Higher-Order Aberrations in Keratoconus

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Optometry
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Abbreviations list

ANOVA= analysis of variance
AC= apical clearance
AT= apical touch
BCVA= best-corrected visual acuity
BFS= best-fitting sphere
BOZR= back optic zone radius
CCD= charged couple device
c/d= cycles per degree
CLEK = Collaborative Longitudinal Evaluation of Keratoconus
COAS= complete ophthalmic analysis system
CPV= corneal p-value
CRF= corneal resistance factor
CSF= contrast sensitivity function
D= dioptres
DAC= definite apical clearance
DAT= definite apical touch
DC= dioptres cylinder
df= degrees of freedom
Dk= oxygen permeability
DS= dioptres sphere
HCA= high-contrast acuity
HEMA= 2-hydroxyethylmethacrylate
HORMS= higher-order RMS error
INTACS= intra-stromal corneal segment rings
IVA= vertical corneal asymmetry index
K= keratometric reading
KC= keratoconus
\( \lambda \) (lambda)= wavelength of light
LASIK= laser-assisted in situ keratomileusis
LCA= low-contrast acuity
LED= light emitting diode
LogMAR= logarithm of the minimum angle of resolution
LoS= line of sight
LRT= laser-ray tracing
MTF= modulation transfer function
OOK= overnight orthokeratology
OPL= optical path length
OR= over-refraction
OSA= Optical Society of America
OTF= Optical transfer function
ORA= Ocular response analyser
PK= penetrating keratoplasty
PMMA= poly-methyl-methacrylate
PoLTF= post-lens tear film
PPR= predicted phoropter refraction
PSF= point spread function
RGP= rigid gas-permeable
RMS= root mean square
RM-ANOVA= Repeated-measures analysis of variance
Rp= Pearson's correlation coefficient
Rs= Spearman's correlation coefficient
SD= standard deviation
SKILL= Smith-Kettlewell Institute Low Luminance
Sw= within-subject standard deviation
Swo= within-observer standard deviation
VB= visual benefit
WSRT= Wilcoxon Signed-Ranks Test
WV= wavefront variance
YAG= Yttrium aluminium garnet
Abstract

The reduction in visual performance typically found in keratoconic patients is believed to be associated with large magnitudes of uncorrected irregular astigmatism and higher-order aberrations (HOAs). Previous studies indicate that correcting HOAs in keratoconus patients may result in an improvement in visual performance. This thesis explores the correction of HOAs using standard sphero-cylindrical and customised aberration-controlling soft contact lenses in 22 patients with keratoconus. The findings of this work may be useful from a clinical perspective, as some keratoconic patients cannot tolerate rigid gas-permeable (RGP) contact lenses and have few alternatives, excluding surgical intervention, for vision correction.

This thesis firstly describes a series of preliminary studies conducted to improve our current understanding of the HOAs manifested in keratoconus. The results of these investigations suggested that alterations in aberrations, due to changes in accommodation or variations in the pre-corneal tear film post-blink, were unlikely to hinder the correction of HOAs for keratoconic patients. Equally, it was ascertained that subjective refraction data provided significantly better visual acuity compared to objective, aberrometry-derived refractions for patients with keratoconus.

The findings also show that both lower-order aberrations (LOAs) and HOAs displayed a larger degree of variability in keratoconic eyes compared to those previously reported for visually-normal subjects. Furthermore, significant increases in 3rd-order coma root mean square aberrations were found after temporarily suspending RGP contact lens wear for 16 keratoconic patients.

The results of two clinical studies suggested that standard sphero-cylindrical soft lenses can, to some extent, mask HOAs in keratoconic patients; however, the visual performances achieved were found to be poorer compared to RGP lenses. Equally, the results showed that RGP lenses provide superior visual performances compared to customised, aberration-controlling lenses, in spite of the customised lenses providing comparable reductions in uncorrected HOAs.

The inducement of superfluous HOAs and LOAs, through customised contact lens translations and rotations, were modelled using MatLab (version 7.6.0.324; The Mathworks, Natick, MA, US). The results confirmed that minimising the decentration of aberration-controlling contact lenses, to less than 5 degrees of rotation and less than 0.50 mm of translation, will help to achieve an optimal correction of HOAs. However, more stringent criteria were required for LOAs, where rotational displacements should be reduced to less than 3 degrees and translational displacements should be limited to less than 0.10 mm.

In conclusion, the correction of HOAs for patients with keratoconus is possible using customised, aberration-controlling soft contact lenses; however, several factors will govern their success, including the repeatability and accuracy of HOA measurements for these irregular corneas, and the stability of the customised lenses on-eye.
Declaration

No portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of The University of Manchester, or any other university or institute of learning.

Thesis Format

This thesis is presented in ‘Alternative Format’. The decision to present the thesis this way was taken as several of the chapters featured here had already been either published, or prepared for submission to peer-reviewed journals. Where manuscripts based on these chapters have been published, or submitted for publication in a refereed journal it is indicated on the first page of the chapter. The author’s contribution to the work presented in each chapter is also identified on the first page of each chapter.
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1. Overview

Keratoconus is a non-inflammatory ectatic disorder of the cornea, typically characterised by stromal tissue thinning which causes the weakened cornea to take on a steepened, conical shape at the anterior surface (Duke-Elder and Leigh, 1965, Kennedy et al., 1986, Lawless et al., 1989). The condition is most usually bilateral in nature, predominantly affecting the inferior-central two thirds of the cornea (Amsler, 1946, Krachmer et al., 1984, Rabinowitz, 1998). Furthermore, several studies have demonstrated an inter-ocular asymmetry in the corneal features of keratoconus patients (Ihalainen, 1986, Lee et al., 1995, Sherafat et al., 2001, Zadnik et al., 2002, Burns et al., 2004, Li et al., 2004, Nichols et al., 2004, Wagner et al., 2007). The retina and the post-retinal neural aspects of the visual system are likely to remain unaffected by keratoconus (Tan et al., 2008). The visual degradation found, compared to in normal eyes (Zadnik et al., 1998), is believed to be attributed to defects at the cornea such as corneal thinning and protrusion, resulting in irregular astigmatism (Edrington et al., 1995, Griffiths et al., 1998, Sorbara et al., 2000, Davis et al., 2006); corneal scarring (Barr and Yackels, 1991, Zadnik et al., 1996, Zadnik et al., 2000, Weed et al., 2007); higher-order aberrations (Negishi et al., 2007, Okamoto et al., 2008, Tan et al., 2008) and forward light scatter (Mihashi et al., 2006a, Jinabhai et al., 2012b).

The introduction of the Hartmann-Shack aberrometer (Liang et al., 1994) has facilitated research exploring the measurement and correction of ocular higher-order aberrations in an attempt to improve visual performance (Liang et al., 1997, Charman, 2004, Charman, 2005a). Several investigations have demonstrated that coma aberrations become significantly elevated in eyes with keratoconus (Maeda et al., 2002, Gobbe and Guillon, 2005, Bühren et al., 2007, Kosaki et al., 2007, Lim et al., 2007, Schlegel et al., 2009), and that these aberrations impact on visual performance (Negishi et al., 2007, Okamoto et al., 2008). Previous studies have attempted to quantify and correct the aberrations manifested in keratoconic patients using aberration-controlling soft contact lenses (López-Gil et al., 2003, Jeong and Yoon, 2006, Chen et al., 2007b, Marsack et al., 2007a, Sabesan et al., 2007b, Marsack et al., 2008, Katsoulos et al., 2009) and adaptive optics devices (Sabesan et al., 2007a, Rocha et al., 2010). At present however, such customised contact lenses are not commercially available to use in clinical practice.

Although numerous studies have been conducted in this field, several key questions regarding the aberrations measured in keratoconic patients remain unanswered, for example, the repeatability of these aberrations is still unexplored using the Hartmann-Shack technique. This research project presents a review of previous studies of keratoconus patients and aims to address some of the gaps in the current literature. The investigations featured in this thesis intend to improve our understanding of the ocular aberrations manifested in keratoconus. More specifically, this project explores the correction of higher-order aberrations in keratoconic eyes using standard and customised soft contact lenses. Before discussing how keratoconus impacts on optical quality and visual performance, it is important to describe what higher-order aberrations are and how they can be measured clinically.
2. Higher-order aberrations

For centuries, spectacles and contact lenses have been recognised as well established optical devices used to correct refractive errors. Higher-order aberrations are complex flaws in an optical system, such as the eye, which cannot be fully corrected using conventional contact lenses or spectacles. This section describes in detail the methods used to describe and measure higher-order aberrations.

2.1 The higher-order aberrations of the eye

Recent advances in optics allow the measurement and correction of higher-order aberrations in addition to lower-order aberrations such as sphero-cylindrical refractive error. The correction of higher-order aberrations was first suggested by Smirnov (1962), who explained that the eye is not a ‘perfect’ optical system. Ocular aberrations are divided into chromatic and monochromatic aberrations. Chromatic aberrations are of longitudinal and transverse forms; arising as red and blue light are focussed at different points due to their difference in wavelength. The most commonly known monochromatic aberrations, in clinical terms, are the ‘Seidel’ aberrations which comprise of distortion, oblique astigmatism, field curvature, coma and spherical aberration (Atchison and Smith, 2000).

2.2 Wavefront aberrations

Ocular aberrations are described by either ‘ray’ or ‘wave’ optics. It is widely accepted that light does not travel in straight lines as geometrical ray optics may suggest. It is more likely to travel in radiating waves emanating from an energy source (Charman, 1991), similar to a stone being thrown in water with the ripples (waves) travelling outwards from where the stone hits the water.

A ‘wavefront’ can thus be described as a surface over which an optical disturbance leaves its’ source; the surface will essentially connect all the different points on the propagating light wave that have an equal phase. If the source is a point, then the wavefront will typically be spherical, however if the source is not a succinct point then the wavefront can take on a whole manner of different shapes, for example it can be planar (straight line), as well as anything in between planar and spherical. The shape of the wavefront can also be altered if the emanating waves hit an irregular refractive surface (Atchison, 2004). This is often referred to as an ‘aberrant’ wavefront. Wavefront aberration, refers to the difference in separation between two surfaces; the ‘ideal’ plane and the ‘aberrant’ wavefront (Thibos et al., 2003a). The larger the separation between these two surfaces, the greater the magnitude of the wavefront aberration. Differences in the separation of these two surfaces at the retina will mean that aberrations cause a detrimental effect on visual performance such that the larger the wavefront aberration, the poorer the optical image quality. These differences in separation between wavefront surfaces are measured in microns (µm).

The effect of aberrations on visual performance depends on several factors, including pupil size and the wavelength of the light. At pupil sizes smaller than 3 mm, higher-order aberrations will show a less detrimental effect on optical quality (Campbell and Green, 1965,
Campbell and Gubisch, 1966, Walsh et al., 1984). Lord Rayleigh’s (1910) ‘quarter wavelength rule’ suggests that, if the wavefront aberration of an optical system is less than a quarter of the wavelength of the light entering the system, then the image would be similar to that of a ‘diffraction-limited’ (i.e. near perfect or ‘aberration-free’) system.

2.3 Zernike polynomials

Wave aberrations are fitted with a mathematical modelling system to help describe their often complex shapes across the pupil (Zernike, 1934). The OSA (Optical Society of America) recommends describing higher-order aberrations using Zernike decomposition polynomials (Thibos et al., 2000, Thibos et al., 2002a). Each Zernike polynomial coefficient term is arranged and recognised by two features; its angular frequency and its radial order (Equation 2.1). The coefficient values have both a magnitude and a sign which describes how that particular term makes up a certain proportion of the total wave aberration. The coefficients can tell us the variation in magnitude for each Zernike term used to describe the aberrations. These properties have made Zernike polynomials very attractive in optics. The ordering system for Zernike polynomials starts from 0 (the 0th order) upwards. Most aberrometers can calculate Zernike coefficients up to the 6th radial order.

The values for ‘piston’ (the 0th radial order coefficient term) and ‘tip’ and ‘tilt’ (the 1st radial order coefficient terms) are usually ignored when analysing aberrometry data for normal and abnormal eyes. This is because these terms relate to the displacement of the image only, consideration of these with respect to image quality is therefore usually not relevant (Applegate et al., 2001, Thibos, 2001, Thibos and Applegate, 2001, Applegate et al., 2002, Iskander et al., 2002, Thibos et al., 2002a, Charman, 2005a). Another useful property of Zernike aberrations are that some of the coefficient terms of the Zernike polynomial expansion series are related to known types of optical aberrations such as defocus and astigmatism (2nd-order), coma (3rd-order), and spherical aberration (4th-order) (Noll, 1976).

Equation 2.1 Total wavefront aberration $W(\rho, \theta) = \sum_{n}^{k} \sum_{m=-n}^{n} C_n^m Z_n^m(\rho, \theta)$

Where,

- $n =$ Radial order (the vertical axis of the Zernike pyramid)
- $m =$ Angular frequency (the horizontal axis of the Zernike pyramid)
- $Z =$ Zernike polynomial term (which represents the shape of the distorted wavefront)
- $C =$ Zernike coefficient (the proportion of the polynomial present in the subject’s eye)
- $k =$ the polynomial order of the expansion
- $\rho =$ the normalised radial distance in the pupil, i.e. $\rho = r/r_{\text{max}}$, where $r_{\text{max}}$ is the maximum pupil diameter for the measured wavefront aberration, and $r =$ radial co-ordinate in the pupil
- $\theta =$ the Azimuthal angle
For Equation 2.1,

a) \( m \leq n \)

b) Positive ‘m’ = \( \cos \theta \) (on the right hand side of the pyramid), negative ‘m’ = \( \sin \theta \) (on the left hand side of the pyramid)

c) \((m - n)\) must always be an even number

d) \( m \) is the number of cycles of sinusoidal variation across 360 degrees

e) \( \rho \) = relative radial co-ordinate; this is a value between 1 and 0

f) \( \theta \) = Angular component (from 0 to 360 degrees)

g) When \( n=0 \), we see rotational symmetry (i.e. for defocus, spherical aberration etc.)

When normalised, by the recommended OSA system, Zernike polynomials are orthogonal, in that they allow us to look at each individual term independent of any other polynomial (Thibos et al., 2000). This is not possible with sphero-cylindrical combinations because the two measurements are intrinsically linked with each other. However, Zernike polynomials are only orthogonal within the unit circle. In these trigonometric-type functions, the unit circle is defined as a circle with a radius of unity (1) which is centred at the origin (0, 0) in the Cartesian coordinate system. It is important to note that Zernike polynomials are not orthogonal over a discrete and finite circle, such as a pupil of a given size (He et al., 1998, Guirao and Artal, 2000).

The Zernike expansion shows us that a given wavefront is composed of individual error coefficients and allows one to investigate a particular terms’ influence on the total RMS (root mean square) error. The total RMS error is the sum (linear combination) of the coefficient components of the wave aberration in root mean square form, over the pupil aperture, as defined in Equation 2.2.

**Equation 2.2**

\[
\text{RMS (root mean square) error} = \sum \sqrt{(C_{m}^{n})^2}
\]

The total RMS error of the ‘higher-order’ aberrations is the vector sum of all the terms from the 3rd radial order and above. The RMS error value allows a brief comparison between different eyes, but the limitation of the RMS error is that it only gives a single number, which does not give information about the precise shape of the wave aberration. Additionally this number is not directly linked to retinal image quality (Marsack et al., 2004).

The Zernike pyramid (Figure 2.1) provides a useful diagrammatic approach to the systematic method of ordering the different Zernike polynomial aberration terms used to describe these complex optical flaws of the eye. As we go further down the Zernike pyramid (past the 2nd-order), we move to the components known as the higher-order aberrations. Figure 2.1 shows that the higher the Zernike order, the more complex the shape of the coefficient term’s wavefront. For example, if we compare the simple wavefront shape of 2nd-order sphere with the more complex wavefront shape of 5th-order secondary coma. This is also the case as we move from the centre of the pyramid laterally towards its edges (i.e. moving from a low angular frequency to a higher angular frequency).
Research has shown that in the normal population most aberrations after the 6th Zernike order are almost zero in magnitude and therefore will not contribute significantly towards determining the retinal image quality achieved (Porter et al., 2001, Castejón-Mochón et al., 2002, Thibos et al., 2002b, Thibos et al., 2002c). Hence Atchison (2004) suggested that for normal eyes, only Zernike terms up to the 6th-order are needed to approximately describe the overall wavefront aberration manifested. The aberrations measured by modern aberrometers are normally depicted in pictorial form using coloured contour maps. Different colours are used to portray positive, negative and neutral aberrations, as shown in Figure 2.2.

Figure 2.1 A pictorial representation of the Zernike pyramid from the 2nd up to the 5th radial order (Zernike, 1934). The red colours here represent positive aberrations, and the blue colours represent negative aberrations.

Figure 2.2 A pictorial power representation of 3rd-order negative vertical coma (Z_{3}^{-1}) from the topographical data of a keratoconic eye (Bühren et al., 2007). The red colours show positive aberration and the blue colours show negative aberration. On this map, the contours join points in the pupil which have the same amount of wave aberration. With vertical coma one should note the difference in aberrations inferiorly and superiorly; in keratoconus the cornea is generally thinner and steeper inferiorly.
2.4 Measurement of ocular aberrations

Smirnov (1962) first suggested the correction of higher-order aberrations using contact lenses. Smirnov's initial experimental setup involved placing a disc very close to the eye (Scheiner, 1619). This disc was opaque with two pinholes at a fixed distance from each other. One of the two pinholes was directly in the centre of the disc; this was known as the reference pinhole. The second pinhole was positioned in the mid-periphery of the disc. The subject was asked to look at a distant point source through the reference pinhole, whilst another ‘mobile’ point source was shone through the second pinhole. Initially this would result in two point images falling on two different parts of the retina, resulting in the subject seeing two lights. The ‘mobile’ point source was then moved by the operator (through positions X and Y in space), whilst still passing through the second pinhole of the disc, until the subject reported that the two lights had married up as a single point image. The spatial displacement of the 'mobile' light source ($\delta X$, $\delta Y$) gave a measure of the ocular aberration at that given pupil point. These measurements were then repeated for different locations within the pupil. Using this ‘subjective aberrometer’, Smirnov (1962) was the first to report that eyes with larger pupils had larger magnitudes of higher-order aberrations than eyes with smaller pupils. Measurements using this technique were laborious for both the examiner and subject.

The next major development was that of an ‘objective’ method to measure aberrations. Berny and Slansky (1970) modified the Foucault knife-edge method (used originally to determine the optical quality of mirrors and lenses) to enable its use as an ophthalmoscope for measurements of the eye. This is where a knife-edge slit source is imaged onto the retina, and the light reflections out of the eye are photographed (similar to retinoscopy). These pictures displayed how higher-order aberrations influenced the distribution of the light reflections across the subject's pupil. Data analyses involved careful scrutiny of all the negatives, in a process which took several hours for the examiner.

Howland and Howland (1977) modified the original Tscherning's (1894) spherical + 5.00 DS aberroscopic method, by using a cylindrical ± 5.00 DC cross-cylinder. Howland and Howland (1977) inserted a grid in between the two lenses. This device was then used to view a point source. The retinal image of the grid was then compared with the actual target grid; any distortions suggested that aberrations were present in the eye under investigation. However, for these comparisons to be made, Howland and Howland (1977) had to rely on the patients' subjective responses in order to measure and calculate how much distortion of the grid had occurred; thus taking measurements was a time-consuming process. Nonetheless, Howland and Howland (1977) were the first to measure the comatic aberrations of the eye.

Walsh and colleagues (1984) further advanced Howland and Howland’s (1977) method, by adding a beam splitter and a camera into the setup, thus allowing a rapid and objective method of acquiring the data. Nevertheless, computation and analysis of the data were still time-consuming. Furthermore, Walsh et al. (1984) were the first to introduce Zernike polynomials; until this point Taylor polynomials were used to describe aberrations. Although useful, Taylor's polynomials are not orthogonal and require all data to be recalculated for simple tasks, such as investigating the effect that a change in pupil size or accommodation might have on a given coefficient term.
Webb and co-workers (1992) further developed Smirnov’s (1962) technique, by sending two beams of light into the pupil at a given time; the first into the centre (reference) and the second to scan the outer pupil area (this second beam entered only a small section of the pupil at a time). The subject then moves this second beam until the two beams intersect, giving a single image. Measuring the angular displacement of the second beam from the reference beam at different pupil positions allows the measurement and calculation of wave aberrations. Webb et al.’s (1992) data suggested that this method was highly repeatable.

The next major development, by Liang and associates (1994), was that of the Hartmann-Shack aberrometer (described further in section 2.5). To enable ocular measurements, modifications were made to the set-up of the initial Hartmann-Shack device that was originally used for measuring atmospheric properties (Platt and Shack, 2001). Laing et al. (1994) described objective measurements using this device on two normal human eyes with computation of wave aberrations using Zernike polynomials up to the 4th-order; this included the primary aberrations such as coma, spherical aberration and secondary astigmatism.

Another method to obtain ocular aberration data is via Laser-Ray Tracing (LRT) (Navarro and Losada, 1997). Briefly in LRT, parallel pencils of laser rays are sequentially sent into the pupil in a series of steps using multiple sample rays in a hexagonal arrangement. For a given pencil of ray beams, the eye’s local aberrations will cause a focal shift of the retinal images with respect to the ‘chief’ ray. The instruments scanners are then used to move the laser to sequentially fire more pencils into different pupil entry positions, until a spread of aberration measurements are made for the whole of the pupil. During the scan, the light reflected off the retina passes back through the optics of the eye and forms an image of the retinal spot, which is captured onto a linear array of photo-detectors. The image spot location, at the detector is used to determine the slope of the WA of the eye under measurement.

Ocular aberrations can also be evaluated using the Tscherning principle (Tscherning, 1904). Mrochen et al. (2000a) further improved upon Walsh et al.’s (1984) technique and developed the modern-day Tscherning aberrometer (Allegretto Wave Light Analyser aberrometer; Alcon, Ft. Worth, Texas, US). With this technique a ‘dot pattern’ mask creates a series of equidistant spots of light (from a Nd-YAG laser at 660 nm) in the pattern of a grid, which are then projected through the pupil onto the retina. The image of the grid spot pattern is formed on the retina using an aberroscopic lens, which sufficiently enlarges the retinal spot pattern to help separate and identify the single spots. The retinal image of the grid spot pattern is then photographed by means of a charge-coupled device (CCD) sensor using the principle of indirect ophthalmoscopy. Each real spot position taken from the retinal image is compared to its corresponding ‘ideal’ spot position, which is calculated using a Gullstrand model eye. From the resulting ray deviations, the wavefront aberrations are mathematically reconstructed into Zernike polynomials.
2.5 Principles and repeatability of the Hartmann-Shack method

The Hartmann-Shack principle is the most commonly employed method for measuring ocular aberrations (Thibos et al., 2003a, Atchison, 2004, Charman, 2004, Charman, 2005a). The device uses a grid of micro-lenslets, each of which independently observes a laser ray projected onto the retina (Liang et al., 1994). The principles of Hartmann-Shack aberrometry are shown schematically in Figure 2.3. Here light (near the infrared range) is sent into the eye and the reflection off the retina outwards is focussed by the linear micro-lenslet array onto a CCD sensor. Before the micro-lenslet array, there are relay lenses which help to focus the 'immediate' light leaving the pupil plane (Platt and Shack, 2001). The Hartmann-Shack system employs many apertures, each corresponding to the face of a tiny lenslet which focuses the emerging pencil of rays onto the image sensor. The micro-lenslet array subdivides the reflected wavefront of light emerging from the eye into a large number of smaller wavefronts, each of which is subsequently focused to a small spot on the sensor. The spatial displacement ($\Delta x$, $\Delta y$) of each spot image 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. Mathematical integration of these slope measurements, by subsequent computer processing of the captured images, reveals the overall shape of the aberrated wavefront. These slopes are then fitted with a Zernike polynomial where the wave aberration is computed using a ‘least-mean square’ fitting procedure. The ‘ideal’ eye would show a perfect lattice with a regular array (Figure 2.3 B), whereas aberrated eyes show an irregular pattern of dots at the CCD sensor (Figure 2.3 C). Several authors have reported that these measurements can prove to be more difficult in patients with keratoconus (Thibos and Hong, 1999, Munson et al., 2001).

Previous studies have attempted to assess the repeatability of aberrations measured using the Hartmann-Shack technique. Repeatability is a measure of precision and is defined as the closeness of the agreement between the results of successive measurements of the same measureand carried out under the same conditions of measurement (McAlinden et al., 2011a). In these studies aberration measurements are usually made over a short period of time using the same instrument and observer. Liang and Williams (1997) measured the eyes of three normal subjects and reported that measurements were highly repeatable with a mean standard deviation approaching Maréchal’s (1947) criterion of $\sim \lambda/14$, i.e. $\sim 0.046 \mu m$ (defined later in section 2.14.5). When evaluating the aberrations of trial lenses, Liang and Williams (1997) report that the mean standard deviation was found to be approximately 35 times smaller (at $\sim \lambda/487$) than the mean standard deviation of a real eye. The data presented suggested that their custom-built Hartmann-Shack device had good repeatability. The accuracy of the lower-order or power measurements of the trial lenses showed only a small difference of $\pm 0.17$ DS (over an 8.00 DS range). Liang and Williams (1997) discussed that changes in accommodation, the tear film and small eye movements (fixational) may play an important role in potentially hindering the repeatability of aberration measurements made for the human eye. However, the authors did not analyse the effect of any of these factors in their study.
A) The lenslet array is focused into the plane of the pupil by relay lenses in order to measure the shape of the wavefront as it leaves the eye’s pupil.

B) A micro-lenslet array subdivides the wavefront into multiple beams. The local slope of the wavefront over each lenslet aperture determines the location of the spot on a video CCD sensor (the image shows an ‘ideal’ eye).

C) An aberrated wavefront produces an irregular pattern of spots on the video sensor. Displacement of each spot from the corresponding lenslet axis is a measure of the slope of the wavefront (the image shows an aberrated eye).

**Figure 2.3** The principles of a Hartmann-Shack aberrometer (Thibos, 2000).

Cheng and colleagues (2003b) assessed the repeatability of aberration measurements using the Complete Ophthalmic Analysis System (COAS) Hartmann-Shack aberrometer (Wavefront Sciences, Albuquerque, N.M., U.S.), using model eyes (simulating 3rd- and 4th-order aberrations) and trial lenses (simulating 2nd-order aberrations). Their results showed very small absolute mean differences between the measured and actual amounts of aberration for spherical aberration (± 0.007 μm), coma (± 0.007 μm) and off-axis astigmatism (± 0.004 μm) in their model eyes, suggesting that their device demonstrated a high degree of precision. The authors also investigated the tolerance of their Hartmann-Shack aberrometer to possible instrument-eye
misalignment. The results showed that there was some tolerance to slight positional
displacements (both axially and laterally) in model eyes and in a normal human eye without
inducing noticeable higher-order aberration. The axial misalignments (of ± 2 mm) were tested in
two models eyes (one emmetropic and one with 4.00 DS of myopia). The data showed that this
range of axial displacement did not induce any noticeable 2nd-, 3rd- or 4th-order aberrations.
Lateral displacement measurements were made for two model eyes and for one normal human
eye. The model eyes included an emmetropic model eye and a model eye with +0.25 μm of
spherical aberration. The data showed that within the range of ± 0.5 mm from the centre of the
pupil, 3rd–order aberration measurements were stable – i.e. this range of lateral displacement did
not induce any noticeable coma aberration. In summary, Cheng et al. (2003b) suggested that
their Hartmann-Shack aberrometer showed high repeatability even amid axial and lateral
misalignment induced by an operator.

Mirshahi et al. (2003) measured 40 normal and two model eyes (one myopic and one
hyperopic – both were aberration and astigmatism free) in order to assess the repeatability of
aberration measurements using the ZyWave Hartmann-Shack aberrometer (Bausch & Lomb,
Rochester, N.Y., U.S.). The authors used the device’s internal software to calculate an objective
refraction value from the 2nd-order aberration coefficients, called the predicted phoropter
refraction (PPR), and compared its repeatability over multiple measurements. Mirshahi et al.
(2003) found that cylindrical prescriptions had greater variability than spherical prescriptions, and
that the smaller cylindrical powers (< 0.50 DC) showed the greatest variability in cylinder axis
measurement. Measurements of higher-order aberrations (up to the 5th-order) were also
repeated and evaluated. The authors reported that the higher the radial order, the smaller the
absolute values of the coefficients, hence the greater the repeatability error. Given that the
population average for the total higher-order aberrations is negligible (Porter et al., 2001, Thibos
et al., 2002b, Thibos et al., 2002c), this result was predicted by Mirshahi et al. (2003), who also
suggested that the correction of low magnitude, higher-order aberrations will always be
challenging because they are difficult to measure in the first instance. All the participants in
Mirshahi et al.’s (2003) study were myopic only, the repeatability in hyperopic patients was not
explored in this study.

Davies et al. (2003) reported significant differences for several Zernike modes between
three sets of 20 repeated measurements using a custom-built Hartmann-Shack aberrometer in
nine normal subjects. The authors repeated their three sets of measurements using a dental bite
bar both with and without pupil-instrument realignment. Davies et al. (2003) discussed that a
combination of small instrument-pupillary misalignment errors, short-term variations in the actual
ocular aberrations (such as tear film changes and accommodative fluctuations) and small drifts in
the measuring equipment were the main causes of their observed variability.

In contrast, Hofer and associates’ (2001) study of three normal subjects suggested that
small eye movements were not the main source of fluctuations in the eyes’ wavefront aberrations.
The authors investigated higher-order aberrations with both natural and paralysed
accommodation using a custom-built Hartmann-Shack aberrometer. The results showed that the
temporal power spectrum shape for higher-order aberrations was different from that of the micro-
fluctuations of accommodation. The origin of the measured fluctuations in higher-order
aberrations was not determined in this report; however, the authors discussed that they could not exclude corneal/lenticular and retinal changes between measurements as likely possibilities. Finally, Hofer et al. (2001) reported no significant difference in the magnitudes of higher-order Zernike coefficient terms between natural-accommodation and cycloplegic states.

Cheng et al. (2004c) used the COAS Hartmann-Shack aberrometer to measure the variation in absolute values of individual coefficient terms, as well as the total RMS error over four different time scales in four normal subjects. The time scales included five consecutive measurements over one second; five sets of five measurements over one hour, five sets of five measurements over one week and finally five sets of five measurements over one year. The authors used the metric of wavefront variance (discussed in section 2.14.6) which is a measure of dispersion that quantifies the average standard deviation between the aberrant wavefront and the ideal wavefront. Cheng et al. (2004c) reported that three out of four eyes had a larger variability in repeated measurements over the longest time span of approximately 10 months (variance = 9.7x10^{-4} \text{ μm}^2) when compared to the shortest time span of one second (variance = 8.1x10^{-5} \text{ μm}^2). This study indicated that the optical fluctuations of the human eye are larger over longer time scales, which includes not only all the fluctuations that exist in shorter time scales, but also fluctuations that may reflect genuine long-term changes in the eye's optics. In contrast to this, Miranda et al. (2009a) reported no clinically significant differences between the initial ocular aberrations measured in 23 visually-normal subjects and repeated measurements made 59 ± 24 seconds, 1.10 ± 0.24 hours and 7.11 ± 0.31 days later. The authors used a commercially available Hartmann-Shack aberrometer in their report (IRX-3; Imagine Eyes, Paris, France). The authors' data analysis, using Bland and Altman plots, showed that measurements made with the IRX-3 device were highly repeatable over the times tested and that ocular aberrations remained stable over these time periods.

Nevertheless, Cheng et al. (2004c) suggested that any variability in aberrations found over a short timescale could be overcome by averaging multiple readings of the aberrations over a short timescale. Compared to measurements made on model eyes, their human eye data showed larger discrepancies upon repetition. It is worth noting that between each set of repeated measurements the model eyes were repositioned by the operator; similarly the instrument was realigned to each subject’s eye each time too. For the measurements made over the one-second time span, the model eye data showed a wavefront variance of 1x10^{-6} \text{ μm}^2, whereas human eyes showed a variance of 81x10^{-6} \text{ μm}^2. The authors proposed that accommodation, small eye movements and variations in the tear film were perhaps important factors in hindering the repeatability of aberration measurements in human eyes. Put more simply, aberration correction in visually-normal eyes equates to attempting to correct a constantly fluctuating value.

Efron et al. (2008) reported that the IRX-3 Hartmann-Shack aberrometer showed a ‘within-observer’ repeatability of 0.082 μm in 13 normal eyes, from three measurements made over 60 seconds, without their habitual contact lenses in place. This repeatability score was derived using the ‘within-observer’ standard deviation value, S_{WO} (calculated as the square root of the average variance). A high repeatability is usually expressed by a low absolute value of within-observer standard deviation. In contrast, Cheng et al. (2004c) reported a repeatability of 0.009 μm in four normal subjects from five measurements, made over one second, using the
COAS aberrometer. The difference in repeatability between these two studies is possibly explained by differences in pupil size as well as the difference in the time periods over which the measurements were made. Cheng et al. (2004c) used a diluted 6-mm pupil, whereas Efron et al. (2008) used an un-dilated 4-mm pupil. It may be argued that the smaller the pupil size used, the smaller the absolute magnitude of the higher-order aberrations measured and therefore the poorer the repeatability, as found by Efron et al. (2008).

In summary, several studies have demonstrated the repeatability of the Hartmann-Shack technique in studies of human (Liang et al., 1994, Liang and Williams, 1997, Hong et al., 2003, Mirshahi et al., 2003, Miranda et al., 2009a) and model eyes (Cheng et al., 2003b, Mirshahi et al., 2003), whilst others report short-term variability in ocular aberrations (Hofer et al., 2001, Davies et al., 2003, Cheng et al., 2004c). Variability in aberrations may result from changes in accommodation (Cheng et al., 2004c), small fixational eye movements (Cheng et al., 2004c) or even fluctuations in the tear film (Hofer et al., 2001, Cheng et al., 2004c).

In another study, Rae and Price (2009) investigated how aberrations altered with and without soft contact lenses for 23 visually-normal, soft lens wearers. The contact lenses used were identical for each participant (Daily disposable lens; Neofilcon A; BC: 8.6; TD: 13.8: power: -1.00 DS). Using the COAS aberrometer, 10 repeated measurements were taken two seconds after blinking for each subject. These measurements were firstly made without lenses and then with the lenses in place approximately five to 15 minutes after insertion. The authors found that the mean magnitudes of the 3rd-order RMS and 5th-order RMS errors increased with contact lens wear, yet no change was found for 4th-order RMS error – 3rd-order RMS: from 0.42 to 0.52 µm; 4th-order RMS: from 0.20 to 0.20 µm; 5th-order RMS: from 0.06 to 0.11 µm. However, only the increase in the 5th-order RMS aberrations was found to be significant (p = 0.009). In this study, the repeatability of aberrations was investigated using standard deviation values. The authors report that the standard deviations of the Zernike coefficients Z(5,-5), Z(5,1) and Z(5,3) increased significantly with contact lens wear (p ≤ 0.003). Rae and Price (2009) concluded that precise assessment of higher-order aberrations may potentially be complicated by contact lens wear in normal subjects.

2.6 Comparing the LRT and Hartmann-Shack methods

Both Moreno-Barriuso and Navarro (2000) and Moreno-Barriuso et al. (2001) compared the LRT technique to the Hartmann-Shack method. The authors found that both methods gave repeatable results on normal human eyes and model eyes. Moreover, the LRT method also gave comparable results to the Hartmann-Shack method for measurements performed with trial lenses and phase plates, (Navarro and Moreno-Barriuso, 1999).

However, each technique does have its own limitations. As expected, Moreno-Barriuso et al. (2001) found that the Hartmann-Shack method of sampling aberrations was limited by the lenslet array’s geometry, which leads to image indexing problems when evaluating highly-aberrated eyes (discussed in detail in section 3.4). Disadvantages of the LRT method include longer acquisition and data computation times (due to limitations in the number of rays entering the eye per second). The longer measurements take, the greater the inaccuracies with respect to
‘time-related’ factors such as small eye movements, accommodation micro-fluctuations, tear film variations and eye-laser-scanner movement. In general, the LRT method uses fewer measuring points in comparison to the Hartmann-Shack method (Thibos, 2000, Moreno-Barriuso et al., 2001), perhaps reducing precision and accuracy. Of the two methods compared, Moreno-Barriuso et al. (2001) suggested that the LRT method could be more accurate at measuring highly-aberrated eyes as the laser scanner can be programmed for any desired sampling pattern. However the authors made these assumptions about highly-aberrated eyes based on measurements from only 2 visually-normal subjects.

Moreno-Barriuso and Navarro's (2000) data, collected from artificial eyes, suggested that the LRT method causes less spot image blurring at larger pupil sizes than the Hartmann-Shack technique. The pupil sizes compared for the Hartmann-Shack measurements were 0.7, 3.0 and 6.0 mm. Moreno-Barriuso and Navarro (2000) described that an increase in pupil size from a 0.7 to a 6.0 mm in diameter resulted in a 17% rise in total RMS error. However, the LRT measurements were made using pupil sizes increasing from 3.0 to 6.0 mm only, which gave just a 4% rise in total RMS error. Although it would have been useful for a better comparison, the authors did not provide the change in aberrations when increasing the pupil size from 3.0 to 6.0 mm using the Hartmann-Shack method. By using only a 3-mm pupil size range for LRT, it could be argued that the authors were bound to find less spot blurring compared to the 5.3-mm pupil size range used for the Hartmann-Shack method; as increasing the pupil size naturally increases the measured image blur (Charman, 1999).

### 2.7 Corneal topography and deriving corneal aberrations

The anterior corneal surface is responsible for ~70% of the power of the unaccommodated eye (Tscherning, 1904). Corneal topography measures the surface shape of the cornea; the fundamental measures of the surface characteristics of the cornea are elevation (or height), slope and curvature data (Turner, 2001). Elevation data measure the corneal height (position in space) relative to some close-fitting reference surface. Slope data measure the orientation of tangential and normal lines with respect to the surface point (Figure 2.4). Curvature data measure the ‘bending’ of the cornea and are inversely proportional to the radius of curvature.

The American National Standards Institute (1999) has defined the ‘keratometric dioptre’ (D) to be a unit of curvature, not optical power. Their standards in corneal topography define an inverse millimetre of curvature equal to 337.5 keratometric dioptries (e.g. an 8 mm radius sphere has a curvature of 42.19 D (= 337.5 / 8)).
Figure 2.4 An illustration of corneal height, slope and curvature. This meridional section through a prolate surface (such as the anterior cornea) illustrates the geometric constructs required to determine the height, slope and curvature of the surface point $P$. The normal line is perpendicular to the surface; it passes through the local centre of curvature, defined by an osculating circle that best fits the sectioned surface at $P$. Height is the three-space position of $P$ (in $\mu$m). Slope refers to the orientation of the tangent line through $P$. Curvature equals the reciprocal radius of the osculating circle. Adapted from Turner (2001).

Although at one time curvature was regarded to be the most important factor when evaluating the cornea (as it is proportional to the paraxial power of a surface), it has now been superseded by elevation data (Turner, 2001). The typical output from a topographer, with regard to corneal elevation data, is in the form of a residual map, which is a plot of the difference between the reference surface and the corneal topography proper (Figure 2.5). The corneal elevation data are considered to be made up of two important components: the reference surface, plus the residual corneal height data. The reference surface describes the regular properties of the cornea, whereas the residual elevation data describe the irregular variations in the corneal structure (Schwiegerling and Greivenkamp, 1997). The maps typically outputted by corneal topographers display the remaining elevation data once a regular best-fitting sphere, or BFS, (a hypothetical spherical surface that matches as closely as possible to the actual corneal profile being measured) is subtracted from the corneal height data. The BFS essentially provides a mathematical way of describing the corneal surface by defining the distance of each elevation point from the reference plane. Most topographers compare the ‘real’ corneal surface to this hypothetical sphere, highlighting areas that are located either ‘above’ ($+\mu$m) or ‘below’ ($-\mu$m) the BFS (Figure 2.5). This BFS method has been shown to improve measurement repeatability against eye movements compared to the Placido method (Módis Jr et al., 2004).
Figure 2.5 The elevation maps of the front (left) and back (right) surface topography data of an eye with moderate keratoconus using the Oculus Pentacam (Oculus, Wetzlar, Germany) – all values shown are in µm. The bluer coloured areas, with + values, represent points above the best fit sphere (BFS), the redder coloured areas, with – values, represent points below the best fit sphere.

A description of corneal higher-order aberrations can be derived from such topographical data using the following methods,

A. Optical Path Length (OPL) ray-tracing

As described above, corneal elevation difference maps represent the distance of a given point on the corneal surface to the reference plane; videokeratoscopes provides a finite number of elevation points from the topographical data captured. The anterior surface corneal wavefront aberration, $W$, can be calculated from the corneal elevation data at each point in the pupil, as the difference in optical path length (OPL) between the principal ray that passes through the centre of the pupil and a marginal ray (Equation 2.3), as represented in Figure 2.6:

Equation 2.3

$$W = nz + (n'd' - n's'),$$

from (Guirao et al., 2002b)

Here $n$ and $n'$ are refractive indices and $d'$ and $s'$ are distances from the cornea. $z$ represents the distance between the cornea and the aberrant wavefront.

The overall anterior surface corneal wavefront aberration can therefore be represented as a weighted sum of the Zernike polynomials, as defined in Equation 2.4, where each Zernike coefficient, $C_n^m$, represents an individual aberration term (Guirao et al., 2002b).

Equation 2.4

$$W(r, \theta) = \sum_{n} \sum_{m=-n}^{n} C_n^m Z_n^m(r, \theta)$$
Where,

- \( n \) = Radial order (the vertical axis of the Zernike pyramid)
- \( m \) = Angular frequency (the horizontal axis of the Zernike pyramid)
- \( Z \) = Zernike polynomial term (which represents the shape of the distorted wavefront)
- \( C \) = Zernike coefficient (the proportion of the polynomial present in the subject’s eye)
- \( k \) = the polynomial order of the expansion
- \( r \) = the radial co-ordinate in the pupil
- \( \theta \) = the Azimuthal angle

In similarity to corneal elevation data, all wavefront aberrations are also specified with respect to an ‘ideal’ reference plane. The OPL technique allows corneal aberrations to be described by considering the differences in OPL between the actual wavefront and the ideal wavefront (Turner, 2001). Thus topographers can use ‘distance’ measurements, in the form of elevation changes at the corneal surface, to analyse the cornea’s optical performance instead of curvature or slope data. For the corneal first surface, the ideal reference plane would be the wavefront that, when combined with the rest of the eye’s optics (corneal back surface and both surfaces of the crystalline lens), creates an aberration-free image of the object of interest at the fovea.

![Figure 2.6](image)

**Figure 2.6** The ray-tracing procedure used to estimate the corneal aberrations \( (W) \), which are computed as the differences in optical path length between the marginal and principal rays (adapted from Villegas et al. (2008)).

X, Y, and Z represent the coordinate axes at the corneal surface; \( r \) (pupil radius) and \( \theta \) (angle), radial coordinates of an arbitrary point at the exit pupil of the eye; \( n \) and \( n' \), refractive indices; and \( z, d', \) and \( s' \) distances.

**B. ‘Remainder lens’ technique**

A simpler technique to derive corneal aberrations is to create a ‘remainder lens’, by subtracting the best-fitting ‘conic’ surface away from the measured corneal curvature. This produces the corneal elevation difference map, which is then multiplied by the refractive index differences (i.e. between air (1.00) and the cornea (1.376), and cornea and aqueous humour (1.336)) (Schwiegerling and Greivenkamp, 1997, Smolek and Klyce, 2003). Although this method allows the calculation of Zernike polynomials, this simplistic approach can neglect some important aberration terms (Guirao and Artal, 2000).
2.8 Instrumentation methods to measure corneal aberrations

The difference between the aberrated wavefront and the reference wavefront, as a function of the exit pupil location, defines the corneal aberration structure. As a matter of convention, wavefront error is set to zero at the centre of the exit pupil. Typically, the difference between the two wavefronts is plotted as a contour map or, for a more quantitative representation, fitted with Zernike polynomials. For corneal first surface optics only (as opposed to the eye’s optics), the exit pupil is placed at the corneal first surface. However, for most topographers the centre of the exit pupil is centred on the eye’s natural pupil as measured by the topographer.

2.8.1 The Placido disc method

Early computer-based methods of attempting to measure corneal dioptric topography used Placido concentric rings (Placido, 1880). Instruments which use this technique include the EyeSys (EyeSys Vision, Houston, T.X., U.S.); TMS-1 (Tomey Technology, Cambridge, M.A., U.S.), Orbscan I (Bausch and Lomb, Rochester, N.Y., U.S.) and the MasterVue Humphrey Atlas corneal topographer (Zeiss-Humphrey, Dublin CA, U.S.). The Placido rings method can only measure anterior corneal curvature (and aberrations). This method does not measure the actual ‘elevation’ directly, but derives it from mathematical computation of curvature data (Applegate et al., 1995). The general technique uses a series of illuminated annular rings projected onto the central 4 mm of the cornea under investigation. Using the anterior tear film as a mirror, the reflected image of these rings is captured by a digital video camera. The captured images are then subjected to a computer algorithm to detect and identify the position of the rings in order to measure the curvature of the cornea (i.e. closely packed rings indicate a steep cornea). So called ‘elevation’ maps are calculated using a co-ordinate system from the curvature data (Liu et al., 1999). The Placido ring method assumes that the corneal apex, videokeratoscopic axis and the line of sight are all the same. As this is not usually the case, descriptive errors using Placido ring-based measurements may occur, where normal eyes may appear to have corneal ‘irregularities’ simply due to eye misalignment/poor fixation (Belin and Holladay, 2007).

2.8.2 Slit scanning method

The Orbscan II (Bausch & Lomb, Rochester, N.Y., U.S.) combines slit-scanning and the Placido rings method, in order to improve the accuracy of topography measurements and allow collection of ‘actual’ height data from the cornea. The slit-beam scanner uses direct stereotriangulation to derive the spatial location of thousands of points on the corneal surface. This technique works by using a slit light source to cause reflections off the cornea. By observing the reflected light (using a high resolution camera) and knowing the positions and orientations of both the camera and the light source, it is possible to determine the distances between the reflected points, the light source and the camera. By ‘sweeping’ the light source (and the camera) across the cornea, a sequence of corneal depth profiles can be generated. Measurements from both the anterior and posterior corneal surfaces are thus possible; the device describes corneal surface data using the BFS method. Pachymetry data can also be derived from the Orbscan II, however...
the instrument has been found to underestimate the corneal thickness compared to the ‘gold standard’ of ultrasonic pachymetry (Kawana et al., 2004).

2.8.3 Scheimpflug imagery

The Oculus Pentacam (Oculus, Wetzlar, Germany) uses Scheimpflug photography to derive the topography of the anterior and posterior corneal surfaces from elevation data (Dubbelman et al., 2001). Once the corneal height data have been measured, the Pentacam generates a three-dimensional mathematical model of the cornea. This model is then used to derive further information. The Pentacam generates elevation data with respect to a ‘reference body’. The reference body can be changed depending on the requirement; it can be ellipsoid, toric ellipsoid or a BFS type. Belin and Holladay (2007) have discussed that compared to a BFS shaped reference body, the toric ellipsoid-shaped reference body may allow a more accurate detection of shape irregularities on a prolate surface such as the human cornea. The authors suggested that this is perhaps advantageous in giving a more accurate detection of ‘forme fruste’ or ‘suspect keratoconus’.

The Pentacam provides corneal wavefront analysis for both surfaces based on the measured corneal elevation data using ray-traced OPLs (Guirao et al., 2002b). The coefficients for the respective Zernike polynomials are calculated using the device’s internal software; these describe the contribution of that polynomial to the height data. When calculating the coefficients, the polynomial terms are matched as accurately as possible to the height data.

2.9 The repeatability of corneal aberration measurements

As explained earlier, corneal aberrations are derived from topographical height data. Applegate et al. (1995) explored the accuracy of topography data obtained from Placido ring-based methods using three model surfaces; one spherical, one elliptical and one cylindrical. The authors back-calculated the instrument’s captured data to derive the measured surface characteristics, which were than compared to the real surface’s actual profile. Applegate et al. (1995) found that on their model surfaces, the TMS-1 had limitations, particularly showing poorer accuracy for measurements of ‘elliptical’ shapes rather than ‘spherical’ ones. The TMS-1 was also found to be limited when the distance from the videokeratoscopic axis increased i.e. in the peripheral cornea (up to an 8 mm corneal diameter). The authors also reported that “dioptric maps appeared to ‘smooth’ over areas of abrupt transition” leading to interpretation inaccuracies. However, for spherical surfaces the TMS-1 gave good accuracy of ‘estimated’ height data, with a RMS error of only 5 µm or less. In contrast, Guirao and Artal (2000) calculated the accuracy of ‘estimated’ height data on 6 model surfaces (three spherical and three elliptical) up to a 6 mm corneal diameter, with a RMS error of 1 to 2 µm using the Humphrey Atlas topographer. These results perhaps showed a better accuracy of ‘estimated’ height data than in Applegate et al.’s (1995) previous study as a smaller corneal area was measured. Guirao and Artal (2000) concluded that the Atlas topographer showed sufficient precision to calculate the wavefront aberrations of the cornea from videokeratoscopic data over an area of 4 to 6 mm in diameter.

Gobbe et al. (2002) carried out a study to investigate the repeatability of the Keratron keratoscope (Optikon, Rome, Italy). Ten examinations were made (each examination consisted of
6 repeated measurements) on 10 different days all within a one-month period. The authors conducted this study on normal subjects aged between 26 to 45 years. Gobbe et al. (2002) reported that some coefficients showed poor repeatability (Z (3,+1) needed five repeated examinations to reliably determine the absolute magnitude of the coefficient), whereas others showed better repeatability (Z (2,-2), Z (2, 0), Z (3,-3) and Z (4,0)), needing only one examination to reliably determine the magnitude of the coefficients. The least repeatable coefficients were the 3rd-order coma terms (Z (3,+1) and (Z (3,-1); where Z (3,-1) needed two repeated examinations).

In this paper repeatability was determined using the standard deviation values of repeated measurements multiplied by the critical value (t) at the 95% confidence interval (t = 2.262 for 10 measurements). The authors discussed that small eye movements made during measurements may have caused the variability. Gobbe et al.’s (2002) data showed that even poorer repeatability was evident at the larger aperture sizes, compared to the smaller sizes. Measuring the higher ‘radial’ order aberrations (i.e. 5th- to 10th-order) also yielded less repeatable results; this was perhaps to be expected, as these coefficients have very small absolute magnitudes.

He et al. (2006) measured the front surface corneal aberrations of 26 normal subjects using the Oculus Pentacam and the Humphrey corneal topographer system (Atlas 995). The authors compared the results obtained from these two devices using correlation analyses. Their results suggested that the two devices were comparable in terms of accuracy for all the aberration terms evaluated, except for the trefoil terms. Significant correlations were found for Z (2,-2) (r =0.90, p<0.0001); Z (2,+2) (r =0.94, p<0.0001); Z (3,-1) (r =0.77, p<0.001); Z (3,+1) (r =0.87, p<0.001) and Z (4,0) (r =0.53, p<0.01). However, Bland and Altman (1986) have previously described how using correlation to compare two different devices can give erroneous results.

Shankar et al. (2008b) reported poor repeatability (using Bland and Altman (1986) coefficients of repeatability – where 95% of the differences should be within ± 1.96 standard deviations) of the front surface corneal aberrations measured in 90 normal subjects and 14 keratoconic patients using the Oculus Pentacam. According to their data, larger absolute magnitudes for all Zernike coefficients were found (even at the ‘higher’ radial orders) than compared to any previous studies of either normal (total higher-order RMS error average of 0.91 ± 0.34 µm) or keratoconic eyes (total higher-order RMS error average of 3.33 ± 2.22 µm). A previous study of 204 normal eyes, using the Orbscan II, found an average total higher-order RMS error of 0.38 ± 0.07 µm (Pesudovs, 2005). Upon investigating their results further, Shankar et al. (2008b) noted that when exporting the data from the Pentacam to their external VOLPro software (v7.08, Sarver and Associates), the output data for some eyes showed ‘missing points’ generally located superior nasally. On the Pentacam elevation data maps, these missing areas were shown as ‘black spots’ which the user guide describes “as points where the device extrapolates values using the surrounding ‘real’ elevation points acquired during imaging” (Oculus Pentacam Manual). In this study, the authors did not discuss why they did not asses the aberration data using the Pentacam’s own internal software.

Whilst assessing a selection of 17 height points from the raw elevation data (in microns), Shankar et al. (2008b) found that the repeatability of the instrument was very good centrally, but poorer even only 4 mm out from the corneal centre. The authors discussed that inaccuracy of the
Pentacam device in measuring the ‘actual’ height of the cornea was the most likely reason for the poor repeatability of the corneal wavefront aberrations. However, it could be possible that the ‘missing points’ in the data may have been due to the eyelids or even the nose obstructing the Scheimpflug camera, i.e. as anatomical hindrance. Another likely source of error would be small eye movements or even incomplete blinking within the 2-second period that the Pentacam acquires its measurements; however, the scans investigated were classified as ‘OK’ using the device’s internal software.

In similarity to Shankar et al.’s (2008b) anterior corneal surface aberrations results, Piñero et al. (2009b) have reported poor repeatability for some of the Zernike coefficients derived from the posterior corneal surface aberrations of 40 normal subjects, also using the Oculus Pentacam. Using the limits of agreement method as suggested by Bland and Altman (1999), the authors found that three repeated measurements by two experienced operators showed good repeatability for spherical aberration and secondary spherical aberration terms. However poorer repeatability was evident for the quadrafoil and trefoil Zernike terms.

In another study, Piñero et al. (2009a) found that many posterior corneal surface Zernike coefficients, from the Pentacam data of 15 keratoconic and 15 normal eyes, showed substantially higher absolute magnitudes than those found at the anterior surface. The authors report that posterior surface vertical coma was as high as +0.32 ± 0.37 µm compared to 0.001 ± 0.23 µm at the anterior surface in the normal subjects. Equally, the results in the keratoconic patients showed that posterior surface vertical coma was as high as -3.70 ± 1.81 µm compared to -1.75 ± 0.98 µm on the anterior surface. These differences are highly unlikely as the refractive index difference between the air (1.0) and the cornea (1.376) is greater than the refractive index difference between the cornea and the aqueous humour (1.336). Therefore, posterior corneal surface aberrations should theoretically be of smaller magnitude than anterior surface aberrations. The exact reason for this anomaly is currently unknown, however, Piñero et al. (2009a) discussed that the Pentacam device’s software may assume that the aqueous humour has the same refractive index as air. The authors thus explain that the Pentacam’s values for the posterior corneal aberrations are likely to be an unrealistic estimation of the real aberration values and should be used with caution.

Despite these studies suggesting otherwise, a review of the literature shows that the Pentacam has been found to be repeatable for many measurements of the anterior eye such as corneal thickness measurements (Lackner et al., 2005a, O'Donnell and Maldonado-Codina, 2005, Miranda et al., 2009b), anterior chamber depth (Lackner et al., 2005b, Shankar et al., 2008a) and posterior corneal curvature (Quisling et al., 2006). Moreover, Miranda et al. (2009a) have reported no significant differences between repeated anterior surface corneal aberrations measured over a minute, an hour, a day and a week in 23 normal subjects using the Oculus Pentacam. The authors’ analysis used Bland and Altman plots and showed that measurements made were highly repeatable over the times tested.
2.10 The accuracy and limitations of Zernike polynomials for calculating corneal aberrations

Despite their useful mathematical properties, Zernike polynomials appear to have limitations in their application of modelling the anterior surface of abnormal corneas (Smolek and Klyce, 2003). Zernike polynomial decompositions can be reversed such that a set of aberration coefficients can be used to reconstruct the original surface profile. In addition to corneal aberration data, corneal topographers also output raw elevation data. In their study, Smolek and Klyce (2003) back-calculated their corneal aberration data and compared the reconstructed surfaces to the raw corneal elevation data to determine the ‘fitting error’. Smolek and Klyce (2003) used the ‘lens subtraction’ method to derive anterior surface corneal aberrations for 88 highly-aberrated eyes (32 keratoconic eyes, 27 post penetrating-keratoplasty eyes and 29 post-conductive keratoplasty eyes), using the TMS-1 instrument. Smolek and Klyce (2003) evaluated the fitting error by comparing the accuracy of Zernike polynomial decomposition at representing the corneal surface for two different scenarios,

a) For the 1st- to 4th-order aberrations (this range contains all the primary higher-order aberrations e.g. coma, spherical aberration etc.)

b) For the 1st- to 10th-order aberrations

Smolek and Klyce (2003) found that increasing the number of radial orders used to represent the corneal surface from 4 to 10 showed a substantial reduction in the fitting error, in that a more accurate representation of the corneal surface is achieved by fitting the corneal height data with more radial orders. The authors discussed that using up to only the 4th-order of Zernike polynomials cannot fully describe highly-aberrated corneas. These problems of inaccuracy mainly arise as Zernike polynomials are global functions, and are perhaps not entirely accurate for characterising very small or subtle changes in the corneal surface. Exactly how many orders would be needed for accurate representation of highly-aberrated eyes remained unanswered in this study.

Iskander et al.’s (2002) research suggested that aberration measurements up to the 10th radial order allows an accurate representation of highly-aberrated keratoconic eyes. In contrast, Pantanelli and Yoon (2006) hypothesised from their study of 56 irregular corneas (including keratoconic, post penetrating-keratoplasty and post-LASIK eyes), that measurements up to the 12th radial order may be needed to accurately represent the aberrations of such abnormal eyes. Carvalho (2005) suggested that ‘capping’ the number of Zernike orders used to describe the aberrations derived from corneal elevation data was not advisable and that one should consider the accuracy required with the numbers of orders to be used (i.e. a greater accuracy requires more radial orders to be used).

2.11 Other methods of describing higher-order aberrations

An isolated study by Iskander et al. (2002) introduced the idea of using Bhatia–Wolf polynomial expansions, for fitting videokeratoscopic height data to describe the anterior corneal surface. The authors found that these polynomial terms gave a more accurate alternative than Zernike’s at describing anterior corneal elevation, by reducing the residual fit error from 0.42 µm
(with Zernike) to 0.25 μm. Unlike Zernike polynomials however, Bhatia–Wolf polynomials are orthogonal in X (horizontal direction), Y (vertical direction), and ρ (radial co-ordinate). But Bhatia–Wolf polynomials are more difficult to calculate than their Zernike equivalents, requiring customised software. Unlike with Zernike polynomials, many of the lower-order terms in the Bhatia–Wolf polynomial expansion series do not represent any commonly known aberrations.

Smolek and Klyce (2005) discussed considering whether Fourier analysis would be more accurate than Zernike polynomials in their conclusions. However, when Yoon et al. (2008) compared Fourier transforms to Zernike polynomials, the data showed that using Zernike polynomials gave less error compared to Fourier analysis.

As a result of the difficulties encountered when using Bhatia–Wolf polynomials or Fourier transformations, Zernike polynomials are still the most commonly used and recognised method of describing higher-order aberrations in optics (for both ocular and corneal aberrations) irrespective of their own limitations.

2.12 Higher-order aberrations in a normal population

Before discussing how aberrations change with the development of keratoconus, it is necessary to appreciate what level of aberrations is considered to be normal. Several studies of normal eyes have found that fourth-order spherical aberration was positively and significantly skewed from zero as shown in Figure 2.7 (Porter et al., 2001, Thibos et al., 2002b, Thibos et al., 2002c, Radhakrishnan and Charman, 2007). Apart from spherical aberration, all four studies showed that the higher the radial order investigated, the smaller the magnitude of the absolute error values for the coefficients.

Thibos et al. (2002b) noted that beyond the 2nd-order, all the Zernike terms came to a population average of almost zero in normal subjects. However, the authors found that hardly any individual Zernike coefficients for any given patient had an absolute error value of exactly zero, i.e. some eyes had positive Zernike coefficient values and some eye had negative values; these findings therefore indicate natural biological variations. Thibos et al.’s (2002b) data also showed that wavefront error increased linearly with pupil size, and that the magnitude of the wavefront error decreased exponentially with increasing radial order. Several authors have also reported that the larger the pupil size, the greater the total RMS error measured (Artal and Navarro, 1994, Liang and Williams, 1997, Castejón-Mochón et al., 2002). Moreover, Castejón-Mochón et al. (2002) found that for larger pupils, the coefficients of the higher radial orders showed greater magnitudes of error than with smaller pupils.
Figure 2.7 Aberrations from a large population of normal human eyes (Porter et al., 2001). The mean values of Zernike modes up to the 5th-order for a 5.7-mm pupil are shown. The error bars represent ± 1 standard deviation from the mean value. The variability of the higher-order modes is shown in the inset of the figure; which excludes all 2nd-order modes and again expands the main ordinate, showing us that spherical aberration (shown as $Z_5^1$) is positively skewed from zero.

2.13 Compensation of corneal aberrations by the internal optics of the eye

The aberration of the eye’s internal optics is the sum of the posterior corneal aberrations and the crystalline lens aberrations. Therefore, ‘whole eye’ or ‘total ocular’ aberrations = internal optics aberrations + anterior corneal aberrations. Artal et al. (2001) evaluated the compensation system of the eye between the internal optics and the cornea in normal eyes. The authors compared ocular (Hartmann-Shack) and corneal (topography) aberrations, they also measured the internal optics of the eye by neutralising the cornea using saline-filled goggles. Artal et al.’s (2001) data show that both the internal optics aberrations and corneal aberrations were both considerably larger in magnitude than the whole eye aberrations, as well as opposite in sign from each other. The authors reported a negative correlation between the internal optics and the anterior corneal aberrations. These results suggested that the internal optics of the eye partially compensate for anterior surface corneal aberrations.

Artal et al.’s (2002) findings suggested that as the eye ages, the compensation between the internal optics and the cornea breaks down. The authors discussed that increases in the aberrations of the internal optics over time were the main reason for this de-harmonisation. This theory has since been contradicted by He et al. (2003a), who also compared ocular (Hartmann-Shack) and corneal (topography) aberrations. He et al. (2003a) reported that subjects who had larger magnitudes of ocular total RMS error, showed larger internal optics aberrations compared to their corneal aberrations, and that these internal optics aberrations were responsible for the majority of the total ocular aberrations. However, the subjects in He et al.’s (2003a) study were all under the age of 29, compared to the age range of 26 to 69 years used by Artal et al. (2002). He
et al. (2003a) concluded that random biological variations between patients was the cause of all eyes having different magnitudes of aberrations for the different components of the eye.

2.14 Ocular aberrations and retinal image quality

A number of important measures of retinal image quality can be derived from the wavefront aberration measurements of an eye, these are known as ‘metrics’ of optical quality. Some of these metrics will now be explained briefly.

2.14.1 Point spread function (PSF)

The PSF is the image that an optical system forms of a point source (target object). This image gives an indication of how aberrated a point becomes once it has passed through the optical system in question. The PSF is a display that represents the intensity distribution of the image which lands on the retina. The PSF of a perfect optical system (diffraction-limited) would be the ‘Airy disc’ i.e. the Fraunhofer diffraction pattern for a circular pupil. The PSF is calculated using the wave aberration, the light transmission of the optical system and the shape and size of the pupil; all of which are measured by Hartmann-Shack aberrometers. The retinal image of any object can be obtained by the complex mathematical process of ‘Convolution’ of the PSF, with the desired object of interest (for example the Snellen letter ‘E’ depicted in Figure 2.8). If we consider that any given object is made up of a substantial number of individual point sources, each with its own intensity, position and colour; then the process of ‘convolution’ transfers the shape and other features of the PSF, onto each one of these points, thus generating a simulated image (Williams et al., 2001). Figure 2.8 displays the wave aberration, PSF and convolved image measured in a normal eye and Figure 2.9 presents the same properties measured in a keratoconic eye.

![Figure 2.8](image-url) The wave aberration, PSF retinal image for a normal eye. From Yoon (2005), “Ocular Wavefront Sensing”, www.cvs.rochester.edu/yoonlab/ocul.html [accessed 7 December 2008].
The uncorrected wavefront aberration of a keratoconic eye.

The corresponding PSF.

The retinal image for this uncorrected keratoconic eye following convolution of the PSF with the letter 'E'.

Figure 2.9 The higher-order wave aberration, PSF and retinal image for a keratoconic eye. From Yoon (2005), “Ocular Wavefront Sensing”, www.cvs.rochester.edu/yoonlab/ocular.html [accessed 7 December 2008].

2.14.2 Modulation transfer function (MTF)

The MTF is the ratio of the Michelson contrast of the image to that of the object, as a function of spatial frequency (Campbell and Gubisch, 1966). This function indicates the ability of an optical system to transfer or reproduce detail at various spatial frequencies from the object to the created image. The MTF is the optical contribution of the contrast sensitivity function (CSF), and can be calculated directly by a complex, mathematical ‘Fourier transform’ of the PSF. Figure 2.10 shows some typical MTF graphs from 17 normal eyes. The larger the area underneath the MTF curve, the better the optical quality of the eye in question.

2.14.3 Visual benefit (VB) scores

The visual benefit is calculated as, the ratio of the MTF with a customised aberration correction in place, to the MTF with just the 2nd-order aberrations corrected (Williams et al., 2000). Therefore the VB indicates the increase in retinal image contrast achieved by correcting all the monochromatic higher-order aberrations in white light, other than just defocus and astigmatism alone (Pantanelli et al., 2007). Values of greater than 1.0 show a positive VB, indicating a gain in visual performance through aberration correction. Eyes with a VB score equal to 1.0 or less will not benefit from the correction of higher-order aberrations. The VB in normal eyes ranges from 1.5 to 8 (Figure 2.10), whereas the VB in some keratoconic eyes has been reported to range from 3 to 25 (Williams et al., 2000). VB scores are normally stated for a set spatial frequency, usually at 16 cycles/degree, this is because it is among the highest frequencies that are detectable by normal subjects viewing visual scenes (Galvin and Williams, 1992).
Figure 2.10 Graphical displays of the modulation transfer function and the associated visual benefit in normal eyes. The data were calculated from the ocular aberrations from 17 normal eyes. The left hand graphs (a) are for a 3-mm pupil and the right hand graphs (b) are for a 6-mm pupil. In the lower two graphs, the dotted lines are the MTFs when correcting the 2nd-order aberrations only. The dashed lines are the MTFs when correcting both the higher-order aberrations as well as the 2nd-order aberrations. The solid line shows the MTFs for an ‘ideal’ or ‘aberration-free’ scenario (Williams et al., 2000).

2.14.4 Strehl ratio

Strehl’s ratio is the ratio of the peak intensity, generally at the centre of the light distribution of the PSF, observed by the imaging system, compared to the theoretical maximum peak intensity of an ‘ideally perfect’, diffraction-limited imaging system’s PSF, (Figure 2.11). If the system is flawless, then Strehl’s ratio will be unity. When the Strehl ratio is 0.8 or higher, a near-optimal image will be obtained from the system, which will show a minimal amount of aberration that will not degrade the retinal image quality substantially (Atchison and Smith, 2000).

Typical Strehl ratio values for visually-normal human eyes (using a 4-mm pupil diameter size) are 0.28 at an age of 25 years, 0.22 at 45 years and finally 0.16 at 65 years of age (Guirao et al., 1999). In contrast, the Strehl ratio of a moderate keratoconic eye with a 6-mm pupil diameter size was found to be as low as 0.005 (Sabesan et al., 2007a).
Figure 2.11 A pictorial definition of the Strehl ratio. The maximum value is one, which occurs when the optical system is diffraction-limited. The left-hand graph shows the diffraction-limited PSF (at unity) and the right-hand graph shows the actual PSF of a human eye for a 6-mm pupil diameter (Williams et al., 2001). (H<sub>dl</sub> = peak ‘diffraction-limited’ value, H<sub>eye</sub> = peak eye value). The ratio of the human eye in this example is 0.20 (or 20%) of the intensity of a diffraction-limited system.

2.14.5 Maréchal’s criterion

Maréchal’s (1947) criterion states that if the RMS error is less than or equal to 1/14 of the wavelength (λ) of the light in question, then the image produced will have no significant difference from that of a ‘diffraction-limited’ system. This criterion is also used to assess instrument accuracy and the repeatability of wavefront aberrations (Liang and Williams, 1997, Liang et al., 1997). Liang and Williams (1997) measured the eyes of three normal subjects and found their Hartmann-Shack measurements to be highly repeatable with a mean standard deviation approaching Maréchal’s criterion of ~λ/14 i.e. ~0.046 μm.

2.14.6 Wavefront variance (WV)

Wavefront variance is measured in μm<sup>2</sup> and quantifies the mean standard deviation between the aberrant wavefront and the ideal reference wavefront. In statistics variance = (standard deviation)<sup>2</sup> and is a measure of dispersion (i.e. averaging the squared distance of all possible values from the expected or mean value).

2.14.7 Contrast sensitivity function (CSF)

The CSF is a measure of how sensitive an eye is to gratings of different spatial frequencies. The CSF is determined by finding the threshold contrast at which the eye just detects a sinusoidal grating at a number of different spatial frequencies. Low spatial frequencies are coarser or ‘thick’ gratings whereas high spatial frequencies are much finer or ‘thin’ gratings. Contrast sensitivity is calculated as the reciprocal of the threshold value (Figure 2.12).
Figure 2.12 The human contrast sensitivity function. Contrast sensitivity values for gratings of different spatial frequencies in a normal human eye in photopic conditions. The normal peak spatial frequency is at 4 cycles/degree (c/d), with a cut off of 60 c/d (due to the retinal photoreceptor array) (Oshika et al., 2006).

2.15 Effect of aberrations on visual performance

An understanding of which aberrations have the most detrimental effect on visual performance is important as not all aberrations have an equal effect (Applegate et al., 2002, Applegate et al., 2003a, Applegate et al., 2003b). Applegate and colleagues (2002, 2003a) developed a psychophysical method for investigating the visual influence of higher-order aberrations based on letter chart simulation. The authors aberrated visual acuity charts by convolving each chart with the PSFs corresponding to a given individual Zernike term using the CTView software program (Sarver and associates Inc., Celebration, FL, US). Six levels of RMS wavefront error were used (0.00, 0.05, 0.10, 0.15, 0.20, and 0.25 µm) for a 6-mm pupil diameter. For each individual chart, each of the 6 levels of RMS error were loaded with each individual coefficient term from the second, third, and fourth radial orders, producing a total of 72 aberrated charts (Applegate et al., 2002, Applegate et al., 2003a). These simulated charts were then viewed by 3 visually-normal subjects through a 3-mm artificial pupil to approximate the retinal images that would have been formed had these aberrations existed in the eye’s pupil plane. These studies showed that increasing the RMS error, for any given Zernike coefficient, reduced the observer’s visual acuity in a linear fashion. Moreover, Applegate et al. (2003a) found that the slopes of the linear fits varied dependant on each Zernike mode; specifically, coefficients nearer the centre of the Zernike pyramid showed steeper slopes than those nearer the pyramid’s ends. This is explained as the higher the Azimuthal (or angular) frequency, the more the aberration ‘power’ is displaced towards the edge of the pupil (or unit circle); hence aberrations located directly in the pupil centre (such as defocus and spherical aberration) will reduce visual performance the most (Applegate et al., 2002).
Applegate et al. (2003b) also report that interactions between Zernike coefficient terms exist. Coefficients in the same radial order, but with different Azimuthal frequencies combined to worsen visual acuity (e.g. Z (3,-1) and Z (3,-3)). Whereas combining coefficients (in the correct proportions) two radial orders apart, at the same Azimuthal frequency and trigonometric function, helped to give a better visual acuity than with either term individually (e.g. Z (3,-1) and Z (5,-1)). However, these investigations were performed for visually-normal subjects only, and for only eight Zernike coefficient terms (i.e. four pairs).

When investigating the relationship between contrast sensitivity and higher-order aberrations, Oshika et al. (2006), using regression analysis, reported that 3rd-order coma aberrations affected contrast sensitivity more than 4th-order spherical aberration. The authors used both sine wave gratings and letter-type contrast sensitivity charts to carry out their analysis. The data collected showed that 3rd-order coma aberrations were significantly associated with reduced grating contrast sensitivity ($p = 0.002$), yet 4th-order spherical aberration was not ($p = 0.20$). Third-order coma aberration was also significantly associated with reduced letter contrast sensitivity ($p < 0.001$), yet 4th-order spherical aberration was not ($p = 0.082$). These tests were performed on visually-normal subjects only.

Okamoto et al. (2008) compared measurements from keratoconic eyes versus age-matched normal controls using regression analysis (Spearman’s coefficients), and found that letter-type contrast sensitivity was significantly lower in keratoconic eyes (average 17.4 ± 3.8 letters) than in normal eyes (average 21.8 ± 1.4 letters), with $p < 0.0001$. The results showed that in keratoconic eyes, there was a more significant correlation between letter-type contrast sensitivity and 3rd-order aberrations ($r = -0.736$, $p < 0.0001$), than between letter contrast sensitivity and 4th-order aberrations ($r = -0.464$, $p < 0.05$). Okamoto et al. (2008) were the first to report a significant association between ocular higher-order aberrations and contrast sensitivity for keratoconic patients; however the authors did not report the severity of their 14 keratoconic subjects.

2.16 The tear film and its effect on higher-order aberrations

An important factor influencing the degree to which higher-order aberrations can be corrected is the stability of ocular aberrations. One factor that contributes to the instability of ocular aberrations is variations in the pre-corneal tear film (Liang and Williams, 1997, Cheng et al., 2003b, Mirshahi et al., 2003, Jeong and Yoon, 2006). Tear film is the most anterior optical surface and hence the most powerful, as it is the boundary of the largest change in refractive indices for light travelling into the eye. Németh et al. (2001) found, when recording corneal topographies using the videokeratoscopic method, that discrepancies due to the tear film hindered the accuracy of measurements approximately 10 seconds after a blink. The authors report that the ‘breaking-up’ of the tear film made the anterior corneal surface asymmetric and irregular.

Ho (2003) investigated the effect of unwanted aberrations from the ‘post-lens tear film’ (PoLTF) in soft contact lens wear using the LRT method. Ho (2003) tested 54 different shaped
models of how the PoLTF could present itself behind a soft lens. Ho (2003) concluded that the PoLTF will only induce statistically significant wavefront aberrations in three very rare cases. These three shapes included a 'ripple-shaped' model, a 'defocus-shaped' model and an 'oblique astigmatism-shaped' model. However the magnitudes of the induced aberrations for these three models were all less than the wavefront aberrations generated from wearing a standard soft contact lens itself. Roberts et al. (2006) found, on average, that habitual spherical soft lenses for myopia induced an additional RMS error of 0.092 μm. All the other PoLTF models investigated did not induce statistically significant amounts of aberration. Hence Ho’s (2003) data suggests that PoLTF aberrations should not significantly reduce the benefits of an aberration correcting soft contact lens. However Ho’s (2003) report was solely based on Strehl ratio data using a model eye only.

Several studies have shown that tear film disruptions measured whilst holding a blink can reduce the optical quality of the eye (Albarrán et al., 1997, Thibos and Hong, 1999, Tutt et al., 2000, Koh et al., 2002). Montés-Micó et al. (2004b) investigated the effect of the post-blink tear film on both ocular and corneal aberrations, measured from 20 normal subjects for twenty seconds after a blink. Montés-Micó et al. (2004b) found that induced post-blink aberrations showed a similar detrimental effect on both ocular and corneal aberrations, particularly at the larger pupil/corneal diameters. Montés-Micó et al. (2004b) discovered that the higher-order RMS error metric increased with time post-blink for both corneal and total ocular aberrations. Their data showed a close relationship between the two, suggesting that tear film aberrations were the major cause of both the ocular and corneal changes measured in their study. The authors also discovered that both corneal and ocular spherical RMS (4th- and 6th-order) and coma RMS aberrations increased with time post-blink. Montés-Micó et al. (2004b) hypothesised that peripheral tear film thinning, coupled with inferior decentration due to gravity, were the possible causes of these two findings. However, the data in Montés-Micó et al.’s (2004b) paper were plotted at 0 seconds, 10 seconds and 20 seconds only; and so exactly how the aberrations fluctuated over the whole of the 20-second time period was not reported in this study.

Figure 2.13 shows an illustration from Montés-Micó et al.’s (2004b) study of how the tear film induced aberrations changed over time for the total ocular and corneal aberrations in their population of normal eyes. Exactly how tear film aberrations of highly-aberrated, keratoconic eyes change with time post-blink currently remains unexplored.
Figure 2.13 Changes in corneal and total ocular aberrations induced by the post-blink tear film (Montés-Micó et al., 2004b). (The top images are at 0, the middle images are at 10 seconds and the bottom images are at 20 seconds post-blink).

Left: the raw Hartmann-Shack images with time post-blink from a normal cornea. Middle: show the changes in total ocular aberrations with time post-blink. Right: the changes in corneal aberrations with time post-blink. (Note that both the total and corneal aberrations increase with increasing time post-blink).

2.17 Changes in higher-order aberrations with accommodation

Several authors have investigated variations in ocular higher-order aberrations with changes in accommodation. As accommodation is achieved by variations in the position and shape of the crystalline lens, it seems reasonable to expect that changes in whole-eye aberrations may occur with alterations in accommodation (Tscherning, 1904, Ivanoff, 1953). Early studies on this topic (using a telescopic, Vernier acuity method) only evaluated changes in spherical aberration and showed that spherical aberration tended to shift from an initially positive value towards a more negative value with increased accommodation (Ivanoff, 1953, van den Brink, 1962). Using more modern techniques, such as the Howland and Howland (1977) aberroscope, LRT and Hartmann-Shack aberrometry, several studies have examined changes in other higher-order aberrations, as well as spherical aberration, with differing results (Howland and Buettner, 1989, Lu et al., 1994, Atchison et al., 1995, He et al., 1998, He et al., 2000, Hazel et al., 2003, Cheng et al., 2004a, Plainis et al., 2005, Radhakrishnan and Charman, 2007, López-Gil et al., 2008). In agreement with the early literature, several groups found that spherical aberration changed in the negative direction upon increased accommodation (He et al., 2000,
Hazel et al., 2003, Cheng et al., 2004a, Plainis et al., 2005, Radhakrishnan and Charman, 2007, López-Gil et al., 2008); whereas Atchison and co-workers (1995) only reported such a shift in approximately half of their participants. Several authors have reported changes in coma aberrations with accommodation; however, these findings showed no clearly defined relationships and varied in both magnitude and direction (Howland and Buettner, 1989, Atchison et al., 1995, He et al., 2000, Cheng et al., 2004a, Plainis et al., 2005, Radhakrishnan and Charman, 2007, López-Gil et al., 2008). The average higher-order RMS error at a fixed pupil diameter was found to remain constant over accommodative levels of 0.00 to 4.00 D by Cheng et al. (2004a), and 0.00 to 3.00 D by both Atchison et al. (1995) and Ninomiya et al. (2002). These results perhaps imply that correction of ocular aberrations for distance vision (to infinity) could also prove useful for a range of near tasks too.

Some studies have suggested that corneal and lenticular changes both occur during accommodation (Pierscionek et al., 2001, He et al., 2003a, Yasuda et al., 2003), although others have found no evidence of corneal variations (Buehren et al., 2003, He et al., 2003b). On balance, it appears likely that changes in aberrations with increased accommodation are mainly attributable to changes in the crystalline lens (Strenk et al., 2005).

López-Gil et al. (2008) suggested that accommodative miosis in both young and old subjects was useful in obtaining good retinal image quality, as a smaller pupil tends to reduce higher-order aberrations. López-Gil et al. (2008) found that this ‘masking effect’ was more effective in younger eyes, particularly for coma and trefoil aberrations. Such masking of aberrations with a smaller pupil was first noted by Calver et al. (1999), and was also reported by Radhakrishnan and Charman (2007).

2.18 Limitations of aberration measurement and representation

There are two major limitations with wavefront representations of higher-order aberrations.

2.18.1 Spot imaging issues

Due to having a fixed number of lenslets in the micro-lenslet array, most commercially-available Hartmann-Shack aberrometers may not provide as dense a sampling in the pupil zone as is needed to identify very small, subtle wavefront disparities (Moreno-Barriuso and Navarro, 2000, Yoon et al., 2004b). When using the Hartmann-Shack device, the aberrated wavefront emerging from the eye is relayed onto a micro-lenslet array, and transformed into a spot pattern which is analysed by a computer program. By measuring the displacement of these spots from a reference, the program reconstructs the original, aberrated wavefront. The measurement performance of the wavefront sensor directly depends on how well the centre of each spot can be detected by the sensor’s centroiding algorithm (Yoon et al., 2004b). Data derived from a Hartmann-Shack sensor does not consider the quality of the individual spots formed by the lenslet array. Only the displacement of spots is needed in computing the local slope of the wavefront over each lenslet aperture, however, the quality of the spot images can vary greatly over the pupil of a human eye (Mihashi et al., 2006a, Lombardo and Lombardo, 2009). A fundamental limitation of the Hartmann-Shack sensor is the requirement that each spot generated
by a given lenslet must land within the ‘virtual sub-aperture’ of certain a photon detector at the CCD. The computer software typically used in Hartmann-Shack aberrometry is usually not capable of correctly identifying a spot image which fully overlaps with another spot, formed by an adjacent lenslet (Figure 2.14 a); two separate spot images formed at the same CCD photon detector sub-aperture (Figure 2.14 b); or a spot image that crosses the allocated path of another spot, known as ‘crossover’ (Figure 2.14 c) (Thibos and Hong, 1999, Munson et al., 2001, Yoon et al., 2004b).

Figure 2.14 Spot imaging issues using the Hartmann-Shack technique: including a) overlapping spots b) multiple spots and c) crossed-over spots. Adapted from Yoon et al. (2004b).

A displaced spot is obviously aberrant from the chief or reference ray, the amount of displacement seen however gives no indication of the image quality. On the other hand, a blurry spot may contain more aberration, optical scatter and refractive blur compared to a sharper spot (Mihashi et al., 2006a, Lombardo and Lombardo, 2009). Figure 2.15 shows a typical example of the Hartmann-Shack spot images from a normal eye and an eye with severe keratoconus.

Figure 2.15 The raw Hartmann-Shack images from a normal eye and an eye with severe keratoconus. The left-hand image shows a regular series of spots typically seen in normal eyes. The right-hand image shows irregularities in the spot array typically seen in keratoconic eyes.
Thibos and Applegate (2001) explain that in the Hartmann-Shack device, the CCD sensor makes the assumption that all the spot images will lie ‘flat’ over the finite diameter of the lenslet in question. This assumption begins to break down even for coarse, lower-order, aberrations when the magnitude of those aberrations is large. In such a case, the wavefront is significantly curved over the lenslet aperture and the result is a blurry spot which is difficult to localise as depicted in Figure 2.16 (lower left-hand image). If the aberrations are large enough, the spots can even overlap, which complicates the analysis considerably. It is also possible that ‘micro-aberrations’ may exist within the device’s spot image, which are too small to be detected by the wavefront sensor’s photon detector; these would still be detrimental to retinal image quality as depicted in Figure 2.16 (lower right-hand image). These micro-aberrations may possibly cause a scattering haze of the spot image, rather than a geographical deviation. Although these blurry spots are problematic, they still contain useful information about the degree and location of scattering sources inside the eye (Mihashi et al., 2006a).

![Figure 2.16](image)

**Figure 2.16** Spot imaging issues in wavefront sensing (Thibos and Applegate, 2001). Upper images show the assumption of how the image produced lies flat over the lenslet aperture. Bottom left: shows how gross aberrations may produce a curved image at the lenslet aperture. Bottom right: shows how unresolvable micro-aberrations may exist in the image produced at the lenslet aperture.

### 2.18.2 Computational errors

The measured Zernike aberration coefficients are mathematically re-constructed from a discrete number of sampling points only, and are therefore not the perfect mirror image of the aberrant wavefront proper. The method classically used in aberrometry is the Zernike polynomial expansion series. This method of modal reconstruction is based on the expansion of the derivatives of the wavefront aberration. The overall wavefront is described as the linear combination of each set of modal functions, and use the ‘least-squares’ fitting method to fit the measured wavefront slope gradients (Ríos et al., 1997). This calculation essentially describes how each aberration coefficient makes up a proportion of the total wavefront. This mathematical process aims to minimise the absolute error between the measured sampled points and the Zernike terms which are fitted to the data. However, Thibos and Applegate (2001) explain that the number of sampling points from the Hartmann-Shack aberrometer will be far greater than the number of Zernike polynomial terms that can be fitted to the wavefront to describe its shape.
It is important to note that direct subtraction or comparison of ‘corneal’ and ‘total ocular’ aberrations can give rise to inaccuracies, as different reference axes may have been used during measurements. Wavefront aberrometers measuring the total ocular aberrations use the patient’s line of sight (the chief ray of the bundle of light entering the eye and passing to the fovea) as the reference axis. Aberrations measured with respect to this axis therefore have the pupil centre as the Cartesian origin (Thibos et al., 2000). On the other hand, corneal topographers generally align the videokeratographic axis with the corneal sighting centre (the intersection of the line of sight with the corneal surface) (Mandell et al., 1995). Essentially the pupillary axis and the line of sight are separated by the angle lambda in the human eye. The magnitude of angle lambda varies in each individual, approximately between 1.4 to 9 degrees in the horizontal meridian (Mandell et al., 1995). Possible inaccuracies in comparing corneal and ocular aberrations may be accounted for (both mathematically and geometrically) and minimised by using an instrument that takes both measurements simultaneously; these instruments are typically custom-built devices (Maeda et al., 2002, Zhou et al., 2004).

In summary, this chapter has described what higher-order aberrations are and how they can be quantified and interpreted. Examples of what levels of aberrations are considered to be normal have also been illustrated. The next chapter will review the literature regarding the measurement and potential correction of higher-order aberrations in patients with keratoconus.
3. Higher-order aberrations in keratoconus

Corneal thinning, apical protrusion, irregular corneal astigmatism and apical scarring typically cause a reduction in visual performance in patients with keratoconus (Zadnik et al., 1998). Additionally, the corneal shape changes in keratoconus induce large amounts of higher-order aberration (Tan et al., 2008), which differ greatly from the aberrations seen in normal eyes (Maeda et al., 2002). This section explains which higher-order aberrations become increased in keratoconic eyes and how the measurement and subsequent correction of these aberrations have been used in previous studies to try and improve visual function in patients with keratoconus.

3.1 Aberrations of the keratoconic eye

Compared to normal eyes, vertical coma ($Z_{3,-1}$) is most commonly found to become elevated in keratoconic eyes, as the corneal thinning classically occurs at either the inferior-temporal (Owens and Watters, 1996, Demirbas and Pflugfelder, 1998, Auffarth et al., 2000, Doh et al., 2000, Núñez and Blanco, 2008) or inferior position (Krachmer et al., 1984, Kennedy et al., 1986, Wilson et al., 1991, Zadnik et al., 1996). This means that light waves from a distant source arriving at the keratoconic eye will be optically distorted by comparatively different amounts by the superior (flatter) and inferior (steeper) cornea. Keratoconic eyes typically show significantly large magnitudes of ‘negative’ vertical coma aberration (Maeda et al., 2002, Lim et al., 2007, Piñero et al., 2009a). The keratoconic cone apex also distorts incoming light waves by ‘rotating’ them, thus inducing trefoil aberrations too (Maeda et al., 2002). Wavefront aberrations have either negative or positive signs as well as a magnitude; a positive sign means that the aberrated wavefront is ahead of the ideal reference wavefront, whereas a negative sign means that the aberrated wavefront is behind the ideal plane. These differences are normally depicted by different colours on a contour map, as shown in Figure 3.1, which portrays the total ocular and anterior corneal aberrations of both a moderate keratoconic and a normal eye.

Several studies have measured either corneal or total ocular higher-order aberrations in keratoconic patients and compared them to normal eyes. However these results are not always exactly comparable because of the different criteria used in selecting the keratoconic patients. Howland et al. (1992) first suggested that the mathematical polynomial decompositions derived from corneal height data may help to distinguish between normal and abnormal corneas. The studies by Schwiegerling et al. (1995) and Schwiegerling and Greivenkamp (1996) both derived corneal aberrations by expanding their collected data, from videokeratoscopic measurements made using the Placido based TMS-1 topographer, into Zernike terms (using the lens subtraction method). Schwiegerling and Greivenkamp (1996) found elevated absolute values of coma RMS $Z_{3,-1}$ and trefoil RMS $Z_{3,±3}$ in 15 keratoconic eyes, compared to 61 normal eyes (over a 6-mm corneal diameter). Schwiegerling and Greivenkamp (1996) acknowledged that any errors in corneal height measurement (e.g. from eye/device misalignment) would induce errors in the derivation of the Zernike polynomial terms. Nevertheless, the authors suggested that this
A technique was complementary to corneal power data, in order to help detect corneal abnormalities.

Figure 3.1 Ocular and corneal higher-order wavefront aberration maps of a moderately keratoconic (A and B) and a visually-normal eye (C and D) for a fixed 6-mm pupil/corneal diameter – all illustrations include a sphero-cylindrical correction (Jinabhai et al., 2009). The vertical coma coefficient in the moderate keratoconic eye was measured at -1.87 μm for the ocular aberrations (A) and -2.91 μm for the corneal aberrations (B). On these maps the coloured contours join points in the pupil (for ocular aberrations), or in the corneal area being measured (for corneal aberrations), which have the same amount of wavefront aberration. A and B show a classic vertical difference in coma-like aberration, which is portrayed by the superior and inferior parts of these two images showing a marked difference in contour colours. Such a marked difference in contours is not found in normal eyes (C and D). The redder colours show positive aberrations, the bluer colours show negative aberrations and the yellower colours show small (close to zero) aberrations.

Gobbe and Guillon (2005) calculated corneal aberrations using the Keratron keratoscope (Optikon, Rome, Italy) and CTView software (over 3.0, 4.5 and 6.0 mm diameters). In support of Schwiegerling and Greivenkamp's (1996) results, Gobbe and Guillon (2005) also revealed significantly elevated amounts of 3rd-order RMS aberrations in 73 keratoconic eyes (3.10 ± 2.28 μm) compared to 870 normal eyes (0.28 ± 0.15 μm), for a 6-mm corneal aperture. Gobbe and Guillon's (2005) results showed that the best differentiator of keratoconus was vertical coma which showed a specificity of 71.9% and a sensitivity of 89.3%. To be deemed ‘abnormal’ (or forme fruste) the magnitude of vertical coma should be more negative than -0.12 μm, to be deemed ‘keratoconic’ the magnitude should be more negative than -0.30 μm – both values are for a 6-mm corneal diameter. Unlike in Schwiegerling and Greivenkamp's (1996) study, which was conducted on pre-diagnosed keratoconic eyes, Gobbe and Guillon (2005) were the first to use the aberration values as a diagnostic tool on undiagnosed patients to help ‘detect’ keratoconus with a
high level of sensitivity. However as yet, no ‘cut-off’ values for vertical coma have been published to help diagnose and differentiate between mild, moderate or severe keratoconus.

In the ‘clinically normal’ fellow eye of 10 newly-diagnosed keratoconic patients, Bühren et al. (2007) reported significantly elevated magnitudes of vertical coma (-0.30 μm; p < 0.001), secondary vertical coma (Z (5,-1): +0.037 μm, where p < 0.05) and 3rd-order RMS error (0.48 μm; p < 0.01), compared to 127 normal control eyes. The authors measured corneal aberrations using the Orbscan II device. Bühren et al.’s (2007) results supported Gobbe and Guillon’s (2005) conclusions, suggesting that corneal aberration data (as well as corneal height and curvature data) can be useful to help detect forme fruste keratoconus. Compared to Gobbe and Guillon’s (2005) results, Bühren et al. (2007) found that the Orbscan gave a vertical coma cut-off value of -0.20 μm (or less) in order to be deemed ‘abnormal’ (or forme fruste) – also using a 6-mm corneal diameter. Bühren et al. (2007) found that mild keratoconic patients had an average vertical coma value of -1.35 μm compared to -0.17 μm measured in the control group. In contrast to Gobbe and Guillon’s (2005) and Bühren et al.’s (2007) studies, Lema et al. (2009a) reported that corneal vertical coma was significantly more positive in magnitude (average of +0.19 μm, with a range of +0.17 to +0.35 μm) in the ‘clinically-normal’ fellow eye of 15 unilateral keratoconus patients, than in 50 normal eyes (average of +0.03 μm, with a range of -0.14 to +0.15 μm) with p = 0.001. Lema et al. (2009a) acknowledged that their findings were not in line with previous studies and discussed that a smaller sample size or even measurement variability inherent to the instrument used (Keratron keratoscope) were possible explanations for their findings (Gobbe et al., 2002).

Alio and Shabayek (2006) investigated anterior corneal surface aberrations using the corneal map analysis system (CSO, Florence, Italy) in 40 eyes of 25 patients with keratoconus and 40 eyes of 20 control subjects (6-mm corneal diameter). The authors used the Amsler (1938) classification system to grade the severity of keratoconus. Of the keratoconic patients, 14 eyes were found to be grade 1, 11 were grade 2, 12 were grade 3 and 3 were grade 4. In the keratoconic group, the mean RMS value for spherical-like aberrations (4th- and 6th-order) was 1.06 ± 0.90 μm (range: 0.26 to 4.90 μm), coma-like RMS (3rd-, 5th- and 7th-order) aberrations was 2.90 ± 1.40 μm (range: 1.09 to 6.69 μm), and higher-order RMS error (up to the 7th-order) was 3.14 ± 1.64 μm (range: 1.20 to 8.31 μm). In the control subjects, the mean RMS value for the spherical-like aberrations was 0.38 ± 0.08 μm (range: 0.24 to 0.54 μm), coma-like RMS aberrations was 0.35 ± 0.11 μm (range: 0.18 to 0.66 μm), and higher-order RMS error was 0.52 ± 0.09 μm (range: 0.24 to 0.76 μm). The authors implemented the magnitudes of corneal coma-like RMS aberrations into Amsler’s (1938) early classification method to create a new grading system where,

Stage 1 keratoconus =

- Mean central K readings < 48.00 D.
- RMS of coma-like aberration from 1.50 to 2.50 μm.
- Absence of scarring.
Stage 2 keratoconus =
- Mean central K readings > 48.00 to < 53.00 D.
- RMS of coma-like aberration from > 2.50 to < 3.50 μm.
- Absence of scarring.
- Minimum corneal thickness > 400 μm.

Stage 3 keratoconus =
- Mean central K readings > 53.00 to < 55.00 D.
- RMS of coma-like aberration from > 3.50 to < 4.50 μm.
- Absence of scarring.
- Minimum corneal thickness 300 to 400 μm.

Stage 4 keratoconus =
- Mean central K readings > 55.00 D.
- RMS of coma-like aberration > 4.50 μm.
- Central corneal scarring.
- Minimum corneal thickness 200 μm.

Maeda et al. (2002) compared total ocular (from Hartmann-Shack data) and corneal aberrations (from videokeratographic, Placido ring based data) measured in 38 normal and 35 keratoconic eyes, using the combined Wavefront Analyser KR-9000 (Topcon Corp., Tokyo, Japan) – this device was customised to measure both sets of aberrations simultaneously. Using a 6-mm diameter, Maeda et al. (2002) found that compared to normal subjects, keratoconic patients showed significantly higher levels of 3rd-order RMS error in both corneal (normal subjects = 0.26 μm and keratoconic patients = 1.99 μm) and ocular aberration measurements (normal subjects = 0.25 μm keratoconic patients = 1.83 μm). Maeda et al. (2002) reported a good correlation between the anterior corneal and ocular aberrations for keratoconic patients and suggested that the anterior surface of the cornea was therefore the ‘major contributor’ of total eye aberrations in keratoconus. The keratoconic eyes investigated ranged from ‘suspect’ (or forme fruste) to ‘mild’ keratoconus cases only; the study did not include moderate or severe cases. Maeda et al. (2002) did not stipulate if the reference planes used in their work were the same for both corneal and ocular measurements, but they do state that simultaneous measurements were made for their subjects.

Barbero et al. (2002) investigated ocular aberrations in two keratoconic patients using the LRT method, the eyes investigated included two moderate and one severe case, mild cases were not evaluated in this paper. The author’s results showed that the mean 3rd-order RMS error values were approximately 3.74 times larger in the keratoconic eyes (2.02 ± 0.41 μm) than in 22 age-matched normal control eyes (0.54 ± 0.30 μm). The authors however, used two different pupil sizes (6.51 mm for the two moderate cases, and 5.5 mm for the one severe case) when calculating the Zernike coefficient terms, meaning that all three eyes could not be directly compared to each other.
Lim et al. (2007) used the Zywave Hartmann-Shack aberrometer (Technolas, Bausch & Lomb, Rochester, NY, US) to measure ocular aberrations in 35 keratoconic, 38 keratoconus-suspect and 166 visually-normal eyes. Lim et al.’s (2007) results concurred with previous studies and found that keratoconic ($1.73 \pm 0.71 \mu m$) and keratoconus-suspect ($0.94 \pm 0.66 \mu m$) eyes showed significantly larger higher-order RMS error than normal eyes ($0.49 \pm 0.16 \mu m$), with $p < 0.001$.

Jafri et al. (2007) evaluated ocular higher-order aberrations (LADARWave aberrometer; Alcon Labs Inc., TX, US) in 10 eyes with suspected keratoconus (defined as no corneal slit-lamp signs of keratoconus but topographical abnormalities), 10 eyes with mild keratoconus and in 50 control eyes (pupil diameter = 6.5 mm). The authors report that corneal vertical coma aberrations were significantly elevated in keratoconus suspect patients ($-0.53 \pm 0.25 \mu m$) compared to the control subjects ($-0.03 \pm 0.28 \mu m$) ($p < 0.02$). Jafri et al. (2007) endorsed the use of ocular aberrometry to supplement corneal topography, aberrometry and slit-lamp findings to help detect early keratoconus.

In summary, Schwiegerling and Greivenkamp (1996), Barbero et al. (2002), Maeda et al. (2002), Gobbe and Guillon (2005), Alio and Shabayek (2006), Lim et al. (2007) Jafri et al. (2007) and Bühren et al. (2007) all found increased higher-order aberrations in keratoconic corneas, suggesting that these eyes are likely to obtain a poorer retinal image than in a normal eye (summarised in Table 3.1).

<table>
<thead>
<tr>
<th>Study</th>
<th>Aberration type and aperture size</th>
<th>Measurement statistic</th>
<th>Keratoconic eyes</th>
<th>Normal eyes</th>
<th>Number of eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gobbe and Guillon (2005)</td>
<td>Anterior corneal (6 mm diam)</td>
<td>Average 3rd-order RMS error</td>
<td>$3.10 \pm 2.28$ SD</td>
<td>$0.28 \pm 0.15$ SD</td>
<td>870 N, 92 KC</td>
</tr>
<tr>
<td>Maeda et al. (2002)</td>
<td>Anterior corneal (6 mm diam)</td>
<td>Average 3rd-order RMS error</td>
<td>1.99</td>
<td>0.26</td>
<td>38 N, 35 KC</td>
</tr>
<tr>
<td>Maeda et al. (2002)</td>
<td>Total Ocular (6 mm diam)</td>
<td>Average 3rd-order RMS error</td>
<td>1.83</td>
<td>0.25</td>
<td>38 N, 35 KC</td>
</tr>
<tr>
<td>Bühren et al. (2007)</td>
<td>Anterior corneal (6 mm diam)</td>
<td>Average 3rd-coma RMS error</td>
<td>1.35 (0.70 to 3.11)</td>
<td>0.17 (0.024 to 0.90)</td>
<td>128 N, 23 KC</td>
</tr>
<tr>
<td>Lim et al. (2007)</td>
<td>Total ocular (6 mm diam)</td>
<td>Average higher-order RMS error</td>
<td>$1.73 \pm 0.71$ SD</td>
<td>$0.48 \pm 0.16$ SD</td>
<td>166 N, 35 KC</td>
</tr>
<tr>
<td>Alio and Shabayek (2006)</td>
<td>Anterior corneal (6 mm diam)</td>
<td>Average higher-order RMS error</td>
<td>$3.14 \pm 1.44$ SD</td>
<td>$0.52 \pm 0.09$ SD</td>
<td>40 N, 40 KC</td>
</tr>
</tbody>
</table>

Kosaki et al. (2007) investigated the magnitude and orientation of ocular aberrations measured in 76 keratoconic eyes wearing RGP lenses using the Wavefront Analyser KR-9000. Firstly, the author’s results concurred with previous studies in that, when uncorrected, they found
unusually high levels of coma RMS error. Secondly, Kosaki et al. (2007) reported that keratoconic eyes also showed significantly higher than normal levels of trefoil RMS \( (Z(3,±3)) \), tetrafoil RMS \( (Z(4,±4)) \) and secondary astigmatism RMS \( (Z(4,±2)) \) aberrations. Thirdly, without RGP lenses in place, Kosaki et al. (2007) found, on average, that trefoil RMS aberrations showed a significantly different orientation in keratoconic eyes (0.19 \( \mu \text{m} \) at 94 degrees) compared to in 105 normal control eyes (0.02 \( \mu \text{m} \) at 35 degrees). The authors discussed that changes in the orientation of trefoil aberrations are perhaps due to alterations in the corneal apex caused by keratoconus. Kosaki et al.’s (2007) data showed that RGP lens wear reduced higher-order RMS error (up to the 4th-order) in keratoconic eyes from an average of 0.72 ± 0.35 \( \mu \text{m} \) to 0.31 ± 0.14 \( \mu \text{m} \) (\( p <0.001 \)). Similar significant reductions were also found for coma RMS, trefoil RMS, tetrafoil RMS and secondary astigmatism RMS error (\( p \leq 0.006 \)). In agreement with previous studies of normal eyes (Hong et al., 2001, Dorronsoro et al., 2003, Lu et al., 2003), Kosaki et al.’s (2007) results demonstrate that RGP lenses can reduce higher-order RMS aberrations in eyes with keratoconus. However, even with these reductions, Kosaki et al. (2007) discussed that residual higher-order RMS aberrations were still larger in the keratoconic group than in normal RGP lens-wearing eyes (0.08 ± 0.02 \( \mu \text{m} \)).

Choi et al. (2007) compared ocular higher-order aberrations measured in 22 normal subjects and 14 keratoconic patients both without and with RGP lenses in place (custom-built Hartmann-Shack aberrometer: pupil diameter of 4 mm). The authors report that only subjects with good RGP lens centration were enrolled to eliminate the effect of RGP lens decentration. Choi et al. (2007) found that in the keratoconic patients, the individual Zernike coefficient vertical coma changed direction from -0.19 ± 0.23 \( \mu \text{m} \) to +0.13 ± 0.15 \( \mu \text{m} \) (\( p = 0.024 \)). In the normal subjects however, no significant changes in either the magnitude or sign of vertical coma were found between with (+0.11 ± 0.13 \( \mu \text{m} \)) and without (+0.04 ± 0.15 \( \mu \text{m} \)) RGP lenses (\( p = 0.36 \)). In agreement with Kosaki et al.’s (2007) report, Choi et al.’s (2007) results showed higher magnitudes of higher-order RMS error in keratoconic eyes with RGP lenses (+0.36 ± 0.12 \( \mu \text{m} \)), than in normal eyes with RGP lenses (+0.33 ± 0.12 \( \mu \text{m} \)), the authors however did not carry out any statistical analysis comparing these values.

In other studies, Marsack et al. (2007b) and Negishi et al. (2007) have also shown that higher-order residual aberrations persist in keratoconic eyes with RGP lenses in situ, and that these residual aberrations may contribute significantly to the reduced visual performance (compared to in normal subjects wearing RGP lenses) mentioned in Zadnik et al.’s (1998) previous study. Marsack et al. (2007b) investigated the effect of these residual higher-order aberrations on high-contrast and low-contrast visual acuity. The authors found, on average, that compared to aged-matched normal subjects, the RGP lens-wearing keratoconic patients achieved poorer logMAR acuities (keratoconic average = 0.15 ± 0.11 log units, normal average = -0.07 ± 0.08 log units) and poorer Pelli Robson contrast sensitivity scores (keratoconic average = 1.61 ± 0.14 log units, normal average = 1.81 ± 0.11 log units).

Marsack et al.’s (2007b) results showed that 3rd-order coma, 4th-order secondary astigmatism and 5th-order secondary coma aberrations were all components of the residual higher-order aberrations measured with RGP lenses in place in the keratoconic group (COAS device). In contrast, Negishi et al.’s (2007) residual higher-order aberrations (measured using the
ARK10000 device; Nidek, Aichi, Japan) were predominantly comprised of 3rd- and 4th-order terms. These results perhaps indicate that the pattern of residual aberrations is unique to each patient, and is likely to be influenced by the lens fitting and the liquid tear film lens. However, neither group of authors provided any specific information regarding the RGP lens fittings for their keratoconic patients. The literature suggests that the majority of keratoconic patients are fitted with flat-fitting RGP lenses (Edrington et al., 1996, Zadnik et al., 1998, Edrington et al., 1999, Barr et al., 2000, Fink et al., 2001, Zadnik et al., 2005). To date, only Jinabhai et al. (2010b) have evaluated how higher-order aberrations alter with different RGP lens fittings. Their results suggested that flatter-fitting RGP lenses provided lower magnitudes of residual aberrations and better visual acuities compared to steeper-fitting RGP lenses. However, these measurements were performed for one patient with moderate keratoconus only.

Both Marsack et al. (2007b) and Negishi et al. (2007) hypothesised that reducing the residual wavefront errors may give an improvement in visual performance. Both groups of authors discussed that the residual errors could be due to the internal optics of the eye (i.e. the posterior cornea and/or the crystalline lens). However, it is also possible that the residual wavefront errors were caused by small RGP lens movements during data capture. Marsack et al. (2007b) assessed 7 keratoconic eyes, one severe case and six moderate cases, whereas Negishi et al. (2007) measured 10 eyes with mild keratoconus only. It would have been interesting to compare the residual aberration errors present in RGP lens-wearing keratoconic patients from cases representing each of the three degrees of disease severity.

Chen and Yoon (2008) suggested that some of the residual aberrations found in the RGP lens-wearing keratoconic eyes from Marsack et al.’s (2007b) and Negishi et al.’s (2007) studies may have been due to the posterior corneal surface, and not the crystalline lens. Chen and Yoon (2008) measured anterior and posterior corneal aberrations in 82 keratoconic eyes and 31 normal eyes, using the Orbscan II (lens-subtraction method) and a 6-mm corneal diameter. Their results revealed that 37 advanced keratoconic eyes showed substantially larger mean posterior corneal higher-order RMS error (1.04 ± 0.31 μm) compared to normal eyes (0.19 ± 0.05 μm). The magnitude of the posterior surface aberrations was found to increase with the severity of the disease, as the 14 mild and 31 moderate keratoconic eyes showed higher-order RMS errors of 0.24 ± 0.05 μm and 0.54 ± 0.21 μm respectively. The average coma RMS error, the most dominant posterior surface aberration term in keratoconic eyes, was found to be substantially higher in advanced cases (0.93 ± 0.35 μm) than in normal control eyes (0.09 ± 0.06 μm). Chen and Yoon (2008) discuss that in keratoconus, some level of compensation may exist between the coma aberrations of the anterior and posterior corneal surfaces. The level of compensation seemed to vary with the severity of disease. The author’s results showed that on average 22 %, 24% and 14% of the anterior surface coma aberrations were compensated for by the posterior surface in severe, moderate and mild keratoconic eyes respectively. No such compensatory effects for coma RMS errors were found in the normal subjects. Hence Chen and Yoon’s (2008) findings supported their initial hypothesis that as the cone begins to protrude with disease progression, stromal thinning also leads to posterior corneal surface protrusion anteriorly, and thus the inducement of posterior corneal coma aberrations.
In concordance with Chen and Yoon's (2008) findings, Nakagawa et al. (2009) also reported that the mean higher-order RMS aberrations from the anterior/posterior corneal surfaces were significantly higher \((p < 0.001)\) in keratoconic eyes \((4.34 / 1.09 \, \mu m,\) respectively) than in control eyes \((0.46 / 0.15 \, \mu m)\) – using the Oculus Pentacam with a 6-mm corneal diameter. The mean magnitudes of trefoil RMS and coma RMS aberrations, for the anterior/posterior corneal surfaces, were significantly \((p < 0.001)\) higher in keratoconic eyes \((\text{trefoil RMS: 0.77 / 0.19 } \mu m\) and \(\text{coma RMS: 3.57 / 0.87 } \mu m)\) than in control eyes \((\text{trefoil RMS: 0.09 / 0.04 } \mu m\) and \(\text{coma RMS: 0.33 / 0.07 } \mu m)\). The authors also discovered that the mean coma axes \((\text{via RMS vector analysis})\) for to the anterior \((63.6 \, \text{degrees})\) and posterior corneal surfaces \((241.9 \, \text{degrees})\) were in opposite directions for patients with keratoconus. Nakagawa et al. (2009) discussed that these results may be explained by some level of aberration compensation between the anterior and posterior corneal surface in patients with keratoconus.

Schlegel et al. (2009) investigated the ocular, anterior corneal, and internal higher-order wavefront aberrations in 100 eyes of patients with keratoconus and 155 visually-normal eyes, using a combined anterior corneal topographer and aberrometer (OPD-Scan II; NIDEK Co. Ltd., Gamagori, Japan). All three sets of aberration measurements were centred on the corneal vertex rather than the more conventional line of sight \((\text{defined as the line passing through the centre of the eye's entrance and exit pupils, which essentially connects the object of regard to the fovea}).\) As expected, the results showed that the corneal, internal and ocular aberrations measured were significantly higher in the keratoconus group than in the normal group. Unlike ocular trefoil RMS aberrations \((3\text{rd- and 5\text{th-order terms}})\), ocular spherical RMS \((4\text{th- and 6\text{th-order}})\), coma RMS \((3\text{rd- and 5\text{th-order}})\), higher-order cylinder RMS \((4\text{th- and 6\text{th-order}})\) and higher-order RMS error \((\text{up to the 6\text{th-order}})\) aberrations were found to be proportionally lower in magnitude than the respective corneal values in the keratoconus group. The authors discussed that this may suggest a partial ‘balancing’ effect of the corneal aberrations by the internal aberrations in keratoconic eyes, as had been previously reported in studies of normal eyes \((\text{Artal et al., 2001}).\) Schlegel et al.’s (2009) results agree with the theories of Nakagawa et al. (2009) and Chen and Yoon (2008) further demonstrating that the posterior corneal surface compensates for higher-order aberrations manifested at the anterior corneal surface.

At present, exactly how 4th-order spherical aberration becomes altered by keratoconus is still subject to debate. Some studies briefly report significant differences in corneal measurements between keratoconic and normal eyes \((\text{Gobbe and Guillon, 2005, Bühren et al., 2007, Bühren et al., 2010}).\) However, Gobbe and Guillon (2005) only reported a significant difference at the largest corneal diameter investigated \((6 \, \text{mm}).\) Similarly, Bühren et al.’s (2007) and Bühren et al.’s (2010) data were also calculated using a 6-mm diameter. Both these studies contradicted the conclusions of Barbero et al. (2002), who had previously suggested that the progression of keratoconus did not seem to significantly affect the magnitude of spherical aberration. Interestingly Barbero et al. (2002) found that, in a moderate keratoconic subject’s right eye, the anterior corneal and ocular spherical aberration values showed opposite signs \((\text{anterior corneal: } +0.44 \, \mu m \text{ and ocular: } -0.30 \, \mu m).\) In the same patient’s left eye however, the authors report that corneal spherical aberration was negative \((-0.55 \, \mu m)\) and that ocular spherical aberration was
zero. In contrast, their severe keratoconic patient showed negligible ocular and anterior corneal spherical aberration. From their results, Barbero et al. (2002) hypothesised that changes in 4th-order corneal spherical aberration, due the progression of keratoconus (from moderate to severe), could be compensated for by the internal optics, as found in previous studies of normal eyes (Artal and Guirao, 1998, Artal et al., 2001, Artal et al., 2002, Kelly et al., 2004, Artal et al., 2006). However Barbero et al.’s (2002) theory was based on data from 3 keratoconic eyes only, two of which were from the same patient.

Maeda et al.’s (2002) paper measured significant differences in RMS spherical-like aberrations at a 4-mm diameter between keratoconic and normal eyes for both corneal and ocular aberrations. However, the data in their paper combined 4th- and 6th-order spherical aberration terms together. Maeda et al. (2002) explained that the differences between the two groups investigated were substantially larger for coma RMS error than for spherical RMS error for both corneal and ocular aberrations.

Some studies have shown that when compared to normal eyes, corneal spherical aberration becomes more positive in keratoconus (Gobbe and Guillon, 2005, Bühren et al., 2007, Bühren et al., 2010), whereas others have reported that ocular spherical aberration becomes more negative (Barbero et al., 2002, Kolibaum et al., 2003). More recently, Pinero et al. (2010) reported a broad range of corneal spherical aberration values amongst mild (37 eyes), moderate (24 eyes) and severe (20 eyes) keratoconus patients, with a mean value of -0.21 µm ± 0.71 µm [SD] and a range between -1.80 to +1.31 µm. It is highly likely that changes in 4th-order spherical aberration with the development of keratoconus will be dependent on the location of the cone apex from the centre of the cornea. On balance, the majority of the literature agrees that spherical aberration is altered by keratoconus.

3.2 The Visual benefit of correcting the higher-order aberrations

Compared to when uncorrected, Liang et al. (1997) reported that correcting higher-order aberrations, by using adaptive optics (described in detail in section 3.3.2), led to an improvement in the calculated PSF, MTF, Strehl ratio and contrast sensitivity functions in their study of 14 normal eyes. To further explore the efficacy of correcting higher-order aberrations, Williams et al. (2000) computed visual benefit scores for 109 normal eyes and 4 patients with keratoconus. The authors reported scores of between 1.5 and 8 in their normal subjects, whereas 3 of the 4 keratoconic eyes showed a potential visual benefit in excess of 8, with one eye showing a visual benefit of 25 (these scores were all calculated for a spatial frequency of 16 cycles/degree (Galvin and Williams, 1992)). Although it would have been useful, Williams et al. (2000) did not state the severity classifications of their four keratoconic eyes.

In a subsequent study, Yoon and Williams (2002) compared the effects of correcting both monochromatic and chromatic aberrations using a deformable mirror in 17 normal eyes. The authors discovered improved contrast sensitivity functions and visual benefit scores when only higher-order monochromatic aberrations were corrected in white light, compared with chromatic aberration correction alone. However, correcting both chromatic and monochromatic aberrations gave the maximal visual benefit (Figure 3.2). However, there is no simple strategy which allows the correction of both aberration types.
Measurements with both the Tscherning and Hartmann-Shack techniques are traditionally made in scotopic conditions, using a light source in the near-infrared range. Kollbaum and Bradley (2007) explain that in order to correct higher-order aberrations for normal visible light, the wavefront errors measured in the ‘near-infrared’ range, will need to be recalculated to account for the visible range. However, Llorente et al. (2003) compared ocular aberrations measured using the Hartmann-Shack and LRT methods; their study design allowed a comparison between aberrations measured in near-infrared light (at ~ 787 nm) and at the middle of the visible range (at ~ 543 nm) respectively. Llorente et al. (2003) made measurements on a range of 36 patients aged between 20-71 years (including some post-surgical eyes). Their results showed equivalence for the higher-order aberrations terms measured with either illumination type.

Since Liang et al. (1994) introduced the Hartmann-Shack aberrometer, the concept of ‘super-vision’, or perfectly correcting all the higher-order aberrations of the eye, has been considered (Liang et al., 1997, Charman and Chateau, 2003, Charman, 2004, Charman, 2005a). However there are several limitations to this concept, as Charman and Chateau (2003) outline:

1. limits that are set by diffraction due to the pupil shape and size
2. the limit of the photoreceptor ‘packing’ density at the foveola
3. accommodative micro-fluctuations
4. tear film fluctuations

Figure 3.2 The MTFs (lower) and VBs (upper) of correcting aberrations in different conditions for a 3- (left) and 6-mm (right) pupil diameter. Yoon and Williams (2002) assumed a perfect correcting method for the calculations to generate the above graphs.
3.3 Correcting monochromatic higher-order aberrations

Several methods can be used to correct monochromatic higher-order aberrations including surgical intervention, adaptive optics and contact lenses. These methods will now be discussed along with the concept of neural adaptations to higher-order aberrations.

3.3.1 Surgical intervention

Refractive surgeons, for some years now, have been using wavefront-guided aberration measurement systems to customise LASIK treatment patterns to a given patient’s cornea (Mrochen et al., 2000b). These treatments not only aim to correct the patient’s refractive error, but also attempt to remove their higher-order aberrations too. Alió and Montés-Micó (2006) and Nuijts et al. (2002) both report that wavefront-guided laser ablation may give better post-operative visual performances than standard LASIK; however corneal laser ablation can also induce unwanted higher-order aberrations whilst attempting to eliminate them (Chalita et al., 2004). A major drawback of refractive surgery is that it is an irreversible procedure. Also, this treatment is not possible for all eyes, for example keratoconus and radial keratotomy are considered as contraindications.

Munson et al. (2001) report the use of the Hartmann-Shack aberrometer to assess the outcome of penetrating keratoplasty (PK) in a 62-year old male patient who had been diagnosed with keratoconus 30 years previously. Before the procedure, the keratoconic eye exhibited extremely large amounts of higher-order aberrations that could not be measured unless the patient wore their habitual RGP contact lens. The authors explain that light scatter from corneal scarring and ‘crossover’ of the spot images at the Hartmann-Shack sensor were probable reasons as to why measurements were not possible without the RGP lens. With the lens however, the computed PSF of the eye was broad and multimodal in shape. The simulated retinal images (derived by convolution of a logMAR letter chart with the patient’s PSF) for this patient confirmed the subjective report of mono-polyopia. At 13 months after surgery, the aberrations of the corrected eye were found to be much smaller compared to before surgery, which correlated with a more compact PSF and sharper simulated retinal images. These optical changes were mirrored by an improvement in spectacle-corrected visual acuity from 1.3 log units before surgery, to 0.0 log units at 13 months. The authors concluded that the Hartmann-Shack aberrometer provided an objective, quantitative assessment of the optical outcome of PK which allows the clinician to measure retinal image quality objectively and to simulate the visual distortions associated with keratoconus.

Pinero et al. (2009) compared the refractive and corneal aberrometric outcomes of intra-corneal ring segment implantation in 106 patients with keratoconus using traditional ‘mechanical tunnelling’ (in 63 eyes) and femtosecond laser-assisted tunnelling (in 83 eyes). Patients were followed-up for between 1 to 24 months after surgery. The authors found that at 6 months, the best-corrected visual acuity improved significantly in the femtosecond group (from 0.51 ± 0.28 log units pre-operatively, to 0.65 ± 0.28 log units post-operatively with p = 0.02) but not in the mechanical group. However, no significant differences in either the cylindrical or spherical equivalent powers were found between the two groups. On the other hand, significant differences
were found between the two groups in terms of spherical aberration ($Z(4, 0)$) and coma RMS, in favour of the laser-assisted group ($p \leq 0.01$).

Baumeister et al. (2009) evaluated changes in corneal aberrations before and 6 months after collagen cross-linking was performed in 20 eyes of 20 keratoconic patients. The authors reported no significant difference in total higher-order RMS aberrations ($3.4 \pm 1.7 \mu m$ to $3.3 \pm 1.8 \mu m$; $p = 0.12$) or coma RMS aberrations ($2.9 \pm 1.5 \mu m$ to $2.8 \pm 1.4 \mu m$; $p = 0.05$) after treatment.

3.3.2 Adaptive optics

The use of deformable mirrors have been shown to give improvements in the visual performance of both normal (Bara et al., 2000, Navarro et al., 2000, Yoon et al., 2004a, Jeong and Yoon, 2006, Villegas et al., 2008) and abnormal eyes (Sabesan et al., 2007a, Rocha et al., 2010). In Sabesan et al.’s (2007a) study a deformable mirror (Mirao 52D, Imagine Eyes) was used for 2 eyes with moderate keratoconus (for a 6-mm pupil diameter), to reduce the higher-order RMS error (3rd- to the 6th-order) from $1.82 \pm 1.06 \mu m$ to $0.05 \pm 0.02 \mu m$, which increased the calculated Strehl ratio from 0.007 to 0.88. Although the patient reported a significant improvement in vision when corrected with the device, the authors did not measure visual acuity in their study.

Rocha et al. (2010) used the crx1 device (Imagine Eyes) in 12 eyes of 8 keratoconic patients and reported a substantial reduction in higher-order RMS error (3rd- to the 5th-order) from $1.88 \pm 0.99 \mu m$ to $0.13 \pm 0.02 \mu m$ for a 6-mm pupil diameter. On average, the keratoconic patients achieved better high-contrast logMAR visual acuity (ETDRS) with the crx1 device ($0.31 \pm 0.18$) compared to a sphero-cylindrical correction alone ($0.44 \pm 0.23$).

Despite their usefulness, there are several disadvantages to using adaptive optics devices,
1. they require very precise alignment of the subject’s pupil with the optical axis of the set-up (i.e., with the wavefront sensor and the deformable mirror)
2. they are unattractive and very obtrusive devices
3. they are expensive to manufacture (especially the deformable mirror type)
4. they always require pupillary dilation (as an artificial pupil is used for measuring visual acuity and aberrations)
5. they require very bright lighting conditions to allow visual acuity measurements to be made through the device

3.3.3 Contact lenses

A more suitable device to correct higher-order aberrations would be the contact lens, which is discrete, simple to use and relatively inexpensive to manufacture compared to adaptive optics devices. Nevertheless, contact lenses too have their respective limitations (further detailed in section 3.7).

The use of computer modelling packages allows researchers to predict the visual outcome and decentration effects of an ‘ideal’ aberration-correcting (or customised) contact lens. Guirao et al. (2001) carried out simulations of customised contact lens decentrations ‘on eye’, and
their corrective effect on wavefront aberrations for 10 normal eyes. The decentrations modelled were a combination of rotation and translation (vertical or lateral displacement) just as in normal soft contact lens wear (Tomlinson et al., 1994, Edrington, 2011). Guirao et al. (2001) showed that the effect of decentration was different for each particular aberration term corrected, and that the benefits yielded were reduced as the decentrations increased in magnitude. Based on their results, the authors hypothesised that perhaps not all higher-order aberration terms are therefore worth correcting. Their data showed that some coefficients were found to be particularly sensitive to decentrations and actually induced superfluous aberrations which may cause a loss in visual performance in an extreme case of on-eye lens decentration.

In another study, Guirao et al. (2002a) mathematically simulated the on-eye translation of a customised lens correcting spherical aberration and reported the inducement of unwanted coma aberrations. The amount of coma induced was dependant on the magnitude of the spherical aberration correction in the lens, as well as the amount of translation. To help keep visual performance as high as possible, even in the presence of decentrations, the authors simulated a partial correction of the measured aberrations. The partial corrections were found to always yield some visual benefit, compared with conventional sphero-cylindrical lenses alone. However, this partial correction theory was tested using just four Zernike coefficient terms (Z (4,0), Z (6,+6), Z (3,+1) and Z (3,+3) and it was not apparent from these results if this idea would work for all Zernike terms. Guirao et al. (2002a) did not state whether the measurements modelled in their paper were for normal eyes or not. Nor do the authors give the pupil size for which the aberrations were calculated. Finally the magnitudes of the translations tested in this investigation were not disclosed in the paper.

de Brabander et al. (2003) simulated the visual performance achieved by correcting higher-order aberrations in nine moderately keratoconic eyes. The authors found that large improvements in retinal image contrast (using MTF data) were possible with the perfect alignment of a customised, aberration-controlling contact lens. Like Guirao et al. (2001) and Guirao et al. (2002a), de Brabander et al. (2003) computed that decentrations of a customised lens led to a partial loss in the visual benefit gained for patients with keratoconus. The authors explained that the loss in visual performance due to decentration was larger when the pupil size was bigger. The authors calculated the effects of rotation and translation separately from each other (as did Bara et al. (2000) using adaptive optics). Clinically, it is widely accepted that soft lenses will translate and rotate upon blinking in tandem (Tomlinson et al., 1994, Young et al., 2009), and that these movements are not mutually exclusive as de Brabander et al.’s (2003) calculations would suggest. Nevertheless, de Brabander et al.’s (2003) results showed that rotations up to a maximum of 5 degrees and decentrations up to a maximum of 1 mm on blinking would be permissible to still yield a benefit from a customised lens. How much tolerance is possible for mild or severe keratoconic eyes remained unexplored in this paper.

Yoon and Jeong (2003) simulated the decentration of customised contact lenses for two post-PK and two keratoconic eyes. They found that compared to in normal eyes (visual benefit = 3), the customised correction gave highly-aberrated eyes a threefold improvement in visual performance (visual benefit = 9). The author’s results also suggested that highly-aberrated eyes were more tolerant to decentrations than normal eyes; for a 0.2 mm decentration vertically, the
visual benefit gained was reduced by only a third for highly-aberrated eyes, but by half in normal eyes.

Hong et al. (2001) evaluated the impact of standard soft and RGP contact lenses on the higher-order aberrations of 4 normal eyes, using the Hartmann-Shack technique. The authors discovered that RGP lenses were the most effective at reducing the uncorrected aberrations. In addition to reductions in coma and trefoil RMS aberrations, the RGP lenses gave higher Strehl ratios, sharper PSFs and larger areas under the MTFs. In agreement with Dorronsoro et al.’s (2003) conclusions, Hong et al. (2001) discussed that the correction of anterior corneal surface aberrations, using RGP lenses, may possibly induce residual ocular aberrations due to the compensatory effects of the eye’s internal optics (Artal et al., 2001).

Using the LRT method, Lu et al. (2003) also compared uncorrected and corrected higher-order aberrations in 54 normal eyes with both soft and RGP contact lenses. In agreement with Hong et al.’s (2001) study, Lu et al. (2003) also found that RGP lenses were more efficient at reducing higher-order RMS aberrations than the standard soft lenses. Moreover, their data showed that standard soft contact lenses induced larger 3rd-, 4th- and 5th-order RMS aberrations, reinforcing the work of Dietze and Cox (2003) and Cox (1990). These findings were also supported by Roberts et al. (2006), who reported a significant increase in higher-order RMS error with soft lenses compared to the uncorrected aberrations of 30 normal eyes. Roberts et al. (2006) also found increased coma RMS, trefoil RMS and spherical aberration RMS with soft lenses compared to the uncorrected eye, however these differences were not found to be significant.

3.3.4 Neural adaptations

The literature suggests that the human brain is likely to be adapted to its own particular pattern of higher-order aberrations. Artal et al.’s (2004) study involved using adaptive optics in 5 normal subjects. The deformable mirror was first used to correct each subject’s manifest aberrations and then to act as an aberration generator, to blur the subject’s vision either with their own aberration pattern or a rotated version of their own aberrations. Eight different aberration patterns were generated for each participant; the first was their own habitual aberration pattern. In addition, 7 similar patterns were created, where each pattern was rotated in 45-degree intervals from 0 through to 315 degrees. Subjects were asked to view a stimulus (a monochromatic binary-noise signal which displayed sharp edges in all orientations) through the mirror with each of the 8 aberration patterns in a randomised order. The author’s results showed that the subjective blur (measured using a matching technique) when viewing the stimulus through one’s own wavefront aberration pattern, was found to be less, than when the aberration pattern was rotated. Based on their findings the authors hypothesised that the human brain is perhaps adapted to its own particular pattern of higher-order aberrations.

Sabesan and Yoon (2009) measured high-contrast acuity and ocular higher-order aberrations through a deformable mirror in 8 normal and 8 keratoconic eyes. The mean ± 1 SD of the manifest higher-order RMS error for the normal eyes was 0.44 ± 0.12 µm (6-mm pupil diameter). With correction, the aberrations were reduced to 0.05 ± 0.01 µm. In the keratoconic
patients, the pre-compensated higher-order RMS error was 2.29 ± 1.15 µm for the same pupil diameter. After compensation, the higher-order RMS error was reduced to 0.08 ± 0.03 µm. The residual higher-order RMS errors measured with the mirror were not found to be significantly different between groups (p = 0.17). With the deformable mirror in place, the logMAR visual acuity was -0.26 ± 0.06 log units in the normal group and -0.07 ± 0.05 log units in the keratoconic group. The adaptive optics-corrected high-contrast acuity (AOHCV) was not found to be correlated with the magnitude of the residual aberrations in the normal group eyes (R² = 0.04), however, significant correlations were found in the keratoconic group (R² = 0.67). Given the relatively larger magnitudes of manifest aberrations in the keratoconic eyes, the improvement in retinal image quality was more pronounced in the keratoconic group than in normal group. However, with an equivalent near-diffraction-limited optical quality in both groups (a residual higher-order RMS error of around ± 0.10 µm), visual performance was found to be significantly worse in the keratoconic group (p = 0.00002). Sabesan and Yoon (2009) concluded that their results are likely to indicate that long-term visual experience with poor retinal image quality, induced by higher-order aberrations in keratoconic eyes, may restrict the visual benefit achievable with near diffraction-limited optical quality. On the other hand, it may also be argued that keratoconic eyes may perhaps show poorer neural processing compared to normal eyes; however, no current studies have investigated this.

In a subsequent study, Sabesan and Yoon (2010) measured ocular aberrations and high-contrast (100 %) and low-contrast (20 %) tumbling ‘E’ visual acuity in four moderately keratoconic eyes wearing their habitual soft-toric contact lenses. Three emmetropic, normal controls (one eye from each participant) were also investigated in their study. A deformable mirror system was used to correct each normal eye’s aberrations, whilst simultaneously inducing each of the 4 keratoconic eye’s wavefront aberration patterns. The authors measured each normal subject’s high-contrast and low-contrast visual acuities through each keratoconic aberration pattern and compared this with the acuities recorded from the keratoconic patients. The authors defined the magnitude of any neural compensation found as the improvement in visual acuity in each keratoconic eye compared to the acuity of the three normal eyes whilst viewing through the keratoconic aberration patterns. Sabesan and Yoon (2010) report that each keratoconic eye had significantly better high- (p < 0.02) and low-contrast acuity (p < 0.03) than the three normal eyes. With equivalent optical quality between the two groups, on average, the neural compensation measured accounted for around 1.2 lines of improvement in both high-contrast and low-contrast acuity in the keratoconic eyes compared to the normal eyes. The authors discussed that in keratoconic eyes, the visual neural system compensates for long-term visual experience with an asymmetrically blurred retinal image, resulting in an improved visual performance in the keratoconic patients compared to the normal subjects.

Although these 2 adaptation studies in keratoconus patients are useful, it is important to appreciate they were all conducted in very unnatural conditions. Firstly, deformable mirrors are obtrusive, bulky devices which must be kept aligned exactly at all times. Secondly, all patients’ pupils in all three investigations were dilated with accommodative paralysis. Thirdly, all the aberration measurements described were conducted in photopic conditions to allow
measurements of visual acuity and aberrations through the mirror. In general, patients would only ever experience scotopic or mesopic light conditions with natural pupil dilation.

Sabesan and Yoon’s (2009) study, does not describe how long any habitual contact lenses were left out for before carrying out their investigation in their one severe and 7 moderately keratoconic patients. This omission may have some impact on the interpretation of the authors’ results because, coma RMS aberrations appear to increase significantly after RGP contact lens wear is suspended for a week (Jinabhai et al., 2012a); it is also possible that further changes in optical quality may continue after this period too. An increase in coma RMS aberrations essentially leads to a more distorted, broader PSF falling on the retina. A further complication in assessing the adaptation to aberrations, is that vertical coma typically shows a positive shift (from an uncorrected negative value to a positive value) with RGP lens wear in patients with keratoconus (Choi et al., 2007, Jinabhai et al., 2010b). A change from a negative to a positive value effectively causes the original PSF shape falling on the retina to become rotated through 180 degrees. Other confounding factors to these adaptation studies is that keratoconus is a progressive disease (Krachmer, 1978, Kennedy et al., 1986), with several authors indicating that corneal aberrations increase in magnitude with keratoconus progression (Gobbe and Guillon, 2005, Alio and Shabayek, 2006, Pinero et al., 2011). Equally, Mihaltz et al. (2010) also proposed that the ‘line of sight’ becomes shifted with keratoconus progression in an attempt to balance spherical aberration with coma. In summary, as coma aberrations vary with and without RGP lens wear and with disease progression it is difficult, at present, to determine exactly what level of retinal image quality keratoconic patients are likely to be adapted to.

3.4 Considerations when measuring aberrations in patients with keratoconus

When attempting to evaluate the optical quality of the keratoconic eye using the Hartmann-Shack technique, the fundamental problem lies in actually acquiring the spot images as the cornea, especially in severe cases of keratoconus, may often become very distorted or even scarred. A simple solution to help reduce the amount of ‘crossover’ or ‘overlapping’ of the aberrated spot images would be to reduce the actual amount of spot displacement possible. This may be achieved by using a shorter focal length for the lenslets in the micro-array (Thibos and Hong, 1999, Thibos, 2000). This concept is however flawed, as the higher powered lenses would result in a loss of sensitivity, as very small spot displacements would be more difficult to measure (Yoon et al., 2004a, Yoon et al., 2004b). Another simple method would be to rearrange the physical spacing of the lenslets to allow maximum resolution (Llorente et al., 2007), however, no commercially available Hartmann-Shack instrument allows this to be done easily.

Rarer and more complex methods have been suggested to help reduce the loss of data in three isolated studies for the Hartmann-Shack technique which included using,

- complex ‘unwrapping’ algorithms in the computational spot detection process; i.e. special mathematical modifications which help to assign spots to their corresponding lenslet, even if they are deviated outside their sub-aperture on the CCD sensor (Pfund et al., 1998)
- a spatial modulator array; this device is placed in front of the lenslet array and allows the 'selective switching on and off' of certain sub-apertures allowing a definite assignment of the spots to their corresponding sub-apertures on the CCD sensor (Lindlein et al., 2001)
- astigmatic lenses in the micro-lenslet array; here the astigmatic lenses produce 'line' rather than 'spot' images, all the cylindrical lenses are orientated at a multitude of different angles allowing simpler recognition of the line image from a given cylindrical aperture lens (Lindlein et al., 2000).

Most Hartmann-Shack aberrometers do not easily allow any of these modifications to be made to the devices’ original setup; as a result these modifications are not routinely used in clinical investigations.

Compared to these three studies, the use of a translatable grid has been considered as a more successful approach for increasing the Hartmann-Shack method's 'dynamic range' - the maximum measurable wavefront slope ($\theta_{\text{max}}$) of an aberrated ray (Yoon et al., 2006, Pantanelli et al., 2007). Equation 3.1 derives $\theta_{\text{max}}$ using $\Delta d_{\text{max}}$, the maximum displacement between the spot image and the optical axis of the lenslet; $f$, the focal length of the micro-lenslet array and $s$, the spacing between the lenslets. The translatable grid essentially works to increase the width of the area that any given aberrated spot can fall onto, by blocking 'every other neighbouring lenslet' for any given lenslet, as depicted in Figure 3.3.

Equation 3.1

$$\theta_{\text{max}} = \frac{\Delta d_{\text{max}}}{f} = \frac{s/2}{f}$$

Figure 3.3 The use of a translatable grid in Hartmann-Shack aberrometry (Yoon et al., 2006). A schematic diagram of capturing the spot images by blocking every other lenslet at each 'plate position' for each 'plate translation'. The figure shows a simplified 5 x 5 lenslet array.
Yoon et al. (2006) used this translatable-grid prototype device on both a normal human eye and an aberrated phase plate. The authors reported no difference in sensitivity, repeatability or accuracy compared to measurements made without the grid. Pantanelli et al. (2007) also used this adapted translatable-grid system on 190 normal control subjects, as well as 21 patients with keratoconus or post-PK. They found higher levels of negative vertical coma aberration, as well as elevated 2nd- and 4th-order astigmatism in the keratoconic eyes than in normal eyes. In the post-PK eyes, they found significantly higher levels of oblique trefoil, quadrafoil, spherical aberration and positive values of vertical coma, than in normal eyes. The potential visual benefits (Williams et al., 2000) calculated from their abnormal subject’s data showed that there is considerable scope for improving the optical performance of very highly-aberrated eyes with bespoke customised corrections.

Nonetheless, there are possible limitations of this translatable-grid adaptation, one of which Pantanelli et al. (2007) acknowledge, in that inaccuracies and errors could arise due to the longer data acquisition times required when using this special technique, as the grid needs to be moved several times during data capture (Figure 3.3). Eye movements, tear film or accommodation variations during the grid repositioning period will undoubtedly confound results. Additionally, neither study discusses that some spots, due to gross corneal distortions, will become deviated away from the wavefront sensor altogether, nor do they acknowledge how their grid could possibly account for this. Finally, some spot images, no matter how many times the grid is moved, are likely to perhaps fall onto the grid itself causing ‘lost’ data (as no image will be registered at the CCD). Nevertheless, the results from Pantanelli et al.’s (2007) work provided a possible solution for measuring the aberrations on highly-aberrated post-PK eyes. It is worth noting that translatable grids can only be used in custom built aberrometers, commercially available instruments will not permit such adaptations of the micro-lenslet array.

3.4.1 The line of sight (LoS) in keratoconus

The line of sight (LoS) is defined as the line passing through the centre of the eye’s entrance and exit pupils connecting the object of regard to the fovea, the LoS has previously been described as the most relevant reference axis for defining retinal image quality at the point of fixation (Applegate et al., 2009). Mihaltz et al. (2010) hypothesised that keratoconus causes a shift in the LoS, which thereby acts as a compensating mechanism for increases in corneal higher-order aberrations. The authors measured the shift in the LoS using the WASCA Hartmann-Shack aberrometer (Carl Zeiss Meditec AG, Jena, Germany). This aberrometer determined the LoS by aligning the subject’s eye with the optical axis of the measurement system by centring the subject’s pupil on the device’s alignment ring (Applegate et al., 2000). The aberrometer provided a measurement of the distance of the LoS from the pupillary centre in the form of $x$ and $y$ coordinate values. The authors used these co-ordinates in trigonometric analyses to measure both the location and the angular axis of the LoS from the vertical meridian (along 90 and 270 degrees) in 55 eyes of 30 keratoconic patients. The angle between the pupillary axis and the LoS is more commonly known as the angle lambda (Charman, 1995). Mihaltz et al.’s (2010) data showed that keratoconic patients had a greater angle lambda than control patients and that the difference was more pronounced in the vertical direction than along the horizontal axis. Their results also show a significant correlation between the distance of LoS from the pupil centre and
the magnitudes of ocular vertical coma and spherical aberration. Guirao et al. (2001) have previously demonstrated that as spherical aberration is decentred, coma is induced. Kollbaum et al. (2008) also state, that depending on the sign of the eye’s inherent coma aberration, typical decentration of spherical aberration-controlling contact lenses could eliminate or change the direction and/or magnitude of the residual coma aberration. From their results, Mihaltz et al. (2010) concluded that a displacement in the LoS in keratoconus may be an internal compensation mechanism of the eye to find the ideal balance between coma and spherical aberration. In addition, the authors report that the axis of the shift of the LoS (measured with the aberrometer) showed a marked correlation with the steepest keratometric reading measured using corneal topography (Tomey corneal topographer; Tomey Corp, Nagoya, Japan). However, the authors do not describe how they adapted measurements centred on the corneal apex (from topography) with the measurements made by the aberrometer (based on the optical axis of the Hartmann-Shack device and the centre of the pupil).

3.5 Keratoconus and aberration-controlling contact lenses

The literature shows that a large proportion of keratoconic patients wear RGP lenses to help correct their visual difficulties (Davis et al., 1998, Szczotka et al., 2001, Kapur et al., 2003, Weed et al., 2007, Bilgin et al., 2009, Mahadevan et al., 2009). The keratoconic patients in these studies tended to wear their RGP lenses for most of their waking day as they were visually-dependent on them. With this in mind, the contact lens material and the anticipated wearing times are of great relevance to ocular comfort when considering fitting patients with keratoconus. Keratoconic hydrogel lenses, such as the KeraSoft2 lens (UltraVision International, Ltd., Bedfordshire, United Kingdom) and the Soft K lens (Soflex Contact Lens Industries Ltd., Misgav, Israel) are generally thick in nature (centre thicknesses of between 0.30 and 0.36 mm), and so the oxygen transmission of a contact lens is also an important aspect to consider when fitting keratoconic patients. White (2010) has suggested that more modern silicone hydrogel materials, such as the KeraSoft IC lens (Filcon III; 74 %water content; Dk 60 – UltraVision International Ltd), are useful for the long contact lens wearing times experienced in patients with keratoconus.

A soft lens design which could achieve maximum on-eye lens comfort as well as providing optimal visual performance would be appealing to many keratoconic patients and practitioners alike as an alternative to a RGP lens. Ideally, this hydrogel contact lens would be silicone-based, of a regular thickness and would have the capabilities to reduce the ocular higher-order aberrations associated with keratoconus.

The idea for higher-order aberration correction was first proposed by Smirnov (1962) who suggested “in principle it is possible to manufacture a lens compensating for the wave aberrations of the eye”. Aware of the fact that the spectacle lens will not conjugately follow the movements of the eye, Smirnov (1962) explained that “these lenses must obviously be contact ones”.

Most of the studies cited in this thesis have concentrated on attempting to make aberration-correcting contact lenses. However, some of the early work in this field designed aberration-generating lenses and compared the aberrations measured both with and without the contact lenses, as well as comparing in vivo and in vitro lens aberration measurements (Lópezm-
Gil et al., 1998, López-Gil et al., 2002). López-Gil et al. (2002) suggested that aberrations can be induced using soft contact lenses, meaning that the converse situation of correcting aberrations with lenses was also plausible. López-Gil et al. (1998) explained that when manufacturing aberration-controlling hydrogel lenses, it is necessary to accurately measure the higher-order aberrations in the lens (in-vitro) prior to dispensing. Both Jeong et al. (2005) and Kollbaum et al. (2008) have reported that this is possible using a Hartmann-Shack aberrometer combined with a ‘wet-cell’, in order to keep the soft lens hydrated.

López-Gil et al. (2003) trialled lathe-cut, front surface aberration-controlling contact lenses, which were made for four normal, four post-PK and two keratoconic patients. Their results showed that there were no significant differences in either visual acuity or contrast sensitivity, between with the customised lenses or with a spectacle-refraction in either the post-PK or normal groups. Equally, the authors found that higher-order aberrations increased in magnitude with the customised lenses for the post-PK and normal subjects. In contrast, their results for the two keratoconic patients showed that the customised lenses reduced the average uncorrected higher-order RMS aberrations from 1.0 µm to 0.5 µm. However, the authors did not indicate if these findings reached statistical significance or not. Moreover, the data showed that the customised lenses also provided significantly better high-contrast acuity (average of +0.80, Snellen decimal) compared to the keratoconic patients’ spectacle refraction acuity (average of +0.55). López-Gil et al. (2003) also compared contrast sensitivity scores achieved with the customised lenses and spectacles (at 3, 6 and 12 cycles/degree). In the manuscript text the authors indicated that the keratoconic patients showed better contrast sensitivity results, particularly at the lower spatial frequencies, however, a misprinted graph was presented in the corresponding figure. Interestingly, the authors suggested that better visual performance was achieved for the keratoconic patients (compared to the post-PK or normal subjects) because “the rotation and translation of the customised lenses is smaller for the keratoconic eye due to the conical shape of the cornea”.

López-Gil et al. (2003) did not state the severity of disease of their two keratoconic patients. Secondly, they do not disclose the outcome of their ‘control method’; which were two sets of separate aberrometry readings, taken six weeks apart, from the patient’s uncorrected eyes (i.e. no comments on the repeatability of these measurements were made in the manuscript). Thirdly, the authors do not explain if an average of the three readings of visual acuity and contrast sensitivity were used, or if they used the ‘best’ of the three in their data. Fourthly, the authors do not disclose which Hartmann-Shack aberrometer or corneal topographer they used in their investigation. Finally, the authors did not state if the RMS values in their figures were from ‘whole eye’ or ‘corneal’ measurements.

Jeong and Yoon (2006) used the Hartmann-Shack method to manufacture a front surface customised aberration-controlling soft lens for a patient with advanced keratoconus. In this study the authors accounted for on-eye lens decentration by firstly fitting a -1.50 DS conventional soft contact lens (the back optic zone radius value was not reported) on the subject’s eye and monitoring its centration on the pupil camera of their aberrometer. The final customised lens fitted in this study was reported to have the same base curve as the -1.50 DS ‘trial’ lens. The aberration correction was transferred onto the customised lens, accounting for the on-eye lens decentration.
and rotation observed with the trial lens. The customised lens produced successfully reduced this subject’s uncorrected higher-order RMS error from 3.89 μm to 1.28 μm. The lens was reported to have given the patient a ‘subjective’ improvement in vision; although it would have been useful to quantify how much of an improvement in vision was achieved, the authors did not measure visual acuity for this patient. Equally, no retinal image quality metrics were computed for the aberrations measured with the lens. Residual wavefront errors were still found for some Zernike terms even with the customised lens. The authors suggested that variations in the tear film or even accommodative micro-fluctuations could have accounted for the residual aberrations measured.

Jeong and Yoon (2006) reported that their customised lens showed typical vertical translations and rotations with blinks. The authors suggested that these small lens decentrations could also have contributed to the residual errors found.

Sabesan et al. (2007b), used the Hartmann-Shack method to carry out a comparison study for three keratoconic eyes (two severe and one moderate case) using front surface customised soft lenses versus conventional soft and RGP lenses. The authors accounted for possible lens decentrations by fitting trial lenses with three different base curves and assessed their fittings to ascertain which was the most stable for that particular eye, before manufacturing their customised soft lenses. In the most successful case, the total RMS error was only reduced from an uncorrected 3.97 μm to 3.28 μm with a conventional soft lens, but with the customised lens this was significantly improved to 0.97 μm. Compared to the conventional lenses, the customised lenses gave improved low-contrast (20 %) logMAR acuities, by an average of 2.1 lines. For one of the severe cases, the customised lens gave an improvement of 3 lines of low-contrast logMAR acuity compared to the patient’s habitual RGP lens. For high-contrast acuity there was very little difference between the subject’s RGP lens and the customised lens, the customised lens still performed best however. In agreement with Jeong and Yoon (2006), Sabesan et al. (2007b) also noted that some small residual errors persisted even with the aberration-correcting custom contact lenses.

Marsack et al. (2007a) produced a front surface customised aberration-controlling soft lens, using the Hartmann-Shack method, for a patient with moderate keratoconus and compared this to the patient’s habitual, conventional soft contact lens. The results showed that both high-contrast and low-contrast acuity were improved compared to the habitual lens. However, in contrast to Sabesan et al.’s (2007b) results, Marsack et al. (2007a) revealed that high-contrast logMAR acuity was improved (by 1.5 lines; p = 0.03) more than low-contrast logMAR acuity (which only improved by one line of letters; p = 0.11). Marsack et al. (2007a) noted that the habitual lens translated on-eye with blinks, but did not incorporate this factor into their design for the final customised lens design ‘L3’. They also, did not explain why the customised lenses ‘L1’ and ‘L2’ were not tested in their paper, even though they were designed specifically to help reduce the higher-order aberrations for this patient. So it is unclear whether ‘L1’ and ‘L2’ gave contradictory/unsatisfactory results. Nonetheless, ‘L3’ successfully reduced the uncorrected higher-order RMS error from 0.99 μm to 0.37 μm, compared to the standard lens 0.77 μm.

Chen et al. (2007b) experimented with a method of enhancing the fitting of their aberration-controlling lens by custom designing the back lens surface (using Orbscan II topography data) to help reduce the residual higher-order aberrations induced by lens
decentrations. They found that the stability of their back surface aberration-controlling soft lenses were better than conventional lenses. These bespoke lenses reduced both horizontal and vertical decentrations by a factor of 2 and reduced rotations by a factor of 5. The customised lenses helped to reduce aberrations for two moderately keratoconic patients. The uncorrected higher-order RMS error was reduced from $1.17 \pm 0.04 \mu m$ to $0.61 \pm 0.04 \mu m$ for the first patient and from $1.66 \pm 0.06 \mu m$ to $1.30 \pm 0.10 \mu m$ for the second patient. However, the authors did not measure visual acuity or any retinal image quality metric in their study. Chen et al. (2007b) measured both anterior and posterior corneal aberrations using the Orbscan II; from these data they performed calculations to model the aberrations of the internal optics. Their results suggested that the posterior corneal surface and the crystalline lens were largely responsible for the residual aberrations measured with the customised lenses in situ. Also the authors acknowledged that variations in the tear film could induce small amounts of unwanted aberrations, to counter these effects the authors standardised their measurements by taking all of their readings two seconds post-blink. Chen et al. (2007b) acknowledged that their customised lenses only had a central 5-mm optical zone of customisation which could possibly cause problems with glare in scotopic conditions. Future studies comparing back surface custom lens designs to front surface designs would arguably be of interest to the scientific community to ascertain which design was superior; as yet no such investigation has been carried out.

In these five studies so far (López-Gil et al. (2003), Jeong and Yoon (2006), Sabesan et al. (2007b), Marsack et al. (2007a) and Chen et al. (2007b)), none of the authors have clearly explained how the lower-order correction was decided upon for their customised lenses. One of following three options is likely to have been used,

a) the subjective over-refraction
b) the refraction derived from the aberrometry data
c) or perhaps a combination of a) and b).

Marsack et al.’s (2008) study compared visual performance and ocular aberrations using bespoke wavefront-guided soft contact lenses versus the subject’s own habitual RGP lenses. The authors produced customised lenses for three keratoconic eyes (two moderate and one severe case) and found that all three customised lenses gave better visual acuity compared to the patient’s habitual RGP lenses. For the subject with severe keratoconus, the habitual RGP lens provided a high-contrast logMAR visual acuity of $0.04 \pm 0.09$ log units, whereas the customised lens gave a score of $-0.05 \pm 0.05$ log units. For this same subject, the average uncorrected higher-order RMS error was reduced from $1.57 \pm 0.03 \mu m$ to $0.76 \pm 0.03 \mu m$ with the customised lens and to $0.50 \pm 0.15 \mu m$ by the habitual RGP lens. For one of the moderate cases, the uncorrected higher-order RMS error was reduced from $0.61 \pm 0.018 \mu m$ to $0.39 \pm 0.018 \mu m$ using their habitual RGP lens, and to $0.38 \pm 0.074 \mu m$ with the customised lens. The high-contrast acuity for this moderately keratoconic subject was measured as $0.20 \pm 0.02$ log units with the RGP lens and $0.14 \pm 0.02$ log units with the customised lens. These two cases demonstrate that customised soft contact lenses have the potential to provide comparable results to RGP lenses in terms of high-contrast visual acuity performance and higher-order RMS error correction.
In a subsequent study, Katsoulos et al. (2009) used a different approach to correct the higher-order aberrations measured in 8 mild to moderate keratoconic eyes. Here the authors designed customised soft lenses which corrected for around 75% of the uncorrected negative vertical coma aberration, as well as correcting 2nd-order (sphere/cylinder) terms extracted from their COAS Hartmann-Shack aberrometry data. In all 8 cases presented, a reduction in higher-order RMS error was seen (the largest reduction was from 0.86 µm to 0.42 µm), however the authors did not report if the differences were significant or not. On the other hand, Katsoulos et al. (2009) revealed a significant reduction in the magnitude of vertical coma aberrations for with and without the customised lenses using the Wilcoxon rank sum test ($p \leq 0.005$); the largest reduction found in their study was from -0.56 µm to -0.15 µm. These reductions in higher-order aberrations were believed to have contributed to the corresponding improvements in high-contrast logMAR visual acuities, compared to the patient's best-corrected spectacle acuities (the largest improvement was from 0.52 log units to 0.06 log units). In agreement with Sabesan et al.'s (2007b) previous results, Katsoulos et al. (2009) reported that greater improvements were found for low-contrast logMAR visual acuities compared to best-corrected spectacle acuities (the largest improvement was from 1.00 log unit to 0.10 log units). The author's rationale for using a 75%-correction was based on previous studies which have shown that decentrations of a partial wavefront aberration correction, rather than the full correction, will still yield a visual benefit compared to conventional contact lenses (Guirao et al., 2002a, de Brabander et al., 2003). Katsoulos et al. (2009) also discussed, as not all keratoconic cones are always decentred in the same position away from the visual axis, that more centrally located cones will require the addition of spherical aberration in order to provide an enhanced visual performance.

### 3.6 Do all aberration terms need correcting?

The literature suggests that correcting every single aberration term may perhaps not be beneficial, as lens decentrations are likely to hinder the visual benefit yielded (Guirao et al., 2001, Guirao et al., 2002a, de Brabander et al., 2003, López-Gil et al., 2009a). As mentioned earlier, very few higher-order aberrations are completely stable in normal human eyes (Cheng et al., 2004c). Nevertheless, López-Gil et al. (2002) showed that the aberrations created by decentration of customised lenses were smaller than the difference between the total RMS error measured with and without customised lenses in place for two normal eyes. Thus López-Gil et al. (2002) hypothesised that "wearing a customised contact lens over a course of time will show a clear benefit … especially for patients with moderate to high amounts of aberration".

Marsack et al.'s (2006) investigation proposed that correcting all the monochromatic higher-order aberration terms of the keratoconic eye are not worthwhile. The authors suggested that only correcting between the 3rd and up to the 5th Zernike orders would give most keratoconic eyes a better visual performance and lessen the likelihood of inducing superfluous aberrations due to lens decentrations. However, when interpreting the data presented by Marsack and co-workers (2006), it is important to note that the authors assumed a 'perfect' alignment of the correction ‘on-eye’. This, however, is an unrealistic assumption for even a prism-ballasted toric soft lens, which typically moves vertically by 0.3 to 1.0 mm upon blink (Tomlinson et al., 1994, Young, 1996, Young et al., 2009), with approximately 2 to 15 degrees of rotation.
modelling simulation results showed that mild and moderate cases of keratoconus would theoretically benefit more than those with severe keratoconus if the number of orders corrected are truncated. This finding was perhaps to be expected however, as severe keratoconus patients are more likely to show larger magnitudes of aberrations at the higher radial orders. With this in mind, in order to successfully correct aberrations in keratoconus with customised lenses, it may be necessary to modify the strategy of correction depending on the subject’s disease severity.

3.7 The drawbacks of customised soft contact lenses

It is evident from the literature reviewed that soft contact lenses can be used to correct higher-order aberrations via wavefront customisation. Nevertheless, soft lenses will suffer from particular disadvantages over spectacles and standard RGP lenses that will limit the potential visual benefit from being entirely successful (Thibos et al., 2003b). These include,

- contact lens dehydration
- decentralisation (rotation and/or translation), thereby inducing unwanted higher-order aberrations; i.e. a contact lens purely correcting spherical aberration only, will induce coma-like aberrations when it translates on the eye (Guirao et al., 2001, Kollbaum et al., 2008)
- errors in the manufacturing process of incorporating the required aberration magnitudes onto the soft lens
- potential light scattering and glare from the boundary of the customised zone(s)
- changes in higher-order aberrations due to disease progression or aging means that the lenses will need upgrading from time to time
- poor lens handling (i.e. damage during cleaning, storing etc.)
- possible complications, such as neovascularisation and/or corneal oedema, if lenses of increased thickness profiles are used
- lenses can only correct for the magnitude of higher-order aberrations measured at a given pupil size

In order to gain the maximum visual benefit from higher-order aberration corrections, a further challenge will be to improve the accuracy of correcting the spherical and cylindrical components of a patient’s prescription with soft customised lenses (Kollbaum and Bradley, 2007). Any under- or over-corrected spherical and cylindrical powers may potentially diminish, or even eliminate, any visual benefits gained by correcting the comparatively smaller higher-order aberration terms.

In summary, this chapter details the type of higher-order aberrations manifested in keratoconic eyes and reviews the literature investigating their potential correction using customised aberration-controlling soft contact lenses. Overall, the studies reviewed indicate that the correction of higher-order aberrations is likely to result in improved visual performance.
3.8 Addressing the gaps in the literature

The literature shows that the vast majority of keratoconic patients are classically fitted with RGP lenses (Edrington et al., 1996, Zadnik et al., 1998, Edrington et al., 1999, Szczotka et al., 2001, Kapur et al., 2003, Zadnik et al., 2005, Weed et al., 2008, Mahadevan et al., 2009). However, even with the wide variety of designs currently available, RGP lenses are often difficult to fit for corneas with keratoconus, with patients sometimes experiencing discomfort due to increased corneal and lid sensitivity (Betts et al., 2002, Edrington et al., 2004), which may eventually lead to RGP lens intolerance. In addition, it has been established that atopy is commonly found amongst patients with keratoconus (Copeman, 1965, Rahi et al., 1977, Gasset et al., 1978, Harrison et al., 1989, McMonnies and Boneham, 2003), perhaps further exacerbating ocular discomfort in RGP contact lens-wearing patients (Bawazeer et al., 2000). Rigid-gas-permeable lenses may also be an inappropriate lens choice in certain instances, for example for keratoconic patients who participate in contact sports. In these cases, other lens modalities may need to be considered. Compared to RGP lenses, hydrogel contact lenses aim to provide improved patient comfort resulting in longer wearing times, in addition, this modality may arguably reduce the likelihood of corneal epithelial staining and apical scarring. However, it is expected that conventional soft lenses may not correct visual performance as effectively as RGP lenses, due to a poorer correction of irregular astigmatism (Tragakis and Brown, 1972, Koliopoulos and Tragakis, 1981) and higher-order aberrations (Griffiths et al., 1998, Sabesan et al., 2007b, Marsack et al., 2008). Although successful results have been reported, previous investigations evaluating aberration-controlling soft lenses for keratoconus patients have generally been carried out in small patient groups (of between 2 and 8 eyes) and have often been limited in the range of disease severity evaluated. Customised aberration-controlling lenses for keratoconus patients are not currently available commercially for use in clinical practice.

At present, several important questions remain unanswered with regard to the measurement and correction of ocular aberrations for patients with keratoconus, these include,

- How repeatable are lower-order and higher-order aberrations measured in patients with keratoconus?
- How do higher-order aberrations alter with variations in the pre-corneal tear film and changes in accommodation for patients with keratoconus?
- What gives the best visual acuity result for patients with keratoconus, an objective aberrometry-derived refraction or a traditional subjective refraction?
- How do higher-order aberrations, visual performance and corneal topography alter when RGP lens wear is suspended for patients with keratoconus?
- How well do standard and aberration-controlling soft contact lenses correct higher-order aberrations in patients at different stages of keratoconus?

These questions are of particular importance, as dynamic (such as alterations with accommodation) and physiological changes (such as with suspending RGP contact lens wear) in the magnitude of higher-order aberrations may potentially hinder the success of aberration-controlling contact lenses. Equally, knowledge of whether subjective or objective (aberrometry-
derived) refraction data provide the best visual performance would be helpful in determining the sphero-cylindrical component of the correction when designing customised lenses. Four preliminary (or pilot) studies were conducted to explore these key areas; these investigations are described in Chapters 4 to 7.

The study featured in Chapter 8 uses a standardised methodology to evaluate the visual performance and correction of higher-order aberrations provided by conventional toric soft lenses in patients with mild, moderate and severe keratoconus. The investigation described in Chapter 9 uses the residual higher-order aberrations measured with toric soft contact lenses to design customised aberration-controlling lenses for the same group of keratoconic patients. Moreover, these clinical studies both compared the visual and optical performances achieved with either soft lens type to the patient’s habitual mode of correction (of either RGP lenses or spectacles). An approximation of the number of keratoconic patients required for these two clinical studies was calculated as the mean value of three separate A-Priori sample size estimations, conducted using a Student’s T-test for an alpha of 0.05 and power of 0.95 (using [http://www.danielsoper.com/statcalc/calc47.aspx](http://www.danielsoper.com/statcalc/calc47.aspx)). These calculations compared the magnitudes of aberrations measured in normal eyes versus eyes with mild, moderate and severe keratoconus (Gobbe and Guillon, 2005, Chen et al., 2007b, Kosaki et al., 2007). The results from these calculations indicated that 10 subjects with mild keratoconus (steep corneal keratometric readings < 45 D), 10 subjects with moderate keratoconus (steep keratometric readings between 45 and 52 D) and 10 subjects with severe keratoconus (steep keratometric readings > 52 D) should be recruited to the studies.

As a final part to this research project, optical modelling simulations were used, as described in Chapter 10, to further develop our current understanding of how accurately lower-order and higher-order aberrations are likely to be corrected with customised corrections for patients with keratoconus. Lastly, Chapter 11 draws together the conclusions of this research project with a view to how this work relates both scientifically and clinically to the visual rehabilitation of keratoconic patients. Suggestions for future studies are also made in Chapter 11.
4. Repeatability of Ocular Aberration Measurements in Patients with Keratoconus

Contributions

I designed this investigation with helpful contributions from my co-authors Clare O’Donnell (COD) and Hema Radhakrishnan (HR). I also completed all the measurements and statistical analyses with useful input from HR and COD. I wrote the published manuscript and this thesis chapter with valuable comments from COD and HR.

Publications

4.1 Abstract

4.1.1 Background: To explore the repeatability of lower-order and higher-order ocular aberrations measured in patients with keratoconus.

4.1.2 Methods and materials: The IRX-3 (Imagine Eyes, Paris, France) aberrometer was used to record lower-order and higher-order aberrations in 31 eyes of 31 patients with keratoconus. Four monocular measurements were taken consecutively for each patient. The aberrometry data were analysed up to the 5th Zernike order for a 4-mm pupil diameter. The data were evaluated using repeated-measures ANOVA. Repeatability was analysed using within-subject standard deviation ($S_W$) and the repeatability limit ($r$) calculated as $1.96 \times \sqrt{2} \times S_W$.

4.1.3 Results: Of the 11 aberration terms evaluated, the repeatability of Z (2,0) (mean = 1.36 µm; $S_W = 0.09$ µm; $r = 0.26$ µm); Z (2,±2) RMS (mean = 1.05 µm; $S_W = 0.09$ µm; $r = 0.24$ µm) and Z (4,0) aberrations (mean = 0.34 µm; $S_W = 0.09$ µm; $r = 0.24$ µm) showed the highest variability. In contrast, Z (3,±1) RMS aberrations (mean = 0.85 µm; $S_W = 0.06$ µm; $r = 0.16$ µm) and Z (4,±2) RMS aberrations (mean = 0.40 µm; $S_W = 0.07$ µm; $r = 0.18$ µm) showed comparatively better repeatability.

4.1.4 Conclusions: The lower-order and higher-order aberrations measured in this group of keratoconic patients showed higher levels of variability compared to previous investigations of visually-normal subjects. These results may be of interest to eyecare practitioners involved in the design and fitting of aberration-controlling contact lenses for patients with keratoconus.
4.2 Introduction

Measurement and analysis of ocular wavefront aberrations enables the assessment of imperfections in the eye’s optical system. Such imperfections are usually caused by the anterior and posterior surfaces of the cornea and crystalline lens. Beyond diffraction, the quality of the retinal image is primarily affected by lower-order aberrations, which can be corrected using spectacles, as well as higher-order aberrations (McAlinden et al., 2011b).

The Hartmann-Shack technique (Liang et al., 1994) has been used to assess the optical quality of the eye in a variety of research areas including the fields of corneal refractive surgery (Alió and Montés-Micó, 2006), intra-ocular lens implantation (Rocha et al., 2006), contact lens fitting (Jinabhai et al., 2010b) and myopia studies (Mathur et al., 2009). Earlier studies have indicated that the Hartmann-Shack method shows good repeatability in both normal human eyes (Liang and Williams, 1997, Salmon and van de Pol, 2005, Visser et al., 2011) and model eyes (Cheng et al., 2003b). However, other investigations have described poor consistency between aberrations measured using the Hartmann-Shack technique and other methods of aberrometry (Rozema et al., 2006, Cervino et al., 2008, McAlinden and Moore, 2010).

Previous reports have shown that the Hartmann-Shack method may be used to differentiate between normal eyes and those with ectatic disorders such as keratoconus (Maeda et al., 2002, Jinabhai et al., 2010a), where vertical coma, (or Z (3,-1) using the nomenclature of Zernike polynomials (Thibos et al., 2002a)), becomes significantly elevated. The increase in Z (3,-1) aberrations is primarily due to an irregular steepening and protrusion of the anterior corneal surface (Barbero et al., 2002, Maeda et al., 2002, Jinabhai et al., 2009). The posterior corneal surface also contributes to the ocular aberrations by partially compensating for some of the anterior corneal surface aberrations (Chen and Yoon, 2008, Nakagawa et al., 2009).

The literature suggests that measurement errors may occur at the Hartmann-Shack wavefront sensor when recording aberrations in patients with keratoconus (Thibos and Applegate, 2001, Katsoulos et al., 2009); however, to date, the repeatability of ocular aberrations in keratoconic patients has not been investigated. Obtaining repeatable aberration measurements in eyes with large magnitudes of ocular aberrations, such as those with keratoconus, is perhaps important from a clinical perspective, especially when attempting to design aberration-controlling contact lenses which optimise optical quality to improve visual performance (Chen et al., 2007b, Marsack et al., 2008, Katsoulos et al., 2009). Equally, Hartmann-Shack aberrometry data may be used to differentiate between different ectatic disorders such as keratoconus and pellucid marginal corneal degeneration (Jinabhai et al., 2011a). Moreover, obtaining repeatable aberration measurements over time would be useful in the early diagnosis (Jafri et al., 2007) and follow-up of patients to help monitor corneal ectatic progression (Kamiya et al., 2003).

The objective of this study was to explore the repeatability of lower-order and higher-order ocular aberrations measured in patients with keratoconus within a single session. This study aims to provide information on the expected repeatability of aberration measurements in patients with keratoconus.
4.3 Methods and materials

Thirty-one previously diagnosed keratoconic patients participated in the investigation; participants were recruited from Manchester Royal Eye Hospital and the University of Manchester's Vision Centre clinic. All experimental data were collected from one eye of each patient during a single session. Nineteen patients habitually wore RGP (rigid gas-permeable) contact lenses, whereas the remaining 12 patients habitually wore spectacles. The mean age of the group was 33 ± 7 [± 1 SD] years (range 19 to 55 years), consisting of 23 males and 8 females. The investigation followed the tenets of the Declaration of Helsinki. All participants gave their informed consent after being told the purpose of the investigation. The study protocol was approved by the National Research Ethics Service, North West 11 Research Ethics Committee. Contact lens-wearing patients were asked to remove their habitual RGP lenses, allowing a slit-lamp biomicroscopic (SL40, Keeler Ltd., Windsor, U.K.) assessment of the patients’ cornea, including the presence or absence of Fleischer’s ring, Vogt’s striae and corneal apical scarring. The presence or absence of a ‘scissors’ retinoscopic reflex was also established (Professional Retinoscope, Keeler Ltd.).

The Oculus Pentacam (Oculus, Wetzlar, Germany) was then used to measure corneal topography, central corneal thickness and central radii of curvature (calculated within a central 3-mm zone). The rotating Scheimpflug camera device uses a monochromatic, blue light emitting diode slit-light source (at 475 nm) and captures 25 images during a 1-second scan, providing 500 true elevation points per image. Four monocular scans were repeated and averaged for each eye. Keratoconus severity was graded from the Pentacam data, using the CLEK (Collaborative Longitudinal Evaluation of Keratoconus) study group’s grading criteria; steep keratometric measurements < 45 D were graded as ‘mild’ keratoconus, between 45 to 52 D were graded as ‘moderate’ keratoconus and readings > 52 D were classed as ‘severe’ keratoconus (Zadnik et al., 1996).

Following this, ocular higher-order aberrations were then measured using the IRX-3 Hartmann-Shack aberrometer (Imagine Eyes, Paris, France), which uses a 32 × 32 lenslet array and near infra-red light with a wavelength of 780 nm. Measurements were made with the patient seated and the head positioned using a chin and forehead rest. Room lights were switched off before the alignment process began, in order to obtain measurements over a large natural pupil without the use of mydriatic drugs. Aberrations were recorded under monocular conditions without any refractive correction in place. Whilst maintaining normal blinking, the operator aligned the patient’s pupil centre with the instrument axis by focusing the corneal Purkinje images displayed on the device’s computer screen. The patient was asked to look at the fixation target (a black 6/12-sized Snellen letter ‘E’ in an elliptical white background field subtending around 0.7 × 1.0 degrees with a luminance of approximately 85 cd/m²). Immediately before each measurement, patients were instructed to blink and then to hold their eyes open to minimise the optical effect of variations in the tear film (Radhakrishnan et al., 2010). Accommodation was relaxed using the device’s internal dynamic fogging method. With regard to the contact lens wearing patients, all aberration measurements were completed within 10 minutes of removing
their habitual lenses. Each aberration measurement took approximately 5 seconds to perform. In total, four monocular measurements were taken consecutively for each patient. Wavefront aberrations were computed up to the 5th Zernike order for a 4-mm pupil diameter using the device’s internal software (version 1.2, Imagine Eyes). A 4-mm pupil diameter was used to analyse the data as this was the largest pupil size common to all the patients evaluated. Total higher-order root mean square (RMS) aberrations were calculated as the RMS error for all the Zernike coefficient terms from the 3rd- to the 5th-order. All the scans performed on each patient evaluated were collected by one observer.

4.3.1 Data analysis

Statistical analyses were carried out to assess the repeatability of 11 Zernike polynomial aberration terms calculated from the four repeated measurements made for each keratoconic patient. Normality of the distributions of these 11 RMS metrics was evaluated using the Shapiro-Wilk’s test, for a critical value of 0.05. The data were investigated using one-way repeated-measures analysis of variance (RM-ANOVA), for a critical value of 0.05. All statistical tests were performed using SPSS Version 16.0 (SPSS Inc., Chicago, IL, US).

In addition to the mean values, the within-subject standard deviation (SW) was estimated for the normally distributed aberration metrics, as the square root of the average variances calculated from each of the four repeated measurements of each keratoconic patient. The SW of repeated measurements on the same subject enables an estimate of the size of the measurement error (McAlinden et al., 2011a). In addition, repeatability limits (r) were calculated as $1.96 \times \sqrt{2 \times SW}$ (McAlinden et al., 2011a).

4.4 Results

Twelve of the 31 keratoconic patients exhibited severe keratoconus, 18 patients had moderate keratoconus and one patient showed mild keratoconus (Zadnik et al., 1996). The average steep keratometric reading was 50.3 ± 4.0 D [± 1 SD] (range 43.4 to 61.8 D), the average flat keratometric reading was 46.8 ± 3.5 D (range 42.4 to 58.2 D) and the average corneal thickness was 445 ± 38 µm (range 324 to 514 µm). All 31 keratoconic patients showed a ‘scissors’ retinoscopic reflex, 30 patients displayed Fleischer’s ring, 18 patients showed Vogt’s striae and 8 patients presented with corneal apical scarring.

As the majority of the aberration terms were found to be non-normally distributed, a square-root transformation was applied to the absolute values of all the collected data (Sakia, 1992). The resulting transformed data were found to be normally distributed using the Shapiro-Wilk’s test ($p \geq 0.12$). The RM-ANOVA within-subject effects analyses showed no significant differences between the 4 repeated measurements ($p \geq 0.28$).

Table 4.1 shows the transformed data’s mean, SW and r values for each of the 11 Zernike aberrations terms evaluated. The Z (2,0) aberrations showed larger mean values compared to the Z (2,±2) RMS aberrations, however the SW and repeatability limit values were
found to be similar for both aberration terms. Compared to the lower-order aberration terms, the total higher-order RMS aberrations showed lower $S_W$ and $r$ values.

Of the 3rd-order aberrations, $Z(3,±1)$ RMS aberrations showed larger mean values compared to $Z(3,±3)$ RMS aberrations, however the $S_W$ and $r$ values were found to be highest for $Z(3,±3)$ RMS aberrations. The $Z(4,0)$ aberration terms showed only slightly higher $S_W$ and $r$ values compared to both $Z(4,±4)$ RMS and $Z(4,±2)$ RMS aberrations. However, $Z(4,±2)$ RMS aberrations showed the largest mean values of all of the 4th-order aberrations investigated. The $Z(5,±1)$ RMS aberrations showed larger mean values than either $Z(5,±3)$ and $Z(5,±5)$ RMS aberrations, however the $S_W$ and repeatability limit values were found to be similar for these three RMS aberration terms. Figure 4.1 presents the transformed data’s mean and $S_W$ values for each of the 11 RMS aberration terms evaluated.

Table 4.1 The transformed data’s mean, within-subject standard deviation ($S_W$), and repeatability limits ($r$) calculated for the 11 Zernike polynomial aberration terms. The table also includes data from Miranda et al.’s (2009a) and Mirshahi et al.’s (2003) studies by way of comparison. (HORMS = higher-order RMS error from the 3rd to 5th Zernike order).

<table>
<thead>
<tr>
<th>Zernike terms</th>
<th>Mean ($µm$)</th>
<th>$S_W$ ($µm$)</th>
<th>$r$ ($µm$)</th>
<th>$S_W$ ($D$)</th>
<th>$S_W$ ($D$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Z(2,0)$</td>
<td>1.36</td>
<td>0.09</td>
<td>0.26</td>
<td>0.16</td>
<td>-</td>
</tr>
<tr>
<td>$Z(2,±2)$</td>
<td>1.05</td>
<td>0.09</td>
<td>0.24</td>
<td>0.15</td>
<td>-</td>
</tr>
<tr>
<td>$Z(3,±1)$</td>
<td>0.85</td>
<td>0.06</td>
<td>0.16</td>
<td>0.10</td>
<td>0.04</td>
</tr>
<tr>
<td>$Z(3,±3)$</td>
<td>0.54</td>
<td>0.07</td>
<td>0.21</td>
<td>0.13</td>
<td>0.04</td>
</tr>
<tr>
<td>$Z(4,0)$</td>
<td>0.34</td>
<td>0.09</td>
<td>0.24</td>
<td>0.15</td>
<td>0.02</td>
</tr>
<tr>
<td>$Z(4,±2)$</td>
<td>0.40</td>
<td>0.07</td>
<td>0.18</td>
<td>0.11</td>
<td>0.03</td>
</tr>
<tr>
<td>$Z(4,±4)$</td>
<td>0.33</td>
<td>0.08</td>
<td>0.21</td>
<td>0.13</td>
<td>0.03</td>
</tr>
<tr>
<td>$Z(5,±1)$</td>
<td>0.26</td>
<td>0.07</td>
<td>0.20</td>
<td>0.13</td>
<td>-</td>
</tr>
<tr>
<td>$Z(5,±3)$</td>
<td>0.24</td>
<td>0.07</td>
<td>0.20</td>
<td>0.12</td>
<td>-</td>
</tr>
<tr>
<td>$Z(5,±5)$</td>
<td>0.22</td>
<td>0.08</td>
<td>0.22</td>
<td>0.14</td>
<td>-</td>
</tr>
<tr>
<td>HORMS</td>
<td>0.93</td>
<td>0.07</td>
<td>0.20</td>
<td>0.13</td>
<td>-</td>
</tr>
</tbody>
</table>

4.5 Discussion

This investigation evaluated the repeatability of both lower-order and higher-order aberrations in a group of keratoconic patients at a single session. An appreciation of the repeatability of ocular aberrations is perhaps useful when designing aberration-controlling corrections designed to optimise optical quality and visual performance for patients with keratoconus. In addition, repeatable aberration measurements over time may be useful in the identification and follow-up of patients with keratoconus and other ectatic corneal conditions.
4.5.1 Lower-order aberrations

The results show that \( Z(2,0) \) and \( Z(2,\pm 2) \) RMS aberrations were the largest in magnitude, followed by \( Z(3,\pm 1) \) RMS, \( Z(3,\pm 3) \) RMS and \( Z(4,\pm 2) \) RMS aberrations. These results were perhaps to be expected as the literature shows that the magnitudes of the Zernike coefficient terms tend to reduce as the radial order increases in both normal subjects (Porter et al., 2001, Thibos et al., 2002c) and keratoconic patients (Maeda et al., 2002, Kosaki et al., 2007, Lim et al., 2007). For all 11 aberration terms tested, no significant differences between the four repeated measurements were found \((p \geq 0.28)\).

To allow interpretation of our results in clinical terms, the \( S_W \) and \( r \) values for the \( Z(2,0) \) and \( Z(2,\pm 2) \) RMS aberrations were converted into dioptres (D) of equivalent defocus, as outlined by Thibos et al. (2002c). Although the converted aberrations do not directly correspond to standard spherical defocus, this methodology allows aberrations which have been measured at different pupil sizes to be compared with one another. The \( Z(2,0) \) aberrations showed a \( S_W \) of ± 0.16 D of equivalent defocus and a \( r \) of 0.45 D. Similarly, the \( Z(2,\pm 2) \) RMS aberrations showed a \( S_W \) of ± 0.15 D and a \( r \) of 0.42 D. These values are similar in magnitude to the repeatability of most autorefractors (Rosenfield and Chui, 1995, Bullimore et al., 1998, Allen et al., 2003). Previously, Rosenfield and Chui’s (1995) results in 12 normal subjects have suggested that a difference of ± 0.31 dioptres of sphere (DS) and ± 0.37 dioptres of cylinder (DC) should be accepted as the minimum value to detect a clinical change in refractive status. Using these values as the threshold, the \( S_W \) and \( r \) results found in the present study suggest that the repeatability of \( Z(2,0) \) and \( Z(2,\pm 2) \) RMS aberrations is reasonably good in patients with keratoconus.

However in contrast to the magnitude of the values presented here, Mirshahi et al. (2003) report a lower \( S_W \) of ± 0.11 D of equivalent defocus (or ± 0.19 \( \mu \)m: with a 7-mm pupil diameter) for \( Z(2,0) \) aberrations and a \( S_W \) of ± 0.08 D (or ± 0.14 \( \mu \)m) for \( Z(2,\pm 2) \) RMS aberrations.
measured in 40 visually-normal eyes using the Zywave aberrometer (Bausch & Lomb, Rochester, NY, US). Similarly, Visser et al. (2011) found a $S_W$ of ± 0.11 D of equivalent defocus (or ± 0.10 µm: for a 5-mm pupil diameter) for $Z_{(2,0)}$ aberrations in 23 normal subjects using the IRX-3 device. The authors also report lower $S_W$ values of ± 0.04 D (or ± 0.03 µm) for $Z_{(2,-2)}$ and ± 0.06 D (or ± 0.05 µm) for $Z_{(2,+2)}$ aberrations.

The higher variability in $Z_{(2,±2)}$ RMS aberrations found in the present study was perhaps to be expected, as patients with keratoconus characteristically show significantly larger magnitudes of irregular corneal astigmatism compared to the visually-normal population (Davis et al., 1998, Oshika et al., 1998). Moreover, this larger variability is in agreement with earlier reports (Raasch et al., 2001, Rubin et al., 2004). Raasch et al. (2001) report poor repeatability of the subjective refraction measurements, performed by one observer on two separate visits, in 92 contact lens-wearing keratoconic patients. The authors found that the 95 % confidence intervals for the power vector terms $J_0$ (± 1.56 D) and $J_{45}$ (± 1.94 D) were significantly larger than in 40 normal subjects ($J_0 = ± 0.23$ D and $J_{45} = ± 0.16$ D). Poor repeatability was also found amongst 32 spectacle-wearing keratoconic patients ($J_0 = ± 2.37$ D and $J_{45} = ± 1.07$ D). Raasch et al. (2001) also performed repeatability analysis in the astigmatic plane in the form of Cartesian co-ordinates. The authors found that the 95 % confidence interval was 0.26 DC in their normal subjects, but 2.57 DC in their contact lens-wearing keratoconic patients and 2.96 DC in their spectacle-wearing keratoconic patients. Rubin et al. (2004) explored the diurnal fluctuations of 50 repeated auto-refractor (Nidek ARK-700A; Nidek Co.) measurements in the left eyes of two normal subjects and a patient with keratoconus. Measurements were made in the mornings and afternoons on two consecutive days. The authors report that the variability of the keratoconic patient’s measurements was considerably higher than in the two normal subjects.

Compared to normal subjects, the large degree of variability in $Z_{(2,0)}$ aberrations presented in this report is in agreement with previous studies in the literature (Raasch et al., 2001, Rubin et al., 2004). Raasch et al. (2001) found that the 95 % confidence intervals for the subjective refraction power vector term $M$, were significantly larger in 92 contact lens-wearing keratoconic patients (± 5.51 D) than in 40 normal subjects (± 0.51 D). Poor repeatability was also found amongst 32 spectacle-wearing keratoconic patients ($M = ± 5.27$ D). Likewise, Rubin et al. (2004) have also reported larger variations in auto-refractor measurements of average spherical power for a keratoconic patient compared to two normal subjects. When evaluating $Z_{(2,0)}$ aberrations, the aberrometer’s software essentially attempts to fit the captured wavefront with a best-fitting spherical surface (Thibos et al., 2004). As the wavefront exiting the keratoconic eye is likely to be grossly distorted, the accuracy of applying a best-fitting sphere is expected to be reduced. This inaccuracy in wavefront fitting may perhaps have led to the poorer repeatability of $Z_{(2,0)}$ aberrations presented in this study compared to in studies of normal eyes.

4.5.2 Higher-order aberrations

The results presented indicate a large variability in higher-order aberrations for patients with keratoconus. To allow a comparison of our findings with previous studies of visually-normal subjects (Mirshahi et al., 2003, Miranda et al., 2009a), the higher-order aberration terms were also converted into dioptres (D) of equivalent defocus (Thibos et al., 2002c) (Table 4.1).
In agreement with the literature (Maeda et al., 2002, Kosaki et al., 2007, Lim et al., 2007, Jinabhai et al., 2012a), our results show that $Z_{(3,\pm 1)}$ RMS aberrations were larger in magnitude than $Z_{(3,\pm 3)}$ RMS aberrations in this group of keratoconic patients. Moreover, the $S_W$ of $Z_{(3,\pm 1)}$ RMS and $Z_{(3,\pm 3)}$ RMS aberrations presented were found to be larger than results from previous studies of visually-normal subjects (Mirshahi et al., 2003, Miranda et al., 2009a). Mirshahi et al.’s (2003) study used 6 repeated measures and a pupil diameter of 7 mm (Zywave device). However, in similarity to our study, Miranda et al. (2009a) also used the IRX-3 device and a 4-mm pupil diameter to investigate the repeatability of ocular aberrations measured in 23 visually-normal subjects. Likewise, the authors also completed their monocular measurements under scotopic conditions. Their results revealed no clinically (or statistically) significant differences between the initial aberration measurements and subsequent measurements recorded 59 ± 24 seconds, 1.10 ± 0.24 hours and 7.11 ± 0.31 days later. Miranda et al. (2009a) used three repeated measures in their study, their Bland and Altman plot analyses showed that measurements made with the IRX-3 device were highly repeatable over the times tested for their 23 subjects and that the ocular aberrations remained stable over these periods.

Expectedly, the mean $Z_{(4,\pm 2)}$ RMS aberration values presented were found to be larger in magnitude than the other 4th-order terms investigated. This finding agrees with previous studies which also report that keratoconic patients show larger magnitudes of secondary astigmatism compared to normal (Oshika et al., 1998, Kosaki et al., 2007, Lim et al., 2007). However unlike the findings of both Miranda et al. (2009a) and Mirshahi et al. (2003), the present study showed a noticeably larger $S_W$ for $Z_{(4,0)}$ aberration. Equally, the $Z_{(4,\pm 2)}$ RMS and $Z_{(4,\pm 4)}$ RMS aberrations results presented also showed larger $S_W$ values compared to Miranda et al.’s (2009a) and Mirshahi et al.’s (2003) findings.

In concordance with previous reports (Maeda et al., 2002, Lim et al., 2007), the $Z_{(5,\pm 1)}$ RMS aberration values presented showed the largest mean values of the 5th-order terms evaluated. However, compared to the results of Mirshahi et al. (2003) the present study shows substantially higher $S_W$ values for $Z_{(5,\pm 1)}$ RMS, $Z_{(5,\pm 3)}$ RMS and $Z_{(5,\pm 5)}$ RMS aberrations.

In similarity to our analysis, Mirshahi et al. (2003) also analysed higher-order RMS error up to the 5th Zernike order, however in contrast to our findings, Mirshahi et al. (2003) reported a lower $S_W$ for higher-order RMS error.

In summary, previous investigations of visually-normal subjects (Mirshahi et al., 2003, Miranda et al., 2009a) have shown a lower variability in higher-order aberrations compared to the present study’s results. These findings were not altogether surprising however, as the literature indicates that 3rd-, 4th- and 5th-order aberrations become significantly elevated in keratoconic eyes compared to normal (Maeda et al., 2002, Kosaki et al., 2007, Lim et al., 2007, Negishi et al., 2007). Nonetheless, the results showed no statistically significant differences between 4 repeated measurements of ocular aberrations in this group of keratoconic patients taken at a single session. The most probable cause of the variability in higher-order aberrations measured in this group of keratoconic patients is Hartmann-Shack spot imaging errors (Yoon et al., 2004b). When measuring aberrations in keratoconic eyes, the spot images landing on the aberrometer’s charge-coupled device (CCD) sensor may overlap with one another and can be difficult to resolve (Yoon
et al., 2004b). Equally, gross deviations at the wavefront sensor may cause two spot images, from two different micro-lenslets, to be formed at the same 'virtual' sub-aperture of a given CCD photon detector. Another complication, also known as ‘crossover’, may lead to a given spot image crossing the allocated path of a neighbouring spot (Thibos and Hong, 1999, Yoon et al., 2004b). Finally, the spot images may become so deviated that they might not actually land on the CCD sensor at all. Each of these scenarios would induce gross errors in the derivation of the wavefront slope values of the aberrant spots deviating away from the ‘chief’ or reference axis (Thibos and Hong, 1999, Yoon et al., 2004b). These spot image errors are believed to arise due to large amounts of irregular corneal distortion and corneal apical scarring in the more severe forms of the disease.

Other possibilities to account for the variability measured in this study include fluctuations in accommodation or even variations in the patient’s tear film between repeated measurements (Radhakrishnan et al., 2010). In addition, Cheng et al. (2004c) have previously suggested that small eye movements may induce variability in aberration measurements for normal subjects. Therefore it is anticipated that small eye movements would induce larger variations in aberrations for eyes with corneal ectasia, however at present this suggestion remains unexplored. Tan et al. (2008) have also indicated that the magnitude of lower-order and higher-order aberrations measured in keratoconic eyes will depend on the location of the cone apex.

Although Hartmann-Shack aberrometry may be performed for keratoconus patients in a clinical setting, the observer should be aware that the repeatability is likely to be worse than in normal subjects and that this is most likely to be due to errors at the wavefront sensor. Nonetheless, the Hartmann-Shack technique may be clinically useful to evaluate changes in ocular aberrations with and without contact lenses for patients with keratoconus. Higher-order aberrations may also be used to detect early corneal ectasia (Jafri et al., 2007), differentiate between different ectatic conditions (Jinabhai et al., 2011a) and to monitor corneal ectasia progression over time (Kamiya et al., 2003). Future studies investigating the inter-session repeatability of ocular aberrations over different time periods could also provide useful information for monitoring patients with corneal disease. Further work in this area could utilise aberrometers which incorporate a corneal topographer (Maeda et al., 2002), such devices would provide additional information with regard to contact lens fitting and keratoconus severity grading.

Repeatable ocular aberration measurements would also prove valuable when designing bespoke optical corrections to reduce coma aberrations for patients with keratoconus. The use of such customised soft contact lenses has already been demonstrated in the literature (Chen et al., 2007b, Marsack et al., 2008, Katsoulos et al., 2009). With the continued development of precise contact lens manufacturing techniques, it plausible that customised aberration-controlling lenses could, in the near future, become widely available to keratoconic patients outside the laboratory setting. It is envisaged that the present study's results may be of interest to eyecare practitioners involved in the design and fitting of aberration-controlling contact lenses for patients with keratoconus.
5. Dynamic Changes in Ocular Higher-Order Aberrations in Patients With Keratoconus

Contributions
I designed this investigation with helpful contributions from my co-authors Hema Radhakrishnan (HR) and Clare O’Donnell (COD). I recruited the keratoconic patients and normal control subjects to this study. I completed all the aberrometry measurements and prepared the data for analysis. I carried out all the statistical analyses, with useful input from HR and COD. I wrote an initial first draft of manuscript, which HR and I rewrote (specifically the introduction and discussion) and restructured into a scientific paper to submit for peer-review and publication. In addition, COD provided valuable comments at all stages of the manuscript/thesis chapter preparation.

Publications

Conference presentations
Poster presentation at the Research Symposium (incorporating the British Congress of Optometry and Vision Science) that was part of the College of Optometrists' Optometry Tomorrow Annual Conference at York Racecourse, April 18th–19th, 2010
5.1 Abstract

5.1.1 Background: The aim was to investigate fluctuations in monochromatic ocular aberrations with accommodation and tear-film changes for eyes with moderate keratoconus.

5.1.2 Methods and materials: We measured changes in ocular higher-order aberrations in 10 eyes with moderate keratoconus and 10 visually-normal eyes to accommodative stimuli ranging from zero to 5.00 DS using a Hartmann-Shack aberrometer. In addition, the changes in ocular higher-order aberrations were measured for up to 15 seconds after a blink in eight keratoconic and eight visually-normal eyes.

5.1.3 Results: Ocular spherical (p = 0.68) and coma (p = 0.71) aberrations did not change significantly with accommodation from zero to 5.00 DS in keratoconic eyes. In contrast to normal eyes, ocular higher-order RMS error tended to decrease in magnitude after a blink in keratoconic eyes. Vertical coma became less negative with time after a blink in the keratoconic group, therefore, reducing the manifest ocular higher-order RMS error by counteracting the negative vertical coma of the cornea.

5.1.4 Conclusions: Compared to the manifest monochromatic higher-order aberrations, any dynamic fluctuations in ocular aberrations due to increased accommodation and tear film changes are relatively small in moderately keratoconic eyes. This implies that the correction of monochromatic higher-order aberrations in keratoconus using customised soft contact lenses will not be significantly hindered by such dynamic aberrational changes.
5.2 Introduction

Ocular aberrations play a key role in influencing retinal image quality. Ectatic disorders such as keratoconus have been shown to produce significantly higher levels of corneal aberrations (Schwiegerling and Greivenkamp, 1996; Gobbe and Guillou, 2005; Alio and Shabayek, 2006) and ocular aberrations (Barbero et al., 2002; Maeda et al., 2002; Kosaki et al., 2007; Lim et al., 2007; Okamoto et al., 2008) in comparison to the normal population. In addition to factors such as spherocylindrical error and corneal scarring, the reduction in visual quality for patients with keratoconus is also likely to be due to large magnitudes of higher-order aberrations (Jinabhai et al., 2009). Correcting higher-order aberrations in patients with keratoconus is therefore likely to improve the quality of vision significantly (Marsack et al., 2008; Katsoulos et al., 2009).

It has been suggested that, by correcting ocular aberrations, it may be possible to obtain ‘supernormal’ vision in patients with normal levels of ocular aberrations (Liang et al., 1997; MacRae, 2000; Mrochen et al., 2000b). However, an important factor influencing the degree to which these aberrations can be corrected is the stability of ocular aberrations. Ocular aberrations differ significantly between individual patients (Porter et al., 2001; Thibos et al., 2002b) and vary throughout the day due to changes in the tear film and accommodation (Howland and Buettner, 1989; Lu et al., 1994; Atchison et al., 1995; He et al., 2000; Hazel et al., 2003; Cheng et al., 2004a; Montés-Micó et al., 2004b; Plainis et al., 2005; Radhakrishnan and Charman, 2007; López-Gil et al., 2008).

The tear film is the most powerful ocular refractive surface as it is at the boundary of the largest change in refractive indices of the eye’s optics. Németh et al. (2001) reported that whilst recording corneal topographies using a videokeratoscope, ‘breaking up’ of the tear film made the anterior corneal surface asymmetric and irregular. Several other studies have also shown that tear film disruptions measured whilst holding a blink can reduce the optical quality of the eye (Albarrán et al., 1997; Thibos and Hong, 1999; Tutt et al., 2000; Koh et al., 2002). Montés-Micó et al. (2004b) evaluated changes in corneal and ocular aberrations after a blink and found significant changes in aberrations over a 20 second timescale. Montés-Micó et al. (2004b) revealed that higher-order root mean square (RMS) error increased with time post-blink for both corneal and total ocular aberrations due to alterations in the tear film. In another study, Montés-Micó et al. (2004a) reported that changes in the post-blink higher-order RMS error in visually-normal subjects could be accounted for by changes in the individual Zernike components. Spherical aberration RMS error (Z(4,0) and Z(6,0)) tended to increase monotonically with time after a blink, whereas the coma RMS aberrations (Z(3±1) and Z(5±1)) passed through a minimum. Montés-Micó et al. (2004a) suggested that the minimum values for the total aberrations were due to the changes in coma RMS aberration.

In addition to the changes in optics caused by instability of the tear film, ocular aberrations are also affected by changes caused as a result of increased accommodation. Since accommodation is achieved by changes in the shape and position of the crystalline lens, the aberrations of the eye are also expected to change with alterations in accommodation (Tscherning, 1904; Ivanoff, 1953). Several studies have shown systematic changes in coma and spherical aberration of the eye with accommodation (Howland and Buettner, 1989; Lu et al.,
The large variability in ocular aberrations caused by factors such as tear film instability and accommodation, make correction of ocular aberrations in the normal population to produce ‘supernormal’ vision a difficult task. Keratoconic patients, on the other hand, have been shown to have significantly high levels of 3rd-order coma aberrations in comparison to normal subjects (Schwiegerling and Greivenkamp, 1996, Barbero et al., 2002, Maeda et al., 2002, Gobbe and Guillon, 2005, Bühren et al., 2007, Kosaki et al., 2007, Lim et al., 2007). Maeda et al. (2002), Gobbe and Guillon (2005) and Bühren et al. (2007) also show a significant difference in spherical-like aberrations between keratoconic and normal eyes for both corneal and ocular aberrations. Correcting these aberrations is therefore likely to improve the visual image quality in keratoconic eyes significantly. However, to correct these aberrations appropriately, it is essential to appreciate the changes in aberrations produced by variations in the tear film and alterations in accommodation in keratoconic eyes. There are relatively few published studies investigating how keratoconus influences the pre-corneal tear film. Some authors report that the disease causes increased tear film instability, squamous cell metaplasia and goblet cell loss (Dogru et al., 2003), whilst others suggest that some of these changes may be attributed to contact lens wear rather than keratoconus per se (Moon et al., 2006). The levels of inflammatory cytokines also appear to be increased in the keratoconic tear film (Lema and Duran, 2005), and may perhaps be related to disease severity (Lema et al., 2009b). To date, there are no published studies addressing how the ocular aberrations of the eye are influenced by possible alterations to the pre-corneal tear film or with accommodation in patients with keratoconus.

This study investigates the dynamics of higher-order aberrations in keratoconic eyes by assessing potential changes in aberrations post-blink and with accommodation in patients with keratoconus and in visually-normal subjects.

5.3 Methods and materials

Nineteen subjects took part in the study, including seven moderately keratoconic participants and 12 visually-normal control subjects. Five of the seven keratoconic participants had been previously diagnosed with bilateral keratoconus, whereas two participants had been diagnosed with unilateral keratoconus. The unilateral keratoconic subjects both showed normal corneal topographies and no clinical signs of keratoconus in their normal contralateral eyes upon slit lamp examination. The subjects were recruited from the University of Manchester’s Vision Centre optometry clinics. Aberrometry data were collected from 12 keratoconic eyes and 12 left normal eyes. Data were collected from both eyes of the bilateral keratoconic patients as the disease tends to be asymmetric in the two eyes (Lee et al., 1995, Sherafat et al., 2001, Zadnik et al., 2002, Burns et al., 2004, Li et al., 2004). Three of the seven keratoconic patients habitually wore rigid gas permeable (RGP) contact lenses to correct their vision. Patient 1 wore Rose K lenses (David Thomas Contact Lenses Ltd., Northampton, U.K.), patient 3 wore a Dyna-Z cone
lens (No 7 Contact Lenses, Hastings, U.K.) and patient 6 wore Jack Allen Aspheri-KD lenses (Jack Allen Contact lenses, Middlesex, U.K.). The other four keratoconic patients were habitually corrected using spectacles only and still achieved reasonable corrected visual acuity. None of the normal subjects wore contact lenses, six wore spectacles and six required no visual correction. No subject enrolled in this study had been diagnosed with dry eyes.

The mean age and standard deviation of the 12 keratoconic patients was 34.1 ± 9.0 years (with a range of 25 to 53 years) and 31.9 ± 10.6 years (with a range of 23 to 55 years) for the 12 normal subjects. None of the keratoconic patients in this study showed corneal scarring detectable upon slit lamp examination. The study inclusion criteria required that all participants had a best-corrected visual acuity of 6/12 or better (to allow them to view the aberrometer’s target), and no history of previous ocular surgery or dry eye. The study followed the tenets of the Declaration of Helsinki. All subjects gave informed consent after being told the purpose of the experiment. The project protocol was approved by the Senate Committee on the Ethics of Research on Human Beings of the University of Manchester.

Firstly, baseline measurements of the subject’s visual acuity with their habitual spectacles or contact lenses in place were taken. A slit lamp bio-microscope (SL40, Keeler Ltd., Windsor, U.K.) was then used to conduct an examination the subject’s external eye and to measure the tear film break-up time using sodium fluorescein in the form of a saline-wetted 1 mg fluoret (Table 5.1 and Table 5.2 show the times at which the tear film just began to destabilise for the keratoconic and normal subjects respectively). The Oculus Pentacam (Oculus, Wetzlar, Germany) was then used to measure the subject’s keratometry readings and corneal thickness. Topography data from the Pentacam were also acquired. The rotating Scheimpflug camera (and a monochromatic slit-light source; a blue LED at 475 nm) provides 25 images during a one second scan; with 500 true elevation points per image. During measurements the patient positioned their chin on the chin-rest and their forehead against the head support bar whilst fixing on the central black circle against the blue LED slit light. The severity of the subjects’ keratoconus was graded using the CLEK study group’s criteria (Zadnik et al., 1996); where steep keratometry readings < 45 D were graded as mild keratoconus, steep keratometry readings between 45 and 52 D were graded as moderate keratoconus and finally steep keratometry readings > 52 D were graded as severe keratoconus. In addition to corneal curvature, central corneal thickness and the presence or absence of Fleischer’s ring, Vogt’s striae and a ‘scissors’ retinoscopic reflex were also recorded.

Total ocular aberrations were measured using a commercially-available Hartmann-Shack aberrometer (IRX-3, Imagine Eyes, Paris, France) with a 32 × 32 sampling array and wavelength of 780nm. Wavefront errors were recorded under monocular conditions. The instrument records pupil diameter at the same time as the aberrations and uses a dynamic fogging method to relax accommodation to the far patient’s point. It also contains an internal Badal system which allows the vergence of the fixation target to be systematically altered with respect to the subject’s far point (i.e., the far point target vergence providing a 0 D accommodative stimulus). Recordings were made with the stimulus, a black 6/12 Snellen letter “E” in an elliptical white background field subtending about 0.7 × 1.0° and having a background luminance of about 85 cd/m2.
Changes in ocular aberrations with accommodation were measured with 1.00 D intervals, to provide accommodative stimuli over the range of zero to 5.00 D. Measurements were taken from 10 keratoconic eyes (from six patients, with mean age and standard deviation of 31.0 ± 3.9 years (range of 25 to 36 years) and 10 normal eyes (from 10 subjects, with mean age and standard deviation of 27.6 ± 3.5 years (range of 23 to 34 years)). One keratoconic patient (aged 53 years) and two normal participants (aged 55 and 52 years respectively) were excluded from these measurements in view of their presbyopic status. The subjects were encouraged to try to keep the letter as clear as possible at all times so that both reflex and voluntary accommodation were employed. If the keratoconic subject habitually wore RGP lenses then these were worn during the measurements (n = 3 eyes). In the case of spectacle wearers, no refractive corrections were worn, instead the measurements started with the determination of the aberrometer target position corresponding to the far point of the eye, followed by the measurement of the associated ocular aberrations. The accommodation demand was then increased in 1.00 D intervals up to 5.00 D with the built-in Badal system. Each axial change in target position took place approximately every 0.75 s, with the target being kept at a constant vergence for approximately 1 s, after which a measurement of the wavefront aberration and pupil size was made. The initial time interval of one second was sufficient for any pupil constriction to be completed (Semmlow and Stark, 1973, Semmlow et al., 1975) and for the subject's accommodation to reach its new level (Campbell and Westheimer, 1960, Tucker and Charman, 1979, Beers and Van der Heijde, 1996, Kasthurirangan and Glasser, 2006). The target was then moved again.

Subjects were given two practice runs to familiarise them with the task, after which three complete runs were recorded. As expected the contact lenses did move over the measurement period, however the instrument was kept aligned with the lens-eye combination as far as possible.

Changes in ocular aberrations over time due to tear film break-up were also measured with the Shack-Hartmann aberrometer without any contact lenses in place. These measurements were taken without the participant’s contact lenses in place. Changes in higher-order ocular aberrations, induced by the tear film ‘breaking-up’, were measured for up to 15 seconds after a blink. Some participants failed to keep their eye open for the full 15 seconds without blinking and the data acquisition was terminated when the subject blinked. For each 15-second run the fixation target was kept at the far point of the eye. The sampling frequency of the post-blink ocular aberration measurements was set to 1 Hz with one measurement being taken every second for the duration of 15 seconds. Each 15-second measurement run was repeated four times per eye with a five minute interval between runs (Figure 5.1).
Figure 5.1 A flow diagram describing the time intervals between measurements of the changes in higher-order aberrations up to 15 seconds post-blink.

5.4 Data analysis

5.4.1 Changes with accommodation

The ‘refraction’ for each accommodative stimulus was deduced using the manufacturer’s software (Version 1.2, Imagine Eyes, Paris, France), which effectively fits the overall wavefront, for the natural or any chosen pupil diameter, with an appropriately tilted sphero-cylinder using the ‘least-squares’ curve fitting principle (Thibos et al., 2004). The wavefront-derived refractive results for the natural pupil size were then vector-averaged (Thibos et al., 1997). The accommodative response for a given near stimulus was taken as the difference between the mean equivalent spherical refraction (i.e. the M power vector) measured with the near stimulus and those at the far point, with the negative sign reversed to make all the responses positive.

Both fourth-order spherical aberration and third-order coma were expressed in their alternative dioptic forms using Equations 5.1 and 5.2, where \( r \) = the pupil radius in mm:

Equation 5.1 Spherical aberration (D/mm²) = \( \frac{24\sqrt{5}}{r^4} \cdot (Z_4^0) \)

from Radhakrishnan and Charman (2007)

Equation 5.2 Coma (D/mm) = \( \frac{9\sqrt{8}}{r^3} \cdot \sqrt{(Z_3^{-1})^2 + (Z_3^{-1})^2} \)

from Radhakrishnan and Charman (2007)
The accommodative response and pupil size data were found to be normally distributed using a Shapiro-Wilk’s normal distribution test; therefore parametric tests were used for the data analysis.

5.4.2 Post-blink aberrations

Since some patients were unable to keep their eyes open, without blinking, for a period of 15 seconds during the measurements with the aberrometer, post-blink aberrations were only measured for eight keratoconic and eight normal eyes. Zernike wavefront aberration coefficients were calculated using the manufacturer’s software for a 4.0-mm pupil diameter (up to the 6th-order). Four sets of measurements were taken from each patient. The average standard deviation was calculated as the square root of the average variance once all the standard deviation values were converted into variances.

5.5 Results

In some keratoconic patients both eyes were used to collect the data as keratoconus is often an asymmetric disease in bilateral cases, with the disease process typically starting in one eye first (Lee et al., 1995, Sherafat et al., 2001, Zadnik et al., 2002, Burns et al., 2004, Li et al., 2004). However, only one eye was used to collect data from the normal participants in all of the experiments conducted. Table 5.1 shows that the left and right eyes of the bilateral keratoconic subjects were not equivalent in terms of the steepest keratometric readings, corneal thicknesses and slit lamp signs of keratoconus. In comparison, Table 5.2 shows a summary of the normal subject’s corneal findings.

Table 5.1 A summary of the seven keratoconic patient’s corneal data. Patient 3 and Patient 4 were unilateral cases.

<table>
<thead>
<tr>
<th>Patient ref.</th>
<th>Eye</th>
<th>Age (years)</th>
<th>CLEK severity</th>
<th>Flat K (D)</th>
<th>Steep K (D)</th>
<th>Corneal thickness (microns)</th>
<th>Fleischer’s ring</th>
<th>Vogt’s striae</th>
<th>Fluorescein tear break up time (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R</td>
<td>53</td>
<td>Moderate</td>
<td>48.5</td>
<td>50.4</td>
<td>392</td>
<td>Present</td>
<td>Present</td>
<td>10</td>
</tr>
<tr>
<td>1</td>
<td>L</td>
<td>53</td>
<td>Moderate</td>
<td>48.9</td>
<td>49.9</td>
<td>419</td>
<td>Present</td>
<td>Absent</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>R</td>
<td>34</td>
<td>Moderate</td>
<td>47.9</td>
<td>48.8</td>
<td>448</td>
<td>Present</td>
<td>Absent</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>L</td>
<td>34</td>
<td>Moderate</td>
<td>47.7</td>
<td>46.8</td>
<td>470</td>
<td>Absent</td>
<td>Absent</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>R</td>
<td>29</td>
<td>Moderate</td>
<td>46.9</td>
<td>48.6</td>
<td>462</td>
<td>Present</td>
<td>Absent</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>L</td>
<td>30</td>
<td>Moderate</td>
<td>42.4</td>
<td>46.8</td>
<td>474</td>
<td>Absent</td>
<td>Absent</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>R</td>
<td>25</td>
<td>Moderate</td>
<td>42.7</td>
<td>47.1</td>
<td>445</td>
<td>Present</td>
<td>Present</td>
<td>11</td>
</tr>
<tr>
<td>5</td>
<td>L</td>
<td>25</td>
<td>Moderate</td>
<td>42.9</td>
<td>45.4</td>
<td>466</td>
<td>Absent</td>
<td>Absent</td>
<td>11</td>
</tr>
<tr>
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<td>R</td>
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<td>Moderate</td>
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<td>51.1</td>
<td>425</td>
<td>Present</td>
<td>Present</td>
<td>9</td>
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<tr>
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<td>Moderate</td>
<td>43.5</td>
<td>46.0</td>
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<td>Present</td>
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<tr>
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<td>L</td>
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<td>46.9</td>
<td>418</td>
<td>Present</td>
<td>Present</td>
<td>9</td>
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</table>
Table 5.2 A summary of the twelve normal subject’s corneal data.

<table>
<thead>
<tr>
<th>Patient ref.</th>
<th>Age (years)</th>
<th>Steep K (D)</th>
<th>Flat K (D)</th>
<th>Corneal thickness (microns)</th>
<th>Fleischer’s ring</th>
<th>Vogt’s striae</th>
<th>Fluorescein tear break up time (s)</th>
</tr>
</thead>
<tbody>
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<tr>
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<td>39.7</td>
<td>517</td>
<td>Absent</td>
<td>Absent</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>32</td>
<td>44.3</td>
<td>43.8</td>
<td>514</td>
<td>Absent</td>
<td>Absent</td>
<td>12</td>
</tr>
<tr>
<td>7</td>
<td>34</td>
<td>44.2</td>
<td>43.4</td>
<td>558</td>
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<td>40.2</td>
<td>576</td>
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<td>Absent</td>
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<td>44.0</td>
<td>537</td>
<td>Absent</td>
<td>Absent</td>
<td>12</td>
</tr>
</tbody>
</table>

5.5.1 Changes in ocular aberrations with accommodation

The mean accommodative response gradient to altering distance stimuli (up to 5 D) was found to be 0.96 in normal eyes and 0.90 in keratoconic eyes. Univariate analysis of variance (ANOVA) showed that normal subjects had significantly higher accommodative response values (ANOVA: $F_{1,119} = 90.28; p < 0.00001$) compared to the keratoconic subjects, as found in a previous report by Ohmi et al. (1990). Figure 5.2 shows the changes in accommodative response and pupil size with accommodative demand in keratoconic and normal participants.

As expected, pupil size changed significantly with accommodation in both groups (ANOVA: $F_{5,119} = 2.90; p = 0.017$). However there were no significant differences in the pupil size between the two subject groups (ANOVA: $F_{1,119} = 1.09; p = 0.30$). In addition, there was also no significant interaction between pupil size in the two groups and accommodative stimulus level (ANOVA: $F_{5,119} = 0.58; p = 0.99$).

5.5.1.1 Spherical aberration

On taking the individual pupil sizes at various levels of accommodation into consideration, the spherical aberration values were calculated in dioptic equivalents and in D/mm$^2$. Figure 5.3 shows the changes in spherical aberration (in D/mm$^2$) as a function of accommodative response for the 10 normal (a) and 10 keratoconic eyes (b) over 5 D of accommodation. At all accommodative levels, spherical aberration varied considerably between individuals in the keratoconic group.

Spherical aberration showed a significant shift towards the negative direction with increased accommodation in the normal group ($R^2 = 0.070; p = 0.043$ – calculated from the average slope for the 10 subjects). The average slope for the 10 normal subjects was -0.018 D/mm$^2$ per dioptre of accommodation. In comparison, the larger variability in the keratoconic group led to no consistent trends being apparent with accommodation ($R^2 = 0.0029; p = 0.68$ – calculated from the average slope for the 10 subjects). The average slope for the 10 keratoconic patients was -0.008 D/mm$^2$ per dioptre of accommodation.
The individual slope values of the lines of best fit, for the averaged spherical aberration data collected over three runs for each participant, were compared between the normal and keratoconic groups using the non-parametric Mann-Whitney test. This showed that the changes in spherical aberration with accommodation were not significantly different between the keratoconic and normal groups ($p = 0.65$).

![Figure 5.2 a)](image1)

**Normal eyes (n=10); keratoconic eyes (n=10)**

![Figure 5.2 b)](image2)

**Normal eyes (n=10); keratoconic eyes (n=10)**

**Figure 5.2** Changes in the accommodative response (a) and pupil size (b) with accommodative demand in normal and keratoconic eyes. The error bars represent ±1 standard deviation (red bars = normal eyes; black bars = keratoconic eyes).
Figure 5.3 Changes in spherical aberration with accommodation in normal (a) and keratoconic (b) eyes using the dioptric form in D/mm².
5.5.1.2 Coma RMS aberrations

Coma RMS aberrations showed minimal changes with accommodation in both subject groups. Figure 5.4 shows the changes in coma RMS aberrations (in D/mm) as a function of accommodative response for the 10 normal (a) and 10 keratoconic eyes (b) over 5 D of accommodation. These measurements take into account the individual pupil diameter of the participants at each accommodative state. In general, it can be noted that the keratoconic eyes had considerably higher levels of coma aberration in comparison to normal eyes. Although coma showed a small positive increase upon accommodation in the normal subjects (an average slope value for the 10 subjects of 0.017 D/mm per dioptre of accommodation), this shift was not found to be significant ($R^2 = 0.030, p = 0.19$). A larger positive increase in coma RMS aberrations with accommodation was found for the keratoconic eyes (an average slope value for the 10 subjects of 0.030 D/mm per dioptre of accommodation); however the data collected showed a larger magnitude of variability with accommodation when compared to the normal eyes, but no significant difference ($R^2 = 0.0025, p = 0.71$). The individual slope values of the lines of best fit for the averaged coma RMS aberration data, collected over three runs for each participant, were compared between the normal and keratoconic groups using the Mann-Whitney test. The changes in coma RMS aberrations with accommodation were not significantly different between the keratoconic and normal groups ($p = 0.94$).

The changes in spherical aberration and coma RMS aberration with accommodation were plotted separately for the 7 keratoconic eyes not wearing lenses (KC-NRGP group), and the 3 keratoconic eyes wearing RGP lenses (KC-RGP group). Both groups of keratoconic patients showed no significant changes in either spherical aberration (KC-NRGP group $R^2 = 0.0038, p = 0.70$ and the KC-RGP group $R^2 = 0.0023, p = 0.85$) or coma aberration (KC-NRGP group $R^2 = 0.0042, p = 0.68$, and the KC-RGP group $R^2 = 0.021, p = 0.57$) with accommodation. Finally, the slope values calculated for the changes in spherical and coma aberrations with accommodation for the KC-NRGP and KC-RGP group were also compared using the Mann-Whitney test. No significant differences were found between the two groups for either the spherical aberration ($p = 0.43$) or the coma RMS aberration ($p = 0.73$) slope values.
Figure 5.4 Changes in coma with accommodation in normal (a) and keratoconic (b) eyes using the dioptic form in D/mm.
5.5.1.3 Post-blink changes in ocular aberrations

Figure 5.5 shows that higher-order RMS aberrations changed in magnitude following a blink in both the normal and keratoconus groups. Figure 5.5 b shows that the higher-order RMS error typically increased in the first 4 to 5 seconds after blink in most keratoconic eyes and following this increase, there was a trend towards a reduction in the magnitude of higher-order RMS error back to almost the baseline value. In contrast, most normal eyes showed relatively stable RMS higher-order aberrations in the first few seconds after blink followed by a subsequent increase in the magnitude of aberrations thereafter (Figure 5.5 a). This increase in higher-order aberrations was linked to modest changes in 3rd- and 4th-order aberrations.

On the other hand, the keratoconic eyes showed a decrease in higher-order RMS error over time after a blink. This was perhaps linked to an increase in vertical coma which shifted from a negative value to a less negative value after a blink. The mean changes in vertical coma (with time after a blink) in normal and keratoconic eyes are shown in Figure 5.6.

Visual image quality is partly dependent on the magnitude and changes in higher-order aberrations after a blink. The average post-blink higher-order RMS error in normal eyes over the 15 seconds of measurement time was 0.13 µm with a mean standard deviation of 0.018 µm for all the normal subjects. The keratoconic eyes showed a significantly higher (ANOVA: F_{1,31} = 55073; p = 0.0001) average post-blink higher-order RMS error of 0.66 µm with a mean standard deviation of 0.022 µm for all the keratoconic patients.
Figure 5.5 Changes in average higher-order RMS error with time post-blink in normal (a) and keratoconic (b) eyes. The solid lines show the best fit 2nd order polynomial curves. The error bars represent ±1 standard error. (Note the magnitude of aberrations in keratoconic eyes in comparison to the normal eyes).
Figure 5.6 Changes in average vertical coma aberration with time post-blink in normal (a) and keratoconic (b) eyes. The solid lines show the best fit 2nd-order polynomial curves. The error bars represent ±1 standard error. (Note the magnitude of aberrations in keratoconic eyes in comparison to the normal eyes).
5.6 Discussion

As found in previous studies, the results presented reveal that spherical aberration tended to show a significant shift in a negative direction with increased accommodation in the normal subjects (van den Brink, 1962, Jenkins, 1963, He et al., 2000, Ninomiya et al., 2002, Hazel et al., 2003, Cheng et al., 2004a, Plainis et al., 2005, Radhakrishnan and Charman, 2007, López-Gil et al., 2008). In contrast, the keratoconic patients showed larger within-subject variations in spherical aberration with accommodation; however no obvious trend was apparent. The magnitudes of both 3rd-order coma and 4th-order spherical aberration seen in the keratoconic group are in line with those already reported in the literature (Barbero et al., 2002, Maeda et al., 2002, Gobbe and Guillon, 2005, Kosaki et al., 2007, Lim et al., 2007), and are believed to be linked to the severity of disease, corneal thickness, corneal curvature and the position of the cone (Jinabhai et al., 2009, Katsoulos et al., 2009, Bühen et al., 2010). Given the large variability in manifest aberrations found in keratoconic group, the systematic changes in higher-order aberrations caused by changes in accommodation appear to be relatively inconsequential. Another possible reason for the larger variability of changes in spherical and coma aberrations with accommodation in the keratoconic group could be that the shape of the cornea in keratoconus can cause computational errors during Hartmann-Shack aberrometry data acquisition (Thibos and Hong, 1999, Thibos and Applegate, 2001, Yoon et al., 2004b, Katsoulos et al., 2009). To help overcome this issue, all aberrometry measurements made in this investigation were repeated several times as suggested by Cheng et al. (2004c). Other studies have suggested that perhaps the laser ray tracing (LRT) method of measuring aberrations may help to reduce some of these computational errors (Moreno-Barriuso and Navarro, 2000, Moreno-Barriuso et al., 2001). However, LRT takes longer to perform and compute compared to the Hartmann-Shack method, therefore LRT is not suitable for measuring dynamic changes in aberrations.

Keratoconus causes a significantly large increase in coma aberrations compared to that of a normal eye. Data from both groups show that each individual subject’s coma aberrations varied in both direction and magnitude with accommodation, as has been found in normal participants in some previous studies (Howland and Buettner, 1989, Lu et al., 1994, Atchison et al., 1995, He et al., 2000, Cheng et al., 2004a, Plainis et al., 2005, Radhakrishnan and Charman, 2007, López-Gil et al., 2008). The results show that the changes in coma aberrations with accommodation were considerably larger in the keratoconic group than in the normal subjects. However the changes in coma aberrations with accommodation did not differ significantly between normal and keratoconic eyes.

These results imply that keratoconus may have no significant influence on the way in which 3rd-order coma and 4th-order spherical aberration change upon accommodation. This concurs with previous research which leads us to believe that during accommodation, coma aberrations change due to alterations in the tilt and vertical positioning of the crystalline lens (Strenk et al., 2005). Similarly the changes in spherical aberration that occur during accommodation are believed to be attributed to changes in the curvature of the crystalline lens surfaces. It is believed that the crystalline lens shows a steepening of the anterior lens curvature centrally and possibly a
flattening of the lens peripherally during accommodation (Brown, 1973, Koretz et al., 1984, Garner and Yap, 1997, Rosales et al., 2006). A negative shift in spherical aberration has been observed in the in vitro lenses of both young humans (Glasser and Campbell, 1998) and monkeys (Roorda and Glasser, 2004). The data presented here, however, show no statistically significant linear effect of the mean accommodative response on either spherical or coma aberrations amongst the keratoconic patients. Additionally, this investigation found that the gradients of the spherical and coma aberration accommodation curves were not significantly different between the normal and keratoconic groups. These findings could perhaps indicate that the optics of the keratoconic eye do not have a mechanism to add negative spherical aberration with increased accommodation. However, previous studies explain that the crystalline lens is principally responsible for the negative shift in spherical aberration with accommodation found in normal eyes. At present, no studies have investigated the accommodative mechanisms of the crystalline lens in keratoconus. Keratoconus is widely accepted as an ectasia of the cornea with no recognised effects on the crystalline lens (Appelbaum, 1936, Krachmer et al., 1984, Kennedy et al., 1986, Rabinowitz, 1998). To date, only one isolated report describes anterior lenticonus, a bulging of the anterior crystalline lens capsule (most commonly associated with Alport’s syndrome (Streeten et al., 1987, Colville et al., 1997, Colville and Savige, 1997, Kato et al., 1998)), in a single keratoconic patient (Shank, 1954). Consequently, it is perhaps more likely that the keratoconic crystalline lens does have a mechanism to add negative spherical aberration with increased accommodation, however such changes may be masked by other sources of spherical aberration (from the conical cornea) and so are harder to identify than in normal subjects.

The purpose of this investigation was to evaluate how higher-order aberrations changed with accommodation, during habitual viewing conditions in keratoconic patients. Therefore, accommodation measurements were made with contact lenses for the patients who habitually wore RGP lenses (n = 3 eyes). For all the other keratoconic patients, their habitual spectacle refraction was inputted into the aberrometer to correct them for distance viewing. Rigid gas-permeable lens movements during the accommodation measurements may possibly have influenced the changes in aberrations measured. However, leaving these subjects uncorrected would have left large amounts of residual blur that may have caused the subject to over- or under-accommodate, perhaps skewing the results. In order to avoid the possibility of contact lens movements from confounding the results, the IRX-3 device was kept aligned with the eye as far as possible. Additionally, the statistical analysis shows that there were no significant differences in the magnitudes of coma or spherical aberration, with accommodation between the keratoconic eyes wearing RGP lenses and those not wearing contact lenses.

In this study, the corneal curvature data were acquired using the Oculus Pentacam within approximately five to ten minutes of the RGP lens-wearing patients (five out of the 12 eyes) removing their lenses. With this in mind, the corneal curvature data recorded in this investigation may perhaps have been flatter, compared to those of previous studies where RGP lenses may have been left out for longer periods or where larger sample sizes were evaluated (average flat keratometric reading = 7.34 ± 0.43 mm, average steep keratometric reading = 6.96 ± 0.32 mm).
In addition, all the keratoconic patients included in the present study had moderate keratoconus only, showing no signs of anterior corneal scarring or hydrops.

Previous studies have shown that tear film changes influence higher-order aberrations after a blink in normal eyes, which in turn, alter the optical quality of the eye dynamically (Albarrán et al., 1997, Thibos and Hong, 1999, Tutt et al., 2000, Koh et al., 2002, Montés-Micó et al., 2004a, Montés-Micó et al., 2004b). In normal eyes, higher-order RMS aberrations were relatively stable in the first few seconds after blink, followed by a subsequent increase in magnitude thereafter. These results agree with these previous reports.

The present study also shows that the higher-order RMS error in keratoconic eyes initially increases in the first few seconds after a blink followed by a subsequent reduction. This reduction appears to be linked to changes in vertical coma aberrations which occur after a blink. In the normal subjects the vertical coma coefficient showed a positive shift as the tears begin to break up ($R^2 = 0.73$), a finding in support of Montés-Micó et al.’s (2004b) previous study. A similar positive shift was also found in the keratoconic eyes after a blink ($R^2 = 0.61$). The positive vertical coma aberration induced by the tear film after a blink effectively reduced the magnitude of the manifest negative vertical coma aberration induced by the patient’s keratoconus. The positive increase in vertical coma after a blink has previously been attributed to vertical gravitational effects on the pre-corneal tear film which may perhaps induce this type of aberration (Buehren et al., 2001, Montés-Micó et al., 2004b). However, other reports have suggested that the keratoconic tear film contains elevated amounts of inflammatory cytokines compared to in normal eyes (Lema and Duran, 2005, Lema et al., 2009b). These inflammatory molecules may perhaps also be responsible for the changes in higher-order aberrations after a blink, however at present, this possibility remains unexplored.

The magnitude of the changes in post-blink higher-order RMS aberrations was found to be similar in both the normal and keratoconic groups. The average standard deviations of the tear film aberrations in the two groups were found to be within 0.04 µm of each other, although the magnitudes of the higher-order aberrations were significantly higher in the keratoconic patients. This difference in the absolute magnitude between the two populations is expected as several studies have shown that keratoconic eyes manifest significantly larger amounts of ocular aberrations when compared to normal eyes (Barbero et al., 2002, Maeda et al., 2002, Kosaki et al., 2007, Lim et al., 2007).

The average higher-order RMS (HORMS) error measured in this study is comparable to values found in other published reports. To allow such comparisons to be made between different studies using different pupil sizes, the HORMS error values (in microns) are converted into dioptic equivalents (in D), as outlined by Thibos et al. (2002c). The present study, which includes 12 moderate keratoconic eyes, found an average HORMS error dioptic equivalent value of 1.17 D. Chen et al. (2007b) found an average HORMS error dioptic equivalent value of 1.12 D from three moderately keratoconic eyes. Lim et al. (2007) found an average HORMS error dioptic equivalent value of 1.33 D from 35 keratoconic eyes, whose disease severity ranged from mild to
severe according to the CLEK study guidelines (Zadnik et al., 1996). In addition, Marsack et al. (2008) report lower values of HORMS error in two moderately keratoconic subjects with dioptric equivalent values of 0.33 D and 0.93 D.

Several studies have suggested that the correction of higher-order aberrations in normal eyes, to help achieve better visual performance, will be limited by tear film and accommodation changes (Charman and Chateau, 2003, Thibos et al., 2003a, Charman, 2004, Charman, 2005a). On the other hand, keratoconic eyes manifest larger magnitudes of corneal (Schwiegerling and Greivenkamp, 1996, Gobbe and Guillou, 2005, Alio and Shabayek, 2006, Bühren et al., 2007) and ocular higher-order aberrations (Barbero et al., 2002, Maeda et al., 2002, Kosaki et al., 2007, Lim et al., 2007, Okamoto et al., 2008). For these patients, correction of aberrations gives significant improvements in visual performance (López-Gil et al., 2003, Jeong and Yoon, 2006, Sabesan et al., 2006, Chen et al., 2007b, Marsack et al., 2007a, Sabesan et al., 2007a, Sabesan et al., 2007b, Marsack et al., 2008, Katsoulos et al., 2009). Overall, the present study of a limited number of moderately keratoconic patients, shows that the variations in aberrations with accommodation and tear film changes are of a similar magnitude in keratoconic patients and normal participants, despite the higher absolute levels of aberrations found in the keratoconic eyes. A larger scale study, including patients with mild and severe keratoconus, is required to assess these effects further. Nonetheless, the results presented here indicate that correcting higher-order aberrations in moderately keratoconic eyes will not be hindered by dynamic changes in ocular aberrations, which typically occur due to tear film fluctuations between blinks or with alterations in accommodation.

In summary, the purpose of this chapter was to explore the changes in higher-order aberrations that occur with accommodation and post-blink in eyes with keratoconus. These results show that 4th-order spherical aberration and 3rd-order coma aberration did not change significantly with accommodation in keratoconic eyes. In contrast to normal eyes, these results show that HORMS error tended to decrease after a blink in keratoconic eyes.

This investigation shows that compared to the large magnitudes of manifest ocular higher-order aberrations, any dynamic changes in aberrations due to variations in accommodation and changes in the tear film are relatively small in keratoconic eyes. It is therefore likely that such aberration changes will not significantly impact on optical quality. On the other hand, there is no evidence to show that the aberration changes due to dynamic variations in the pre-corneal tear film and alterations in accommodation are smaller than those measured in normal eyes. In conclusion, our results imply that the correction of higher-order aberrations in keratoconus using a customised soft contact lens will not be hindered by dynamic changes in the tear film or with increased accommodation.
6. A comparison between subjective refraction and aberrometry-derived refraction in keratoconus patients and control subjects

Contributions
I designed this investigation with helpful contributions from my co-authors Clare O'Donnell (COD) and Hema Radhakrishnan (HR). I also completed all the measurements and statistical analyses with useful input from HR and COD. I wrote the published manuscript and this thesis chapter with valuable comments from COD and HR.

Publications

Conference presentations
Paper presentation at the American Academy of Optometry Conference (San Francisco, CA, US: November 17-20; 2010)
6.1 Abstract

6.1.1 Background: This study compares the differences in the magnitude of the subjective refraction and 3 aberrometry-derived refractions along with the visual acuity achieved with these refractions in a group of keratoconic patients and age-matched normal subjects.

6.1.2 Methods and materials: Subjective refraction and Hartmann-Shack aberrometry were performed on 6 patients with keratoconus and 12 normal subjects. In addition, the logMAR visual acuity achieved using the subjective and aberrometry auto-refraction data were measured in the 6 keratoconic subjects.

6.1.3 Results: The subjective and aberrometry-derived spherical equivalent (M) refraction data were significantly different in the keratoconus group ($p = 0.015$) but not in the normal group ($p = 0.10$). In the keratoconic patients, subjective refraction data gave significantly better logMAR acuity than the aberrometry-derived auto-refraction data ($p = 0.031$). The magnitudes of vertical coma and higher-order RMS (root mean square) error showed significant correlations with the subjective refraction logMAR visual acuities ($p \leq 0.008$). Significant correlations were also found between the magnitudes of manifest vertical coma and higher-order RMS error, and the difference in M power vector terms between the subjective and aberrometry-derived auto-refraction data in the keratoconic group ($p \leq 0.034$).

6.1.4 Conclusions: The subjective and aberrometry-derived spherical equivalent refraction data were significantly different in the keratoconus group. The larger the magnitude of the higher-order aberrations in keratoconic eyes, the poorer the subjective refraction acuity achieved and the larger the difference between the subjective and aberrometry-derived M power vector terms. Further investigation into deriving objective refraction data from aberrometry measurements is warranted in keratoconus.
6.2 Introduction

Although subjective refraction is regarded as the ‘gold standard’, the literature shows that the precision of a subjective refraction is somewhat poor, with 95 % limits of inter-examiner agreement for spherical equivalent terms being quoted as between ± 0.51 D and ± 0.63 D (Zadnik et al., 1992, Raasch et al., 2001, Pesudovs et al., 2007). This is almost twice the limits of agreement reported for auto-refractor (Zadnik et al., 1992) or aberrometry-derived refraction data (Salmon et al., 2003). If accurate, automated ‘objective’ refraction data may potentially provide more reliable refraction results than the current gold standard. It may be reasonable to expect that in the absence of neural or retinal disease, optical quality data could be predictive of visual performance and sphero-cylindrical refraction. Since the advent of the Hartmann-Shack aberrometer (Liang et al., 1994), researchers have attempted to derive ‘objective’ refraction data from higher-order aberration measurements. The literature reports that in visually-normal eyes, aberrometry-based refraction data match reasonably well with subjective refraction data (Cheng et al., 2003a, Cheng et al., 2003c, Guirao and Williams, 2003, Salmon et al., 2003, Cheng et al., 2004b, Marsack et al., 2004, Thibos et al., 2004, Chen et al., 2005, Pesudovs et al., 2007, Watson and Ahumada, 2008). Several studies have evaluated the use of visual metrics (single-value terms descriptive of optical quality) based on ocular aberrations in normal subjects (Cheng et al., 2003c, Guirao and Williams, 2003, Cheng et al., 2004b, Thibos et al., 2004, Chen et al., 2005, Applegate et al., 2006). However, Schoneveld et al. (2009) have previously attempted to use visual metrics to predict the optical quality of 26 keratoconic patients using anterior surface corneal wavefront aberration data (Orbscan II, Bausch & Lomb, Rochester, NY, US) rather than ocular aberrations. The authors report that with smaller pupils, image plane metrics gave the best correlations with visual performance. With larger pupils however, pupil plane metrics gave improved correlations with visual performance. Although useful, the authors made no compensation for the posterior corneal surface or crystalline lens aberrations in the derivation of their pupil and image plane metrics. This may affect the interpretation of the study’s results, as reports in the literature have shown that the posterior corneal surface and the crystalline lens compensate for the aberrations of the anterior cornea in both normal subjects (Artal and Guirao, 1998, Artal et al., 2002) and patients with keratoconus (Barbero et al., 2002, Chen and Yoon, 2008, Nakagawa et al., 2009, Schlegel et al., 2009).

The auto-refraction measurement from aberrometric data is characteristically derived using an appropriately tilted spherocylinder that compensates for the best-fitting wavefront across all the measured monochromatic aberrations (using the method of least-squares) (Thibos et al., 2004). The 2nd-order Zernike terms can be converted into dioptric equivalent forms to derive refraction data using the defocus (Z(2,0)) and astigmatism (Z(2,±2)) Zernike coefficients. Furthermore, these second-order terms can also be combined with third-order (Z(3,±1)) and fourth-order (Z(4,0)) dioptric equivalent Zernike coefficient terms to derive objective refraction data.

The most common type of aberrometer used in clinical research is based on the Hartmann-Shack principle (Thibos and Hong, 1999, Charman, 2005a, Maeda, 2009). In a
comparison of the Hartmann-Shack aberrometer and the objective cross-cylinder aberroscope, Hong et al. (2003) report that the Hartmann-Shack device showed better test-retest reliability. However, the authors found little evidence of a correlation between the individual Zernike aberration coefficients measured by the two methods in the same eye. Hong et al. (2003) suggest that the differences in measurements between the two devices may have been due to differences in sampling densities, patient-instrument alignment errors and temporal aberration fluctuations. However, Hong et al.’s (2003) canonical variate analysis data showed that the Hartmann-Shack aberrometer was better at discriminating between different subjects compared to the objective cross-cylinder aberroscope.

In another study, Salmon and van de Pol (2005) report that the lower-order terms derived from Hartmann-Shack aberrometry (COAS device; Wavefront Sciences, Albuquerque, NM, U.S.) were, in the majority of their 28 normal subjects, capable of the same level of accuracy as can be expected for a subjective refraction. However, the authors report that in some eyes the aberrometer gave errors equivalent to 0.50 D for both sphere and cylinder powers with a 30-degree axis error. In agreement with Mirshahi et al. (2003), Salmon and van de Pol (2005) explain that 5th-order aberrations are often difficult to estimate as their magnitudes are usually smaller than the Hartmann-Shack instrument’s measurement error while measuring aberrations in visually-normal eyes. However, Salmon and van de Pol (2005) acknowledged that clinicians are often interested in measuring large magnitudes of higher-order aberration in abnormal eyes, which they suggested can be easily measured using the Hartmann-Shack principle. The authors reported that the best agreement between subjective and aberrometry-derived refractions was found when using the sphere power directly from the 2nd-order (Z(2,0)), rather than the Seidel sphere power term (paraxial curvature-matching method defined by Thibos et al. (2004)), which also incorporates the 4th-order spherical aberration term Z(4,0). This finding was in agreement with a previous study conducted in 20 visually-normal eyes (Salmon et al., 2003). Both Salmon et al. (2003) and Salmon and van de Pol (2005) reported poorer repeatability (5 measurements made within 1 minute) of the Seidel sphere power term compared to the 2nd-order sphere power term measured using the COAS device.

Using Bland-Altman limits of agreement (at 95 %), Pesudovs et al. (2007) compared the precision (repeatability) of power vector terms derived using subjective refraction data, Hartmann-Shack aberrometry refraction data (using the COAS G200 device) and conventional auto-refraction data (using the Nidek AR-800 device – Nidek, Gamagori, Japan, and the Topcon KR-8000 device – Topcon Corp., Tokyo, Japan). In their study of 16 visually-normal subjects, the authors report that paraxial curvature-matched wavefront refractions were not as precise as standard auto-refractions, although they were not clinically worse. In agreement with the literature, Pesudovs et al. (2007) also reported poorer repeatability (3 measurements made with 1 minute) of the Seidel sphere power terms compared to the 2nd-order sphere terms. Moreover, the authors found that 2nd-order refraction data (derived from the Z(2,0) and Z(2±2) terms) showed better inter-examiner repeatability for M (± 0.17 D), J0 (± 0.10 D) and J45 (± 0.06 D) terms, than the subjective and Nidek AR-800 auto-refraction data. In addition, Pesudovs et al. (2007) reported better within-examiner repeatability for M (± 0.11 D), J0 (± 0.07 D) and J45 (± 0.04 D) terms, than the subjective and Nidek AR-800 auto-refraction data.
In a more recent paper, Navarro (2009) discusses a different method of deriving the objective refraction from aberrometry measurements, by using the domain of geometrical optics based on ray bundles and beams, rather than image quality metrics. Such metrics are predominantly derived from the wavefront aberration itself; thus, the predicted objective refraction is the refractive power providing the optimal image quality under the conditions of the particular chosen metric only. Navarro (2009) suggests the application of matrix formalism to represent lens power and light beam vergences, in clinical sphere-plus-cylinder terms, to describe the vergence error of aberrated skew rays. Under this formulation, aberrometry data may be interpreted as a clinical, sphero-cylindrical refraction, with the difference being that the refraction is particular to each ray of the complete bundle passing through the pupil. Thus Navarro (2009) explains that one can perform 'micro-refraction' in order to obtain the corresponding 'micro-lens' prescription. At present no clinical study has adopted this method, however such calculations may mean that aberration correction via standard refraction might be possible for individual rays which could prove useful, particularly in the fields of adaptive optics.

In keratoconus, monochromatic higher-order aberrations are substantially elevated compared to normal eyes, with the 3rd-order Zernike coefficient, vertical coma (Z(3,-1)), being significantly higher than in normal eyes (Schwiegerling and Greivenkamp, 1996, Barbero et al., 2002, Maeda et al., 2002, Gobbe and Guillón, 2005, Alio and Shabayek, 2006, Bühren et al., 2007, Lim et al., 2007, Negishi et al., 2007, Pantanelli et al., 2007, Jinabhai et al., 2009). A recent study by Radhakrishnan et al. (2010) suggests that these large magnitudes of higher-order aberrations do not change significantly with tear film fluctuations or accommodation changes. However, the presence of these aberrations may perhaps reduce the accuracy of standard auto-refractors and the auto-refraction result given by aberrometers. If higher-order aberrations are taken into account, it could be hypothesised that objective aberrometry auto-refraction data could correlate well with subjective refraction data for eyes with keratoconus.

This chapter aims to compare subjective refraction data to auto-refraction data obtained from an aberrometer, using Thibos et al.’s (2004) least-squares fitting method, and with refraction data derived from the Zernike coefficient terms obtained using the Hartmann-Shack principle in a group of keratoconic and visually-normal participants. Finally, the logMAR visual acuity obtained with the subjective and aberrometry auto-refraction data will be compared in the keratoconic subjects, as well as exploring possible relationships between subjective visual acuity and the magnitude of higher-order aberrations measured in keratoconic eyes.

### 6.3 Methods and materials

Six keratoconic and twelve visually-normal subjects took part in this study. The keratoconic patients included one subject with severe keratoconus and five moderately keratoconic subjects (Zadnik et al., 1996). The subjects were all recruited from the University of Manchester’s Vision Centre optometry clinic. Both eyes of each participant were refracted and measured using the IRX-3 aberrometer (Imagine Eyes, Paris, France), however only the left eye
data were analysed. The average age of the six keratoconic participants was 32.4 ± 5.4 years [± 1 SD] and 33.6 ± 4.2 years for the twelve normal subjects. All participants had no previous history of ocular surgery. This study followed the tenets of the Declaration of Helsinki. All participants gave their informed consent after being told the purpose of the experiment. The project protocol was approved by the Senate Committee of Research on Human Beings of the University of Manchester.

A slit lamp bio-microscope examination was conducted for the six keratoconic participants to confirm that no corneal scarring was present. A rotating Scheimpflug camera (Oculus Pentacam, Oculus, Wetzlar, Germany) was used to measure the subject’s keratometry readings (Oculus software version 1.17r46). The patient was asked to blink before every measurement to help avoid blinking during data capture. The severity of the subjects’ keratoconus was graded using the CLEK study groups’ criteria; where steep keratometry readings < 45 D were graded as mild keratoconus, steep keratometry readings between 45 and 52 D were graded as moderate keratoconus and steep keratometry readings > 52 D were graded as severe keratoconus (Zadnik et al., 1996). Table 6.1 shows a brief summary of the corneal data for all the keratoconic subjects enrolled in this study.

### Table 6.1 A summary of the left eye corneal data for the keratoconic participants.

<table>
<thead>
<tr>
<th>Subject ref.</th>
<th>CLEK severity</th>
<th>Flat ‘K’ (D)</th>
<th>Steep ‘K’ (D)</th>
<th>Corneal scarring</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Moderate</td>
<td>43.3</td>
<td>46.9</td>
<td>None</td>
</tr>
<tr>
<td>B</td>
<td>Moderate</td>
<td>42.9</td>
<td>45.4</td>
<td>None</td>
</tr>
<tr>
<td>C</td>
<td>Severe</td>
<td>48.6</td>
<td>52.7</td>
<td>None</td>
</tr>
<tr>
<td>D</td>
<td>Moderate</td>
<td>46.8</td>
<td>47.7</td>
<td>None</td>
</tr>
<tr>
<td>E</td>
<td>Moderate</td>
<td>48.2</td>
<td>50.9</td>
<td>None</td>
</tr>
<tr>
<td>F</td>
<td>Moderate</td>
<td>42.4</td>
<td>46.8</td>
<td>None</td>
</tr>
</tbody>
</table>

A monocular subjective refraction was performed on all subjects to an accuracy of ± 0.25 D for sphere and cylinder powers. The maximum plus lens accepted whilst maintaining optimal visual acuity was used to arrive at the endpoint refraction (Borisch, 1970, Rabbetts and Bennett, 2000). The endpoint refraction was checked with a + 1.00 DS blur test. Once the endpoint refraction was reached, the back vertex distance was recorded in millimetres – average of 12.1 ± 0.70 mm. The subject’s logMAR visual acuity was measured and scored to the letter using a Bailey–Lovie letter chart (Berkeley, California, U.S.). A score of + 0.02 log units was added for each letter that was read incorrectly on the endpoint line. The subjective refraction routine lasted for approximately 12 minutes for each subject. Each routine was conducted in a laboratory with a constant room illumination of approximately 310 lux; the Bailey–Lovie logMAR chart was externally illuminated using two fluorescent tubes, aligned in such a way that they uniformly illuminated to approximately 750 lux without causing glare. In addition, the subject’s pupil size was also measured using a pupil gauge – average of 5.0 ± 0.5 mm. By measuring the pupil size during the subjective refraction, it was possible to ascertain an average habitual pupil size for
typical ‘in-door’ viewing conditions for all the study’s participants. Zernike aberration coefficient terms were also calculated for a fixed pupil size of 5 mm to ensure that the aberrometry-derived auto-refraction results were comparable to the subjective refraction data.

Measurements of the subject’s total ocular aberrations were made using the IRX-3 Hartmann-Shack aberrometer using a 32 X 32 lenslet array and near infra-red light with a wavelength of 780 nm. All aberrometry measurements were made within two minutes of completing the subjective refraction routine and pupil size measurements. Wavefront errors were recorded under monocular conditions with the room lighting switched off. The IRX-3 instrument records pupil diameter at the same time as the aberrations and uses a dynamic fogging method to relax accommodation to the far point. All recordings were made using the fixation stimulus, a black 6/12-sized Snellen letter “E” in an elliptical white background field subtending approximately 0.7 x 1.0 degrees and having a luminance of about 85 cd/m². Four monocular measurements were made for each participant. Ocular aberrations were calculated up to the 6th Zernike order for a 5-mm pupil size using the IRX-3 device’s software (Imagine Eyes software version 1.2).

For the keratoconic participants, the ‘calculated’ aberrometer auto-refraction result was derived using the manufacturer’s software, which fits the measured wavefront of a chosen pupil diameter with an appropriately tilted sphero-cylinder in 0.01 D intervals (Thibos et al., 2004). For this calculation, the vertex distance was set to the spectacle plane at +12 mm using the device’s software, as this value was as close as was possible to the average vertex distance measured for all the study participant’s subjective refraction values. The ‘calculated’ aberrometer auto-refraction prescription was then transferred to a trial frame and fitted at a vertex distance of +12 mm, using reduced aperture trial lenses, in 0.12 D intervals for both sphere and cylinder. This refraction result will be referred to as the ‘aberrrometer auto-refraction’ hereafter. The subject’s logMAR acuity was then measured through these lenses and scored to the letter using a Bailey–Lovie letter chart. To prevent subjects from memorising the letters, a different Bailey–Lovie letter chart was used than for the subjective refraction, however the room (approximately 310 lux) and chart (approximately 750 lux) illumination remained constant throughout the investigation. All aberrometry auto-refraction acuity measurements were made within approximately 8 minutes of measuring the subjective refraction acuities.

6.3.1 Data analysis

The subjective refraction and aberrometer auto-refraction data were converted to the power vector coordinates M, J0 and J45 using Equations 6.1 to 6.3, from Thibos et al. (1997). Where S’ is the spherical component, C’ is the cylindrical component and \( \alpha \) is the axis in radians.

\[
M = \frac{S' + C'}{2}
\]
The 2nd-order aberration terms were converted into a conventional refraction result, for comparison to the subjective refraction and aberrometer auto-refraction data, using the Zernike coefficient terms $Z(2,0)$, $Z(2,-2)$ and $Z(2,2)$ via Equations 6.4 to 6.6. These refraction data were then also converted into their respective power vector terms using Equations 6.1 to 6.3.

**Equation 6.2**

$$J_0 = \frac{C'}{2}(\cos 2\alpha)$$

**Equation 6.3**

$$J_{45} = \frac{C'}{2}(\sin 2\alpha)$$

**Equation 6.4**

Sphere in D = \[4\sqrt{3} \cdot \frac{Z_2^0}{r^2}\]

Adapted from Thibos et al. (2004)

**Equation 6.5**

Cylinder in D = \[4\sqrt{3} \cdot \frac{\sqrt{(Z_{2}^{-2})^2 + (Z_2^2)^2}}{r^2}\]

Adapted from Thibos et al. (2004)

**Equation 6.6**

Cylinder axis in degrees = \[\tan^{-1}\left(\frac{Z_{2}^{-2}}{Z_2^2}\right)\]

To maintain optometric angular convention,

A) if $\theta < 0$, then 180 degrees were added

B) if $\theta$ is > 0, then 90 degrees were added

Adapted from Thibos et al. (2004)

The final refraction result compared to the subjective, aberrometry auto-refraction and 2nd-order refraction data, was derived by combining the power vector components of the Zernike coefficients $Z(2,0)$, $Z(2,2)$, $Z(2,-2)$, $Z(3,1)$, $Z(3,-1)$ and $Z(4,0)$, calculated from their respective dioptric equivalent forms using Equations 6.4 to 6.9. Equations 6.7 and 6.8 provide a cylindrical power and axis respectively, from the coma aberration terms, whilst Equation 6.9 provides a spherical power from the spherical aberration term.
Equation 6.7  \[
\text{Coma in } D = 4\sqrt{3}\cdot \frac{\sqrt{(Z_{3}^{-1})^2 + (Z_{3}^{1})^2}}{r^2}
\]
Adapted from Thibos et al. (2004)

Equation 6.8  \[
\text{Coma angle in degrees } = \tan^{-1}\left(\frac{Z_{3}^{-1}}{Z_{3}^{1}}\right)
\]
To maintain optometric angular convention, when \( \theta < 0 \), then 180 degrees were added
Adapted from Tahir et al. (2009)

Equation 6.9  \[
\text{Spherical aberration in } D = 4\sqrt{3}\cdot \frac{Z_{4}^{0}}{r^2}
\]
Adapted from Thibos et al. (2004)

All data were analysed using SPSS version 16.0 (SPSS Inc., Chicago, U.S.) and Microsoft Excel 2003 (Microsoft Corp., Redmond, Washington, U.S.). All non-normally distributed data were analysed using non-parametric tests (Friedman analysis and Spearman’s correlation coefficients).

6.4 Results

6.4.1 Comparing the magnitudes of M, J0 and J45 power vector terms in keratoconic eyes

Figure 6.1 shows the spherical equivalent, M, and astigmatic components, J0 and J45, measured with the subjective refraction, the aberrometer auto-refraction and the refraction data derived from the aberrometry terms in the keratoconic group. The spherical equivalent refraction, M, was not equal in magnitude for the subjective and aberrometer auto-refraction data amongst the keratoconic group. In comparison to the subjective data, the aberrometer auto-refraction M power vector terms tended to be substantially more negative for the majority of the keratoconic subjects. The data also show that neither the M-components derived from the 2nd-order terms, nor from a combination of the 2nd-, 3rd- and 4th-order terms, gave results equal to that of the subjective refraction M-components. These two aberrometry-derived refractions also tended to show more negative M-components in 5 out of the 6 cases evaluated.

Similarly, the aberrometer auto-refraction J0- and J45-components were also not equal in magnitude to the subjective refraction results. Compared to the subjective refraction data, the aberrometer auto-refraction results tended to give slightly more positive J0-component (in 4 out of 6 patients) and J45-component (in 4 out of 6 patients) values. Compared to the subjective
refraction J0- and J45-components, the J0- and J45-components derived from the 2nd-order terms and from a combination of the 2nd-, 3rd- and 4th-order terms showed large amounts of variability between individual subjects in the keratoconic group.

Table 6.2 shows the mean differences between the subjective refraction and the aberrometer auto-refraction, the 2nd-order term’s refraction and the combined 2nd-, 3rd- and 4th-order term’s refraction data for the M, J0 and J45 power vector terms in the keratoconic group.

Table 6.2 The mean differences between the subjective and ‘aberrometry-derived’ refractions in the keratoconic group.

<table>
<thead>
<tr>
<th>Keratoconic group</th>
<th>Subjective vs. aberrometer auto-refraction data (D)</th>
<th>Subjective vs. the 2nd-order terms refraction data (D)</th>
<th>Subjective vs. the 2nd, 3rd and 4th-order terms refraction data (D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M mean difference</td>
<td>2.35</td>
<td>2.94</td>
<td>3.49</td>
</tr>
<tr>
<td>J0 mean difference</td>
<td>-1.24</td>
<td>-0.93</td>
<td>-0.49</td>
</tr>
<tr>
<td>J45 mean difference</td>
<td>-0.40</td>
<td>-0.76</td>
<td>-0.62</td>
</tr>
</tbody>
</table>

A Shapiro-Wilk’s test showed that the power vector components of refractive error were not normally distributed in the keratoconic group ($p < 0.05$). A non-parametric Friedman test showed that the M-component data were significantly different for the four refraction types compared ($p = 0.015$; $\chi^2 = 10.8$, df = 3 and n = 6). The J0-component ($p = 0.08$) and J45-component ($p = 0.07$) data calculated for the four refraction types showed large magnitudes of variation amongst the individual subjects in the keratoconic group that was approaching statistical significance.

A post-hoc power analysis, for the M-component data, gave a power of 0.82 for the keratoconic group, where $\chi^2 = 10.8$, n = 6 and df = 3 using an alpha of 0.05 (G-power 3.1.2; Kiel, Germany).
Figure 6.1 The M, J0 and J45 power vector terms and logMAR visual acuities in six keratoconic eyes (On the ‘M’ graph the upper values = subjective refraction acuities, lower values = aberrometer auto-refraction acuities).
6.4.2 Comparing the magnitudes of M, J0 and J45 power vector terms in visually-normal eyes

Figure 6.2 shows the spherical equivalent, M, and astigmatic components, J0 and J45, measured with the subjective refraction, the aberrometer auto-refraction and the refraction data derived from the aberrometry terms in the normal group. It is apparent from Figure 6.2 that compared to the subjective refraction data, the aberrometer auto-refraction results gave slightly more negative M power vector terms by a mean difference of around 0.19 D. A non-parametric Friedman test showed that the M power vector terms were not significantly different for the four refraction types compared ($p = 0.10$). The data also show that neither the M-components derived from the 2nd-order terms, nor from a combination of the 2nd-, 3rd- and 4th-order terms, gave results equal to that of the subjective refraction M power vectors. However, the differences between the subjective refraction and aberrometer auto-refraction M-component terms were considerably smaller in the normal group than in the keratoconic group.

The aberrometer auto-refraction J0- and J45-components were similar in magnitude to the subjective refraction data. The results also show that the J0- and J45-components derived from the 2nd-order terms and from a combination of the 2nd-, 3rd- and 4th-order terms, gave results similar to that of the subjective refraction J0- and J45-components. A non-parametric Friedman test showed that the J0- and J45-component data were not significantly different for the four refraction types compared for the normal subjects (J0-component $p = 0.41$ and J45-component $p = 0.84$).

Table 6.3 shows the mean differences between the subjective refraction data and the aberrometer auto-refraction, the 2nd-order terms refraction and the combined 2nd-, 3rd- and 4th-order terms refraction data, for the M, J0 and J45 power vector terms in the normal group.
Figure 6.2 The M, J0 and J45 power vector terms in twelve visually-normal subjects.
Table 6.3 The mean differences between the subjective and ‘aberrometry-derived’ refractions in the normal group.

<table>
<thead>
<tr>
<th>Normal group</th>
<th>Subjective vs. aberrometer auto-refraction data (D)</th>
<th>Subjective vs. the 2nd-order terms refraction data (D)</th>
<th>Subjective vs. the 2nd, 3rd and 4th-order terms refraction data (D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M mean difference</td>
<td>0.19</td>
<td>0.18</td>
<td>0.18</td>
</tr>
<tr>
<td>J0 mean difference</td>
<td>-0.08</td>
<td>-0.09</td>
<td>-0.09</td>
</tr>
<tr>
<td>J45 mean difference</td>
<td>-0.03</td>
<td>-0.03</td>
<td>-0.02</td>
</tr>
</tbody>
</table>

6.4.3 Correlation between logMAR visual acuities and higher-order aberrations in keratoconic eyes

Visual acuities measured with the subjective refraction and aberrometer auto-refraction values for each keratoconic individual are shown in Figure 6.1. The data show that the subjective refractions gave substantially better logMAR acuities (average of 0.06 ± 0.17 log units) compared to the aberrometer auto-refraction data (average of 0.53 ± 0.24 log units) for the six keratoconic patients.

Table 6.4 shows the average vertical coma, higher-order RMS (root mean square) error and logMAR acuity data (with the subjective and aberrometer auto-refraction results) for the six keratoconic participants.

Table 6.4 Average vertical coma (µm), higher-order RMS error (µm) and logMAR visual acuities in the keratoconic participants

<table>
<thead>
<tr>
<th>Subject ref.</th>
<th>Average vertical coma (µm)</th>
<th>Standard deviation</th>
<th>Average higher-order RMS error (µm)</th>
<th>Standard deviation</th>
<th>Subjective logMAR acuity</th>
<th>Aberrometer logMAR visual acuity</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>-0.71</td>
<td>0.06</td>
<td>0.86</td>
<td>0.077</td>
<td>-0.02</td>
<td>0.32</td>
</tr>
<tr>
<td>B</td>
<td>-0.77</td>
<td>0.007</td>
<td>0.87</td>
<td>0.006</td>
<td>-0.02</td>
<td>0.58</td>
</tr>
<tr>
<td>C</td>
<td>-0.94</td>
<td>0.03</td>
<td>1.15</td>
<td>0.005</td>
<td>0.26</td>
<td>0.62</td>
</tr>
<tr>
<td>D</td>
<td>-0.21</td>
<td>0.01</td>
<td>0.25</td>
<td>0.009</td>
<td>-0.10</td>
<td>0.20</td>
</tr>
<tr>
<td>E</td>
<td>-0.97</td>
<td>0.06</td>
<td>1.09</td>
<td>0.06</td>
<td>0.28</td>
<td>0.88</td>
</tr>
<tr>
<td>F</td>
<td>-0.40</td>
<td>0.01</td>
<td>0.57</td>
<td>0.007</td>
<td>-0.06</td>
<td>0.56</td>
</tr>
</tbody>
</table>

A Wilcoxon signed-rank test (two-tailed) showed that the subjective refraction acuities were significantly different from the aberrometer auto-refraction acuities for the keratoconic patients \( p = 0.031; \ Z = -2.2 \).

Figure 6.3 shows the LogMAR visual acuities achieved with the subjective refraction and aberrometry auto-refraction data as a function of vertical coma in the six keratoconic eyes. The data show that as the magnitude of vertical coma aberration reduced, the logMAR acuity achieved improved with both the subjective refraction and the aberrometer auto-refraction. There was a significant negative correlation between the subjective logMAR acuity achieved and the magnitude of the subject’s vertical coma aberration (Spearman’s correlation coefficient,
In contrast, no significant correlation was found between the aberrometer auto-refraction logMAR acuities and the magnitude of the keratoconic subjects’ vertical coma aberration (Pearson’s correlation coefficient, $R_p = -0.74$, $p = 0.09$).

The average vertical coma aberration was measured at $-0.67 \pm 0.3\, \mu m$ in the keratoconic group and at $0.03 \pm 0.06\, \mu m$ in the normal group. The Mann-Whitney test showed that the magnitudes of the vertical coma aberrations were significantly different between the two groups ($p = 0.0008; Z = -3.4$).

![Figure 6.3](image)

**Figure 6.3** The correlation between subjective and aberrometry auto-refraction logMAR visual acuity and vertical coma ($\mu m$) in the keratoconic patients. ($R_p = \text{Pearson's correlation coefficient}$ and $R_s = \text{Spearman's correlation coefficient}$).

Figure 6.4 shows the LogMAR visual acuity achieved with subjective refraction and aberrometry auto-refraction data as a function of higher-order RMS error (from the 3rd- up to 6th-order) in the six keratoconic eyes. These results show that as the higher-order RMS error reduced in magnitude, the logMAR acuity achieved improved with both the subjective refraction and the aberrometer auto-refraction result. There was a significant positive correlation between the subjective logMAR acuity achieved and the subject’s higher-order RMS error ($R_s = 0.93$, $p = 0.008$). In contrast, there was no significant correlation between the aberrometer auto-refraction logMAR visual acuities and the magnitude of the subject’s higher-order RMS error ($R_p = 0.74$, $p = 0.10$).

The average higher-order RMS error was measured at $+0.80 \pm 0.34\, \mu m$ in the keratoconic group and at $+0.13 \pm 0.05\, \mu m$ in the normal group. The Mann-Whitney test showed that the magnitudes of the higher-order RMS aberrations were significantly different between the two groups ($p = 0.0007; Z = 3.4$).
Figure 6.4 The correlation between subjective and aberrometry auto-refraction logMAR visual acuity and higher-order RMS error (µm) in the keratoconic patients. ($R_p = $ Pearson’s correlation coefficient and $R_S = $ Spearman’s correlation coefficient).

6.4.4 Correlation between power vector terms and higher-order aberrations in keratoconic eyes

Figure 6.5 shows the relationships for the difference in spherical equivalent terms, between the subjective and aberrometer auto-refraction data, and the magnitudes of both vertical coma and higher-order RMS error. These data show that as the magnitude of negative vertical coma and higher-order RMS error increases, the difference between the subjective and aberrometer auto-refraction M-component terms also increases. There was a significant correlation between the difference in the M-component terms and the magnitude of the subject’s negative vertical coma aberrations ($R_p = -0.93, p = 0.007$). Similarly, a significant correlation was also found between the difference in M-component terms, and the magnitude of the subject’s higher-order RMS error ($R_p = 0.95, p = 0.004$).

However, no significant correlation was found for the differences in J0-components between these two refraction types, and the magnitudes of either vertical coma or higher-order RMS aberrations ($R_p \leq 0.31, p \geq 0.55$). Similarly, there was no significant correlation for the differences in J45-components between these two refraction types and the magnitudes of either vertical coma or higher-order RMS error ($R_p \leq 0.52, p \geq 0.29$).
Difference between subjective refraction and aberrometry auto-refraction

![Graph showing correlations between subjective and aberrometry auto-refraction](image)

**Figure 6.5** Correlations of the difference between the subjective and aberrometry ‘auto-refraction’ M power vector terms, and vertical coma and higher-order RMS aberrations in the keratoconic patients. ($R_p = $ Pearson’s correlation coefficient).

Figure 6.6 shows the relationship for the differences in spherical equivalent terms, between the subjective refraction and aberrometry-derived refraction data (i.e. from the 2nd-order terms – Figure 6.6 A, and a combination of the 2nd-, 3rd- and 4th-order terms – Figure 6.6 B), and the magnitudes of both vertical coma and higher-order RMS aberrations. These data also show that the larger the magnitudes of vertical coma and higher-order RMS aberrations, the larger the difference between the subjective and two aberrometry-derived M power vector terms.

In contrast, no significant correlations were found for the differences in J0 terms, between the subjective and two aberrometry-derived refractions, and the magnitudes of either vertical coma or higher-order RMS aberrations ($R_p \leq 0.30, p \geq 0.56$). Similarly, no significant correlations were found for the differences in the J45 terms between the subjective and two aberrometry-derived refractions, and the magnitudes of either vertical coma or higher-order RMS aberrations ($R_p \leq 0.61, p \geq 0.20$).
Figure 6.6 Correlations of the difference between the subjective and aberrometry-derived refraction M power vector terms, and vertical coma and higher-order RMS aberrations in the keratoconic patients. 

A) shows the difference in M-components between the subjective refraction and 2nd-order terms ($R_p = \text{Pearson's correlation coefficient}$), and B) shows the difference in M-components between the subjective refraction and a combination of the 2nd-, 3rd- and 4th-order terms ($R_s = \text{Spearman's correlation coefficient}$).
6.5 Discussion

This study confirms that in keratoconic eyes, the subjective refraction data were not equal to the aberrometry auto-refraction data, which effectively fit the overall wavefront with an appropriately tilted sphero-cylindrical correction for a chosen pupil diameter (Thibos et al., 2004). The mean differences between the subjective and three ‘aberrometry-derived’ refractions (i.e. the aberrometer auto-refraction, the 2nd-order term’s refraction and the combined 2nd-, 3rd- and 4th-order term’s refraction data) were found to be substantially larger in the keratoconic group, than in the normal group. The data from the keratoconic group showed that the subjective and three ‘aberrometry-derived’ M power vector terms were significantly different from each other. Amongst the normal participants however, the M, J0 and J45 power vector terms calculated from the subjective and three ‘aberrometry-derived’ refractions were not significantly different from each other.

In the keratoconic group, neither the 2nd-order aberration terms, nor a combination of the 2nd, 3rd and 4th-order aberration terms (all in their respective dioptric equivalent forms), gave results equal to that of the subjective refraction. Therefore, at present, it is not known exactly which ocular, aberrometry-derived visual metric helps to give results equivalent in magnitude to a subjective refraction in patients with keratoconus; perhaps suggesting that further research into the use of visual metrics to estimate refraction data objectively in keratoconus is warranted.

The data collected from the keratoconic group showed that when compared to the subjective refraction, the ‘aberrometry-derived’ refraction data tended to substantially over-minus the M power vector terms. A similar trend, although to a much smaller magnitude, was also found amongst the normal participants, where the difference in the M power vector terms between the subjective and aberrometry auto-refraction data was approximately 0.19 D; which is within the clinically recognised measurement accuracy of ± 0.25 D for a subjective refraction. Such small differences may perhaps be attributed to the differences in target distance between the subjective refraction and aberrometry measurements, as well as small amounts of residual accommodation often found in young hyperopes. These findings are in agreement with the results of Thibos et al.’s (2004) study of 200 visually-normal eyes, which also found that the method of least-squares fitting data gave an average M-component value of 0.39 D of more myopia than subjective refraction data. However, the authors report that the method of least-squares fitting was accurate at predicting the astigmatic components J0 and J45 (using scatter plots and 95% confidence ellipses).

The repeatability of the Hartmann-Shack aberrometer may also play an important role when comparing such refraction data. Several studies have demonstrated good repeatability of the Hartmann-Shack aberrometer in studies of human (Liang et al., 1994, Liang and Williams, 1997, Hong et al., 2003, Mirshahi et al., 2003, Miranda et al., 2009a) and model eyes (Cheng et al., 2003b, Mirshahi et al., 2003), whilst others report short-term variability in ocular aberrations (Hofer et al., 2001, Davies et al., 2003, Cheng et al., 2004c). This variability may result from changes in accommodation (Hofer et al., 2001), small fixational eye movements (Cheng et al.,
or even fluctuations in the tear film (Hofer et al., 2001, Cheng et al., 2004c). Efron et al.’s (2008) study showed that the IRX-3 device had a repeatability (within-observer SD) of 0.082 µm in 13 normal eyes from three measurements made over 60 seconds. Cheng et al. (2004c) report a repeatability of 0.009 µm in 4 normal subjects from five measurements made over one second using a Hartmann-Shack device. This large difference in repeatability between the two studies is possibly explained by differences in pupil size as well as the difference in the time periods over which the measurements were made. Cheng et al. (2004c) used a dilated 6-mm pupil, whereas Efron et al. (2008) used an un-dilated 4 mm pupil. It may be argued that the smaller the pupil size used, the smaller the absolute magnitude of the higher-order aberrations measured and, therefore, the poorer the repeatability; as demonstrated by Efron et al. (2008). In addition, Cheng et al.’s (2004c) data shows that the repeatability of higher-order aberrations reduces as the time over which the repeated measurements are made is increased. In contrast to this, Miranda et al. (2009a) reported no significant differences between the initial ocular aberrations and the aberrations measured 59 ± 24 seconds, 1.10 ± 0.24 hours and 7.11 ± 0.31 days later in 23 normal subjects using the IRX-3 device. In line with the conclusions from studies by Mirshahi et al. (2003), Efron et al. (2008) and Cheng et al. (2004c), the aberrometry readings in this investigation were repeated four times for each subject to help improve measurement repeatability.

The small differences in the subjective and aberrometer auto-refraction M-components in the normal group may also perhaps be explained by the fact that all objective aberrometers make their measurements using infra-red light (Liang et al., 1994, Navarro and Losada, 1997). In order to compensate for the eyes' longitudinal chromatic aberration, and to give an appropriate correction for a visible monochromatic wavelength (generally in the yellow or green part of the visible spectrum), aberrometer manufacturers commonly add an appropriate amount of negative spherical power to the estimated infra-red correction (Llorente et al., 2003, Cheng et al., 2004b, López-Gil et al., 2009b) (of approximately -0.40 DS in normal eyes (Charman, 2005b)).

An additional reason for the discrepancies between the M power vectors in the keratoconic group could be that Zernike polynomials are known to have limitations in their application of modelling the anterior surface and higher-order aberrations of abnormal corneas (Smolek and Klyce, 2003, Klyce et al., 2004, Carvalho, 2005). These limitations arise as there are not an infinite number of Zernike polynomials or coefficient terms to describe all of the information being sampled over the CCD (charge-coupled device) wavefront sensor of the Hartmann-Shack aberrometer. The resultant ‘fitting-error’ associated with using Zernike polynomials to describe the curvature and aberrations of abnormal corneas, may therefore also be responsible for the differences in the magnitude of the power vector terms between the subjective and aberrometry-derived refractions (Smolek and Klyce, 2003, Klyce et al., 2004, Carvalho, 2005). Irrespective of their limitations however, Zernike polynomials are still the most commonly used and recognised method of describing monochromatic higher-order aberrations (Yoon et al., 2008).
A final possible explanation for these results, particularly amongst the keratoconic group, where the differences in the M power vectors terms were found to be significant, is that the large magnitudes of higher-order aberrations manifested may have caused gross mathematical and computational inaccuracies in fitting the overall wavefront with an appropriately tilted spherocylindrical correction (Thibos and Hong, 1999, Thibos and Applegate, 2001, Yoon et al., 2004b). When measuring aberrations in keratoconic eyes, the spot images landing on the aberrometer’s CCD sensor may often be very close together and difficult to resolve. The images could also overlap or ‘crossover’, resulting in only one image being registered instead of two. Finally, the spot images may even become deviated so greatly that they might not actually land on the sensor at all. Each of these scenarios would induce gross errors in the derivation of the wavefront slope values of the aberrant spots deviating away from the ‘chief’ or reference axis (Thibos and Applegate, 2001, Yoon et al., 2004b). These errors are believed to arise due to irregular corneal distortion and scarring in the more severe forms of the disease. These mathematical and computational errors in the measurement of wavefront aberrations, due to keratoconus, are therefore likely to lead to inaccuracies in deriving the auto-refraction data from the aberrometry measurements. Jinabhai et al. (2011b) have reported that both lower-order and higher-order aberrations show poorer repeatability in keratoconic patients compared to previous reports in visually-normal subjects. The authors hypothesised that spot-imaging errors at the wavefront sensor were the primary cause for the poor repeatability measured in 31 keratoconic patients. The spot image data collected in this investigation showed varying degrees of local irregularities across the CCD sensor in all the keratoconic eyes investigated. The literature suggests that spot detection difficulties at the CCD sensor would be most erroneous in highly irregular eyes such as those with advanced keratoconus (Thibos and Hong, 1999, Munson et al., 2001, Thibos and Applegate, 2001, Yoon et al., 2004b). Most of subjects in this study had moderate keratoconus and reasonable corrected logMAR visual acuity (average of 0.06 ± 0.17), and so it would be expected that spot image irregularities would not have as severe an impact amongst these participants.

The use of matrix formalism as described by Navarro (2009) could perhaps be useful when applied to derive objective refraction data from aberrometry measurements. The use of such matrices would by-pass the use of image quality or visual metrics; although such methods were not implemented in this study, they could prove useful in future studies of both normal and keratoconic subjects.

For the six keratoconic patients, the subjective refraction gave significantly better logMAR acuity, with an average of 0.06 ± 0.17, compared to average aberrometer auto-refraction logMAR acuity of 0.53 ± 0.24. This study shows that visual acuity worsened as the magnitude of the manifest higher-order aberrations increased in keratoconic eyes. This finding was to be expected, with previous studies explaining that the higher-order aberrations associated with keratoconus, namely coma, cause a reduction in visual performance (Sabesan et al., 2007a, Okamoto et al., 2008, Rocha et al., 2010). The results presented here indicate that in keratoconic eyes there was a significant correlation between the magnitude of the manifest vertical coma aberration and higher-order RMS error, and the visual acuity achieved with a subjective
refraction. The data showed that as the magnitude of aberrations increased, the subjective refraction visual acuity achieved reduced. Similar trends were found between the aberrometer auto-refraction logMAR acuities and the magnitudes of the manifest vertical coma aberration and higher-order RMS error. However, unlike with the subjective refraction acuities, there were no significant correlations between either the magnitudes of vertical coma aberration or higher-order RMS error, and the aberrometry auto-refraction logMAR acuities. These trends were perhaps not significant as the aberrometry auto-refraction power vectors were often very different in magnitude from the subjective refraction terms; the results show that the subjective refraction data gave significantly better acuities.

Finally, this investigation reveals significant correlations between the magnitudes of vertical coma and higher-order RMS error, and the difference in M power vector terms between the subjective refraction and aberrometer auto-refraction data in the keratoconic group. The general trend showed that the higher the magnitudes of negative vertical coma and higher-order RMS error, the larger the difference in the M power vector terms between these two refraction types. This finding is perhaps also explained by the fact that the large magnitudes of higher-order aberration typically found in keratoconic eyes can cause serious computational and mathematical errors at the Hartmann-Shack CCD sensor (Thibos and Hong, 1999, Thibos and Applegate, 2001, Yoon et al., 2004b).

In summary, the data presented show that the mean differences between subjective and aberrometry-derived refraction data are substantially larger in keratoconic eyes than in normal eyes. The subjective refraction data also gave significantly better logMAR acuity than the aberrometer's auto-refraction data. In the keratoconic group, the refraction data derived from the 2nd-order aberration terms and by combining the 2nd-, 3rd- and 4th-order aberration terms were different to the subjective refraction data. In addition, the results show that in keratoconic eyes, the larger the magnitudes of manifest vertical coma and higher-order RMS error, the poorer the subjective logMAR acuity achieved. These results perhaps warrant the further investigation of aberrometry-derived metrics to objectively estimate refraction in keratoconus, as an objective method of accurately predicting refraction would be clinically useful in saving time when assessing patients with keratoconus.

This chapter reports a significant finding in keratoconus research as objective refraction obtained with an aberrometer (even after accounting for the higher-order aberrations) does not match with subjective refraction findings in keratoconus patients, despite optical defects such as higher-order aberrations being considered as an important cause of poor visual quality in keratoconus. The results also indicate that a subjective refraction is likely to provide the best visual performance, which may be useful when designing bespoke aberration-controlling contact lenses for patients with keratoconus.
7. Changes in Refraction, Ocular Aberrations and Corneal Structure after Suspending RGP Contact Lens Wear in Keratoconus

Contributions
I designed this investigation with helpful contributions from my co-authors Hema Radhakrishnan (HR) and Clare O'Donnell (COD). I also completed all the measurements and statistical analyses with useful input from HR and COD. I wrote the published manuscript and this thesis chapter with valuable comments from HR and COD.

Publications

Conference presentations
Poster presentation at the Association for Research in Vision and Ophthalmology Conference (Fort Lauderdale, FL, US: April 29 – May 5; 2011)
7.1 Abstract

7.1.1 Background: This investigation reports on changes in visual acuity, ocular higher-order aberrations and refraction, after suspending rigid gas-permeable (RGP) lens wear for one week in 16 patients with moderate to severe keratoconus. Alterations in the anterior surface central corneal powers and axes and central corneal thickness were also investigated.

7.1.2 Methods and materials: Scheimpflug photography and Shack-Hartmann aberrometry were performed at two visits, seven days apart, after the patients had removed their habitual RGP lenses. Subjective refraction and both high-contrast and low-contrast logMAR visual acuities were also recorded at both visits.

7.1.3 Results: Reductions in both high- (p = 0.001) and low-contrast visual acuity (p = 0.005), along with an increase in third-order RMS aberrations (p = 0.006), occurred after RGP lens wear was suspended in these keratoconic patients. However, no significant changes in subjective refraction were found over the one-week period (p ≥ 0.082). Significant correlations were observed between third-order coma RMS aberrations and the measured high-contrast (Pearson correlation coefficient, R_p ≥ 0.53, p ≤ 0.034) and low-contrast visual acuities (R_p ≥ 0.55, p ≤ 0.027). In addition to increases in the anterior surface central corneal powers (p ≤ 0.02), a reduction in central corneal thickness was also found between the two visits (p = 0.00012).

7.1.4 Conclusions: Changes in the optical and structural parameters of the keratoconic cornea occur after suspending RGP contact lens wear. This information may be of interest to practitioners involved with prescribing aberration-controlling soft contact lenses for such patients.
7.2 Introduction

Keratoconus, is classically described as an ectatic corneal condition (Krachmer et al., 1984) characterised by maximal stromal thinning occurring at the same point as the greatest corneal protrusion (Rabinowitz, 1998). The condition predominantly affects the inferior-paracentral two thirds of the cornea, which, over time, progressively steepens, exhibiting a more conical profile (Li et al., 2007). As keratoconus progresses, spectacles provide inadequate best-corrected visual acuity due to irregular myopic astigmatism. As a result, keratoconus is primarily managed using rigid gas-permeable (RGP) contact lenses (Lawless et al., 1989, Zadnik et al., 1998). From time to time, patients with keratoconus may be required to leave out their RGP lenses for example if they develop corneal abrasion, infection or persistent epithelial desiccation or perhaps because of RGP lens breakage or loss. In addition, practitioners may also request that lenses are left out before conducting a subjective refraction. Prior to refitting keratoconic patients with an alternative lens type (e.g. a specialist soft lens) or design, clinicians may require that RGP lens wear is suspended for a short time to act as a 'wash-out' period, as RGP lens wear has been shown to induce corneal topographical changes in normal control subjects (Wilson et al., 1990) and keratoconic patients (Szczotka et al., 1996). By leaving the RGP lenses out, the patient's cornea would theoretically adopt its truest and perhaps most irregular shape. This ultimately would allow the practitioner the best opportunity to achieve the most accurate lens fitting, potentially resulting in optimal lens comfort and visual performance.

Because the literature does not address how the optical properties of the keratoconic cornea change when RGP contact lens wear is suspended, the present study was performed in an attempt to investigate this. Zadnik and Mutti (1987) have previously discussed that flat-fitting RGP lenses may ‘mould’ the keratoconic cornea by exerting pressure on the cone apex, thereby forcing the anterior surface to align to a shape similar to that of the RGP lens back surface. Therefore, it is likely that the keratoconic corneal profile will alter after RGP lenses are removed. Moreover, changes in the curvature or thickness of the cornea may lead to changes in subjective refraction and higher-order aberrations and such variations could potentially impact on visual acuity.

In contrast to normal eyes, patients with keratoconus typically show large magnitudes of irregular astigmatism (Zadnik et al., 1998, Li et al., 2007) and both corneal (Gobbe and Guillon, 2005, Alio and Shabayek, 2006) and ocular higher-order aberrations (Maeda et al., 2002, Kosaki et al., 2007, Lim et al., 2007). Of the higher-order aberrations, 3rd-order vertical coma is typically negative in sign and, usually, is significantly elevated compared with normal eyes. The large magnitudes of aberration reflect the nature and position of the corneal thinning and subsequent protrusion (Tan et al., 2008, Jinabhai et al., 2009). Previous studies have shown that higher-order aberrations affect visual performance in keratoconus. Moreover, Negishi and colleagues (2007) and Okamoto and co-workers (2008) report significant correlations between the magnitudes of 3rd-order RMS aberrations and letter contrast sensitivity in keratoconus patients compared to in age-matched control subjects. Negishi et al. (2007) measured contrast sensitivity in keratoconic patients with RGP lenses in situ, whereas Okamoto et al. (2008) made their measurements using...
a trial lens refraction in keratoconus patients who had left their RGP lenses out for at least two weeks before evaluation.

In visually-normal subjects, corneal curvature changes, which occur upon contact lens removal, are influenced by the type of lens worn (Wilson et al., 1990, Budak et al., 1999), the modality of wear (Wang et al., 2002) and the number of years of lens wear (Wang et al., 2002, Tsai et al., 2004). It would appear that corneal topography takes longer to stabilise after RGP lens wear compared to soft lens wear (Wilson et al., 1990, Budak et al., 1999, Wang et al., 2002, Tsai et al., 2004). Perhaps surprisingly, there is no consensus in the literature about the expected time period that is necessary to achieve corneal stability after RGP lens removal. For example, Budak et al. (1999) report that up to 5 weeks were required before consistent measurements of corneal topography could be obtained in 18 RGP lens-wearing subjects, whereas Wilson et al. (1990) found that up to 21 weeks were required in three RGP lens-wearing eyes. Other authors have reported that up to 9 weeks were required to achieve topographical stability after discontinuing RGP lens wear (Wang et al., 2002, Tsai et al., 2004). Both Wang et al. (2002) and Tsai et al. (2004) report that longer recovery times were required in patients with a higher mean number of years of RGP lens wear. The results of these studies are perhaps influenced by the sensitivity of the measurement techniques employed in the various investigations.

Overnight orthokeratology (OOK) studies have previously investigated how the optical and structural properties of the cornea change after suspending contact lens wear. Hiraoka et al. (2009) have shown that after discontinuing reverse-geometry RGP lens wear, parameters such as subjective refraction, uncorrected visual acuity and higher-order ocular aberrations returned to baseline measurements at one week. Equally, Soni et al. (2004) report that central corneal curvature (in both meridians) returned to baseline measurements 7 days after discontinuing reverse-geometry RGP lens wear. These reports suggest that a period of 7 days is sufficient to measure noticeable changes in the refractive and topographical properties of normal myopic corneas after RGP lens removal.

The present study aimed to evaluate possible changes in the optical and structural properties of the cornea in 16 eyes of 16 keratoconic patients after suspending RGP lens wear for a period of one week. Changes in subjective refraction, ocular higher-order aberrations and both high-contrast and low-contrast visual acuity were measured. In addition, central corneal radii, central corneal thickness and corneal asphericity were also investigated.

### 7.3 Methods and materials

Sixteen patients with previously diagnosed keratoconus participated in the investigation; all participants were recruited from Manchester Royal Eye Hospital. All experimental data were collected from one eye of each of the 16 patients. All participants habitually wore RGP contact lenses. The mean age of the group was $34 \pm 6$ [SD] years (range 26 to 43 years), consisting of 11 males and 5 females. The investigation followed the tenets of the Declaration of Helsinki. All participants gave their informed consent after being told the purpose of the investigation. The
study protocol was approved by the National Research Ethics Service, North West 11 Research Ethics Committee.

A slit-lamp biomicroscope (SL40, Keeler Ltd., Windsor, U.K.) examination was conducted to assess the fitting of the subjects’ habitual RGP lenses using sodium fluorescein. The lens fittings were graded as definite apical clearance, apical clearance, apical touch or definite apical touch, using the criteria outlined by Fink and associates (2001). Participants were then asked to remove their habitual RGP lenses to allow a slit-lamp biomicroscopic assessment of the patients’ cornea, including the presence or absence of Fleischer’s ring, Vogt’s striae, prominent corneal nerves and apical scarring.

A baseline monocular subjective refraction was performed on all subjects, at a distance of 6 metres, to obtain the subjective refraction result that maintained optimal visual acuity. The final refraction result was checked with a + 1.00 DS blur test. Once the endpoint refraction was reached, the back vertex distance was recorded in millimetres. Baseline high- (95 %) and low-contrast (15 %) acuity measurements were then taken using two Bailey-Lovie logMAR letter charts (National Vision Research Institute, Melbourne, Australia). Both charts were positioned at 3 meters from the patient and were illuminated externally using two fluorescent tubes, aligned in such a way that they uniformly illuminated to approximately 750 lux without causing glare. The high-contrast and low-contrast acuity measurements at 3 metres were scored to the letter in log units and were corrected for a distance of 6 metres using the manufacturer’s conversion chart.

The Oculus Pentacam (Oculus, Wetzlar, Germany) was used to measure each subject’s corneal topography, central corneal thickness and central radii of curvature (calculated in the central 3 mm zone). The rotating Scheimpflug camera-based device works in conjunction with a blue light-emitting diode, monochromatic slit-light source (at 475 nm) and captures 25 images during a 1-second scan, which provides up to 500 true elevation points per image. Four monocular scans were repeated and averaged for each eye. The severity of keratoconus was graded from the Pentacam data, immediately after lens removal at this initial visit, using the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) study group’s criteria, where steep keratometric measurements between 45 to 52 D were graded as ‘moderate’ keratoconus and readings > 52 D were classed as ‘severe’ keratoconus (Zadnik et al., 1996). In addition, the Pentacam’s internal software (Version 1.17r46, Oculus) was used to calculate measurements of the anterior corneal surface asphericity in an 8-mm diameter peripheral ring zone – corneal surface asphericity will be referred to as the corneal P-value (CPV). The CPV gives an index of peripheral flattening and describes the degree to which an aspheric surface differs from the equivalent spherical form by indicating how rapidly the surface flattens from the apex (Lam and Douthwaite, 1994). The CPV is the current American National Standards Institute standard for representing the corneal shape within a conic section (American National Standard for Ophthalmics, 1999).

Measurements of ocular higher-order aberrations were made with the IRX-3 Hartmann-Shack aberrometer (Imagine Eyes, Paris, France), which uses a 32 X 32 lenslet array and near infra-red light (wavelength = 780 nm). Ocular aberrations were recorded under monocular conditions with the room lights switched off. Accommodation was relaxed using the dynamic fogging method whilst patients fixated on a black 6/12-sized Snellen letter “E” in an elliptical white
background field subtending an approximate $0.7 \times 1.0$-degree angle with a luminance of approximately $85 \text{ cd/m}^2$. An average of four monocular measurements was calculated for all participants. The wavefront aberrations were computed up to the 6th Zernike order for a 4-mm pupil diameter (using the device’s internal software – Version 1.2, Imagine Eyes), as this was the largest pupil size common to all 16 patients.

At the end of the day 1 visit, each patient was asked to leave out their habitual RGP lenses for a period of seven days. All patients had spectacles which had been prescribed within the previous 18 months and were asked to use these until the next appointment (one week later). At the second visit, evaluation of the subjects was repeated by the same examiner. The subjective refraction, high-contrast and low-contrast acuities, central corneal radii, central corneal thickness, anterior surface CPV and ocular aberrations obtained at the two visits were compared for each participant.

7.3.1 Data analysis
To facilitate statistical analysis, all subjective refraction data were converted into the power vector coordinates $M$, $J_0$ and $J_{45}$ as outlined by Thibos and co-workers (1997). Normality tests were performed for all the data collected using the Shapiro-Wilk’s test for a critical value of 0.05 (SPSS Version 16.0; SPSS Inc., Chicago, US). All normally distributed data were analysed using one-way repeated-measures analysis of variance (RM-ANOVA), whilst non-normally distributed data were analysed using the Wilcoxon signed-rank test (WSRT). Similarly, all normally distributed data were evaluated using Pearson’s correlation coefficients (two-tailed) for a critical value of 0.05, whereas all non-normally distributed data were analysed using Spearman’s correlation (Rho) coefficients (two-tailed) for a critical value of 0.05.

7.4 Results
Table 7.1 summarises the anterior surface central radii and axes, central corneal thicknesses, CLEK study group severity grades, corneal slit-lamp appearance and RGP lens fitting grades for the 16 keratoconic patients at the initial examination. The group constituted of 6 patients with severe keratoconus and 10 patients with moderate keratoconus, 7 of the participants displayed apical scarring. All 16 patients showed Fleischer’s ring and prominent corneal nerves. Fifteen patients presented with a flat RGP lens fitting whilst only one participant showed an apical clearance fit. The average number of years since the diagnosis of keratoconus among the patients was $9 \pm 5$ years, with an average number of years of contact lens wear of $7 \pm 5$ years. The average contact lens wearing time was $10 \pm 3$ hours per day and $6 \pm 1$ day per week.
Table 7.1 A summary of the average anterior surface central radii and axes, central corneal thicknesses, CLEK study group severity grades (Zadnik et al., 1996), corneal slit-lamp appearance and RGP lens fittings for the 16 keratoconic patients at the initial examination. (DAT = definite apical touch; AT = apical touch and AC = apical clearance (Fink et al., 2001)).

<table>
<thead>
<tr>
<th>Patient ref.</th>
<th>Flat K (D)</th>
<th>Steep K (D)</th>
<th>Flat meridian axis (degrees)</th>
<th>Central corneal thickness (microns)</th>
<th>CLEK severity grade</th>
<th>Vogt's striae</th>
<th>Apical scarring</th>
<th>RGP lens fitting grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>49.78</td>
<td>56.03</td>
<td>16</td>
<td>455</td>
<td>Severe</td>
<td>Present</td>
<td>Absent</td>
<td>DAT</td>
</tr>
<tr>
<td>2</td>
<td>45.55</td>
<td>49.95</td>
<td>116</td>
<td>451</td>
<td>Moderate</td>
<td>Absent</td>
<td>Absent</td>
<td>AT</td>
</tr>
<tr>
<td>3</td>
<td>42.83</td>
<td>45.10</td>
<td>70</td>
<td>440</td>
<td>Moderate</td>
<td>Absent</td>
<td>Absent</td>
<td>AT</td>
</tr>
<tr>
<td>4</td>
<td>45.60</td>
<td>48.43</td>
<td>31</td>
<td>434</td>
<td>Moderate</td>
<td>Absent</td>
<td>Absent</td>
<td>AC</td>
</tr>
<tr>
<td>5</td>
<td>58.15</td>
<td>61.75</td>
<td>124</td>
<td>324</td>
<td>Severe</td>
<td>Present</td>
<td>Present</td>
<td>AT</td>
</tr>
<tr>
<td>6</td>
<td>45.60</td>
<td>47.28</td>
<td>136</td>
<td>505</td>
<td>Moderate</td>
<td>Absent</td>
<td>Absent</td>
<td>AT</td>
</tr>
<tr>
<td>7</td>
<td>47.80</td>
<td>52.00</td>
<td>112</td>
<td>419</td>
<td>Moderate</td>
<td>Present</td>
<td>Present</td>
<td>DAT</td>
</tr>
<tr>
<td>8</td>
<td>52.20</td>
<td>55.88</td>
<td>20</td>
<td>503</td>
<td>Severe</td>
<td>Present</td>
<td>Present</td>
<td>DAT</td>
</tr>
<tr>
<td>9</td>
<td>44.20</td>
<td>47.95</td>
<td>125</td>
<td>453</td>
<td>Moderate</td>
<td>Present</td>
<td>Absent</td>
<td>DAT</td>
</tr>
<tr>
<td>10</td>
<td>44.10</td>
<td>49.20</td>
<td>91</td>
<td>461</td>
<td>Moderate</td>
<td>Absent</td>
<td>Absent</td>
<td>DAT</td>
</tr>
<tr>
<td>11</td>
<td>43.85</td>
<td>49.38</td>
<td>138</td>
<td>386</td>
<td>Moderate</td>
<td>Present</td>
<td>Present</td>
<td>DAT</td>
</tr>
<tr>
<td>12</td>
<td>48.63</td>
<td>51.85</td>
<td>142</td>
<td>415</td>
<td>Moderate</td>
<td>Present</td>
<td>Present</td>
<td>DAT</td>
</tr>
<tr>
<td>13</td>
<td>43.38</td>
<td>47.33</td>
<td>13</td>
<td>484</td>
<td>Moderate</td>
<td>Absent</td>
<td>Present</td>
<td>AT</td>
</tr>
<tr>
<td>14</td>
<td>51.38</td>
<td>56.43</td>
<td>27</td>
<td>416</td>
<td>Severe</td>
<td>Present</td>
<td>Present</td>
<td>DAT</td>
</tr>
<tr>
<td>15</td>
<td>49.08</td>
<td>52.90</td>
<td>25</td>
<td>435</td>
<td>Severe</td>
<td>Present</td>
<td>Present</td>
<td>DAT</td>
</tr>
<tr>
<td>16</td>
<td>47.73</td>
<td>53.20</td>
<td>16</td>
<td>420</td>
<td>Severe</td>
<td>Present</td>
<td>Absent</td>
<td>DAT</td>
</tr>
</tbody>
</table>

7.4.1 Changes in subjective refraction

Table 7.2 summarises the subjective refraction power vector terms M, J0 and J45 measured at both visits. No significant changes in M, J0 and J45 were found between the two assessments.

Table 7.2 A summary of the subjective refraction power vector terms measured at both visits. Statistical analysis was performed using repeated-measures ANOVA.

<table>
<thead>
<tr>
<th>Vector</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>p</th>
<th>F_{1,15}</th>
</tr>
</thead>
<tbody>
<tr>
<td>M (D)</td>
<td>-2.44 ± 1.79</td>
<td>-2.44 ± 1.85</td>
<td>0.96</td>
<td>0.003</td>
</tr>
<tr>
<td>J0 (D)</td>
<td>-1.52 ± 1.06</td>
<td>-1.72 ± 1.15</td>
<td>0.082</td>
<td>3.47</td>
</tr>
<tr>
<td>J45 (D)</td>
<td>-0.23 ± 1.27</td>
<td>-0.07 ± 1.39</td>
<td>0.34</td>
<td>0.95</td>
</tr>
</tbody>
</table>

7.4.2 Changes in higher-order aberrations

Figure 7.1 displays box and whisker plots of the various higher-order aberrations measured at the two visits and shows that 3rd-order coma RMS error increased (from 0.89 ± 0.36 µm to 1.12 ± 0.42 µm; p = 0.01, F_{1,15} = 8.55; RM-ANOVA) between visits. Similarly, increases in total 3rd-order RMS aberrations (from 0.97 ± 0.35 µm to 1.19 ± 0.41 µm; p = 0.006, F_{1,15} = 10.17; RM-ANOVA) and higher-order RMS (HORMS) error (from 1.06 ± 0.37 µm to 1.27 ± 0.43 µm; p = 0.003, Z = -2.94, WSRT) were also measured. In contrast, no significant changes in the 3rd-order trefoil RMS (from 0.33 ± 0.15 µm to 0.34 ± 0.17 µm; p = 0.88, Z = -0.16, WSRT) and the 4th-order RMS aberrations (from 0.34 ± 0.20 µm to 0.34 ± 0.17 µm; p = 0.75, F_{1,15} = 0.11;
RM-ANOVA) were found between assessments. Upon investigating individual Zernike coefficient terms, 3rd-order vertical coma showed an increase in magnitude from $-0.84 \pm 0.36 \, \mu m$ to $-1.09 \pm 0.43 \, \mu m$ ($p = 0.009$, $F_{1,15} = 9.06$; RM-ANOVA) between the two visits; however, 4th-order spherical aberration showed a non-significant negative shift from $+0.014 \pm 0.23 \, \mu m$ to $-0.015 \pm 0.23 \, \mu m$ ($p = 0.52$, $F_{1,15} = 0.44$; RM-ANOVA).

Figure 7.1 Box and whisker plots showing the difference in RMS (root mean square) aberrations between the two visits for a 4-mm pupil diameter. Statistical analysis was carried out using parametric (repeated-measures ANOVA) and non-parametric (Wilcoxon signed-ranks test *) tests. The box edges depict the upper and lower quartile values. The solid line within the box shows the median value. The whiskers represent the ranges between which the upper and lower 25% of the data fall (*) indicates a significant difference between visits).

7.4.3 Changes in visual performance

Table 7.3 summarises the high-contrast and low-contrast visual acuity data measured at the two visits. Reductions in both high-contrast and low-contrast acuity were measured after RGP lens wear was suspended.

<table>
<thead>
<tr>
<th>Acuity type (log units)</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>$p$</th>
<th>$F_{1,15}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-contrast</td>
<td>$+0.33 \pm 0.14$</td>
<td>$+0.40 \pm 0.16$</td>
<td>$0.001^*$</td>
<td>17.86</td>
</tr>
<tr>
<td>Low-contrast</td>
<td>$+0.70 \pm 0.21$</td>
<td>$+0.79 \pm 0.19$</td>
<td>$0.005^*$</td>
<td>10.62</td>
</tr>
</tbody>
</table>
7.4.4 Changes in corneal structure

Table 7.4 summarises the corneal parameters measured at the two visits. Both the flat and steep central corneal powers increased over the 1-week period. In contrast, the CPV and central corneal thickness showed reductions in magnitude between the two visits. However, the flat meridian axes showed no significant change.

Table 7.4 A summary of the corneal parameters evaluated at the two visits. Both parametric (repeated-measures ANOVA; RM-ANOVA) and non-parametric (Wilcoxon signed-ranks test; WSRT) tests were used to analyse the data (* indicates a significant difference between visits). n = number of patients, df = degrees of freedom.

<table>
<thead>
<tr>
<th>Keratometric data</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>p</th>
<th>Test</th>
<th>Statistic</th>
<th>n or df</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flat central radius (D)</td>
<td>47.49 ± 4.04</td>
<td>48.11 ± 4.18</td>
<td>0.020*</td>
<td>WSRT</td>
<td>Z = -2.32</td>
<td>n = 16</td>
</tr>
<tr>
<td>Steep central radius (D)</td>
<td>51.54 ± 4.36</td>
<td>52.24 ± 4.72</td>
<td>0.003*</td>
<td>RM-ANOVA</td>
<td>F = 13.13</td>
<td>(1,15)</td>
</tr>
<tr>
<td>Flat meridian axis (degrees)</td>
<td>75.03 ± 52.39</td>
<td>73.72 ± 53.85</td>
<td>0.33</td>
<td>WSRT</td>
<td>Z = -0.98</td>
<td>n = 16</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>p</th>
<th>Test</th>
<th>Statistic</th>
<th>n or df</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central corneal thickness (µm)</td>
<td>437.38 ± 44.21</td>
<td>428.91 ± 47.54</td>
<td>0.00012*</td>
<td>RM-ANOVA</td>
<td>F = 27.06</td>
<td>(1,15)</td>
</tr>
<tr>
<td>Corneal P-value</td>
<td>-0.21 ± 0.46</td>
<td>-0.32 ± 0.49</td>
<td>0.002*</td>
<td>RM-ANOVA</td>
<td>F = 14.56</td>
<td>(1,15)</td>
</tr>
</tbody>
</table>

When the differences in both high-contrast and low-contrast acuities measured between the two visits were plotted against the differences in the steep central corneal powers, Spearman’s correlation analyses showed no significant relationships between the variables (p ≥ 0.22). Similarly, no significant correlations were found between the differences in flat central corneal powers and the differences in both high-contrast (p = 0.75) and low-contrast acuities (p = 0.89) measured between the two visits. Equally, when the differences in both the flat and steep keratometric readings measured between the two examinations were plotted against the differences in coma RMS aberrations, no significant correlations were found between the variables (p ≥ 0.70).

7.4.5 Correlations between high-contrast and low-contrast visual acuities and ocular aberrations

Figure 7.2 shows the Pearson correlations (R_p) between total 3rd-order RMS aberrations (Z (3±3) and Z (3±1)) and high-contrast and low-contrast visual acuities measured at both visits. At the first assessment (baseline measurements), significant correlations were found between the magnitudes of total 3rd-order RMS aberrations and both high-contrast and low-contrast visual acuities. A small increase in the level of correlation between high-contrast visual acuity and total 3rd-order RMS aberrations was found at the second visit. A stronger correlation was evident between low-contrast acuity and total 3rd-order RMS aberrations at the second visit compared to at baseline.
Figure 7.2 The Pearson correlations ($R_p$) (two-tailed) between total 3rd-order RMS (root mean square) aberrations and high-contrast and low-contrast acuity measured at both visits. The upper graphs represent high-contrast acuity and the lower graphs represent low-contrast acuity. The left-hand graphs show the correlations at baseline and the right-hand graphs show the correlations at day 7. The solid lines represent the lines of best fit.

Figure 7.3 shows the Pearson correlations between 3rd-order coma RMS aberrations ($Z (3±1)$) and high-contrast and low-contrast visual acuity measured at either visit. The initial assessment data showed significant correlations between the magnitudes of 3rd-order coma RMS aberrations and both high-contrast and low-contrast visual acuity. A small increase in the level of correlation between high-contrast visual acuity and 3rd-order coma RMS aberrations was found at the second assessment compared to at baseline. A higher level of correlation was apparent between low-contrast visual acuity and 3rd-order coma RMS aberrations at day 7 than at baseline.

In contrast, no significant correlations (using Spearman’s correlation coefficients) were found between both high- or low-contrast visual acuity scores and the magnitudes of 3rd-order trefoil RMS aberrations measured at either assessment ($p \geq 0.53$).
7.5 Discussion

This study investigated possible changes in high-contrast and low-contrast visual acuity, subjective refraction, ocular aberrations and the structural properties of the cornea in 16 patients with moderate to severe keratoconus. These parameters were evaluated at two separate visits made 7 days apart following suspension of RGP lens wear.

The findings of this study established that both high-contrast and low-contrast visual acuity reduced between visits. However, no significant changes in subjective refraction power vector terms were found over the 1-week period. The results reveal that higher-order RMS aberrations increased in magnitude after suspending RGP lens wear for one week. These changes were primarily due to alterations in 3rd-order coma RMS aberrations, which showed a noticeable increase between the two sets of measurements. In contrast, no significant change in 3rd-order trefoil RMS error was measured between visits.

Using the IRX-3 aberrometer, Miranda et al. (2009a) found that 3rd-order coma RMS aberrations showed a mean difference of 0.005 µm (with 95% confidence limits of -0.049 µm and +0.059 µm) between measurements made seven days apart in visually-normal, non-contact lens wearers. The aberrometry data presented in this study show considerably larger variations in...
RMS coma aberrations at both examinations, which is agreement with previous studies of patients with keratoconus (Shankar et al., 2008b, Piñero et al., 2009a, Jinabhai et al., 2011b).

Statistical analysis showed that total 3rd-order RMS aberrations and 3rd-order coma RMS error were significantly correlated with both high- and low-contrast acuity measurements. However, no significant correlations were found between 3rd-order trefoil RMS aberrations and high-contrast and low-contrast acuity measurements. To date, only Okamoto et al. (2008) appear to have investigated higher-order aberrations and letter contrast sensitivity in keratoconic eyes after suspending RGP lens wear; however, no baseline measurements of visual performance or aberrations were made immediately after RGP lens removal in their study. Okamoto et al. (2008) report significant correlations between letter contrast sensitivity and ocular 3rd-order RMS aberrations. In their study, the authors measured letter contrast sensitivity using the CSV-1000LV chart (Vector Vision, Columbus, OH, US) at 2.4 cycles/degree using 8 different contrast levels, ranging from standard contrast to 1.1% contrast. Their correlation data used the number of letters correctly identified (out of 24 letters) rather than using the actual contrast threshold or contrast sensitivity, and plotted these values against ocular aberrations. In support of the findings of Okamoto et al. (2008), the results of the present study also showed significant correlations between the magnitude of 3rd-order RMS aberrations and low-contrast visual acuity at both day 1 and day 7. However, Okamoto et al. (2008) found no significant correlation between 3rd-order RMS error and high-contrast visual acuity (measured using a Bailey-Lovie logMAR letter chart).

In conflict with these results, the present investigation found a significant correlation between 3rd-order RMS aberrations and high-contrast visual acuity at both day 1 and day 7. Differences between the results of the present study and those of Okamoto et al. (2008) may have arisen from a number of possibilities such as the disease severity of the participants. Okamoto et al. (2008) did not disclose the disease severity of their keratoconic patients; however, the authors did report that eyes with scarring were not included for evaluation, perhaps suggesting that their patients had more early-stage keratoconus. Alio and Shabayek (2006) have previously shown that the magnitude of higher-order aberrations is dependent on the severity of keratoconus, in that patients with moderate to severe keratoconus show larger magnitudes of aberrations than patients with mild disease. Therefore, it was perhaps to be expected that different relationships between high-contrast and low-contrast acuities and ocular aberrations were found compared to the results presented here. Okamoto et al. (2008) used a 6-mm pupil diameter size to calculate their wavefront aberrations after pupil dilation using 1% tropicamide. In the present study none of the participants had their pupils dilated and a 4-mm pupil diameter size (common to all 16 patients evaluated) was used to compute the aberrations. Using dioptric equivalent calculations (Thibos et al., 2002c), to account for the differences in pupil size used between the two studies, the average total 3rd-order RMS error measured by Okamoto et al. (2008) was 1.22 D, in contrast to 1.68 D (at day 1) and 2.06 D (at day 7) measured in the present study. As the present study patients showed a higher magnitude of 3rd-order aberrations, significant correlations with visual performance is not altogether surprising (Applegate et al., 2002, Negishi et al., 2007, Jinabhai et al., 2010a).

Seven out of the 16 patients in this study showed visible apical scarring upon slit-lamp examination. Such apical corneal scarring will affect both forward and backward light scatter
(Pesudovs et al., 2004, Mihashi et al., 2006b, Patel et al., 2008), which, in addition to higher-order aberrations, is likely to have influenced the contrast acuity scores achieved (Zadnik et al., 2000). Another possible factor to account for the differences between the studies could be the length of the lens wear suspension. Okamoto et al. (2008) stated that patients were asked to cease contact lens wear for at least two weeks before evaluation, whereas the keratoconic patients in the present study were asked to leave their lenses out for 7 days. It is possible that further alterations in the optical properties of these keratoconic corneas may have occurred if RGP lenses were left out for longer than one week. In addition to contact lens wear, ocular aberrations are also influenced by fluctuations in accommodation and the pre-corneal tear-film (Radhakrishnan et al., 2010), as well as instrument noise (Thibos and Hong, 1999, Moreno-Barriuso and Navarro, 2000). Nevertheless, in a previous OOK study, Hiraoka et al. (2009) reported that subjective refraction, uncorrected visual acuity and higher-order aberrations all returned to baseline measurements one week after terminating reverse-geometry, RGP lens wear. Their study proposed that normal myopic corneas adopt their habitual refractive state after one week without RGP lens wear.

In similarity to Okamoto et al.’s (2008) study, our results also showed significant correlations between total 3rd-order RMS aberrations and low-contrast visual acuity after only 7 days without RGP lenses. This may imply that important information regarding aberrations and visual performance can be obtained by leaving lenses out for just one week. Furthermore, it may be argued, that measurements of changes to the cornea over a period of more than a week without lenses could prove difficult for patients with keratoconus, as they primarily rely on their RGP lenses since spectacles tend not to provide comparable visual acuity.

The results presented here reveal that 3rd-order trefoil RMS aberrations showed a poorer level of correlation with both high-contrast and low-contrast acuity at either visit. This finding was expected as aberration coefficients closer to the centre of the Zernike pyramid, such as 3rd-order coma, produce a more destructive influence on visual performance than coefficients located further away from the pyramid’s centre, such as 3rd-order trefoil (Applegate et al., 2002, Applegate et al., 2003a, Applegate et al., 2003b). It was therefore anticipated that any increases in 3rd-order coma RMS error between the two assessments would potentially worsen visual performance further. In support of this, the level of correlation between 3rd-order coma RMS and low-contrast acuity at the second examination ($R_p = 0.65, p = 0.007$) showed a noticeable increase from that calculated at baseline ($R_p = 0.55, p = 0.027$). On the other hand, the level of correlation found between 3rd-order coma RMS and high-contrast acuity showed a comparatively smaller increase between assessments (from $R_p = 0.53, p = 0.034$ at day 1, to $R_p = 0.61, p = 0.012$ at day 7). These findings perhaps indicate that increases in 3rd-order coma RMS aberrations have a more destructive influence on low-contrast acuity than on high-contrast acuity in patients with moderate to severe keratoconus. This supports the results of Fernandez-Sanchez et al.’s (2008) study of 11 visually-normal eyes, whose ocular aberrations were measured with and without aberration-inducing soft contact lenses in place. The lenses fitted induced 1.03 µm of 3rd-order coma RMS aberration, resulting in a mean change in high-contrast logMAR acuity of 0.19 ± 0.10 [±1 SD] log units, and a mean change in low-contrast acuity of 0.39 ± 0.14 log units;
suggesting that increases in coma RMS aberrations cause more impairment of low-contrast acuity than high-contrast acuity in normal eyes.

Alongside these changes in visual performance and ocular aberrations, variations in the structural properties of the cornea were also found in the keratoconic patients after suspending RGP lens wear. These included steepening of the anterior surface central radii of curvature, a reduction in the central corneal thickness and a negative increase in the anterior surface CPV (measured in an 8-mm diameter peripheral ring zone). Of these corneal changes, steepening of the central cornea after RGP lens wear suspension may be attributed to the lens fitting. Fifteen of the 16 keratoconic patients showed an apical-touch type fitting (Fink et al., 2001), which is in agreement with previous reports (Edrington et al., 1999, Zadnik et al., 2005). Apical touch lens fittings could principally centre the majority of the lens weight over the cone apex, causing the anterior surface of the cone to conform to a shape similar to the back surface of the contact lens. Upon removing the lens, there could be a reduction in the pressure exerted on the cone’s anterior surface; a relaxation of this pressure would perhaps enable the cone to protrude forward without obstruction. More peripherally, measurements of the CPV showed an average negative value, indicating a hyperboloid corneal contour. Between the two assessments, a small negative increase in the CPV was measured, suggesting that the peripheral corneal profile showed a small degree of flattening at the second examination. This peripheral flattening is likely to be due to steepening of the central cone after apical touch lens removal. The reductions in central corneal thickness observed after suspending RGP lens wear may perhaps be related to recovery from subtle levels of corneal oedema (Swarbrick et al., 1998). All the patients enrolled in this study tended to wear their RGP lenses for the majority of their working day and for most of the week.

It could be argued that the noticeable differences in 3rd-order ocular aberrations measured between the two visits are perhaps related to the changes in the structural properties of the cornea over the 7-day period. The results suggest that without the RGP lens, the keratoconic cornea displays an increase in anterior surface steepening at the central cornea as well as a reduction in central corneal thickness. This steeper and more conical corneal profile may have directly resulted in the inducement of additional 3rd-order RMS aberrations, in particular for the Zernike coefficient vertical coma, which sequentially led to the measureable reduction in both high-contrast and low-contrast acuities recorded between visits.

The phenomenon of corneal moulding using RGP contact lenses is purposely employed in OOK (Swarbrick, 2006), where reverse-geometry RGP lenses are fitted to reduce myopia by inducing corneal curvature and epithelial thickness changes (Nichols et al., 2000, Rah et al., 2002, Soni et al., 2003). Several investigations have shown that OOK increases corneal (Hiraoka et al., 2005, Hiraoka et al., 2006) and ocular (Joslin et al., 2003, Berntsen et al., 2005, Hiraoka et al., 2007, Stillitano et al., 2007) higher-order aberrations. Most investigations report significant increases in 3rd-order coma, 4th-order spherical aberration and total higher-order RMS aberrations (Hiraoka et al., 2005, Hiraoka et al., 2006, Hiraoka et al., 2007, Stillitano et al., 2007). In another OOK study, Soni et al. (2004) explain that central corneal curvature (in both meridians) returned to baseline values 7 days after suspending reverse-geometry RGP lens wear. It is plausible that similar changes in corneal curvature, corneal thickness and ocular aberrations may have
occurred for the keratoconic patients in the present study as a result of suspending their habitual RGP lens wear.

A possible limitation to this investigation is that all the lenses worn by the patients were of different designs and materials; this could not have been avoided as the participants were recruited from a hospital population and had typically been fitted by different practitioners at different times. Similarly, the keratoconic patients were heterogeneous in terms of the duration of disease and lens wear experience.

In summary, the results of this investigation show that changes in both high-contrast and low-contrast visual acuities and ocular higher-order aberrations occur after RGP lens wear is suspended in patients with keratoconus. However, no significant changes in subjective refraction power vector terms were found over the one-week period. Increases in 3rd-order coma RMS aberrations showed significant correlations with the measured reductions in both high-contrast and low-contrast visual acuity in these patients with moderate to severe keratoconus.

It is envisaged that the findings of this investigation could be useful for practitioners who are considering refitting RGP lens-wearing keratoconic patients with alternative lens types. Understanding how refraction and visual performance change upon removal of RGP lenses may also be of general interest to clinicians managing patients with keratoconus. Moreover, the results of this investigation may be helpful to researchers concerned with designing and fitting aberration-controlling soft contact lenses to keratoconus patients. As the concept of customised contact lenses becomes a reality, understanding how ocular aberrations vary after RGP contact lens removal will be important in the fitting process, particularly as the literature explains that higher-order aberration measurements show poor repeatability in keratoconic eyes (Shankar et al., 2008b, Piñero et al., 2009a, Jinabhai et al., 2011b) and that the measurement of ocular aberrations is prone to error in these patients (Thibos and Applegate, 2001, Yoon et al., 2004b).
8. Visual Performance and Optical Quality with Sphero-Cylindrical Soft Contact Lenses in Keratoconus Patients

Contributions

I designed this investigation with helpful contributions from my co-authors Hema Radhakrishnan (HR), Clare O'Donnell (COD) and Cindy Tromans (CT). I also completed all the measurements and statistical analyses with useful input from HR and COD. I wrote the scientific manuscript and this thesis chapter with valuable comments from HR, COD and CT.

Publications submitted


Acknowledgements

I would like to thank the optometrists at Manchester Royal Eye Hospital for their help with patient recruitment.
8.1 Abstract

8.1.1 Purpose: To investigate how toric soft contact lenses correct visual performance and ocular higher-order aberrations in keratoconic patients, compared to habitual RGP (rigid-gas-permeable) contact lenses or spectacles.

8.1.2 Methods and materials: Twenty-two keratoconic patients (16 habitual RGP lens wearers and 6 spectacle wearers) were fitted with toric hydrogel lenses. Ocular aberrations were measured with and without the patient’s habitual RGP lenses using a Hartmann-Shack aberrometer. Measurements were also made with the patient wearing the toric soft lenses. In the spectacle-wearing group, ocular aberrations were measured with and without the toric hydrogel lenses. Visual performance was evaluated with the patient’s habitual correction (of either RGP lenses or spectacles) and with the soft lenses, using high-contrast and low-contrast logMAR charts and the Smith-Kettlewell Institute Low Luminance (SKILL) card (Smith-Kettlewell Eye Research Institute, CA, US).

8.1.3 Results: In the RGP lens-wearing group, both the patients’ habitual lenses and the toric soft lenses significantly reduced coma RMS, trefoil RMS, 3rd-order RMS, 4th-order secondary cylinder RMS and higher-order RMS aberrations ($p \leq 0.015$). In the spectacle-wearing patients, the toric soft lenses significantly reduced coma RMS, 3rd-order RMS and higher-order RMS aberrations ($p \leq 0.01$). The patients’ habitual RGP lenses gave significantly better low-contrast acuity and SKILL card scores ($\leq 0.006$) when compared to the toric soft lenses, however, no significant difference was found between lens types for high-contrast acuity ($p = 0.10$). In the spectacle-wearing group, no significant differences in visual performance measurements were found between the patients’ spectacles and the toric soft lenses ($p \geq 0.06$).

8.1.4 Conclusions: The results show that RGP lenses provided superior visual performances and greater reduction of 3rd-order aberrations compared to toric hydrogel lenses in this group of keratoconic patients. In the spectacle-wearing group, visual performance with the toric soft lenses was found to be comparable to that measured with spectacles. Nevertheless, with the exception of 4th-order spherical aberration, the soft lenses were successful in significantly reducing uncorrected higher-order aberrations. These results may be of interest to eyecare practitioners involved in the visual rehabilitation of keratoconic patients who seek an alternative to RGP lenses.
8.2 Introduction

Keratoconus is a progressive, ectatic disorder of the cornea which is typically bilateral, yet asymmetric in nature (Krachmer et al., 1984). The condition is characterised by corneal protrusion, stromal thinning, irregular corneal astigmatism and variable degrees of corneal scarring (Rabinowitz, 1998). Protrusion of the corneal surfaces leads to higher-order aberrations, in particular vertical coma (Schoneveld et al., 2009, Jinabhai et al., 2010a), which can be evaluated using Hartmann-Shack aberrometry (Jinabhai et al., 2011b).

The method of visual correction utilised in keratoconus alters depending on the severity of the condition. In the earliest stages patients may achieve satisfactory visual acuity using spectacles, however, as the corneal surface becomes more distorted, spectacle correction becomes progressively unsuccessful. Currently, rigid gas-permeable (RGP) contact lenses are the primary method of non-surgical visual rehabilitation employed in patients with moderate to severe keratoconus (Lim and Vogt, 2002, Kapur et al., 2003, Wagner et al., 2007, Weed et al., 2008, Bilgin et al., 2009, Mahadevan et al., 2009). When applied to the eye, RGP lenses can mask most of the corneal aberrations induced by keratoconus by replacing the irregular, keratoconic corneal surface with the regular refractive surfaces of the RGP lens and a liquid ‘tear-lens’ (Griffiths et al., 1998). Three major RGP lens-fitting strategies have been described in the literature including ‘apical clearance’ (steeper fitting), ‘apical touch’ (flatter fitting) and ‘three-point touch’ (Leung, 1999). The most commonly adopted strategy is the apical touch type lens fit (Edrington et al., 1999). It has been suggested that this fitting technique facilitates good visual acuity (Zadnik and Mutti, 1987, Jinabhai et al., 2010b); however, excessive apical contact and lens movement between blinks may lead to chronic epithelial abrasion perhaps leading to epithelial thinning and sub-epithelial scarring (Barr et al., 2000).

Even with the variety of designs currently available, RGP lenses are often difficult to fit for corneas with keratoconus, with patients sometimes experiencing discomfort perhaps due to increased lid sensitivity (Betts et al., 2002, Edrington et al., 2004), which may lead to RGP lens intolerance. Moreover, it has been established that atopy is commonly found amongst patients with keratoconus (Copeman, 1965, Rahi et al., 1977, Gasset et al., 1978), perhaps further exacerbating ocular discomfort in RGP contact lens-wearing patients (Bawazeer et al., 2000). Rigid gas-permeable lenses may also be an inappropriate choice in certain instances, for example for keratoconic patients who participate in contact sports. In these cases, other lens modalities may need to be considered. Pullum and Buckley (1997) have previously suggested the use of scleral contact lenses to improve lens comfort, however, relatively few practitioners are skilled in fitting this lens type and these lenses typically reduce the amount of oxygen available to the cornea due to their large diameter and centre thickness (Tan et al., 1995). Other reports have also described the use of spherical, soft contact lenses as an alternative for keratoconic patients who achieve poor acuity with spectacles and have developed RGP lens intolerance (Lobascher, 1975, Koliopoulos and Tragakis, 1981). These studies demonstrate that soft lenses can, to some extent, mask irregular corneal astigmatism.
When comparing the visual performance of RGP lenses with four different spherical soft lenses, in a study of 13 keratoconic patients, Griffiths et al. (1998) found that the RGP lenses gave better high-contrast (by approximately 1 line) and low-contrast (by approximately 1.5 lines) logMAR acuity results. The authors also revealed that RGP lenses significantly reduced residual corneal RMS aberrations, at diameters of 4 and 6 mm, compared to all four soft lenses evaluated (p < 0.01). Yamazaki et al. (2006) fitted 80 eyes of 66 RGP lens-intolerant, keratoconic patients using spherical and sphero-cylindrical soft contact lenses (Perfect Keratoconus lenses, Xyloficon material; water content 67 %; centre thickness 0.36 mm; World Vision Ophthalmic, Sao Paulo, Brazil). The authors found that 73 out of 80 eyes fitted, obtained visual acuities of 6/12 or better. Gonzalez-Meijome et al. (2006) also described the successful rehabilitation of three eyes of two keratoconic patients using spherical Soft K lenses (Acofilcon A material; water content 58 %; centre thickness 0.32 mm; Soflex Contact Lens Industries Ltd., Misgav Israel). Both patients achieved visual acuities of 6/4.5.

These reports indicate that hydrogel lenses may be useful in patients with RGP lens intolerance. The major advantage over RGP lenses is improved comfort, but in order to mask astigmatism successfully, soft lenses typically require thicker optical zones (often between 0.3 to 0.4 mm) (Gonzalez-Meijome et al., 2006; Yamazaki et al., 2006), which, in some cases, can lead to hypoxia and corneo-limbal neovascularisation. As keratoconic patients may require corneal transplantation, this is to be avoided, since corneal vascularisation may contribute to graft rejection. More recently, White (2010) has described the use of silicone hydrogel lenses to improve oxygen permeability in soft lenses designed for keratoconus (KeraSoft IC; Filcon V 3 material; water content 74 %; Dk = 60; centre thickness 0.4 mm; UltraVision CLPL, Leighton Buzzard, UK). These lenses were fitted to a patient with bilateral keratoconus and provided visual acuities of 6/8 in both eyes.

In summary, soft contact lenses offer certain advantages over RGP lenses e.g. better comfort in cases of RGP lens intolerance. Equally, Pesudovs et al. (2006) have shown that young ametropic adults are likely to achieve a better ‘quality of life’ whilst wearing contact lenses compared with spectacles, indicating that contact lenses could offer a significant benefit to young adults. Previous studies of spherical hydrogel lenses have shown that soft lenses can mask irregular corneal astigmatism to a limited extent; however, there are relatively few studies that have compared the effect of toric soft lenses on ocular aberrations and visual performance versus measurements made with RGP lenses and spectacles in patients with keratoconus. The present study aimed to investigate the changes in high-contrast and low-contrast visual acuity and ocular aberrations, in a cohort of keratoconic patients fitted with toric soft contact lenses in comparison to their habitual RGP lens or spectacle lens correction.

8.3 Methods and materials

Twenty-two patients with previously diagnosed keratoconus took part in this investigation; participants were recruited from the Optometry Department at the University of Manchester's Vision Centre clinic and Manchester Royal Eye Hospital. Inclusion criteria for the study participants included a ‘scissors’ retinoscopic reflex, distorted mires on keratometry and slit
lamp signs of keratoconus such as corneal apical protrusion, Vogt’s striae, stromal scarring and Fleischer’s ring. Patients with corneal transplants, cataracts, intra-ocular lens implants, macular disease or optic nerve disease, in either eye, were excluded from participating. All experimental data were collected from one eye of each patient; the selected for investigation showed more advanced disease than the fellow eye. Sixteen participants were successful habitual RGP contact lens wearers; the remaining 6 patients habitually wore spectacles to correct their vision. Each of the spectacle-wearers wanted to wear contact lenses and had not been fitted with lenses previously. Successful lens wearers were defined as patients who experienced no more than a slight lens awareness and/or an occasional foreign body sensation whilst wearing their RGP lenses and regularly wore their lenses for minimum of 8 hours a day (Sarver and Harris, 1971). The mean age of the group was 34 ± 8 [SD] years (range 19 to 55 years), consisting of 17 males and 5 females. The investigation followed the tenets of the Declaration of Helsinki. All participants gave their informed consent after being told the purpose of the study. The investigation protocol was approved by the National Research Ethics Service, North West 11 Research Ethics Committee. The flowcharts presented in Figure 8.1 and Figure 8.2 summarise the sequence of investigative steps for the RGP lens- and spectacle-wearing patients respectively.

8.3.1 Visual performance

High-contrast (95 %) and low-contrast (15 %) visual acuities were measured using two Bailey-Lovie logMAR letter charts (National Vision Research Institute, Melbourne, Australia). Both letter charts were positioned at a distance of 3 meters from the patient and were illuminated externally using two fluorescent tubes, aligned such that they uniformly illuminated to approximately 750 lux without causing glare. All high-contrast and low-contrast acuity measurements recorded at 3 metres were scored to the letter in log units and were corrected for a distance of 6 metres. In addition, the Smith-Kettlewell Institute Low Luminance (SKILL) card, (Smith-Kettlewell Eye Research Institute, San Francisco, CA, US) was used to evaluate the patient's near vision logMAR acuity in both high-contrast and simulated, reduced-luminance conditions (black-on-grey letters) (Haegerstrom-Portnoy et al., 1997). First, the high-contrast letters were presented at the specified viewing distance of 40 cm, and the near logMAR acuity recorded. The card was then turned over, and the near logMAR acuity recorded, using the simulated, reduced-luminance characters presented at the same distance. Acuity measurements for each side of the chart were recorded using the ‘letter-by-letter’ method, as outlined by Haegerstrom-Portnoy et al. (1997). The SKILL card ‘score’ was calculated as the difference in the number of letters correctly identified between the high-contrast and low-contrast sides (in log units). All measurements were made in a consulting room with a constant illumination of approximately 310 lux. The patient's pupil size whilst viewing the high-contrast acuity logMAR chart was recorded using a pupil gauge. Where necessary, SKILL card acuity measurements were made using an appropriate subjective ‘reading addition’ over-refraction for the working distance of 40 cm (using trial lenses).
**RGP-wearers (n = 16)**

<table>
<thead>
<tr>
<th>DAY 1: Baseline data</th>
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<tbody>
<tr>
<td>Day 1</td>
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<tr>
<td>Baseline data</td>
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<tr>
<td>Visual performance assessment with RGP lenses (HCA, LCA &amp; SKILL card score)</td>
</tr>
<tr>
<td>Higher-order aberration measurement with RGP lenses (IRX-3)</td>
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<tr>
<td>RGP lens fitting assessment and lens removal</td>
</tr>
<tr>
<td>Corneal slit-lamp examination without lenses</td>
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<tr>
<td>Higher-order aberration measurement without lenses (IRX-3)</td>
</tr>
<tr>
<td>Corneal topography evaluation without lenses (Pentacam)</td>
</tr>
<tr>
<td>(RGP lenses left out for 1 week to act as a washout period)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>DAY 7: Initial trial lens fitting appointment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 7</td>
</tr>
<tr>
<td>Initial trial lens fitting appointment</td>
</tr>
<tr>
<td>Corneal slit-lamp examination (without RGP lenses)</td>
</tr>
<tr>
<td>Plano soft trial lens fitting assessment (&amp; OR)</td>
</tr>
<tr>
<td>RGP lens wear resumed as normal</td>
</tr>
<tr>
<td>(Sphero-cylindrical soft lenses ordered)</td>
</tr>
<tr>
<td>(RGP lenses left out overnight before fitting the sphero-cylindrical soft lenses)</td>
</tr>
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</table>

**Sphero-cylindrical soft lens collection appointment**

<table>
<thead>
<tr>
<th>Day 7</th>
<th>Initial trial lens fitting appointment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 7</td>
<td>Initial trial lens fitting appointment</td>
</tr>
<tr>
<td>Corneal slit-lamp examination</td>
<td></td>
</tr>
<tr>
<td>Higher-order aberrations measured without spectacles (IRX-3)</td>
<td></td>
</tr>
<tr>
<td>Corneal topography evaluation (Pentacam)</td>
<td></td>
</tr>
<tr>
<td>Plano soft trial lens fitting assessment (&amp; OR)</td>
<td></td>
</tr>
<tr>
<td>(Sphero-cylindrical soft lenses ordered)</td>
<td></td>
</tr>
<tr>
<td>Visual performance assessment with sphero-cylindrical soft lenses (HCA, LCA &amp; SKILL card score)</td>
<td></td>
</tr>
<tr>
<td>Higher-order aberrations measured with the sphero-cylindrical soft lenses (IRX-3)</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 8.1** A flow diagram summarising the different stages of the investigation in the RGP lens-wearing group (n = 16).

**Spectacle-wearers (n = 6)**

<table>
<thead>
<tr>
<th>Initial trial lens fitting appointment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
</tr>
<tr>
<td>Initial trial lens fitting appointment</td>
</tr>
<tr>
<td>Visual performance assessment with spectacles (HCA, LCA &amp; SKILL card score)</td>
</tr>
<tr>
<td>Corneal slit-lamp examination</td>
</tr>
<tr>
<td>Higher-order aberrations measured without spectacles (IRX-3)</td>
</tr>
<tr>
<td>Corneal topography evaluation (Pentacam)</td>
</tr>
<tr>
<td>Plano soft trial lens fitting assessment (&amp; OR)</td>
</tr>
<tr>
<td>(Sphero-cylindrical soft lenses ordered)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sphero-cylindrical soft lens collection appointment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 7</td>
</tr>
<tr>
<td>Sphero-cylindrical soft lens collection appointment</td>
</tr>
<tr>
<td>Corneal slit-lamp examination</td>
</tr>
<tr>
<td>Sphero-cylindrical soft lens fitting assessment (&amp; OR)</td>
</tr>
<tr>
<td>Visual performance assessment with sphero-cylindrical soft lenses (HCA, LCA &amp; SKILL card score)</td>
</tr>
<tr>
<td>Higher-order aberrations measured with the sphero-cylindrical soft lenses (IRX-3)</td>
</tr>
</tbody>
</table>

**Figure 8.2** A flow diagram summarising the different stages of the investigation in the spectacle-wearing group (n = 6).
8.3.2 Ocular aberrations

Ocular aberrations were evaluated using the IRX-3, Hartmann-Shack aberrometer (Imagine Eyes, Paris, France). The IRX-3 device uses a 32 X 32 lenslet array and near infra-red light with a wavelength of 780 nm. Aberrations were recorded under monocular conditions with the room lights switched off. Accommodation was relaxed using the dynamic fogging method (via the device’s internal Badal system), whilst patients fixated on a black 6/12-sized Snellen letter “E” in an elliptical white background field subtending an approximate 0.7 × 1.0-degree angle with a luminance of around 85 cd/m². Wavefront aberrations were computed up to the 6th Zernike order for a 4-mm pupil diameter, as this was the largest pupil size common to all 22 patients evaluated, using the device's internal software (Version 1.2, Imagine Eyes). An average of four monocular readings was calculated for each set of measurements made for all 22 patients. Each measurement was made approximately 1 second after a blink to standardise the measurements and to limit the variations in wavefront aberrations due to alterations in the tear film over time (Radhakrishnan et al., 2010).

8.3.3 RGP lens fitting assessment and corneal slit-lamp examination

A slit-lamp biomicroscope (SL40, Keeler Ltd., Windsor, U.K.) was used to assess the fitting of the subjects’ habitual RGP lenses using sodium fluorescein. The RGP lens fittings were graded as definite apical clearance, apical clearance, apical touch or definite apical touch using the criteria defined by Fink and associates (2001). The surface quality, cleanliness and overall condition of the lenses were also inspected to ensure that the lenses were not damaged (either through chips or scratches) or heavily deposited. The contact lens-wearing patients were then asked to remove their habitual RGP lenses, to facilitate further biomicroscopic assessment of the cornea, including the presence or absence of Fleischer’s ring, Vogt’s striae, prominent corneal nerves and apical scarring. A similar corneal examination was also performed for the spectacle-wearing patients.

8.3.4 Corneal topography

The Oculus Pentacam (Oculus Inc., Wetzlar, Germany) was used to evaluate each subject's corneal topography, central corneal thickness and central radii of curvature (calculated within a central 3-mm zone). The rotating Scheimpflug camera device works in conjunction with a monochromatic, blue light-emitting diode slit-light source (at a wavelength of 475 nm) and captures 25 images during a 1-second scan, which provides up to 500 true elevation points per image. Four monocular scans were repeated and averaged for each patient. The CLEK (Collaborative Longitudinal Evaluation of Keratoconus) study group’s criteria was used to grade the severity of keratoconus using the Pentacam’s topographical data, where steep keratometric measurements < 45 D were graded as ‘mild’ keratoconus, values between 45 to 52 D were graded as ‘moderate’ keratoconus and readings > 52 D were classed as ‘severe’ keratoconus (Zadnik et al., 1996).
After collecting the baseline data, the 16 contact lens-wearing patients were instructed to leave their RGP lenses out for a period of 7 days to act as a ‘wash-out’ period (Jinabhai et al., 2012a) prior to fitting the soft trial contact lenses. All 16 patients had spectacles, which had been prescribed within the previous 18 months and were asked to use these until the trial lens fitting appointment one week later.

8.3.5 Plano soft trial lens fitting assessment and over-refraction

Using the patient’s corneal topography as a starting point, a series of different Plano trial lenses were applied and evaluated on-eye to ascertain the best fitting lens characteristics with regards to lens comfort, centration (horizontally and vertically), movement (digital push-up test and movement with blink in the primary position, up-gaze and upon horizontal lag) and corneal coverage, using established criteria outlined in the literature (Maldonado-Codina et al., 2005). Lens rotations in the primary position and upon blinking were also evaluated during the fitting process, by observing the position of the lens orientation marker (usually located at the 6-o’clock position) by projecting a narrow vertical slit lamp beam onto the lens to align with the lens marking. After a settling period of approximately 30 minutes, a monocular over-refraction routine was performed through the best-fitting trial lens, at a distance of 6 metres (using a Snellen letter chart (National Eye Institute, Bethesda, MD, US), with a luminance of 120 cd/m²), to obtain the subjective sphero-cylindrical refraction result that maintained optimal visual acuity. Retinoscopy with the trial contact lens was firstly carried out to establish a starting point for the over-refraction. This refraction result was then refined using standard subjective techniques (Rabbetts and Bennett, 2000) with some modification – for example, larger power steps between lenses and a high-powered Jackson crossed-cylinder (±1.00 DC - dioptre cylinder), tailored to keratoconic patients with poorer vision (Zadnik et al., 1998, Boxer-Wachler et al., 2003). The refraction endpoint was the maximum ‘plus’ sphero-cylindrical refraction which allowed the patient to read their threshold visual acuity. Once the endpoint over-refraction was reached, the vertex distance was recorded in millimetres. Both high-contrast and low-contrast logMAR visual acuity measurements were then recorded at 3 metres (scored to the letter in log units) and were corrected for a distance of 6 metres. The best-fitting trial lens’ back optic zone radius, peripheral lens design, laser marker orientation and subjective over-refraction were used to order a sphero-cylindrical soft lens for each patient. The lens manufacturer appropriately adjusted the final contact lens powers to compensate for any small rotations (up to a maximum of 5 degrees or less) observed during the fitting process.

On completion of the trial lens fitting, the 16 RGP lens-wearing patients were then asked to resume contact lens wear as normal whilst the soft lenses were ordered. However, before the toric soft lens collection appointment, the lens-wearing patients were instructed to leave their habitual RGP lenses out overnight and to attend their appointment wearing their spectacles. Similarly, the spectacle-wearing patients attended their collection appointments wearing their spectacles.
8.3.6 Final sphero-cylindrical soft lens collection appointment

On average, the final lens collection appointment took place 2 weeks after the trial lens fitting appointment. Five minutes after applying each toric soft lens, a slit-lamp biomicroscopic evaluation was performed to ensure that each lens was positioned acceptably with regard to lens centration (horizontal and vertical), movement (with push-up, in the primary position, upon up-gaze and with horizontal lag) and toric marker alignment. Each lens fitted was designed with a prism-ballasted toric front surface design, a spherical back surface and a total diameter of 14.50 mm. All the lenses fitted were manufactured using a Filcon II-based material (water content 77 %, Dk = 53 and centre thickness of 0.40 mm).

A period of 30 minutes was allowed for the patient’s tear film to stabilise after lens application before measuring each patient’s over-refraction and visual performance. The slit-lamp biomicroscope was used to reassess the lens position to ensure this had not altered substantially over time. A spherical over-refraction was then performed at 6 metres (Snellen chart). For patients where a spherical over-refraction was required to maximise acuity, the trial lens was kept in place whilst recording high-contrast and low-contrast acuities (at 3 metres) and SKILL card scores (at 40 cm). Using the IRX-3 device, ocular aberrations were evaluated with the toric soft lenses in place.

8.4 Data analysis

Total higher-order root mean square (RMS) aberrations were calculated as the root mean square of all the Zernike coefficient terms from the 3rd- to the 6th-order inclusive. Tests of normality were performed using the Shapiro-Wilk’s test and a critical value of 0.05 (SPSS version 16.0; SPSS, Chicago, IL, US). Normally distributed data were analysed with 1-way repeated-measures analysis of variance (RM-ANOVA) using a critical value of 0.05. Non-normally distributed data were evaluated with either the Wilcoxon signed-ranks test (WSRT) or the Friedman test (both for a critical value of 0.05).

In the RGP lens-wearing group, post-hoc analyses for the normally distributed aberrometry data were carried out using paired dependant t-tests with a Bonferroni adjustment for three multiple comparisons (critical value of 0.05/3 = 0.017). For the non-normally distributed aberrometry data, post-hoc analyses were carried out using individual WSRT, also using a critical value of 0.017.

For the correlation data, all normally distributed values were analysed using the 2-tailed Pearson’s correlation (Rₚ) method (critical value of 0.05), whereas all non-normally distributed values were evaluated using the 2-tailed Spearman’s correlation (Rₛ) method (critical value of 0.05).
8.5 Results

8.5.1 Patient demographics

Table 8.1 summarises the anterior surface central radii, central corneal thicknesses, CLEK study group severity grades, corneal slit-lamp appearance and RGP lens fitting grades for the keratoconic patients at the initial examination. The participants recruited to the study included 7 patients with severe keratoconus, 14 patients with moderate keratoconus and one patient with mild keratoconus. All 22 patients showed Fleischer's ring and prominent corneal nerves. Eight of the 22 patients exhibited corneal apical scarring, as expected these patients were graded with either moderate or severe disease. Fifteen of the RGP lens-wearing patients presented with a flat-fitting RGP lens and one patient had an apical clearance type lens fit.

Table 8.1 A summary of the average anterior surface central radii, central corneal thicknesses, CLEK (collaborative longitudinal evaluation of keratoconus) study group severity grades, corneal slit-lamp appearance and RGP lens fittings for the keratoconic patients at the initial examination. (DAT = definite apical touch; AT = apical touch and AC = apical clearance).

<table>
<thead>
<tr>
<th>Patient ref.</th>
<th>Flat K (D)</th>
<th>Steep K (D)</th>
<th>Central corneal thickness (microns)</th>
<th>CLEK severity grade</th>
<th>Vogt's striae</th>
<th>Apical scarring</th>
<th>RGP lens fitting grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>49.8</td>
<td>56.0</td>
<td>455</td>
<td>Severe</td>
<td>Present</td>
<td>Absent</td>
<td>DAT</td>
</tr>
<tr>
<td>2</td>
<td>45.6</td>
<td>50.0</td>
<td>451</td>
<td>Moderate</td>
<td>Absent</td>
<td>Absent</td>
<td>AT</td>
</tr>
<tr>
<td>3</td>
<td>42.8</td>
<td>45.1</td>
<td>440</td>
<td>Moderate</td>
<td>Absent</td>
<td>Absent</td>
<td>AT</td>
</tr>
<tr>
<td>4</td>
<td>45.6</td>
<td>48.4</td>
<td>434</td>
<td>Moderate</td>
<td>Absent</td>
<td>Absent</td>
<td>AC</td>
</tr>
<tr>
<td>5</td>
<td>58.2</td>
<td>61.8</td>
<td>324</td>
<td>Severe</td>
<td>Present</td>
<td>Present</td>
<td>AT</td>
</tr>
<tr>
<td>6</td>
<td>45.6</td>
<td>47.3</td>
<td>505</td>
<td>Moderate</td>
<td>Absent</td>
<td>Absent</td>
<td>AT</td>
</tr>
<tr>
<td>7</td>
<td>47.8</td>
<td>52.0</td>
<td>419</td>
<td>Moderate</td>
<td>Present</td>
<td>Present</td>
<td>DAT</td>
</tr>
<tr>
<td>8</td>
<td>52.2</td>
<td>55.9</td>
<td>503</td>
<td>Severe</td>
<td>Present</td>
<td>Present</td>
<td>DAT</td>
</tr>
<tr>
<td>9</td>
<td>44.2</td>
<td>48.0</td>
<td>453</td>
<td>Moderate</td>
<td>Present</td>
<td>Absent</td>
<td>DAT</td>
</tr>
<tr>
<td>10</td>
<td>44.1</td>
<td>49.2</td>
<td>461</td>
<td>Moderate</td>
<td>Absent</td>
<td>Absent</td>
<td>DAT</td>
</tr>
<tr>
<td>11</td>
<td>43.9</td>
<td>49.4</td>
<td>386</td>
<td>Moderate</td>
<td>Present</td>
<td>Present</td>
<td>DAT</td>
</tr>
<tr>
<td>12</td>
<td>48.6</td>
<td>51.9</td>
<td>415</td>
<td>Moderate</td>
<td>Present</td>
<td>Present</td>
<td>DAT</td>
</tr>
<tr>
<td>13</td>
<td>43.4</td>
<td>47.3</td>
<td>484</td>
<td>Moderate</td>
<td>Absent</td>
<td>Absent</td>
<td>AT</td>
</tr>
<tr>
<td>14</td>
<td>51.4</td>
<td>56.4</td>
<td>416</td>
<td>Severe</td>
<td>Present</td>
<td>Present</td>
<td>DAT</td>
</tr>
<tr>
<td>15</td>
<td>49.1</td>
<td>52.9</td>
<td>435</td>
<td>Severe</td>
<td>Present</td>
<td>Present</td>
<td>DAT</td>
</tr>
<tr>
<td>16</td>
<td>47.7</td>
<td>53.2</td>
<td>420</td>
<td>Severe</td>
<td>Present</td>
<td>Absent</td>
<td>DAT</td>
</tr>
<tr>
<td>17</td>
<td>43.9</td>
<td>46.9</td>
<td>422</td>
<td>Moderate</td>
<td>Present</td>
<td>Absent</td>
<td>-</td>
</tr>
<tr>
<td>18</td>
<td>50.7</td>
<td>53.0</td>
<td>494</td>
<td>Severe</td>
<td>Present</td>
<td>Present</td>
<td>-</td>
</tr>
<tr>
<td>19</td>
<td>44.9</td>
<td>48.0</td>
<td>477</td>
<td>Moderate</td>
<td>Absent</td>
<td>Absent</td>
<td>-</td>
</tr>
<tr>
<td>20</td>
<td>43.2</td>
<td>46.7</td>
<td>462</td>
<td>Moderate</td>
<td>Absent</td>
<td>Absent</td>
<td>-</td>
</tr>
<tr>
<td>21</td>
<td>45.7</td>
<td>49.3</td>
<td>432</td>
<td>Moderate</td>
<td>Absent</td>
<td>Absent</td>
<td>-</td>
</tr>
<tr>
<td>22</td>
<td>42.7</td>
<td>43.4</td>
<td>514</td>
<td>Mild</td>
<td>Absent</td>
<td>Absent</td>
<td>-</td>
</tr>
</tbody>
</table>

8.5.2 Visual performance

The mean pupil size recorded for all 22 patients whilst measuring visual performance was 4.3 ± 0.4 mm. In the RGP lens-wearing group high-contrast acuity, low-contrast acuity and SKILL card scores with the patient’s habitual lenses were compared to measurements made with the
toric soft lenses. Compared to the toric soft lenses, the RGP lenses provided significantly better low-contrast acuity (RM-ANOVA: $F_1, 5 = 10.0; p = 0.006$, Figure 8.3) and SKILL card scores (RM-ANOVA: $F_1, 5 = 36.8; p = 0.00002$, Figure 8.3). Although the RGP lenses provided better results, no significant differences in high-contrast acuity were found between the two lens types (WSRT: $Z = -1.6; p = 0.10$).

In the 6 spectacle-wearing patients, visual performance measured with the patient's habitual spectacles was compared to that measured with the toric soft lenses. No significant differences in high-contrast acuity, low-contrast acuity and SKILL card scores were found between measurements made with the patient's spectacles and with the toric soft lenses ($p \geq 0.06$, Figure 8.3).

The spherical over-refractions used to measure visual performance with either the patient's habitual RGP lenses or the soft lenses ranged from -0.50 to +0.75 D.

**Figure 8.3** A comparison of the visual performance achieved using the patient's habitual mode of correction and the soft toric lenses. Error bars represent ± 1 standard deviation. HCA = high-contrast acuity; LCA = low-contrast acuity and RM-ANOVA = repeated-measures analysis of variance.
8.5.3 Ocular aberrations in the RGP lens-wearing patients (n = 16)

In the RGP lens-wearing patients, three sets of aberrometry data were compared, these included measurements made with the patient’s habitual RGP lenses in place, measurements without any contact lenses in place and measurements with the toric soft lenses in place. Table 8.2 displays the statistical analysis for the ocular aberrations evaluated. Second-order cylinder RMS, coma RMS, 3rd-order RMS, total higher-order RMS (3rd- to 6th-order) and 4th-order spherical aberration all showed significant differences between the 3 sets of measurements using RM-ANOVA (p ≤ 0.002). Post-hoc analyses showed significantly lower 2nd-order cylinder RMS, coma RMS, 3rd-order RMS and total higher-order RMS aberrations with the patient’s habitual RGP lenses in place compared to the uncorrected data (p ≤ 0.001; Figure 8.4, and Figure 8.5). Equally, with the toric soft lenses in place, post-hoc tests also showed significantly lower coma RMS, 3rd-order RMS, higher-order RMS and 4th-order spherical aberration compared to the uncorrected data (p ≤ 0.011, Figure 8.5). However, in contrast to the RGP lenses, the toric soft lenses induced a non-significant increase in 2nd-order cylinder RMS error compared to the uncorrected values (p = 0.16).

Compared to the uncorrected values (+0.01 ± 0.23 µm [SD]), the RGP lenses did not significantly alter 4th-order spherical aberration (p = 0.35). With the RGP lenses in place, the spherical aberration values recorded were all positive in sign (+0.07 ± 0.08 µm). In contrast, the toric soft lenses induced a significant magnitude of negative spherical aberration (-0.12 ± 0.18 µm) compared to without lenses in place (p = 0.005; Figure 8.5).

When comparing the aberrations measured with RGP lenses to those with toric soft lenses, post-hoc results showed significantly lower magnitudes of 2nd-order cylinder RMS, 3rd-order RMS and higher-order RMS error with the RGP lenses (p ≤ 0.015; Figure 8.4 and Figure 8.5). Compared to the RGP lenses, the toric soft lenses also induced a considerable level of negative spherical aberration (p = 0.001, Figure 8.5).

In the RGP lens-wearing patients, Friedman analyses also showed significant differences between the 3 sets of measurements for trefoil RMS, secondary cylinder RMS, 4th-order RMS and 5th-order RMS aberrations (p ≤ 0.03, Table 8.2). With the RGP lenses, post-hoc analyses showed significantly lower trefoil RMS, secondary cylinder RMS, 4th-order RMS and 5th-order RMS aberrations compared to the uncorrected aberrations (p ≤ 0.005, Figure 8.5). Post-hoc tests also showed that the toric soft lenses significantly reduced trefoil RMS, secondary cylinder RMS, and 5th-order RMS aberrations compared to the uncorrected measurements. In comparison to the toric soft lenses, post-hoc analyses showed that the RGP lenses significantly reduced trefoil RMS aberrations (p = 0.008, Figure 8.5), however no significant differences were found for the 4th-order secondary cylinder RMS, 4th-order RMS and 5th-order RMS aberrations (p ≥ 0.06).

Upon evaluating individual Zernike coefficients, Friedman analyses showed a significant difference in vertical coma aberration between the three sets of data evaluated ($\chi^2 = 27.1; \text{degrees of freedom} = 2; p = 0.000001$). Post-hoc analyses of the vertical coma coefficient terms in the 16 RGP lens wearers showed a significant positive shift from an uncorrected value of $-0.85 \pm 0.35 \mu m$ to $+0.38 \pm 0.17 \mu m$ with the RGP lenses ($Z = -3.5, p = 0.0004; \text{WSRT}$). Post-hoc tests
showed that the RGP lenses provided significantly better correction of vertical coma \((Z = -3.5, p = 0.0004; \text{WSRT})\) compared to the toric soft lenses \((-0.63 \pm 0.43 \mu m)\).

However, no significant differences in horizontal coma were found between the three sets of aberration measurements \((p = 0.27)\).

Table 8.2 Comparing the root mean square (RMS) aberrations measured with no lenses, with the patient's habitual RGP lenses and with the soft toric lenses using repeated-measures ANOVA (RM-ANOVA) and Friedman analysis. (See Figure 8.4 and Figure 8.5 for the post-hoc analysis data). \(\chi^2\) = Chi-squared and df = degrees of freedom.

<table>
<thead>
<tr>
<th>Ocular aberrations</th>
<th>Test</th>
<th>Statistic</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd-order cylinder RMS</td>
<td>RM-ANOVA</td>
<td>(F_{2, 30} = 12.1)</td>
<td>(* 0.0001)</td>
</tr>
<tr>
<td>3rd-order coma RMS</td>
<td>RM-ANOVA</td>
<td>(F_{2, 30} = 12.4)</td>
<td>(* 0.0001)</td>
</tr>
<tr>
<td>3rd-order trefoil RMS</td>
<td>Friedman</td>
<td>(\chi^2 = 15.1, \text{df} = 2)</td>
<td>(^* 0.001)</td>
</tr>
<tr>
<td>3rd-order RMS</td>
<td>RM-ANOVA</td>
<td>(F_{2, 30} = 17.0)</td>
<td>(* 0.00001)</td>
</tr>
<tr>
<td>4th-order spherical aberration</td>
<td>RM-ANOVA</td>
<td>(F_{2, 30} = 7.6)</td>
<td>(* 0.002)</td>
</tr>
<tr>
<td>4th-order secondary cylinder RMS</td>
<td>Friedman</td>
<td>(\chi^2 = 12.9, \text{df} = 2)</td>
<td>(^* 0.002)</td>
</tr>
<tr>
<td>4th-order RMS</td>
<td>Friedman</td>
<td>(\chi^2 = 7.1, \text{df} = 2)</td>
<td>(^* 0.03)</td>
</tr>
<tr>
<td>5th-order RMS</td>
<td>Friedman</td>
<td>(\chi^2 = 12.5, \text{df} = 2)</td>
<td>(^* 0.002)</td>
</tr>
<tr>
<td>Higher-order RMS (3rd to 6th)</td>
<td>RM-ANOVA</td>
<td>(F_{2, 30} = 18.2)</td>
<td>(* 0.00001)</td>
</tr>
</tbody>
</table>

*Indicates a significant difference using repeated-measures ANOVA (RM-ANOVA).

\(^\dagger\)Indicates a significant difference using Friedman analysis.

Figure 8.4 Comparing the correction of 2nd-order cylinder RMS aberrations using RGP and soft toric lenses in the RGP lens-wearers \((n = 16)\) and the spectacle-wearers \((n = 6)\). Error bars represent ± 1 standard deviation. RMS = root-mean-square and RM-ANOVA = repeated-measures analysis of variance.
Figure 8.5 Comparing the correction of higher-order aberrations using RGP and soft toric lenses in the contact lens-wearing group (n = 16). Error bars represent ±1 standard deviation. RMS = root-mean-square; RM-ANOVA = repeated-measures analysis of variance and WSRT = Wilcoxon signed-ranks test.
Figure 8.6 Comparing the correction of higher-order aberrations using soft toric lenses in the spectacle-wearing group (n = 6). Error bars represent ±1 standard deviation. RMS = root-mean-square and RM-ANOVA = repeated-measures analysis of variance.
8.5.4 Ocular aberrations in the spectacle-wearing patients (n = 6)

In the six spectacle-wearing patients, ocular aberrations were compared both with and without the toric soft lenses in place using RM-ANOVA; significant reductions were found for coma RMS, 3rd-order RMS and higher-order RMS aberrations (p ≤ 0.01, Figure 8.6), whereas 4th-order spherical aberration showed a negative shift in magnitude from +0.06 ± 0.10 µm to -0.05 ± 0.03 µm (p = 0.015, Figure 8.6). In contrast, no significant differences were found for trefoil RMS, 4th-order cylinder RMS, 4th-order RMS and 5th-order RMS aberrations (p ≥ 0.06). In similarity to the RGP-lens-wearing group, RM-ANOVA showed that toric soft lenses also induced a non-significant increase in 2nd-order cylinder RMS compared to the uncorrected values in the spectacle-wearing patients (p = 0.22; Figure 8.4).

8.5.5 Ocular aberrations with and without toric soft lenses (n = 22)

Table 8.3 shows the results of the statistical analysis when comparing the ocular aberrations evaluated with and without the toric soft lenses in place for all 22 patients investigated. Compared to the uncorrected values, the data show that the toric soft lenses significantly reduced 7 out of the 8 RMS aberration metrics evaluated (p ≤ 0.01). In contrast, the toric soft lenses significantly induced a larger magnitude of negative 4th-order spherical aberration (p = 0.003). The toric soft lenses also induced an increase in 2nd-order cylinder RMS error, however this change in aberrations did not reach statistical significance (p = 0.09).

When comparing individual Zernike terms with and without toric soft lenses for all 22 patients investigated, the results show that the soft lenses significantly reduced uncorrected vertical coma aberration from -0.77 ± 0.36 µm to -0.54 ± 0.41 µm (F1, 21 = 13.2, p = 0.002; RM-ANOVA).

Table 8.3 Comparing the mean (± 1 SD) root mean square (RMS) aberrations measured with and without the soft toric lenses for all 22 patients. Statistical test performed included repeated-measures ANOVA (RM-ANOVA) and the Wilcoxon signed-ranks test (WSRT).

<table>
<thead>
<tr>
<th>Ocular aberrations</th>
<th>Test</th>
<th>Statistic</th>
<th>p</th>
<th>No lens average</th>
<th>±1 SD</th>
<th>Soft toric lens average</th>
<th>±1 SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd-order cylinder RMS</td>
<td>RM-ANOVA</td>
<td>F1, 21 = 3.3</td>
<td>0.09</td>
<td>1.21</td>
<td>0.64</td>
<td>1.61</td>
<td>1.03</td>
</tr>
<tr>
<td>3rd-order coma RMS</td>
<td>RM-ANOVA</td>
<td>F1, 21 = 15.1</td>
<td>*0.001</td>
<td>0.90</td>
<td>0.34</td>
<td>0.65</td>
<td>0.35</td>
</tr>
<tr>
<td>3rd-order trefoil RMS</td>
<td>RM-ANOVA</td>
<td>F1, 21 = 19.9</td>
<td>*0.0002</td>
<td>0.32</td>
<td>0.14</td>
<td>0.21</td>
<td>0.09</td>
</tr>
<tr>
<td>3rd-order RMS</td>
<td>RM-ANOVA</td>
<td>F1, 21 = 21.9</td>
<td>*0.0001</td>
<td>0.82</td>
<td>0.35</td>
<td>0.60</td>
<td>0.37</td>
</tr>
<tr>
<td>4th-order RMS</td>
<td>RM-ANOVA</td>
<td>F1, 21 = 18.0</td>
<td>*0.0003</td>
<td>+0.03</td>
<td>0.20</td>
<td>-0.10</td>
<td>0.16</td>
</tr>
<tr>
<td>4th-order spherical aberration</td>
<td>WSRT</td>
<td>Z = -3.1</td>
<td>*0.002</td>
<td>0.21</td>
<td>0.15</td>
<td>0.12</td>
<td>0.12</td>
</tr>
<tr>
<td>4th-order secondary cylinder RMS</td>
<td>WSRT</td>
<td>Z = -2.7</td>
<td>*0.007</td>
<td>0.30</td>
<td>0.19</td>
<td>0.21</td>
<td>0.16</td>
</tr>
<tr>
<td>5th-order RMS</td>
<td>WSRT</td>
<td>Z = -2.6</td>
<td>*0.01</td>
<td>0.11</td>
<td>0.07</td>
<td>0.08</td>
<td>0.06</td>
</tr>
<tr>
<td>Higher-order RMS (3rd to 6th)</td>
<td>WSRT</td>
<td>Z = -3.7</td>
<td>*0.0002</td>
<td>0.97</td>
<td>0.37</td>
<td>0.71</td>
<td>0.38</td>
</tr>
</tbody>
</table>

* Indicates a significant difference using repeated-measures ANOVA (RM-ANOVA).
^ Indicates a significant difference using the Wilcoxon signed-ranks tests (WSRT).
8.5.6 Correlation between visual performance and corneal parameters

High-contrast and low-contrast logMAR acuities measured using each patient’s habitual mode of correction (either RGP lenses or spectacles) were plotted against the steep keratometric readings measured using the Oculus Pentacam. No significant correlation was found for the high-contrast acuity scores (p = 0.55), whereas a significant correlation was found for the low-contrast acuities and steep keratometric readings (gradient = +0.02 log units/dioptre (D), R_p = +0.59, p = 0.004, Figure 8.7 A).

High-contrast and low-contrast acuities measured with the toric soft lenses were also plotted against the steep keratometric readings for all 22 patients evaluated. Significant correlations were found for both the high-contrast (gradient = +0.03 log units/D, R_S = +0.69, p = 0.0004, Figure 8.7 B) and low-contrast acuity scores and steep keratometric readings (gradient = +0.03 log units/D, R_p = +0.72, p = 0.0002, Figure 8.7 B). Overall, the visual performance results, with either the subject’s habitual mode of correction or the toric soft lenses, showed that patients with steeper keratometric values achieved poorer high-contrast and low-contrast acuity scores.

8.5.7 Correlation between visual performance and ocular aberrations

High-contrast and low-contrast logMAR visual acuities measured using each patient's habitual mode of correction (either RGP lenses or spectacles) were plotted against the 9 aberration terms measured with the correction for all 22 patients investigated. The analyses showed no significant correlations between either the high-contrast or low-contrast acuity scores achieved or the computed aberration terms (p ≥ 0.13).

Both the high-contrast and low-contrast acuities achieved with the toric soft lenses were plotted against the 9 aberration terms measured with the lenses in situ. Significant correlations were found between the low-contrast acuity scores and the 2nd-order cylinder RMS (gradient = +0.10 log units/µm, R_p = +0.65, p = 0.001); 3rd-order RMS (gradient = +0.25 log units/µm, R_p = +0.50, p = 0.018); coma RMS (gradient = +0.24 log units/µm, R_p = +0.49, p = 0.019); higher-order RMS (gradient = +0.25 log units/µm, R_S = +0.55, p = 0.008) and spherical aberration terms (gradient = -0.50 log units/µm, R_p = -0.50, p = 0.017) as shown in Figure 8.8 and Figure 8.9. In contrast, no significant correlations were found between the high-contrast acuity scores and the 9 aberration terms evaluated (p ≥ 0.07).
Figure 8.7 The correlations between the steep keratometric readings and visual performance measured with A) the habitual correction (of either spectacles or RGP lenses) and with B) the soft toric contact lenses for all 22 patients. The grey squares represent the low-contrast acuity scores and the black diamonds represent the high-contrast acuity scores. The coloured solid lines represent the line-of-best fit for each corresponding data set.
Figure 8.8 The correlation between the low-contrast acuities achieved and the 2nd-order cylinder RMS aberrations measured with the soft toric contact lenses for all 22 patients. The solid line represents the line-of-best fit.

Figure 8.9 The correlations between the low-contrast acuities achieved and the higher-order aberrations measured with the soft toric contact lenses for all 22 patients. The black triangles represent 3rd-order coma RMS, the red squares represent 3rd-order RMS, the green crosses represent higher-order RMS and the purple circles represent 4th-order spherical aberration. The coloured dashed lines each represent the line-of-best for each corresponding data set.
8.6 Discussion

This study investigated how sphero-cylindrical soft contact lenses corrected visual performance and ocular aberrations compared to RGP contact lenses or spectacles in 22 patients with keratoconus. The results show that in the contact lens-wearing patients, RGP lenses gave significantly better low-contrast acuity and SKILL card scores compared to toric soft lenses. Although high-contrast acuity scores were also found to be better with the patient’s habitual RGP lenses (versus the toric soft lenses), the differences were not found to be significant.

These findings were not unexpected as two previous studies have also established that RGP lenses provide better visual performance than soft lenses in patients with keratoconus (Griffiths et al., 1998, Marsack et al., 2008). Griffiths et al. (1998) compared the visual performance of RGP lenses against four different soft spherical contact lenses in 13 patients with keratoconus. The authors reported that RGP lenses gave better high-contrast and low-contrast acuities compared to all four soft lenses evaluated. Similarly, Marsack et al. (2008) have also demonstrated that RGP lenses give better high-contrast and low-contrast acuities compared to a sphero-cylindrical soft lens in their investigation of three patients with keratoconus.

The improvement in visual performance afforded by RGP lenses is most likely to be due the superior correction of irregular corneal astigmatism for patients with keratoconus (Jupiter and Katz, 2000, Nepomucenoa et al., 2003). In comparison, larger magnitudes of residual corneal astigmatism would still persist with a soft contact lens in place, as less pressure is exerted onto the cone apex (Buxton, 1978, Sorbara et al., 2000, McMonnies, 2005). The improvement in visual performance found with RGP lenses may perhaps also be attributed to the greater reduction of ocular aberrations (Griffiths et al., 1998, Marsack et al., 2008). Rigid gas-permeable lenses are likely to mask the corneal aberrations induced by keratoconus by ‘replacing’ the irregular corneal surface with smooth and regular refractive surfaces (Griffiths et al., 1998, Marsack et al., 2008).

The patient’s tear film typically creates a ‘liquid-lens’ which fills the gap between the RGP lens back surface and the irregular anterior cornea, thereby reducing optical aberrations (Kosaki et al., 2007, Negishi et al., 2007, Marsack et al., 2008, Jinabhai et al., 2010b). The refractive index of the ‘tear-fluid lens’ (n = 1.336) formed beneath the RGP lens back surface is close to that of the cornea (n = 1.376), consequently reducing the vast majority of the aberrations at the anterior corneal surface (1.336/1.376 ≈ 97 %) (Hong et al., 2001, Dorronsoro et al., 2003). Moreover, the literature suggests that flatter-fitting RGP lenses give better visual performance compared to steeper-fitting lenses (Zadnik and Mutti, 1987, Sorbara et al., 2000, Jinabhai et al., 2010b). Fifteen of the 16 lens-wearing patients in the present study displayed an apical-bearing RGP lens fitting (Fink et al., 2001). Zadnik and Mutti (1987) originally hypothesised that the back surface of a flat-fitting RGP lens may ‘mould’ and ‘flatten’ the corneal distortion induced by keratoconus. This corneal moulding may lead to the anterior corneal surface adopting a more ‘normal’ curvature contour by exerting pressure onto the corneal apex, perhaps regularising its profile. Jinabhai et al.’s (2010b) results also indicate that flat-fitting lenses may reduce residual higher-order aberrations compared to steeper lens fits. The authors hypothesised that 3rd-order coma RMS aberrations, reduce in magnitude as the anterior corneal surface conforms to a more regular profile underneath an apical-bearing lens.

In the contact lens-wearing group, the results show that RGP lenses reduced 2nd-order cylinder RMS, coma RMS, trefoil RMS, 3rd-order RMS and higher-order RMS aberrations more
effectively than the toric soft lenses. These results corroborate with findings from previous studies that compared optical quality in patients with keratoconus using both RGP and soft lenses (Griffiths et al., 1998, Kosaki et al., 2007, Negishi et al., 2007, Sabesan et al., 2007b, Marsack et al., 2008). Using corneal topographical analysis, Griffiths et al. (1998) found that RGP lenses significantly reduced uncorrected, corneal total RMS (both lower-order and higher-order) aberrations compared to four different spherical soft lenses in 13 keratoconus patients. Similarly, both Marsack et al. (2008) and Sabesan et al. (2007b) have also reported that ocular total higher-order RMS aberrations were reduced more effectively by RGP lenses compared to sphero-cylindrical soft lenses for patients with moderate and severe keratoconus.

In concordance with our results, both Kosaki et al. (2007) and Negishi et al. (2007) have also previously demonstrated that RGP lenses significantly reduce both uncorrected coma RMS and higher-order RMS aberrations in patients with keratoconus. The present study’s results are also in agreement with Kosaki et al.’s (2007) findings, which showed that uncorrected 4th-order secondary cylinder RMS aberrations were significantly reduced by RGP lenses in their study of 76 keratoconic eyes. Equally, our findings corroborate with Kosaki et al. (2007) and Choi et al. (2007), who also found no significant changes in 4th-order spherical aberration between measurements made with and without RGP lenses in their keratoconic patients. In agreement with the findings of both Choi et al. (2007) and Jinabhai et al. (2010b), our results also found a positive shift in vertical coma with RGP lenses in place compared to the uncorrected values. Furthermore, the results show that RGP lenses provided significantly better correction of vertical coma compared to the toric soft lenses.

In the spectacle-wearing group, no statistically significant differences in high-contrast acuity, low-contrast acuity or SKILL card scores were obtained with the patients’ spectacle refraction versus the toric soft lenses. The data presented show that both low-contrast acuity and SKILL card scores were slightly better with the spectacle refractions than with the toric soft lenses. However, the mean high-contrast acuity scores were found to be similar with both modes of visual correction, although with a larger degree of variance for the spectacle acuities. These results were perhaps due to large magnitudes of irregular corneal astigmatism persisting with the toric hydrogel lenses in place, as soft lenses tend to drape over the irregular anterior corneal surface without producing a significant masking effect at the corneal apex (Buxton, 1978, Sorbara et al., 2000). To help quantify this effect it may perhaps be useful to measure toric over-refractions (White, 2010). However, due to possible lens movements toric over-refractions are likely to show reduced repeatability. In an attempt to overcome this, residual astigmatic errors were evaluated objectively using the 2nd-order cylinder RMS data measured with the IRX-3 device. Compared to the uncorrected values, the toric soft lenses induced a non-significant increase in 2nd-order cylinder RMS error in both the spectacle-wearing patients and in the RGP lens group. In contrast, the data in the contact lens-wearing patients show that RGP lenses provided significantly lower 2nd-order cylinder RMS aberrations compared to the uncorrected data and to measurements made with the toric soft lenses. Correlation analyses showed a significant correlation between the low-contrast visual acuities and the residual 2nd-order cylinder RMS aberrations measured with the toric soft lenses for all patients. However, in agreement with Jinabhai et al.’s (2011b) results, the 2nd-order cylinder RMS aberrations recorded in the present study also showed a large amount of variability.
Moreover, both Jinabhai et al. (2010a) and Katsoulos et al. (2009) have previously demonstrated that 2nd-order cylinder RMS errors measured using the Hartmann-Shack technique do not correspond with cylindrical powers measured using subjective refraction in keratoconus patients. Both studies suggest that the large variability in cylinder RMS aberrations is most likely to be due to spot imaging errors at the wavefront sensor (Yoon et al., 2004b).

Other possible reasons for these results include small rotational and translational movements of the sphero-cylindrical soft lenses upon blinking (Tomlinson et al., 1994). In agreement with previous studies of soft contact lenses for patients with keratoconus (Chen et al., 2007b, Sabesan et al., 2007b), we found that small amounts of rotation and translation were unavoidable in some patients owing to the irregularity of the corneal profile. During the initial fitting process, the best fitting lens was chosen for each patient to ensure that the toric alignment marker was correctly positioned and remained relatively stable during blinks. The maximum lens rotation recorded in the primary position was found to be 5 degrees or less (found in only four out of the 22 patients evaluated). However, the contact lens manufacturers appropriately adjusted the final contact lens powers in order to compensate for these rotations. Vertical lens centration was evaluated using the grading system outlined by Maldonado-Codina et al. (2005), where 0 = optimal centration, the lens sits symmetrically about the centre of the cornea; -1 = a slightly decentred lens inferiorly, where the limbus is not exposed superiorly and -2 = an extremely decentred lens inferiorly, leaving the superior limbus exposed. The vertical lens centration was found to be 0 for 19 of the 22 patients evaluated, with the remaining three patients displaying a vertical lens centration graded as -1. In comparison, the horizontal lens centration was found to be 0 for all 22 patients. The lens movement with blink in the primary position was also graded as described by Maldonado-Codina et al. (2005), where 0 = optimal movement of between 0.2 mm and 0.4 mm; +1 = slightly excessive movement, where the lens moves between 0.4 mm and 1.0 mm and +2 = extremely excessive movement, where the lens moves more than 1.0 mm upon blinking. The lens movement in primary gaze was found to be 0 for 21 of the 22 patients evaluated, with the remaining patient showing a lens movement of +1. The movement with blink upon up-gaze was also graded using the same criteria, 17 of the 22 patients assessed showed a lens movement of 0, whilst the remaining 5 patients showed a lens movement of +1. These measurements suggest that the lens fittings achieved in this report were clinically acceptable in all 22 cases presented.

As the toric soft lenses were only worn for approximately 1 hour, it is perhaps unlikely that the measured reductions in low-contrast acuity, compared to the patient's habitual correction, occurred due to corneal oedema or hypoxia. However, a possible factor which may have contributed to these findings is a reduction in the quality of the tear film due to soft contact lens wear (Alonso-Caneiro et al., 2009). It is plausible that, between blinks, high-water content hydrogel lenses rapidly dehydrate causing increased forward light scattering (Thai et al., 2002). This scattered light may potentially act as a veiling luminance, thereby reducing the contrast of the image formed at the retina (Timberlake et al., 1992). Previous studies have also established that the tear film in keratoconic patients exhibits significantly elevated amounts of inflammatory mediators compared to in normal control subjects (Lema et al., 2009b). The optical effect of this altered tear chemistry remains unexplored at present; however, it could influence the surface wettability of soft contact lenses thereby impacting on visual performance.
Nevertheless, the toric soft lenses did mask a proportion of the uncorrected ocular aberrations; in particular, the lenses significantly reduced coma RMS, 3rd-order RMS and total higher-order RMS aberrations. When analysing the data for all 22 keratoconic patients, the soft lenses significantly reduced 7 out of the 8 higher-order aberration terms investigated, with the exception of 4th-order spherical aberration. As with RGP lenses, it is expected that the tear film underneath a soft lens would partially fill the space between the anterior corneal surface and the back surface of the hydrogel lens (Ho, 2003). However, unlike with a RGP lens, it is anticipated that a soft lens would perhaps drape over the keratoconic cornea without exerting any pressure on the corneal apex. As a result, it is expected that 3rd-order coma RMS may not be corrected as effectively using soft lenses (Buxton, 1978, Sorbara et al., 2000, McMonnies, 2005). On the other hand, scleral contact lenses are typically fitted to vault the corneal apex, thereby avoiding mechanical trauma and providing improved comfort. Due to their large diameter and scleral-bearing design, these lenses retain a pre-corneal fluid reservoir which provides neutralisation of the underlying irregular corneal surface (Pullum and Buckley, 1997). However to date, no study has investigated the correction of higher-order aberrations using this lens type in keratoconus patients.

The results presented also reveal significant correlations between the coma RMS, 3rd-order RMS and higher-order RMS aberrations measured with the toric soft lenses and the resultant low-contrast acuities achieved. Figures 8.5, 8.6 and 8.9 show that the vast majority of 3rd-order RMS and higher-order RMS error were comprised of coma RMS aberrations. In contrast, no significant correlations were found for the high-contrast acuity scores. These results suggest that the residual coma RMS aberrations left uncorrected by the toric soft lenses may have a more destructive influence on low-contrast acuity than on high-contrast acuity in patients with keratoconus. These results agree with the findings of a study of 11 normal eyes, where ocular aberrations, high-contrast acuity and low-contrast acuity were evaluated with and without coma aberration-inducing soft contact lenses (Fernández-Sánchez et al., 2008).

Moreover, our results also show that compared to when uncorrected, the toric soft lenses induced significant negative 4th-order spherical aberration. This alteration in spherical aberration is most likely to be due to an inherent correction for positive spherical aberration, which is a design feature typically used for fitting toric soft lenses to highly irregular corneas. The amount of negative spherical aberration induced will be dependent on the lens’ spherical power and asphericity (p-value). The spherical aberration measured with the toric soft lenses in place, was also found to be significantly correlated with the low-contrast acuities achieved. The residual spherical aberration values ranged from -0.53 µm to +0.24 µm. On inspection of the data, it was evident that the low-contrast acuity scores were best for low levels of spherical aberration (of around zero) and any increase in spherical aberration (either positive or negative) reduced the acuity levels. This finding is in line with previous studies which show that high levels of ocular aberrations reduce visual acuity (Rocha et al., 2007, Li et al., 2009).

The residual coma aberrations measured with the toric soft lenses on-eye may either be linked to the wavefront error not corrected by the soft lenses, or could be a result of small lens movements on-eye (Guirao et al., 2001, Kollbaum et al., 2008). Due to their optical design, these toric soft lenses showed an inherent level of negative spherical aberration. Both Guirao et al.
(2001) and Kollbaum et al. (2008) have discussed that decentring a lens containing negative spherical aberration will induce negative coma aberrations.

The CLEK study group's classification system uses steep keratometric measurements to classify the degree of disease severity in keratoconus (Zadnik et al., 1996). Significant correlations were found between the steep keratometric readings and both the high-contrast and low-contrast acuity scores measured with the soft lenses. This finding agrees with the results of Koliopoulos and Tragakis (1981), who reported that 28 out of 57 keratoconic eyes with steep average corneal curvatures (of 52.1 D and above), achieved visual acuities of 6/20 or worse, when fitted with soft lenses. In contrast, the authors found that 30 out of 39 keratoconic eyes with flatter steep meridian curvatures (between 42 and 52 D), achieved visual acuities of 6/8.5 or better when fitted with soft lenses.

As the number of patients with mild (1) and severe disease (7) investigated were substantially lower than the number of moderate cases (14 patients), the present study cannot fully quantify the usefulness of toric soft lenses at different stages of keratoconus. Therefore additional investigations of the visual and optical performance of soft lenses in the early stages of keratoconus are perhaps warranted. In further support of this, 8 of the patients evaluated (patient reference 2, 3, 6, 10 and 19 to 22) achieved high-contrast acuity scores ranging between +0.12 and +0.20 log units, which equates to between 6/8 and 6/10 in Snellen acuity terms. This level of acuity approximates the current UK visual requirement for driving (Charman, 1985). These 8 patients' steep keratometric readings ranged between 43.4 and 50.0 D.

A potential limitation of this investigation is the accuracy with which ocular aberrations can be measured for keratoconus patients using the Hartmann-Shack technique. The literature suggests that spot imaging errors at the wavefront sensor (such as overlapping spots, spot ‘crossover’ or even missing spots and scatter) are likely to occur when evaluating patients with keratoconus, due to irregular corneal distortion and scarring (Yoon et al., 2004b, Katsoulos et al., 2009, Jinabhai et al., 2010a, Jinabhai et al., 2011b). Such errors are likely to cause mathematical and computational inaccuracies in deriving the shape of the aberrant wavefront at the Hartmann-Shack sensor. Moreover, Jinabhai et al. (2011b) have also reported that ocular aberrations show a higher variability in keratoconus patients compared to in visually-normal subjects.

Another possible limitation is that the RGP lenses worn by the 16 contact lens-wearing patients were made of different materials and designs. Similarly, the patients were heterogeneous in terms of their duration of disease and RGP lens wear experience. In addition, RGP and toric soft lens movements, whilst recording ocular aberrations, may have influenced the measurements. However, to minimise the possibility of contact lens movements confounding the results, the IRX-3 device was kept aligned with the eye as far as possible and we believe that this had minimal influence on the results.

This study was designed to evaluate the performance of toric soft contact lenses for keratoconus patients using a research protocol and lens-fitting strategy which enabled comparisons between different patients. However, in clinical practice it is likely that the toric soft lens fitting and prescription may need to be optimised on a case-by-case basis to maximise visual performance when refitting keratoconus patients with soft lenses from RGP lenses (White, 2010).
In conclusion, the findings presented show that RGP lenses gave better visual performance results and a more effective reduction of 3rd-order aberrations compared to the toric soft lenses trialled. Nevertheless, with the exception of 4th-order spherical aberration, the toric soft lenses significantly reduced the uncorrected higher-order aberrations manifested in all the keratoconic participants. Toric soft lenses performed better for the keratoconic patients with less advanced disease and could be trialled for such patients, especially for those who do not achieve adequate comfort or acceptable wear times with RGP lenses. In addition, this modality may arguably help to reduce the likelihood of corneal epithelial staining and apical scarring. However, if toric soft lenses are manufactured from a low-Dk material or the lens profile is too thick, then the patient is more likely to develop possible complications such as corneo-limbal neovascularisation.

The findings presented show relationships between the residual coma RMS, 3rd-order RMS, spherical aberration and higher-order RMS aberrations measured with the toric soft lenses in situ and the resultant low-contrast acuities achieved, perhaps advocating the use of aberration-controlling technology to further improve visual performance in patients with keratoconus. It is envisaged that the results of this investigation may be of interest to eyecare practitioners involved in the visual rehabilitation of keratoconic patients who seek an alternative to RGP contact lens wear.
Contributions

I designed this investigation with helpful contributions from my co-authors Hema Radhakrishnan (HR), Clare O'Donnell (COD) and Cindy Tromans (CT). I also completed all the measurements and statistical analyses with useful input from HR and COD. I wrote the scientific manuscript and this thesis chapter with valuable comments from HR, COD and CT.

Publications submitted

JINABHAI, A., RADHAKRISHNAN, H., O'DONNELL, C. & TROMANS, C. (*manuscript currently in preparation*).

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9.1 Abstract

9.1.1 Background: This study investigates how aberration-controlling soft contact lenses corrected ocular aberrations and visual performance in keratoconic patients compared to other forms of refractive correction.

9.1.2 Methods and materials: Twenty-two keratoconic patients (16 RGP lens wearers and 6 spectacle wearers) participated in this investigation. Patients were fitted with standard toric soft lenses and aberration-controlling soft lenses (designed to correct 3rd-order coma). In the RGP lens-wearing patients, aberrations were measured using a Hartmann-Shack aberrometer, without lenses, with the patient's habitual RGP lenses and with the study contact lenses. In the spectacle-wearing patients aberrations were measured both with and without the study lenses. Visual performance (high-contrast and low-contrast logMAR acuity) was evaluated with the patient wearing their habitual correction and with the study lenses.

9.1.3 Results: In the contact lens-wearing patients, the habitual RGP lenses and the customised aberration-controlling lenses provided comparable, significant reductions in uncorrected coma root-mean-square (RMS) error, 3rd-order RMS error and higher-order RMS (HORMS) error ($p \leq 0.004$). In the spectacle-wearing patients both the standard toric and customised contact lenses significantly reduced uncorrected 3rd-order RMS error and HORMS error ($p \leq 0.005$). The spectacle-wearing patients showed no significant differences in visual performance obtained with their habitual spectacles versus the study lenses. In contrast, both the standard toric soft lenses and the habitual RGP lenses provided significantly better high-contrast acuities compared to the aberration-controlling lenses ($p \leq 0.006$).

9.1.4 Conclusions: In this group of keratoconic patients aberration-controlling soft contact lenses provided comparable reductions in higher-order aberrations to RGP contact lenses. However, the patient's habitual RGP lenses provided superior visual performance.
9.2 Introduction

The optimal mode of visual correction for patients with keratoconus varies depending on the disease severity (Kennedy et al., 1986). In the milder forms, patients may achieve satisfactory visual acuity using spectacles alone (Kastl et al., 1987, Mahadevan et al., 2009). However, as the corneal surface becomes more irregular, spectacle correction becomes progressively unsuccessful due to large magnitudes of irregular corneal astigmatism (Zadnik et al., 2002), corneal apical scarring (Barr and Yackels, 1991) and higher-order aberrations, in particular vertical coma (Maeda et al., 2002, Kosaki et al., 2007, Lim et al., 2007, Jinabhai et al., 2010a). At present, rigid gas-permeable (RGP) contact lenses are the principle method of non-surgical visual rehabilitation used for patients with moderate to severe keratoconus (Lim and Vogt, 2002, Kapur et al., 2003, Wagner et al., 2007, Weed et al., 2008, Bilgin et al., 2009, Mahadevan et al., 2009). When applied to the eye, RGP lenses can mask most of the anterior corneal surface lower-order and higher-order aberrations induced by keratoconus, by replacing the irregular, keratoconic corneal surface with the smooth and regular refractive surfaces of the RGP lens and a liquid tear-lens (Griffiths et al., 1998, Jinabhai et al., 2010b). Nevertheless, a review of the literature shows that residual ocular higher-order aberrations persist even with RGP contact lens wear in patients with keratoconus (Kosaki et al., 2007, Marsack et al., 2007b, Negishi et al., 2007, Jinabhai et al., 2012c). Studies by Chen and Yoon (2008) and Nakagawa et al. (2009) have indicated that these residual aberrations may be attributed to the posterior surface of the cornea in eyes with keratoconus.

In an attempt to optimise the optical quality of the keratoconic eye, several authors have evaluated the use of customised aberration-controlling soft contact lenses to help reduce ocular aberrations for keratoconic patients (López-Gil et al., 2003, Jeong and Yoon, 2006, Chen et al., 2007b, Marsack et al., 2007a, Sabesan et al., 2007b, Marsack et al., 2008, Katsoulos et al., 2009). However, some investigations did not fully evaluate visual performance, whereas others predominantly used the metric of higher-order RMS error to evaluate changes in optical quality. Although useful, higher-order RMS error does not provide information regarding changes in individual Zernike coefficient terms (Cheng et al., 2004c, Marsack et al., 2004, Thibos et al., 2004).

It is expected that aberration-controlling soft contact lenses may offer certain advantages over RGP lenses, e.g. better comfort in cases of RGP lens intolerance. Previous reports have suggested that optimal correction of higher-order aberrations will be achieved using a bespoke correction which corrects only certain Zernike coefficient terms (Guirao et al., 2002a, de Brabander et al., 2003). To date, only Katsoulos et al. (2009) have adopted such an approach for patients with keratoconus. The purpose of the present study was to investigate how standard toric soft contact lenses and customised aberration-controlling soft contact lenses correct ocular higher-order aberrations and visual performance in patients with keratoconus, compared to either RGP lenses or spectacles. The customised lenses were designed to either fully (100 %) or partially (50 %) correct 3rd-order coma aberrations. In addition to a ‘full’ correction, our rationale for using a ‘partial’ correction was based on previous calculations (Guirao et al., 2001, Guirao et al., 2002a, de Brabander et al., 2003, Thibos et al., 2003b, López-Gil et al., 2009a), which have confirmed that decentration (either by rotation or translation) of a ‘full’ wavefront aberration correction induces unwanted residual aberrations, which are likely to diminish visual performance. Moreover, both Guirao et al. (2002a) and de Brabander et al. (2003) have reported that decentration of a partial
correction of wavefront aberrations will still yield a more useful visual benefit than a conventional spherocylindrical correction.

In addition to higher-order RMS error, the present investigation explores changes in coma RMS, trefoil RMS and spherical aberration. The investigation also uses the same natural pupil size to evaluate the changes in aberrations across all patients investigated (without the use of a mydriatic agent, which may cause changes in wavefront analysis by causing a shift in the location of the pupil centre (Yang et al., 2002, Carkeet et al., 2003)).

### 9.3 Methods and materials

Twenty-two patients with previously diagnosed keratoconus took part in this study; participants were recruited from the Optometry clinic at the University of Manchester and Manchester Royal Eye Hospital. Inclusion criteria for the study participants included a ‘scissors’ retinoscopic reflex, distorted mires on keratometry and slit lamp signs of keratoconus such as corneal apical protrusion, Vogt’s striae and Fleischer’s ring. Patients with corneal transplants, cataracts, intra-ocular lens implants, macular disease or optic nerve disease, in either eye, were excluded. All experimental data were collected from one eye of each patient (Thibos et al., 2002c); the eye selected showed more advanced disease than the fellow eye. Sixteen participants were successful habitual RGP contact lens-wearers; the remaining 6 patients habitually wore spectacles to correct their vision. Successful lens wearers were defined as patients who experienced no more than a slight lens awareness and/or occasional foreign body sensation whilst wearing their RGP lenses and who regularly wore their lenses for minimum of 8 hours a day (Sarver and Harris, 1971). The mean age of the group was 34 ± 8 [SD] years (range 19 to 55 years), consisting of 17 males and 5 females. The investigation followed the tenets of the Declaration of Helsinki. All participants gave their informed consent after being told the purpose of the study. The investigation was approved by the National Research Ethics Service, North West 11 Research Ethics Committee. The flowchart presented in Figure 9.1 summarises the sequence of investigative steps for the RGP lens- and spectacle-wearing patients.

#### 9.3.1 Visual performance

High-contrast (95 %) and low-contrast (15 %) visual acuities were measured using Bailey-Lovie logMAR letter charts (National Vision Research Institute, Melbourne, Australia). Both letter charts were positioned at a distance of 3 meters from the patient and were illuminated externally using two fluorescent tubes, aligned such that they uniformly illuminated to approximately 750 lux without causing glare. All high-contrast and low-contrast acuity measurements at 3 metres were scored to the letter in log units and were corrected for a distance of 6 metres. In addition, the SKILL (the Smith-Kettlewell Institute Low Luminance) card (Smith-Kettlewell Eye Research Institute, San Francisco, CA, U.S.) was also used to evaluate the patient’s near vision logMAR acuity in both high-contrast and simulated, reduced-luminance conditions, i.e. black-on-grey letters (Haegerstrom-Portnoy et al., 1997). First, the high-contrast letters were presented at the specified viewing distance of 40 cm, and the near logMAR acuity recorded. The card was then turned over, and the near logMAR acuity was recorded using the simulated, reduced-luminance characters presented at the same distance. Acuity measurements for each side of the chart were made using the ‘letter-by-letter’ method, as outlined by Haegerstrom-Portnoy et al. (1997). The SKILL card
‘score’ was calculated as the difference in the number of letters correctly identified between the high-contrast and low-contrast sides (in log units). All measurements were made in a consulting room with a constant illumination of approximately 310 lux. The patient’s pupil size whilst viewing the high-contrast acuity logMAR chart was recorded using a pupil gauge. Where necessary, SKILL card acuity measurements were made using an appropriate subjective ‘reading addition’ over-refraction for the working distance of 40 cm (using trial lenses).

9.3.2 Ocular higher-order aberrations

Ocular aberrations were evaluated using the IRX-3, Hartmann-Shack aberrometer (Imagine Eyes, Paris, France). The IRX-3 device uses a 32 x 32 lenslet array and near infra-red light with a wavelength of 780 nm. Aberrations were recorded under monocular conditions with the room lights switched off. Accommodation was relaxed using the dynamic fogging method (via the device’s internal Badal system), whilst patients fixated, monocularly, on a black 6/12-sized Snellen letter “E” in an elliptical white background field subtending an approximate 0.7 x 1.0-degree angle with a luminance of around 85 cd/m². Wavefront aberrations were computed up to the 6th Zernike order, for a 4-mm pupil diameter, using the device’s software (Version 1.2, Imagine Eyes). A 4-mm diameter was chosen as this was the largest pupil size common to all 22 patients evaluated. An average of four monocular readings was calculated for each set of measurements made for all 22 participants. Each measurement was made approximately 1 second after a blink to standardise the measurements and to limit the variations in wavefront aberrations due to alterations in the tear film over time (Radhakrishnan et al., 2010).

9.3.3 RGP lens fitting assessment and corneal slit-lamp examination

A slit-lamp biomicroscope (SL40, Keeler Ltd., Windsor, U.K.) was used to assess the fitting of the subjects’ habitual RGP lenses using sodium fluorescein. The RGP lens fittings were graded as definite apical clearance, apical clearance, apical touch or definite apical touch using the criteria defined by Fink et al. (2001). The surface quality, cleanliness and overall condition of the lenses were also inspected to ensure that the lenses were not damaged (either through chips or scratches) or heavily deposited. The contact lens-wearing patients were then asked to remove their habitual RGP lenses, to facilitate further biomicroscopic assessment of the cornea, including the presence or absence of Fleischer’s ring, Vogt’s striae, prominent corneal nerves and apical scarring. A similar corneal examination was also performed for the spectacle-wearing patients.
**RGP-wearers (n = 16)**

**Visual performance assessment with RGP lenses (HCA, LCA & SKILL card score)**

**Higher-order aberration measurement with RGP lenses (IRX-3)**

**RGP lens fitting assessment and lens removal**

**Corneal slit-lamp examination without lenses**

**Higher-order aberration measurement without lenses (IRX-3)**

**Corneal topography evaluation without lenses (Pentacam)**

*RGP lenses left out for 1 week to act as a washout period*

**Day 7: Initial trial lens fitting appointment**

**Corneal slit-lamp examination (without RGP lenses)**

**Plano soft trial lens fitting assessment (& OR)**

**RGP lens wear resumed as normal**

*Sphero-cylindrical soft lenses ordered*

---

**Spectacle-wearers (n = 6)**

**Visual performance assessment with spectacles (HCA, LCA & SKILL card score)**

**Corneal slit-lamp examination**

**Higher-order aberrations measured without spectacles (IRX-3)**

**Corneal topography evaluation (Pentacam)**

**Plano soft trial lens fitting assessment (& OR)**

*Sphero-cylindrical soft lenses ordered*

---

**Standard soft lens collection appointment**

**Sphero-cylindrical soft lens fitting assessment (& OR)**

**Visual performance assessment (HCA, LCA & SKILL card score)**

**Higher-order aberrations measured with the spherocylindrical soft lenses (IRX-3)**

**Residual aberrations used to order customised lenses**

---

**Customised lenses collection appointment**

**100% Coma correction lens fitting assessment (& OR)**

**Visual performance assessment (HCA, LCA & SKILL card score)**

**Higher-order aberrations measured with the 100% Coma correction lenses (IRX-3)**

**100% Coma correction lenses removed (& procedure repeated for the 50% Coma correction lenses)**

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*Figure 9.1 A flow diagram summarising the different stages of the investigation for both patient groups.*
9.3.4 Corneal topography

The Oculus Pentacam (Oculus Inc., Wetzlar, Germany) was used to evaluate each subject's corneal topography, central corneal thickness and central radii of curvature (calculated within a central 3-mm zone). The rotating Scheimpflug camera device works in conjunction with a monochromatic, blue light-emitting diode slit-light source (at a wavelength of 475 nm) and captures 25 images during a 1-second scan, which provides up to 500 true elevation points per image. Four monocular scans were repeated and averaged for each patient. The CLEK (Collaborative Longitudinal Evaluation of Keratoconus) study group's criteria was used to grade the severity of keratoconus using the Pentacam's topographical data, where steep keratometric measurements < 45 D were graded as ‘mild’ keratoconus, values between 45 to 52 D were graded as ‘moderate’ keratoconus and readings > 52 D were classed as ‘severe’ keratoconus (Zadnik et al., 1996).

After collecting the baseline data, the 16 contact lens-wearing patients were instructed to leave their RGP lenses out for a period of 7 days to act as a ‘wash-out’ period prior to fitting the study lenses (Jinabhai et al., 2012a). Plano trial lenses were used to assess the optimal back optic zone radius and sphero-cylindrical powers so that higher-order aberrations could then be assessed to design customised lenses to correct the aberrations accordingly. All 16 patients had spectacles, which had been prescribed within the previous 18 months and were asked to use these until the trial lens fitting appointment one week later.

9.3.5 Soft trial lens fitting assessment and over-refraction (OR)

Using each patient’s corneal topography as a starting point, a series of different Plano trial lenses were applied and evaluated on-eye to ascertain the best fitting lens characteristics with regards to lens comfort, centration (horizontally and vertically), movement (digital push-up test and with blink in the primary position, up-gaze and horizontal lag) and corneal coverage, using established criteria outlined in the literature (Maldonado-Codina et al., 2005). Lens rotations in the primary position and upon blinking were also evaluated during the fitting process, by observing the position of the lens orientation marker (usually located at the 6-o’clock position) by projecting a narrow vertical slit lamp beam onto the lens and rotating the beam to align with the lens marking. After a settling period of approximately 30 minutes, a monocular over-refraction (OR) was performed through the best-fitting trial lens, at a distance of 6 metres (using a Snellen letter chart (National Eye Institute, Bethesda, MD, U.S.), with a luminance of 120 cd/m²), to obtain the subjective sphero-cylindrical refraction result that maintained optimal visual acuity. Retinoscopy with the trial contact lens was firstly carried out to establish a starting point for the over-refraction. This refraction result was then refined using standard subjective techniques (Rabbetts and Bennett, 2000) with some modification – for example, larger power steps between lenses and a high-powered Jackson crossed-cylinder (±1.00 DC - dioptre cylinder), tailored to keratoconic patients with poorer vision (Zadnik et al., 1998, Boxer-Wachler et al., 2003). The refraction endpoint was the maximum ‘plus’ sphero-cylindrical refraction power which allowed the patient to read their threshold visual acuity. Once the endpoint refraction was reached, the back vertex distance was recorded in millimetres. Both high-contrast and low-contrast logMAR visual acuity measurements were then recorded at 3 metres (scored to the letter in log units) and were corrected for a distance of 6 metres. The best-fitting trial lens back optic zone radius, peripheral lens design, laser marker
orientation and subjective OR result were used to order a standard toric soft lens for each patient. The lens manufacturer appropriately adjusted the final contact lens powers to compensate for any small rotations (up to a maximum of 5 degrees or less) observed during the fitting process.

On completion of the trial lens fitting, the 16 RGP lens-wearing patients were then asked to resume RGP lens wear as normal whilst the soft lenses were ordered. However, before the toric soft lens collection appointment, the lens-wearing patients were instructed to leave their habitual RGP lenses out overnight and to attend their appointment wearing their spectacles. Similarly, the spectacle-wearing patients attended their collection appointments wearing their habitual spectacles.

9.3.6 Standard toric soft lens collection appointment

On average, the final lens collection appointment took place 2 weeks after the trial lens fitting appointment. Five minutes after applying the toric soft lens, a slit-lamp biomicroscopic evaluation was performed to ensure that each lens was positioned acceptably with regard to lens centration (horizontal and vertical), movement (with push-up, in the primary position, upon up-gaze and with horizontal lag) and toric marker alignment. Each lens fitted was designed with a prism-ballasted toric front surface design, a spherical back surface and a total diameter of 14.50 mm. All the lenses fitted were manufactured using a Filcon II-based material (water content 77 %, Dk = 53 and centre thickness of 0.40 mm).

A period of 30 minutes was allowed for the patient's tear film to stabilise after lens application before measuring each patient's OR and visual performance. The slit-lamp biomicroscope was used to reassess the lens position to ensure this had not altered substantially over time. A spherical OR was then performed at 6 metres (Snellen chart). For patients where a spherical OR was required to maximise acuity, the lens was also kept in place whilst recording high-contrast and low-contrast acuities (at 3 metres) and SKILL card scores (at 40 cm). Using the IRX-3 device, ocular aberrations were evaluated with the toric soft lenses in place.

The standard toric soft lenses fitted in this investigation were used to design the aberration-controlling customised lenses, equally these lenses also served as a control. The IRX-3 device was used to measure the residual ocular higher-order aberrations with the standard toric lenses in place. These residual aberrations were then incorporated into a modified version of the standard toric lens design to produce two additional customised lenses for each patient. The customised lenses were manufactured with non-rotationally symmetric surfaces, containing the already established sphero-cylindrical correction, along with either a 100 % correction (referred to as 100 % lens) or a 50 % correction (referred to as 50 % lens) of the residual 3rd-order coma aberrations measured with the IRX-3 device. On average, the residual vertical and horizontal coma aberrations recorded with the standard toric soft lenses in either patient group were negative in sign; therefore the customised lenses were all designed to include the required magnitude of positive coma to reduce the magnitude of the residual aberrations.

The aberrations of the 100 % and 50 % lenses were verified against the designed aberrations using the ClearWave instrument (Wavefront Sciences, Albuquerque, NM, US) which is based on the Hartmann-Shack principle (Jeong et al., 2005, Kollbaum et al., 2008).
Before the customised lens collection appointment, the RGP lens-wearing patients were again instructed to leave their habitual lenses out overnight and to attend their appointment wearing their spectacles. Equally, the spectacle-wearing patients attended their collection appointments wearing their habitual spectacles.

9.3.7 Customised lens collection appointment

Five minutes after applying the 100 % coma correcting lenses, a slit-lamp biomicroscopic evaluation was performed to ensure that the lenses were positioned acceptably with regard to lens centration, movement and toric marker alignment. A further period of 30 minutes was allowed for the patient’s tear film to stabilise after lens application before measuring each patient’s OR and visual performance. The slit-lamp biomicroscope was used to reassess the lens position to ensure this had not altered substantially over time. A spherical OR was then performed at 6 metres (Snellen chart). For patients where a spherical OR was required to maximise acuity, the lens was also kept in place whilst recording high-contrast and low-contrast acuities (at 3 metres) and SKILL card scores (at 40 cm). Ocular higher-order aberrations were then repeated with the 100 % coma-correcting lenses in situ. These lenses were then removed and the same procedures and measurements, as outlined above, were repeated using the 50 % coma-correcting lenses.

9.3.8 Data analysis

The total higher-order root mean square (RMS) aberrations were calculated as the root mean square of all the Zernike coefficient terms from the 3rd- to the 6th-order inclusive. Tests of normality were performed using the Shapiro-Wilk’s test and a critical value of 0.05 (SPSS version 16.0; SPSS, Chicago, IL, US). Normally distributed data were analysed with 1-way repeated-measures analysis of variance (RM-ANOVA) using a critical value of 0.05. Non-normally distributed data were evaluated with either the Wilcoxon signed-ranks test (WSRT) or the Friedman test (both for a critical value of 0.05).

In the RGP lens-wearing group, post-hoc analyses for the normally distributed aberrometry data were conducted using paired dependant t-tests with a Bonferroni adjustment for 10 multiple comparisons (critical value of 0.05/10 = 0.005). For the non-normally distributed aberrometry data, post-hoc analyses were carried out using individual WSRT, also using a critical value of 0.005. In the spectacle-wearing group, post-hoc analyses for the normally distributed aberrometry data were conducted using paired dependant t-tests with a Bonferroni adjustment for 6 multiple comparisons (critical value of 0.05/6 = 0.0083).

For the correlation data, all normally distributed values were analysed using the 2-tailed Pearson’s correlation (R<br/>2</br>) method (critical value of 0.05), whereas all non-normally distributed values were evaluated using the 2-tailed Spearman’s correlation (R<br/>S</br>) method (critical value of 0.05).
9.4 Results

9.4.1 Patient demographics

Table 9.1 summarises the anterior surface central radii, central corneal thickness, CLEK study group severity grade, corneal slit-lamp appearance and RGP lens fitting grade for the keratoconic patients at the initial examination. The participants recruited to the study included 7 patients with severe keratoconus, 14 patients with moderate keratoconus and one patient with mild keratoconus. All 22 patients showed Fleischer's ring and prominent corneal nerves. Eight of the 22 patients exhibited corneal apical scarring, as expected these patients were graded with either moderate or severe disease. Fifteen of the RGP lens-wearing patients presented with a flat RGP lens fitting and one patient had an apical clearance type lens fit.

Table 9.1 A summary of the average anterior surface central radii, central corneal thicknesses, CLEK (collaborative longitudinal evaluation of keratoconus) study group severity grades, corneal slit-lamp appearance and RGP lens fittings for the keratoconic patients at the initial examination. (DAT = definite apical touch; AT = apical touch and AC = apical clearance).

<table>
<thead>
<tr>
<th>Patient ref.</th>
<th>Flat K (D)</th>
<th>Steep K (D)</th>
<th>Central corneal thickness (microns)</th>
<th>CLEK severity grade</th>
<th>Vogt's striae</th>
<th>Apical scarring</th>
<th>RGP lens fitting grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>49.8</td>
<td>56.0</td>
<td>455</td>
<td>Severe</td>
<td>Present</td>
<td>Absent</td>
<td>DAT</td>
</tr>
<tr>
<td>2</td>
<td>45.6</td>
<td>50.0</td>
<td>451</td>
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<td>Absent</td>
<td>AT</td>
</tr>
<tr>
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<td>Absent</td>
<td>AT</td>
</tr>
<tr>
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<td>48.4</td>
<td>434</td>
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<td>Absent</td>
<td>AC</td>
</tr>
<tr>
<td>5</td>
<td>58.2</td>
<td>61.8</td>
<td>324</td>
<td>Severe</td>
<td>Present</td>
<td>Present</td>
<td>AT</td>
</tr>
<tr>
<td>6</td>
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<td>AT</td>
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<td>Present</td>
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</tr>
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</tr>
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<td>Absent</td>
<td>DAT</td>
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<td>461</td>
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<td>Absent</td>
<td>DAT</td>
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<td>Present</td>
<td>DAT</td>
</tr>
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<td>46.7</td>
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<td>-</td>
</tr>
<tr>
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<td>Absent</td>
<td>Absent</td>
<td>-</td>
</tr>
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<td>43.4</td>
<td>514</td>
<td>Mild</td>
<td>Absent</td>
<td>Absent</td>
<td>-</td>
</tr>
</tbody>
</table>

All 16 RGP lens-wearing patients were fitted with the standard toric soft lenses. Customised coma-correcting lenses could not be manufactured for patient number 3, as the mean residual vertical and horizontal coma aberrations measured with the standard toric soft lens were measured to be very low, at +0.008 and +0.02 microns respectively. Equally, a few measurements with the customised lenses could not be obtained as some patients were unable to attend all of the
scheduled visits. Consequently, only 14 out of the 16 RGP lens-wearing patients were fitted with the 100 % coma correction lenses (patient reference 1, 2, 4 and 6 to 16) and 13 patients were fitted with the 50 % coma correction lenses (patient reference 1, 2, 4 and 6 to 11 and 13 to 16). Moreover, aberration measurements could not be acquired with either customised lens for patient number 4; however visual performance measurements were possible with both customised lenses. With regard to the statistical analysis, unobtainable data were treated as ‘missing data’. Consequently, the aberrometry data compared across the four different lens types (the RGP lenses, standard soft toric lenses, 100 % lenses and the 50 % lenses) could only be analysed for 12 of the 16 RGP lens-wearing patients, whereas visual performance data were analysed for 13 patients. All visual acuity and aberration measurements were successfully obtained from the 6 spectacle wearers.

9.4.2 Higher-order aberrations

9.4.2.1 RGP lens-wearers

In the RGP lens-wearing patients 5 sets of aberrometry data were compared, these included measurements made with the patient’s habitual RGP lenses, without any contact lenses in place, with the standard toric soft lenses, with the 100 % lenses and with the 50 % lenses. Table 9.2 shows the statistical analysis for the ocular aberrations evaluated. Second-order cylinder RMS, coma RMS and spherical aberration all showed significant differences between the 5 sets of aberrometry measurements using RM-ANOVA (p ≤ 0.006).

Compared to the uncorrected data, the RGP lenses significantly reduced 2nd-order cylinder RMS error (p = 0.003, Figure 9.2). Compared to the RGP lenses, all three soft lenses induced a significant increase in cylinder RMS error (p ≤ 0.001); however, only the 100 % lenses induced significantly more 2nd-order cylinder RMS error compared to the uncorrected aberration measurements (p = 0.004).

Compared to the uncorrected values, post-hoc analyses (displayed in Figure 9.3) showed significantly lower magnitudes of coma RMS error with the RGP lenses (p = 0.001), the 100 % lenses (p = 0.001) and the 50 % lenses (p = 0.0002). However, no significant difference in coma RMS was found between the uncorrected values and those measured with the standard toric soft lenses (p = 0.016). No other significant differences in coma RMS aberrations were found between the different lens types evaluated (p ≥ 0.005). The lowest residual coma RMS aberrations were achieved with the 50 % lenses, closely followed by the RGP lenses and the 100 % lenses respectively.

Compared to the uncorrected measurements, post-hoc tests showed that the standard toric soft lenses induced a significant magnitude of negative spherical aberration (p = 0.003; Figure 9.3). Equally, both the 100 % and 50 % lenses also induced a significant magnitude of negative spherical aberration compared to the RGP lenses (p ≤ 0.002; Figure 9.3). However, no significant differences in spherical aberration were found between the uncorrected data and with either the 100 % lenses (p = 0.02), the 50 % lenses (p = 0.01) or the RGP lenses (p = 0.94). No other significant differences in spherical aberration were found between the different lens types evaluated (p ≥ 0.005).
In the RGP lens-wearing patients, Friedman analyses also showed significant differences between the 5 sets of measurements for trefoil RMS, 3rd-order RMS, 4th-order cylinder RMS and higher-order RMS aberrations (p ≤ 0.033, Table 9.2). Compared to the uncorrected values, post-hoc analyses showed that the RGP lenses and the standard toric soft lenses significantly reduced trefoil RMS aberrations (p ≤ 0.002, Figure 9.3). However, no significant differences in trefoil RMS aberrations were found between the uncorrected values and those measured with either the 100 % or 50 % lenses (p ≥ 0.03). No other significant differences in trefoil RMS aberrations were found between the different lens types evaluated (p > 0.005).

Compared to the uncorrected values, post-hoc analyses also revealed that the RGP lenses, and both the 100 % and 50 % lenses, significantly reduced 3rd-order RMS aberrations (p ≤ 0.004, Figure 9.3). However, no significant differences in 3rd-order RMS error were found between the uncorrected values and those measured with the standard toric soft lenses (p = 0.008). No other significant differences in 3rd-order RMS aberrations were found between the different lens types investigated (p ≥ 0.005). The lowest magnitude of residual 3rd-order RMS error was achieved with the 50 % lenses, closely followed by the habitual RGP lenses and the 100 % lenses respectively.

Post-hoc tests showed that both the RGP lenses and the 50 % lenses significantly reduced 4th-order cylinder RMS error (p ≤ 0.003, Figure 9.3). However, no significant differences were found between the uncorrected 4th-order cylinder RMS values and those measured with either the standard toric soft lenses or with the 100 % lenses (p ≥ 0.007). No other significant differences in 4th-order cylinder RMS error were found between the different lens types evaluated (p ≥ 0.005).

Compared to the uncorrected values, post-hoc analyses show that all four lens types evaluated significantly reduced higher-order RMS error (p = ≤ 0.004, Figure 9.3). However, no other significant differences in higher-order RMS aberrations were found between the different lens types investigated (p ≥ 0.005). The lowest residual higher-order RMS aberrations were achieved with the 50 % lenses, closely followed by the RGP lenses and the 100 % lenses respectively.

Upon evaluating individual Zernike coefficient terms, Friedman analysis showed a significant difference in vertical coma between the 5 sets of aberration data analysed (χ² = 40.3; degrees of freedom (df) = 4; p = 0.0000001). Post-hoc analyses, using the WSRT, showed significant reductions in uncorrected vertical coma from -0.93 ± 0.34 µm [±1 SD] to +0.18 ± 0.39 µm with the 100 % lenses (Z = -3.1 , p = 0.002); to -0.17 ± 0.30 µm with the 50 % lenses (Z = -3.1, p = 0.002) and to +0.39 ± 0.14 µm with the RGP lenses (Z = -3.1 , p = 0.002). However, the standard toric lenses did not significantly reduce uncorrected vertical coma aberrations (-0.66 ± 0.43 µm; p = 0.04).

In comparison to the standard toric soft lenses, both the 100 % and 50 % lenses provided significantly better reductions in vertical coma (Z ≥ -3.1, p ≤ 0.002). A significant difference in vertical coma was also found between the RGP lenses and both the 50 % lenses (Z = -3.1, p = 0.002) and the standard toric lenses (Z = -3.1, p = 0.002). Both the RGP lenses and the 100 % lenses produced a positive shift in vertical coma; although the RGP lenses showed higher residual values, the differences were not found to be significant (p = 0.14). Likewise, both the 100 % lenses and the 50 % lenses also produced a positive shift in vertical coma (compared to the uncorrected values); although, on average, the 100 % lenses showed higher residual values, the differences were not found to be significant (p = 0.01).
Freidman analysis showed no significant differences in horizontal coma between the 5 sets of aberration measurements evaluated (p = 0.10).

Table 9.2 Comparing the root mean square (RMS) aberrations measured with and without the patients’ habitual RGP lenses, with the standard toric soft lenses and with both the 100 % and 50 % lenses using repeated-measures analysis of variance (RM-ANOVA) and the Friedman test. (See Figure 9.2 and Figure 9.3 for the post-hoc analyses).

<table>
<thead>
<tr>
<th>Aberration metric</th>
<th>Test</th>
<th>Statistic</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd-order cylinder RMS</td>
<td>RM-ANOVA</td>
<td>F&lt;sub&gt;4,44&lt;/sub&gt; = 8.4</td>
<td>*0.006</td>
</tr>
<tr>
<td>Coma RMS</td>
<td>RM-ANOVA</td>
<td>F&lt;sub&gt;4,44&lt;/sub&gt; = 11.1</td>
<td>*0.000003</td>
</tr>
<tr>
<td>Trefoil RMS</td>
<td>Friedman</td>
<td>χ² = 11.3 df =4</td>
<td>^0.023</td>
</tr>
<tr>
<td>3rd-order RMS</td>
<td>Friedman</td>
<td>χ² = 20.7 df =4</td>
<td>^0.0004</td>
</tr>
<tr>
<td>4th-order spherical aberration</td>
<td>RM-ANOVA</td>
<td>F&lt;sub&gt;4,44&lt;/sub&gt; = 6.7</td>
<td>*0.0003</td>
</tr>
<tr>
<td>4th-order cylinder RMS</td>
<td>Friedman</td>
<td>χ² = 23.3 df =4</td>
<td>^0.0001</td>
</tr>
<tr>
<td>Higher-order RMS (3rd to 6th)</td>
<td>Friedman</td>
<td>χ² = 24.3 df =4</td>
<td>^0.000007</td>
</tr>
</tbody>
</table>

* Indicates a significant difference using repeated-measures ANOVA (RM-ANOVA).

^ Indicates a significant difference using Friedman analysis.

Figure 9.2 Comparing 2nd-order cylinder RMS using the patients’ habitual RGP lenses, standard toric soft lenses and the 100 % and 50 % lenses in the contact lens-wearing group. Error bars represent ±1 standard deviation. RMS = root mean square and RM-ANOVA = repeated-measures analysis of variance.
Figure 9.3 Comparing higher-order aberrations using the patients’ habitual RGP lenses, standard toric soft lenses and the 100% and 50% lenses in the contact lens-wearing group. Error bars represent ±1 standard deviation.

RMS = root mean square; RM-ANOVA = repeated-measures analysis of variance and WSRT = Wilcoxon signed-ranks tests.
9.4.2.2 Spectacle-wearers

In the spectacle wearers, four sets of aberrometry measurements were compared, these included measurements made without any contact lenses in place, with the standard toric soft lenses, with the 100 % lenses and with the 50 % lenses. Table 9.3 displays the statistical analysis for the 7 ocular aberration terms evaluated using RM-ANOVA. Significant differences were found between each of the 4 sets of higher-order aberration measurements analysed (p ≤ 0.033). In contrast, no significant differences were found between the 4 sets of 2nd-order cylinder RMS data (p = 0.37).

Compared to the uncorrected values, post-hoc analyses showed that the 100 % lenses significantly reduced coma RMS aberrations (p = 0.005, Figure 9.4), however, no significant differences were found between the uncorrected data and those measured with either the standard toric soft lenses or the 50 % lenses (p ≥ 0.01). Although both customised lenses achieved lower magnitudes of residual coma RMS error compared to the standard toric lenses, the differences did not reach statistical significance (p ≥ 0.03). The lowest residual coma RMS aberrations were achieved with the 50 % lenses, closely followed by the 100 % lenses.

Uncorrected 3rd-order RMS aberrations were significantly reduced by each of the three soft lenses (p ≤ 0.004, Figure 9.4). However, post-hoc tests showed no significant differences in 3rd-order RMS error between the standard toric lenses and either of the two customised lenses (p ≥ 0.04). The lowest residual 3rd-order RMS aberrations were achieved with the 50 % lenses, closely followed by the 100 % lenses.

Similarly, the uncorrected higher-order RMS error values were significantly reduced by all three lenses (p ≤ 0.005, Figure 9.4). However, post-hoc tests showed no significant differences in higher-order RMS aberrations between the standard toric lenses and either of the two customised lenses (p ≥ 0.08). The lowest residual higher-order RMS aberrations were achieved with the 50 % lenses, closely followed by the 100 % lenses.

At a significance level of 0.0083, post-hoc analyses showed no significant differences between the 4 sets of aberration measurements made for trefoil RMS and 4th-order cylinder RMS aberrations (Figure 9.4). Likewise, the differences in spherical aberration between these 4 sets of measurements were not found to be statistically significant; however, compared to the uncorrected values, all three lens types induced a negative shift in spherical aberration.

Upon evaluating individual Zernike aberration terms, RM-ANOVA showed a significant difference in vertical coma between the 4 sets of measurements analysed (F3,15 = 9.6, p = 0.001). Compared to the uncorrected values (-0.53 ± 0.29 µm [±1 SD]), post-hoc analyses showed that the 100 % lenses induced a significant positive shift in vertical coma aberration (+0.21 ± 0.24 µm) – p = 0.007. Likewise, the 50 % lenses also, on average, induced positive shift in vertical coma (+0.001 ± 0.30 µm), however this difference did not reach statistical significance (p = 0.04). Post-hoc analyses also showed a non-significant reduction in uncorrected vertical coma with the standard toric lenses (p = 0.009). No significant differences in vertical coma were measured between the standard toric soft lenses and either of the two customised lenses (p ≥ 0.02) in this patient group.

Freidman analysis showed no significant differences in horizontal coma between the 5 sets of aberration measurements evaluated (p = 0.20).
Table 9.3 Comparing the root mean square (RMS) aberrations measured without any lenses in place, with the standard toric soft lenses and with both the 100 % and 50 % lenses using repeated-measures analysis of variance (RM-ANOVA). (See Figure 9.2 and Figure 9.4 for the post-hoc analyses). * Indicates a significant difference.

<table>
<thead>
<tr>
<th>Aberration metric</th>
<th>Test</th>
<th>Statistic</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd-order cylinder RMS</td>
<td>RM-ANOVA</td>
<td>$F_{3,15} = 1.5$</td>
<td>0.37</td>
</tr>
<tr>
<td>Coma RMS</td>
<td>RM-ANOVA</td>
<td>$F_{3,15} = 9.7$</td>
<td>*0.001</td>
</tr>
<tr>
<td>Trefoil RMS</td>
<td>RM-ANOVA</td>
<td>$F_{3,15} = 6.3$</td>
<td>*0.006</td>
</tr>
<tr>
<td>3rd-order RMS</td>
<td>RM-ANOVA</td>
<td>$F_{3,15} = 16.2$</td>
<td>*0.00006</td>
</tr>
<tr>
<td>4th-order spherical aberration</td>
<td>RM-ANOVA</td>
<td>$F_{3,15} = 6.6$</td>
<td>*0.005</td>
</tr>
<tr>
<td>4th-order cylinder RMS</td>
<td>RM-ANOVA</td>
<td>$F_{3,15} = 3.8$</td>
<td>*0.033</td>
</tr>
<tr>
<td>Higher-order RMS (3rd to 6th)</td>
<td>RM-ANOVA</td>
<td>$F_{3,15} = 14.7$</td>
<td>*0.0001</td>
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</tbody>
</table>

9.4.3 Visual performance

The average pupil size recorded for all 22 patients whilst measuring visual performance was 4.3 ± 0.4 mm [±1 SD]. In the RGP lens-wearing group RM-ANOVA showed significant differences in high-contrast acuity ($F_{3, 36} = 11.1$ $p = 0.00003$), low-contrast acuity ($F_{3, 36} = 10.3$ $p = 0.00005$) and SKILL card scores ($F_{3, 36} = 7.9$ $p = 0.0003$) between the four different lens types evaluated. Figure 9.5 displays the post-hoc test results in the RGP lens-wearing group. The RGP lenses gave significantly better high-contrast acuity than the 100 % lenses ($p = 0.002$). Equally, the standard toric soft lenses provided significantly better results than both the 100 % ($p = 0.002$) and the 50 % ($p = 0.006$) lenses. However, no significant differences in high-contrast acuity were found between the RGP lenses and either the standard toric soft or 50 % lenses ($p \geq 0.01$). No other significant differences in high-contrast acuity were found between the different lens types evaluated ($p \geq 0.0083$).

The low-contrast acuity results also show that the RGP lenses performed significantly better than the 100 % lenses ($p = 0.001$). However, no significant differences in low-contrast acuity were found between the RGP lenses and either the standard toric soft or 50 % lenses ($p \geq 0.01$). No other significant differences in low-contrast acuity were found between the different lens types evaluated ($p \geq 0.0083$).

The SKILL card results revealed significantly lower scores with the RGP lenses compared to either the standard toric soft lenses ($p = 0.0004$) or the 100 % lenses ($p = 0.001$). In contrast, no significant differences were found between the RGP lenses and the 50 % lenses ($p = 0.01$). No other significant differences in SKILL card scores were found between the different lens types evaluated ($p \geq 0.0083$).

In the spectacle-wearing group, RM-ANOVA showed no significant differences between the high-contrast acuities ($p = 0.07$), low-contrast acuities ($p = 0.06$) and SKILL card scores ($p = 0.11$) measured with the patient’s spectacles, the standard toric soft lenses and the two customised lenses.

The spherical ORs used to measure visual performance with either the patient’s habitual RGP lenses or the standard soft lenses ranged from -0.50 to +0.75 D. The OR data measured with the customised lenses showed larger variations ranging between -1.50 and +0.75 D for the 100 % lenses and between -1.00 and +1.00 D for the 50 % lenses.
Figure 9.4 Comparing higher-order aberrations using the standard toric soft lenses and the 100 % and 50 % lenses in the spectacle-wearing group. Error bars represent ±1 standard deviation. RMS = root mean square and RM-ANOVA = repeated-measures analysis of variance.

* Indicates a significant difference (RM-ANOVA: *p < 0.0003)
Figure 9.5 A comparison of the visual performance achieved using the patient’s habitual mode of correction, the standard toric soft lenses and the 100% and 50% lenses using repeated-measures analysis of variance (RM-ANOVA). Error bars represent ±1 standard deviation. RMS = root mean square; HCA = high-contrast acuity and LCA = low-contrast acuity.

9.4.4 Correlation between visual performance and corneal parameters

High-contrast and low-contrast logMAR acuities measured using each patient’s habitual mode of correction (either RGP lenses or spectacles) were plotted against the steep keratometric readings measured using the Oculus Pentacam for all 22 patients evaluated. No significant correlation was found for the high-contrast acuity scores ($p = 0.55$), whereas a significant correlation was found for the low-contrast acuities (gradient = +0.02 log units/dioptre (D); $R_p = +0.59, p = 0.004$).

The high-contrast and low-contrast acuities with the standard toric soft lenses were also plotted against the steep keratometric readings for all 22 patients evaluated. Significant correlations were found for both the high-contrast (gradient = +0.03 log units/D; $R_s = +0.69, p = 0.0004$) and low-contrast acuity scores (gradient = +0.03 log units/D; $R_p = +0.72, p = 0.0002$).
The high-contrast and low-contrast acuities achieved with the 100 % lenses were plotted against the steep keratometric readings for 20 patients. Significant correlations were observed for both the high-contrast (gradient = +0.04 log units/D; R\text{p} = +0.58, p = 0.007) and low-contrast acuity data (gradient = +0.03 log units/D; R\text{p} = +0.48, p = 0.03).

The high-contrast and low-contrast acuities measured with the 50 % lenses were also plotted against the steep keratometric readings for 19 patients. Significant correlations were found for both the high-contrast (gradient = +0.04 log units/D; R\text{p} = +0.58, p = 0.009) and low-contrast acuity data (gradient = +0.04 log units/D; R\text{p} = +0.62, p = 0.005).

9.4.5 Correlation between visual performance and ocular aberrations

High-contrast and low-contrast logMAR acuities measured using each patient’s habitual mode of correction (either RGP lenses or spectacles) were plotted against the 7 aberration terms measured with the correction in place for all 22 patients investigated. The analyses showed no significant correlations between either the high-contrast or low-contrast acuity scores achieved or the computed aberration terms (p ≥ 0.13).

Both the high-contrast and low-contrast acuities achieved with the standard toric soft lenses were plotted against the 7 aberration terms measured with the lenses in situ for all 22 patients evaluated. Significant correlations were found between the low-contrast acuity scores and the 2nd-order cylinder RMS (gradient = +0.10 log units/µm; R\text{p} = +0.65, p = 0.001); 3rd-order RMS (gradient = +0.25 log units/µm, R\text{p} = +0.50, p = 0.018); coma RMS (gradient = +0.24 log units/µm; R\text{p} = +0.49, p = 0.019); higher-order RMS (gradient = +0.25 log units/µm; R\text{S} = +0.55, p = 0.008) and spherical aberration terms (gradient = -0.50 log units/µm; R\text{p} = -0.50, p = 0.017). In contrast, no significant correlations were found between the high-contrast acuity scores and the 7 aberration terms evaluated (p ≥ 0.10).

The high-contrast and low-contrast acuities measured with the 100 % lenses were also plotted against the 7 aberration terms measured with the lenses for 19 patients. No significant correlations were found between either the high-contrast and low-contrast acuity scores achieved or the computed higher-order aberration terms (p ≥ 0.23). However, significant correlations were found between the 2nd-order cylinder RMS aberrations and the high-contrast (gradient = +0.22 log units/µm; R\text{p} = +0.77, p = 0.0001) and low-contrast acuities (gradient = +0.19 log units/µm; R\text{p} = +0.76, p = 0.0002) recorded with the 100 % lenses.

In addition, the high-contrast and low-contrast acuities achieved with the 50 % lenses were also plotted against the 7 aberration terms measured with the lenses for 18 patients. Again, no significant correlations were observed between the high-contrast acuity scores achieved and the computed higher-order aberration terms (p ≥ 0.12). However, significant correlations were found between the low-contrast acuities recorded and the coma RMS aberrations (gradient = +0.53 log units/µm; R\text{p} = +0.48, p = 0.04); higher-order RMS aberrations (gradient = +0.57 log units/µm; R\text{p} = +0.49, p = 0.04) and the spherical aberration terms (gradient = -0.99 log units/µm; R\text{S} = -0.51, p = 0.03). Likewise, significant correlations were also found between the 2nd-order cylinder RMS aberrations and both the high-contrast (gradient = +0.19 log units/µm; R\text{p} = +0.69, p = 0.002) and low-contrast acuities (gradient = +0.14 log units/µm; R\text{p} = +0.67, p = 0.002) recorded with the 50 % lenses.
9.5 Discussion

This study investigated how standard toric soft and customised coma-correcting hydrogel contact lenses corrected visual performance and ocular aberrations compared to RGP contact lenses or spectacles in patients with keratoconus. The results show that in the contact lens-wearing group, the patient’s habitual RGP lenses provided significantly better SKILL card scores than the standard toric soft lenses. Although the high-contrast and low-contrast acuity scores were also found to be better with RGP lenses (versus the standard toric soft lenses), these differences did not reach statistical significance. These findings were not unexpected as two previous studies have also reported that RGP lenses provide better visual performance than conventional soft lenses in patients with keratoconus (Griffiths et al., 1998, Marsack et al., 2008).

The literature suggests that the improvement in visual performance afforded by RGP lenses is most likely to be due the superior correction of irregular corneal astigmatism for patients with keratoconus (Fowler et al., 1988, Kastl and Johnson, 1989, Jupiter and Katz, 2000, Nepomuceno et al., 2003, Wietham and Driebe, 2004). In comparison, larger magnitudes of residual corneal astigmatism would still persist with a soft contact lens in place, as less pressure is exerted onto the cone apex (Buxton, 1978, Sorbara et al., 2000, McMonnies, 2004, McMonnies, 2005). The improvement in visual performance found with RGP lenses may perhaps also be attributed to the greater reduction of optical aberrations, as RGP lenses are likely to mask the corneal aberrations induced by keratoconus by replacing the irregular corneal surface with the smooth and regular refractive surfaces of the RGP lens (Griffiths et al., 1998, Marsack et al., 2008). Furthermore, the patient’s tear film typically creates a ‘liquid tear-lens’ which fills the gap between the RGP lens back surface and the irregular anterior cornea, thereby reducing optical aberrations. The refractive index of the ‘tear-fluid lens’ (n = 1.336) formed beneath the RGP lens back surface is close to that of the cornea (n = 1.376), consequently reducing the vast majority of the aberrations at the anterior corneal surface (1.336/1.376 = 97 %) (Hong et al., 2001, Dorronsoro et al., 2003, Lu et al., 2003). Moreover, the literature suggests that flatter-fitting RGP lenses give better visual performance compared to steeper-fitting lenses (Zadnik and Mutti, 1987, Sorbara et al., 2000, Jinabhai et al., 2010b). Fifteen of the 16 lens-wearing patients in the present study displayed an apical-bearing RGP lens fitting (Fink et al., 2001). Zadnik and Mutti (1987) originally hypothesised that the back surface of a flat-fitting RGP lens may ‘mould’ and ‘flatten’ the corneal distortion induced by keratoconus. This corneal moulding may lead to the anterior corneal surface adopting a more ‘normal’ curvature profile by exerting pressure onto the corneal apex, perhaps regularising its profile. Jinabhai et al.’s (2010b) results also indicate that flat-fitting lenses may reduce residual higher-order aberrations compared to steeper lens fits. The authors hypothesised that 3rd-order coma RMS aberrations, reduce in magnitude as the anterior corneal surface conforms to a more regular profile underneath an apical-bearing lens.

In the contact lens-wearing group, the results showed that RGP lenses reduced 2nd-order cylinder RMS, coma RMS, trefoil RMS, 3rd-order RMS, 4th-order secondary cylinder RMS and higher-order RMS aberrations more effectively than the standard toric soft lenses. These findings support the results of previous studies that compared optical quality in patients with keratoconus using both RGP and conventional soft lenses (Griffiths et al., 1998, Kosaki et al., 2007, Negishi et al., 2007, Sabesan et al., 2007b, Marsack et al., 2008). Using corneal topographical analysis, Griffiths et al. (1998) found that RGP lenses significantly reduced uncorrected, corneal total RMS
(both lower-order and higher-order) aberrations compared to four different spherical soft lenses in 13 patients with keratoconus. Equally, Marsack et al. (2008) and Sabesan et al. (2007b) have also demonstrated that ocular, total higher-order RMS aberrations are reduced more effectively by RGP lenses compared to sphero-cylindrical soft lenses for patients with moderate and severe keratoconus.

In agreement with our results, Kosaki et al. (2007) and Negishi et al. (2007), have demonstrated that RGP lenses significantly reduce both uncorrected coma RMS and higher-order RMS aberrations in patients with keratoconus. The results presented here are also in agreement with Kosaki et al.’s (2007) findings, which showed that uncorrected 4th-order secondary cylinder RMS aberrations were significantly reduced by RGP lenses in their study of 76 keratoconic eyes. Equally, our findings corroborate with Kosaki et al. (2007) and Choi et al. (2007), who also found no significant changes in 4th-order spherical aberration between measurements made with and without RGP lenses in keratoconic patients. In concordance with both Choi et al. (2007) and Jinabhai et al. (2010b), our results also found a positive shift in vertical coma with RGP lenses compared to the uncorrected values. Furthermore, the data presented show that RGP lenses provided significantly better correction of vertical coma compared to the standard toric soft lenses.

In the spectacle-wearing patients, no statistically significant differences in high-contrast acuity, low-contrast acuity or SKILL card scores were obtained with the patients’ spectacle refraction versus the standard toric soft lenses. The data presented show that both low-contrast acuity and SKILL card scores were slightly better with the spectacle refractions than with the standard toric soft lenses. However, the mean high-contrast acuity scores were found to be similar with both modes of visual correction, although with a larger degree of variance for the spectacle acuities. These results were perhaps due to large magnitudes of irregular corneal astigmatism persisting with the standard toric lenses in place, as hydrogel lenses tend to drape over the irregular anterior corneal surface without producing any significant masking effect at the corneal apex (Buxton, 1978, Sorbara et al., 2000). To help quantify this effect it may perhaps be useful to measure toric over-refractions (White, 2010). However, due to possible lens movements, toric over-refractions are likely to show reduced repeatability. In an attempt to overcome this, residual astigmatic errors were evaluated objectively using the 2nd-order cylinder RMS data measured with the IRX-3 device. Compared to the uncorrected values, the standard toric soft lenses induced a non-significant increase in 2nd-order cylinder RMS error in both the spectacle-wearing patients and in the RGP lens group. In contrast, the data in the contact lens-wearing patients show that RGP lenses provided significantly lower 2nd-order cylinder RMS aberrations compared to the uncorrected data and to measurements made with the standard toric soft lenses. Correlation analyses showed a significant correlation between the low-contrast visual acuities and the residual 2nd-order cylinder RMS aberrations measured with the standard toric soft lenses for all patients. However, in agreement with Jinabhai et al.’s (2011b) results, the 2nd-order cylinder RMS aberrations recorded in the present study also showed a large amount of variability. Moreover, both Jinabhai et al. (2010a) and Katsoulos et al. (2009) have previously demonstrated that 2nd-order cylinder RMS errors measured using the Hartmann-Shack technique do not correspond with cylindrical powers measured using subjective refraction in keratoconus patients. Both studies
suggest that the large variability in 2nd-order cylinder RMS aberrations is most likely to be due to spot imaging errors at the wavefront sensor (Yoon et al., 2004b).

In the RGP lens-wearing patients, the results reveal substantially poorer high-contrast acuity, low-contrast acuity and SKILL card scores with both customised lenses compared to with either the RGP or standard toric soft lenses. In particular, the post-hoc results reveal that both the 100 % and 50 % lenses provided significantly poorer high-contrast acuities compared to the standard soft toric lenses. The 100 % lenses also provided significantly poorer low-contrast acuities, high-contrast acuities and SKILL card scores compared to the RGP lenses. In the spectacle-wearing group, the 100% and 50 % lenses also provided poorer high-contrast acuity, low-contrast acuity and SKILL card scores compared to the patient’s habitual spectacles; however, these differences did not reach statistical significance. Both customised lenses also provided poorer high-contrast acuities compared to the standard toric soft lenses. However, the customised lenses provided low-contrast acuity and SKILL card scores comparable to those measures with the standard toric soft lenses.

Nonetheless, the 100 % and 50 % coma-correcting lenses significantly reduced uncorrected coma RMS, 3rd-order RMS and higher-order RMS error in the RGP lens-wearing patients and significantly reduced 3rd-order RMS and higher-order RMS aberrations in the spectacle-wearing group. However, only the 100 % lenses significantly reduced uncorrected coma RMS aberrations in the spectacle wearers. These results are in agreement with previous studies which have also investigated aberration-controlling contact lenses for patients with keratoconus (López-Gil et al., 2003, Jeong and Yoon, 2006, Chen et al., 2007b, Marsack et al., 2007a, Sabesan et al., 2007b, Marsack et al., 2008). In the RGP lens-wearing group the most successful correction of the uncorrected higher-order aberration terms was achieved by the 50 % lenses, however no significant differences in coma RMS, trefoil RMS, 3rd-order RMS, 4th-order cylinder RMS and higher-order RMS aberrations were found between the four lens types evaluated (p ≥ 0.005). Likewise, in the spectacle-wearing patients the most successful correction of the uncorrected higher-order aberration terms was achieved by the 50 % lenses, however no significant differences in coma RMS, trefoil RMS, 3rd-order RMS, 4th-order spherical aberration, 4th-order cylinder RMS and higher-order RMS aberrations were found between the four lens types evaluated (p ≥ 0.0083).

Compared to previous investigations of customised lenses for patients with keratoconus, Katsoulos et al. (2009) used a different approach to reduce the uncorrected ocular aberrations measured in their study of 8 mild to moderate keratoconic patients. The authors produced customised soft lenses which not only fully corrected for spherico-cylindrical refraction, but also partially corrected (by around 75 %) for manifest negative vertical coma aberrations measured using the Hartmann-Shack technique. In all 8 cases, a reduction in higher-order RMS error was seen (the largest reduction reported was from 0.86 μm to 0.42 μm), however the authors did not report if the differences were significant or not. On the other hand, Katsoulos et al. (2009) revealed a significant reduction in the magnitude of vertical coma aberrations with and without customised lenses (p ≤ 0.005); the largest reduction found in their study was from -0.56 μm to -0.15 μm. In agreement with Katsoulos et al.’s (2009) findings, our results show significant reductions in uncorrected vertical coma with both the 100 % and 50 % lenses in the RGP lens-wearing group and with the 100 % lenses in the spectacle-wearing group. Although the 50 % lenses also reduced
uncorrected vertical coma in the spectacle-wearing group, the differences did not reach statistical
significance; this difference between groups is likely to be due to the difference in sample sizes.

Our findings on changes in high-contrast and low-contrast visual acuity with aberration-
results showed that customised lenses provided significantly better high-contrast acuity (average of
+0.80, Snellen decimal) compared to the patients’ spectacle refraction (average of +0.55). Sabesan
et al. (2007b) found that customised lenses gave an average improvement of 2.1 lines of low-
contrast logMAR acuity compared to conventional soft lenses in three keratoconic patients. For one
of their patients with severe keratoconus, the customised lens provided an improvement of 3.5
lines of low-contrast acuity compared to the patient’s habitual RGP lens. In comparison, very little
difference in high-contrast acuity was found between the subject’s RGP lens and the customised
soft lens, although the customised lens still performed best. Marsack et al. (2007a) report that both
high-contrast and low-contrast acuity were improved with the customised lenses compared to the
conventional lens. However, in contrast to Sabesan et al.’s (2007b) study, Marsack et al. (2007a)
found that high-contrast acuity was improved (by 1.5 lines (logMAR); p = 0.03) more than low-
contrast acuity (which only improved by one line; p = 0.11). Marsack et al. (2008) revealed that
their patient with severe keratoconus achieved a high-contrast acuity score of +0.04 ± 0.09 log
units with their habitual RGP lens, which improved to -0.05 ± 0.05 log units with the customised
lens. The authors also report that one of their two moderately keratoconic patients achieved a high-
contrast acuity score of +0.20 ± 0.02 log units with their RGP lens and +0.14 ± 0.02 log units with
the customised lens. Katsoulos et al.’s (2009) results also suggested that customised lenses
provided improved high-contrast acuity compared to the patient’s habitual spectacles (the largest
improvement reported was from +0.52 log units to +0.06 log units). In accordance with Sabesan et
al.’s (2007b) study, Katsoulos et al. (2009) reported larger still improvements in low-contrast acuity
with customised lenses compared to the patient’s spectacles (the largest improvement reported
was from +1.00 log unit to +0.10 log units).

As with the standard toric soft lenses, the poorer visual performance measured with the
customised contact lenses may also be attributed to large magnitudes of uncorrected corneal
astigmatism persisting with the customised hydrogel contact lenses in place. Residual astigmatic
errors with the customised lenses were evaluated objectively using the IRX-3 device. The results in
the contact lens group showed that RGP lenses provided significantly better correction of 2nd-order
cylinder RMS error than both customised lenses. In contrast, both the 100 % and 50 % lenses
induced substantially larger magnitudes of 2nd-order cylinder RMS aberrations compared to the
uncorrected values. Likewise, in the spectacle-wearing group, both customised lenses also induced
higher levels of 2nd-order cylinder RMS aberrations compared to the uncorrected data; however,
these differences did not reach statistical significance. In accordance with Jinabhai et al.’s (2011b)
findings, the 2nd-order cylinder RMS aberrations recorded with the customised lenses showed a
large degree of variability. Correlation analyses revealed significant correlations between the 2nd-
order cylinder RMS aberrations measured with both the 100 % and 50 % lenses, and their
corresponding high-contrast and low-contrast acuity scores. However, previous investigations have
demonstrated that 2nd-order cylinder terms measured with the Hartmann-Shack technique to not
correspond with cylindrical powers measured using subjective refraction (Katsoulos et al., 2009, Jinabhai et al., 2010a).

In contrast to the RGP lenses, the all three study lenses induced a negative shift in spherical aberration compared to the uncorrected data in the contact lens group. This alteration in spherical aberration is most likely to be due to an inherent correction for positive spherical aberration, which is a design feature typically used for fitting soft lenses to highly irregular corneas. The amount of negative spherical induced will be dependent on the lens spherical power and asphericity (corneal p-value). A similar trend was also found in the spectacle-wearing patients, but to a lesser extent. This difference between patient groups is likely to be due to differences in sample size. The residual spherical aberration values measured with the standard toric soft lenses (n = 22) and the 50 % coma correction lenses (n = 18) were found to be significantly correlated with the low-contrast acuities achieved. On careful inspection of the data, it was evident that the low-contrast acuity scores measured with either the standard lenses or the 50 % lenses were best for low levels of spherical aberration (of around zero) and any increase in spherical aberration (in either a positive or negative direction) reduced the acuity levels. This finding is in line with previous studies that show that high levels of ocular aberrations reduce visual acuity (Applegate et al., 2002, Applegate et al., 2003a, Rocha et al., 2007, Li et al., 2009).

The results presented also show significant correlations between 3rd-order coma RMS aberrations and the resultant low-contrast acuities measured with both the standard lenses (n = 22) and the 50 % coma correction lenses (n = 18). However, no significant correlations were found for the corresponding high-contrast acuity scores. These results suggest that the residual coma aberrations left uncorrected by the standard toric lenses and the 50 % lenses may have a more destructive influence on low-contrast acuity than on high-contrast acuity in patients with keratoconus. These results corroborate with the findings of a study of 11 normal eyes, where high-contrast acuity, low-contrast acuity and ocular aberrations were evaluated with and without coma aberration-inducing soft contact lenses in place (Fernández-Sánchez et al., 2008).

Other factors that may be responsible for the poor visual performance measured with the customised lenses include limitations in the accuracy of measuring ocular aberrations in patients with keratoconus, and even perhaps inaccuracies in reproducing the desired aberration correction onto the customised lenses. It is plausible that computational errors may have occurred whilst measuring the residual aberrations with the standard soft toric lenses in these keratoconic patients (Thibos, 2000, Yoon et al., 2004b, Katsoulos et al., 2009, Jinabhai et al., 2011b). The higher-order aberrations measured using the IRX-3 device in these keratoconic patients, especially the measurements of coma and higher-order RMS aberrations, showed a large degree of variability (as demonstrated by the large standard error bars in Figure 9.2, Figure 9.3 and Figure 9.4). Moreover, the substantial residual sphero-cylindrical refractive errors, measured by the IRX-3 with all three soft lenses in place, were not verified in the subjective ORs performed for each patient. These ORs, in the vast majority of cases, revealed only minor alterations in spherical power in order to maximise visual performance. These differences are most likely to be due to the inability of the Hartmann–Shack wavefront sensor to measure highly-aberrated eyes (Thibos, 2000). Several authors have previously acknowledged that errors may arise at the sensor in patients with keratoconus due to overlapping spot images, spot image crossover or even missing spots (Thibos
and Hong, 1999, Munson et al., 2001, Thibos and Applegate, 2001, Yoon et al., 2004b, Katsoulos et al., 2009, Jinabhai et al., 2011b) and scatter (Mihashi et al., 2006a). Such computational errors may have caused an underestimation or overestimation of the residual wavefront errors measured with contact lenses in place (Katsoulos et al., 2009, Jinabhai et al., 2010a). Alternative techniques, such as high-dynamic range Hartmann-Shack wavefront sensors (Pantanelli et al., 2007) or laser-ray tracing methods (Navarro and Moreno-Barriuso, 1999, Moreno-Barriuso and Navarro, 2000) may provide less variable data in patients with keratoconus.

The residual aberrations measured with the standard soft toric lenses were used to design the aberration-controlling lenses. Therefore, any miscalculations in the magnitude of these residual aberrations may have led to inaccuracies in determining the magnitude of the aberration correction of the final customised lenses, thereby possibly inducing a reduction in visual performance. In support of this theory, previous studies have revealed significant corrections between high-contrast (Jinabhai et al., 2012a) and low-contrast acuity (Okamoto et al., 2008, Jinabhai et al., 2012a) and 3rd-order RMS aberrations in patients with keratoconus, where patients with the highest aberrations achieved the poorest acuity scores. Similarly, upon examining the individual Zernike coefficients measured with the customised lenses, it was apparent that the 100 % lenses, on average, tended to overcorrect vertical coma from an initially negative value (uncorrected) to a positive value in either patient group. A similar trend, but to a lesser extent, was also found for the 50 % lenses, with the results revealing residual vertical coma values which were substantially more positive than the expected values (which, in principle, would have equated to approximately half the uncorrected magnitudes of vertical coma). These findings perhaps indicate that the precision required to produce such customised lenses is not yet possible using the current techniques employed to manufacture these customised lenses.

Although the higher-order aberrations of each customised lens were verified using the ClearWave device, any small lens misalignments during the measurement process would have induced superfluous lower-order and higher-order aberrations (Guirao et al., 2001, Guirao et al., 2002a, López-Gil et al., 2002, de Brabander et al., 2003, Thibos et al., 2003b, López-Gil et al., 2009a), thereby causing variations between the design specified aberration values and the ClearWave measurements.

The inducement of unwanted aberrations is also likely to occur with small translational and rotational movements upon blinking when the lenses are applied on-eye. Terry et al. (1993) have previously shown that small lens movements are necessary to allow some tear exchange underneath the lens which ultimately supplies the cornea with essential lubrication and nutrients. Depending on their magnitude, as well as the eye’s inherent aberrations, these induced aberrations may either enhance or reduce the effectiveness of the correction (Bara et al., 2000, Guirao et al., 2001, Guirao et al., 2002a, López-Gil et al., 2009a). The literature indicates that aberrations induced by the rotation or translation of an ‘ideal’ aberration correction are proportional to the amount of displacement as well the magnitude of the original, displaced aberration (Guirao et al., 2001, de Brabander et al., 2003, Kollbaum and Bradley, 2007, Kollbaum et al., 2008). The exact effects will also depend upon the pupil diameter analysed.

Previous studies report that horizontal and vertical translations typically induce more residual aberration compared to rotational movements, thereby causing larger degradations in optical image quality (Guirao et al., 2001, Guirao et al., 2002a, Kollbaum and Bradley, 2007,
Rotational movements of an ‘ideal’ correction will induce residual aberration of the opposite meridional frequency (Guirao et al., 2001, Guirao et al., 2002a, Kollbaum and Bradley, 2007, Lundstrom and Unsbo, 2007, Kollbaum et al., 2008), i.e. rotating 3rd-order vertical coma aberration \( (Z(3, -1)) \) will induce 3rd-order horizontal coma aberration \( (Z(3, +1)) \). On the other hand, translation of a given Zernike coefficient term will induce residual aberration, diagonally up the Zernike pyramid, of one order lower than the original term.

For example, translating 4th-order spherical aberration \( (Z(4, 0)) \) induces either horizontal or vertical 3rd-order coma aberration depending on the direction of translation (Guirao et al., 2001, Kollbaum and Bradley, 2007, Kollbaum et al., 2008). Equally, it is expected that translating either 3rd-order vertical or horizontal coma will induce superfluous 2nd-order defocus and cylinder aberration, which may potentially reduce visual performance. To help overcome the potentially destructive influence of ‘ideal’ lens decentrations, Guirao and co-workers (2002a) suggested that correcting only a limited number of Zernike coefficient terms can yield more beneficial results compared to correcting every single higher-order term. Similarly, de Brabander et al. (2003) reported that decentration of a partial correction of wavefront aberrations will still yield a more useful visual benefit than a conventional sphero-cylindrical correction. This approach has been successfully demonstrated by Katsoulos et al. (2009). In support of de Brabander et al.’s (2003) study, our results reveal that the 50 % lenses yielded slightly lower coma RMS, 3rd-order RMS and higher-order RMS aberrations than the 100 % lenses. However, the 50 % lenses provided only slightly better visual performance results compared to the 100 % lenses.

The residual coma aberrations measured with the customised lenses on-eye may either be linked to some inaccuracies in the customised lens design and manufacturing process, or could be a result of small lens movements on-eye (Guirao et al., 2001, Kollbaum et al., 2008). Due to their optical design, all three study lenses showed an inherent level of negative spherical aberration. Both Guirao et al. (2001) and Kollbaum et al. (2008) have previously suggested that decentring a lens containing negative spherical aberration will induce negative coma aberrations.

In agreement with previous studies of soft contact lenses for patients with keratoconus (Jeong and Yoon, 2006, Chen et al., 2007b, Sabesan et al., 2007b, López-Gil et al., 2009a), we found that small amounts of rotation and translation were unavoidable with both the standard and customised soft lenses in a few patients owing to the irregularity of the corneal profile. During the initial fitting process, the best fitting Plano trial lens was chosen for each patient to ensure that the toric alignment marker was correctly positioned and remained relatively stable during blinks. For all participants, the maximum lens rotations in the primary position with the standard soft toric lenses were found to be 5 degrees or less (found in only four out of the 22 patients evaluated). However, the manufacturers appropriately adjusted the final contact lens powers in order to compensate for these rotations. The contact lens coverage, centration and movement measurements recorded suggested that the standard toric and customised soft lens fittings achieved in this report were clinically acceptable for all the cases presented. However, it is expected that translation of the customised lenses with blinks will induce unwanted 2nd-order and 3rd-order aberrations, which may have led to the reduction in visual performance measured in this report.

The literature suggests that the human brain is likely to be adapted to its own particular pattern of higher-order aberrations in both visually-normal subjects (Artal et al., 2004, Chen et al.,
2007a) and keratoconus patients (Sabesan and Yoon, 2009, Sabesan and Yoon, 2010). Sabesan and Yoon (2009) used a deformable mirror to correct the manifest higher-order aberrations of 8 normal subjects and 8 keratoconic patients. The authors found that visual performance was significantly worse in the keratoconic patients even with an equivalent ‘near-diffraction-limited’ optical quality in both groups. The authors concluded that long-term visual experience with poor retinal image quality, induced by higher-order aberrations, may restrict the visual benefit achievable with higher-order aberration correction in patients with keratoconus. In a subsequent study, Sabesan and Yoon (2010) also reported that 4 keratoconic eyes achieved better high-contrast and low-contrast acuities (by approximately 1.2 lines), compared to 3 normal subjects who viewed the same targets (tumbling ‘E’ letters) through each of the 4 keratoconic patients wavefront aberration patterns (the aberration patterns were induced for the normal subjects using a deformable mirror). The authors hypothesised that in keratoconic eyes, the visual neural system may compensate for long-term visual experience to an asymmetrically blurred retinal image, thereby resulting in an improved visual performance compared to normal subjects. Therefore, the poor visual performance achieved with the customised lenses in the present study, even though 3rd-order coma RMS aberrations were well corrected, may perhaps be attributed to some level of neural adaptation in both groups of keratoconic patients. At present, however, the time required to reverse any adaptations to ocular aberrations is unknown (Artal et al., 2004, Chen et al., 2007a). As the customised lenses were not worn for more than an hour each, it is likely that the patients’ neural system did not have enough time to adapt to the altered point-spread function patterns (produced by the customised lenses) falling on the retina. On average, the vertical coma coefficient terms measured with the patient’s habitual RGP lenses (+0.39 ± 0.14 µm [±1 SD]) were most closely matched by the 100 % lenses (+0.18 ± 0.39 µm), compared to the 50 % lenses (-0.17 ± 0.30 µm); however on average, the 100 % lenses provided poorer high-contrast acuity, low-contrast acuity and SKILL card scores compared with the 50 % lenses.

Another factor perhaps influencing the visual performance achieved with the aberration-controlling lenses could be related to the diameter of customised optical zone. The customised lenses were each designed for a 4-mm pupil diameter, as this pupil size was the largest pupil diameter common to all 22 patients whilst recording higher-order aberrations. Therefore, the same pupil diameter was used for each patient to enable comparisons between groups. However, the average pupil size measured whilst evaluating high-contrast and low-contrast logMAR acuity was found to be 4.3 ± 0.4 [±1 SD] mm. This highlights a major limitation for customised lenses, in that the optimal correction of aberrations is only possible at a single pupil size (Charman and Chateau, 2003, Thibos et al., 2003b). To overcome this issue, future studies should aim to produce customised lenses with a pupil size bespoke to each individual patient.

It is unlikely that the measured reductions in low-contrast acuity, compared to the patient's habitual correction, occurred due to corneal oedema or hypoxia, as the standard and customised soft lenses were only worn for approximately 1 hour each. Equally, the patient’s RGP lenses were left out overnight before either soft lens collection appointment. However, a possible factor which may have contributed to these findings is a reduction in the quality of the tear film due to soft contact lens wear (Kopf et al., 2008, Alonso-Caneiro et al., 2009). It is plausible that, between blinks, high-water content hydrogel lenses rapidly dehydrate causing increased forward light
scattering (Lohmann et al., 1993, Thai et al., 2002). This scattered light may potentially act as a veiling luminance, thereby reducing the contrast of the image formed at the retina (Kirkpatrick and Roggenkamp, 1985, Ridder and Tomlinson, 1991, Timberlake et al., 1992). Previous studies have also established that the tear film in keratoconic patient’s exhibits significantly elevated amounts of inflammatory mediators compared to in normal control subjects (Dogru et al., 2003, Lema et al., 2008, Lema et al., 2009b). The optical effect of this altered tear chemistry remains unexplored at present; however it could influence the surface wettability of soft contact lenses thereby impacting on visual performance.

A potential limitation of this investigation is that the RGP lenses worn by the 16 contact lens-wearing patients were made of different materials and designs. Similarly, the patients were heterogeneous in terms of their duration of disease and RGP lens wear experience. In addition, RGP lens and soft lens movements, whilst recording the ocular aberrations, may have influenced the measurements. However, to minimise the possibility of contact lens movements confounding the results, the IRX-3 device was kept aligned with the eye as far as possible and we believe that this had minimal influence on the results.

The present study was designed to evaluate the performance of standard and customised soft lenses for patients with keratoconus using a research protocol and contact lens-fitting strategy which allowed comparisons between patients. In clinical practice however, it is likely that the soft contact lens fitting, refractive prescription and magnitude of aberration correction may need to be optimised on a case-by-case basis to maximise visual performance when refitting keratoconus patients with soft lenses from RGP lenses.

As the numbers of mild and severe patients investigated were substantially lower than the number of moderate cases evaluated, the present study cannot fully predict the usefulness of standard toric and customised soft lenses at each of the different stages of keratoconus. Therefore additional investigations of the visual and optical performance of standard toric and customised soft lenses in the earlier stages of keratoconus are perhaps warranted. In support of this, our results reveal significant correlations between the steep keratometric readings and both the high-contrast and low-contrast visual acuity scores achieved with the standard toric soft lenses and both customised lenses. These results may imply that patients with less advanced disease would achieve the best visual performance using either standard toric or customised soft lenses compared to more advanced cases. Our results agree with the findings of Koliopoulos and Tragakis (1981), who reported that 28 out of 57 keratoconic eyes with steep average corneal curvatures (of 52.1 D and above), achieved visual acuities of 6/20 or worse, when fitted with spherical soft lenses. In contrast, the authors found that 30 out of 39 keratoconic eyes with flatter curvatures in the steep meridian (between 42 and 52 D), achieved visual acuities of 6/8.5 or better when fitted with spherical soft lenses. Equally, Katsoulos et al. (2009) reported improvement in both high-contrast and low-contrast acuity with customised coma-correcting lenses in patients with mild to moderate keratoconus.

In conclusion, this investigation shows that the two customised lenses substantially reduced uncorrected coma RMS and higher-order RMS aberrations in both groups of keratoconic patients evaluated. However, the visual performance measured with the patient’s habitual RGP lenses was
found to be better than with either customised lens in the contact lens group. In the spectacle-wearing patients, no significant differences were found between the visual performances measured with the patient’s habitual spectacles, the standard soft toric lenses or the two customised lenses. The results indicate that keratoconic patients with less advanced disease may achieve better visual performance with customised lenses compared to those with severe keratoconus.
10. Modelling Lower-order and Higher-order Aberrations Using Customised Corrections in Keratoconus

Contributions
I designed this investigation with helpful contributions from my co-authors W. Neil Charman (WNC), Hema Radhakrishnan (HR) and Clare O’Donnell (COD). I completed all of the modelling and statistical analyses with useful input from WNC. I wrote the scientific manuscript and this thesis chapter with valuable comments from WNC, HR and COD.

Publications submitted

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10.1 Abstract

10.1.1 Background: This investigation theoretically explores the limitations of ‘ideal’ aberration-controlling contact lens corrections in 3 patients with keratoconus.

10.1.2 Methods and materials: Ocular aberrations were measured with and without each patient’s habitual rigid gas-permeable lenses using a Hartmann-Shack aberrometer. Customised lens corrections were calculated for each patient’s uncorrected wavefront aberrations. Higher-order and lower-order aberrations induced by decentring these customised corrections were modelled using MatLab (Mathworks, Natick, MA, US). Rotations were evaluated up to 15 degrees and translations up to 1 mm both horizontally and vertically.

10.1.3 Results: Rotations and translations induced both higher-order and lower-order residual aberrations. Vertical translations induced the largest residual higher-order root-mean-square (RMS) aberrations (up to 0.50 µm) and 2nd-order RMS aberrations (up to 4.80 D), followed by horizontal translations and rotations respectively. As expected, the residual higher-order and lower-order aberrations were found to be largest for the patient with severe keratoconus.

10.1.4 Conclusions: The results suggest that minimising the decentration of aberration-controlling contact lenses, to less than 5 degrees of rotation and 0.50 mm of translation, will help to achieve an optimal higher-order aberration correction, where residual RMS errors are likely to be less than 0.15 µm. However, more stringent criteria are required for lower-order aberrations, where rotational displacements should be reduced to less than 3 degrees and translational displacements should be limited to less than 0.10 mm.
10.2 Introduction

The human eye experiences a multitude of optical imperfections which degrade visual quality, including scatter, reflection, chromatic aberration, lower-order (i.e. spherocylindrical refractive errors) and higher-order monochromatic aberrations. These defects play a crucial role in imposing a limit on the eye’s visual quality (Charman, 1995). The literature shows that higher-order monochromatic aberrations have a significant impact on retinal image quality, particularly for eyes with a large pupil diameter (Artal and Navarro, 1994, Liang and Williams, 1997) and in cases of corneal abnormality, such as keratoconus (Negishi et al., 2007, Okamoto et al., 2008, Jinabhai et al., 2009, Jinabhai et al., 2010a). Several authors report that aberrations from the 3rd to 5th Zernike order are significantly larger in keratoconic eyes compared to normal control subjects (Barbero et al., 2002, Maeda et al., 2002, Gobbe and Guillot, 2005, Bühren et al., 2007, Lim et al., 2007). These studies all agree that the magnitudes of 3rd-order coma and trefoil aberrations are the most significantly affected.

Since the introduction of the Hartmann-Shack aberrometer, and other similar devices which allow rapid measurements of a patient’s ocular wavefront aberrations in a clinical setting, researchers have attempted to measure, evaluate and correct the higher-order aberrations of the eye in the hope of improving visual quality (Liang et al., 1997, Charman, 2005a). Ideally, by enhancing the optics of the eye it may be possible to improve vision up to the eye’s spatial resolution limit, which is governed purely by the diffraction-limited optical quality or the pupil size in use and the spacing between the photoreceptors at the macula.

In principle, modern day methods of correcting both higher-order and lower-order aberrations include corneal refractive laser surgery (Mrochen et al., 2000b), intra-ocular lens implants (Holladay et al., 2002), adaptive optics (Liang et al., 1997) and customised contact lenses (López-Gil et al., 2003, Marsack et al., 2007a, Sabesan et al., 2007b, Katsoulos et al., 2009). Corneal refractive surgery is a non-reversible treatment and is usually prohibited in subjects with keratoconus. Similarly, IOL implants are also non-reversible and require invasive surgery. Adaptive optics devices are still essentially for laboratory rather than everyday use. Aberration-controlling customised contact lenses, on the other hand, could yet prove to be a useful form of correction, as these are portable, reversible, cosmetically acceptable and may be worn in conditions such as keratoconus. However, compared to the adaptive optics or corneal refractive surgery methods, a major disadvantage of a contact lens is the necessary requirement of small lens movements to allow suitable tear exchange underneath the lens which ultimately supplies the cornea with essential lubrication and nutrients (Terry et al., 1993). Unfortunately, as the ‘ideal’ correcting lens becomes displaced, its movement will induce additional, superfluous higher-order (Cox, 1990, Guirao et al., 2002a, López-Gil et al., 2002, de Brabander et al., 2003, Thibos et al., 2003b, López-Gil et al., 2009a) and lower-order aberrations (Bara et al., 2000, Guirao et al., 2001). Depending on their magnitude, as well as the eyes inherent aberrations, these induced aberrations may either enhance or reduce the effectiveness of the correction (Bara et al., 2000, Guirao et al., 2001, Guirao et al., 2002a, López-Gil et al., 2009a). Previous studies evaluating such ‘ideal’ lens displacements report that horizontal and vertical translations typically induce more residual aberration compared to rotational movements, thereby causing larger degradations in optical image quality (Guirao et al., 2001, Guirao et al., 2002a, Kollbaum and Bradley, 2007, Kollbaum et al., 2008, López-Gil et al.,
However, Guirao et al. (2001) explain that not every coefficient term in a given Zernike order produces the same amount of residual aberration. For instance, terms with equal meridional and angular frequencies are less sensitive to translation (although they are more sensitive to rotation). The literature also shows that rotational movements of an ideal correction induce aberrations of the opposite meridional frequency (Guirao et al., 2001, Guirao et al., 2002a, Kollbaum and Bradley, 2007, Lundstrom and Unsbo, 2007, Kollbaum et al., 2008), i.e. rotating 3rd-order vertical coma aberration ($Z(3,-1)$) will induce 3rd-order horizontal coma aberration ($Z(3,+1)$).

On the other hand, translation of a given Zernike coefficient term will induce residual aberration, diagonally up the Zernike pyramid, of one order lower than the original term. For example, translating 4th-order spherical aberration ($Z(4,0)$) induces 3rd-order coma aberration (Guirao et al., 2001, Kollbaum and Bradley, 2007, Kollbaum et al., 2008). Kollbaum and Bradley (2007) explain that the magnitude of the decentred spherical aberration remains unchanged despite the inducement of superfluous coma aberration. The authors discovered that if a lens containing 4th-order spherical aberration translates by 0.5 mm, an amount of coma approximately equivalent to the amount of spherical aberration is induced. However, if the lens is translated by 1 mm, a magnitude of coma approximately equal to twice the level of spherical aberration is induced.

Several studies have revealed that aberrations induced by the rotation or translation of an ‘ideal’ aberration correction are proportional to the amount of displacement as well as the magnitude of the original, displaced aberration (Guirao et al., 2001, de Brabander et al., 2003, Kollbaum and Bradley, 2007, Kollbaum et al., 2008). The exact effects will also depend upon the pupil diameter analysed. To help overcome the potentially destructive influence of lens decentrations, previous authors have suggested that correcting only a limited number of Zernike coefficient terms can yield more beneficial results compared to correcting every single higher-order term (Guirao et al., 2001, Guirao et al., 2002a). This approach has been successfully demonstrated by Katsoulos et al. (2009), who implemented a 75% correction of the manifest negative vertical coma aberrations measured using a Hartmann-Shack aberrometer.

The aim of this investigation was to explore, theoretically, the limitations of an ‘ideal’ aberration-controlling correction in three real patients with varying degrees of keratoconus. In order to avoid tear lens effects, we assumed the aberration corrections were applied to soft contact lens materials, so that the ‘on-eye’ lens aberrations are equal to the ‘off-eye’ values. Specifically, this study models how the correction of ocular aberrations becomes affected when an ‘ideal’ aberration correction either rotates or decentres (analogous to lens movements typically observed between blinks or with eye movements in toric soft lens wearers). Potential changes in optical quality with lens decentrations will be evaluated using point spread function (PSF) images and wavefront aberration maps. The literature reports that translations of between 0.04 mm (Tomlinson and Bibby, 1980) and 2.5 mm (Tomlinson et al., 1994), as well as rotations of between 3 degrees (López-Gil et al., 2009a) and 15 degrees (Tomlinson et al., 1994), characteristically occur during blinking whilst wearing prism-ballasted toric soft contact lenses. To date, no studies have reported the expected increase in 2nd-order aberrations induced by decentring a contact lens containing a correction for 3rd-order aberrations.

In this investigation rotations and translations were considered independently of each other in order to evaluate which of these two types of dynamic movement induced the largest
aberrations. The outcomes of this investigation could provide valuable information in evaluating the effectiveness of producing and fitting aberration-controlling contact lenses for eyes with keratoconus.

10.3 Methods and materials

Three patients (average age 30 ± 6 years) with different degrees of keratoconus participated in this investigation; these patients were recruited from the contact lens clinics at Manchester Royal Eye Hospital. All three patients had previously been diagnosed with bilateral keratoconus and habitually wore rigid gas permeable (RGP) contact lenses. The study followed the tenets of the Declaration of Helsinki. All patients gave their informed consent after being told the purpose of the investigation. The study protocol was approved by the National Health Service Research Ethics Committee.

Baseline logMAR visual acuity measurements were taken for each patient with their habitual contact lenses in place. The patients were then instructed to remove their lenses. A slit-lamp examination of the patient’s external eye was conducted, recording the presence or absence of Fleischer’s ring and Vogt’s striae. None of the patients evaluated showed corneal scarring detectable upon slit-lamp examination.

The Oculus Pentacam (Oculus, Wetzlar, Germany) was used to measure each patient’s keratometric readings and corneal thickness. Topographic data from the Pentacam were also acquired. The rotating Scheimpflug camera provides 25 images during a one-second scan, with 500 true elevation points per image. During measurements the patients positioned their chins on the chin-rest and their foreheads against the head support bar, while fixing on the central black circle against the blue LED slit light (475 nm). Four repeated measurements were made for each patient under monocular conditions with the room illumination switched off. The mean of the four measurements were used for analysis. The severity of the patients’ keratoconus was graded using the CLEK study group’s criteria, where steep keratometric readings less than 45 D were graded as mild keratoconus, steep keratometric readings between 45 and 52 D were moderate keratoconus and finally steep keratometric readings greater than 52 D were graded as severe keratoconus (Zadnik et al., 1996). The three patients studied included single examples of mild, moderate and severe keratoconus.

Following this, ocular wavefront aberrations were measured using a Hartmann-Shack aberrometer (IRX-3; Imagine Eyes, Paris, France). The IRX-3 device uses a 32 × 32 lenslet array and near infra-red light with a wavelength of 780 nm. The wavefront errors were recorded under monocular conditions with the room illumination switched off. The instrument records pupil diameter at the same time as the wavefront aberrations and uses a dynamic fogging method to relax accommodation to the far point of the eye. All recordings were made using the instrument’s internal fixation stimulus, a black 6/12 sized Snellen letter ‘E’ in an elliptical white background field subtending approximately 0.7 × 1.0° and having a luminance of about 85 cd/m². Four repeated monocular measurements were made for all three patients. The Zernike coefficients for each of the four measurements were then averaged. All aberrations were calculated up to the 5th Zernike order for a 6-mm pupil diameter (the largest pupil size common to all three patients), using the
IRX-3 device’s software (version 1.2, Imagine Eyes). The captured aberrometry data were exported and analysed using Microsoft Excel (version 2003; Microsoft Corp., Redmond, WA, U.S.) and MatLab (version 7.6.0.324; The Mathworks, Natick, MA, US).

The wavefront aberrations of each patient’s eye, \( WFA_{\text{EYE}} \), were described as a combination of Zernike polynomials, \( Z_n^{\pm m} \) (Thibos et al., 2000), up to the 5th-order over both a 6-mm pupil and a condensed pupil diameter of 4 mm with coefficients \( (A_n^{\pm m}) \):

**Equation 10.1**

\[
WFA_{\text{EYE}}(\rho, \theta) = \sum_{n, \pm m} A_n^{\pm m} Z_n^{\pm m}(\rho, \theta)
\]

where \( \rho \) and \( \theta \) are the radial and Azimuthal coordinates respectively (Table 10.1). For each patient assessed, an ‘ideal’ aberration-controlling correction (ACC) which would completely correct each patient’s wave aberrations when perfectly aligned with the patient’s eye, was also evaluated for a 4-mm circular zone (Figure 10.1). It was also assumed that, when not rotated or translated, the wavefront aberration of this ‘ideal’ correction would partially correct the eye over the full 6-mm pupil diameter for which the original wavefront error was evaluated.

**Equation 10.2**

\[
WFA_{\text{ACC}}(\rho, \theta) = - \sum_{n, \pm m} A_n^{\pm m} Z_n^{\pm m}(\rho, \theta)
\]

The residual aberration when the ideal correction is applied to the eye with a rotation or translation, with respect to the pupil centre, was also considered for a 4-mm circular zone (Figure 10.1).

**Equation 10.3**

\[
WFA_{\text{residual}} = WFA_{\text{EYE}} + WFA_{\text{ACC}} \text{(translated or rotated)} = \sum_{n, \pm m} A_n^{\pm m} Z_n^{\pm m}(\rho, \theta) - \sum_{n, \pm m} C_n^{\pm m} Z_n^{\pm m}(\rho, \theta)
\]

As outlined by Guirao et al. (2001), the Zernike coefficients \( C_n^{\pm m} \) represent the translated or rotated versions of the aberration coefficients for the ideal aberration correction. The WFA ACC (translated or rotated) was derived by considering a 4-mm diameter circular section of the original wavefront aberrations (6-mm diameter) at the pupil centre, and then applying either a rotation or translation of the required magnitude (Guirao et al., 2001, Lundstrom and Unsbo, 2007). As translations of up to 1 mm were evaluated both horizontally and vertically, evaluation of a central 4-mm circular zone meant that the translated movements did not fall outside of the original pupil diameter of 6 mm.

This model assumes that the ideal correction is conjugate to the patient’s pupil plane; however, in reality this aberration correction would be conjugate with the corneal plane in the form of a contact lens. With this in mind, some small additional compensation would need to be made in order to account for the shift from the pupil plane to the anterior corneal plane.

Guirao et al. (2001) also outlined that introducing a change in the pupil co-ordinates

**Equation 10.4**

\[
\begin{align*}
x' &= (x - \Delta x) \cos \alpha + (y - \Delta y) \sin \alpha, \\
y' &= (y - \Delta y) \cos \alpha - (x - \Delta x) \sin \alpha,
\end{align*}
\]
where \( \alpha \) is the angle of rotation and \( \Delta x, \Delta y \) are translations along the X- and Y-axis respectively) of the monomial representations of each Zernike polynomial (Table 10.1), allows the WFA ACC (translated or rotated) to be expressed in a new Zernike expansion after rearranging the terms. The coefficients \( (C_i) \) of the new expansion are systematically obtained from the original coefficients \( (A_k) \) using the matrix product:

\[
C_i = \sum_{j,k} T_{ij} R_{jk} A_k
\]

Equation 10.5 from Guirao et al. (2001)

where \([T]\) and \([R]\) are the matrices for rotation and translation respectively (Guirao et al., 2001). Hence the coefficients for the residual WFA are

\[
(1 - T_{ij} R_{jk}) A_k
\]

Equation 10.6 from Guirao et al. (2001)

### Table 10.1
A description of Zernike coefficient terms represented in polynomial and monomial formats from the 3rd-order to the 5th-order.

<table>
<thead>
<tr>
<th>Radial order (n)</th>
<th>Frequency (m)</th>
<th>Name</th>
<th>Zernike polynomial</th>
<th>Monomial representation</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>-3</td>
<td>Oblique trefoil</td>
<td>( \sqrt{8}p^3\sin(3\theta) )</td>
<td>( \sqrt{8}(3x^2y-y^3) )</td>
</tr>
<tr>
<td>3</td>
<td>-1</td>
<td>Vertical coma</td>
<td>( \sqrt{8}(3p^3-2p)\sin(\theta) )</td>
<td>( \sqrt{8}(3x^2y+3y^3-2y) )</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>Horizontal coma</td>
<td>( \sqrt{8}(3p^3-2p)\cos(\theta) )</td>
<td>( \sqrt{8}(3x^3+3xy^2-2x) )</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>Regular trefoil</td>
<td>( \sqrt{8}p^3\cos(3\theta) )</td>
<td>( \sqrt{8}(x^3-3xy^2) )</td>
</tr>
<tr>
<td>4</td>
<td>-4</td>
<td>Oblique quadrafoil</td>
<td>( \sqrt{10}p^4\sin(4\theta) )</td>
<td>( \sqrt{10}(4x^3y-4xy^2) )</td>
</tr>
<tr>
<td>4</td>
<td>-2</td>
<td>Oblique secondary astigmatism</td>
<td>( \sqrt{10}(4p^4-3p^2)\sin(2\theta) )</td>
<td>( \sqrt{10}(8x^3y+8xy^3-6xy) )</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>Spherical aberration</td>
<td>( \sqrt{5}(6p^4-6p^2+1) )</td>
<td>( \sqrt{5}(6x^4+12x^2y^2+6y^4-6x^2-6y^2+1) )</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>Regular secondary astigmatism</td>
<td>( \sqrt{10}(4p^4-3p^2)\cos(2\theta) )</td>
<td>( \sqrt{10}(4x^4+4x^2y^2-4x^2y^2-4y^4+3y^2) )</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>Regular quadrafoil</td>
<td>( \sqrt{10}p^4\cos(4\theta) )</td>
<td>( \sqrt{10}(x^4-6x^2y^2+y^4) )</td>
</tr>
<tr>
<td>5</td>
<td>-5</td>
<td>Oblique pentfoil</td>
<td>( \sqrt{12}p^5\sin(5\theta) )</td>
<td>( \sqrt{12}(5x^5y-10x^3y^2+y^3) )</td>
</tr>
<tr>
<td>5</td>
<td>-3</td>
<td>Oblique secondary trefoil</td>
<td>( \sqrt{12}(5p^5-4p^3)\sin(3\theta) )</td>
<td>( \sqrt{12}(15x^5y+10x^3y^2-12x^2y^3+5x^3y^3+4y^5) )</td>
</tr>
<tr>
<td>5</td>
<td>-1</td>
<td>Secondary vertical coma</td>
<td>( \sqrt{12}(10p^5-12p^3+3p)\sin(\theta) )</td>
<td>( \sqrt{12}(10x^5y+20x^3y^3+10y^5-12x^2y^3+3y) )</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>Secondary horizontal coma</td>
<td>( \sqrt{12}(10p^5-12p^3+3p)\cos(\theta) )</td>
<td>( \sqrt{12}(10x^5y+20x^3y^3+10xy^5-12x^2y^3+3x) )</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>Regular secondary trefoil</td>
<td>( \sqrt{12}(5p^5-4p^3)\cos(3\theta) )</td>
<td>( \sqrt{12}(5x^5-4x^3-10x^3y^2-15xy^4-12xy^4) )</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>Regular pentafoil</td>
<td>( \sqrt{12}p^5\cos(5\theta) )</td>
<td>( \sqrt{12}(x^5-10x^3y^2+5xy^3) )</td>
</tr>
</tbody>
</table>
10.4 Results

10.4.1 Corneal profile and aberrometry data

Table 10.2 summarises the corneal parameters, visual acuities and ocular higher-order aberrations measured with and without RGP lenses for each keratoconic patient’s right eye. Slit-lamp examinations found that all three patients displayed Fleischer’s ring, with the moderate and severe cases also showing Vogt’s striae. None of the patients showed any apical scarring.

In line with the literature, all three patients showed abnormally large magnitudes of vertical coma aberration. The patient with severe keratoconus also showed a large magnitude of oblique trefoil. Other aberration coefficient terms made only minor contributions to the overall total higher-order root-mean-square (HORMS) wavefront error. Note too that the conventional RGP lens is quite successful in reducing the higher-order aberrations, even for the severely keratoconic eye; this emphasises the optical advantages of such lenses in the visual rehabilitation of keratoconus. A spectacle correction would not be expected to have much effect on the higher-order ocular aberrations as they provide a sphero-cylindrical correction only.
Table 10.2 A summary of the corneal parameters (Oculus Pentacam), visual acuities and higher-order aberrations (IRX-3) evaluated for each keratoconic patient. The corneal and aberration measurements shown are the mean of 4 repeated measurements. The data presented are for a 4-mm pupil diameter.
(K = keratometric reading; LogMAR = logarithm of the minimum angle of resolution; RMS = Root mean square; HORMS = higher-order RMS error).

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flat K (D)</td>
<td>41.0</td>
<td>43.8</td>
<td>47.0</td>
</tr>
<tr>
<td>Steep K (D)</td>
<td>44.2</td>
<td>47.9</td>
<td>53.1</td>
</tr>
<tr>
<td>Corneal Thickness (µm)</td>
<td>476</td>
<td>432</td>
<td>410</td>
</tr>
<tr>
<td>Visual acuity with RGP lenses</td>
<td>LogMAR scores (log units)</td>
<td>-0.10</td>
<td>0.08</td>
</tr>
<tr>
<td>Higher-order aberrations (µm)</td>
<td>RGP lens</td>
<td>No lens</td>
<td>RGP lens</td>
</tr>
<tr>
<td>Oblique trefoil</td>
<td>0.042</td>
<td>0.100</td>
<td>0.065</td>
</tr>
<tr>
<td>Vertical coma</td>
<td>0.054</td>
<td>-0.409</td>
<td>0.054</td>
</tr>
<tr>
<td>Horizontal coma</td>
<td>0.044</td>
<td>-0.025</td>
<td>0.023</td>
</tr>
<tr>
<td>Regular trefoil</td>
<td>-0.006</td>
<td>0.104</td>
<td>-0.044</td>
</tr>
<tr>
<td>3rd-order RMS error</td>
<td>0.082</td>
<td>0.434</td>
<td>0.098</td>
</tr>
<tr>
<td>Oblique tetrafoil</td>
<td>-0.004</td>
<td>-0.025</td>
<td>-0.013</td>
</tr>
<tr>
<td>Oblique secondary cylinder</td>
<td>-0.025</td>
<td>0.032</td>
<td>0.024</td>
</tr>
<tr>
<td>Spherical aberration</td>
<td>0.029</td>
<td>-0.074</td>
<td>0.052</td>
</tr>
<tr>
<td>Regular secondary cylinder</td>
<td>0.000</td>
<td>-0.018</td>
<td>-0.005</td>
</tr>
<tr>
<td>Regular tetrafoil</td>
<td>0.017</td>
<td>0.037</td>
<td>0.002</td>
</tr>
<tr>
<td>4th-order RMS error</td>
<td>0.042</td>
<td>0.093</td>
<td>0.059</td>
</tr>
<tr>
<td>Oblique pentafoil</td>
<td>-0.001</td>
<td>-0.005</td>
<td>0.000</td>
</tr>
<tr>
<td>Oblique secondary trefoil</td>
<td>-0.001</td>
<td>-0.003</td>
<td>0.000</td>
</tr>
<tr>
<td>Secondary horizontal coma</td>
<td>-0.003</td>
<td>-0.012</td>
<td>0.000</td>
</tr>
<tr>
<td>Secondary vertical coma</td>
<td>-0.001</td>
<td>0.012</td>
<td>0.001</td>
</tr>
<tr>
<td>Regular secondary trefoil</td>
<td>0.000</td>
<td>-0.006</td>
<td>0.003</td>
</tr>
<tr>
<td>Regular pentafoil</td>
<td>0.000</td>
<td>-0.005</td>
<td>0.000</td>
</tr>
<tr>
<td>5th-order RMS error</td>
<td>0.003</td>
<td>0.020</td>
<td>0.003</td>
</tr>
<tr>
<td>Total HORMS error</td>
<td>0.092</td>
<td>0.445</td>
<td>0.114</td>
</tr>
</tbody>
</table>

10.4.2 ‘Ideal’ aberration-controlling corrections

Figure 10.2 shows the higher-order (from the 3rd to the 5th order) wavefront aberration maps generated for each keratoconic patient’s uncorrected eye and the maps for the ‘ideal’ aberration correction required to correct each eye’s aberrations.
Figure 10.2 The higher-order wavefront aberration maps for each uncorrected keratoconic patient’s right eye (left-hand images) plus the eye’s ‘ideal’ higher-order aberration-controlling correction (central images) results in the formation of ‘ideal’ planar wavefronts (right-hand images) when each correction is perfectly aligned. Each wavefront map represents the aberrations from the 3rd- to the 5th-order and includes a sphero-cylindrical correction. All aberrations were calculated using a 4-mm pupil diameter. The darker colours represent negative aberrations, whereas the lighter colours represent positive aberrations. The scale bar shown is in microns. The mild keratoconic patient’s data are displayed across the top row, the moderate patient’s data across the middle row and the severe patient’s data across the bottom row.

Figure 10.3 displays the monochromatic point-spread function (PSF) images for each patient’s uncorrected eye and the diffraction-limited functions generated when all the higher-order aberrations have been corrected using a perfectly aligned, ‘ideal’ aberration correction (diffraction-limited Airy disk). Note the relatively blurred, comatic form of the uncorrected PSF in comparison with the Airy disk of the corrected PSF.
Figure 10.3 The point spread function (PSF) images for each keratoconic patient’s uncorrected eye and the PSF images generated when all the higher-order aberrations have been fully corrected using a perfectly aligned ‘ideal’ aberration-controlling correction. The mild patient’s functions are shown in the upper images, the moderate patient’s functions in the middle images and the severe patient’s PSFs in the lower images. All functions were calculated for a 4-mm pupil diameter from the 3rd to the 5th Zernike order.

10.4.3 Rotational displacements

Figure 10.4 A) to D) display the residual higher-order wavefront aberration maps and PSFs generated for each patient by rotating an ideal aberration correction, from the ‘correctly aligned’ position, in a clockwise direction, by 1, 5, 10 and 15 degrees respectively. Rotations of up to 5 degrees produce little degradation in the PSF for the mild and moderate keratoconic eyes but there is noticeable blurring for the eye with severe keratoconus when the rotation is 5 degrees. For the 10 and 15 degree rotations, considerable magnitudes of positive coma are induced in all three cases, the largest magnitude of which was seen for the severe case: this induced coma is predominantly horizontal whereas the original, uncorrected coma was predominantly vertical. However, a comparison of Figure 10.4 D) with Figure 10.3 suggests that, even with the 15 degree rotation of the customised correction, the PSF is always less aberrated than in the original, uncorrected eye.
Figure 10.4 The residual higher-order wavefront aberration maps (upper) and PSFs (lower), generated when the ideal aberration correction is rotated from the ‘aligned’ position by 1 (A), 5 (B), 10 (C) and 15 degrees (D) in a clockwise direction for all three keratoconic patients. Each wavefront map represents the aberrations from the 3rd- to the 5th-order and includes a sphero-cylindrical correction. All aberrations were calculated using a 4-mm pupil diameter. The darker colours represent negative aberrations, whereas the lighter colours represent positive aberrations. The scale bar shown is in microns. The left hand images display the aberrations induced for the mild keratoconic patient, the central images for the moderate keratoconic patient and the right-hand images for the severe keratoconic patient.
As well as considering the effects of lens rotation on the PSF, it is helpful to examine the corresponding changes in the magnitudes of the individual Zernike aberrations. Figure 10.5 shows the magnitude of the residual higher-order aberrations when rotating the ideal aberration-controlling correction in a clockwise direction by up to 15 degrees for all three patients. As the ideal correction rotates, equally small amounts of residual coma RMS and trefoil RMS aberrations were seen for the mild keratoconic patient. A similar finding was also apparent for the moderate patient, but with slightly higher coma RMS aberrations compared to trefoil RMS aberrations. In contrast, substantially larger magnitudes of both trefoil RMS and coma RMS aberrations were induced with rotation for the severe keratoconic patient. Note, however, that the uncorrected HORMS values for a 4-mm pupil diameter were 0.45, 0.60 and 1.01 microns for the mild, moderate and severe cases respectively (Table 10.2), so that even for rotations of 15 degrees the aberrations of the corrected eye were smaller than those of the uncorrected eye (or the eye when corrected with a spectacle lens).

To set the magnitude of the residual aberrations in context, the Marechal (1947) criterion suggests that the PSF is almost perfect if the wavefront aberration is less than 1/14 of a wavelength, i.e. around 0.04 microns at the middle of the visible spectrum. Figure 10.5 shows that this is almost the case for rotations up to 5 degrees for the mild and moderate cases; but not for the severe keratoconic patient. Alternatively, a criterion based on a magnitude of refractive spherical blur which gives a similar level of wavefront aberration could be used. For a 4-mm pupil diameter a wavefront aberration of about 0.144 microns corresponds to an equivalent defocus of 0.25 D. Assuming that the latter is tolerable, it can be seen that the PSF for the mild and moderate keratoconic eyes may be acceptable even if their corrections rotate through 10 degrees, whereas rotation should not exceed about 5 degrees in the severe keratoconic eye.

To summarise, Figure 10.5 shows that the largest change in the magnitude of aberrations induced by rotating an ideal correction was evident for the severe keratoconic patient. The wavefront maps and PSF images also support this finding. The severe keratoconic patient's wavefront maps showed higher magnitudes of horizontal coma and trefoil aberrations compared to the mild and moderate cases. The severe patient's PSF images also showed broader, odd-symmetric distributions compared to the other two patients. However, the manifest HORMS aberrations were always reduced by the correction in comparison to the uncorrected levels, even for a 15-degree rotation, in all three eyes.
Figure 10.5 The magnitude of the residual trefoil RMS, coma RMS, 3rd-order RMS and higher-order RMS aberrations induced by rotating the ideal aberration-controlling correction (from the ‘aligned’ position) in a clockwise direction by up to 15 degrees for the three keratoconic patients. Higher-order RMS aberrations were calculated from the 3rd- to the 5th-order. All data were calculated using a 4-mm pupil diameter. The solid green horizontal line represents 0.144 microns of RMS error.

10.4.4 Translational displacements

Figure 10.6 A) to C) display the residual higher-order wavefront aberration maps and PSFs generated for each patient by translating an ideal aberration correction (from the ‘correctly aligned’ position) horizontally, in the nasal direction by 0.1, 0.5 and 1.0 mm respectively. Note that, even with 1 mm of decentration, the PSFs are still more compact than the corresponding uncorrected PSF images displayed in Figure 10.3.
Figure 10.6 The residual higher-order wavefront aberration maps (upper half) and PSFs (lower half), generated when an ideal correction is translated from the ‘aligned’ position by 0.1 (A), 0.5 (B) and 1.0 mm (C) horizontally for all three keratoconic patients. Each wavefront map represents the aberrations from the 3rd- to the 5th-order and includes a sphero-cylindrical correction. All aberrations were calculated using a 4-mm pupil diameter. The darker colours represent negative aberrations, whereas the lighter colours represent positive aberrations. The scale bar shown is in microns. The left hand images display the aberrations induced for the mild keratoconic patient, the central images for the moderate keratoconic patient and the right-hand images for the severe keratoconic patient.
Figure 10.7 The residual higher-order wavefront aberration maps (upper half) and PSFs (lower half), generated when an ideal correction is translated from the ‘aligned’ position by 0.1 (A), 0.5 (B) and 1.0 mm (C) vertically for all three keratoconic patients. Each wavefront map represents the aberrations from the 3rd- to the 5th-order and includes a sphero-cylindrical correction. All aberrations were calculated using a 4-mm pupil diameter. The darker colours represent negative aberrations, whereas the lighter colours represent positive aberrations. The scale bar shown is in microns. The left-hand images display the aberrations induced for the mild keratoconic patient, the central images for the moderate keratoconic patient and the right-hand images for the severe keratoconic patient.
Figures 10.7 A) to C) display the residual higher-order wavefront aberration maps and PSFs generated for each patient by translating an ideal aberration correction (from the ‘correctly aligned’ position) vertically, in the superior direction by 0.1, 0.5 and 1.0 mm respectively. Again, note that, even with 1 mm of decentration, the PSFs are still more compact than the corresponding uncorrected PSF images displayed in Figure 10.3.

Horizontal and vertical translations of around 0.1 mm produced very little degradation in the PSF for all three keratoconic eyes; however, there was a noticeable blurring when translations approached and exceeded 0.5 mm in magnitude. Translating an ideal aberration correction by up to 1 mm horizontally, induced substantial negative vertical coma and negative oblique trefoil aberrations in the moderate patient’s PSF images. In contrast, the severe and mild patient’s PSF images displayed the inducement of positive horizontal coma aberrations. With respect to vertical translations, the moderate patient’s PSF images showed broad distributions both horizontally and vertically, whereas the mild patient’s functions showed broad, negative comatic distributions, predominantly along the y-axis. The severe patient’s functions showed a classic positive oblique trefoil or triangular astigmatic pattern.

However, a comparison of Figure 10.6 C) and Figure 10.7 C) with Figure 10.3 suggests that, even with up to 1 mm of horizontal or vertical translations of the customised correction, the PSF is always better than it was in the original, uncorrected eye.

As well as considering the effects of lens translation on the PSF, it is again helpful to examine the corresponding changes in the magnitudes of the individual aberrations. Figure 10.8 shows the magnitude of the residual higher-order RMS aberrations induced when translating the ideal aberration correction, from the ‘correctly aligned position’ horizontally (nasally) and vertically (upwards) by up to 1 mm for all three keratoconic patients.
Figure 10.8 The magnitude of the residual higher-order aberrations when translating the ideal aberration-controlling correction, from the ‘aligned position’, horizontally (nasally) and vertically (upwards), by up to 1 mm for all three keratoconic patients. The upper graphs display the horizontal translations, whereas the lower graphs show the vertical translations. The left-hand graphs display the mild keratoconic patient’s data, the central graphs the moderate keratoconic patient’s data and the right-hand graphs the severe keratoconic patient’s data. Higher-order RMS aberrations were calculated from the 3rd- to the 5th-order. All data were calculated using a 4-mm pupil diameter. The uncorrected HORMS values for a 4-mm pupil diameter were (Table 10.2) 0.45, 0.60 and 1.01 microns for the mild, moderate and severe keratoconic patients respectively. The solid green horizontal line represents 0.144 microns of RMS error.
In support of the wavefront aberration maps and PSF images shown in Figure 10.6 and Figure 10.8 also shows that the largest magnitudes of residual aberrations, when translating an ideal aberration-controlling correction either horizontally or vertically, were evident for the moderate and severe cases. Figure 10.8 shows that, as the ideal correction decentres horizontally, equally small amounts of residual coma RMS and trefoil RMS aberrations were seen for the severe keratoconic patient. A similar finding was also apparent for the moderate keratoconic patient, but with slightly higher coma RMS aberrations than trefoil RMS aberrations. Similar magnitudes of coma RMS aberrations were also induced in the mild case; however this patient was less sensitive to the inducement of trefoil RMS aberrations compared to the moderate and severe patients.

As the ideal correction translates vertically, similar magnitudes of residual coma RMS aberrations were induced for both the mild and moderate patients. Slightly higher amounts of trefoil RMS aberrations were found for the moderate case than for the mild case. On the other hand, vertical translations showed a substantially lower magnitude of residual coma RMS aberrations for the severe case, but a noticeably higher magnitude of trefoil RMS aberrations compared to the mild and moderate patients.

A comparison between Figure 10.5 and Figure 10.8 would suggest that vertical translations induced larger magnitudes of 3rd-order and HORMS aberrations than either horizontal translations or rotations for the mild and moderate keratoconic patients. The severe case, on the other hand, showed a higher sensitivity to both vertical translations and rotations compared to horizontal translations. However, the uncorrected HORMS error values for a 4-mm pupil diameter were 0.45, 0.60 and 1.01 microns for the mild, moderate and severe cases respectively (Table 10.2), so that even for 1 mm of horizontal or vertical decentration, the aberrations of the corrected eye were smaller than those of the uncorrected eye.

Figure 10.8 shows that horizontal or vertical translations of up to 0.1 mm meet the Marechal (1947) criterion, yielding HORMS error values less than or equal to 0.04 microns for all three keratoconic patients. However, the literature suggests that soft contact lenses are likely to show larger magnitudes of decentration upon blinking (Tomlinson and Bibby, 1980, Tomlinson et al., 1994, Chateau et al., 1996, Young et al., 2009). Alternatively, using the spherical blur criterion described earlier, Figure 10.8 shows that decentrations of up to 0.5 mm horizontally may be acceptable in all three cases. However, this criterion suggests that vertical decentrations should be minimised to less than 0.5 mm for all three keratoconic patients evaluated.

Table 10.3 shows the magnitude of higher-order RMS aberrations corrected or induced, for each of the maximum decentrations evaluated in all three patients evaluated. The values were calculated as the ratio of the residual aberrations, when the correction becomes decentred, compared to the patient’s manifest aberrations, expressed as a percentage. In this table values > 100 % depict an inducement of higher-order aberrations greater than the patient’s manifest values, whereas a value of 100 % would indicate a case of perfect correction. Values < 100 %, e.g. 25 %, indicate that the decentred ‘ideal lens’ corrected only a quarter of the original value of the uncorrected eye’s wavefront aberrations.
Table 10.3 A summary of the correction or inducement of higher-order aberrations for each of the maximum decentrations evaluated for all three keratoconic patients.

<table>
<thead>
<tr>
<th>Severe keratoconus patient</th>
<th>% Correction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aberration metric</td>
<td>Rotation (15 degs)</td>
</tr>
<tr>
<td>HORMS error (3rd to 5th)</td>
<td>56.4</td>
</tr>
<tr>
<td>3rd-order RMS</td>
<td>57.2</td>
</tr>
<tr>
<td>Coma RMS</td>
<td>73.9</td>
</tr>
<tr>
<td>Trefoil RMS</td>
<td>23.5</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderate keratoconus patient</th>
<th>% Correction</th>
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</thead>
<tbody>
<tr>
<td>Aberration metric</td>
<td>Rotation (15 degs)</td>
</tr>
<tr>
<td>HORMS error (3rd to 5th)</td>
<td>66.3</td>
</tr>
<tr>
<td>3rd-order RMS</td>
<td>66.9</td>
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<tr>
<td>Coma RMS</td>
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<tr>
<td>Trefoil RMS</td>
<td>23.5</td>
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<table>
<thead>
<tr>
<th>Mild keratoconus patient</th>
<th>% Correction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aberration metric</td>
<td>Rotation (15 degs)</td>
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<tr>
<td>HORMS error (3rd to 5th)</td>
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</tr>
<tr>
<td>3rd-order RMS</td>
<td>64.6</td>
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<td>Coma RMS</td>
<td>73.9</td>
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<tr>
<td>Trefoil RMS</td>
<td>23.4</td>
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</tbody>
</table>

10.4.5 Lower-order aberrations

As mentioned earlier, horizontal or vertical translation of a correction containing 4th-order spherical aberration induces superfluous 3rd-order coma aberrations. Similarly, translating 3rd-order coma aberrations will also induce unwanted 2nd-order defocus and cylindrical aberrations. With this in mind, an understanding of the inducement of lower-order aberrations when decentring an ideal aberration-correcting lens is also desirable.

Figure 10.9 displays the magnitude of the lower-order aberrations induced by rotating the ideal aberration-controlling correction, from a ‘perfectly aligned position’, by up to 15 degrees for all three keratoconic patients. As expected, the analysis for rotational displacements of the customised correction showed no changes in 2nd-order defocus RMS (all defocus aberrations were converted into RMS errors (in dioptres) using $\sqrt{Z_{2,0}^2}$; this converted negative defocus values into positive values). However, 2nd-order astigmatic RMS error (i.e. the combined cylinder RMS terms, Z(2,±2) converted into dioptres (D) (Thibos et al., 2002c)) showed a significant linear increase in magnitude with increasing rotational misalignment for all three patients. The severe keratoconic patient showed the largest magnitude of induced astigmatic RMS aberrations, whereas the mild case showed the smallest magnitude. Using the criterion of 0.25 D of spherical blur, the results propose that the mild and moderate keratoconic patients may be able to tolerate rotations of up to 5 degrees. However, Figure 10.9 suggests that rotations need to be minimised to no more than 3 degrees to provide stable vision for the severe keratoconic patient.
The magnitude of the residual astigmatic RMS aberrations induced by rotating the ideal aberration-controlling correction (from the ‘aligned’ position) in a clockwise direction by up to 15 degrees for the three keratoconic patients. Astigmatic RMS aberrations were calculated from the 2nd-order Zernike cylinder terms. All data were calculated using a 4-mm pupil diameter. The horizontal black line represents 0.25 D of refractive blur.

Figure 10.10 displays the magnitude of the lower-order aberrations induced by translating the ideal aberration-controlling correction, from a ‘perfectly aligned position’, both horizontally (nasally) and vertically (upwards) by up to 1 mm for all three keratoconic patients. Horizontal translations induced increases in both astigmatic RMS and defocus RMS errors in the mild and moderate cases. The astigmatic RMS errors induced were found to be larger in magnitude compared to the defocus RMS errors for both patients. In contrast, horizontal decentrations predominantly induced astigmatic RMS aberrations for the severe keratoconic patient, with a comparatively smaller increase in defocus RMS error. Horizontal translations of up to 0.5 mm induced comparable magnitudes of 2nd-order RMS aberrations in all three patients, with the severe case showing the highest values at 1 mm of decentration. Using the criterion of 0.25 D of spherical blur, the results suggest that horizontal translations of up to only 0.1 mm could be tolerated in all three patients evaluated.

Vertical translations, on the other hand, tended to induce larger increases in both defocus RMS and astigmatic RMS aberrations in all three patients. For the mild and moderate cases, the magnitudes of the induced defocus RMS errors were found to be slightly higher than the astigmatic RMS aberrations. However, vertical decentrations induced an equivalent amount of defocus RMS and astigmatic RMS error for the severe keratoconic patient. Of the three patients evaluated, the severe case showed the largest magnitude of induced 2nd-order RMS aberrations, whereas the moderate case showed the smallest magnitude. Using the criterion of 0.25 D of spherical blur, the results suggest that vertical translations of up to 0.1 mm may perhaps be tolerated by the mild and moderate patients; conversely vertical decentrations should be kept to less than 0.1 mm for the severe keratoconic patient. However, the literature suggests that soft contact lenses are likely to show larger magnitudes of decentration upon blinking (Tomlinson and Bibby, 1980, Tomlinson et al., 1994, Chateau et al., 1996, Young et al., 2009).
Figure 10.10 The magnitude of the residual lower-order aberrations when translating the ideal aberration-controlling correction, from the ‘aligned position’, horizontally (nasally) and vertically (upwards) by up to 1 mm for all three keratoconic patients. The upper graphs display the horizontal translations, whereas the lower graphs show the vertical translations. The left-hand graphs display the mild keratoconic patient’s data, the central graphs the moderate keratoconic patient’s data and the right-hand graphs the severe keratoconic patient’s data. Lower-order RMS aberrations were calculated from the 2nd-order coefficient terms. All data were calculated using a 4-mm pupil diameter. The horizontal black line represents 0.25 D of refractive blur.
10.5 Discussion

The results of this investigation demonstrate that surplus higher-order and lower-order aberrations become induced when an ‘ideal’ aberration-controlling correction becomes decentred for highly-aberrated, keratoconic eyes. The magnitudes of decentration evaluated in this study were chosen to be similar in magnitude to the small vertical, rotational and horizontal lens movements characteristically seen between blinks and with versional eye movements in toric soft contact lens wearers (Tomlinson and Bibby, 1980, Tomlinson et al., 1994, López-Gil et al., 2009a, Young et al., 2009). The findings of this report are in agreement with the literature and show that the amount of aberration induced by such movements is dependent on the magnitude of the aberrations in the correction, as well as the direction and amount of decentration applied (Bara et al., 2000, Guirao et al., 2001, de Brabander et al., 2003, Kollbaum and Bradley, 2007, Kollbaum et al., 2008, López-Gil et al., 2009a). Since the correction is designed to nullify the aberrations of the individual eye, sensitivity to such induced aberrations is also dependent on the magnitude of the patient’s original, habitual aberrations. With this in mind, the magnitude of higher-order and lower-aberrations induced by decentration of an ideal correction will be unique to each individual patient’s eye. In the mild and moderate keratoconic patients evaluated, it was apparent that vertical translations induced the largest magnitude of residual higher-order aberrations, followed by horizontal translations and rotations respectively. However in the severe case, both rotations and vertical translations induced comparatively larger magnitudes of superfluous higher-order aberrations compared to horizontal translations.

Although surplus higher-order and lower-order aberrations are induced with rotations, our findings indicate that all three keratoconic patients would still experience a reasonable correction of 3rd-order coma RMS aberrations even with rotations of up to 15 degrees (of approximately 74 %). However, vertical decentrations of 1 mm led to a poorer correction of coma RMS aberrations for the mild and moderate patients (≤ 34 %), than for the severe patient (of approximately 83 %). Vertical translations of 1 mm also tended to induce a substantial increase in trefoil RMS aberrations in all three cases, particularly for the moderate and mild patients. Compared to the severe and mild cases, horizontal decentrations of 1 mm induced a noticeable increase in trefoil RMS aberrations for the moderately keratoconic patient. Nevertheless, over the ranges of rotation and translation studied, the overall HORMS errors for a 4-mm pupil diameter were always less than those of the uncorrected eye, so that the correction was always theoretically beneficial.

This investigation focused primarily on modelling the inducement of superfluous higher-order aberrations by correcting the Zernike terms of the 3rd- to the 5th-order. It is important however, to also appreciate that translation of a correction purely neutralising higher-order aberrations would also generate unwanted lower-order aberrations. The literature reports that 2nd-order coefficient terms have a greater impact on visual performance compared to the 3rd-, 4th- and 5th-order coefficient terms (Applegate et al., 2002, Applegate et al., 2003a, Oshika et al., 2006). In general, our results showed that the magnitude of 2nd-order RMS aberrations, induced through horizontal and vertical translations, were substantially larger than both the induced and manifest higher-order aberrations in all three keratoconic patients. This finding perhaps reinforces the
importance of optimally correcting any manifest lower-order aberrations before even considering the correction of higher-order aberrations, as outlined by Kollbaum and Bradley (2007).

de Brabander et al.’s (2003) study suggested that translational displacements of an ‘ideal’ lens of less than 0.75 mm still yielded an improvement in the modulation transfer function for a pupil diameter of 4.5 mm. The maximum allowable translation was reduced to less than 0.5 mm for pupil sizes up to 7 mm in diameter. On the other hand, the authors explain that rotations of up to a maximum of 10 degrees could be tolerated even for pupil sizes of up to 7 mm in diameter. However, de Brabander et al. (2003) did not investigate the inducement of lower-order aberrations through rotation and translation in their paper. Their study evaluated corneal aberrations derived from anterior surface, Placido-ring based topographical measurements only. Recent studies have shown that the posterior corneal surface compensates for the anterior corneal aberrations in patients with keratoconus (Chen and Yoon, 2008, Nakagawa et al., 2009). Finally, de Brabander et al. (2003) did not explore eyes with mild keratoconus in their study.

Lopez-Gil et al.’s (2009a) study concluded that highly-aberrated, keratoconic eyes would still benefit from a reduction in aberrations despite ‘ideal’ lens rotations of up to 5 degrees and translation displacements of up to 0.5 mm both horizontally and vertically over a 5-mm pupil diameter.

In agreement with the literature, our results suggest that rotational displacements should be minimised to no more than 5 degrees and translational displacements to no more than 0.5 mm in magnitude, to avoid the inducement of superfluous higher-order aberrations with decentration. With regard to the inducement of superfluous lower-order aberrations, the results indicate that rotational displacements should be reduced to no more than 5 degrees in mild to moderate keratoconus and to less than 3 degrees in more severe cases, whereas translational displacements should not exceed 0.1 mm. As lower-order aberrations have the greatest impact on visual performance, inevitable reductions in optical quality will arise as the ‘ideal’ contact lens displaces, even by small amounts. The findings of this report provide an enlivening challenge to contact lens designers in the quest to provide the ideal correction of highly-aberrated, keratoconic eyes. However, it is important to appreciate that ‘on-eye’ contact lens movements are dynamic, in which it is expected that displacements and rotations occur around the ideal, ‘aligned’ position. In this case, it is anticipated that for most of the time, the lens will be correctly positioned and the maximum displacements or rotations, with their higher levels of aberration, will only occur for a small fraction of the time.

When designing aberration-controlling contact lenses, previous studies have already demonstrated that not all higher-order aberration terms should be corrected, thus reducing the likelihood of inducing superfluous higher-order and lower-order aberrations (Guirao et al., 2001, Guirao et al., 2002a, de Brabander et al., 2003, Katsoulos et al., 2009). The results presented further support this idea of ‘partial correction’; in particular, our results suggest that it is sensible not to include a correction for 4th-order spherical aberration when designing aberration-controlling contact lenses for keratoconus patients, as vertical translations upon blinking will induce unwanted 3rd-order vertical coma aberration (Kollbaum et al., 2008). Such induced aberrations are likely to reduce the effectiveness of the intended correction.
This study chiefly investigated clockwise rotations, nasal decentrations and translations superiorly. It is obvious that temporal decentrations, anti-clockwise rotations and translations inferiorly would yield different numerical results to those described in this report. Similarly, this model investigated rotations and translations independently of each other. This effectively allows the reader to differentiate between each type of decentration and to explore their individual effects in inducing unwanted aberrations. In reality however, contact lens translations and rotations occur simultaneously upon blinking (Tomlinson and Bibby, 1980, Tomlinson et al., 1994, Chateau et al., 1996, López-Gil et al., 2009a), with eye versinal movements (Young et al., 2009) and with head rotations (for example if a patient is lying down flat and watching television with their contact lenses in situ) (McIlraith et al., 2010). Future studies modelling the effects of decentration on aberration correction may wish to explore the combined effects of both translations and rotations in tandem.

The literature shows that the ocular higher-order aberrations measured in keratoconus will alter with both RGP contact lens wear (Jinabhai et al., 2010b, Jinabhai et al., 2012a), and disease progression (Alio and Shabayek, 2006, Jafri et al., 2007). Several authors have also revealed that aberrations are dynamic in nature and vary between blinks (Montés-Micó et al., 2004b, Radhakrishnan et al., 2010), with increased accommodation (Radhakrishnan and Charman, 2007, Radhakrishnan et al., 2010), small eye movements (Cheng et al., 2003b, Cheng et al., 2004c) and changes in pupil size (Liang and Williams, 1997, Maeda et al., 2002). For simplicity, variations in aberrations due to such dynamic alterations were not evaluated in this study. Similarly, in practice it is unlikely that the aberrations of any lens as manufactured will exactly match those of the ‘ideal’ correcting lens.

The monochromatic aberrations explored in this investigation were all derived using a wavelength of 780 nm, as this was the output of the aberrometer’s laser beam. However, the V-lambda spectral sensitivity curve shows that the human eye is most sensitive to yellow-green light. No compensations were made to account for the shift from infra-red light to the middle of the visible spectrum for any the PSF images displayed in this report. Similarly, no defocus compensations were made to account for the eye’s longitudinal chromatic aberrations. It is expected that changes in wavelength, both with and without a defocus compensation for longitudinal chromatic aberration, would alter the appearance of the PSF images generated in this study; however at present this remains uninvestigated.

A further limitation to this study is that higher-order aberrations, for each of the three keratoconic patients evaluated, were measured using the Hartmann-Shack technique. Jinabhai et al. (2011b) have reported that higher-order aberrations measured with the IRX-3 device show poorer repeatability in keratoconic patients compared to visually-normal subjects. The most likely reason for this poorer repeatability is spot imaging error errors at the Hartmann-Shack wavefront sensor such as spot crossover, overlapping spots and multiple spot images falling within the ‘virtual sub-aperture’ of a given photon detector at the charge-coupled device sensor (Thibos and Hong, 1999, Munson et al., 2001, Yoon et al., 2004b). These spot imaging errors would therefore cause inaccuracies in reconstructing the aberrant wavefront’s shape. Such errors are believed to be attributed to irregular corneal distortion and corneal apical scarring (Thibos, 2000, Munson et al.,
To help reduce the effects of these potential complications, only patients without corneal scarring were recruited to the study. Equally, all aberration measurements were repeated four times per eye for each patient (Cheng et al., 2004c).

In summary, this report systematically modelled the magnitudes of higher-order and lower-order aberrations induced by decentring an ideal aberration-controlling correction in three patients with varying degrees of keratoconus. The decentrations evaluated were typical of the small contact lens movements seen in toric soft contact lens wearers. Our results suggest that minimising the decentration of customised aberration-controlling contact lenses, to less than 5 degrees of rotation and less than 0.50 mm of translation, will help to achieve an optimal higher-order aberration correction. However, more stringent criteria are required to reduce the inducement of lower-order aberrations, where rotational displacements should be reduced to less than 3 degrees and translational displacements should be limited to less than 0.10 mm. These findings may be of interest to the scientific community and to contact lens manufacturers designing customised contact lenses for patients with keratoconus.
11. Conclusions and future work

11.1 Summary of key findings

The main purpose of this project was to improve our current understanding of the higher-order aberrations manifested in keratoconus and to explore their potential correction using standard and customised soft contact lenses.

Chapter 4 explored the repeatability of lower-order and higher-order aberration measurements in 31 keratoconic patients, within a single session, using the Hartmann-Shack technique. The results indicate that defocus and cylinder RMS error showed poorer repeatability compared to previous studies of visually-normal subjects. As expected, the results also revealed that 3rd-order coma and trefoil RMS aberrations, as well as 4th-order spherical aberration, showed higher variability than in normal eyes. Equally, 4th-order cylinder RMS, tetrafoil RMS, 5th-order coma RMS, 5th-order trefoil RMS and pentafoil RMS aberrations also showed poorer repeatability compared to normal subjects. In addition to the aberration values being high, the most probable cause for the larger variability in higher-order aberrations in keratoconic eyes is spot imaging errors at the wavefront sensor. Nonetheless, repeated-measures ANOVA results showed no significant differences between 4 repeated measurements of either lower-order or higher-order aberrations in this group of keratoconic patients. Therefore, the findings presented perhaps indicate that the Hartmann-Shack technique may be clinically useful when evaluating changes in higher-order aberrations in patients with keratoconus.

Chapter 5 investigated the changes in higher-order aberrations with alterations in the tear film post-blink and with increasing accommodation in normal subjects and patients with moderate keratoconus. The results showed that coma RMS and spherical aberration did not change significantly with accommodation in this group of keratoconic patients. In contrast to normal eyes, the results showed that higher-order RMS error tended to decrease after a blink in keratoconic eyes. These changes are likely to be due to a positive increase in vertical coma aberration post-blink, a similar trend was also observed in the normal subjects. Previous authors suggested that these changes are likely to be due to vertical gravitational effects on the pre-corneal tear film (Buehren et al., 2001, Montés-Micó et al., 2004b). Nonetheless, the magnitude of the changes in post-blink higher-order RMS aberrations was found to be similar in both groups, despite the higher absolute levels of aberrations found in the keratoconic patients. Compared to the manifest ocular higher-order aberrations, any dynamic variations in aberrations with accommodation and tear film changes are relatively small in keratoconic eyes. From a clinical perspective, it is therefore expected that these aberration changes will not significantly impact on optical quality, perhaps indicating that the correction of aberrations in eyes with moderate keratoconus is unlikely to be hindered by dynamic changes in ocular aberrations.

Chapter 6 compared the differences between the subjective refraction and three objective aberrometry-derived refractions, along with visual acuity achieved with these refractions, in keratoconic patients and age-matched normal subjects. These findings show that the objective refraction results obtained with a Hartmann-Shack aberrometer (even after accounting for the higher-order aberrations) differ from the subjective refraction data measured in keratoconus patients, despite optical defects such as higher-order aberrations being considered as an important cause of poor visual quality in keratoconus. The results reveal that the larger the magnitude of the
higher-order aberrations in keratoconic eyes, the poorer the subjective refraction logMAR acuity and the larger the difference between the subjective and aberrometry-derived spherical equivalent results. The data also suggest that subjective refraction results provide the best visual performance, which may be clinically useful when designing bespoke aberration-controlling contact lenses for patients with keratoconus. Therefore, the customised lenses evaluated in this thesis were designed using subjective refraction results, as detailed in Chapter 9.

Chapter 7 describes the changes in visual acuity, ocular higher-order aberrations and subjective refraction, after suspending RGP contact lens wear for one week in 16 patients with moderate to severe keratoconus. Alterations in the anterior surface central corneal powers and axes and central corneal thickness were also investigated. Reductions in both high-contrast and low-contrast acuity, along with an increase in 3rd-order RMS aberrations, occurred after RGP lens wear was suspended. The measured reductions in visual performance equated to a mean loss of around 5 letters of low-contrast logMAR acuity and around 4 letters of high-contrast logMAR acuity. Although these differences were found to be statistically significant, it may be argued that these changes were perhaps only approaching a clinically significant difference in visual performance. However, the results presented showed no significant changes in subjective refraction between the two visits. Significant correlations were observed between third-order coma RMS aberrations and the measured high-contrast and low-contrast acuities. In addition to increases in the anterior surface central corneal powers, a reduction in central corneal thickness was also found. These alterations in corneal structure are likely to be attributed to corneal ‘unmoulding’ after suspending RGP lens wear, which is perhaps related to the lens fitting strategy employed and the duration of lens wear (Szczotka et al., 1996). The literature shows that the vast majority of keratoconic patients are fitted with flat-fitting RGP lenses to correct their vision (Edrington et al., 1999, Zadnik et al., 2005), and that patients tend to wear their lenses every day. Therefore, the results presented in Chapter 7 may be useful when considering refitting RGP lens-wearing keratoconic patients with soft contact lenses. Consequently, the RGP lens-wearing patients featured in Chapters 8 and 9 were asked to suspend RGP lens wear for a period of one week before they were refitted with soft lenses.

Chapter 8 investigated how conventional toric soft contact lenses corrected visual performance and ocular higher-order aberrations in comparison to RGP contact lenses or spectacles in patients with keratoconus. The results revealed that RGP lenses provided clinically superior visual performances, where improvements in low-contrast acuity and SKILL card scores reached statistical significance. The RGP lenses also provided clinically significant reductions in 3rd-order aberrations compared to the toric soft lenses in the contact lens-wearing group. Nonetheless, the toric soft lenses were successful in significantly reducing the uncorrected higher-order aberrations. The results presented suggest that the visual performance achieved with toric soft lenses is likely to be related to disease severity, where patients with less advanced keratoconus achieved better results.

The purpose of the study reported in Chapter 9 was to investigate how conventional toric soft contact lenses and customised aberration-controlling soft contact lenses corrected ocular higher-order aberrations and visual performance in patients with keratoconus, compared to either RGP lenses or spectacles. The customised lenses were designed to either fully (100 %) or partially (50 %) correct ocular coma aberrations. The results showed that the two customised lenses
provided clinically significant reductions in uncorrected coma RMS and higher-order RMS aberrations in the contact lens-wearing group, which reached statistical significance. On the other hand, the visual performances measured with the patient’s habitual RGP lenses were found to be clinically better than with either of the two aberration-controlling customised lenses. The results also indicated that keratoconic patients with less advanced disease may achieve better visual performance with customised lenses compared to those with severe keratoconus.

The investigation described in Chapter 10 systematically modelled the magnitudes of higher-order and lower-order aberrations induced by decentring an ideal aberration-controlling correction in three patients with mild, moderate and severe keratoconus respectively. The decentrations evaluated were typical of the small contact lens movements seen in soft toric lens wearers. The results presented suggest that minimising the decentration of customised aberration-controlling contact lenses, to less than 5 degrees of rotation and less than 0.50 mm of translation, will help to achieve an optimal higher-order aberration correction. However, more stringent criteria are required to minimise the inducement of lower-order aberrations, where rotational displacements should be reduced to less than 3 degrees and translational displacements should be limited to less than 0.10 mm.

In summary, the findings of this thesis reveal that the correction of higher-order aberrations for keratoconus patients is possible using customised soft contact lenses. Such customised corrections are unlikely to be hindered by dynamic variations in aberrations due to changes in the pre-corneal tear film and accommodation. For the optimal correction of manifest coma aberrations, it is advisable not to include a correction for spherical aberration, as on-eye lens decentrations will induce superfluous coma aberrations which are likely to reduce the efficacy of the correction. Moreover, a 100 % correction of coma aberrations will induce significant 2nd-order errors with blink-related contact lens rotations and translations. In this regard, a partial correction of coma aberration may be useful to help minimise the effects of lens decentrations, but still offer improved optical quality compared to a sphero-cylindrical correction alone.

When designing the lower-order aberration correction for customised lenses, a subjective refraction is likely to provide better visual performance compared to objective, aberrometry-derived refractions. Equally, the results presented show that the repeatability of lower-order and higher-order aberrations is poorer in keratoconic patients compared to results reported in previous studies of visually-normal subjects.

The results of this project reveal that RGP lenses provided the best visual performance compared to both sphero-cylindrical and customised aberration-controlling soft contact lenses. It is possible that the visual performance and optical quality measured with RGP lenses is linked to the contact lens fitting technique employed (Jinabhai et al., 2010b). The most common strategy adopted when fitting RGP lenses for keratoconus patients is the ‘flat-fitting’ technique. Moreover, the findings presented indicate that flat-fitting RGP lenses may mould the anterior corneal surface in patients with keratoconus. In this regard, it is plausible that the keratoconic cornea may undergo a period of ‘unmoulding’ after RGP lens wear is suspended in patients who are to be refitted with soft contact lenses. During the unmoulding phase it is probable that alterations in higher-order aberrations, visual performance, corneal curvature and corneal thickness may occur. Such alterations may impact on the soft contact lens fitting and optical correction. In order to overcome
these alterations, it may be necessary to make subsequent adjustments to the customised soft lens parameters after the initial fitting.

Although aberration-controlling contact lenses would be a valuable tool in the management of keratoconic patients, their use may be limited by disease progression, which will lead to changes in corneal curvature, corneal thickness and higher-order aberrations. In addition to on-eye lens decentrations, aberration-controlling lenses are also restricted by the size of the customised optical zone, in that changes in the patient’s pupil size will reduce the efficacy of the correction. However, unlike some surgical corrections which are typically permanent, customised contact lenses do provide a reversible option for visual rehabilitation.

With the advent of new silicone hydrogel lens materials, aberration-controlling soft contact lenses could provide longer wearing times, improved corneal physiology (such as reduced staining and scarring) and enhanced patient comfort compared to RGP lenses. Such lenses could therefore provide a useful alternative for keratoconic patients who participate in contact sports or who develop RGP lens intolerance.

11.2 Suggestions for future work

This project has attempted to improve our current understanding of the higher-order aberrations manifested in keratoconus. However, the featured studies show some limitations which have already been outlined in each chapter presented. In brief, these limitations include smaller numbers of mild and severe keratoconic patients (compared to moderate cases); the RGP lenses evaluated here were of different designs and materials to one another; the aberration-controlling contact lenses fitted each showed a fixed customised optical zone diameter of 4 mm; the customised lenses each included a correction for spherical aberration which induced coma aberrations upon lens decentration and finally the lens translations modelled in Chapter 10 were restricted to a maximum of 1 mm. The remainder of the present thesis chapter aims to highlight areas for future investigation in patients with keratoconus.

Ocular higher-order aberrations may perhaps be a useful tool in grading the different severity stages of keratoconus. Although previous studies have considered using anterior corneal aberrations to grade keratoconus (Alio and Shabayek, 2006), the literature suggests that the internal optics may compensate for the anterior corneal aberrations in keratoconic patients (Chen and Yoon, 2008, Nakagawa et al., 2009, Schlegel et al., 2009). Therefore, it is likely that ocular aberrations represent a truer picture of optical quality in keratoconus patients. Equally, the results presented in Chapter 4 indicate that the repeatability of ocular aberrations is perhaps better compared to the corneal aberrations in keratoconic eyes (Shankar et al., 2008b, Piñero et al., 2009a). At present, the concept of grading keratoconus using ocular aberrations remains unexplored in the literature.

The repeatability results presented in Chapter 4 were limited to a single session only. Future investigations of keratoconic patients could evaluate repeatability over longer time frames such as a week or a month. Such studies may determine how useful higher-order aberration measurements are in monitoring keratoconus progression over time. This methodology could also be extended to explore the repeatability of corneal and internal aberrations over longer time frames; such studies may improve our current understanding of how the compensation between
the corneal surfaces alters as the condition progresses. However, for RGP lens-wearing keratoconic patients, the results of repeatability studies over longer time periods may be confounded by changes in the corneal structure after contact lens removal (Jinabhai et al., 2012a).

The results presented in Chapter 5 explored dynamic variations in aberrations due to change in the pre-corneal tear film and accommodation in patients with moderate keratoconus only. The magnitudes of such dynamic variations have not yet been investigated in patients with forme fruste, mild or severe keratoconus. As the magnitude of manifest higher-order aberrations is expected to be lower in less advanced cases, it is probable that different results may be found informe fruste and mild keratoconic patients, than those of the moderate cases featured in Chapter 5. However in contrast, severe cases are likely to show higher magnitudes of manifest aberrations, therefore it may be assumed that dynamic variations could have a lesser optical effect in these patients compared to those with moderate keratoconus.

In Chapter 6 three different Zernike RMS metrics were tested to explore the possibility of deriving refraction data objectively from Hartmann-Shack aberrometry measurements in keratoconic patients. The three metrics evaluated did not provide as good visual acuity as subjective refraction data. Nevertheless, several studies have used specialised software programs (such as GetMetrics – v2.02.006 (University of Houston, College of Optometry)) to identify optical quality metrics to predict refractive error (Cheng et al., 2004b, Thibos et al., 2004) and visual performance (Cheng et al., 2003c, Marsack et al., 2004, Chen et al., 2005, Applegate et al., 2006) in visually-normal subjects. To date, optical quality visual metrics based on the optical transfer function, modulation transfer function and point spread function have not been investigated using ocular aberrations measured in eyes with keratoconus. It is envisaged that investigations of image quality metrics in keratoconus patients would be of interest to the scientific community, particularly as retinoscopy and subjective refraction can often be difficult for these patients. Therefore, an objective method of deriving refraction and estimating visual performance would be useful clinically.

The data presented in Chapter 7 show that the corneal profile and ocular aberrations alter significantly after RGP lens wear is suspended for 7 days. However at present, it is unclear exactly how long is required for the keratoconic cornea to stabilise again after RGP lenses are removed and lens wear is suspended. It is expected that the time required will perhaps be related to the lens fitting strategy used and the number of years of RGP lens wear. Future investigations in this area may aim to review ocular aberrations and corneal topographies over time periods greater than one week. However, it may be considered unethical to ask keratoconic patients to leave their RGP lenses out for long periods as they are typically reliant on their lenses for everyday visual tasks such as driving and computer screen work (Szczotka et al., 2001, Edrington et al., 2004, Davis et al., 2006, Wagner et al., 2007). On the other hand, it would also be of interest to investigate how the topography of the keratoconic cornea changes over time after refitting patients with soft contact lenses from RGP lenses.

The results of the investigations described in Chapters 8 and 9 suggest that the success of sphero-cylindrical and customised soft contact lenses is likely to be related to the patient’s disease severity, where less advanced cases achieve better visual performance than more severe cases. However, these studies included only one patient with mild keratoconus (compared to 7 severe cases and 14 moderate cases). In this regard, future studies evaluating the use of standard and customised aberration-controlling soft lenses could aim to explore the visual performance and
optical quality achieved in patients with earlier forms of keratoconus. Moreover, keratoconic patients with mild disease are likely to show less corneal distortion and apical scarring, which may help to reduce the variability of higher-order aberration measurements and may perhaps even improve soft contact lens stability on-eye.

Further research exploring possible relationships between the biomechanical properties of the keratoconic cornea and the magnitude of the higher-order aberrations manifested may be useful in investigating any association between the patient’s disease severity and optical quality. To date only one study has considered this idea (Pinero et al., 2010). Pinero et al. (2010) reported significant correlations between the corneal resistance factor (CRF), measured using the Ocular Response Analyser – ORA (Reichert, DePew, NY, US), and corneal spherical aberration measured in patients with severe keratoconus. In agreement with studies by Shah et al. (2007) and Ortiz et al. (2007), Pinero et al.’s (2010) results also suggested that biomechanical properties, such as the CRF, are useful in differentiating between normal and keratoconic corneas. Therefore, long term studies using the ORA device and higher-order aberration measurements may be useful in potentially grading the severity of keratoconus and monitoring disease progression.

In addition to corneal transplantation procedures, other surgical methods used to manage patients with keratoconus include intra-stromal corneal segment rings, or INTACS (Colin et al., 2000), and corneal collagen cross-linking (Wollensak et al., 2003). To date, only a few studies have investigated changes in higher-order aberrations before and after conducting these techniques (Pinero et al., 2009, Vinciguerra et al., 2009, Caporossi et al., 2010). These reports suggest that INTACS and collagen cross-linking can both reduce astigmatism and higher-order aberrations, thereby providing improved visual performance for keratoconic patients. Chan et al. (2007) and Coskunseven et al. (2009) have also demonstrated that collagen cross-linking was significantly more effective in improving corrected visual acuity, reducing spherical equivalent refraction and reducing mean keratometric readings when carried out in conjunction with INTACS inserts than without them. Currently no study has explored how higher-order aberrations alter when both procedures have been performed together. It is also unclear, at present, if higher-order aberrations would be corrected more effectively if collagen cross-linking was performed either before or after INTACS implantation.

Several reports in the literature have investigated the mode of inheritance of keratoconus but none provide a definitive conclusion. Autosomal recessive inheritance has been demonstrated (Wang et al., 2000), however, most reports show an autosomal dominant model (Ihalainen, 1986, Rabinowitz et al., 1992, Tyynismaa et al., 2002). Some authors have also confirmed the involvement of different individual gene loci (a fixed position on a chromosome) in patients with keratoconus (Fullerton et al., 2002, Tyynismaa et al., 2002, Hutchings et al., 2005). Moreover, Bisceglia et al. (2009) have reported that loci on the 5th, 14th and 15th chromosomes exhibited strong evidence of a link with keratoconus. Further genetic studies to potentially isolate keratoconus genes may perhaps be useful in providing future gene therapy treatments for patients with keratoconus.
Appendix 1: Research ethics committee approval letters
Document 1.1 Ethical approval letter for the studies presented in Chapters 4, 5, 6 and 7

Secretary to the Ethics Committee
Room 2.085 John Owens Building
Tel: 0161 275 2206/2046
Fax: 0161 275 5697
Email: timothy.stibbs@manchester.ac.uk
ref: TPCS/ethics/08276

Mr Amit Jinabhai,
Room C4(d) Moffat Building,

16th January 2009

Dear Amit,

Committee on the Ethics of Research on Human Beings
Jinabhai, Radhakrishnan, O'Donnell: Investigating ocular and corneal aberrations in keratoconic and normal eyes (ref 08276)

I write to thank you and Hema for coming to meet the Committee today and to confirm that the Committee gave ethical approval to the above project, subject to:

- Toning down the first paragraph of the advert. It should preferably say, “You are invited to help a study investigating…”
- Adding a ‘complaint’ paragraph to the information sheet on the following lines:
  “If there are any issues regarding this research that you would prefer not to discuss with members of the research team, please contact the Research Practice and Governance Co-ordinator by either writing to The Research Practice and Governance Co-ordinator, Research Office, Christie Building, The University of Manchester, Oxford Road, Manchester M13 9PT, by emailing: ResearchGovernance@manchester.ac.uk, or by telephoning 0161 275 7583 or 275 8093”

This approval is effective for a period of five years and if the project continues beyond that period it must be submitted for review. It is the Committee’s practice to warn investigators that they should not depart from the agreed protocol without seeking the approval of the Committee, as any significant deviation could invalidate the insurance arrangements. We also ask that any information sheet should carry a University logo or other indication of where it came from.

Finally, I would be grateful if you could complete and return the attached forms at the end of the project or by January 2009 whichever is earlier. We hope the research goes well.

Yours sincerely

Dr T P C Stibbs
Secretary to the Committee

The University of Manchester, Oxford Road, Manchester M13 9PT Royal Charter Number: RC000797
Document 1.2 Ethical approval letter for the studies presented in Chapters 8, 9 and 10

National Research Ethics Service
North West 11 Research Ethics Committee - Preston

05 March 2010

Mr Amit N. Jinabhai
Ph.D. Student
University of Manchester
Ph.D. Student
Faculty of Life Sciences
Moffat Building
PO Box 88
M60 1QD

Dear Mr Jinabhai

Study title: Measuring Corneal and Ocular Higher Order Aberrations in Keratoconus to Investigate and Optimise Visual Function Using Customised Soft Contact Lenses

REC reference: 09/H1016/100
Amendment number: 01
Amendment date: 18 February 2010

The above amendment was reviewed by the Sub-Committee in correspondence on 02 March 2010.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

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<td>Participant Information Sheet</td>
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Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

This Research Ethics Committee is an advisory committee to North West Strategic Health Authority.

The National Research Ethics Service (NRES) represents the NRES Directorate within the National Patient Safety Agency and Research Ethics Committees in England.
R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

09/H1016/100: Please quote this number on all correspondence

Yours sincerely

Rowen Callaghan
Committee Co-ordinator

E-mail: rowen.callaghan@northwest.nhs.uk

Enclosures: List of names and professions of members who took part in the review

Copy to: Dr Karen Shaw Research Office, The University of Manchester

Alison Robinson, R&D office for Central Manchester University Hospitals NHS Foundation Trust

North West 11 Research Ethics Committee - Preston

Attendance at Sub-Committee of the REC meeting on 02 March 2010

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<td>Dr Patricia Wilkinson</td>
<td>General Practitioner</td>
<td>Expert</td>
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Appendix 2: List of other peer-reviewed scientific publications associated with this research project


12. References


SHANKAR, H., TARANATH, D., SANTHIRATHELAGAN, C. T. (1954) Monocular coexistence of anterior lenticonus, posterior keratoconus, and

SEMMLOW, J. & STARK, L. (1973) Pupil movements to light and accommodative stimulation: A


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