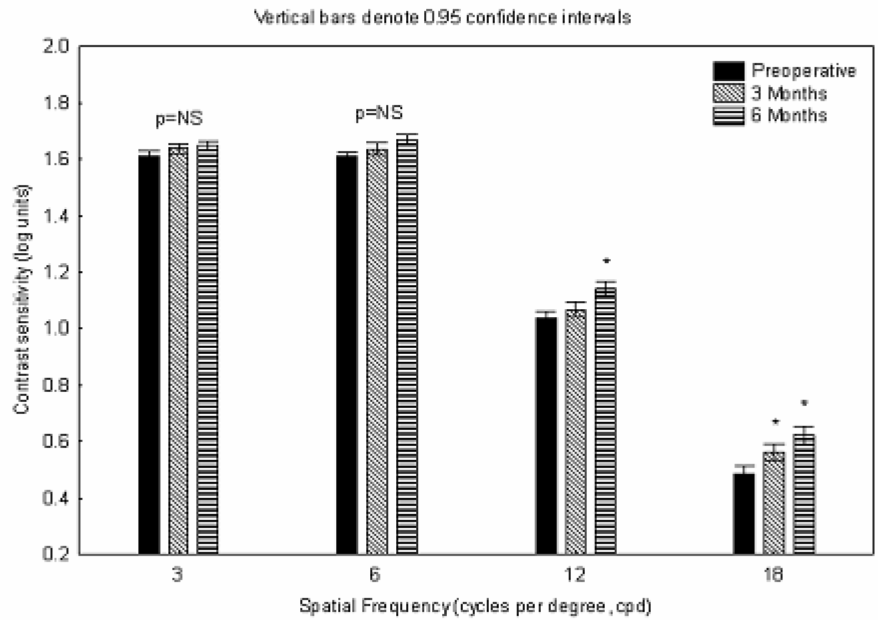


Figure 27: Mesopic contrast sensitivity for the myopic group. Statistically significant changes ($p<0.005$) from the preoperative visit are marked *.

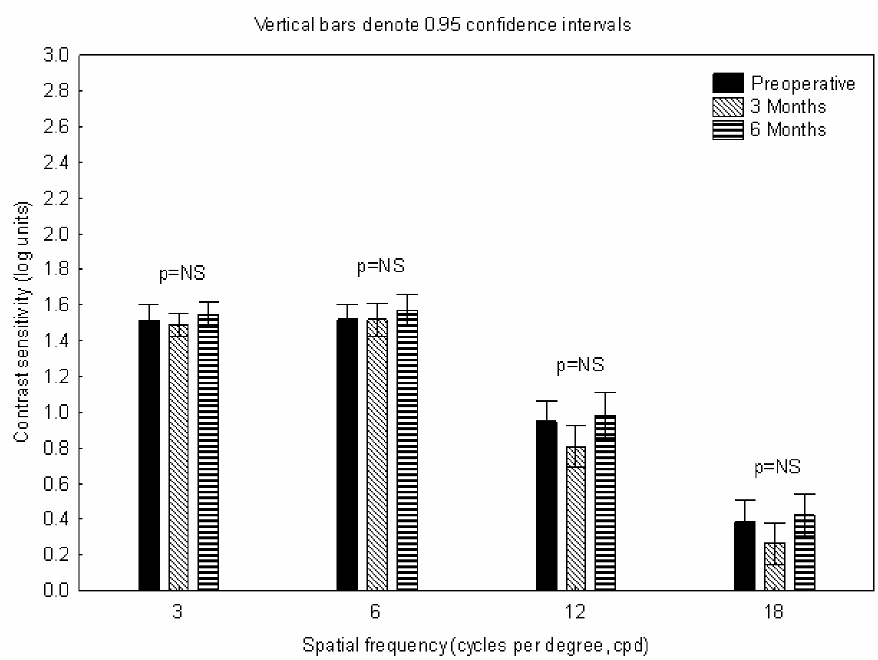


Figure 28: Mesopic contrast sensitivity for the hyperopic group. There were no statistically significant changes over time (all $p>0.05$).

Table 11: Mesopic contrast sensitivity results at the preoperative and six month visit for the myopic and hyperopic groups. Statistically significant differences ($p<0.005$) are shown in bold.

	Mesopic contrast sensitivity for the myopic group (mean ± SEM)			
Visit	3 cpd	6 cpd	12 cpd	18 cpd
Preoperative	1.612 ± 0.017	1.611 ± 0.016	1.037 ± 0.025	0.487 ± 0.026
Six month	1.649 ± 0.015	1.670 ± 0.017	1.140 ± 0.024	0.623 ± 0.029
	p=0.83	p=0.15	**p<0.001**	**p<0.001**
	Mesopic contrast sensitivity for the hyperopic group (mean ± SEM)			
Visit	3 cpd	6 cpd	12 cpd	18 cpd
Preoperative	1.514 ± 0.042	1.520 ± 0.040	0.947 ± 0.057	0.383 ± 0.060
Six month	1.546 ± 0.036	1.569 ± 0.044	0.982 ± 0.063	0.423 ± 0.057
	p>0.99	p>0.99	p>0.99	p>0.99

Table 12: The percentage of subjects in the myopic and hyperopic groups who achieved the maximum contrast sensitivity score under mesopic conditions.

	% (# eyes) Myopic group			% (# eyes) Hyperopic group	
Spatial Frequency (cpd)	Maximum Log CS	maximum at baseline	maximum at six months	maximum at baseline	maximum at six months
3	2.08	4.3% (7)	4.3% (7)	3.2% (1)	3.2% (1)
6	2.29	0.6% (1)	0.6% (1)	3.2% (1)	0
12	1.99	0	0.6% (1)	0	0
18	1.55	0	1.9% (3)	0	0

Correlation between mesopic contrast sensitivity and higher order aberrations

Metrics used to predict visual performance from wavefront aberration measurements have been shown to correlate better with tests performed under mesopic conditions.[246] Therefore, the association between mesopic contrast sensitivity and six month higher order aberrations was investigated, in an attempt to determine whether a larger magnitude or change in higher order aberrations was associated with a worsening of contrast sensitivity.

There were no statistically significant correlations in the hyperopic group (all $p>0.005$). However, negative correlations between mesopic contrast sensitivity and higher order aberrations were found for the myopic group, as shown in Table 13 and Table 14. All of the statistically significant associations suggest that larger magnitudes, or greater changes, in certain higher order aberrations were associated with a worsening of mesopic contrast sensitivity at specific spatial frequencies. Figure 29 shows the correlation plot between the change in mesopic contrast sensitivity at 12 cpd and the absolute change in Z^3_3 for the myopic group (r=-0.310, p<0.001). When the outlier was removed, the correlation was no longer statistically significant (r=-0.214, p=0.007).

Table 13: Correlation between six month mesopic contrast sensitivity and the absolute magnitude of higher order Zernike coefficients for the myopic group. Statistically significant (p<0.005) p-values are shown in bold.

Spatial frequency	Higher order Zernike coefficient terms (correlation coefficient, p-value)								
	6M Z^{-1}_3	6M Z^1_3	6M Z^{-3}_3	6M Z^3_3	6M Z^0_4	6M Z^{-2}_4	6M Z^2_4	6M Z^{-4}_4	6M Z^4_4
3 cpd	-0.003 p=0.973	-0.046 p=0.561	0.038 p=0.632	-0.117 p=0.138	-0.004 p=0.963	-0.103 p=0.192	-0.058 p=0.466	-0.140 p=0.075	-0.180 p=0.022
6 cpd	-0.065 p=0.409	-0.172 p=0.029	-0.192 p=0.014	**-0.292** **p<0.001**	-0.160 p=0.042	-0.136 p=0.084	-0.153 p=0.051	-0.072 p=0.363	**-0.293** **p<0.001**
12 cpd	-0.112 p=0.157	-0.218 p=0.005	-0.151 p=0.055	**-0.296** **p<0.001**	**-0.261** **p=0.001**	-0.174 p=0.027	-0.222 p=0.004	-0.125 p=0.114	**-0.220** **p<0.005**
18 cpd	-0.119 p=0.130	-0.150 p=0.056	-0.143 p=0.070	**-0.249** **p=0.001**	**-0.260** **p=0.001**	-0.182 p=0.020	-0.136 p=0.084	-0.110 p=0.163	-0.209 p=0.008

Table 14: Correlation between the change in mesopic contrast sensitivity and the absolute change of higher order Zernike coefficients for the myopic group. Statistically significant (p<0.005) p-values are shown in bold.

Spatial frequency change	Higher order Zernike coefficient terms (correlation coefficient, p-value)								
	6M Z^{-1}_{3}	6M Z^{1}_{3}	6M Z^{-3}_{3}	6M Z^{3}_{3}	6M Z^{0}_{4}	6M Z^{-2}_{4}	6M Z^{2}_{4}	6M Z^{-4}_{4}	6M Z^{4}_{4}
3 cpd	-0.061 p=0.441	0.318 p=0.688	0.017 p=0.831	-0.081 p=0.307	0.039 p=0.621	-0.122 p=0.123	-0.047 p=0.553	-0.009 p=0.913	-0.108 p=0.172
6 cpd	-0.131 p=0.096	-0.157 p=0.046	**-0.267** **p=0.001**	-0.155 p=0.048	-0.154 p=0.050	-0.180 p=0.022	-0.158 p=0.045	-0.044 p=0.577	-0.146 p=0.065
12 cpd	-0.059 p=0.454	-0.049 p=0.540	-0.163 p=0.038	**-0.310** **p<0.001**	-0.125 p=0.112	-0.088 p=0.268	-0.207 p=0.008	-0.060 p=0.450	-0.202 p=0.010
18 cpd	-0.043 p=0.585	0.067 p=0.397	-0.095 p=0.229	-0.185 p=0.019	-0.043 p=0.584	-0.186 p=0.018	-0.079 p=0.318	-0.081 p=0.303	-0.089 p=0.259

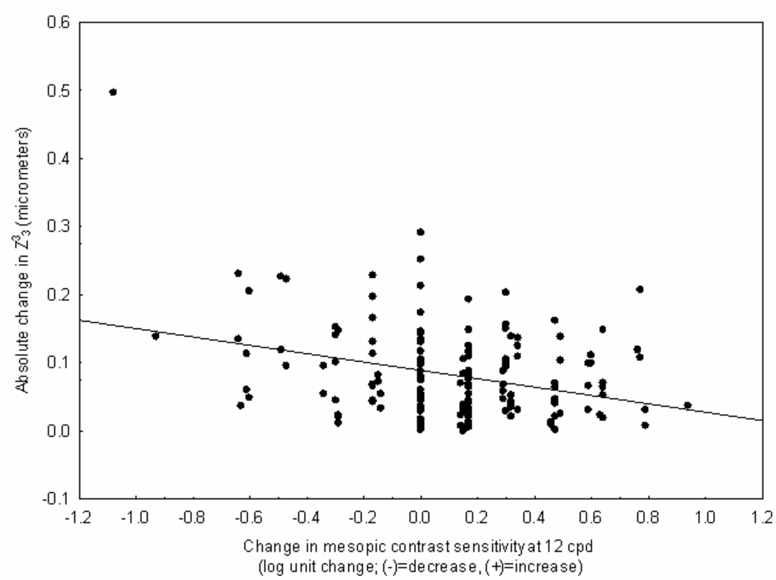


Figure 29: Correlation between the change in mesopic contrast sensitivity at 12 cpd and the absolute change in Z^3_3 for the myopic group (r=-0.310, p<0.001). Univariate regression is shown.

Discussion

Safety and efficacy

No eye lost two or more lines of HC BCVA in either group. Visual acuity results following WFG LASIK for the myopic and hyperopic group were excellent, with more than 80% achieving 0.00 logMAR (6/6) or better UCVA. These outcomes are very similar to a review of FDA outcomes for WFG LASIK reported by Sakimoto et al,[233] who reported 89% with 0.00 logMAR (6/6) or better UCVA and a loss of two or more lines of HC BCVA in 0.5%.

Visual acuity

The preoperative mean (± SD) HC BCVA in this study was -0.09 ± 0.07 logMAR for the myopic group and -0.07 ± 0.09 logMAR for the hyperopic group. A study of healthy, pre-presbyopic eyes reported average values of HC BCVA between -0.20 logMAR (6/3.8) and -0.10 logMAR (6/4.5).[263] The results of this study were slightly less, which could be due to HC BCVA being measured under ambient lighting conditions, whereas the previous study measured HC BCVA under high luminance.

The preoperative mean (± SD) LC BCVA was 0.17 ± 0.07 logMAR and 0.18 ± 0.09 logMAR for the myopic and hyperopic group, respectively. There are very few reports of typical LC BCVA values in the literature. Pesudovs et al.[246] investigated LC BCVA under high illumination for 148 subjects with a range of crystalline lens changes and found a similar mean LC BCVA of 0.18 ± 0.15 logMAR. The reason LC BCVA was not better in my study could also be due to differences in lighting conditions.

An increase in HC BCVA has been previously reported following WFG LASIK,[264] although there have been mixed reports following non-WFG surgery, with a greater loss reported for higher myopic corrections.[265] Looking at the effect of WFG LASIK on HC BCVA in this study, we measured a small, but statistically significant improvement in the myopic group. The mean increase from preoperative levels at six months was 0.05 logMAR (approximately two letters). When the effect of magnification was taken into account[266] this change was reduced to 0.02 logMAR (one letter), but remained statistically significant. Regardless, it is unlikely that this small improvement in HC BCVA for the myopic group is clinically relevant. For the hyperopic group there was no statistically significant change in HC BCVA over time, including no overall loss. This is an improvement over non-WFG LASIK, where loss of HC BCVA has been previously reported.[267, 268]

While it has been suggested that LC BCVA provides little additional information to HC BCVA,,[269] other reports in the literature have shown that a decrease in LC BCVA can occur with little effect on HC BCVA.[135, 270] In my study, LC BCVA for the myopic group showed a statistically significant improvement after surgery, with a mean increase of 0.04 logMAR (two letters). This finding is in agreement with another report of improved LC BCVA following WFG LASIK.[271] Varying results have been reported following non-WFG LASIK, with numerous publications reporting LC BCVA loss, [135, 272-274] especially for higher myopic corrections.[275] For the hyperopic group there was no statistically significant change in LC BCVA over time. There are no reports in the literature following hyperopic refractive surgery and thus LC BCVA results following non-WFG or WFG LASIK are not available for comparison.

Statistically significant correlations were found in this study between BCVA and higher order aberrations. In all cases the correlations were stronger for LC BCVA compared to HC BCVA. There are mixed results in the literature regarding the association between higher order aberrations and visual acuity. Yamane et al.[272] reported that LC BCVA was associated with an increase in Z^1_3/Z^{-1}_3 (coma) and Z^0_4 (spherical aberration) following non-WFG LASIK. We did not find spherical aberration to be associated with either HC or LC BCVA in the myopic group; however we did find a positive association between spherical aberration and LC BCVA in the hyperopic group. Applegate et al.[54] have also reported that an increase in surgically-induced spherical aberration is associated with a reduction in LC BCVA. Despite these individual associations, there was no overall decrease in visual acuity.

Contrast sensitivity

Contrast sensitivity testing is not commonly conducted in a clinical setting. Consequently, this test is less familiar than HC and LC BCVA. As it evaluates visual performance across low and high spatial frequencies, it is said to better reflect the performance of visual tasks under a variety of conditions.[276] Previous studies investigating photopic contrast sensitivity following non-WFG LASIK report either a decrease, which can be temporary or permanent, or little change from preoperative levels.[129, 273, 277-281] Significant temporary reductions in mesopic contrast sensitivity have been found following non-WFG LASIK, particularly at high spatial frequencies.[278, 281, 282] More recently, contralateral studies comparing non-WFG LASIK with WFG LASIK have shown improved contrast sensitivity with WFG surgery.[137, 138, 283] In my study there were no reductions in photopic or mesopic contrast sensitivity.

While there was no increase in contrast sensitivity for the hyperopic group, contrast sensitivity for the myopic group improved at low to mid spatial frequencies under photopic conditions and at mid to high spatial frequencies, under mesopic conditions.

Mesopic testing results in a larger physiologic pupil size. As higher order aberrations increase with larger pupils,[54, 136, 284] it would be intuitive that testing under these reduced light levels would better reflect optical quality. It has been reported that mesopic testing is better for detecting small differences in retinal image quality than photopic testing.[246, 285] Neither group had reductions in contrast sensitivity at any spatial frequency six months following WFG LASIK. Although not statistically significant, the hyperopic group did exhibit a mild decrease in mesopic contrast sensitivity which improved by six months.

Statistically significant correlations were found in this study between mesopic contrast sensitivity and individual Zernike coefficient terms for the myopic group. No significant correlations were found for the hyperopic group. There have been mixed reports in the literature regarding the association between higher order aberrations and contrast sensitivity. While some studies have reported no association,[278, 281, 286, 287] others have found reductions in contrast sensitivity associated with increases in higher order aberrations following non-WFG LASIK.[272, 288] The majority of the statistically significant correlations found in this study were at mid to high spatial frequencies (6 cpd, 12 cpd and 18 cpd). There were no significant associations at 3 cpd. This finding is in agreement with the literature, where mid to high spatial frequency targets have been shown to be more affected by low levels of aberrations than low spatial frequency targets.[134, 272, 289] Similar to the visual acuity results, despite these individual associations, there was no overall decrease in mesopic contrast sensitivity. Based on these results, clinical testing of LC BCVA and mesopic mid-spatial frequencies (6 cpd and 12 cpd) is recommended.

When reporting visual outcomes, it is important to ensure that a specific test measures a change in optical quality effectively. Pesudovs et al.,[290] investigated the effectiveness of two types of contrast sensitivity tests on detecting changes in optical quality. They concluded that the Vistech chart suffered from ceiling effects for post-LASIK patients and floor effects for post-cataract patients. In this study, photopic contrast sensitivity suffered from greater than 20% ceiling effects, suggesting that testing contrast sensitivity under photopic conditions was not an adequate visual outcome measure. This might explain why improvements occurred for HC BCVA, but not for high spatial frequency photopic contrast sensitivity.

The discrepancy between the results in this study for visual acuity, contrast sensitivity and higher order aberrations requires further examination. A possible reason why improvements in visual acuity and contrast sensitivity were found, despite an increase in higher order aberrations, could be due to the difference in the way these tests were conducted. The vision tests were viewed best corrected with the phoropter in place, therefore aberrations induced by the phoropter could influence these results. In order to truly make a direct comparison between these measures before and after surgery, the total optical system would have to be included for both measurements (personal communication, David W. Evans, PhD Consultant Faculty, University of Alabama Birmingham, School of Optometry). Along the same lines, it is possible that the effects of the higher order aberrations were balanced by the subjective manifest refraction with the appropriate amount of sphere and/or astigmatism correction during vision testing.[291] There has also been work undertaken on the measurement of higher order aberrations for individuals with better than $\geq$ 6/4.5 vision.[292, 293] Despite having excellent visual acuity, these individuals have a considerable amount of higher order aberrations, including coma (Z^{1}_{3}, Z^{-1}_{3}). Applegate et al.,[291] have shown that aberrations can combine to either improve or reduce vision. Consequently, contributing to these results may be some type of interaction between aberrations.

An advantage of this study is that it was conducted in a research setting and data were collected in a controlled manner. A limitation is that the average amount of myopia was low to moderate. It has been shown that higher amounts of correction can result in a significant loss of visual quality following non-WFG LASIK.[272] Therefore, additional large scale studies looking at quality of vision outcomes after WFG LASIK for higher levels of myopia are needed to determine whether these visual outcomes remain. We were also unable to determine whether changes in vision occur after the six month visit, since no further data were collected after this time. This is particularly important when attempting to counsel patients regarding their vision and/or if an enhancement is indicated. Interestingly, higher order aberrations did not exhibit the same temporal change. It is possible that these improvements in vision are related to learning effects, which have been reported in the literature for the CSV-1000E test,[294] or wound healing. Other studies have suggested that neural adaptation might also play a role.[295]

With improvements in technology and more precise measures of retinal image quality, it is not surprising that current methods of vision testing may also need to be improved. A few ways to increase sensitivity of currently available tests is to have multiple trials at each level, use random target generation and incorporate pupil size monitoring. Until the ideal test can be developed, increasing the level of difficulty could improve the sensitivity of currently available tests. This could potentially be done by increasing the number of letters, reducing the size progression of letters, or repeating the measurements.[296] An improved association between vision testing and higher order aberration results could be achieved by measuring vision and analyzing wavefront aberration data over the same pupil size. Contrast sensitivity tests incorporating various orientations of sinusoidal gratings could be tested against gratings that are oriented in only one direction, to determine whether orientation is a factor, which may be particularly relevant for reflecting changes in asymmetric higher order aberrations. Finally, using vision tests that are sensitive to phase information is also important, to provide a more accurate representation of the visual interpretation of retinal image quality.[297]

In summary, both myopic and hyperopic WFG LASIK resulted in either no change or slight improvements in visual acuity and contrast sensitivity. LC BCVA and mesopic contrast sensitivity were better visual outcome measures than HC BCVA and photopic contrast sensitivity, in this study. The relationship between higher order aberrations and visual acuity and contrast sensitivity found in this study implies that certain higher order aberrations are associated with reduced visual performance. Regardless, there was no loss in visual acuity or contrast sensitivity despite an overall increase in higher order aberrations following surgery. Ultimately, this suggests that more sensitive measures of visual performance following WFG LASIK are required. A description of the higher order aberrations before and after WFG LASIK will be described in detail in the following two chapters.

Chapter 4

Investigation of monochromatic higher order aberrations prior to wavefront-guided LASIK

Introduction

Recent studies have shown that there is a great deal of variability in the distribution of higher order aberrations between individuals.[55, 298] Large-scale studies conclude that higher order aberrations are not associated with low order sphere and astigmatism,[299, 300] in contrast to other researchers, who have demonstrated an association between higher order aberrations and higher degrees of myopia.[301, 302] Regardless of refractive error, spherical aberration is larger and slightly positive for most individuals.[298, 303, 304] Additionally, mirror symmetry of individual aberrations between left and right eyes has been reported.[55, 298]

The aim of this investigation was to describe and explore the magnitude of higher order aberrations prior to wavefront-guided (WFG) LASIK for subjects with myopic and hyperopic refractive errors. Bilateral symmetry and the relationship between manifest refraction, central corneal curvature and higher order aberrations before and after surgery were also investigated.

Methods

As described in Chapter 2, wavefront aberrations were measured over a 7.0 mm minimum pupil diameter and computed over a 5.0 mm pupil diameter using Zernike polynomials up to the fourth order. Simple t-tests were used to calculate differences between means, with a significance level of $p<0.05$. Associations were determined using Pearson correlation coefficients and a Bonferroni correction was applied to account for multiple comparisons, resulting in an adjusted level of significance of 0.05/18. Calculations were undertaken using Statistica 7 software (StatSoft Inc, Tulsa, OK). Standard deviations (SD) are used for preoperative information to show the spread of the data in the population.[261] Vector components were calculated for sphere, regular astigmatism (J_0) and oblique astigmatism (J_{45}) using the manifest refraction as described by Thibos and Horner.[305] Similarly, vector components for corneal M (M_k), corneal J_0 (J_{0k}) and corneal J_{45} (J_{45k}) were calculated using steep and flat central corneal curvature readings, determined by auto-keratometry.[305]

Results

Magnitude of preoperative higher order monochromatic aberrations

Figure 30 illustrates the mean of each Zernike coefficient up to the fourth order for the myopic group. As seen by the large standard deviations, there was a great deal of inter-subject variability in the data. Most of the Zernike terms averaged close to zero, but t-tests revealed that the mean Zernike coefficients were statistically different from zero for all terms (all $p<0.03$) except horizontal coma, Z^1_3 ($p>0.05$). Spherical aberration had the largest value, with a mean (± SD) positive value of 0.073 ± 0.093 µm. Figure 31 exhibits the absolute magnitude of the Zernike coefficients for the myopic group and illustrates that despite positive and negative values averaging close to zero, the absolute magnitude of individual aberrations ranged between 0.02 µm and 0.10 µm preoperatively. Thibos et al.[304] suggest that the tendency for human eyes is to be aberration-free (with the exception of having slight positive spherical aberration) but that an individual eye is likely to suffer from positive or negative aberrations due to biological variability. In the myopic group, the largest absolute magnitudes (mean ± SD) were for Z^{-1}_3 (0.096 ± 0.076 µm), followed by Z^0_4 (0.082 ± 0.085 µm), Z^{-3}_3 (0.065 ± 0.052 µm), Z^1_3 (0.060 ± 0.053 µm) and Z^3_3 (0.055 ± 0.044 µm).

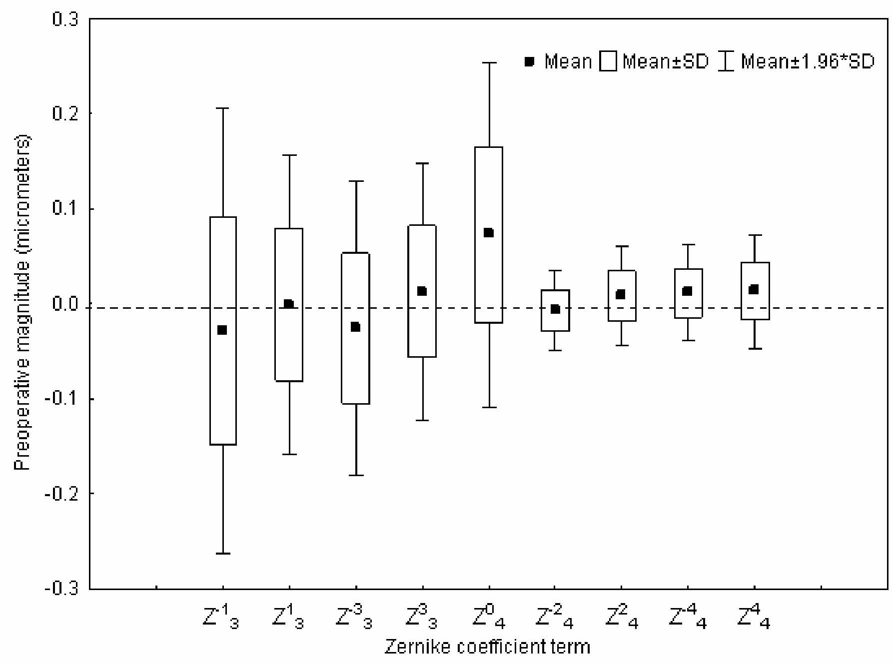


Figure 30: The mean preoperative third and fourth order Zernike coefficients for the myopic group (n=162 eyes) over a 5.0 mm pupil.

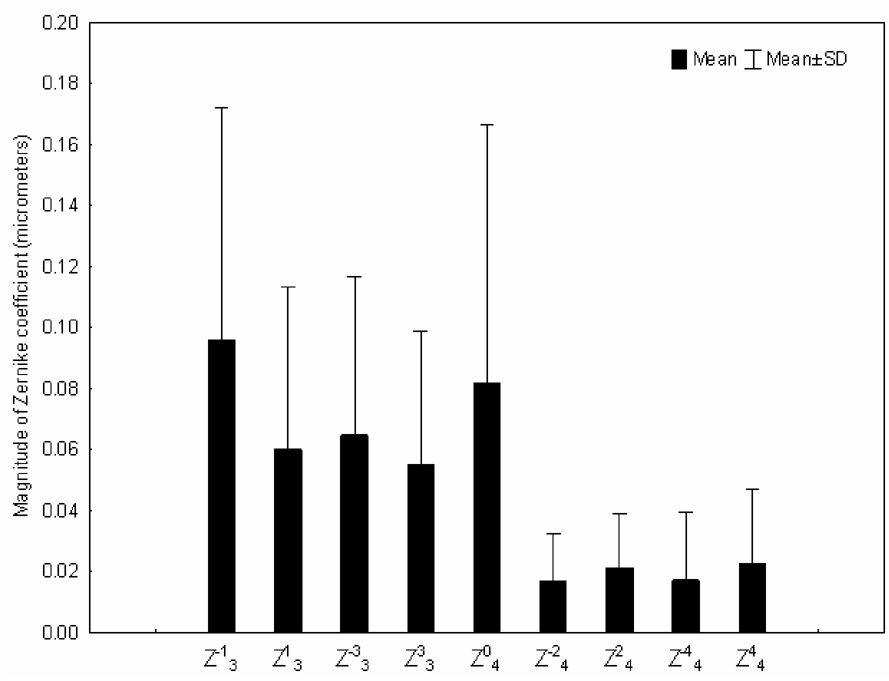


Figure 31: The absolute magnitude for preoperative third and fourth order Zernike coefficients for the myopic group.

Figure 32 illustrates the mean values for third and fourth order Zernike coefficients for the hyperopic group. Similar to the myopic group, there was a large amount of inter-subject variability. Only the means of Z^{-3}_3, Z^0_4 and Z^{-4}_4 were statistically different from zero (all $p<0.05$), with spherical aberration being the most different from zero with a mean (± SD) value of 0.120 ± 0.067 µm. Figure 33 shows the mean absolute magnitudes of the Zernike coefficients, which ranged between 0.02 µm and 0.12 µm. Similar to the myopic group, the third order terms and the fourth order term spherical aberration (Z^0_4) contributed the most to the variance of the wavefront aberration. The largest absolute magnitudes (mean ± SD) for the hyperopic group were for Z^0_4 (0.120 ± 0.067 µm), followed by Z^{-1}_3 (0.083 ± 0.055 µm), Z^{-3}_3 (0.077 ± 0.057 µm), Z^1_3 (0.061 ± 0.052 µm) and Z^3_3 (0.045 ± 0.030 µm).

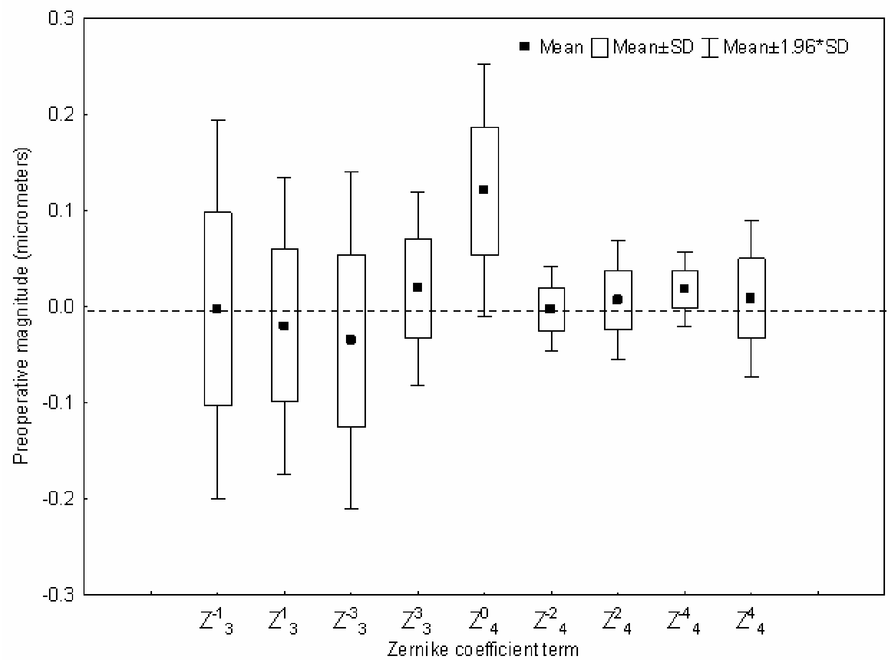


Figure 32: The mean preoperative third and fourth order Zernike coefficients for the hyperopic group (n=31 eyes) over a 5.0 mm pupil.

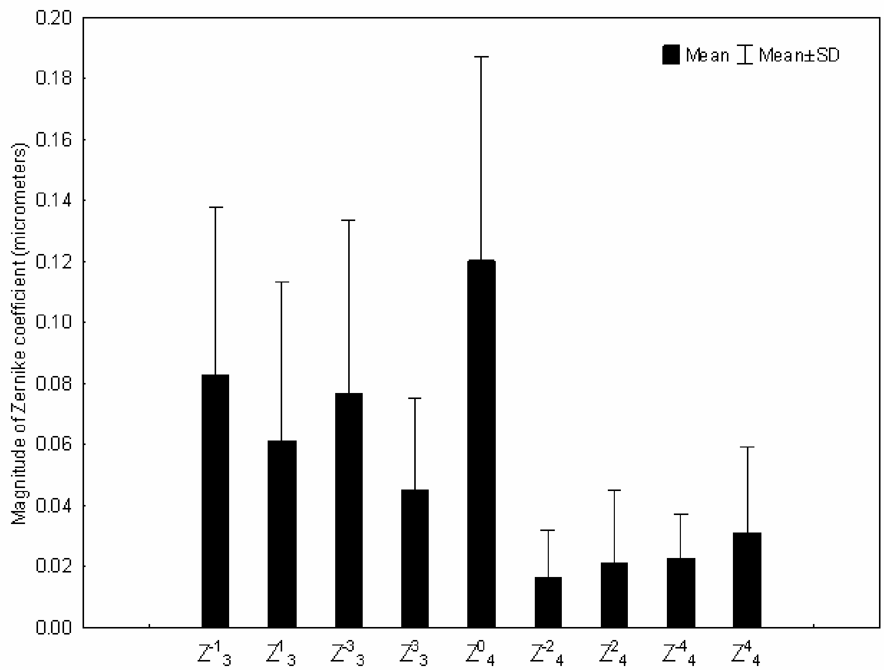


Figure 33: The absolute magnitude for preoperative third and fourth order Zernike coefficients for the hyperopic group.

A comprehensive review has been reported in the literature describing population norms for monochromatic higher order aberrations from pooled data for 2560 eyes (1433 subjects).[306] A comparison of our data for individual Zernike terms and the results reported by Salmon et al.[306] (all analyzed over a 5.0 mm pupil diameter) can be found in Table 15. The means were compared using known standard deviations to see how our results compared. The greatest difference was for Z^0_4 (spherical aberration) in both the myopic and hyperopic groups.

Table 15: Comparison of absolute magnitudes for the myopic and hyperopic group with population norms from the literature.[306] A statistically significant difference (p<0.05) between the means is shown in bold.

Zernike coefficient term	Mean absolute magnitude of Zernike coefficient (± standard deviation)		
	Myopic group (n=162 eyes)	Hyperopic group (n=31 eyes)	Population norms (n=2008 eyes)
Z^{-1}_{3}	**0.096 ± 0.076, p=0.014**	0.083 ± 0.055, p=0.857	0.082 ± 0.069
Z^{1}_{3}	0.060 ± 0.053, p=0.302	0.061 ± 0.052, p=0.197	0.056 ± 0.047
Z^{-3}_{3}	0.065 ± 0.052, p=0.380	0.077 ± 0.057, p=0.080	0.069 ± 0.056
Z^{3}_{3}	0.055 ± 0.044, p=0.394	**0.045 ± 0.030, p=0.042**	0.052 ± 0.043
Z^{0}_{4}	**0.082 ± 0.085, p<0.001**	**0.120 ± 0.067, p<0.001**	0.064 ± 0.049
Z^{-2}_{4}	0.017 ± 0.015, p>0.999	0.016 ± 0.016, p=0.417	0.017 ± 0.015
Z^{2}_{4}	**0.021 ± 0.018, p=0.007**	**0.021 ± 0.023, p=0.008**	0.026 ± 0.023
Z^{-4}_{4}	**0.017 ± 0.022, p<0.001**	0.022 ± 0.014, p=0.533	0.023 ± 0.020
Z^{4}_{4}	0.023 ± 0.024, p=0.269	**0.031 ± 0.028, p=0.001**	0.025 ± 0.022

Symmetry between left and right eyes

If bilateral symmetry were present, all Zernike terms that are symmetrical about the vertical (y) axis would be equal in magnitude and terms that are asymmetrical about the vertical (y) axis would be equal in magnitude between the eyes, but opposite in sign.[304] To test the hypothesis of bilateral symmetry in our study, we looked at the symmetric (Z^{-1}_3, Z^{-3}_3, Z^0_4, Z^2_4 and Z^4_4) and asymmetric (Z^1_3, Z^3_3, Z^{-2}_4, Z^{-4}_4) Zernike coefficients separately and determined the correlation between the left and right eyes, both before and after surgery. Results for the symmetric and asymmetric Zernike coefficients for the myopic group before and after WFG LASIK can be found in Figure 34 and Figure 35, respectively. Results for the hyperopic group can be found in Figure 36 and Figure 37. My results support the observation that strong correlations exist for higher order aberrations between eyes prior to surgery for both groups, with a stronger correlation between the symmetric Zernike terms compared to the asymmetric terms. Six months following WFG-LASIK, however, the symmetry between the eyes was weakened, particularly for the asymmetric components, which were no longer statistically significantly correlated between eyes ($p>0.05$ for both the myopic and hyperopic groups).

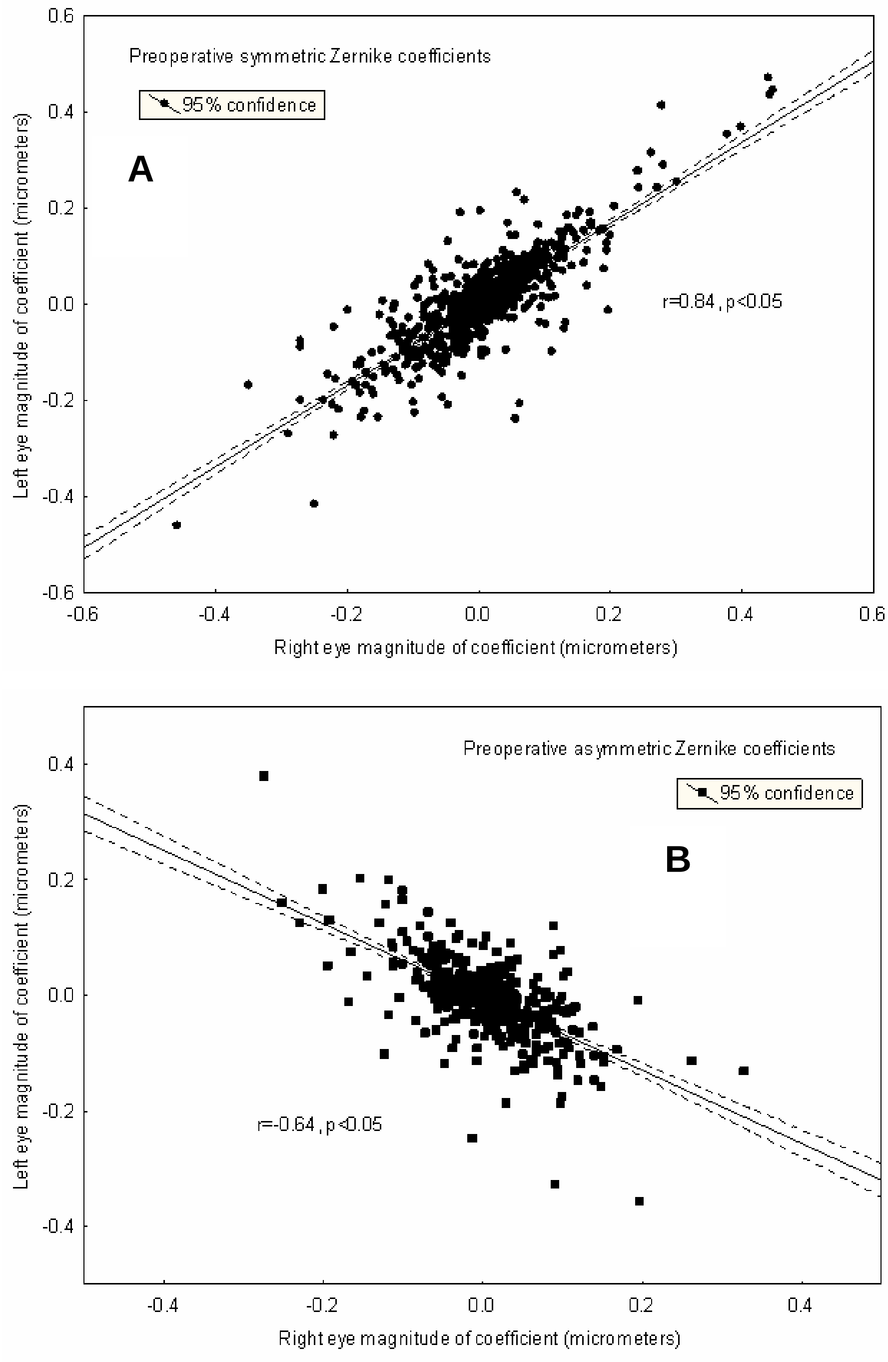
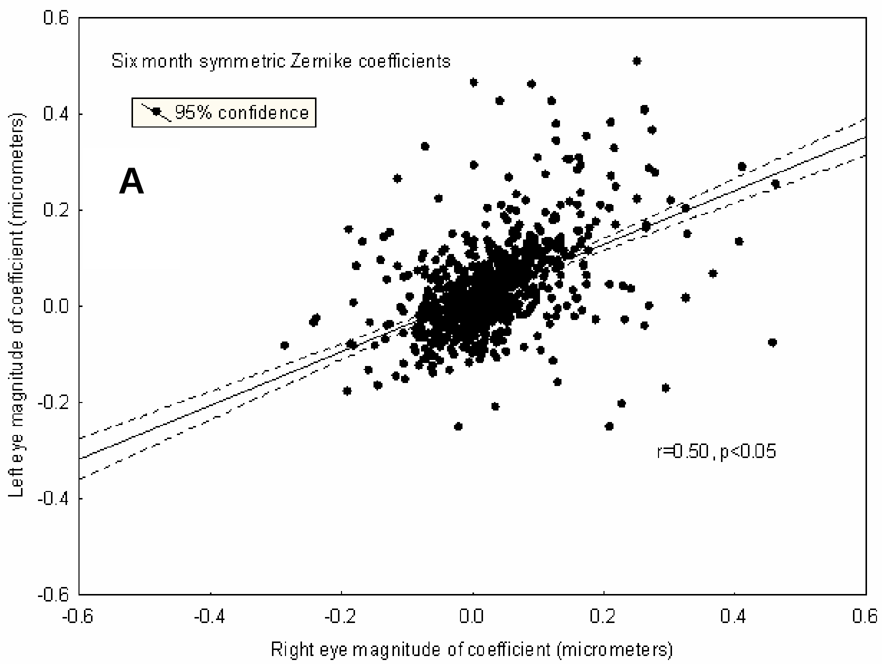


Figure 34: Correlation between higher order aberrations prior to surgery for the myopic group. A) symmetric third and fourth order aberrations B) asymmetric third and fourth order aberrations



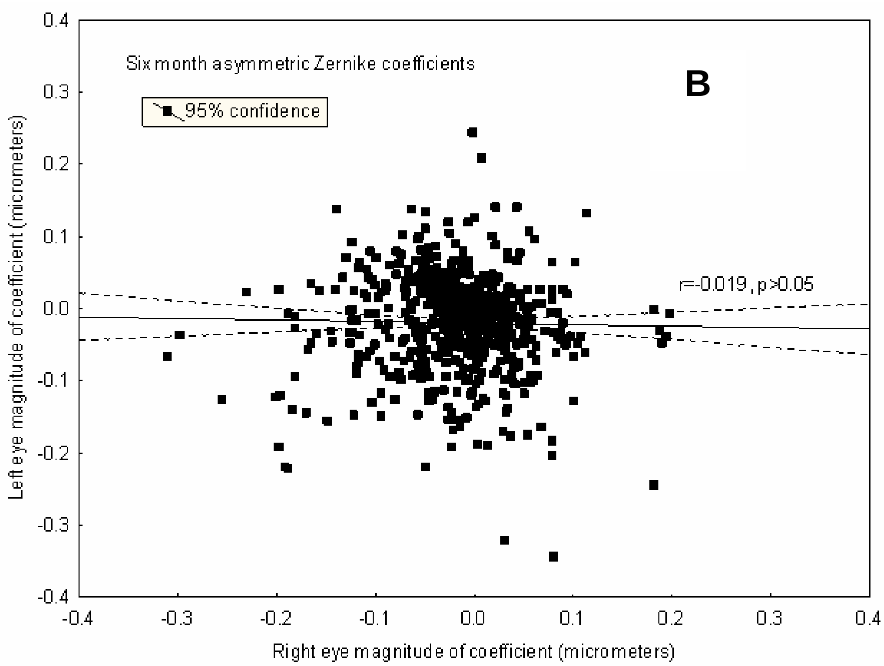


Figure 35: Correlation between higher order aberrations six months following WFG-LASIK for the myopic group. A) postoperative symmetric third and fourth order aberrations B) postoperative asymmetric third and fourth order aberrations

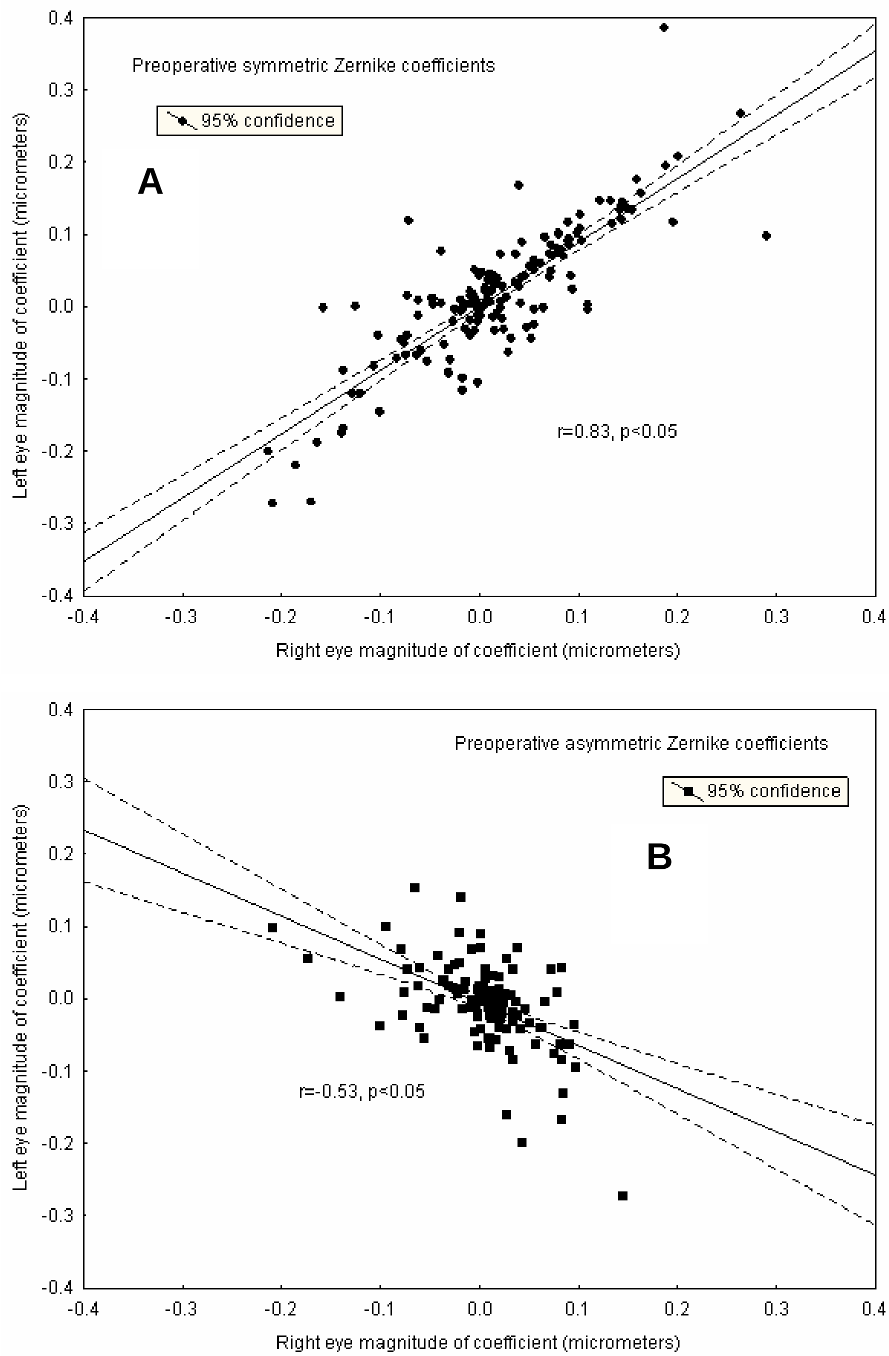


Figure 36: Correlation between higher order aberrations preoperatively for the hyperopic group. A) symmetric third and fourth order aberrations B) asymmetric third and fourth order aberrations

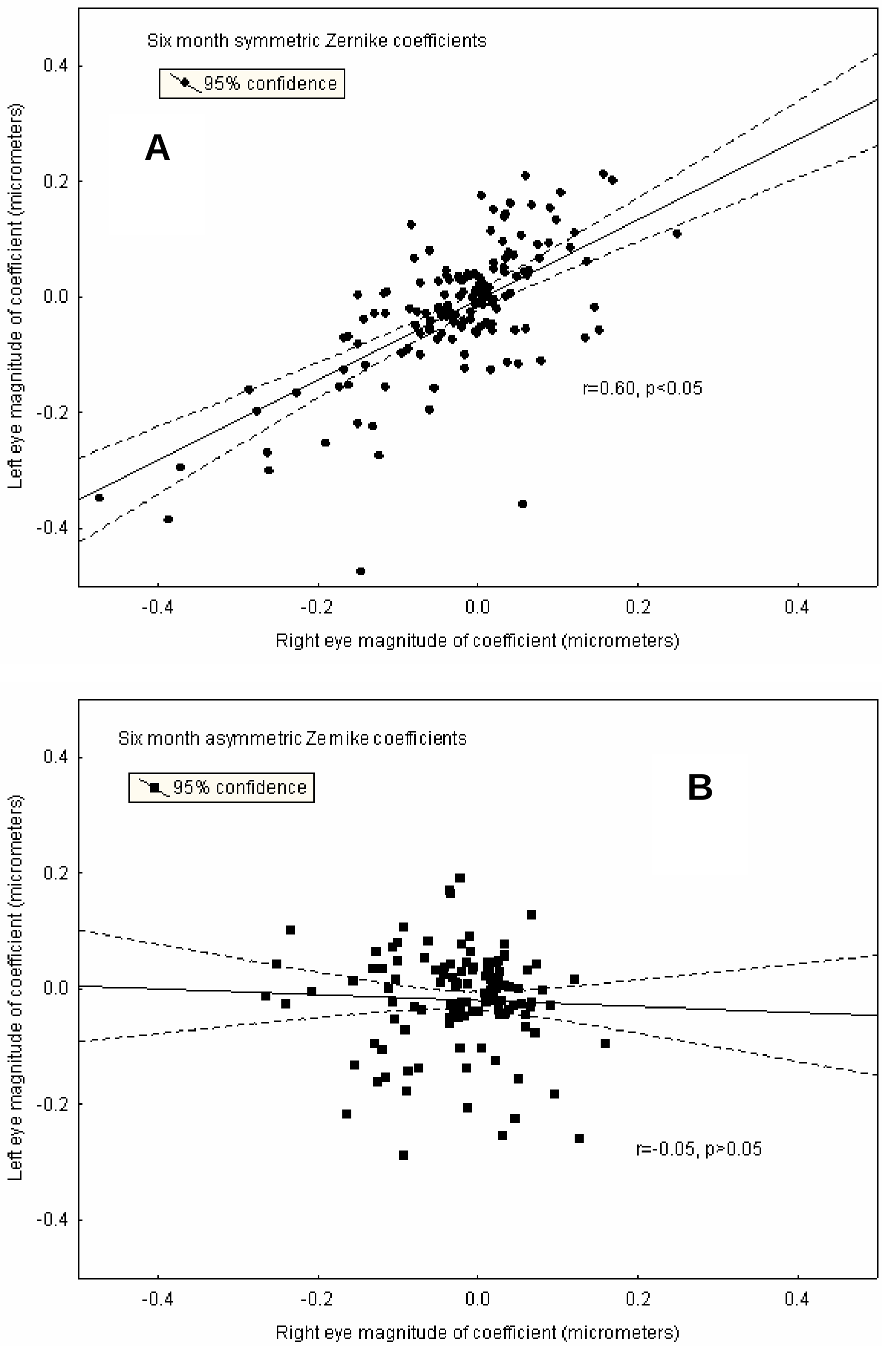


Figure 37: Correlation between higher order aberrations six months following WFG-LASIK for the hyperopic group. A) postoperative symmetric third and fourth order aberrations B) postoperative asymmetric third and fourth order aberrations

Vector analysis

Associations between preoperative manifest refraction, central corneal curvature, and ocular aberrations are shown in Table 16 and Table 17 for the myopic and hyperopic group, respectively. Statistically significant correlations were found between preoperative sphere (M) and the Zernike term for defocus (Z^0_2) and between preoperative refractive astigmatism (J_0 and J_{45}), corneal curvature (J_{0k} and J_{45k}) and the Zernike terms for astigmatism (Z^2_2 and Z^{-2}_2). Sphere (M) was not associated with central corneal curvature (M_k), which indicates that differences in refractive power were due mainly to differences in the axial length. The strong association between refractive astigmatism (J_0 and J_{45}) and corneal curvature (J_{0k} and J_{45k}) suggests that most of the refractive astigmatism in this study was corneal in nature. There were no statistically significant correlations between higher order aberrations and the manifest refraction or central corneal curvature prior to surgery (all $p>0.002$).

Table 16: Correlations between preoperative vector components of manifest refraction, central corneal curvature and mean ocular aberrations for the myopic group. Only statistically significant r-values (p<0.002) are shown.

Preoperative variables	Myopic group Preoperative vectors for refraction and keratometry					
	M	J_0	J_{45}	M_k	J_{0k}	J_{45k}
M	-	-	-	-	-	-
J_0	-	-	-	-	0.86	-
J_{45}	-	-	-	-	-	0.63
M_k		-	-	-	-	-
J_{0k}	-	0.86	-	-	-	-
J_{45k}	-	-	0.63	-	-	-
Z^0_2	-0.86	-	-	-	-	-
Z^{-2}_2	-	-	-0.88	-	-	-0.66
Z^2_2	-	-0.94	-	-	-0.86	-
Z^{-1}_3	-	-	-	-	-	-
Z^1_3	-	-	-	-	-	-
Z^{-3}_3	-	-	-	-	-	-
Z^3_3	-	-	-	-	-	-
Z^0_4	-	-	-	-	-	-
Z^{-2}_4	-	-	-	-	-	-
Z^2_4	-	-	-	-	-	-
Z^{-4}_4	-	-	-	-	-	-
Z^4_4	-	-	-	-	-	-

Table 17: Correlations between preoperative vector components of manifest refraction, central corneal curvature and mean ocular aberrations for the hyperopic group. Only statistically significant r-values (p<0.002) are shown.

Preoperative variables	Hyperopic group Preoperative vectors for refraction and keratometry					
	M	J_0	J_{45}	M_k	J_{0k}	J_{45k}
M	-	-	-	-	-	-
J_0	-	-	-	-	0.95	-
J_{45}	-	-	-	-	-	0.89
M_k	-	-	-	-	-	-
J_{0k}	-	0.95	-	-	-	-
J_{45k}	-	-	0.89	-	-	-
Z^0_2	-0.87	-	-	-	-	-
Z^{-2}_2	-	-	-0.97	-	-	-0.84
Z^2_2	-	-0.96	-	-	-0.91	-
Z^{-1}_3	-	-	-	-	-	-
Z^1_3	-	-	-	-	-	-
Z^{-3}_3	-	-	-	-	-	-
Z^3_3	-	-	-	-	-	-
Z^0_4	-	-	-	-	-	-
Z^{-2}_4	-	-	-	-	-	-
Z^2_4	-	-	-	-	-	-
Z^{-4}_4	-	-	-	-	-	-
Z^4_4	-	-	-	-	-	-

Pearson correlation results between postoperative manifest refraction and postoperative higher order aberrations are shown in Table 3 and Table 4 for the myopic and hyperopic group, respectively. Postoperative central corneal curvature data were not available. For the myopic group, the statistically significant associations that were present preoperatively remained, however a statistically significant positive correlation was found between Z^0_4 and manifest sphere (M) and between Z^{-2}_4 and oblique astigmatism (J_{45}) (both p<0.002). A correlation plot for six month Z^0_4 and six month sphere (M) is shown in Figure 38. For the hyperopic group, fewer statistically significant associations existed postoperatively. Oblique astigmatism (J_{45}) was negatively correlated with Z^{-2}_2, and regular astigmatism (J_0) was positively correlated with Z^0_4 (both p<0.002). A correlation plot for six month Z^0_4 and six month J_0 is shown in Figure 39.

Table 18: Correlation between six month manifest refraction and mean Zernike coefficient terms for the myopic group. Statistically significant r-values (p<0.002) are shown.

	Myopic group											
	Six month Zernike coefficient terms											
	6M Z^0_2	6M Z^{-2}_2	6M Z^2_2	6M Z^{-1}_3	6M Z^1_3	6M Z^{-3}_3	6M Z^3_3	6M Z^0_4	6M Z^{-2}_4	6M Z^2_4	6M Z^{-4}_4	6M Z^4_4
6M M	-0.38	-	-	-	-	-	-	0.37	-	-	-	-
6M J_0	-	-	-0.42	-	-	-	-	-	-	-	-	-
6M J_{45}	-	-0.51	-	-	-	-	-	-	0.31	-	-	-

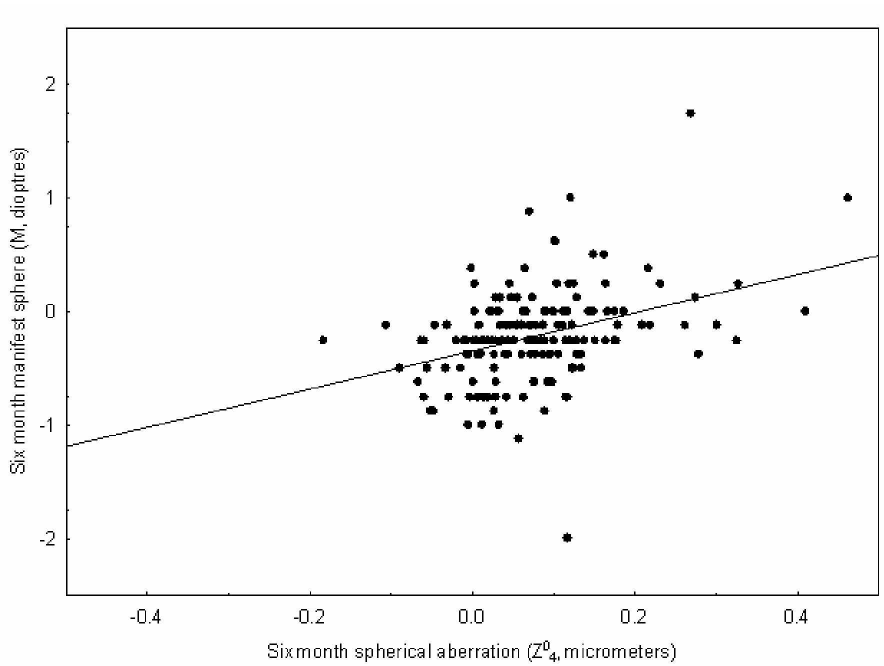


Figure 38: Scatterplot for six month manifest sphere (M) versus six month spherical aberration (Z^0_4) for the myopic group (r=0.37, p<0.002). Univariate regression is shown.

Table 19: Correlation between six month manifest refraction and mean Zernike coefficient terms for the hyperopic group. Statistically significant r-values (p<0.002) are shown.

	Hyperopic group Six month Zernike coefficient terms											
	6M Z^0_2	6M Z^{-2}_2	6M Z^2_2	6M Z^{-1}_3	6M Z^1_3	6M Z^{-3}_3	6M Z^3_3	6M Z^0_4	6M Z^{-2}_4	6M Z^2_4	6M Z^{-4}_4	6M Z^4_4
6M M	-	-	-	-	-	-	-	-	-	-	-	-
6M J_0	-	-	-	-	-	-	-	-0.61	-	-	-	-
6M J_{45}	-	-0.74	-	-	-	-	-	-	-	-	-	-

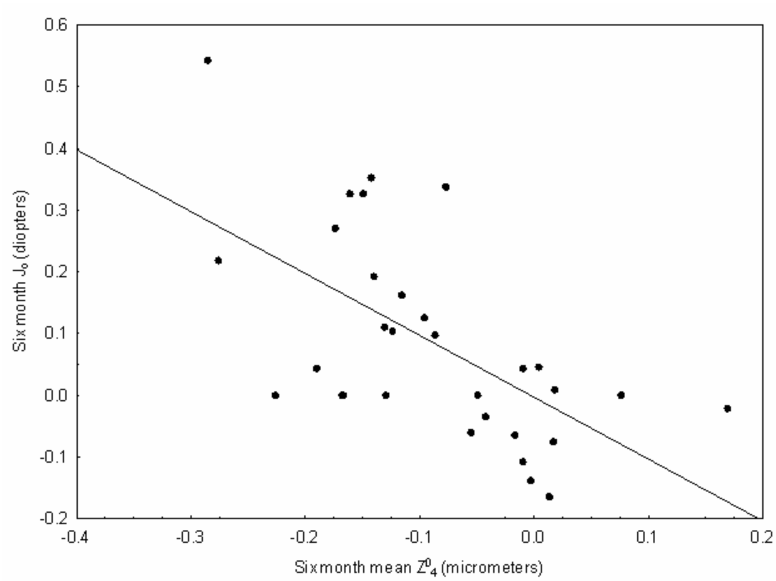


Figure 39: Scatterplot for six month regular astigmatism (J_o) versus six month spherical aberration (Z^0_4) for the hyperopic group (r=-0.61, p<0.002). Univariate regression is shown.

Discussion

Preoperative monochromatic higher order aberrations

Preoperatively, the distributions of monochromatic third and fourth order aberrations for the myopic and hyperopic groups were similar, with mean values close to zero, except for spherical aberration (Z^0_4), which had a positive value for both groups. This is in agreement with other studies reporting population characteristics of higher order aberrations in the unaccommodated eye.[298, 303, 304] It has been suggested that this mean positive amount of spherical aberration is due mainly to the aspheric prolate shape of the cornea, which is steeper centrally and flatter in the periphery.[59] The absolute magnitude (mean ± SD) for spherical aberration in this study was 0.073 ± 0.093 µm for the myopic group and 0.120 ± 0.068 µm for the hyperopic group. The magnitude of spherical aberration for the myopic group was similar to that reported by Cheng et al[300] of a mean (± SD) of 0.065 ± 0.083, but slightly less than that reported by Porter et al.[298] of a mean (± SD) of 0.138 ± 0.103 µm. This difference could be due our results being analyzed over a 5.0 mm pupil size, similar to Cheng et al,[303] whereas Porter et al.[298] used a 5.7 mm pupil size for their data analysis. Increasing the pupil diameter over which aberrations are measured has been found to cause an overall increase in higher order aberrations, particularly spherical aberration.[307-309] Spherical aberration was slightly larger for the hyperopic group compared to the myopic group in this study, which could be partially explained by the difference in age between the groups, since spherical aberration has been shown to increase with age.[310] The mean (± SD) age was 37.7 ± 9.3 years for the myopic group and 45.4 ± 11.3 years for the hyperopic group. Normal aging disrupts the balance between spherical aberration caused by the corneal and internal optics,[57] due mainly to a change in spherical aberration of the crystalline lens going from negative to positive values.[58] Comparing the clinical preoperative monochromatic higher order aberration data to data provided by Salmon et al.,[306] we see that most of the data were similar, with a few differences in the means found for individual Zernike coefficient terms for either the myopic or the hyperopic group. Spherical aberration, however, was larger for both groups in my study. As mentioned previously, this difference could be due to a younger mean age of their population, which was 33.8 ± 7.8 years. Spherical aberration is also influenced by accommodation and has been shown to become less positive/more negative with accommodation at near. The amount of change in spherical aberration has been shown to be linearly related to the amplitude of accommodation, with a mean change of -0.044 µm per dioptre of accommodation.[303] Cheng et al.[303] reported that changes in other higher order aberrations with accommodation were more variable, exhibiting no apparent trends. The influence of accommodation on spherical aberration in this study was not likely a significant factor, due to the cycloplegic effect of the dilating drops and the fogging of the target during aberration measurements.

In addition to spherical aberration, studies on ocular aberrations in normal healthy eyes have reported higher magnitudes of coma (Z^{-1}_3 and Z^1_3).[59, 311, 312] Interestingly, we found a greater amount (mean ± SD) of vertical coma (Z^{-1}_3) in the myopic group (-0.02 ± 0.12 μm) compared to the hyperopic group (-0.003 ± 0.10 μm) and a greater amount of horizontal coma (Z^1_3) in the hyperopic group (-0.02 ± 0.08 μm) compared to the myopic group (-0.001 ± 0.08 μm) preoperatively. Horizontal coma can be due to angle kappa (the angular distance between the line of sight and the pupillary axis), the eccentricity of the pupil, or a decentred or tilted lens.[304] The compensation of horizontal coma by the internal optics of the eye has been reported in previous studies[312, 313] with a larger angle kappa and a greater amount of compensation found in hyperopic eyes.[314] This might explain why horizontal coma was greater in the hyperopic group. With respect to vertical coma, Kelly et al.[312] investigated 30 undilated subjects with a mean refractive error between -2D and +1D and found that ocular vertical coma was greater in magnitude than corneal vertical coma, implying that both the cornea and the internal optics are contributing factors. Regardless, it is not clear why preoperative vertical coma was slightly greater in the myopic group compared to the hyperopic group in this study.

In order to increase the pupil size over which wavefront aberrations can be measured and to minimize accommodation, it is common to dilate the pupil using mydriatics. It has been reported that pupil dilation and mydriasis can affect aberrometry measurements.[74] Yang et al.[315] found that the pupil centre moved temporally from photopic to mesopic conditions (mean distance 0.13 ± 0.07 mm) and moved supero-temporally from photopic to pharmacologically-dilated conditions (1% cyclopentolate) (mean distance 0.18 ± 0.09 mm), suggesting that mydriasis causes a bigger shift of pupil centre location than natural pupil dilation. A study by Awwad et al.[316] investigated the effect of pharmacologic dilation and mild cycloplegia (1% tropicamide and 2.5% phenylephrine) on higher order aberration measurements with the LADARWave aberrometer. They found that higher order aberrations measured in eyes with physiologic pupils were similar to those in pharmacologically dilated pupils, when the line of sight was taken as the reference. As the line of sight was taken as the reference for these measurements, I feel that the effect of dilation on our aberration results was negligible and cannot explain the difference in vertical coma between groups.

Following spherical aberration and coma, trefoil (Z^{-3}_3 and Z^3_3) was the next largest higher order aberration for both the myopic and hyperopic groups. Preoperatively, the mean (± SD) values for vertical (Z^{-3}_3) and horizontal (Z^3_3) trefoil were -0.026 ± 0.079 µm and 0.012 ± 0.069 µm, respectively for the myopic group and -0.036 ± 0.089 µm and 0.019 ± 0.051 µm, respectively for the hyperopic group. Trefoil has a shape that is characteristically flatter in the center, with shape changes occurring along the edge or closer to the pupil margin. Applegate et al.[56] investigated the impact of different higher order aberrations on visual performance and found that not all aberrations have an equal effect on vision. They demonstrated that trefoil has less visual impact compared to equal amounts of spherical aberration or coma.[56] A study by Villegas et al.[317] found a negative correlation between vertical coma and vertical trefoil and reported that this coupling improved retinal image quality. Interestingly, when we investigate the association between preoperative higher order aberrations, we also found a moderate, negative correlation between vertical coma and vertical trefoil in the myopic group ($r= -0.41$, $p<0.002$). This association was not observed in the hyperopic group.

Bilateral symmetry

The bilateral symmetry present prior to surgery has been previously reported, and is attributed to the development of the ocular system, similar to other parts of the body, which shows symmetry about the midline.[304] The disruption in bilateral symmetry following surgery is not surprising due to refractive surgery altering corneal shape; but to my knowledge this disruption has not been discussed in the literature and the clinical significance of this alteration is unknown. It has been shown that differences can exist between binocular and monocular vision testing before and after non-WFG LASIK.[318] What is not known, however, is whether this symmetry is important for neural processing or visual performance. Artal et al.[285] have shown that a stimulus seen with an individual's own aberrations was sharper than when seen through aberrations that have been rotated. This supports the hypothesis that the neural visual system is adapted to the eye's aberrations, which could be just as important for binocular vision as it is for monocular vision. Jimenez et al.[319] recently investigated the role of higher order aberrations in binocular visual performance and found that as the inter-ocular differences in aberrations increased, stereopsis and binocular summation (measured using the ratio between the binocular and monocular contrast sensitivity function) performance decreased. Taken together, this work suggests that the impact of the disruption of bilateral symmetry is worth exploring following surgery, particularly for individuals who are symptomatic or who have specific visual demands.

Vector analysis and correlation results

We investigated the relationship between preoperative manifest refraction, central corneal curvature and preoperative Zernike coefficient terms. Prior to surgery, there was a strong relationship between all measures of astigmatism, including J_{0k} and J_{45k}. Interestingly, we did not find an association between manifest sphere (M), central corneal curvature (M_k) or defocus (Z^0_2). In the literature, myopes tend to have steeper corneal curvature than hyperopes.[30] Our data agree, with slightly steeper corneal curvature in the myopic group (flat and steep meridians, mean ± SD = 43.24 ± 1.45D and 44.20 ± 1.52D, respectively) compared to the hyperopic group (flat and steep meridians = 42.28 ± 1.16D and 43.35 ± 1.15D, respectively). Despite this difference in curvature, there have been mixed reports regarding the association between corneal curvature and refractive error,[24-26, 28, 29] as described in Chapter 1. It is possible that the range of defocus in both groups (-0.25D to -6.50D for the myopes and +1.00D to +5.00D for hyperopes) was not large enough to show an association.

Postoperatively, associations were fewer and weaker. There was a positive association between spherical aberration and manifest sphere (M). This may be explained by the results of previous studies, where in the presence of positive spherical aberration, visual acuity was maximized by a positive amount of defocus.[291, 320] There was a strong correlation between regular astigmatism (J_o) and negative spherical aberration (Z^0_4) for the hyperopic group, which has not been reported in the literature. It is not clear why this association exists, therefore further investigation is warranted.

In summary, higher order monochromatic aberrations were similar between the myopic and hyperopic groups and there was strong bilateral symmetry prior to surgery. Following WFG LASIK, there was a disruption in bilateral symmetry, particularly for the asymmetric higher order aberrations; however the clinical relevance of this alteration is unknown. Vector analysis revealed that components of the preoperative manifest refraction and central corneal curvature were not associated with preoperative higher order aberrations in either group. The impact of WFG on higher order aberrations and the association between preoperative and postoperative higher order aberrations will be discussed in detail in Chapter 5.

Chapter 5

Impact of wavefront-guided LASIK on monochromatic higher order aberrations

Introduction

It has been shown that higher order optical aberrations increase following non-wavefront-guided (WFG) refractive laser procedures, despite the accurate correction of spherocylindrical errors.[125, 134, 138, 162, 247, 259, 307, 321-323] Non-WFG LASIK has a tendency to induce positive spherical aberration with myopic corrections and negative spherical aberration with hyperopic corrections.[324] Non-WFG LASIK for hyperopia has also been shown to result in more horizontal coma[325] and a greater overall increase in higher order aberrations[326] compared to non-WFG LASIK for myopia. Improvements in technology, including the development of eye tracking systems and small-beam scanning lasers, have enabled the delivery of more precise treatments and have improved results.[172, 327, 328] WFG LASIK is an additional advancement in technology, with the goal of reducing the amount of post-surgical higher order aberrations and, ultimately, enhanced visual performance.

Early comparisons have reported fewer surgically-induced higher order aberrations following WFG LASIK compared to non-WFG LASIK.[137-139] Despite promising initial results,[137, 138, 271, 329-332] there have been no large scale studies comprehensively reporting changes in monochromatic higher order Zernike coefficients following WFG LASIK procedures for both myopic and hyperopic corrections.

The aim of this investigation was to determine the impact of WFG LASIK on third and fourth order monochromatic aberrations for myopic and hyperopic corrections. Additional assessments were conducted in order to investigate associations between postoperative higher order aberrations and preoperative refraction and central corneal curvature.

Methods

Repeated Measures analyses and post-hoc tests were used to determine significance, which was set at $p<0.05$. Descriptive statistics were reported using mean and standard error of the mean (SEM). Vector components were calculated for sphere, regular astigmatism (J_0) and oblique astigmatism (J_{45}) using the manifest refraction, as described by Thibos and Horner.[305] Similarly, vector components for corneal M (M_k), corneal J_0 (J_{0k}) and corneal J_{45} (J_{45k}) were calculated using steep and flat central corneal curvature readings, determined by auto-keratometry.[305] Correlations were determined using the Pearson product-moment correlation coefficient and a Bonferroni correction was applied to account for multiple comparisons, resulting in an adjusted level of significance of 0.05/20. Calculations were undertaken using Statistica 7 software (StatSoft Inc, Tulsa, OK).

Results

Magnitude of higher order monochromatic aberrations following WFG LASIK

Figure 40 displays the distribution of higher order aberrations for the myopic group six months following WFG LASIK. The means for all higher order terms are statistically significantly different from zero (all $p<0.05$), however spherical aberration, Z^0_4, and vertical coma, Z^{-1}_3, are the most different, with means (± SEM) of 0.076 ± 0.007 µm and 0.051 ± 0.010 µm, respectively. Figure 41 shows the postoperative absolute magnitudes for the individual Zernike coefficients. These ranged between 0.03 and 0.10 µm, with the largest absolute magnitude for Z^{-1}_3 (0.100 ± 0.007 µm), followed by Z^0_4 (0.089 ± 0.006 µm).

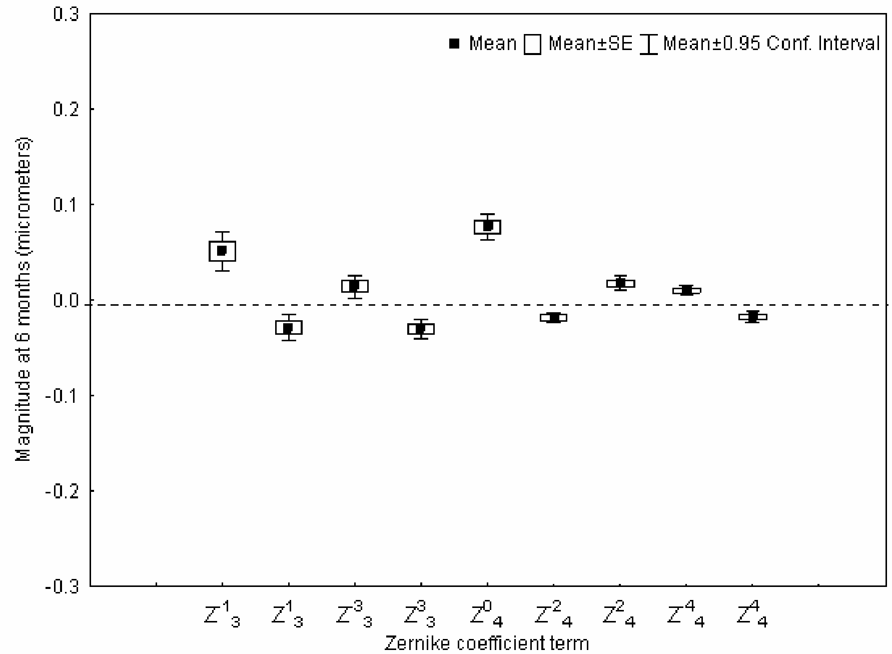


Figure 40: Mean third and fourth order Zernike coefficient values at six months for the myopic group.

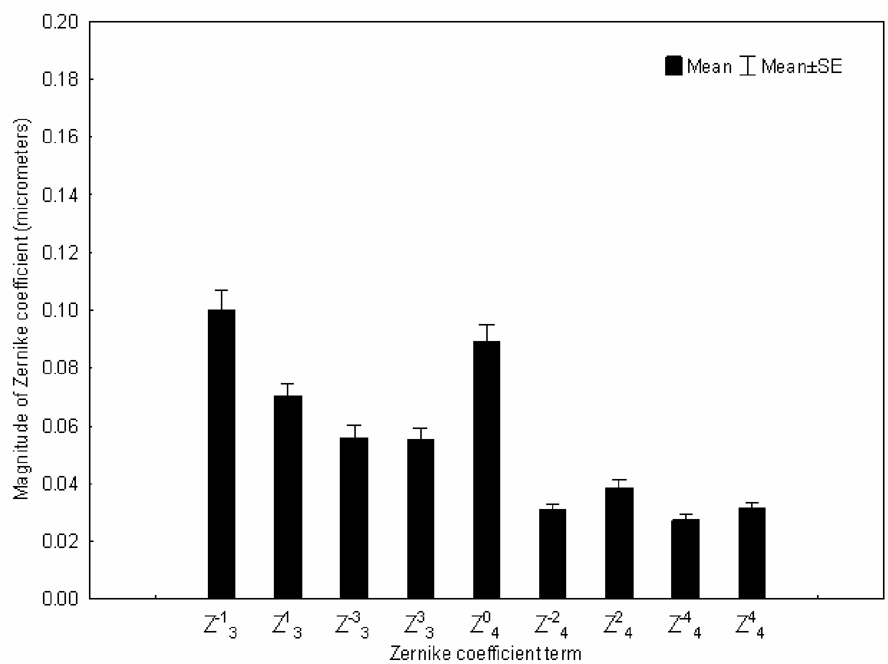


Figure 41: Absolute magnitude of third and fourth order Zernike coefficients at six months for the myopic group.

Figure 42 displays the distribution of higher order aberrations for the hyperopic group six months following WFG LASIK. The means for all higher order terms were statistically significantly different from zero (all $p<0.05$), except for Z^1_3, Z^{-2}_4 and Z^2_4 (all $p>0.05$). Spherical aberration, Z^0_4, horizontal trefoil, Z^3_3, and vertical coma, Z^{-1}_3, were the largest and most negative, with mean (± SEM) values of -0.087 ± 0.018 µm, -0.070 ± 0.016 µm and -0.070 ± 0.031 µm, respectively. Figure 43 shows the absolute magnitude for the individual Zernike coefficients. These ranged between 0.03 and 0.13 µm, the largest for Z^{-1}_3 (0.134 ± 0.023 µm) and Z^0_4 (0.107 ± 0.014 µm).

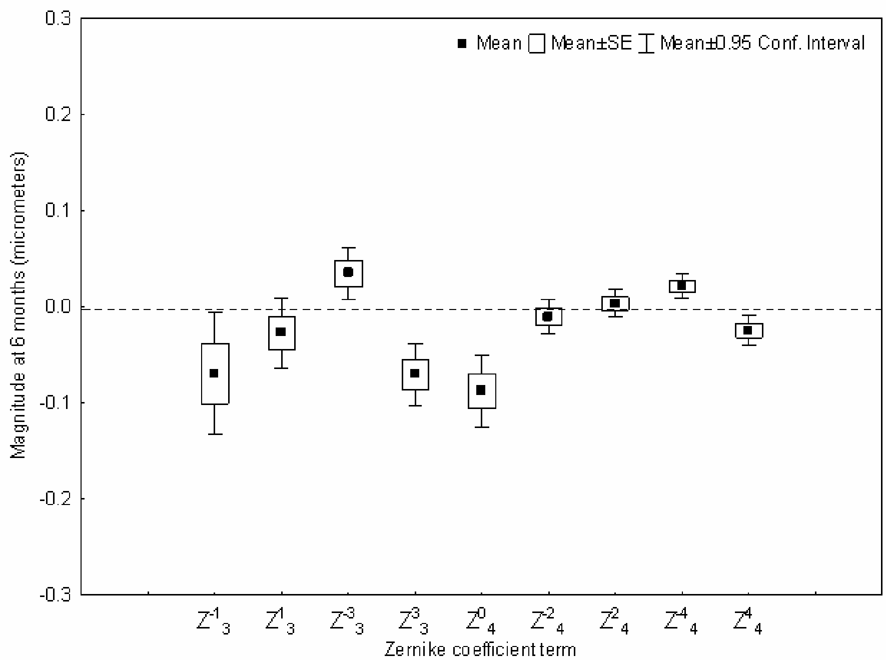


Figure 42: Mean third and fourth order Zernike coefficient values at six months for the hyperopic group.

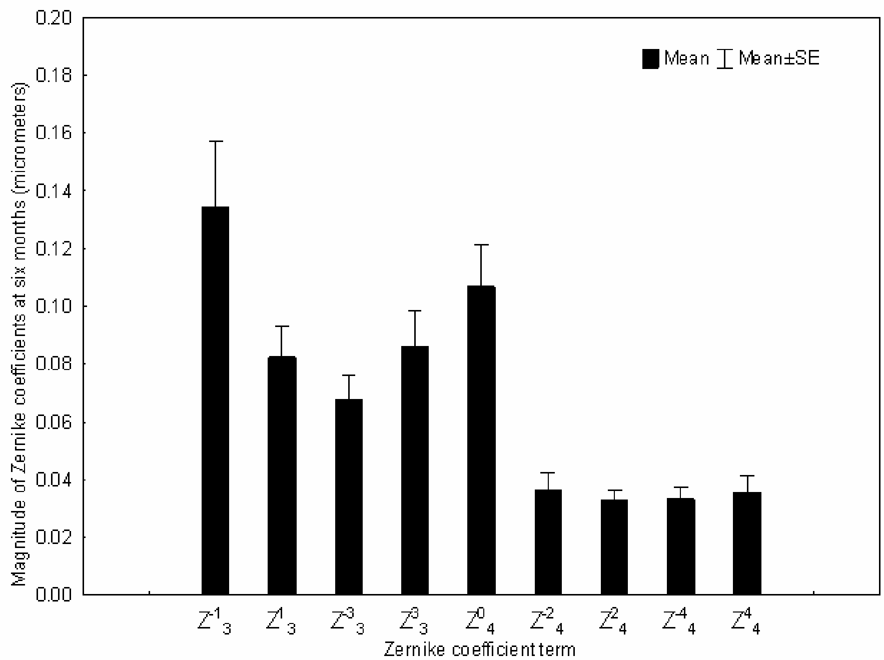


Figure 43: Absolute magnitude of third and fourth order Zernike coefficients at six months for the hyperopic group.

Change in higher order monochromatic aberrations

Figure 44 displays the mean third and fourth order Zernike coefficients across study visits. There was a statistically significant change in all third order terms (Z^{-1}_3, Z^{1}_3, Z^{-3}_3, Z^{3}_3) and the fourth order term Z^{4}_4 from the preoperative to the three and six month visits (all $p<0.05$). No significant change was observed between three and six months (all $p>0.05$). As shown in Figure 44, these changes were in the opposite direction to preoperative values (i.e. Z^{-1}_3 was negative preoperatively and positive postoperatively). Data for the mean change in higher order Zernike coefficients from baseline can be found in Table 20. Figure 45 shows the absolute magnitude of the change in Zernike coefficient terms from the preoperative visit to the six month visit. The greatest absolute change from baseline (± SEM) occurred for the third order term Z^{-1}_3 (0.142 ± 0.009 µm) followed by Z^{-3}_3 (0.093 ± 0.006 µm), Z^{3}_3 (0.083 ± 0.005 µm), and Z^{1}_3 (0.078 ± 0.005 µm).

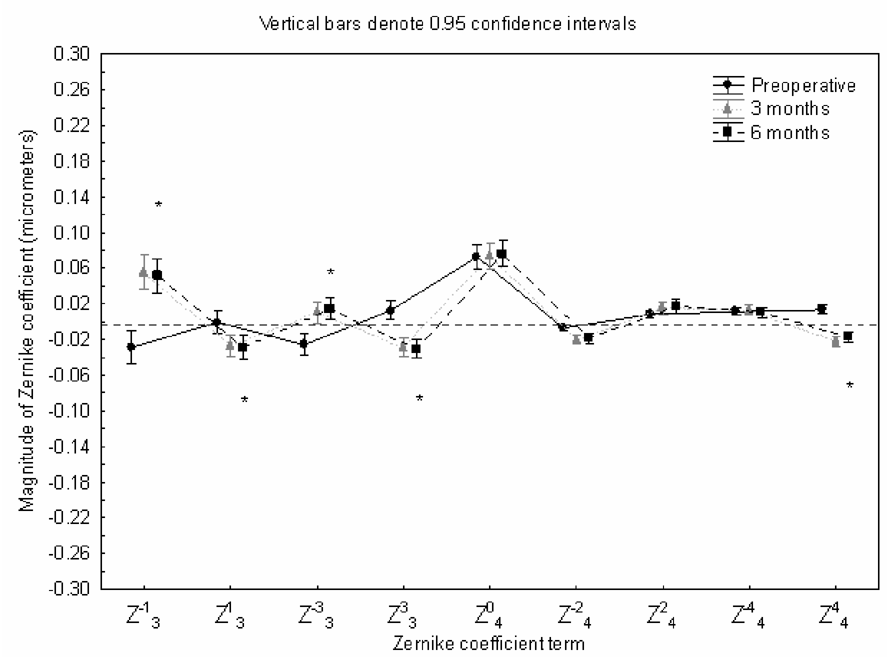


Figure 44: Mean third and fourth order Zernike coefficients for the myopic group before and after surgery. Statistically significant differences (p<0.05) from preoperative values are marked *.

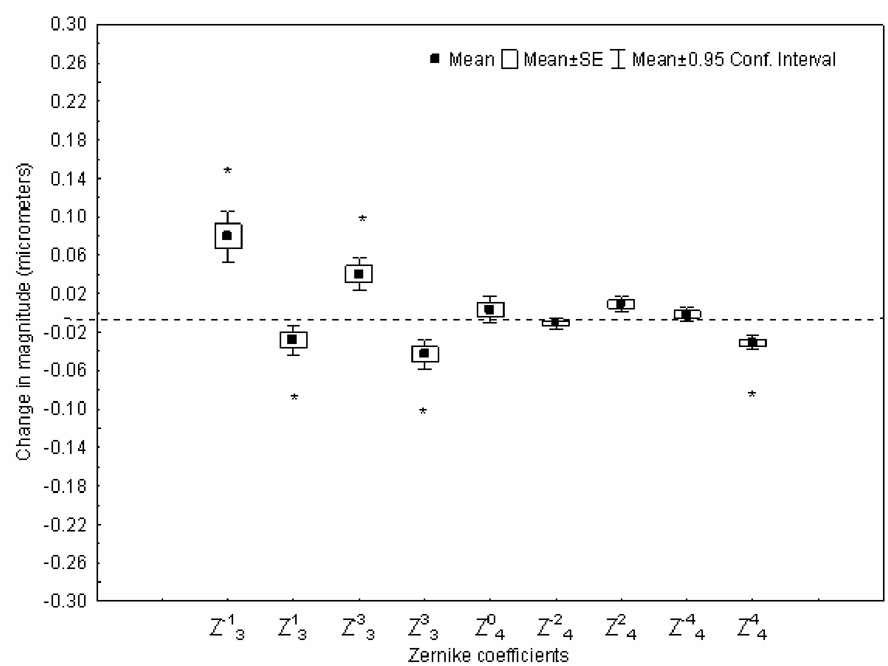


Figure 45: Mean change in third and fourth order Zernike coefficients from baseline for the myopic group. Statistically significant changes (p<0.05) are marked *.

Table 20: Change in magnitude from baseline of the higher order Zernike coefficients six months following WFG LASIK for the myopic group. Mean ± SEM are reported. Statistically significant p-values (p<0.05) are shown in bold.

	Zernike coefficient terms (mean ± SEM)								
	Z^{-1}_3	Z^{1}_3	Z^{-3}_3	Z^{3}_3	Z^{0}_4	Z^{-2}_4	Z^{2}_4	Z^{-4}_4	Z^{4}_4
Mean change	0.080 ±0.013	-0.028 ±0.007	0.040 ±0.009	-0.043 ±0.008	0.004 ±0.007	-0.011 ±0.003	0.009 ±0.004	-0.001 ±0.003	-0.031 ±0.004
p-value	**p<0.001**	**p=0.002**	**p<0.001**	**p<0.001**	p>0.05	p>0.05	p>0.05	p>0.05	**p<0.001**

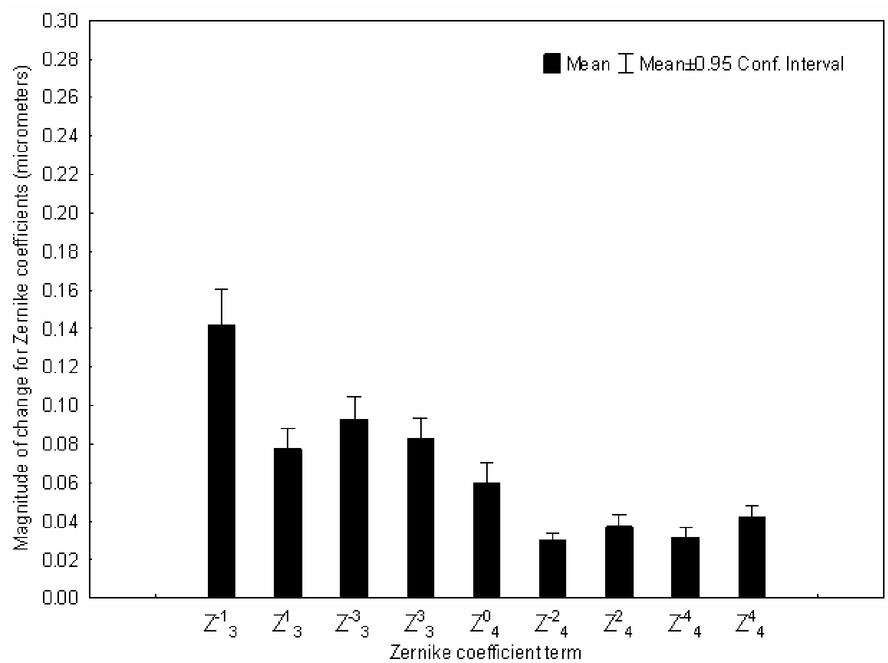


Figure 46: Absolute change from baseline in third and fourth order Zernike coefficients following WFG LASIK for the myopic group.

Figure 47 displays the mean third and fourth order Zernike coefficients for the hyperopic group. There was a statistically significant change in the third order terms Z^{-1}_3, Z^{-3}_3, Z^{3}_3 and the fourth order term Z^{0}_4 from the preoperative to the three and six month visits (all $p<0.05$). No significant change was observed between three and six months (all $p>0.05$). Similar to the myopic group, the Zernike coefficients which were significantly different following surgery had a change in sign. Data for the change in higher order Zernike coefficients can be found in Table 21. Figure 48 shows the magnitude of change from the preoperative visit to the six month postoperative visit. The greatest absolute change (± SEM) was for the fourth order term, Z^{0}_4 (0.208 ± 0.018 μm) followed by the third order terms Z^{3}_3 (0.101 ± 0.014 μm), Z^{-3}_3 (0.092 ± 0.013 μm) and Z^{-1}_3 (0.144 ± 0.022 μm).

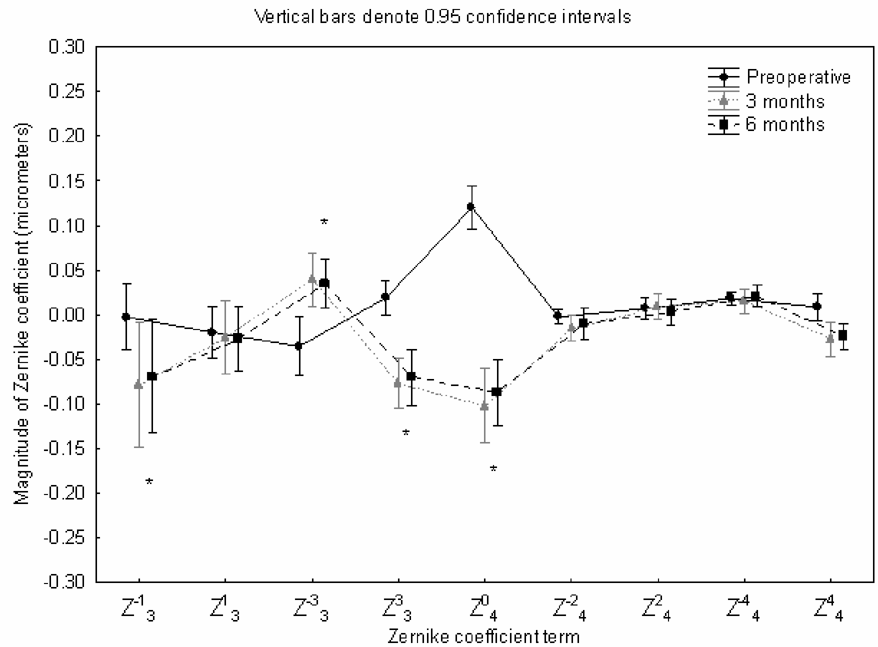


Figure 47: Mean third and fourth order Zernike coefficients for the hyperopic group before and after surgery. Statistically significant differences (p<0.05) from preoperative values are marked *.

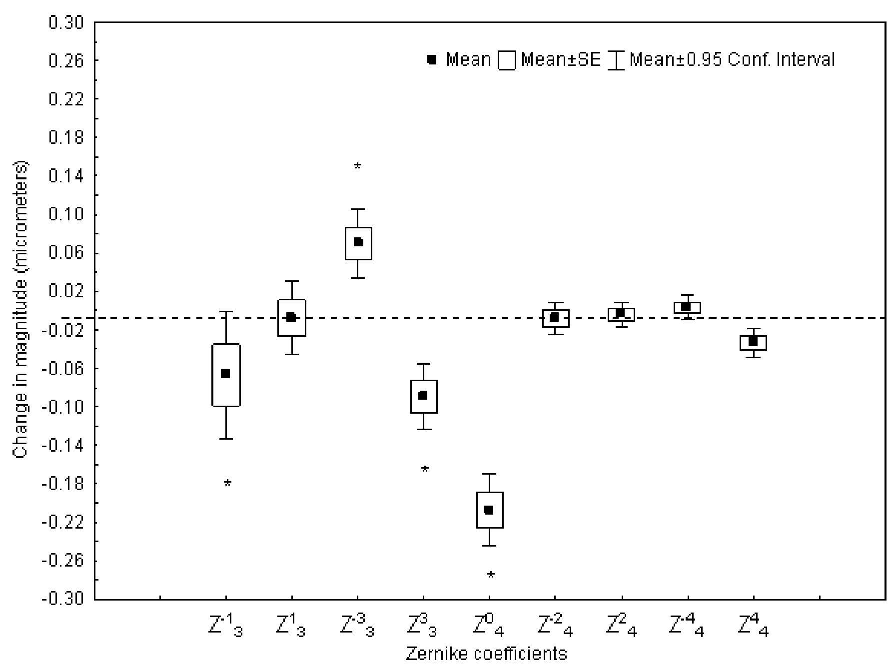


Figure 48: Mean change in third and fourth order Zernike coefficients following WFG LASIK for the hyperopic group. Statistically significant changes (p<0.05) are marked *.

Table 21: Change in magnitude of the higher order Zernike coefficients six months following WFG LASIK for the hyperopic group. Mean ± SEM are reported. Statistically significant p-values (p<0.05) are shown in bold.

	Zernike coefficient terms (mean ± SEM)								
	Z^{-1}_3	Z^{1}_3	Z^{-3}_3	Z^{3}_3	Z^{0}_4	Z^{-2}_4	Z^{2}_4	Z^{-4}_4	Z^{4}_4
Mean change	-0.067 ±0.032	-0.008 ±0.019	0.070 ±0.017	-0.089 ±0.017	-0.208 ±0.018	-0.008 ±0.008	-0.004 ±0.006	0.003 ±0.006	-0.033 ±0.007
p-value	**0.002**	>0.05	**<0.001**	**<0.001**	**<0.001**	>0.05	>0.05	>0.05	>0.05

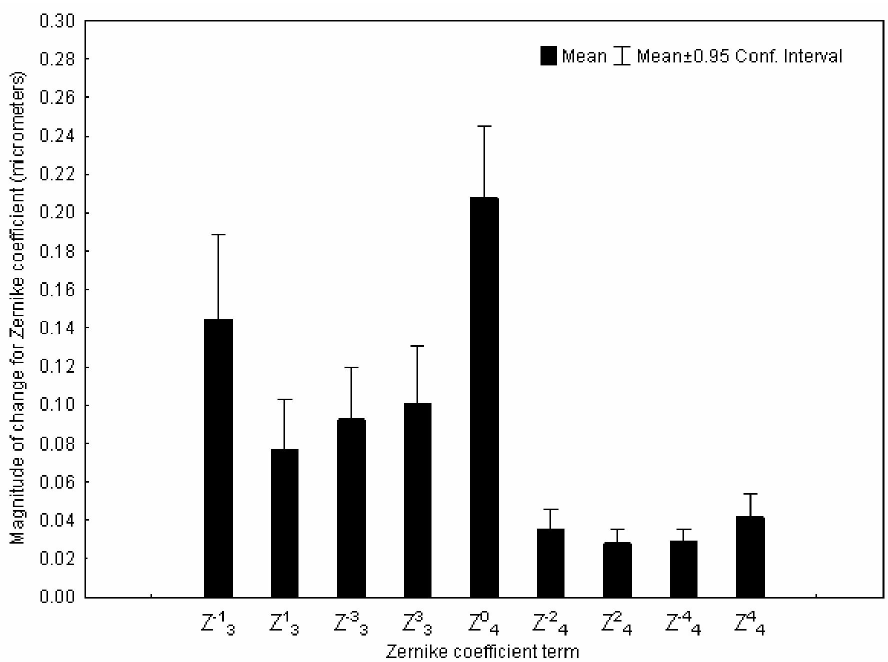


Figure 49: Absolute change in third and fourth order Zernike coefficients following WFG LASIK for the hyperopic group.

Directional changes in third order terms, coma and trefoil

As previously described, a significant change in the third order monochromatic aberrations coma (Z^{-1}_3, Z^{1}_3) and trefoil (Z^{-3}_3, Z^{3}_3) occurred following myopic and hyperopic WFG LASIK in this study. Figure 50 and Figure 51 display the scatterplots for coma and trefoil before and after surgery for right eyes (top) and left eyes (bottom) for the myopic group. A 95% probability ellipse has been used to assist in visually observing the changes. As described by Thibos et al.,[333] the magnitude of the aberration can be determined by the radial distance of the data point from the origin and the axis of the aberration is determined by the polar angle of the symbol. The scatterplots for Z^{-1}_3 versus Z^1_3 in Figure 50 show a tendency for vertical coma (Z^{-1}_3) to become more positive after surgery, however the points on the scatterplots remain fairly centered about the horizontal axis. A slight shift of horizontal coma in the positive direction can be observed postoperatively for left eyes (see Figure 50 D). Figure 51 displays the results for trefoil, where the data take on more of an elliptical pattern. There was a trend for postoperative vertical trefoil (Z^{-3}_3) values to become more positive after surgery. In addition, there was a tendency for horizontal trefoil (Z^3_3) to become more negative in the right eyes and more positive in the left eyes following surgery.

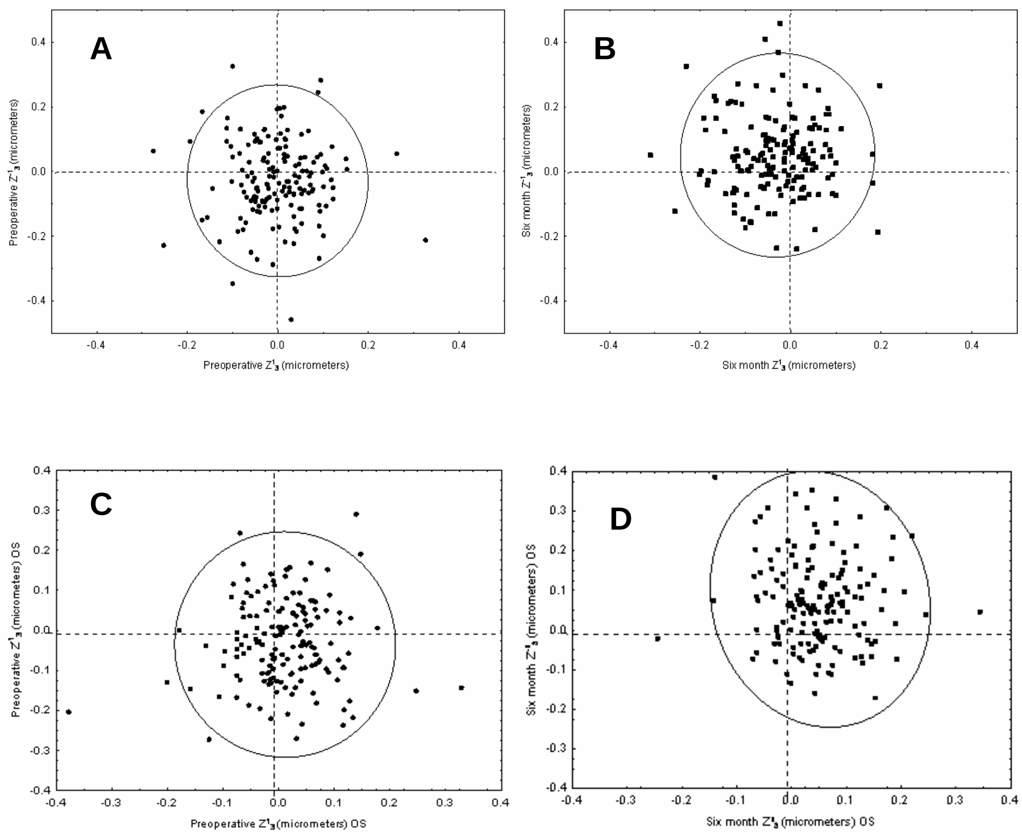


Figure 50: Covariation of the orthogonal components for coma preoperatively and at six months for the right eye (A and B, respectively) and preoperatively and at six months for the left eye (C and D, respectively) for the myopic group.

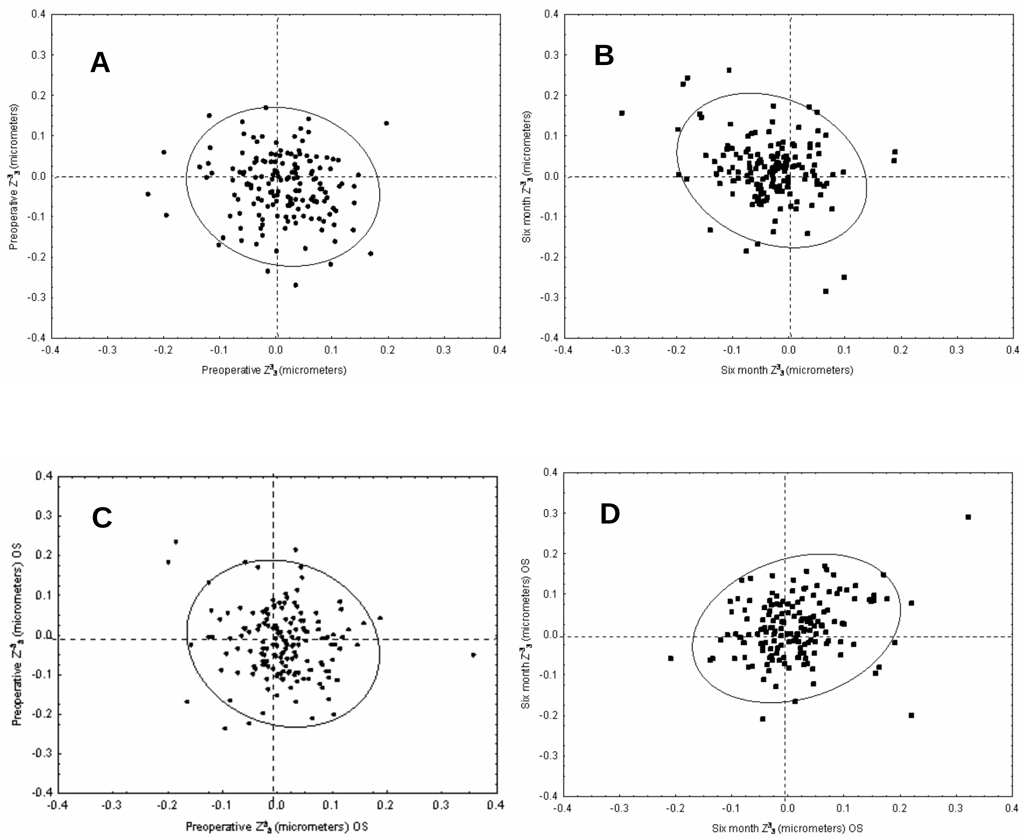


Figure 51: Covariation of the orthogonal components for trefoil preoperatively and at six months for the right eyes (A and B, respectively) and preoperatively and at six months for the left eyes (C and D, respectively) for the myopic group.

Figure 51 and Figure 52 display the scatterplots for coma and trefoil before and after surgery for right eyes (top) and left eyes (bottom) for the hyperopic group. There are fewer eyes in the hyperopic group; however directional changes are still observed. As is seen in the scatterplots in Figure 52, the values for vertical coma (Z^{-1}_3) became more negative after surgery and there was a slight trend for horizontal coma (Z^{1}_3) to become more negative in the right eyes and more positive in the left eyes. Figure 53 shows the results for trefoil. The findings are similar to the myopic group; where there was a trend for postoperative vertical trefoil (Z^{-3}_3) values to become more positive after surgery. Additionally, there was a tendency for horizontal trefoil (Z^{3}_3) to become more negative in the right eyes and more positive in the left eyes following surgery.

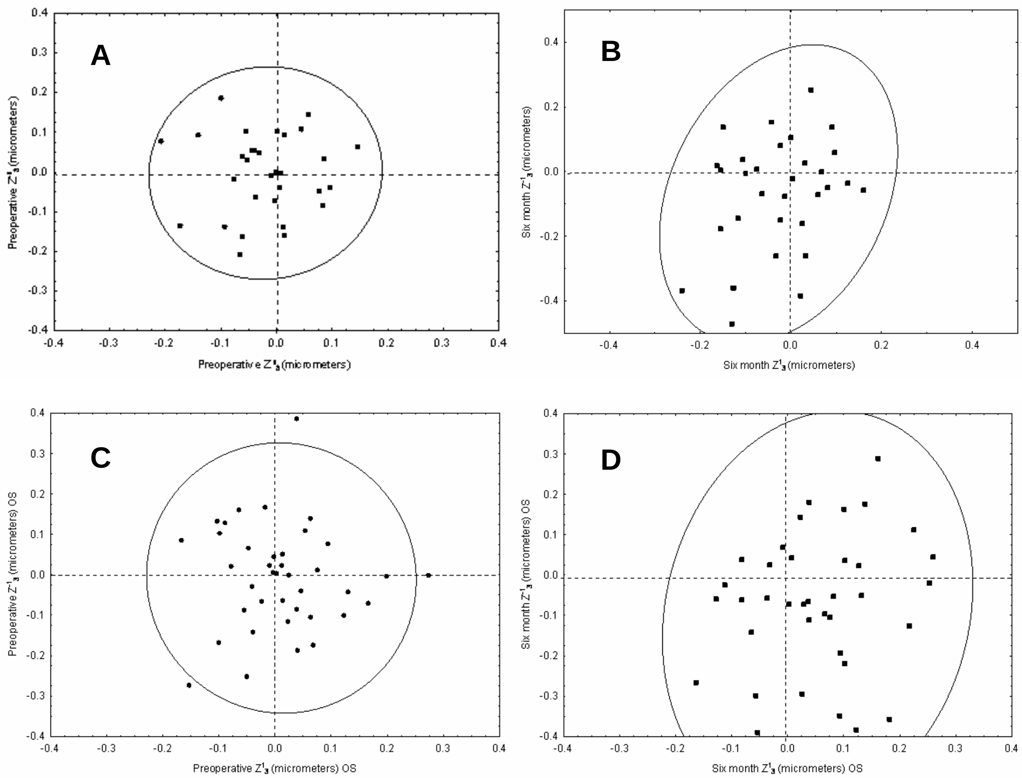


Figure 52: Covariation of the orthogonal components for coma preoperatively and at six months for the right eye (A and B, respectively) and preoperatively and at six months for the left eye (C and D, respectively) for the hyperopic group.

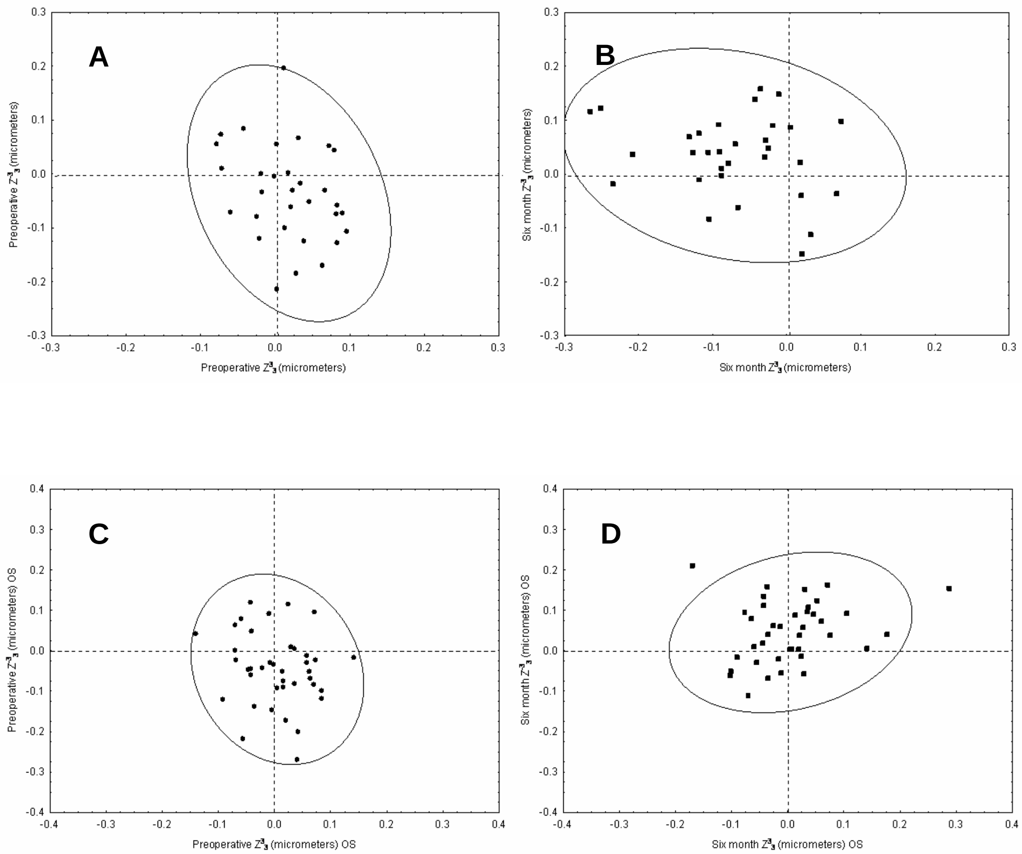


Figure 53: Covariation of the orthogonal components for trefoil preoperatively and at six months for the right eyes (A and B, respectively) and preoperatively and at six month for the left eyes (C and D, respectively) for the hyperopic group.

Correlations

Chapter 4 investigated the relationship for preoperative variables and postoperative variables, separately. In this Chapter, correlations have been calculated between preoperative and postoperative variables, as shown in Table 22. For the myopic group, the strongest correlations were between preoperative defocus (Z^0_2) and six month spherical aberration (Z^0_4) (r=0.54, p<0.002) and between preoperative spherical aberration (Z^0_4) and six month spherical aberration (Z^0_4) (r=0.54, p<0.002).

Table 23 shows the results for the hyperopic group. Preoperative defocus (Z^0_2) was positively correlated with six month spherical aberration (Z^0_4) (r=0.77, p<0.002) and preoperative oblique astigmatism (Z^{-2}_2) was positively correlated with six month oblique secondary astigmatism (Z^{-2}_4) (r=0.61, p<0.002).

Table 22: Correlations between the preoperative and six month postoperative Zernike coefficients for the myopic group. Only statistically significant correlations (p<0.002) are shown.

	Preoperative vs. six month Zernike coefficients for the myopic group											
	6M Z^0_2	6M Z^{-2}_2	6M Z^2_2	6M Z^{-1}_3	6M Z^1_3	6M Z^{-3}_3	6M Z^3_3	6M Z^0_4	6M Z^{-2}_4	6M Z^2_4	6M Z^{-4}_4	6M Z^4_4
Z^0_2	-	-	-	-	-0.29	-	-	0.54	-	-	-	-
Z^{-2}_2	-	-	-	-	-	-	-	-	0.40	-	-	-
Z^2_2	-	-	-	-	-	-	-	-	-	0.29	-	-
Z^{-1}_3	-	-	-	-	-	-	-	-	-	-	-	-
Z^1_3	-	-	-	-	0.29	-	-	-	-	-	-	-
Z^{-3}_3	-	-	-	-	-	-	-	-	-	-	-	-
Z^3_3	-	-	-	-	-	-	-	-	-	-	-	-
Z^0_4	-	-	-	-	-	-	-	0.54	-	-	-	-
Z^{-2}_4	-	-	-	-	-	-	-	-	-	-	-	-
Z^2_4	-	-	-	-	-	-	-	-	-	-	-	-
Z^{-4}_4	-	-	-	-	-	-	-	-	-	-	-	-
Z^4_4	-	-	-	-	-	-	-	-	-	-	-	-

Table 23: Correlations between the preoperative and six month postoperative Zernike coefficients for the hyperopic group. Only statistically significant correlations (p<0.002) are shown.

	Preoperative vs. six month Zernike coefficients for the hyperopic group											
	6M Z^0_2	6M Z^{-2}_2	6M Z^2_2	6M Z^{-1}_3	6M Z^1_3	6M Z^{-3}_3	6M Z^3_3	6M Z^0_4	6M Z^{-2}_4	6M Z^2_4	6M Z^{-4}_4	6M Z^4_4
Z^0_2	-	-	-	-	-	-	-	0.77	-	-	-	-
Z^{-2}_2	-	-	-	-	-	-	-	-	0.61	-	-	-
Z^2_2	-	-	-	-	-	-	-	-	-	-	-	-
Z^{-1}_3	-	-	-	-	-	-	-	-	-	-	-	-
Z^1_3	-	-	-	-	-	-	-	-	-	-	-	-
Z^{-3}_3	-	-	-	-	-	-	-	-	-	-	-	-
Z^3_3	-	-	-	-	-	-	-	-	-	-	-	-
Z^0_4	-	-	-	-	-	-	-	-	-	-	-	-
Z^{-2}_4	-	-	-	-	-	-	-	-	-	-	-	-
Z^2_4	-	-	-	-	-	-	-	-	-	-	-	-
Z^{-4}_4	-	-	-	-	-	-	-	-	-	-	-	-
Z^4_4	-	-	-	-	-	-	-	-	-	-	-	-

Vector analysis

Correlation results between preoperative manifest refraction and six month higher order aberrations are shown for the myopic and hyperopic group in Table 24 and Table 25, respectively. For the myopic group, the strongest relationships were found between preoperative sphere (M) and six month spherical aberration (Z^0_4) and between preoperative astigmatism (J_0 and J_{45}) and six month secondary astigmatism (Z^{-2}_4 and Z^2_4) (all r>-0.36, p<0.002). For the hyperopic group, a strong correlation was found between preoperative sphere (M) and six month spherical aberration (Z^0_4) (r=-0.75, p<0.002).

Table 24: Correlation between vector components of the preoperative manifest refraction and six month third and fourth order Zernike coefficient terms for the myopic group. Only statistically significant (p<0.002) correlations are shown.

Preoperative refraction	Myopic group Six month Zernike coefficient terms								
	6M Z^{-1}_3	6M Z^1_3	6M Z^{-3}_3	6M Z^3_3	6M Z^0_4	6M Z^{-2}_4	6M Z^2_4	6M Z^{-4}_4	6M Z^4_4
M	-	-	-	-	-0.36	-	-	-	-
J_0	-	-	-	-	-	-	-0.36	-	-
J_{45}	-	-	-	-	-	-0.44	-	-	-

Table 25: Correlation between vector components of the preoperative manifest refraction and six month third and fourth order Zernike coefficient terms for the hyperopic group. Only statistically significant (p<0.002) correlations are shown.

Preoperative refraction	Hyperopic group Six month Zernike coefficient terms								
	6M Z^{-1}_3	6M Z^1_3	6M Z^{-3}_3	6M Z^3_3	6M Z^0_4	6M Z^{-2}_4	6M Z^2_4	6M Z^{-4}_4	6M Z^4_4
M	-	-	-	-	-0.75	-	-	-	-
J_0	-	-	-	-	-	-	-	-	-
J_{45}	-	-	-	-	-	-	-	-	-

Correlation results between preoperative central keratometry readings and six month third and fourth order aberrations are shown for the myopic group in Table 26. R-values are shown for statistically significant correlations. For the myopic group, J_{0k} was significantly associated with postoperative regular secondary astigmatism (Z^2_4) ($r=-0.35$, $p<0.002$). There were no statistically significant correlations between preoperative central keratometry readings and six month higher order aberrations for the hyperopic group (all $p>0.002$).

Table 26: Correlation between vector components of the preoperative central keratometry readings and six month third and fourth order Zernike coefficient terms for the myopic group. Only statistically significant (p<0.002) correlations are shown.

Preoperative keratometry	Myopic group Six month Zernike coefficient terms								
	6M Z^{-1}_3	6M Z^{1}_3	6M Z^{-3}_3	6M Z^{3}_3	6M Z^{0}_4	6M Z^{-2}_4	6M Z^{2}_4	6M Z^{-4}_4	6M Z^{4}_4
M_k	-	-	-	-	-	-	-	-	-
J_{0k}	-	-	-	-	-	-	-0.35	-	-
J_{45k}	-	-	-	-	-	-	-	-	-

Discussion

Magnitude of postoperative higher order aberrations

Postoperatively, there was an overall increase in higher order aberrations following WFG LASIK, which has been previously reported in the literature.[271, 286] The absolute magnitude of change was greater for the hyperopic group compared to the myopic group, which has been reported following non-WFG LASIK.[324, 326] The higher order aberration with the largest absolute magnitude following WFG LASIK in the myopic group was vertical coma (Z^{-1}_3), which also exhibited the greatest change. Notably, there was little change in spherical aberration (Z^0_4) for the myopic group in this study, which is an improvement over non-WFG LASIK, where moderate increases in positive spherical aberration have been reported.[56, 334] For the hyperopic group, vertical coma (Z^{-1}_3) had the largest absolute magnitude following WFG LASIK; however spherical aberration (Z^0_4) exhibited the greatest change. The magnitude of postoperative spherical aberration (Z^0_4) was similar to the preoperative amount; however there was a reversal of sign. This means that preoperatively spherical aberration was positive and postoperatively it was negative. This directional change is in agreement with previous findings reported in the literature.[309, 324, 335-337] Possible etiologies for these changes are described below.

Change in spherical aberration following WFG LASIK

There has been a great deal of work investigating the relationship between the change in corneal asphericity following refractive surgery.[278, 336, 338-345] Asphericity (Q) quantifies how the radius of curvature changes from the center to the peripheral cornea. When $Q < 0$, peripheral corneal curvature is flatter than the central curvature and is termed prolate. When $Q > 0$, peripheral corneal curvature is steeper than the central curvature and is termed oblate (Figure 54). Most eyes exhibit a naturally prolate corneal shape ($Q < 0$),[2] which is thought to neutralize the negative spherical aberration of the internal crystalline lens in the pre-presbyopic eye.[59] Therefore, changing the shape of the corneal surface through laser refractive surgery also alters its asphericity, which is thought to contribute to surgically-induced spherical aberration.[346] Llorente et al.[30] investigated differences in geometrical properties in a group of age-matched hyperopes and myopes with similar refractive error and found that hyperopic eyes tended to have higher (less negative) Q values and higher spherical aberration than myopic eyes. Corneal asphericity has been shown to change after non-WFG LASIK in proportion to the amount of correction for both myopic and hyperopic treatments, but in an amount different than predicted by mathematical models, indicating that additional factors are involved.[341, 346]

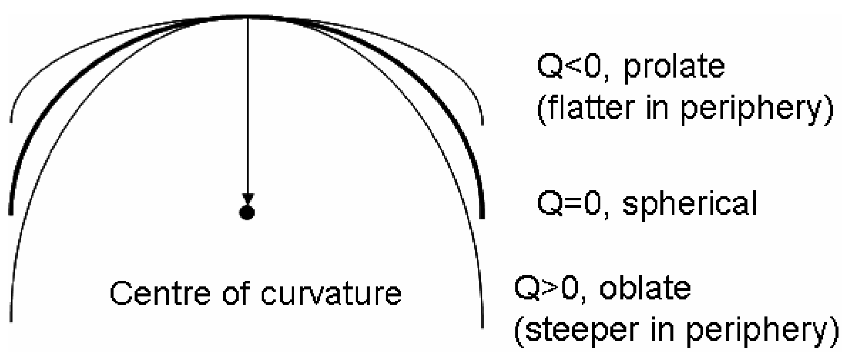


Figure 54: Description of asphericity.

Factors that have been related to the impact of LASIK on spherical aberration include surface smoothing as a result of the corneal wound-healing process,[347] biomechanical changes[200] and variation in the laser ablation depth per pulse across the treatment area in relation to corneal curvature.[175, 346, 348] Yoon et al.[176] developed a model to explain how spherical aberration is induced by refractive surgery for myopia and hyperopia. Their model fitted with clinical data when it combined the effects of variable ablation depth per pulse with biomechanical changes. The biomechanical response they propose is that the central cornea becomes flatter and the peripheral cornea becomes steeper following a myopic treatment and that the central cornea becomes steeper and the peripheral cornea becomes flatter following a hyperopic treatment. This model explains the differences in surgically-induced spherical aberration for myopic and hyperopic treatments. Roberts et al.[200] introduce a different model for the biomechanical response of the cornea to surgery, based on structural changes of the cornea. They suggest that central corneal flattening and peripheral corneal steepening occurs for both myopic and hyperopic treatments, as a result of the severing of corneal lamellae. This model, however, does not explain the negative spherical aberration induced by hyperopic treatments. Regardless of the exact etiology, refractive surgery results in a shape change to the cornea that disrupts the balance between the cornea and internal optics, which results in positive ocular spherical aberration following myopic LASIK and negative ocular spherical aberration following hyperopic LASIK.

Change in coma following WFG LASIK

An interesting finding in this study was the difference in postoperative vertical coma (Z^{-1}_{3}) between the myopic and hyperopic groups. Positive vertical coma was induced in the myopic group and negative vertical coma in the hyperopic group. Kohnen et al.[324] investigated corneal higher order aberrations following non-WFG LASIK and they also found positive coma induced in myopes and negative vertical coma induced in hyperopes. Flap creation with a Hansatome microkeratome, which produces a superiorly placed hinge, has been shown to result in an increase in higher order aberrations, specifically vertical coma.[203] Ginsberg et al.[349] assessed the effect of the LASIK flap on corneal shape using corneal topography analysis and found that the flap retracted asymmetrically toward the hinge, producing measurable meridional differences in corneal curvature. Other studies have not found a significant increase in coma following flap creation.[162, 164] It is suggested in the literature that surgically-induced coma is due to treatment decentration or misalignment errors.[125, 259, 350] Wavefront errors and laser ablation are centered on the line of sight, which coincides with the center of the natural pupil. As a function of luminance, however, the center of the pupil shifts, commonly in the temporal direction.[315, 351] The shift in pupil center is in the same direction, with similar magnitudes, for myopes and hyperopes.[352] Therefore, we would expect a similar change in coma for both myopes and hyperopes. Since this was not the case, it is unlikely that these results are solely due to decentration shifts of the pupil center. Guirao et al.[353] found that decentering a higher order aberration primarily results in induced aberrations with a radial order that is one less (i.e. n-1). For example, decentering spherical aberration (a fourth order aberration, n=4) would theoretically result in induced coma (a third order aberration, n=3).[353] Therefore, if a systematic vertical decentration occurred for both myopic and hyperopic treatments (i.e. something inherent in the wavefront device or registration system) it is possible that this could cause an increase in positive vertical coma for the myopic group (who have positive spherical aberration) and an increase in negative vertical coma in the hyperopic group (who have negative spherical aberration). There was no correlation between vertical coma and spherical aberration was found in this study for either group, however. Another explanation could be differences in the biomechanical or wound healing response of the cornea following flap creation and stromal ablation for myopic and hyperopic treatments; however corneal topographical data are not available from this study for analysis, and so conclusions directly from surface shape change are not possible.

Change in trefoil following WFG LASIK

Unlike the change in coma, the change in vertical (Z^{-3}_{3}) and horizontal (Z^{3}_{3}) trefoil occurred in the same direction for the myopic and hyperopic group. The surgery induced positive vertical trefoil and negative horizontal trefoil. While it is possible that these changes could be due to an overcorrection of both terms, the ablation profiles are very different for myopic and hyperopic treatments and it would be unexpected that the different treatments would result in similar changes in trefoil. Therefore, these changes could be related to surgical factors, rather than the correction of refractive error. The rotation of the Hansatome® microkeratome (Bausch & Lomb Incorporated) has been suggested as a possible cause for induced trefoil following LASIK surgery.[162] The motion of the Hansatome microkeratome head is in an arc in the nasal to temporal direction for both eyes as it passes the cornea to create a flap with a superior hinge (refer to Figure 55). These results show that both the myopic and hyperopic group exhibited a slight shift in the axis of trefoil in the same head-centric direction postoperatively. It is possible that this motion may have contributed to the shift in trefoil found in this study. Intralase® (Intralase® Corp), which uses a different method for flap creation does not have a rotary component and uses a femtosecond laser instead of a blade. Interestingly, there have been reports of surgically-induced trefoil following flap creation with the Hansatome microkeratome, but not with Intralase, however the axis of trefoil change was not reported in the literature.[354, 355] It has been shown that flaps created with a mechanical microkeratome have a meniscus shape, being thicker in the periphery and thinner centrally, compared to an Intralase flap which is planar.[356] This difference in thickness could also play a role in how the flap sits on the underlying cornea following surgery. Additional investigations are necessary to explore these possible explanations further.

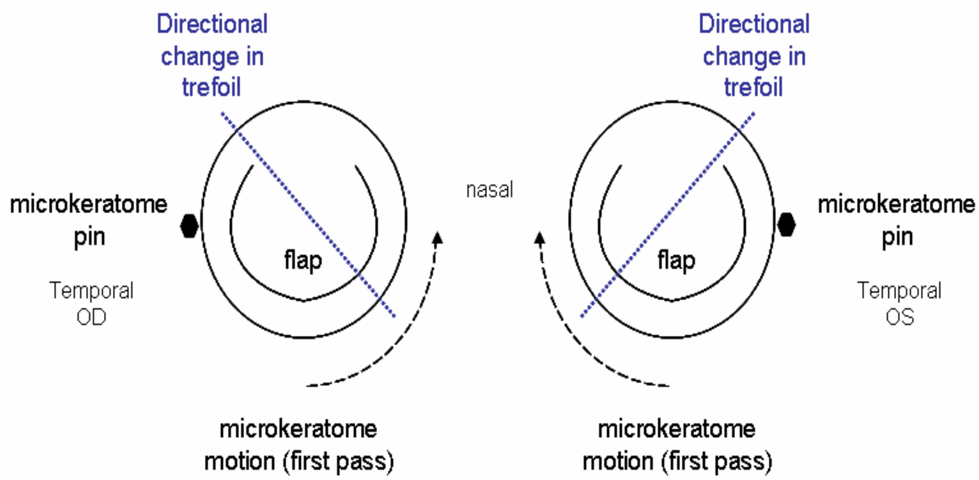


Figure 55: Description of the motion of the Hansatome microkeratome in this study and the directional change in trefoil following WFG LASIK.

Vector analysis and correlation results

The correlation results for preoperative and postoperative Zernike coefficients showed that postoperative spherical aberration (Z^0_4) was positively associated with preoperative defocus (Z^0_2) for both the myopic and hyperopic groups. This is in agreement with the literature, which has reported larger amounts of surgically-induced spherical aberration with larger amounts of attempted spherical correction.[176, 309, 357, 358] The remainder of the correlations between preoperative and postoperative variables indicate that the optics of the eye become more complex following surgery and are explained by more complicated wavefront shapes. More associations were found between postoperative higher order aberrations and preoperative refractive components (manifest refraction and low order aberrations) than preoperative central corneal curvature. This is likely because the treatment is aimed to reduce refractive error and applies an ablation profile in order to correct this, taking central corneal curvature into account minimally.

It is interesting that aside from spherical aberration (Z^0_4), the other higher order aberrations that showed the greatest change following surgery, vertical coma (Z^{-1}_3) and both trefoil terms (Z^{-3}_3, Z^3_3), were not associated with preoperative manifest refraction or central corneal curvature. Consequently, other sources or explanations for these surgically-induced changes need to be determined before they can be minimized. Some of the possible factors include flap creation, wound healing, biomechanical changes, and registration or decentration errors, as mentioned previously.

Despite WFG LASIK having a statistically significant impact on higher order aberrations in this study for both the myopic and hyperopic groups; it is unknown from this study whether these changes are clinically meaningful. As described in Chapter 3, visual acuity and contrast sensitivity measures did not seem to be affected by these surgically-induced higher order aberrations. While it is possible that these tests are not sensitive enough to reflect these changes in optical quality, it is also possible that these changes were not of sufficient magnitude to detrimentally impact vision. It is also possible that the effects of these aberrations were minimized as a result of their interactions, which has been previously reported.[291] The subsequent Chapter describes the symptoms following surgery, in order to explore the impact of WFG LASIK on qualitative vision and patients' overall satisfaction with surgery.

Chapter 6

Qualitative vision following WFG LASIK

Introduction

Despite excellent visual acuity and a high level of satisfaction, many patients still report reduced quality of vision following refractive surgery.[174, 359-361] Subjective complaints vary, but often include symptoms of glare, halos, starbursts and double vision, particularly at night.[131-134, 362] A study by Levinson et al.[363] states poor distance vision, dry eye, pain, glare and halos as the major reasons for dissatisfaction following surgery.

There are many factors related to refractive surgery that can impact postoperative quality of vision. In non-wavefront-guided (non-WFG) LASIK patients, Pop et al[130] investigated the preoperative risk factors for developing night vision complaints after surgery and found that attempted correction (sphere > -5.00D), optical zone size (≤ 6.00mm) and residual spherical equivalent refraction (> 0.50D) were all associated factors. O'Brart et al[117] have demonstrated that smaller treatment zone diameters are associated with an increase in symptoms of halos. Lee et al.[129] investigated non-WFG LASIK for myopia and found symptoms of halos and glare were correlated with the preoperative spherical equivalent refraction and the amount of astigmatism correction, respectively. Miller et al.[364] reviewed 174 charts for patients who had non-WFG LASIK for myopia and found that uncorrected visual acuity (UCVA) and lower preoperative astigmatism correlated positively with satisfaction, while increased postoperative ocular dryness correlated negatively with satisfaction.[364] Individual attributes, such as tolerance to blur and blur adaptation, are also potential factors affecting subjective ratings.[295]

An increase in higher order aberrations has been shown to result in poor subjective image quality following non-WFG LASIK.[125, 260, 365] Sharma et al.[301] investigated higher order aberrations and the relative risk for symptoms and found that symptomatic subjects had a greater amount of higher order aberrations following non-WFG LASIK than those without symptoms. McCormick et al.[366] reported higher order aberrations were more than two times greater in symptomatic subjects than asymptomatic subjects following non-WFG LASIK.

The goal of WFG LASIK is to improve optical quality following surgery by minimizing the amount of surgically-induced higher order aberrations. In a retrospective analysis of 274 eyes that underwent WFG LASIK for myopia, Tuan[367] found that most individuals were as satisfied or more satisfied with their postoperative UCVA than their preoperative best corrected vision (BCVA). Furthermore, contralateral studies comparing non-WFG LASIK with WFG LASIK have found better subjective quality of vision results with WFG LASIK.[138, 139]

The aim of this section of my study was to explore the impact of WFG LASIK on qualitative vision and sensory complaints, following myopic and hyperopic treatments, and to compare these findings to reports in the literature.

Methods

A closed-ended categorical questionnaire was administered prior to surgery and at each follow-up visit. Spectacles were worn when filling in the questionnaire prior to surgery and the postoperative questionnaires were completed while uncorrected. Four-point scales (none, mild, moderate, severe) were used at the preoperative visit and five-point scales (significantly better, better, same, worse, significantly worse) were used at the follow-up visits. Spearman rank order correlations were calculated between 46 six month variables, therefore a Bonferroni correction was applied, resulting in a level of significance of 0.05/46. Calculations were undertaken using Statistica 7 software (StatSoft Inc, Tulsa, OK).

Results

The subjective responses for the myopic group for questions relating to ocular sensory information and various aspects of vision can be found in Figure 56 and Figure 57, respectively. These results indicate that the majority of subjects noticed either no change or an improvement following surgery. Table 27 shows the percent of subjects with either better or worse symptoms following surgery. Figure 58 displays the results for overall vision and satisfaction following myopic WFG LASIK.

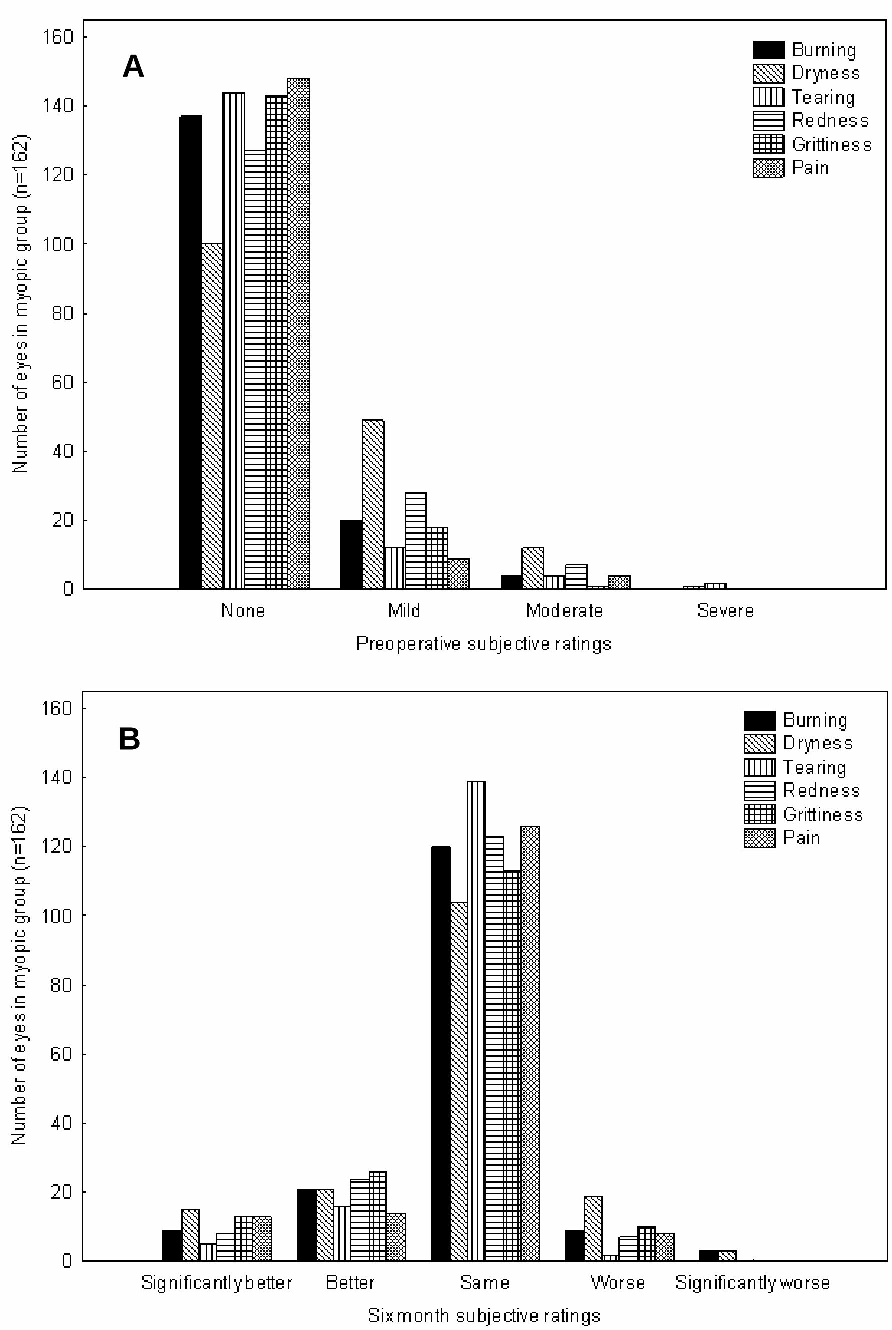


Figure 56: Subjective responses to questions regarding sensory information for the myopic group. A) preoperative subjective ratings and B) postoperative subjective ratings.

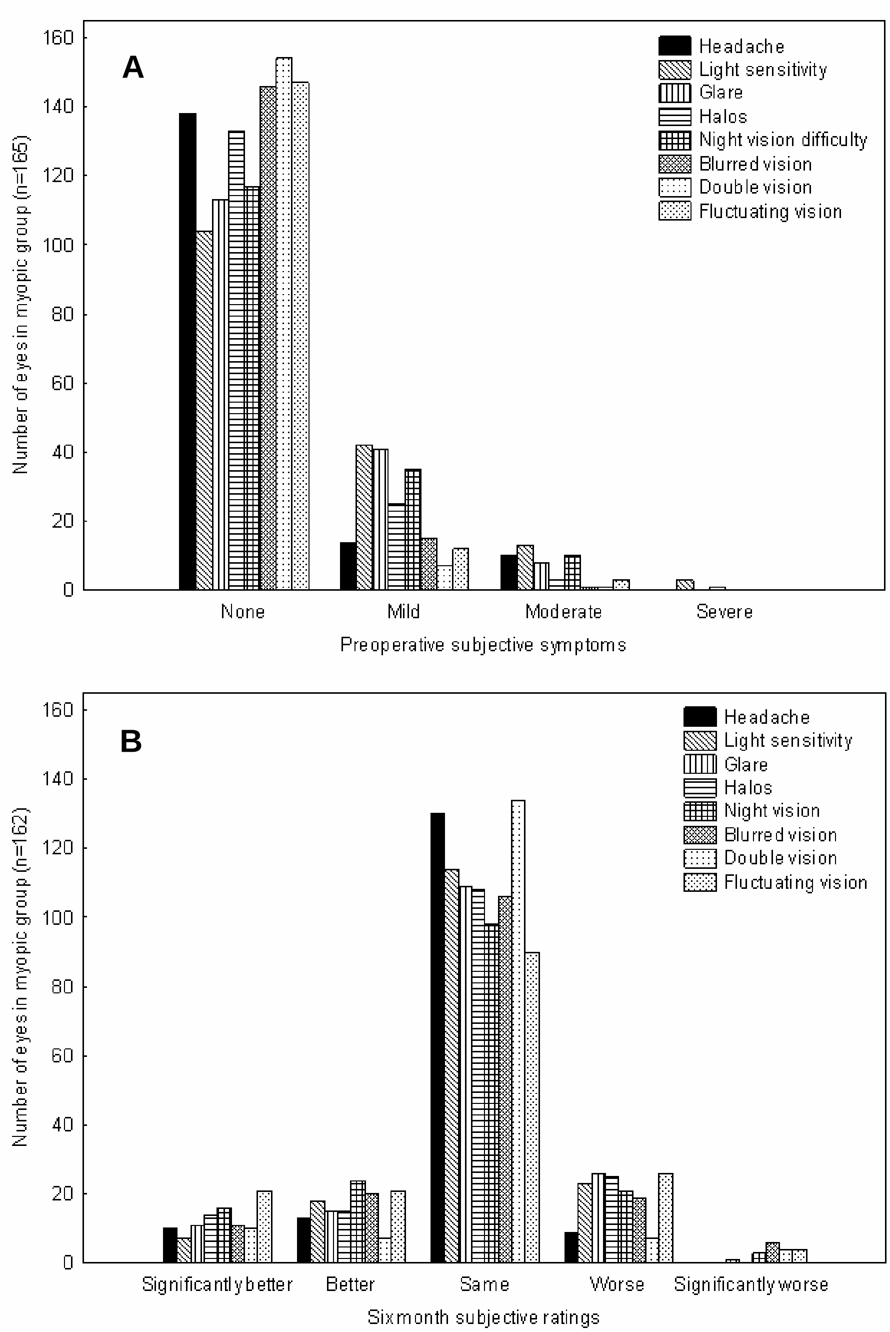


Figure 57: Subjective responses to questions regarding aspects of vision for the myopic group A) preoperative subjective ratings and B) postoperative subjective ratings

Table 27: % change in subjective symptoms six months following WFG LASIK for the myopic group (n=162).

	Six month subjective ratings for the myopic group % (number of subjects)	
Symptom	Better than preoperative level	Worse than preoperative level
Burning	18.5% (30)	7.4% (12)
Dryness	22.2% (36)	13.6% (22)
Tearing	13.0% (21)	1.2% (2)
Redness	19.8% (32)	4.3% (7)
Grittiness	24.1% (39)	6.2% (10)
Pain	16.7% (27)	4.9% (8)
Headache	14.2% (23)	5.6% (9)
Light sensitivity	15.4% (25)	14.2% (23)
Glare	16.0% (26)	**16.7% (27)***
Halos	17.9% (29)	15.4% (25)
Night vision difficulty	24.6% (40)	14.8% (24)
Blurred vision	19.1% (31)	15.4% (25)
Double vision	10.5% (17)	6.8% (11)
Fluctuating vision	25.9% (42)	18.5% (30)
Average	17.2% (27.9)	10.4% (16.8)

***** indicates "worse than preoperative level" rating was greater than "better than preoperative level" rating for that symptom.

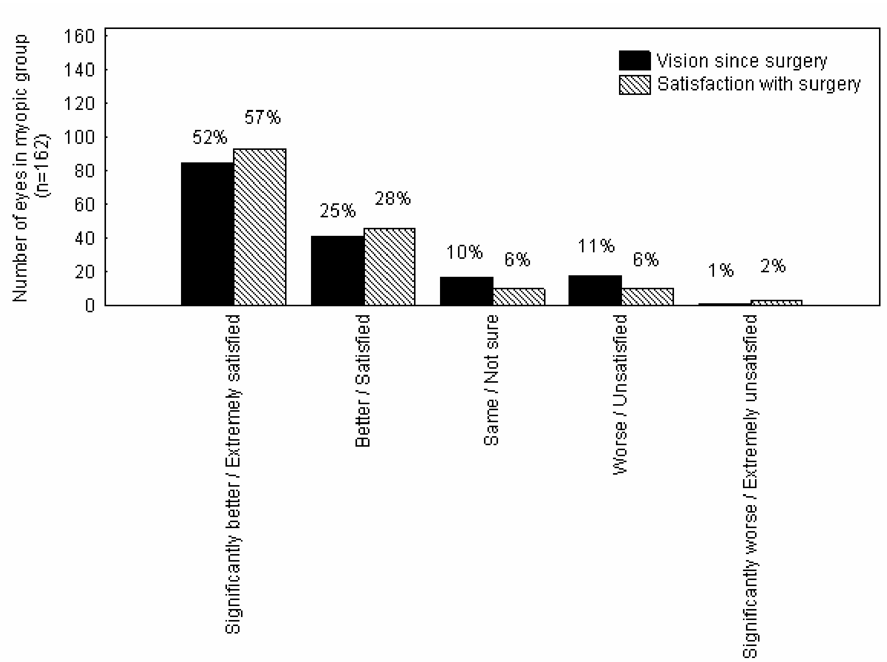


Figure 58: Subjective responses to questions regarding overall vision and satisfaction following WFG LASIK for the myopic group

For the hyperopic group, Figure 59 and Figure 60 display the responses to questions relating to ocular sensory information and aspects of vision, respectively. Table 28 shows the percent of subjects that reported either better or worse subjective symptoms following surgery. Figure 61 shows the overall vision and satisfaction results for this group. As for the myopic group, most subjects reported either no change or a slight improvement in their subjective ratings and were generally satisfied following their hyperopic WFG LASIK procedure.

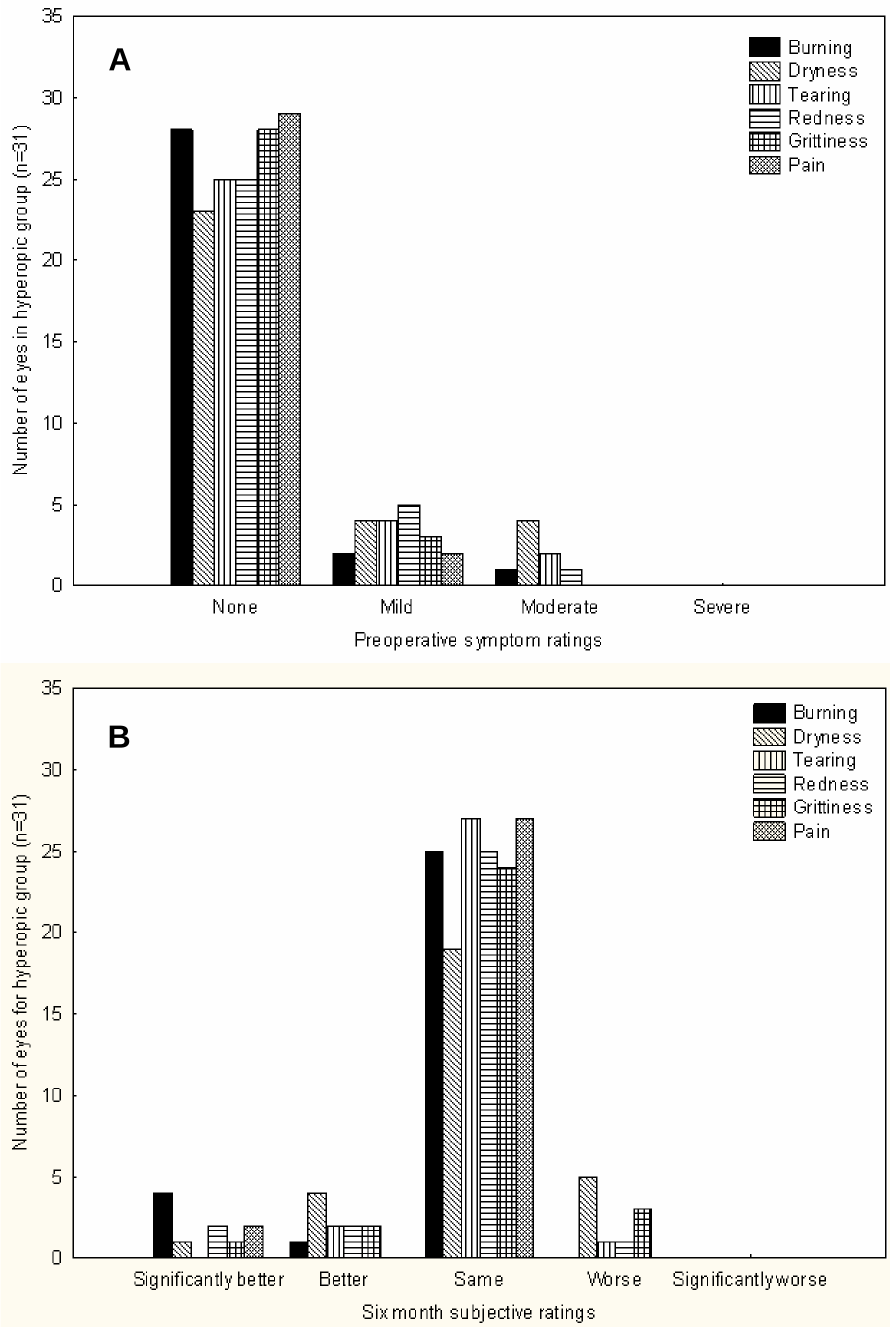


Figure 59: Subjective responses to questions regarding sensory information for the hyperopic group. A) preoperative subjective ratings and B) postoperative subjective ratings.

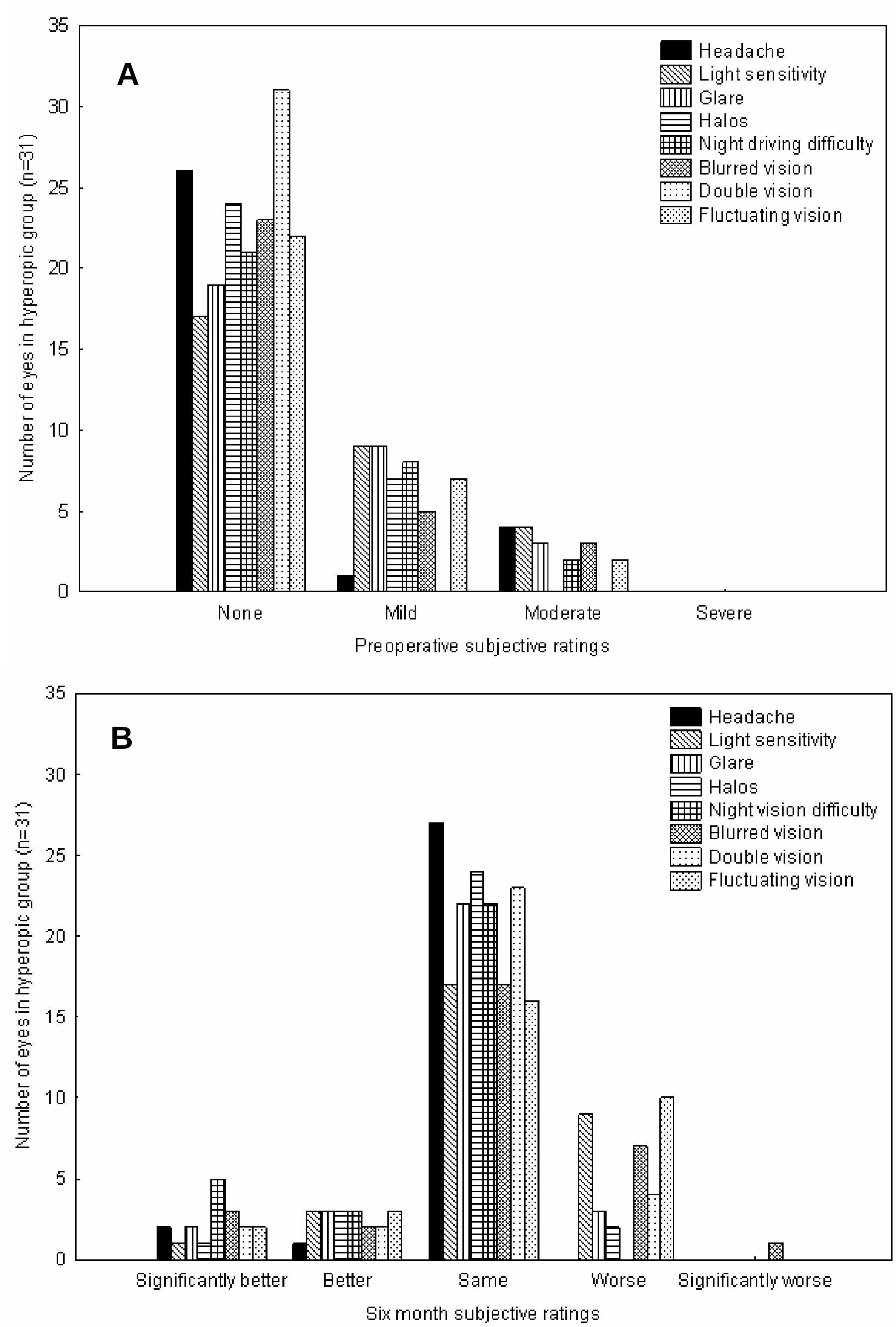


Figure 60: Subjective responses to questions regarding aspects of vision for the hyperopic group. A) preoperative subjective ratings and B) postoperative subjective ratings.

Table 28: % change in subjective symptoms six months following WFG LASIK for the hyperopic group (n=31)

	Six month subjective ratings for the myopic group % (number of subjects)	
Symptom	Better than preoperative level	Worse than preoperative level
Burning	16.1% (5)	0
Dryness	16.1% (5)	16.1% (5)
Tearing	6.5% (2)	3.2% (1)
Redness	12.9% (4)	3.2% (1)
Grittiness	12.9% (4)	9.7% (3)
Pain	6.5% (2)	0
Headache	9.7% (3)	0
Light sensitivity	12.9% (4)	**29.0% (9)***
Glare	16.1% (5)	9.7% (3)
Halos	12.9% (4)	6.5% (2)
Night vision difficulty	25.8% (8)	0
Blurred vision	16.1% (5)	**25.8% (8)***
Double vision	12.9% (4)	12.9% (4)
Fluctuating vision	16.1% (5)	**32.3% (10)***
Average	12.9% (4)	10.6% (3.3)

***** indicates “worse than preoperative level” rating was greater than “better than preoperative level” rating for that symptom.

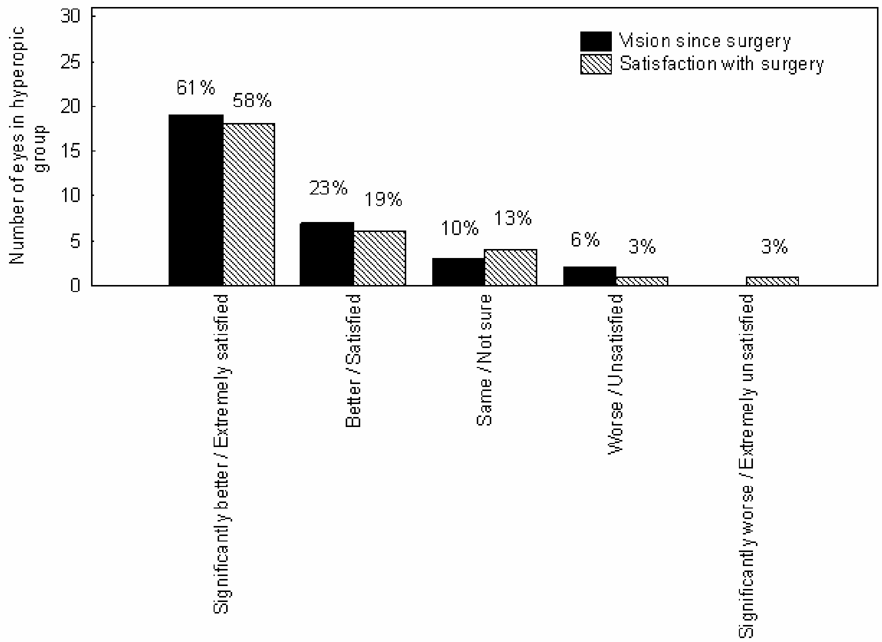


Figure 61: Subjective responses to questions regarding overall vision and satisfaction following WFG LASIK for the hyperopic group

Correlations

For the myopic group, six month ratings for vision since surgery and satisfaction with surgery were statistically significantly associated with six month UCVA ($r=0.30$ and 0.37, respectively; both $p<0.001$). Six month vision since surgery was statistically significantly associated with burning, dryness, night vision, blur, and fluctuation of vision ($r=0.26$ to 0.70; all $p<0.001$). Six month satisfaction with surgery was statistically significantly associated with burning, dryness, glare, halos, night vision, blur, double vision, and fluctuation of vision ($r=0.27$ to 0.70; all $p<0.001$). Statistically significant associations were found between subjective ratings ($r=0.27$ to 0.67; all $p<0.001$). There were no statistically significant correlations between subjective ratings and BCVA, contrast sensitivity or higher order aberrations (all $p>0.001$). Additionally, there were no statistically significant associations between six month mesopic pupil size measurements and six month subjective quality of vision ratings for the myopic group (all $p>0.001$).

Findings for the hyperopic group were different from the myopic group. Ratings for vision since surgery and satisfaction with surgery were not associated with any of the other six month variables (all $p>0.001$). This could be due in part to the small sample size. Taking a less conservative approach and setting statistical significance at $p<0.01$, six month satisfaction with surgery was associated with UCVA and high contrast BCVA ($r=0.55$ and 0.47, respectively; both $p<0.01$). With statistical significance set at $p<0.01$ there were many correlations between subjective ratings, however six month vision since surgery and six month satisfaction with surgery were still not associated with any of the other subjective ratings (all $p>0.01$). There were no statistically significant correlations between subjective ratings and low contrast BCVA, contrast sensitivity, higher order aberrations or mesopic pupil size (all $p>0.01$).

Discussion

Our results indicate that the majority of myopic and hyperopic subjects found no change in subjective ratings related to sensory information or different aspects of vision following WFG LASIK. Overall, more than 75% of those in the myopic and hyperopic group were happy with their vision following surgery and were satisfied overall. This is similar to high levels of satisfaction (ranging from 82% to 98%) reported in the literature following non-WFG LASIK surgery.[131] McGhee et al.[368] found that more than 95% of patients were satisfied with their UCVA, visual recovery, quality of life and overall outcome following surgery. Despite this, however, reduced quality of vision can occur regardless of high satisfaction ratings. A study emphasizing this fact was an informal survey of satisfaction following non-WFG LASIK reported by Hill.[369] This study found that 48 (24%) of 200 subjects reported that their night vision was worse after surgery, however 195 (98%) in the same study were extremely happy with their results. In this study, approximately 10% reported a worsening of one or more symptoms in both the myopic and hyperopic group. Only 2% of those in the myopic group indicated that they were still satisfied with surgery. In the hyperopic group, 4% of those who had one or more symptoms indicated that they were still satisfied with surgery.

For the myopic group the main symptoms that worsened following surgery were fluctuating vision, glare, halos and light sensitivity (range 14% to 18%). For the hyperopic group, the main symptoms that worsened after surgery were fluctuating vision, light sensitivity, blurred vision and double vision (range 13% to 32%). Visual symptoms following non-WFG LASIK, particularly at night, are quite prevalent and range from 12% to 57%.[368, 370] A recent review of FDA studies across different lasers for non-WFG LASIK for myopia found that night vision was worse following surgery for approximately 15% of patients.[174] In a retrospective study comparing symptomatic to asymptomatic subjects following non-WFG LASIK for myopia, blurred vision was the most common symptom followed by double vision, halos, and fluctuation in vision (range 14% to 42%).[301] Another study investigated symptoms following non-WFG LASIK for 841 myopic subjects and found symptoms of halos (30%), glare (27%) and starburst (25%) following surgery. These values are slightly higher than the percentages in our myopic group, which could be due to the fact it was a non-WFG treatment, differences in the method of data collection and/or differences in the study population. A contralateral study between non-WFG and WFG myopic LASIK found fewer symptoms reported in the WFG group.[371] In hyperopic non-WFG LASIK patients, Jaycock et al.[372] reported that approximately 88% of them were happy with the results and that the 12% who were unhappy tended to have residual hyperopic refractive error and poor night vision. Salz et al.[373] reported outcomes for 295 hyperopic eyes with or without astigmatism treated with non-WFG LASIK and used a postoperative questionnaire similar to the one used in this study. They found that greater than 68% of subjects were satisfied with the results of their surgery and that the symptoms commonly reported as significantly worse after surgery were dryness, difficulty with night driving, fluctuation of vision, halos, blurred vision, double vision, grittiness, redness and pain. In the same study, greater than 95% of the subjects reported unchanged or improved quality of vision, conveying that overall satisfaction following surgery cannot be based on quality of vision ratings alone.

Examining the ratings of ocular sensory symptoms in this study revealed that, dryness was the main symptom for both groups, worsening postoperatively in 14% of the subjects in the myopic group and 16% of the subjects in the hyperopic group. It has previously been reported that dryness symptoms significantly increase following non-WFG LASIK surgery and can persist for as long as 16 months.[374, 375] Bailey and Zadnik[174] reported that 20% of patients experienced worse dryness symptoms following non-WFG LASIK and found no difference between laser types, including WFG surgery. It is not surprising that there is minimal difference between non-WFG LASIK and WFG LASIK for the prevalence of postoperative dryness symptoms, since both surgically interfere with the anterior corneal surface.

Uncorrected visual acuity was associated with worse subjective ratings, sometimes previously reported.[359, 376] There was no association between mesopic pupil size and subjective ratings, which is in agreement with other studies.[367, 377] It could be that improvements in technology, such as advanced ablation profiles, better choice of treatment zone parameters, including larger optic zones and blended transition zones,[378] and careful pre-selection of refractive surgery candidates has resulted in less impact of pupil size on subjective vision ratings. Additionally, there were no associations between subjective ratings and higher order aberrations, low contrast BCVA or contrast sensitivity for either group.

In this study the evaluation of qualitative vision was performed binocularly; however vision testing and higher order aberration measurements were done monocularly. Binocular vision has been shown to be superior to monocular vision and has been attributed to inter-ocular neural summation.[379, 380] Boxer Wachler et al.[381] assessed whether there was a difference in vision with monocular and binocular testing for post LASIK patients and found that monocular testing resulted in a larger pupil size and slightly reduced visual acuity and contrast sensitivity. Therefore, it is possible binocular testing masked differences in visual quality between the eyes, which could underestimate reports of reduced subjective visual quality following WFG LASIK in this study.

Psychometric testing of visual complaints prior to surgery could help to determine whether there was a worsening (or an improvement) following surgery. In this study, the preoperative evaluation revealed mild symptoms such as dryness, burning, light sensitivity, glare and night vision difficulty in both groups. These could be due to the optics of the eye, habitual refractive correction (spectacles or contact lenses), environmental conditions, among other factors. Further insight into the cause for these preoperative symptoms might lend insight into changes following surgery. For instance, a study has suggested that preoperative dry eye may be a risk factor for severe dry eye following surgery.[382] Studies of this nature are beneficial for counseling regarding risk factors and managing expectations prior to surgery.

A limitation of this investigation was the nature of the questionnaire provided. The questions were related to refractive surgery; however rating whether these symptoms improved or worsened following surgery might be difficult after six months has elapsed. The questionnaire has also not been validated. However, it does provide insight into whether someone feels they are doing better or worse following surgery, but further interpretation should be undertaken with caution. It would be valuable if standard questionnaires to assess postoperative visual quality[361] were more commonly used, so that comparisons between studies could be made.

Attempts have been made to improve subjective testing following refractive surgery. The National Eye Institute Visual Function Questionnaire (NEI-VFQ) has been created to capture the effect of a wide range of eye diseases.[383] Unfortunately, however, this questionnaire does not include symptoms specific for refractive surgery patients, such as halos, fluctuations in vision, and convenience.[384] As a result, the National Eye Institute sponsored the development of the Refractive Error Correction Quality of Life questionnaire (NEI-RQL), which was specifically designed to measure the vision-targeted, health-related quality of life for persons with well-corrected refractive error.[385] In addition, Vitale et al[386] have constructed a questionnaire (the Refractive Status and Vision Profile or RSVP) designed to measure the visual, functional, and psychological consequences of refractive error. Vitale et al.[386] reported that certain subscales, as well as the overall test score, were more strongly correlated with patient satisfaction and overall assessment of vision than visual acuity or refractive error measures. Nichols et al.[387] investigated the NEI-RQL and the RSVP and both questionnaires had acceptable reliability and validity. Use of these instruments will hopefully allow patients to better explain their subjective visual experiences following surgery. Ultimately, improved evaluation of qualitative outcomes will aid in the development of new technology to optimize visual function and provide improved insight into patient satisfaction following refractive surgery.

So far in this thesis WFG LASIK outcomes have been measured in terms of visual acuity, contrast sensitivity, wavefront aberrations and subjective ratings. The goal of the following chapter is to provide insight into the relationships between these outcome measures.

Chapter 7

Factor analysis and case examples

Factor analysis

Factor analysis was invented over one hundred years ago by psychologist Charles Spearman to evaluate the many tests of mental ability.[388] He used factor analysis to explain the relationships between various tests in terms of a few conceptually meaningful, relatively independent factors.[388] Clinical trials often include many different variables in order to ensure that important information is not overlooked. However, collecting information using many different variables can be difficult and also impractical, for reasons such as time constraints and cost. Therefore, it would be beneficial to understand the relationship between multiple variables in order to determine whether it was possible to identify new, perhaps more effective variables.

The primary objective of this analysis was to determine whether key factors exist to explain the relationship between the variables used to measure outcomes following WFG LASIK and to gain insight into which variables were the most important in explaining the data.

Methods

The six month postoperative outcomes including age, manifest refraction, visual acuity, contrast sensitivity, monochromatic aberrations and subjective ratings were included in the analysis (41 variables in total). Based on eigenvalues, a scree plot was used to determine the number of factors. The number of factors and the correlations were taken from the Varimax rotated solution. Variables with factor loadings of >0.50 were used to interpret and classify the individual factors. Calculations were undertaken using Statistica 7 software (StatSoft Inc, Tulsa, OK).

For the myopic group, Figure 62 displays a plot of the eigenvalues. As shown by a sharp bend in the scree plot, three separate factors were distinct and had larger values than the rest. Table 29 displays the exact eigenvalue for these three factors and the percentage of the variance of the data explained by each. In total, approximately 41% of the variance of the data in the myopic group could be explained by these three factors.

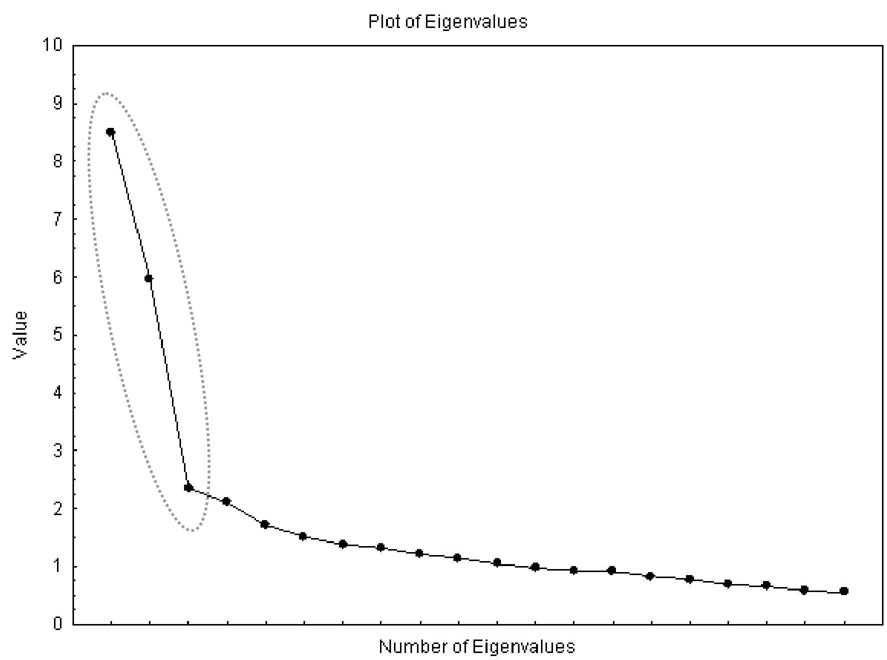


Figure 62: Scree plot of the eigenvalues for the myopic group.

Table 29: Eigenvalues and % total variance for factor analysis using principal component extraction for the myopic group.

Factor	Eigenvalue	% total variance	Cumulative Eigenvalue	Cumulative %
1	8.50	20.74	8.50	20.74
2	5.96	14.54	14.47	35.29
3	2.35	5.73	16.82	41.02

Figure 63 is a plot of Factor 1 versus Factor 2 for the myopic group. The variables with the highest factor loadings (> 0.5) for each factor can be found in Table 30. Using these variables, general concepts for each factor were subjectively determined and are listed in the first row of the table. The primary factor for the myopic group was *subjective ratings* (glare, halos, and double vision), followed by *vision* (HC BCVA, LC BCVA and contrast sensitivity) and finally *optical quality* (Z^0_4, Z^{-2}_4, and Z^{-4}_4).

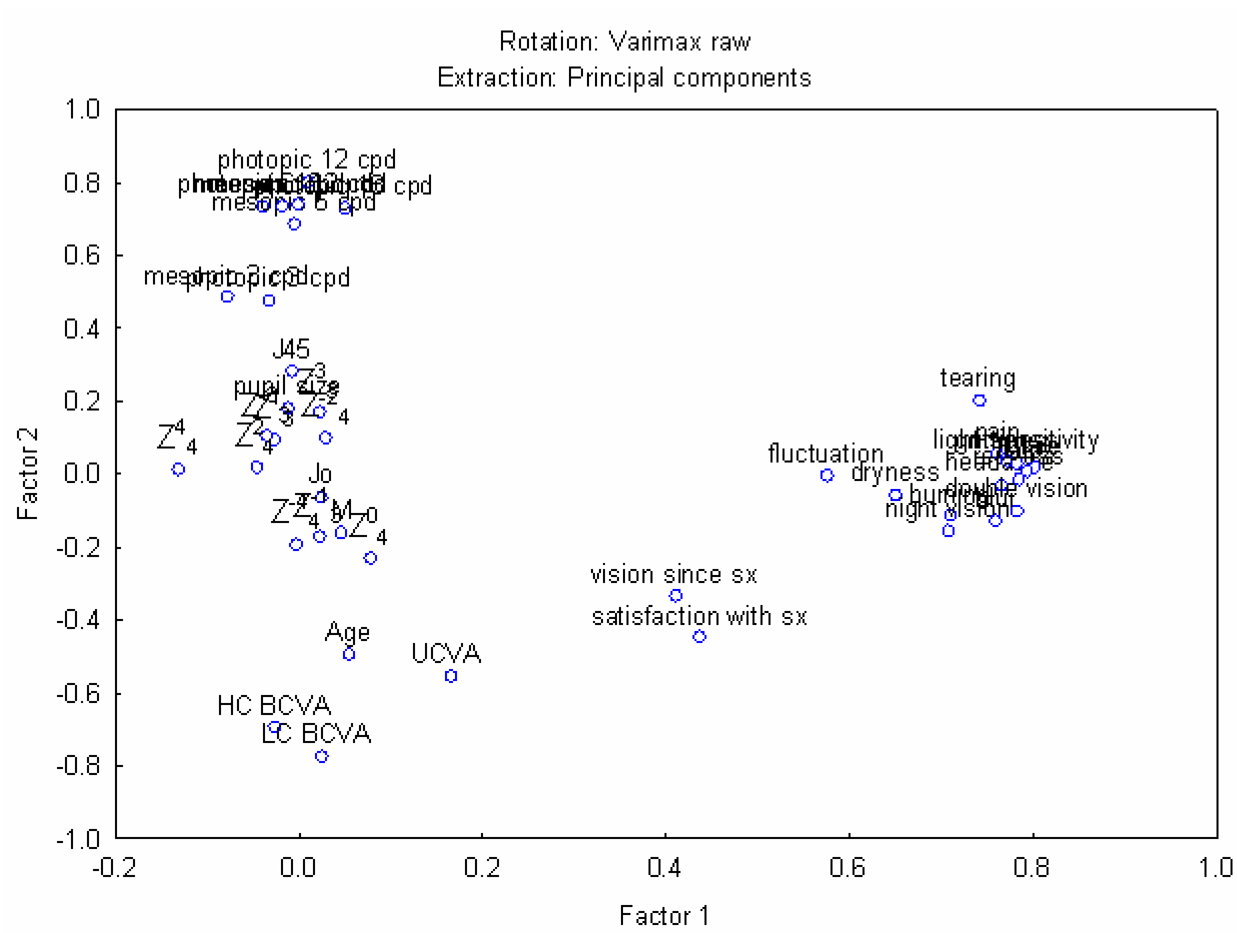


Figure 63: Plot of factor loadings for the myopic group.

Table 30: List of the variables with the largest factor loadings for the myopic group (all loadings > 0.5).

FACTOR 1 subjective ratings	FACTOR 2 vision	FACTOR 3 optical quality
glare	photopic cs	Z^{0}_{4}
halos	(6, 12, 18 cpd)	manifest sphere
double vision	LC BCVA	Z^{-2}_{4}
light sensitivity	mesopic cs	Z^{-4}_{4}
redness	(6, 12, 18 cpd)	
grittiness	HC BCVA	
headache		
pain		
blur		
tearing		
burning		
night vision		
dryness		
fluctuation		

For the hyperopic group, the matrix was ill-conditioned. This was likely due to the fact that there were so few cases compared to variables and that some of the variables had no variance (i.e. pain ratings were all "2 = no change"). Regardless, there were four factors that explained a large percentage of the variability of the data (approximately 52%). A plot of the eigenvalues can be seen in Figure 64.

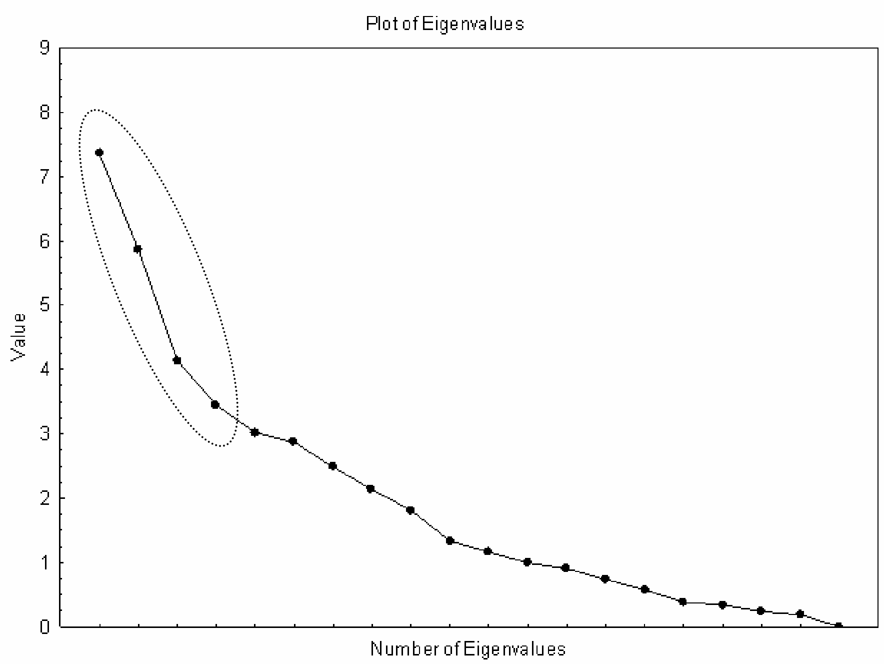


Figure 64: Scree plot of the eigenvalues for the hyperopic group.

Table 31: Eigenvalues and % total variance for factor analysis using principal component extraction for the hyperopic group.

Factor	Eigenvalue	% total variance	Cumulative Eigenvalue	Cumulative %
1	7.35	18.38	7.35	18.38
2	5.86	14.65	13.21	33.03
3	4.13	10.34	17.35	43.37
4	3.45	8.62	20.80	52.00

Figure 65 is a plot of Factor 1 versus Factor 2 for the hyperopic group. The variables with the highest factor loadings (> 0.5) for each factor can be found in Table 32. Using these variables, general concepts for each factor were subjectively determined and are listed in the first row of the table. Although the data for the hyperopic group were not ideal for factor analysis, cursory findings suggest that important factors were similar to those found in the myopic group: *subjective ratings* (burning, grittiness, and headache), *high spatial frequency vision* (UCVA, HC BCVA and contrast sensitivity at 18 cpd), *low spatial frequency vision* (mesopic contrast sensitivity at 3 and 6 cpd) and *optical quality* (Z^{-2}_4, Z^{2}_4, Z^{-4}_4 and Z^{4}_4).

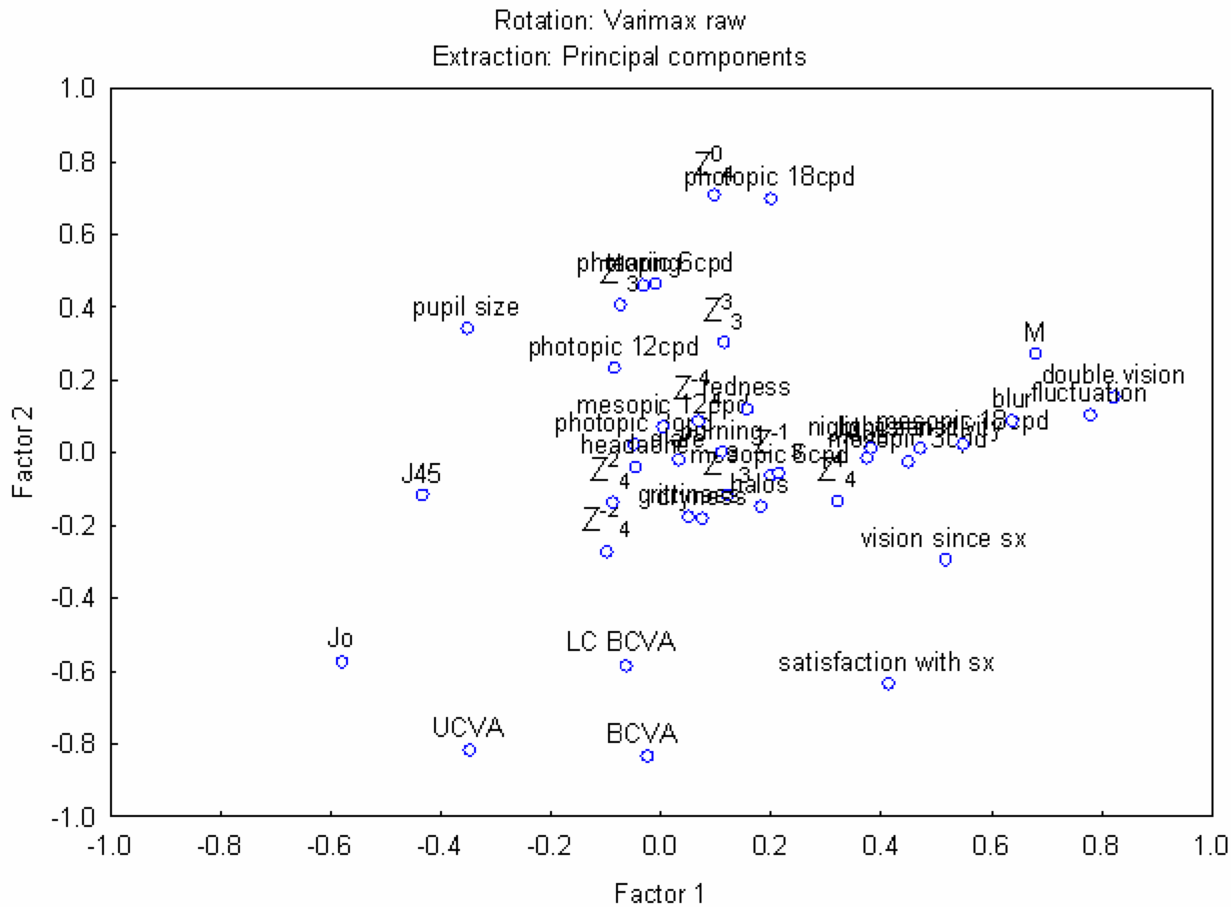


Figure 65: Plot of factor loadings for the hyperopic group.

Table 32: List of the variables with the largest factor loadings for the hyperopic group (all loadings > 0.5).

FACTOR 1 subjective ratings	FACTOR 2 high spatial frequency vision	FACTOR 3 low spatial frequency vision	FACTOR 4 optical quality
burning	UCVA	mesopic contrast	Z^{-2}_{4}
grittiness	HC BCVA	sensitivity	Z^{2}_{4}
headache	J_o	(3 and 6 cpd)	Z^{-4}_{4}
dryness	photopic contrast		Z^{4}_{4}
glare	sensitivity (18 cpd)		night vision
blur	Z^{0}_{4}		

Case examples

A large sample size is important to determine overall results, following a treatment or a procedure. Unfortunately, however, small, inconsistent and/or irregular results can get lost within a large amount of data. The purpose of this section was to look at two specific cases where the subjects were unsatisfied after surgery in an attempt to determine which variables were the most affected.

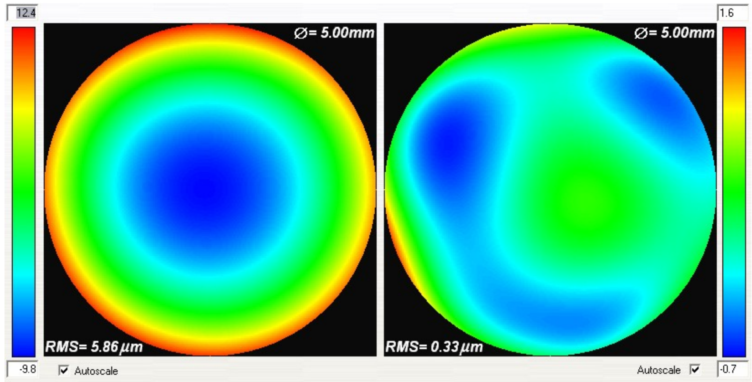
Methods

Two subjects, one from the myopic group and one from the hyperopic group, were arbitrarily selected based on reduced satisfaction ratings reported in Chapter 6. General preoperative and postoperative information has been provided. Total ocular and higher order aberration wavefront maps are shown, as well as the corresponding point spread function (PSF) derived using third and fourth order aberrations. Images were obtained using the LADARVision software (Alcon Laboratories, Inc., Fort Worth, TX).

Results

Case 1: CML-272

CML-272 was a 52 year old female who had a history of soft contact lens wear. Her preoperative manifest refraction was -6.25-0.75x172. High contrast (HC) and low contrast (LC) best-corrected visual acuities (BCVAs) were -0.08 and 0.20 logMAR, respectively. Central keratometry readings were 42.25 @ 165 and 44.0 @ 078 for the flat and steep meridians, respectively. Preoperative wavefront aberrations can be seen in Figure 66. Subjective ratings prior to surgery revealed mild dryness.



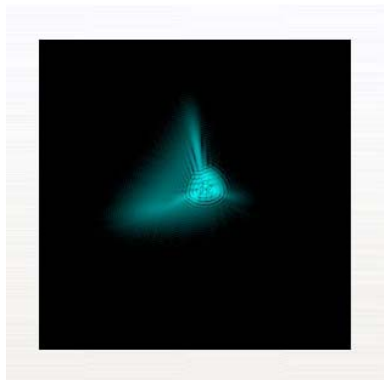


Figure 66: CML-272 preoperative 2-D wavefront aberration map (top) with total ocular aberrations shown on the left and higher order aberrations shown on the right. The impact of higher order aberrations on the PSF is also shown (bottom).

Six months following WFG LASIK, CML-072 was unsatisfied with surgery and felt that her vision was worse than it was before surgery. Subjective ratings included significantly worse dryness, worse tearing, significantly worse double vision and worse fluctuation in vision. Uncorrected visual acuity (UCVA) was 0.00 logMAR. Manifest refraction was +2.00-0.50x175 and HC and LC BCVAs were -0.06 and 0.34 logMAR, respectively. Mesopic contrast sensitivity was improved at 3 cpd (0.15 log units), reduced at 6 and 12 cpd (-0.93 and -0.64 log units, respectively) and unchanged at 18 cpd. Postoperative wavefront aberrations and the PSF can be seen in Figure 67.

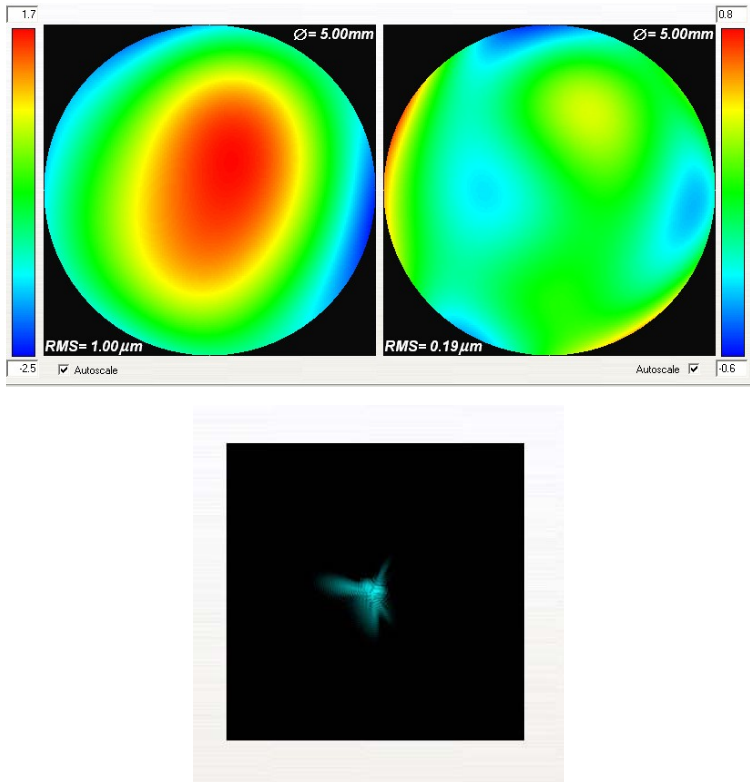


Figure 67: CML-272 six month 2-D wavefront aberration map (top) with total ocular aberrations shown on the left and higher order aberrations shown on the right. The impact of higher order aberrations on the PSF is also shown (bottom).

Subject CML-272 had a moderate (approximately 2.00D) over-correction. HC BCVA was relatively unchanged; however LC BCVA and mesopic contrast sensitivity were worse following surgery. Subjective ratings indicated mild double vision and fluctuation of vision. Despite these findings, however, higher order aberrations were less following surgery (see Figure 67). As discussed previously in Chapter 3, it is possible that the optics of the phoropter containing the six month manifest refraction had an effect on LC BCVA and contrast sensitivity results. Although these results do not indicate why such a large over-correction occurred, different possibilities, such as reduced stromal hydration during treatment,[168] wound healing and/or biomechanical changes, might have played a role.[115] Additionally, this subject had a moderate amount of preoperative spherical aberration (Z^0_4 = 0.44 µm), which has been associated with an overcorrection of myopia with WFG LASIK[389] and WFG LASIK enhancements.[390, 391]

Case 2: CHL-309

CHL-309 was a 54 year old female who had no history of contact lens wear. Her preoperative manifest refraction was +1.00-0.75x091. HC and LC BCVAs were -0.02 and 0.30 logMAR, respectively. Central keratometry readings were 42.75 @ 172 and 43.50 @ 082 for the flat and steep meridians, respectively. Preoperative wavefront aberrations and PSF can be seen in Figure 68. Subjective ratings prior to surgery revealed moderate dryness, mild redness, moderate headaches, very severe light sensitivity, moderate night driving difficulty, moderate blur and moderate fluctuation in vision.

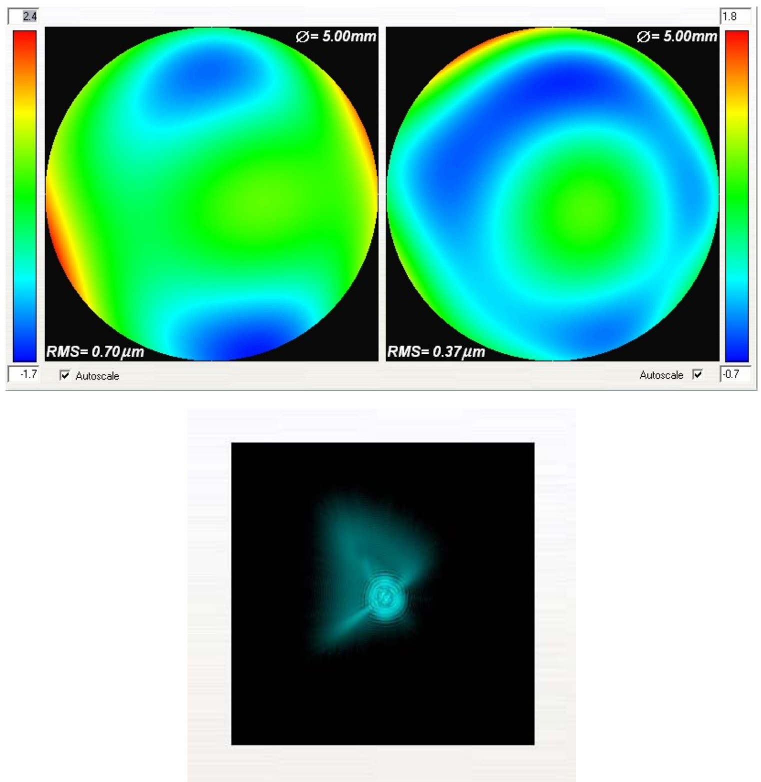


Figure 68: CHL-309 preoperative 2-D wavefront aberration map (top) with total ocular aberrations shown on the left and higher order aberrations shown on the right. The impact of higher order aberrations on the PSF is also shown (bottom).

Six months following WFG LASIK, CHL-309 reported that her vision was the same as it was before surgery and that she was extremely unsatisfied. Subjective ratings included worse dryness, worse light sensitivity, worse double vision, and worse fluctuation in vision. All other symptoms were rated as being the same as they were prior to surgery. Uncorrected visual acuity (UCVA) was 0.04 logMAR. Postoperative manifest refraction was +1.75-0.25x075 and HC and LC BCVAs were -0.06 and 0.22 logMAR, respectively. Mesopic contrast sensitivity was unchanged at 3 cpd and was improved at 6, 12 and 18 cpd (0.49, 0.77 and 0.60 log units, respectively). Postoperative wavefront aberrations and PSF can be seen in Figure 69.

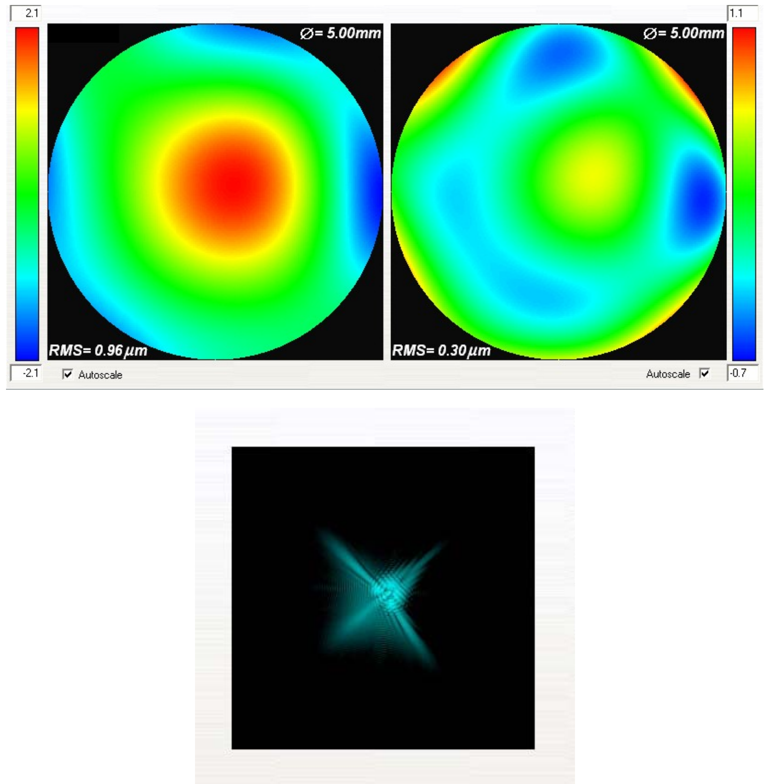


Figure 69: CHL-309 six month 2-D wavefront aberration map (top) with total ocular aberrations shown on the left and higher order aberrations shown on the right. The impact of higher order aberrations on the PSF is also shown (bottom).

Subject CHL-309 experienced an under-correction, resulting in similar preoperative and postoperative manifest refractions. Preoperative sensory and vision ratings were poor and postoperative ratings even worse. There was little change from baseline in the total amount of higher order aberrations; however the PSF looks somewhat different at six months. Not unlike the case for CML-272, it is unknown why there was an under-correction for this subject. Possible causes include excessive stromal hydration during treatment,[168] wound healing and/or biomechanical factors.[115]

Discussion

The previous four chapters explored the effect of WFG LASIK on visual acuity, contrast sensitivity, higher order aberrations and subjective ratings. The purpose of this chapter was to investigate the structure between these outcome measures and to provide case examples in order to put these results into clinical perspective. It can be concluded from the factor analysis that there were a variety of factors that contributed to the outcome measures for this data set, with the three main factors being: *subjective ratings, vision* and *optical quality*. It was interesting that the variables that made up these separate factors were distinct, as intuitively one might have expected these to be strongly related. Optical quality, for example, has been associated with subjective ratings[260, 392] and vision.[134, 393] It should be kept in mind, however, that a large percentage (>50%) of the data was not explained by these three factors.

Similar factors were identified for the hyperopic group; however the interpretation of this finding should be cautionary as the data were not well-suited for the analysis. Regardless, it was interesting that the variables that made up the *subjective ratings* factor were different for the myopic and hyperopic groups. The variables with the largest factor loadings for the myopic group were "sensory-type" ratings, including glare, halos, double vision and light sensitivity, while the variables that contributed the most for the hyperopic group were "comfort-type" ratings, such as burning, grittiness, headache and dryness. This might be an important difference in subjective outcome measures between groups and should be considered when setting criteria for subjective ratings in future studies.

Despite factors providing unique and important information; redundancy between variables can exist within a factor. Pesudovs et al.[290] investigated ten results for two contrast sensitivity charts and reported that two factors, high spatial frequency vision and low spatial frequency vision, existed. The authors concluded that perhaps a different test that is normally performed, such as HC BCVA, could capture high spatial frequency information, and a more efficient test specifically designed to capture low spatial frequency information could be used.[290] Similarly, it is possible that HC BCVA, LC BCVA, and photopic and mesopic contrast sensitivity are not all necessary to capture information relating to vision in the myopic group. Until this is tested, however, it is recommended that a variety of objective and subjective clinical tests be performed in order to fully describe information following WFG LASIK.

The case examples presented in this chapter somewhat coincide with the factor analysis results and imply that subjective information, vision and optical quality provide different information and can change independently of one another. Reductions (or improvements) in one area does not necessarily mean that reductions (or improvements) will occur in the other. For example, subject CML-272 experienced an improvement in optical quality; however subjective ratings and vision measures were reduced. Subject CHL-309 experienced improved vision and little change in optical quality; however subjective ratings following surgery were worse. The case studies also illustrate that unpredictable, less than optimal outcomes can occur despite careful preoperative selection. This is one of the main factors that can make refractive surgery so daunting. Future work in this field, which will be discussed in the next chapter, will hopefully help to minimize the number of unpredictable outcomes.

Chapter 8

Conclusions and future work

There were three specific aims of this dissertation to investigate the clinical outcomes of myopic and hyperopic WFG LASIK. The first aim was to *determine the impact of WFG LASIK on visual acuity and contrast sensitivity and to determine the ability of these tests to reflect post-surgical changes in higher order aberrations.* The results described in Chapter 3 indicate that HC and LC BCVA and photopic and mesopic contrast sensitivity were relatively unaffected by WFG LASIK for both the myopic and hyperopic group. Despite the fact that an increase in higher order aberrations has been shown to result in reduced optical quality,[54, 125, 134, 272] our findings suggest that the testing strategy used in this study did not adequately reflect the postoperative change in monochromatic higher order aberrations. In light of this, the relationship between higher order aberrations and their impact on vision requires further analysis. It would also be beneficial to determine what level of change in visual acuity or contrast sensitivity is clinically relevant.

The second aim of this dissertation was to *describe and explore the monochromatic higher order aberrations before and after WFG LASIK for myopia and hyperopia.* It was reported in Chapter 4 that preoperatively, the magnitude of higher order aberrations for the myopic and hyperopic groups in this study were similar to published reports.[298, 303, 304] Most of the higher order aberrations averaged close to zero, with the exception of spherical aberration which was slightly positive for both groups. A statistically significant increase in higher order aberrations following WFG LASIK for the myopic group did occur, particularly for the third order terms, coma and trefoil. This was also true for the hyperopic group, with the greatest postoperative increase being spherical aberration. Aside from increases in magnitude, directional changes in higher order aberrations also occurred following surgery and were discussed in Chapter 5. Of particular interest were the directional changes in spherical aberration and coma, which differed between the myopic and the hyperopic groups, and the directional change in trefoil, that was the same for the myopic and hyperopic group. Further investigation into the etiology and predictability of these changes is warranted if surgically-induced higher order aberrations following WFG LASIK are to be reduced further.

The third aim of this dissertation was to *assess the visual impact of WFG LASIK on qualitative vision following surgery.* On average, there was a high level of satisfaction following surgery and the majority of myopic and hyperopic subjects reported no change in their subjective ratings. For certain individuals, however, subjective ratings uncovered a worsening of sensory information or different aspects of vision, which was particularly noticeable in the hyperopic group. These ratings were not associated with higher order aberrations, low contrast BCVA or contrast sensitivity for either group. The implementation of validated questionnaires in a larger number of studies would be helpful to provide more insight into the postoperative symptoms associated with WFG LASIK. Preoperative psychometric testing might also prove to be a worthwhile endeavor, since our findings suggest that different criteria might be used by individuals when reporting "satisfaction" following surgery.

Chapter 7 was included in this dissertation to determine whether key factors exist to explain the relationship between the outcome variables following WFG LASIK and to gain insight into which variables were the most important in explaining the data. This work implies that a variety of objective and subjective variables are necessary in order fully capture information following WFG LASIK. Subjective ratings, vision, and optical quality measures are all important. The next logical step would be to determine which of the current tests are the most useful and to determine whether additional tests (either new or modified) can be developed in order to improve postoperative testing strategies.

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