The Changes of Posterior Corneal Curvature, Topographic Corneal Thickness and Corneal Biomechanical Properties from Overnight Orthokeratology Lens Wear and Recoveries of These Parameters

DAVIE CHEN

Doctor of Philosophy

The Hong Kong Polytechnic University

Hong Kong 2011

The Hong Kong Polytechnic University
School of Optometry

The Changes of Posterior Corneal Curvature, Topographic Corneal Thickness and Corneal Biomechanical Properties from Overnight Orthokeratology Lens Wear and Recoveries of These Parameters

by

DAVIE CHEN

A thesis submitted in partial fulfillment of

the requirements for the degree of

Doctor of Philosophy

August 2010

CERTIFICATE OF ORIGINALITY

I hereby declare that this thesis is my own work and that, to my best of knowledge and belief, it reproduces no material previously published or written, nor material that has been accepted for the award of any other degree or diploma, except where due acknowledgement has been made in the text.

Signed __________________

Davie Chen

(Candidate)

Abstract

Title of thesis: **The Changes of Posterior Corneal Curvature, Topographic Corneal Thickness and Corneal Biomechanical Properties from Overnight Orthokeratology Lens Wear and Recoveries of These Parameters**

Chief supervisor: **Dr. Andrew K.C. LAM**

Orthokeratology (ortho-k) is a clinical technique to temporarily reduce refractive error (mainly for myopia correction) using specially designed rigid lenses. Anterior corneal flattening, central corneal thinning and mid-peripheral corneal thickening have been documented in myopic ortho-k treatment. Researchers assumed that the posterior corneal curvature was not affected and therefore adopted the Munnerlyn's formula to predict the ortho-k effect. In contrast, overall corneal bending involving the posterior corneal curvature has been reported to account for the ortho-k changes. To date, limited information regarding the posterior corneal changes after ortho-k treatment has been reported. Also, the recovery of topographical corneal thickness has not been fully studied after successful ortho-k treatment, even though changes of corneal thickness were previously demonstrated.

On the other hand, measurement of corneal biomechanical properties required sophistical calculations. Clinical measurement of these properties (in terms of corneal hysteresis: CH, and corneal resistance factor: CRF) are now possible which may play a role to predict the efficacy of ortho-k treatment. The long-term corneal biomechanical changes from ortho-k and its recovery after the treatment have not been previously studied. This project aimed to evaluate the effect of ortho-k treatment on the posterior corneal changes, topographical corneal thickness, and corneal biomechanics variations so as to understand the mechanism of ortho-k treatment. The recoveries of these changes were also evaluated.

In this project, three studies [two short-term studies (up to one overnight) and one long-term study (up to 6 months)] were undertaken. For the short-term studies, the corneal changes after 15, 30, 60 minutes, and one overnight of ortho-k lens wear were evaluated. Short-term study I involved wearing ortho-k lenses in both eyes whereas in short-term study II, one eye (treatment eye) wore ortho-k lens and the fellow eye (control eye) wore conventional alignment fitted lens. The long-term study consisted of three phases, including a 6-month treatment period (Phase I), monitoring of diurnal changes after immediate lens removal (up to 8 hours) on the day after 6-month treatment period (Phase II), and a 2-month recovery period after cessation of successful treatment (Phase III).

In the short-term study I, significant posterior corneal steeping was found after 60 minutes and overnight ortho-k lens wear. There was significant reduction of CRF after overnight ortho-k lens wear. Significant central corneal thinning and mid-peripheral corneal thickening were found after 60 minutes and one overnight ortho-k lens wear respectively. The posterior corneal steepening has been confirmed from the short-term study II where similar posterior corneal steepening was found in the treatment eyes only. Significant corneal thickening was also found at mid-peripheral cornea after one overnight ortho-k lens wear with no significant change in the control eyes.

In the long-term study (Phase I), significant posterior corneal steepening was seen only at the first overnight visit. A significant reduction of CRF was found after one week of lens wear and gradually reduced throughout the treatment period. Significant central corneal thinning was shown after one month of lens wear while mid-peripheral thickening was shown after overnight and one-week

visits only. During the monitoring of diurnal changes (Phase II), the posterior cornea was found steepest after immediate lens removal but significantly flattened 2 hours after lens removal. Corneal biomechanical properties were stable throughout the day. The cornea was the thickest at mid-peripheral regions after immediate lens removal and significantly reduced 2 hours after lens removal. In the 2-month recovery period (Phase III), posterior corneal curvatures, topographic corneal thickness, and CRF returned to baseline level one week after cessation of lens wear.

The present study clearly shows that ortho-k treatment has transient steepening effect on the posterior corneal curvatures, which disappeared 2 hours after lens removal. Its contribution to myopia reduction was not significant clinically. The topographic corneal thickness changes are associated with the transient posterior corneal steepening. Also, the ortho-k treatment has some short-term effects on the corneal biomechanical properties. On the other hand, all these changes from ortho-k treatment are reversible and are able to return to baseline level one month after cessation of successful ortho-k treatment. It could further evident that the ortho-k treatment has no permanent influence on these corneal parameters.

List of publications and presentations

Paper published:

Chen D, Lam AK. Intrasession and intersession repeatability of the Pentacam system on posterior corneal assessment in the normal human eye. J Cataract Refract Surg. 2007;33:448-454.

Chen D, Lam AK. Reliability and repeatability of the Pentacam on corneal curvatures. Clin Exp Optom. 2009;92:110-118.

Chen D, Lam AK, Cho P. A pilot study on the corneal biomechanical changes in short-term orthokeratology. Ophthalmic Physiol Opt. 2009;29:464-471.

Chen D, Lam AK, Cho P. Posterior corneal curvature change and recovery after 6 months overnight orthokeratology treatment. Ophthalmic Physiol Opt. 2010;30:274-280.

Lam AK, Chen D. Pentacam pachometry: comparison with non-contact specular microscopy on the central cornea and inter-session repeatability on the peripheral cornea. Clin Exp Optom. 2007;90:108-114.

Conference presentations:

Chen D, Lam AK, Cho P. The effect of short-term orthokeratology treatment on corneal biomechanics and posterior corneal shape. Presented at The 16th Asia Pacific Optometric Congress, 2007. Goa, India.

Chen D, Lam AK, Cho P. Posterior corneal shape and corneal biomechanics changes with orthokeratology lens wear and their recovery. Presented at American Academy of Optometry Meeting, 2008. Anaheim, United States.

Chen D, Lam AK, Cho P. Posterior corneal shape changes with orthokeratology lens wear and its recovery. Presented at 33rd Clinical Conference & Exhibition by British Contact Lens Association, 2009. Manchester, United Kingdom.

Acknowledgements

I would like to express my gratitude to my chief supervisor, Dr. Andrew Lam for his advices and guidance throughout my postgraduate study period. I am grateful for his timeless support and endless patience during last few years. I would also sincerely thank my co-supervisor, Prof. Pauline Cho and acknowledge the help in proofreading this thesis by Professor Peter Swann and Professor Barry Collin.

I would like to truly thank my residency mentor, Mr. Vincent Chui, who taught me the technique of orthokeratology. Colleagues and friends from both research and clinic teams have given me substantial assistance and encouragement during my studies. Special thanks are given to Connie, Emily, Hang, Karry, Marco, Mavis, Maymay, Peggy, Thomas, Rachel, Forrest, Patrick, Carol, and Victoria. Sincere gratitude extends to my friends, included Frankie, Kim, Wing, Grace, Tom, Calvin, Edwin, Terence, Ruby, Cindy, Kanden, Winnie, John, Kent, Titan, Ivy, and Heidi. The friendships among them are valuable and essential to me during the past two decades. All of their supports are always the best "adrenaline" when I felt tired, sad and lonely during the difficult times.

Last, I must give my deep thanks to my family and Novem, who have given me endless care and support. They have also provided me a very high degree of freedom and let me achieve my goals in my postgraduate life.

Davie Chen

Table of Contents

Chapter 1

Review and updates on Orthokeratology

1.1 Introduction

Orthokeratology [also known as ortho-k, corneal reshaping, corneal refractive therapy (CRT), and vision shaping treatment (VST)] is a clinical technique to temporarily reduce or modify refractive error with the use of specially designed rigid lenses (Caroline, 2001). The concept of ortho-k emerged in the early 1960s. The ortho-k lens designs evolved significantly in the following decades, though the development was occasionally abandoned due to different obstacles, such as unpredictable lens centration, lens effect and non-permanent. The ortho-k treatment can be accomplished by either traditional or modern ortho-k lens designs depending on the construction of the lens curves. For the traditional ortho-k lens design, a flat-fitted lens was used to flatten the cornea (to reduce the corneal power) in order to reduce the myopia. For the modern ortho-k lens design, the flat base curve is surrounded by a much steeper reverse curve, which is specially constructed to improve the lens centration. It is termed a “reverse geometry lens”. The sophisticated lathing technology has significantly aided the development of ortho-k treatment and boosted the research interests. Clinical applications of modern ortho-k have contributed mainly to the temporary reduction of myopia (Mountford, 1997, Nichols et al., 2000) and the control of myopic progression (Cho et al., 2005, Walline et al., 2009, Kakita et al., 2011). Some ortho-k researchers reported that this treatment has a tendency to slow down the myopic progression, which is one of the main reasons why the modern ortho-k treatment is popular in the Asian Pacific region. The latest lens designs have also been developed to strive for the correction of hyperopia and astigmatism. There is a growing number of reports on hyperopic ortho-k treatment in the last three years (Lu et al., 2007b, Gifford and Swarbrick, 2008, Haque et al., 2008, Lu et al., 2008, Gifford et al., 2009, Gifford and Swarbrick, 2009) in addition to a case study for astigmatic corrections (Chan et al., 2009). The reverse geometry lens has also been adopted for fitting the post-surgical cornea to restore vision (Burns-LeGros and Wagner, 2007, Tan et al., 2010).

1.2 History and development

1.2.1 Origin of traditional ortho-k and its early development

The concept of traditional ortho-k treatment was first suggested by Jessen (1962) and known as "orthofocus" in the literature. He introduced an innovative concept of lens fitting, which was different from the conventional alignment fitting. A plano lens with base curve (BC) flatter than the corneal curvatures was used to create a tear lens (carrying negative power) between the posterior lens surface and the anterior corneal surface to correct myopia. After wearing the lenses for two months, the cornea was flattened and unaided vision was improved after lens removal. A similar idea by Jessen (1962) was applied in hyperopic cases using lenses with steeper base curve compared with the corneal curvature. Unfortunately, the technique was preliminary and not very successful probably because of the limited extent of the refractive correction, poor lens centration, and the corneal oedema caused by the impermeable lens materials. However, it undoubtedly introduced an innovative idea and a breakthrough in contact lens fitting philosophy, which has already built up a foundation for later development in ortho-k.

Hyperopic correction with a steep-lens fitting was also introduced. It was relatively easier to achieve the lens centration to provide the hyperopic correction in comparison to flat-fitting lens for myopic correction. The central corneal oedema induced by central pooling obtained in steep-fitting lenses and oxygen-impermeable lens materials was another reason, which favours hyperopic correction. It was difficult to predict the lens centration with the flat-fitting lenses and significant with-the-rule astigmatism was induced with superiorly decentred lenses. After the emergence of the concept of orthofocus, many cases of suggested lens fitting and refractive error correction were reported (Ziff, 1968a, Ziff, 1968b, Nolan, 1969, Fontana, 1972, May, 1974, Grant, 1975, Patterson, 1975, Ziff, 1976). The term “orthokeratology” was introduced by a group of enthusiastic contact lens specialists (Ziff, 1968a, Ziff, 1968b, Nolan, 1969, May, 1974, Grant, 1975, Patterson, 1975). It was also known as traditional ortho-k. This lens fitting modality was not common and was still anecdotal until the first clinical study reported by Kerns (1976). Four major series of clinical studies, including Kerns (1976), Binder et al. (1980), Polse et al. (1983b), and Coon (1984), were released to give scientific support to the previous anecdotal evidence. These studies concluded that the reduction of myopia (mean amount of refractive change) from ortho-k was limited (ranged from 0.39 D to 1.51 D), and not vastly different from conventional lenses with alignment fitting (ranged from 0.23 D to 0.96 D). In addition, the clinical outcomes were variable and unpredictable owing to poor lens centration and the regular induction of with-the-rule corneal astigmatism. Permanent elimination of refractive errors by deforming the corneal shape with traditional ortho-k lens wear was the ultimate goal of orthokeratologists.

However, only temporary reduction could be achieved with daytime wearing of retainer lenses for one to eight hours continuously or in a split schedule. It was not very useful as the exact wearing time required for the refractive correction varied and was largely dependent on the patients, who needed to wear the retainer lenses during the day. Therefore, practitioners gradually lost their interest in the traditional ortho-k treatment. Even though this technique included a certain degree of corneal oedema due to the limited oxygen permeability of the lens, it was safe, since there were no significant adverse compromises to corneal physiology, such as corneal inflammation, disruption of corneal structure, from the flattening of corneal curvatures (Polse et al., 1983a).

1.2.2 From traditional ortho-k to modern ortho-k

The development of traditional ortho-k was very limited between 1970s and 1980s. Poor lens centration with flat-fitting lenses was one of the main drawbacks in the original traditional ortho-k fitting philosophy. To address this problem, Jessen (1964) described a lens design with a flatter base curve surrounded with a steeper peripheral curve. This steeper peripheral curve aimed at improving lens centration with better lens-to-cornea alignment between the lens curvature and peripheral cornea. This concept was not implemented due to limited lens lathing technology. Fontana (1972) tried to adopt this idea to manufacture a prototypal “reverse geometry” lens, which was called “one piece bifocal” lens design, however, this lens was not accepted as a true “reverse geometry” lens but was considered to be a recessive lens design with the peripheral curve one dioptre steeper than the base curve (Mountford et al., 2004). The lens was not easy to manufacture with the lathing techniques at that time and therefore, was not popular.

In the early 1990s, there was a resurgence of ortho-k treatment due to the advances in lens design and lathing technique, availability of lens materials with higher oxygen permeability, and the computer-assisted keratography (also known as computer-assisted corneal topography).

With the advances in lens lathing technology, the first reverse geometry lenses were successfully produced (Wlodyga and Bryla, 1989, Harris and Stoyan, 1992). This started the new generation of ortho-k lens designs and was classified as “modern ortho-k”. The flat base curve created an apparent central bearing area surrounded by a wide annulus of tear reservoir, which was created by the steeper reverse curve (RC). The peripheral curve was similar to that found in ordinary conventional lens designs, which created an edge lift for tear exchange and ease of lens removal. This modern ortho-k lens design revived ortho-k researchers' interests in this technique due to the faster and more predictable clinical results. Several well-controlled clinical trials were conducted to evaluate the efficacy, predictability, and safety of treatment when wearing this new lens. The efficacy in reducing myopia with this modern ortho-k lens design was reported to be two times faster, in terms of treatment period, than the traditional ortho-k lens design, which took 60 to 300 days to complete the refractive error changes (Mountford, 1997, Swarbrick et al., 1998, Fan et al., 1999, Lui and Edwards, 2000, Nichols et al., 2000). Therefore, this modern design was named "accelerated orthokeratology". Although the lens material used in modern ortho-k lens was improved from oxygen impermeable material to low to moderate oxygen permeable material, most of the wearing modalities were still restricted to daytime only, due to insufficient oxygen permeability for overnight wear. Therefore, it was still inconvenient because the lenses had to be worn during daytime and improved unaided vision was achieved after lens removal during the rest of the day. Furthermore, good lens centration could not be predicted or achieved readily with the modern ortho-k lens design, which was still a major concern (Mountford et al., 2004).

1.2.3 Modern ortho-k at present

To ensure good lens centration, the reverse geometry lens has been redesigned to incorporate a much steeper and narrower reverse curve. An alignment curve (AC) was introduced adjacent to the reverse curve to provide a larger area for corneal contact to support the lens weight on the peripheral cornea. The centration of the lens has been much improved and this design has been renamed as “advanced orthokeratology” (Lui et al., 2000, Mountford et al., 2004). Many ortho-k lens manufacturers have adopted this design and further modified it into spherical or aspheric alignment curves. The terminology in describing the BC, RC and ACs can differ, but most of the designs of the different lens manufacturers are basically similar. Lens materials with higher oxygen permeability have considerably boosted the development of ortho-k treatment. Traditional and early modern ortho-k treatments were limited to daytime wear only due to insufficient (zero to low) oxygen permeability. Higher oxygen permeable material allows overnight wear which largely increases the convenience and popularity of this treatment (Mountford, 1997, Nichols et al., 2000), especially in the younger age groups. Children can enjoy good unaided vision upon lens removal after overnight wear. They can participate in different kinds of sports or activities without spectacles. Also, recent studies have documented its potential to retard the progression of myopia (Cho et al., 2005, Walline et al., 2009, Kakita et al., 2011). This is one of the major reasons why ortho-k lens wear is so popular in the Asian Pacific region (Cho et al., 2002a, Cho et al., 2003).

1.3 Advances in modern ortho-k development

The popularity of modern ortho-k has increased in the last two decades largely due to advanced lens designs, materials and instrumental improvement.

1.3.1 Development of lens designs from traditional to modern

The evolution of lens designs, from the original flat-fitting to the contemporary 5-curve reverse geometry lens designs, has largely boosted the popularity of the ortho-k treatment (Cheung et al., 2009). The history of the development in lens designs has been discussed in the previous section (Section 1.2).

1.3.2 Improved lens materials

The lens material in traditional ortho-k (or originally called “orthofocus”) lenses was polymethyl methacrylate (PMMA), which was oxygen impermeable. Corneal oedema was induced after wearing the lens for several hours. These lenses were not suitable for prolonged daytime wear let alone night time wear. Holden and Mertz (1984) demonstrated that the oxygen transmissibility of any lens material should reach the value of 87×10^{-9} (cm × mlO_2)/(sec × ml × mmHg) to limit corneal oedema to 4%. Harvitt and Bonanno (1999) further updated the oxygen transmissibility to 125×10^{-9} (cm × mlO_2)/(sec × ml × mmHg) to limit the corneal oedema to 3%, which is the level normally found after sleeping. There are now lens materials with higher oxygen permeability, for example, Boston XO [Dk = 100 (ISO/FATT), Material name: Hexafocon A, Bausch and Lomb, US] has been widely used in many overnight ortho-k studies (Soni et al., 2004, Alharbi et al., 2005, Cho et al., 2005, Johnson et al., 2007, Stillitano et al., 2007, Hiraoka et al., 2008). There has been no clinical study reporting significant undesirable corneal physiology in ortho-k treatment using Boston XO (Soni and Nguyen, 2006). Other lens materials with high oxygen permeability including Boston XO_2 [Dk = 141 (ISO/FATT), Material name: Hexafocon B, Bausch and Lomb, US], FluoroPerm 151 [Dk = 151 (ISO/FATT), Material name: Paflufocon D, Paragon Vision Sciences, US] and Menicon Z [Dk = 189 Fatt (Polarographic), Material name: Tisilfocon A, Menicon Co. Ltd, Japan] are currently available. The availability of these super-permeable materials could boost the development of overnight ortho-k treatment significantly. Swarbrick and Lum (2006) demonstrated that the efficacy of ortho-k treatment after wearing lower oxygen transmissibility lenses (Boston EO) was significantly slower than wearing lenses with higher oxygen transmissibility (Boston XO), in terms of uncorrected vision (UCV), refractive error, corneal apical radius, and asphericity. They also demonstrated greater corneal stromal oedema in ortho-k treatment after wearing lenses with lower oxygen transmissibility than wearing lenses with higher oxygen transmissibility. Therefore, practitioners are encouraged to use lenses with high oxygen transmissibility.

After sleeping with the lenses overnight without compromising corneal physiology, wearers can enjoy good unaided vision upon lens removal the next morning. Compared with ordinary rigid lens wear, ortho-k provides more benefits to wearers, especially for children. Overnight ortho-k is easier for lens adaptation without extensive lens awareness during the closed eye condition, and there are reduced eyelid and lens interaction, and no disturbance by wind or dust being trapped under the lens during sleep.

1.3.3 Computer-assisted keratography

Computer-assisted keratography provides comprehensive corneal information including anterior and posterior corneal topography, apical radius, eccentricity and topographic corneal thickness. Different topographic maps are available and can be compared by modern corneal topographers. This enhances the ease of monitoring the modern ortho-k effect. The relationship between alignment curves and the peripheral cornea is important to determine good lens centration. Lens selection and modification are greatly dependent on the simulated keratometric readings and eccentricity values (Mountford et al., 2004). The topographic corneal curvature data from contemporary corneal topographers have significantly contributed in the achievement of good lens centration (Mountford, 1997, Caroline, 2001).

1.4 Current objectives of modern ortho-k

There are several main objectives of fitting modern ortho-k lenses. The first is to temporarily reduce refractive errors, including myopia, hyperopia, and astigmatism. Another clinical application of ortho-k (or reverse geometry lens) lenses could be for restoring residual vision in post-surgical corneas (Burns-LeGros and Wagner, 2007, Tan et al., 2010). The development of modern ortho-k for myopic correction is well established and the popularity of hyperopic and astigmatic corrections is increasing with more and more clinical studies and case reports becoming available (Lu et al., 2007b, Gifford and Swarbrick, 2008, Haque et al., 2008, Lu et al., 2008, Chan et al., 2009, Gifford et al., 2009, Gifford and Swarbrick, 2009).

Another objective is to control the myopic progression during early childhood. Cho et al. (2005) first reported that ortho-k treatment has the potential to slow down the progression of myopia. Recent studies reported similar reduced axial elongation in an ortho-k group, which further supports the proposal that ortho-k treatment can reduce eye growth (Walline et al., 2009, Kakita et al., 2011). A series of animal studies by Smith et al. (2005, 2007, 2009) suggested that the peripheral retina might play a more significant role in the myopia progression. Deprivation of signals from the fovea through photocoagulation did not affect the emmtropization in primates. In contrast, induced by hyperopic defocus by minus lens on the retina could trigger eyeball elongation. Relative myopia at the periphery induced by ortho-k treatment might possibly account for the potential influence in retarding myopia progression. Previous study by Charman et al. (2006) compared the refractive changes along the horizontal meridian and up to ± 34 degree with reference to the fixation axis after ortho-k treatment. They found ortho-k is a good way to correct relative hyperopia to myopia at the retinal periphery after the lens wear. A recent study by Mathur and Atchison (2009) not only found changes in peripheral refraction (from hyperopia to myopia), but also a dramatic increase in peripheral higher-order aberrations after ortho-k lens wear. These refractive changes (increase of peripheral myopia and higher-order aberrations) induced by the ortho-k treatment, have been suggested as a means of slowing down progression of myopia. However, further studies are required to warrant ortho-k treatment on the basis of these findings.

1.5 Latest studies on corneal changes with modern ortho-k treatment

Many recent studies used ortho-k lenses with the current ortho-k lens designs [with base curve, reverse curve, one or two alignment curves and PC (peripheral curve)], which are 4- and 5-curve designs. Several clinical studies have reported on the effect of ortho-k on vision, refractive error, corneal thickness, corneal curvature, corneal recovery after cessation of treatment, control of myopia and changes in corneal or ocular aberrations. The following sections focus on the recent studies on the efficacy of ortho-k treatment, corneal changes, corneal biomechanics and topographic corneal thickness.

1.5.1 Corneal changes with modern ortho-k treatment

Anterior corneal curvatures rapidly flattened following as little as 10 minutes of lens wear with the modern ortho-k lens design (Sridharan and Swarbrick, 2003). Most of the previous studies demonstrated that it took seven to 10 days to achieve a target refractive error change, of approximately 2.50 D (Walline et al., 2004, Johnson et al., 2007, Kang et al., 2007, Stillitano et al., 2008). Correspondingly, the refractive errors and unaided vision are reduced and improved respectively. All of the above corneal changes can occur rapidly, which helps to achieve the targeted refractive error. The major benefit of these rapid corneal responses is allowing good unaided vision during the day. Also, if there is any undesirable lens performance from the treatment, ortho-k practitioners can immediately modify the lens parameters to achieve a better effect.

On the other hand, the flattened cornea starts to return to its original shape during the day after lens removal in the morning, which results in regression to myopia. After four weeks of treatment, the effect can be sustained for at least eight hours after lens removal, which is adequate to provide good unaided vision throughout the day (Kang et al., 2007). Reports of the duration of recovery from ortho-k effect vary within the literature. Soni et al. (2004) found that the ortho-k effect in spherical equivalent refraction (SER) vanished completely one week after cessation of lens wear while Kobayashi et al. (2008) reported that a longer discontinuation period (2 months) was required for complete recovery. Wu et al. (2009) recently reported that the residual flattening from ortho-k treatment in terms of mean keratometric reading remained even after 2 weeks of discontinuation.

Visual acuity (VA) at high contrast levels is not affected by the modern ortho-k treatment. However, the VA at low contrast level is reduced. The deterioration of low contrast visual acuity is attributed to the increased higher-order aberrations, such as spherical aberrations and coma (Berntsen et al., 2005). With the modern ortho-k treatment, the central cornea is flattened, while the mid-peripheral cornea is steepened, which has been termed as ‘sphericalization’

(Sridharan and Swarbrick, 2003). The cornea becomes an oblate ellipse and therefore spherical aberration is induced. Also, the centration of the treatment zone may not be located exactly on the central cornea. The slightly decentred treatment zone would induce coma, either vertical or horizontal. These induced aberrations can significantly affect the VA at low contrast level.

Anterior corneal flattening, the main contributor to myopic reduction in ortho-k treatment, has been well documented in the literature (Alharbi et al., 2005, Jayakumar and Swarbrick, 2005, Kang et al., 2007, Stillitano et al., 2008). Myopic reduction from both ortho-k treatment and photorefractive surgery is achieved by flattening the anterior corneal curvature to redirect the light rays to the retina. Some corneal researchers have attempted to demonstrate corneal changes from ortho-k treatment and photorefractive keratectomy using similar experimental methods (Swarbrick et al., 1998, Caroline, 2001). Munnerlyn's formula has been widely used to predict the corneal power change in photorefractive surgery, where the corneal power change is derived from the depth and diameter of the ablation zone (Munnerlyn et al., 1988). Swarbrick et al. (1998), used Munnerlyn's formula to predict the reduction of myopia with the change of corneal sagittal height and treatment zone diameter in ortho-k treatment. However, the formula assumes that the posterior corneal curvature does not alter after photorefractive surgery (Munnerlyn et al., 1988, Owens et al., 2004b). Swarbrick et al. (1998) found epithelial thinning in the central cornea and thickening at the periphery (including mid-periphery). Therefore, they suggested that the mechanism of ortho-k treatment is solely due to a redistribution of the anterior corneal tissues rather than an overall corneal bending. Although they used the Holden-Payor optical micropachometer, their measurements of corneal epithelial thickness could be questionable since the optical resolution is not high enough to identify the corneal layers. Choo et al. (2004) successfully demonstrated that the histological changes with ortho-k lens wear at the cellular level in a cat model. The epithelial cells are rapidly compressed in the central cornea and thickened in the mid-periphery. The cell structures are remained intact, which indicated an exchange of intra-cellular contents between cells, and migration of cells from central to mid-periphery. Their important work has supported the suggested mechanism of redistribution of the anterior corneal tissue in ortho-k treatment. However, this was an animal study and the epithelial cells investigated were limited to only a few time points. The gradual changes or recovery of epithelial cells were not observed. In addition, only one lens design was used in that study and other lens designs might generate different results. No investigation of posterior corneal changes after ortho-k treatment was reported in their study.

With the use of Purkinje image technique, Owens et al. (2004) derived the posterior corneal curvature and first reported that it was significantly flattened with ortho-k treatment, but only after 1 week and not at any other visit within a month. More recent studies have demonstrated that short (e.g. 1 week) (Stillitano et al., 2007) or long (e.g. 1 year) (Tsukiyama et al., 2008) ortho-k treatments have no effect on the posterior corneal surface. Different instruments were utilized in their studies, while Orbscan and Pentacam were used by Stillitano et al. (2007) and Tsukiyama et al., (2008) respectively. However, the reduction in myopia with ortho-k treatment cannot be explained fully by the change to anterior corneal curvature (Lu et al., 2007a). It might be attributed, in part, to a change in posterior corneal curvature, which is yet to be fully understood.

Perhaps more studies on the effect on the posterior corneal curvature could help to understand the mechanism of ortho-k treatment and refractive changes. Posterior corneal curvature changes have not been studied fully because it was not easy to measure. Orbscan was commonly used to study the changes in posterior corneal shape (Wang et al., 1999, Kamiya et al., 2000, Naroo and Charman, 2000, Baek et al., 2001, Seitz et al., 2001, Miyata et al., 2002), but Maloney (1999) has questioned its accuracy in evaluating posterior corneal displacement. Recently, Read and Collins (2009) studied the diurnal variation of posterior corneal curvature with the use of Scheimpflug image-based corneal topography. They found that the posterior cornea changes significantly in non-contact lens wearers throughout 24 hours. The posterior cornea steepened immediately after sleep and it returned to baseline level within 2 to 3 hours after eye opening. Further study applying this instrument to measure and monitor posterior corneal change with modern ortho-k treatment is required.

1.5.2 Corneal biomechanics

Corneal biomechanical properties include corneal viscosity, elasticity, hydration, connective tissue position and regional corneal thickness (Liu and Roberts, 2005). Clinical measurement of corneal biomechanics was difficult since sophisticated calculations were required that were inconvenient for clinicians.

The Ocular Response Analyzer (ORA, Reichert Inc., US) is a non-contact tonometer which provides in vivo measurements of corneal biomechanical properties (Luce, 2005). The instrument measures both inward and outward corneal responses with a metered air-pulse and an electro-optical monitoring system. An air pulse deforms the cornea until it reaches a pre-defined flattened shape and the emitted infra-red light rays are maximally reflected by the flattened cornea to the receiver. This is the first peak signal and the corresponding flattening pressure is the first applanation pressure (P1). The air pulse strength increases continuously to deform the cornea until it reaches a slight concavity. The concave cornea reflects the light rays in different directions away from the receiver. Subsequently, the air pulse generator stops increasing the strength of the air pulse. The cornea then gradually returns to the pre-defined flattened shape and back to its original convexity. When the cornea has returned to the pre-defined flattened state, the light rays are reflected maximally to the receiver. The corresponding pressure is the second applanation pressure (P2). For a perfectly elastic material, there should be no pressure difference in the air-pulse between the first and second applanation signals. The cornea does not act like an elastic material. A difference between the first and second applanation pressures has been demonstrated. The manufacturer of ORA termed the difference between P1 and P2 as corneal hysteresis (CH), which is a new parameter measuring the viscous damping of the cornea. Corneal resistance factor (CRF) is another parameter determined with a formula (P1 minus k * P2), where k is a constant. This constant factor is 0.7, which is determined by P1, P2 and central corneal thickness (CT) (Kotecha et al., 2006). The CRF is suggested as a measurement of “overall resistance” of the cornea (Luce, 2005).

After the first report by Luce (2005), ORA has gained more and more popularity and has recently aroused the interest of corneal researchers in the biomechanical properties of the cornea. Several recent studies have reported CH and CRF in normal patients. A number of studies have investigated the variations of CH and CRF with age (Kotecha et al., 2006, Kida et al., 2008), their relationships with the central corneal thickness (Kida et al., 2006, Kotecha et al., 2006, Shah et al., 2006, Lam et al., 2007, Lu et al., 2007c), and with axial length (Lim et al., 2008, Shen et al., 2008, Wells et al., 2008). Changes of CH and CRF after refractive surgery (Luce, 2005, Ortiz et al., 2007, Pepose et al., 2007, Kirwan and Okeefe, 2008), from contact lens wear (Lu et al., 2007c), from ocular massage (Lam and Chen, 2007a), from photodynamic collagen cross-linking treatment (Goldich et al., 2009), from short-term ortho-k (Gonzalez-Meijome et al., 2008b) and after glaucoma treatment (Sun et al., 2009) have also been reported (Table 1.1). Corneal biomechanical properties could also be different in pathological ocular conditions, for example, a cornea with keratoconus (Luce, 2005, Ortiz et al., 2007, Shah et al., 2007), Fuchs' dystrophy (Luce, 2005) and glaucoma (Mangouritsas et al., 2008, Kotecha et al., 2009).

Table 1.1. Summary of corneal hysteresis and corneal resistance factor changes with different interventions in previous studies.

Studies	Intervention	Corneal biomechanics (mmHg)					
		Corneal hysteresis (CH)			Corneal resistance factor (CRF)		
		Before	After	Changes	Before	After	Changes
Luce, 2005	LASIK	-	-	(Decrease)	-	-	-
Ortiz et al., 2007	LASIK	10.4 ± 1.7	9.3 ± 1.9	-1.1 (Decrease)	10.1 ± 2.0	8.1 ± 1.8	-2.0 (Decrease)
Pepose et al., 2007	LASIK	9.7 ± 1.8	8.0 ± 1.6	*-1.7 ± 1.5 (Decrease)	9.5 ± 1.9	6.7 ± 1.7	*-2.8 ± 1.6 (Decrease)
Kirwan and Okeefe, 2008	LASIK	10.8 ± 1.4	9.0 ± 1.3	*-1.9 ± 1.2 (Decrease)	-	-	-
	LASEK	10.7 ± 1.7	8.6 ± 2.1	*-2.2 ± 1.3 (Decrease)	-	-	-
Lu et al, 2007c	Contact lens patching (3 hours)	11.5 ± 1.4	11.6 ± 1.1	+0.1 (Increase)	9.6 ± 1.9	10.2 ± 1.5	*+0.6 (Increase)
Lam and Chen, 2007a	Ocular massage (10 minutes)	11.0 ± 1.3	11.6 ± 1.5	*+0.5 (Increase)	11.0 ± 1.6	10.7 ± 1.7	*-0.3 (Decrease)
Goldich et al., 2009	Photodynamic collagen cross-linking treatment (6 months)	8.4 ± 1.3	8.1 ± 1.3	-0.3 (Decrease)	7.2 ± 1.8	7.2 ± 1.5	0.0 (No change)
Sun et al., 2009	Treatment for chronic primary angle closure glaucoma (4 weeks)	6.8 ± 2.1	9.5 ± 1.7	*+2.7 (Increase)	-	-	-

LASIK and LASEK = Laser in situ keratomileusis and Laser-assisted subepithelial keratectomy respectively.
* indicates significant difference obtained before and after intervention in the study reported.

The role of corneal biomechanics in long-term ortho-k is still unclear. Could corneal biomechanics be used to predict the ortho-k effect? In the 1980s, Polse et al. (1983b) reported that the cornea could return to its original shape after cessation of lens wear due to its elastic property. They were probably the first group to consider the biomechanical properties of the cornea in ortho-k treatment. Carkeet et al. (1995) attempted to correlate ocular rigidity with the efficacy of the ortho-k effect. They were unable to ascertain any relationship with ocular rigidity in various responders. The derived ocular rigidity, obtained by Friedenwald's formula, was a measure of the elastic properties of the whole eyeball, rather than just corneal biomechanics (Carkeet et al., 1995).

Presently, modern ortho-k lens design possesses a much steeper reverse curve, and one or two alignment curves, compared with the previous 3-curve lens design (Carkeet et al., 1995, Dave and Ruston, 1998, Swarbrick et al., 1998, Lui and Edwards, 2000). The profile of tear layer thickness is no longer identical to the 3-curve design while a narrower and deeper tear reservoir is formed under the reverse curve (Mountford et al., 2004). The differential thickness of the tear layer between the posterior lens surface of these reverse geometry lenses and the anterior corneal profile creates a relative positive pressure at the corneal centre and a negative pressure at the mid-periphery. This pressure difference is believed to reshape the cornea causing a dramatic change, including both the anterior (Alharbi et al., 2005, Cho et al., 2005, Hiraoka et al., 2006, Johnson et al., 2007, Tsukiyama et al., 2008) and possibly posterior corneal curvatures (Owen et al., 2004). Alharbi et al. (2005) hypothesized that the relative positive pressure under the lens centre of the reverse geometry lens generates a clamping effect, which restricts hypoxic oedema induced from sleeping whilst wearing ortho-k lenses. This positive pressure may alter corneal biomechanics.

Gonzalez-Meijome et al. (2008b) were the first group to study the correlations of CH and CRF with the changes in keratometry after 3-hours of ortho-k lens wear. They demonstrated a positive relationship between steepest keratometry reading change in ortho-k treatment phase and corneal hysteresis, while negative relationship was obtained in recovery phase. Based on the results, they suggested that the mechanism of ortho-k treatment involves corneal bending in addition to corneal epithelial change. However, no posterior corneal measurement was involved in their study to support their suggestion of corneal bending with ortho-k treatment. Also, the sample size was small and the short duration of ortho-k lens wear was limited to 3 hours only. Long-term changes in corneal biomechanics with ortho-k treatment were not studied.

Knowledge of the short- and long-term corneal biomechanical changes when undergoing ortho-k treatment and recovery is still very limited: the corneal parameters CH and CRF may be affected in ortho-k. Could they play a role in predicting the efficacy of ortho-k?

1.5.3 Topographic corneal thickness

Swarbrick et al. (1998) were the first to report epithelial thinning after one week of ortho-k treatment and hypothesized that the myopic reduction during ortho-k is achieved by the redistribution of the epithelial cells and the anterior stroma. Both compression of epithelial cells and loss of the superficial epithelial layer have also been suggested. Some studies on overnight ortho-k treatment further demonstrated induced epithelial thinning in the central cornea, but without the involvement of the corneal stroma (Alharbi and Swarbrick, 2003, Wang et al., 2003). Mid-peripheral corneal thickening, which originates in the corneal stroma after ortho-k lens wear, has been further revealed (Alharbi and Swarbrick, 2003, Wang et al., 2003). Choo et al. (2004) have shown compression and thickening of epithelial cells at different corneal regions with ortho-k lens wear, which has been discussed in the previous section (Section 1.5.1).

For the endothelium, no changes in cell density or morphology were found (Fan et al., 1999, Hiraoka et al., 2004). Most of these studies measured the corneal thickness along the horizontal meridian only, while other locations were not reported. This might be due to the limitations of the instruments since the eye is required to look up and down for the vertical meridian measurement, which might be hindered by the eyelids. Modified optical pachymeter or optical coherence tomographer (OCT) was used, which might limit the measurements of corneal thickness along the horizontal meridian. Further study is required to investigate topographic corneal thickness changes with ortho-k lens wear.

1.6 Conclusions

The technique of ortho-k has being developing for nearly five decades. It is a clinical technique to reduce refractive error temporarily, improve unaided vision and possibly control myopic progression. The efficacy of this technique is well documented. Many uncertainties and problems with this technique have been raised in previous studies. In particular, the involvement of the posterior cornea and corneal biomechanics in ortho-k treatment are still unclear. These uncertainties aroused the author’s interest to investigate the short- and long-term changes in posterior corneal shape and corneal biomechanics with the modern ortho-k treatment.

Chapter 2

Aims of the study

2.1 Knowledge gaps

The uncertainties regarding changes in the posterior corneal curvature, corneal biomechanics and topographic corneal thickness with ortho-k lens wear have been pointed out in the previous chapter. This is the first study to investigate changes in all these parameters with ortho-k lens wear.

2.2 Aims of the study

The aims of this study are to investigate the short-term and long-term ortho-k effects on corneal parameters including posterior corneal curvature, corneal biomechanical properties and topographical corneal thickness. In addition, the long-term ortho-k effects and recovery from cessation of successful lens wear on these corneal parameters are investigated.

The questions asked include:

1. What are the short-term effects of ortho-k on the posterior corneal curvature, corneal biomechanical properties and topographical corneal thickness?

To address this question, the above parameters will be measured with the use of a new corneal topographer and ORA, after short-term (from minutes up to one overnight) ortho-k lens wear.

Null hypothesis: There is no change in the posterior corneal curvature, corneal biomechanical properties and topographical corneal thickness after short-term ortho-k treatment.

2. What are the long-term ortho-k effects on posterior corneal curvature, corneal biomechanical properties and topographical corneal thickness?

   To address this question, the above parameters will be measured, with the use of the corneal topographer and ORA, after a long-term (6 months) ortho-k lens wear.

   Null hypothesis: There is no change in the posterior corneal curvature, corneal biomechanical properties and topographical corneal thickness after long-term ortho-k treatment.

3. How do posterior corneal curvature, corneal biomechanical properties and topographical corneal thickness return to normal during the daytime after lens removal with ortho-k treatment?

To address this question, the above parameters will be monitored after lens removal, with the use of the corneal topographer and ORA, on the first day after 6 months of ortho-k lens wear.

Null hypothesis: There is no change in the posterior corneal curvature, corneal biomechanical properties and topographical corneal thickness during the first day after lens removal from successful ortho-k lens wear.

4. How do posterior corneal curvature, corneal biomechanical properties and topographical corneal thickness return to their original state after the cessation of lens wear after long-term of ortho-k treatment?

   To address this question, with the use of the corneal topographer and ORA, the above parameters will be measured over a 2-month recovery period after cessation of long-term ortho-k treatment.

   Null hypothesis: There is no change in the posterior corneal curvature, corneal biomechanical properties and topographical corneal thickness within 6 months after ortho-k treatment.

Chapter 3

An evaluation of a rotating Scheimpflug based corneal topography, the Pentacam system

3.1 Introduction

This chapter will evaluate the performance of a rotating Scheimpflug based corneal topographer, the Pentacam system. The Pentacam is an essential instrument used in this project to assess the longitudinal changes in anterior and posterior corneal curvatures, and topographic corneal thickness with ortho-k lens wear. Therefore, an instrument giving repeatable measurements is very important. Detailed investigations of its performance, in terms of intra-observer reliability and inter-session repeatability, on a number of corneal parameters including, anterior and posterior corneal curvatures at the corneal centre and mid-periphery, and topographic corneal thickness will be discussed in this chapter.

3.2 Methodology

3.2.1 Subjects

Thirty-nine subjects (20 males and 19 females) were recruited, who were free from ocular and general diseases. One eye was randomly selected from each of these subjects (19 right and 20 left eyes). All subjects were aged from 20 to 26 years [mean ± standard deviation (SD): 22.3 ± 1.9 years]. They had normal VA (6/6 or better) with a mean ± SD SER of −3.28 ± 2.93 D. The exclusion criteria included a history of corneal abnormality, refractive surgery or orthokeratology treatment. All procedures followed the Declaration of Helsinki and the protocol was reviewed and approved by the Ethics Committee of the university. Informed consent was obtained from the subjects after the procedures were explained.

3.2.2 Instrument

The Pentacam system (Oculus, Germany) is a rotating Scheimpflug imaging-based corneal topographer. Figure 3.1 shows the instrument used in the current study. The system can be selected to capture 25 or 50 slit images per scan each containing 500 data points per image. In 2005, an updated version, Pentacam HR (Oculus, Germany) was commercially launched, which is slightly different from the original version. The new version is equipped with a 1.45 megapixel camera to maximally capture up to 100 Scheimpflug images per scan and 1,380 data points per image.

In the current study, the original system with the "25 image mode" was used and the software version was 1.12. Subjects were asked to fixate on an internal target inside the instrument. The joystick was adjusted until a perfect alignment was obtained. The instrument automatically took one scan by rotating the camera 360 degrees. Twenty-five Scheimpflug images were captured within 2 seconds from each scan. A 3-dimensional mathematical model of the anterior segment was constructed. The corneal parameters were automatically generated. Only scans registered as ‘‘OK’’ according to the Examination Quality Specifications of the Pentacam were stored. If the quality of scan was affected by different errors, including poor fixation, misalignment or missing segments, yellow or red colour with the error was shown. According to the user’s manual, examiner is suggested repeating the scan if the Examination Quality Specifications is not registered as “OK”.

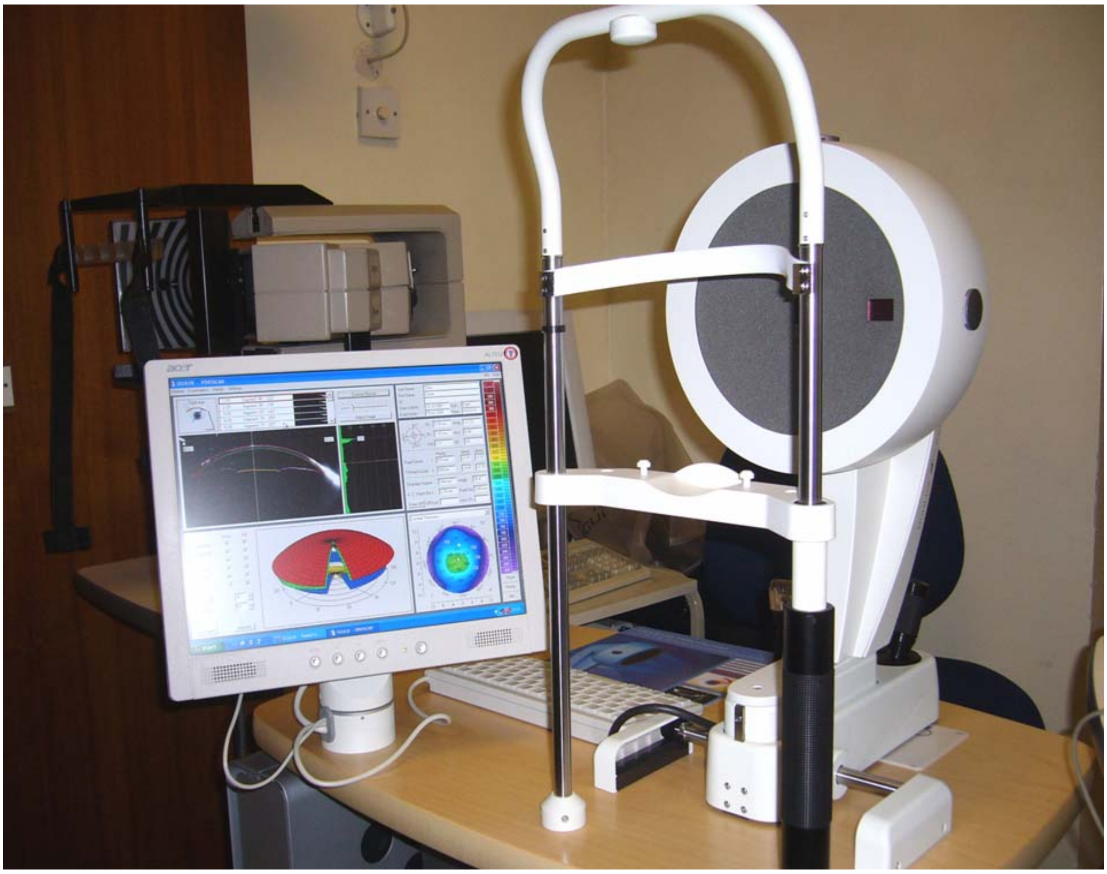


Figure 3.1. The front view of the Pentacam system.

3.2.3 Study protocol

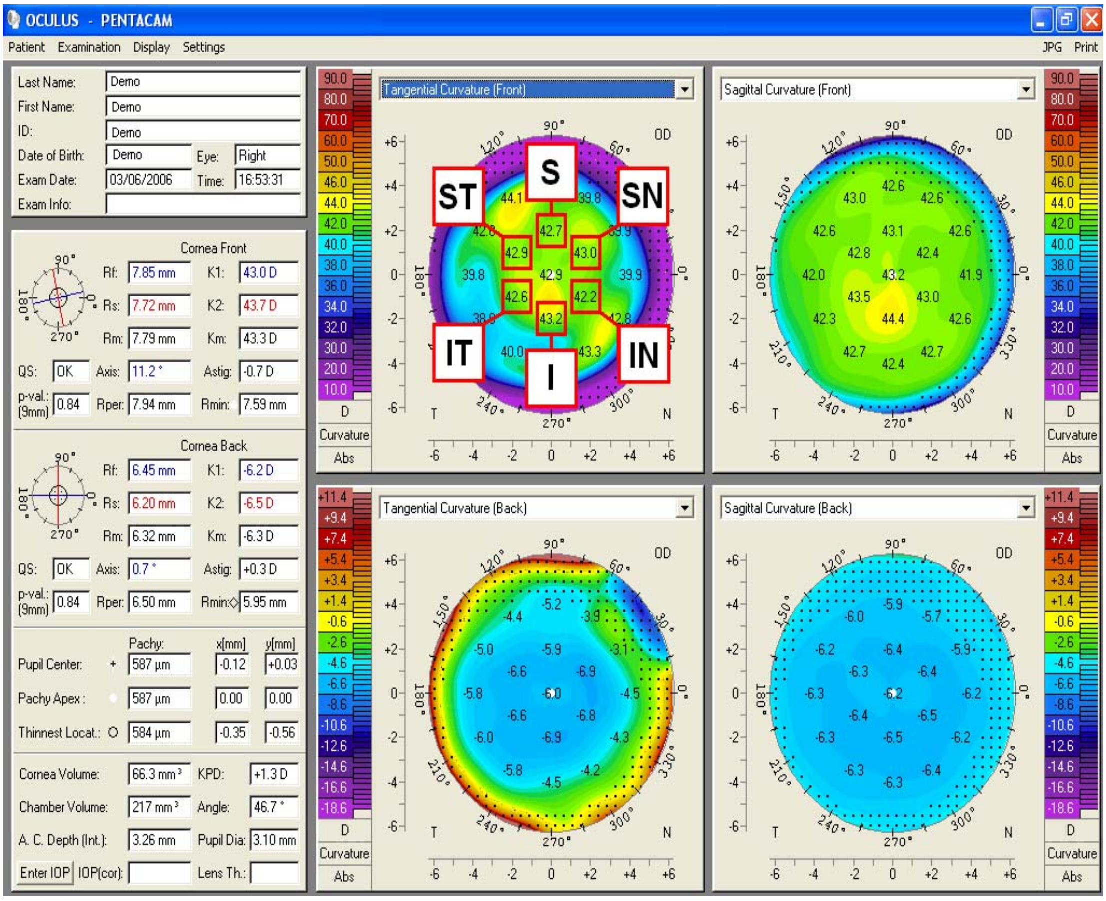
Three consecutive images were captured for intra-observer reliability analysis. For inter-session repeatability analysis, the same procedures were repeated on a separate day, one to two weeks apart, at approximately the same time of day to minimize the diurnal effects. All the measurement data were stored in the computer system on the measurement day and retrieved for analysis on another day.

3.2.4 Measurements

3.2.4.1 Anterior and posterior simulated keratometric readings and mid-peripheral corneal curvatures

The simulated keratometric (Sim K) readings along the flattest and steepest meridians were studied in the central 3.0 mm zone. The Sim K readings were further converted into rectangular Fourier form using the orthogonal power vector methods developed by Thibos et al. (1997). The vector presentation included M, J_0 and J_{45}, which are mean keratometric reading, power vectors along horizontal or vertical meridians, and along oblique meridians, respectively. For the mid-peripheral corneal curvatures (mPCC), six automated mPCC measurements in the 4.0 mm zone were extracted. These were 60 degrees apart and generated at a 2.0 mm radius from the corneal apex. Figure 3.2 shows the locations at which the six mPCC were extracted from the Pentacam. As either right or left eye was included; all of the left eye data were transposed into the same convention with reference to the right eye in the data analysis. Figures 3.3 and 3.4 are schematic diagrams demonstrating how the Sim K readings and mPCC from the right and left eyes were matched in the transposition. The six mPCC were categorised as superior, superior nasal, inferior nasal, inferior,

inferior temporal and superior temporal. Both tangential and axial curvatures were analysed.



Last Name: Demo
First Name: Demo
ID: Demo
Date of Birth: Demo Eye: Right
Exam Date: 03/06/2006 Time: 16:53:31
Exam Info:

Cornea Front
Rf: 7.85 mm K1: 43.0 D
Rs: 7.72 mm K2: 43.7 D
Rm: 7.79 mm Km: 43.3 D
QS: OK Axis: 11.2 ° Astig: -0.7 D
p-val.: (9mm) 0.84 Rper: 7.94 mm Rmin: 7.59 mm

Cornea Back
Rf: 6.45 mm K1: -6.2 D
Rs: 6.20 mm K2: -6.5 D
Rm: 6.32 mm Km: -6.3 D
QS: OK Axis: 0.7 ° Astig: +0.3 D
p-val.: (9mm) 0.84 Rper: 6.50 mm Rmin: 5.95 mm

	Pachy:	x[mm]	y[mm]
Pupil Center: +	587 µm	-0.12	+0.03
Pachy Apex :	587 µm	0.00	0.00
Thinnest Locat.: ○	584 µm	-0.35	-0.56

Cornea Volume: 66.3 mm³ KPD: +1.3 D
Chamber Volume: 217 mm³ Angle: 46.7 °
A. C. Depth (Int.): 3.26 mm Pupil Dia: 3.10 mm
Enter IOP IOP(cor): Lens Th.:

Figure 3.2. An example of the Pentacam printout (Right eye) extracted from the system. The numbers squared are corneal curvatures at the 4 mm zone defaulted by the system.

S = Superior, SN = Superior nasal, IN = Inferior nasal, I = Inferior, IT = Inferior temporal, ST = Superior temporal

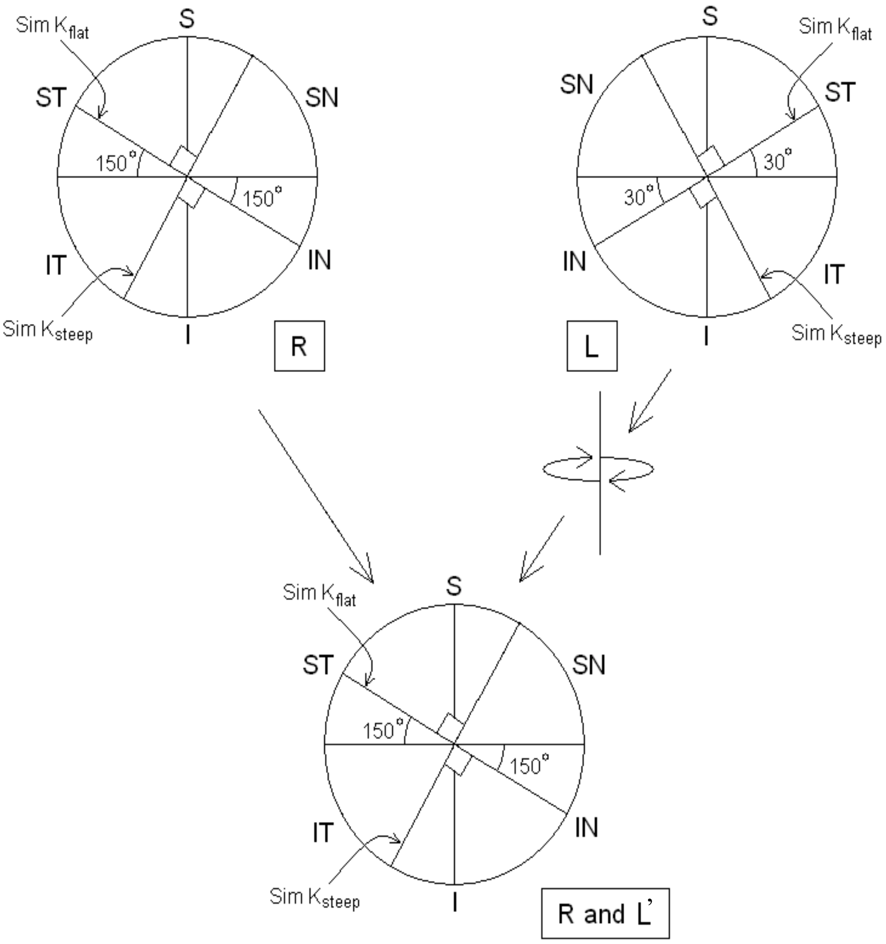


Figure 3.3. The central simulated keratometric readings. Data from the left eye has been transposed to match with that from the right eye for data analysis.

R and L = Right and left eyes respectively, L' = Transposed left eye.

Sim K$_{flat}$ and Sim K$_{steep}$: Flattest and steepest simulated keratometric reading respectively

S = Superior, SN = Superior nasal, IN = Inferior nasal, I = Inferior, IT = Inferior temporal, ST = Superior temporal

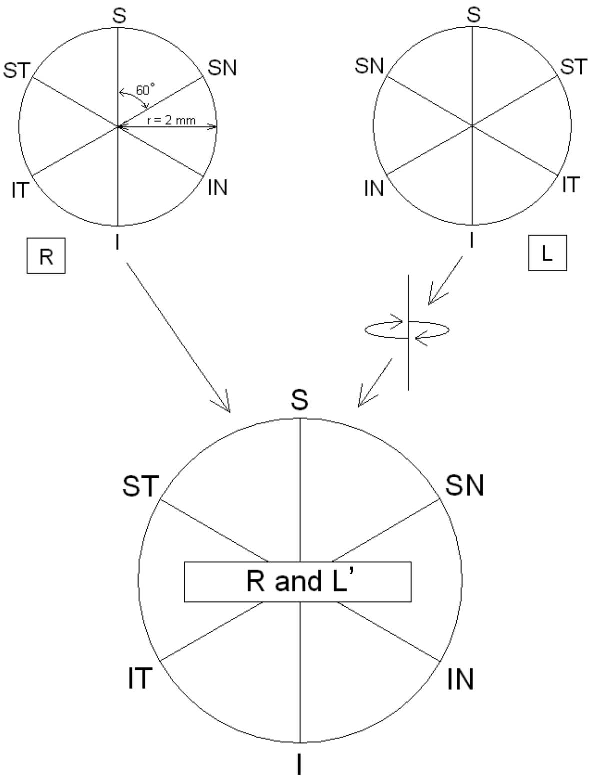


Figure 3.4. The peripheral corneal curvatures at 6 locations. Data from the left eye has been transposed to match with that from the right eye for data analysis.

R and L = Right and left eyes respectively, L’ = Transposed left eye.

S = Superior, SN = Superior nasal, IN = Inferior nasal, I = Inferior, IT = Inferior temporal, ST = Superior temporal

3.2.4.2 Anterior and posterior best-fit spheres

The anterior and posterior reference best-fit spheres (BFS) were automatically generated by the system software at central 5 mm and 8 mm diameter zones, respectively. The average BFS, calculated from 3 consecutive readings, was compared between visits.

3.2.4.3 Topographic corneal thickness

Topographic corneal thickness was measured. The central corneal thickness refers to corneal thickness measured at the corneal apex and the mid-peripheral corneal thickness refers to corneal thickness at the nasal, inferior, temporal and superior regions at distances of 1.5 mm and 2.5 mm from the corneal apex, respectively. Corneal thickness at different regions was determined and compared at the two visits.

3.2.5 Statistical analysis

Statistical analysis was performed using the SPSS software (version 13.0, SPSS, Inc.). The intra-observer reliability of all parameters was tested using the Cronbach's alpha test (α) and the intra-class correlation coefficient (ICC). In general, an α value of 0.70 is considered satisfactory but a value of 0.90 is required in clinical applications (Bland and Altman, 1997). For the ICC, a value above 0.75 indicates good intra-observer reliability. Most clinical applications require a value of at least 0.90 (Portney and Watkins, 2000). For inter-session repeatability analysis, all parameters were compared between visits. All the data were tested for normality using the Kolmogorov-Smirnov test. The level of significance was set at 5%. Agreements between the two visits were studied using the Bland-Altman limits of agreement (Bland and Altman, 1986). The coefficient of repeatability (COR; ± 1.96 * SD of the differences) was calculated to provide an interval in which 95% of the differences between visits fell. Agreement between two visits was studied using two approaches. The first approach compared the first readings of the two visits, whereas, the second used the average of three consecutive readings from each visit for comparison. Relative repeatability (RR) was calculated as a percentage of the ratio of COR to the mean value of the measure to enhance the ease of clinical interpretation of the results (Shankar et al., 2008).

3.3 Results

3.3.1 Intra-observer reliability

3.3.1.1 Anterior and posterior simulated keratometric readings and mid-peripheral corneal curvatures

The intra-observer reliability of the Pentacam system was shown to be very good in the anterior and posterior Sim K measurements ($\alpha \geq 0.990$; ICC ≥ 0.972) (Table 3.1). It was also reliable in the power vectors (M, J_0 and J_{45}) at the anterior corneal surface ($\alpha \geq 0.960$; ICC ≥ 0.888) but was generally decreased at the posterior corneal surface ($\alpha \geq 0.896$; ICC ≥ 0.742). Comparable results were also demonstrated in the six mPCC calculated from the tangential map at the anterior corneal surface, and was very reliable ($\alpha \geq 0.965$; ICC ≥ 0.901) (Table 3.2). The results for the anterior axial mPCC were similar and even more reliable ($\alpha \geq 0.995$; ICC ≥ 0.984). For the posterior mPCC, the tangential corneal curvatures indicated good reliability ($\alpha \geq 0.950$; ICC ≥ 0.863) except at the superior region ($\alpha = 0.891$; ICC = 0.732). The reliability indices were higher for the axial posterior corneal curvatures at all regions ($\alpha \geq 0.970$; ICC ≥ 0.916).

Table 3.1. The reliability indices of simulated keratometric readings along the flattest and steepest meridians, power vectors (M, J_0 and J_{45}) at the anterior and posterior corneal surfaces.

	Parameters	**α**	**ICC**
Anterior	**Sim K_{flat}**	0.999	0.996
	Sim K_{steep}	0.999	0.997
	M	0.998	0.995
	J_0	0.993	0.979
	J_{45}	0.960	0.888
Posterior	**Sim K_{flat}**	0.990	0.972
	Sim K_{steep}	0.994	0.983
	M	0.990	0.970
	J_0	0.925	0.804
	J_{45}	0.896	0.742

α = Cronbach's alpha; ICC = Intra-class Correlation Coefficient

Sim K_{flat} and Sim K_{steep} = Simulated keratometric readings along flattest and steepest meridians respectively

M = Mean of the Flattest and Steepest simulated keratometric readings, J_0 = Power vector along 90° / 180°; J_{45} = Power vector along 45° / 135°

Table 3.2. The reliability indices of mid-peripheral corneal curvatures at the anterior and posterior corneal surfaces.

		Tangential		**Axial**	
	Regions	**A**	**ICC**	**α**	**ICC**
Anterior	**S**	0.965	0.901	0.997	0.990
	SN	0.988	0.965	0.995	0.986
	IN	0.984	0.953	0.997	0.990
	I	0.987	0.963	0.995	0.984
	IT	0.994	0.982	0.997	0.990
	ST	0.972	0.919	0.995	0.986
Posterior	**S**	0.891	0.732	0.970	0.916
	SN	0.961	0.892	0.979	0.940
	IN	0.952	0.869	0.979	0.940
	I	0.968	0.909	0.982	0.948
	IT	0.950	0.863	0.982	0.947
	ST	0.954	0.874	0.987	0.961

α = Cronbach's alpha; ICC = Intra-class Correlation Coefficient

S = Superior, SN = Superior nasal, IN = Inferior nasal, I = Inferior, IT = Inferior temporal, ST = Superior temporal

S, SN, IN, I, IT and ST are 6 automated mid-peripheral corneal curvatures, 60 degree apart, taken clockwise from 12 o'clock at a 2.0 mm radius from the corneal apex and are given for tangential and axial topography maps.

3.3.1.2 Anterior and posterior best-fit spheres

For the best fit spheres at the 5 mm and 8 mm zones, the performance was very good at the anterior corneal surface (α ≥ 0.999; ICC ≥ 0.998). Although the performance was slightly decreased at the posterior corneal surface, the intra-observer reliability indices were also high (α = 0.997; ICC ≥ 0.990) (Table 3.3).

Table 3.3. The reliability indices of best-fit spheres at the anterior and posterior corneal surfaces.

	Best-fit sphere	**α**	**ICC**
Anterior	**5.0 mm zone**	0.999	0.998
	8.0 mm zone	1.000	0.999
Posterior	**5.0 mm zone**	0.997	0.990
	8.0 mm zone	0.997	0.991

α = Cronbach's alpha; ICC = Intra-class Correlation Coefficient

3.3.1.3 Topographic corneal thickness

The reliability of the central corneal thickness measurement at the apex was high (α = 0.995; ICC = 0.986). Topographic CT from Pentacam at different regions all had α ≥ 0.988 and ICC ≥ 0.966 (Table 3.4).

Table 3.4. The reliability indices of topographic corneal thickness measurements.

	α	**ICC**
Corneal apex	0.995	0.986
Nasal	0.997	0.972
Mid-nasal	0.993	0.980
Inferior	0.992	0.977
Mid-inferior	0.994	0.983
Temporal	0.988	0.966
Mid-temporal	0.993	0.980
Superior	0.990	0.970
Mid-superior	0.993	0.980

α = Cronbach's alpha; ICC = Intra-class Correlation Coefficient

3.3.2 Inter-session repeatability

3.3.2.1 Anterior and posterior simulated keratometric readings and mid-peripheral corneal curvatures

The Pentacam's inter-session repeatability was evaluated using the first reading from each visit and the average result of three readings from each visit. Table 3.5a shows the anterior mean value (visits 1 and 2), difference (visit 1 minus visit 2), COR, RR of Sim K, power vectors (M, J_0 and J_{45}) and mPCC between the two visits. Two approaches (first reading versus average result) also showed good repeatability for the Sim K, but using the average result could ensure the COR would be within 0.25 D, with a corresponding RR of less than 0.5%. For the power vectors, M had a similar performance to the Sim K measurement. Although greater RR was shown in J_0 and J_{45}, their COR were within ± 0.25 D using both approaches.

For the mPCC, axial curvatures were more repeatable than the tangential curvatures. The superior region yielded the worst repeatability. When using the average result, all COR of the tangential curvatures were less than ± 1.00 D, whereas using the first reading, the COR was slightly over ± 1.00 D at the superior and superior temporal regions. Comparing the repeatability of the axial curvatures using the two approaches, the COR was as great as ± 1.03 D (for the superior region) when using the first reading with a corresponding RR of 2.37%. When using the average result, the COR at all regions were within 0.50 D with the RR around 1.0%.

Table 3.5b shows the analysis of repeatability of the posterior corneal curvatures. The central posterior Sim K and power vectors (M, J_0 and J_{45}) showed good repeatability. All COR of the Sim K and power vectors were within 0.15 D using the first reading and the COR reduced to within 0.09 D using the average result. Similar to the anterior cornea, the RR values were very large for J_0 and J_{45}. The posterior tangential curvatures were more variable than the axial curvatures, similar to the anterior mPCC. The tangential curvature at the superior region was still the least repeatable (first reading approach: COR = ± 0.50 D, RR = −7.96%) compared to the other regions. In the "first reading" approach (that is comparing the first reading from each visit), the COR of the tangential curvatures (except the superior region) were within 0.35 D and RR within −5.31%. The average result approach reduced the COR to ± 0.37 D or lower for all regions. On the axial curvatures, the COR from using the first reading for all regions were within 0.23 D, whereas they were within 0.16 D using the average result.

Table 3.5a. The anterior mean value (visits 1 and 2), difference (visit 1 minus visit 2), COR and RR of simulated keratometric readings along the flattest and steepest meridians, power vectors (M, J_0 and J_{45}), and mid-peripheral corneal curvatures (S, SN, IN, I, IT and ST) between the 2 visits.

Anterior		**Approach 1: First reading from each visit**				**Approach 2: Average of 3 readings from each visit**			
		Mean ± SD				**Mean ± SD**			
		Mean value (D)	**Difference (D)**	**COR (D)**	**RR (%)**	**Mean value (D)**	**Difference (D)**	**COR (D)**	**RR (%)**
Sim K_{flat}		42.37 ± 1.18	−0.03 ± 0.10	±0.19	0.46	42.37 ± 1.17	0.00 ± 0.10	±0.20	0.48
Sim K_{steep}		43.68 ± 1.38	−0.03 ± 0.18	±0.34	0.79	43.69 ± 1.37	−0.02 ± 0.11	±0.21	0.48
M		43.01 ± 1.22	−0.02 ± 0.12	±0.23	0.53	43.01 ± 1.21	0.00 ± 0.09	±0.17	0.40
J_0		0.60 ± 0.42	0.00 ± 0.10	±0.20	32.88	0.60 ± 0.42	−0.01 ± 0.06	±0.11	18.85
J_{45}		0.05 ± 0.18	0.02 ± 0.10	±0.20	382.31	0.07 ± 0.19	0.03 ± 0.10	±0.20	291.11
Tangential Power	**S**	43.16 ± 1.73	0.03 ± 0.59	±1.15	2.66	43.19 ± 1.77	0.09 ± 0.48	±0.95	2.20
	SN	41.91 ± 1.35	−0.02 ± 0.39	±0.76	1.82	41.92 ± 1.36	−0.03 ± 0.32	±0.63	1.51
	IN	41.92 ± 1.33	−0.10 ± 0.46	±0.90	2.14	41.88 ± 1.29	−0.06 ± 0.38	±0.74	1.77
	I	43.26 ± 1.65	−0.08 ± 0.46	±0.90	2.08	43.28 ± 1.61	−0.06 ± 0.31	±0.60	1.39
	IT	42.83 ± 1.39	0.00 ± 0.30	±0.58	1.36	42.84 ± 1.37	0.01 ± 0.26	±0.51	1.19
	ST	42.88 ± 1.42	0.11 ± 0.56	±1.10	2.56	42.93 ± 1.43	0.01 ± 0.41	±0.81	1.88
Axial Power	**S**	43.45 ± 1.53	−0.04 ± 0.53	±1.03	2.37	43.48 ± 1.51	−0.05 ± 0.23	±0.44	1.02
	SN	42.33 ± 1.24	−0.07 ± 0.20	±0.38	0.90	42.33 ± 1.23	−0.04 ± 0.16	±0.32	0.75
	IN	42.67 ± 1.21	0.01 ± 0.26	±0.51	1.20	42.71 ± 1.23	0.04 ± 0.22	±0.44	1.03
	I	43.86 ± 1.42	0.02 ± 0.35	±0.68	1.56	43.87 ± 1.41	0.06 ± 0.23	±0.45	1.02
	IT	42.74 ± 1.26	0.01 ± 0.24	±0.46	1.09	42.74 ± 1.26	−0.01 ± 0.19	±0.36	0.85
	ST	42.70 ± 1.26	−0.02 ± 0.28	±0.55	1.29	42.69 ± 1.22	0.00 ± 0.20	±0.40	0.93

Sim K_{flat} and Sim K_{steep} = Simulated keratometric readings along flattest and steepest meridians respectively

M = Mean of the Flattest and Steepest simulated keratometric readings, J_0 = Power vector along 90° / 180°; J_{45} = Power vector along 45° / 135°

S = Superior, SN = Superior nasal, IN = Inferior nasal, I = Inferior, IT = Inferior temporal, ST = Superior temporal

S, SN, IN, I, IT and ST are 6 automated mid-peripheral corneal curvatures, 60 degree apart, taken clockwise from 12 o'clock at a 2.0 mm radius from the corneal apex and are given for tangential and axial topography maps.

COR = Coefficient of repeatability (±1.96 * standard deviation of the difference); RR = Relative repeatability

Table 3.5b. The posterior mean value (visits 1 and 2), difference (visit 1 minus visit 2), COR and RR of simulated keratometric readings along the flattest and steepest meridians, power vectors (M, J_0 and J_{45}), and mid-peripheral corneal curvatures (S, SN, IN, I, IT and ST) between the 2 visits.

Anterior		**Approach 1: First reading from each visit**				**Approach 2: Average of 3 readings from each visit**			
		Mean ± SD				**Mean ± SD**			
		Mean value (D)	**Difference (D)**	**COR (D)**	**RR (%)**	**Mean value (D)**	**Difference (D)**	**COR (D)**	**RR (%)**
Sim K_{flat}		−6.03 ± 0.22	0.00 ± 0.06	±0.12	−1.92	−6.03 ± 0.22	0.01 ± 0.03	±0.06	−1.02
Sim K_{steep}		−6.45 ± 0.23	0.01 ± 0.08	±0.15	−2.29	−6.45 ± 0.24	0.00 ± 0.05	±0.09	−1.39
M		−6.23 ± 0.22	0.00 ± 0.05	±0.10	−1.64	−6.23 ± 0.22	0.00 ± 0.03	±0.06	−0.88
J_0		−0.20 ± 0.07	0.00 ± 0.05	±0.10	−49.64	−0.20 ± 0.07	0.00 ± 0.03	± 0.06	−32.45
J_{45}		−0.03 ± 0.05	0.00 ± 0.04	±0.08	−246.75	−0.04 ± 0.05	−0.01 ± 0.03	± 0.06	−169.73
Tangential Power	**S**	−6.34 ± 0.35	0.03 ± 0.26	±0.50	−7.96	−6.32 ± 0.33	−0.01 ± 0.19	±0.37	−5.80
	SN	−6.59 ± 0.31	0.03 ± 0.18	±0.35	−5.31	−6.58 ± 0.29	0.03 ± 0.11	±0.22	−3.38
	IN	−6.48 ± 0.27	−0.01 ± 0.14	±0.28	−4.35	−6.46 ± 0.27	0.00 ± 0.14	±0.27	−4.11
	I	−6.54 ± 0.29	0.04 ± 0.18	±0.35	−5.30	−6.54 ± 0.28	0.02 ± 0.12	±0.24	−3.74
	IT	−6.45 ± 0.25	0.03 ± 0.16	±0.32	−4.92	−6.45 ± 0.24	−0.01 ± 0.11	±0.22	−3.39
	ST	−6.53 ± 0.26	0.04 ± 0.16	±0.32	−4.84	−6.54 ± 0.26	0.00 ± 0.14	±0.28	−4.27
Axial Power	**S**	−6.46 ± 0.25	0.02 ± 0.12	±0.23	−3.55	−6.46 ± 0.26	−0.01 ± 0.08	±0.16	−2.40
	SN	−6.20 ± 0.23	0.01 ± 0.07	±0.14	−2.20	−6.19 ± 0.23	0.01 ± 0.06	±0.12	−1.97
	IN	−6.26 ± 0.21	0.02 ± 0.08	±0.15	−2.35	−6.27 ± 0.22	0.01 ± 0.06	±0.12	−1.94
	I	−6.48 ± 0.24	0.02 ± 0.07	±0.14	−2.14	−6.48 ± 0.24	0.02 ± 0.07	±0.13	−2.04
	IT	−6.22 ± 0.25	0.00 ± 0.08	±0.16	−2.52	−6.23 ± 0.24	0.01 ± 0.05	±0.09	−1.43
	ST	−6.17 ± 0.24	0.00 ± 0.07	±0.14	−2.27	−6.17 ± 0.23	−0.01 ± 0.06	±0.11	−1.85

Sim K_{flat} and Sim K_{steep} = Simulated keratometric readings along flattest and steepest meridians respectively

M = Mean of the Flattest and Steepest simulated keratometric readings, J_0 = Power vector along 90° / 180°; J_{45} = Power vector along 45° / 135°

S = Superior, SN = Superior nasal, IN = Inferior nasal, I = Inferior, IT = Inferior temporal, ST = Superior temporal

S, SN, IN, I, IT and ST are 6 automated mid-peripheral corneal curvatures, 60 degree apart, taken clockwise from 12 o'clock at a 2.0 mm radius from the corneal apex and are given for tangential and axial topography maps.

COR = Coefficient of repeatability (±1.96 * standard deviation of the difference); RR = Relative repeatability

3.3.2.2 Anterior and posterior best-fit spheres

Table 3.6 lists the mean values, the mean difference, COR and RR of the anterior and posterior BFS between 2 visits. When comparing the first reading from each visit, the difference was greater with a larger COR than that when comparing the average from 3 consecutive readings. The COR using the first reading BFS were 71.5 µm at the 5 mm zone and 81.3 µm at the 8 mm zone, while the COR using averaged posterior BFS were 47.0 µm at the 5 mm zone and 63.5 µm at the 8 mm zone. All of the RR were minimal (limited to within 0.10%). Similarly, the RR generally improved with the second approach.

Table 3.6. The mean value (visits 1 and 2), difference (visit 1 minus visit 2), COR and RR of anterior and posterior best-fit spheres at 5 mm and 8 mm zones between the 2 visits.

	Approach 1: First reading from each visit				**Approach 2: Average of 3 readings from each visit**			
	Mean ± SD				**Mean ± SD**			
Best-fit sphere	**Mean value (mm)**	**Difference (µm)**	**COR (µm)**	**RR (%)**	**Mean value (mm)**	**Difference (µm)**	**COR (µm)**	**RR (%)**
Anterior								
5.0 mm Zone	7.86 ± 0.22	5.6 ± 18.3	35.9	0.07	7.86 ± 0.22	0.7 ± 13.4	26.3	0.009
8.0 mm Zone	7.91± 0.23	1.8 ± 13.5	26.5	0.02	7.91 ± 0.23	0.1 ± 11.8	23.1	0.001
Posterior								
5.0 mm Zone	6.41 ± 0.23	6.4 ± 36.5	71.5	0.10	6.41 ± 0.23	5.3 ± 24.0	47.0	0.08
8.0 mm Zone	6.43 ± 0.21	4.4 ± 41.5	81.3	0.07	6.42 ± 0.21	2.6 ± 32.4	63.5	0.04

COR = Coefficient of repeatability (±1.96 * standard deviation of the difference); RR = Relative repeatability

3.3.2.3 Topographic corneal thickness

Table 3.7 shows the topographic CT from the two visits. When comparing the first reading from each visit, the difference was greater with a larger COR than that when comparing the average from 3 consecutive readings. All COR using the “first reading” approach were generally greater than the COR using the “average result” approach except at the mid-superior region. Also, all RR were limited to 2.7% when using the “average result” approach, except at the superior region (3.90%).

Table 3.7. The mean value (visits 1 and 2), difference (visit 1 minus visit 2), COR and RR of topographic corneal thickness between the 2 visits.

	Approach 1: First reading from each visit				**Approach 2: Average of 3 readings from each visit**			
	Mean ± SD				**Mean ± SD**			
	Mean value (µm)	**Difference (µm)**	**COR (µm)**	**RR (%)**	**Mean value (µm)**	**Difference (µm)**	**COR (µm)**	**RR (%)**
Corneal apex	557.9 ± 33.0	4.2 ± 7.7	15.1	2.71	558.5 ± 33.3	2.1 ± 6.9	13.5	2.43
Nasal	617.5 ± 35.1	4.1 ± 9.3	18.2	2.94	617.9 ± 35.6	3.5 ± 7.8	15.3	2.47
Mid-nasal	576.0 ± 33.0	4.2 ± 7.5	14.7	2.55	576.9 ± 33.4	2.7 ± 6.8	13.4	2.32
Inferior	605.5 ± 34.8	5.2 ± 10.5	20.6	3.40	605.1 ± 35.4	3.2 ± 7.6	14.8	2.45
Mid-inferior	569.2 ± 33.1	4.4 ± 8.9	17.4	3.06	569.4 ± 33.5	2.1 ± 6.5	12.7	2.23
Temporal	599.3 ± 37.8	4.3 ± 9.4	18.3	3.06	600.3 ± 38.6	1.9 ± 8.1	15.8	2.64
Mid-temporal	566.7 ± 35.0	4.2 ± 8.0	15.6	2.75	567.6 ± 35.5	2.0 ± 7.0	13.7	2.41
Superior	641.3 ± 34.9	5.4 ± 14.3	28.1	4.38	641.8 ± 34.8	2.3 ± 12.9	25.2	3.90
Mid-superior	590.0 ± 33.3	3.7 ± 7.8	15.3	2.60	591.0 ± 33.5	1.9 ± 8.0	15.7	2.65

COR = Coefficient of repeatability (±1.96 * standard deviation of the difference); RR = Relative repeatability

3.4 Discussion

3.4.1 Intra-observer reliability

The Sim K, power vectors (M, J_0 and J_{45}) and BFS at both 5 mm and 8 mm zones show very good intra-observer reliability at the anterior corneal surface ($\alpha \geq 0.960$ and ICC ≥ 0.888). Although the intra-observer reliability was high, taking three readings to generate an average result for analysis is better than just taking one reading, as most of the previous studies did using either Orbscan or Pentacam. The reliability on posterior corneal measurements in terms of power vectors and BFS was not as good as the anterior cornea but the performance on the Sim K measurements was still good ($\alpha \geq 0.990$ and ICC ≥ 0.972). The M vector was as reliable as the Sim K but J_0 and J_{45} were less reliable ($\alpha \geq 0.896$ and ICC ≥ 0.742). J_0 and J_{45} were converted into rectangular Fourier form from the Sim K (Thibos et al., 1997). The BFS at the posterior corneal surface were at least $\alpha = 0.997$ and ICC = 0.990. This is in line with the suggestion that the α and ICC should be at least 0.90 (Portney and Watkins, 2000).

The larger variability of measurements on the posterior corneal surface could be explained by the assumptions made to remedy the distortion in the Scheimpflug image (geometrical distortion due to the camera's configuration) and the magnification of the posterior corneal surface by the anterior corneal surface (optical distortion of the image due to the anterior corneal surface preceding the posterior corneal surface). The variability could also be attributed to the small refractive index difference at the cornea/aqueous humour interface (a difference of 0.04) compared to the difference at the air/cornea interface (a difference of 0.376), which can lead to a difficulty in identifying the posterior corneal surface given the lower contrast difference (Shankar et al., 2008). The intensity from the light emitting diode decreases after passing through the anterior corneal surface, which may decrease the resolution at the posterior corneal surface on the captured Scheimpflug image. The decrease in performance of posterior J_0 and J_{45} (Table 3.1) could also be accounted for by a greater variability of the cylinder axis in repeated measurements. The Pentacam system provided reliable Sim K measurements at both surfaces. The anterior and posterior mPCC also showed good reliability ($\alpha \geq 0.950$ and ICC ≥ 0.863), except in the superior region at the posterior cornea ($\alpha = 0.891$ and ICC = 0.732). Similar to the central corneal measurements, the posterior mPCC varied slightly more than the anterior mPCC in repeated within-session measurements. Although the tangential mPCC had slightly lower reliability compared with the axial mPCC (Table 3.2), almost all

ICC values were close to 0.900, which ensures a reasonable clinical reliability (Portney and Watkins, 2000). A greater variability in the tangential mPCC is due to a greater rate of change at the mid-peripheral cornea from tangential curvature as a function of calculating it locally compared to the axial curvature (Salmon and Horner, 1995, Shankar et al., 2008). In addition, the variability of the superior region was greatest at both corneal surfaces. The discrepancy in repeated measurements could be explained by corneal distortion exerted by the static pressure from the upper eyelid (Buehren et al., 2001) and by the shadows of eyelashes.

For the CT measurement, the intra-observer reliability was good at all corneal regions. All of the α and ICC were at least 0.960. Table 3.4 lists the reliability coefficients of topographic corneal thickness measurements. The Pentacam system demonstrated stable CT measurements, probably because an internal fixation target is provided by the Pentacam whereas ultrasonic pachymetry does not. There is another camera in the Pentacam system that repeatedly monitors any minute eye movements during the rotational imaging process (Barkana et al., 2005). One important benefit may be the short acquisition time for numerous readings with Pentacam. Pentacam is superior to Orbscan in central pachymetry because it uses 25 slit images on each acquisition with all the images involving the central corneal region. In contrast, the Orbscan takes 40 independent images (20 scans to the right, 20 to the left) but not all the images are scanned through the central region (Modis et al., 2004) and its long acquisition time might be difficult for the subjects to hold still.

3.4.2 Inter-session repeatability

Two approaches were used (comparing the first reading from each visit and comparing the average of three consecutive readings from each visit) to analyse the inter-session repeatability in the current study. Shankar et al. (2008) reported good inter-observer repeatability with the Pentacam. Only one reading was taken for each subject, which is similar to the first approach. The inter-session repeatability (from the first approach) of Sim K is comparable with the inter-observer repeatability reported by Shankar et al. (2008). Both the anterior and posterior J_0 and J_{45} showed a large relative repeatability compared with the Sim K measurements. The large RR is due to a relatively small mean J_0 and J_{45}. By definition, RR will approach infinity if the denominator is close to zero (Shankar et al., 2008). J_0 and J_{45} represent power vectors along the vertical/horizontal and oblique meridians, respectively. The subjects in the current study had limited amounts of corneal astigmatism with an even smaller number of subjects having oblique astigmatism, which might further account for the extreme RR of J_{45} (over 300%) shown in the current results (Topuz et al., 2004). COR is a better parameter to demonstrate good inter-session repeatability of J_0 or J_{45} (Table 3.5a and 3.5b).

For mPCC, comparable performance also applies to the anterior surface (Table 3.5a). Using the second approach could further reduce the COR of anterior mPCC (within 1.0 D for tangential curvatures and within 0.25 D for axial curvatures), with good corresponding RR (around 2.0% for tangential curvatures and 1.0% for axial curvatures). The current study extended the investigation in the inter-session repeatability to the posterior mPCC. Although all of the COR of posterior mPCC were smaller than the anterior mPCC, these might not indicate that the measurements of posterior mPCC were more repeatable. It was attributed to the fact that COR is not a parameter sensitive enough to reflect repeatability precisely because the mean mPCC values at the posterior corneal surface were smaller (approximately –6.0 D). Shankar et al. (2008) recommended using the RR and greater variations between visits were found (Tables 3.5a and 3.5b). Although the posterior mPCC has poorer inter-session repeatability than the anterior mPCC, improvement is shown with the second approach. The relatively poor inter-session repeatability in the posterior mid-peripheral tangential curvatures may be of concern, if tangential curvatures were used to monitor longitudinal corneal change (Tsukiyama et al., 2008). The superior region varied a great deal compared to other mid-peripheral corneal regions (Tables 3.5a and 3.5b), which could be attributed to reasons similar to those discussed in the performance of intra-observer reliability.

For the BFS measurement, the COR of anterior BFS was similarly better than the posterior BFS. They were also reduced by using an average result rather than using just the first BFS from each visit. The inter-session repeatability is increased with the use of the average BFS. A similar improvement in the posterior BFS measurement from Pentacam between visits is therefore anticipated.

Corneal ectasia is a serious corneal complication after refractive surgery, characterized by corneal thinning and reduced visual performance. Most previous studies used the elevation of the posterior cornea for comparison (Wang et al., 1999, Kamiya et al., 2000, Baek et al., 2001, Miyata et al., 2002).

Some compared the posterior BFS (Naroo and Charman, 2000) or the posterior corneal power and eccentricity (Seitz et al., 2001). Orbscan is a commonly used device (Wang et al., 1999, Kamiya et al., 2000, Naroo and Charman, 2000, Baek et al., 2001, Seitz et al., 2001, Miyata et al., 2002) but Maloney (1999) has questioned its accuracy in evaluating posterior corneal displacement. Maldonado et al. (2006) reported good intra-session and inter-session repeatability of Orbscan on posterior BFS at the 5 mm zone. The ICC was 0.980 within-visit and the COR was 250 μm between-visits. Therefore, Pentacam demonstrated a better performance, with ICC of 0.990 and the COR being 47 μm. It could be partly due to normal subjects recruited here instead of post-myopic laser in situ keratomileusis (LASIK) patients; and partly by taking three readings to generate an average result. Even if the first reading from each visit were used, the COR was only 71.5 μm (Table 3.6). The interval between visits was also too long in Maldonado's study, 6 to 9 months. Pentacam could be better than Orbscan for studying the central cornea because Pentacam has a better acquisition method.

For topographic corneal thickness measurements, a better inter-session repeatability was found at the corneal apex (COR: 13.5 μm, Table 3.7) than the results demonstrated by O'Donnell and Maldonado-Codina (2005) (COR: 21.1 μm). It might be due to only one reading being taken during each visit in their study, while the current study took an average from 3 readings. Also, they did not state if they referred to the corneal apex or the thinnest corneal region. In topographic CT, the superior cornea is the thickest, with the cornea being thicker at the nasal than the temporal. This is similar to previous findings using Orbscan (Modis et al., 2004, Sanchis-Gimeno et al., 2004) or Pentacam (Rufer et al., 2005). The thinnest corneal region was located infero-temporal to the corneal apex. Several studies using Orbscan have confirmed this (Liu et al., 1999, Lam and Chan, 2003, Jonsson and Behndig, 2005, Gao et al., 2006). On average, the thinnest region is within the central one millimetre zone of the cornea. It is important and especially for refractive surgeons to know the thinnest corneal region, rather than the region of mean central corneal thickness. Many previous studies using Pentacam took either one (O’Donnell and Maldonado-Codina, 2005, Buehl et al., 2006) or two readings (Lackner et al., 2005) for central CT evaluation, while one previous study took three successive readings (Ucakhan et al., 2006). One reading could be acceptable for assessing the central cornea because each acquisition contains 25 slit images all covering the central cornea. The latest Pentacam can obtain 100 images. When only the first reading was considered from the two visits, the agreement on corneal apex was 15.1 µm (1.96 × ± 7.7 µm, Table 3.7). For topographic CT measurement, one measurement might not be enough. From the data in Table 3.7, the COR of mid-peripheral corneal thickness using the second approach were around 15.0 µm (except at the superior corneal region). Cho and Cheung (2002) measured the mid-peripheral corneal thickness with the Orbscan system and also reported the greatest variability at the superior region. This is the limitation of the instrument which should be acknowledged. The repeatability of topographic CT at the superior region is poor and it might be attributed to the influence of the upper eyelid.

The Pentacam system can measure the topographic corneal thickness. It is superior to other non-contact pachymetry such as specular microscopy, because the latter can measure mid-peripheral CT only at several predetermined locations (Cho and Cheung, 2000). Similarly, at least three repeated measurements were suggested if topographic CT analysis is required. The Pentacam uses a Scheimpflug camera rotating over 360 degrees that can finish one measurement within two seconds. Ciolino and Belin (2006) and Ciolino et al. (2007) recently reported that when using the Pentacam, no posterior corneal protrusion was found within the first month after patients who had refractive surgery (Ciolino and Belin, 2006) or even after one year (Ciolino et al., 2007). Placido disc-based corneal topographers are commonly used for corneal research (Sridharan and Swarbrick, 2003, Gonzalez-Meijome et al., 2004, Lam et al., 2004a, Lam et al., 2004b, Franklin et al., 2006, Read et al., 2006, Gonzalez-Meijome et al., 2007, Huang and Lam, 2007, Iskander et al., 2003, Lam and Lam, 2007) because of their superior performances in measuring corneal curvature and corneal eccentricity (Tang et al., 2000, Chui and Cho, 2005, Cho et al., 2002b). The corneal parameters are derived from the reflection of the Placido disc at the tear film, which cannot provide any information about the posterior corneal surface. The Pentacam is easy to use because its automatic release mode can minimize the confounding factor in alignments between observers. During each acquisition, minute eye movements are closely monitored by another camera in the system. If the examined eye blinks extensively or fixates poorly, misalignment is detected and the practitioner is notified. To monitor longitudinally any progressive corneal change, such as after refractive surgery or orthokeratology treatment, a repeatable instrument is required. Myopic regression after refractive surgery is widely known. Some researchers have suggested that the posterior corneal shift is one of the factors contributing to the myopic regression (Naroo and Charman, 2000, Kamiya and Oshika, 2003). Therefore, posterior corneal change is frequently analyzed after refractive surgery. However, there might be a limitation in the corneal curvature measurement after refractive surgery or ortho-k treatment. The corneal apex could no longer be identical at the original (pre-treatment) location. However, the error introduced might probably be random.

This part of the project demonstrated good intra-observer reliability and inter-session repeatability of Pentacam on anterior and posterior corneal measurements in terms of Sim K readings, mid-peripheral corneal curvatures, best-fit spheres and topographic corneal thickness. The Pentacam system could be used to monitor longitudinal corneal changes with orthokeratological treatment. However, the current study is limited in that testing was with the Pentacam system with no comparison with the most updated Orbscan. This is because an updated version of Orbscan was not available in the Optometry Clinic of The Hong Kong Polytechnic University. An earlier study on the Orbscan has found poor performance in measuring the mid-peripheral cornea (Cho and Cheung, 2002). Also, only normal subjects were measured in the current study. Further studies including both the latest models of Pentacam (Pentacam HR) with the incorporation of the Orbscan (Orbscan IIz) would be useful. Further studies recruiting subjects with a range of corneal conditions to warrant the superior performance by the Pentacam system are also anticipated.

3.5 Conclusions

The Pentacam system has demonstrated very good intra-observer reliability and inter-session repeatability. The intra-observer reliability indices for the corneal parameters indicated that the Pentacam system performed very well and was clinically acceptable. For inter-session repeatability, an average of 3 readings should be adopted for comparison between visits. This can increase the sensitivity to monitor any change longitudinally, as in the current study that involved long-term orthokeratology.

Papers published:

Chen D, Lam AK. Intrasession and intersession repeatability of the Pentacam system on posterior corneal assessment in the normal human eye. J Cataract Refract Surg. 2007;33:448-454.

Chen D, Lam AK. Reliability and repeatability of the Pentacam on corneal curvatures. Clin Exp Optom. 2009;92:110-118.

Lam AK, Chen D. Pentacam pachometry: comparison with non-contact specular microscopy on the central cornea and inter-session repeatability on the peripheral cornea. Clin Exp Optom. 2007;90:108-114.

Chapter 4

Methodology

4.1 Introduction

In this chapter, three experimental studies are reported, which shared similar subject inclusion criteria, instruments, measurements and lens designs. The general (or common) methodology is reported first and then the detailed description of each of these three studies. The main difference among these three studies is the wearing modalities. They are specifically described in the sections (Sections 4.4 to 4.6) following the general information in Sections 4.2 and 4.3 in this chapter. The aims of this study are to understand the short-term and longer term changes of corneal parameters including posterior corneal curvature, corneal biomechanical properties and topographical corneal thickness with ortho-k treatment, and their recoveries after 6-months of successful lens wear.

4.2 General methodology

4.2.1 Subjects

Subjects were recruited from friends and university students by advertisements posted on notice boards at The Hong Kong Polytechnic University and City

University of Hong Kong. Inclusion criteria were young Chinese adult myopes, aged from 18 to 30 years. Any subjects with pathological conditions in general and ocular health, history of corneal surgery, rigid contact lens wear of any kind, myopia more than 5.00 D, astigmatism more than 1.50 D or corneal toricity more than 1.75 D were excluded. Soft contact lens wearers were required to stop lens wear for at least 1 week (Machat, 1996) before any baseline measurement. All procedures followed the Declaration of Helsinki and the protocol was reviewed and approved by the Ethics Committee of The Hong Kong Polytechnic University. An information sheet regarding the project title, aims, measurement protocol, potential adverse effects and right of terminating the study without penalty, were explained to each subject before commencement of any measurement. After explanation of the information about the study, subjects were asked to sign a statement of informed consent.

4.2.2 Measurements

4.2.2.1 Visual acuity

Distance uncorrected vision and VA were measured at 3 metres using a Bailey-Lovie (logMAR) chart with five letters per line. All visual acuity measurements were obtained under normal room illumination (365 lx), which was checked regularly (every 6 months).

4.2.2.2 Refractive error

Subjective refraction was performed with the criterion of maximum plus correction giving maximum acuity. The same examination room was used throughout the study to minimize variations. The measured refractive error was transposed to SER with the following formula:

$$SER = S + C / 2;$$

where SER is spherical equivalent refraction, S is spherical power and C is cylindrical power.

4.2.2.3 Corneal topography

Two corneal topographers were used in the current studies. The first corneal topographer was the Medmont E300, Version 3.9.3 (Medmont, Camberwell, Victoria, Australia), which was used in all three studies for fitting the ortho-k lenses, which ensured good lens centration from ortho-k treatment. The Medmont topographer was used in the current study, since it is a well established corneal topographer widely used in ortho-k studies (Cho et al., 2002b, Sridharan and Swarbrick, 2003, Soni et al., 2004, Jayakumar and Swarbrick, 2005, Mountford et al., 2005, Chan et al., 2008). The instrument is shown in Figure 4.1.

Figure 4.1. The Medmont system.

One of the main emphases of the whole study was the change in the anterior and posterior corneal curvatures, in terms of Sim K readings. Topographic corneal thickness was also evaluated. These were measured using a second corneal topographer, the Pentacam system, Version 1.12 (Oculus, Germany).

The repeatability of the Pentacam for measuring posterior corneal curvature and topographic corneal thickness have been evaluated and covered in the previous section (Chapter 3). The 50-image mode was used and three scans were captured to generate an average result for analysis (See Chapter 3). Each subject was asked to fixate on an internal target, while the joystick was adjusted until perfect alignment was achieved. Only scans registered as ''OK'' according to the Examination Quality Specifications of the Pentacam were included. This was to ensure that the scans were not affected by poor fixation, misalignment or missing segments. The Sim K along the flattest (Sim K_{flat}) and steepest (Sim K_{steep}) meridians in the central 3.0 mm zone were studied. Corneal thickness was analysed topographically from the apex to the mid-peripheral regions, with radii of 0.5 to 2.5 mm from the apex at a 0.5 mm intervals along the vertical and horizontal meridians. For example, CT at the superior, inferior, temporal and nasal regions at a distance of 1.0 mm from the corneal apex were averaged for data analysis. An example of CT extraction from four locations (1.0 mm from apex) is shown in Figure 4.2. This was named as the 1.0 mm annulus.

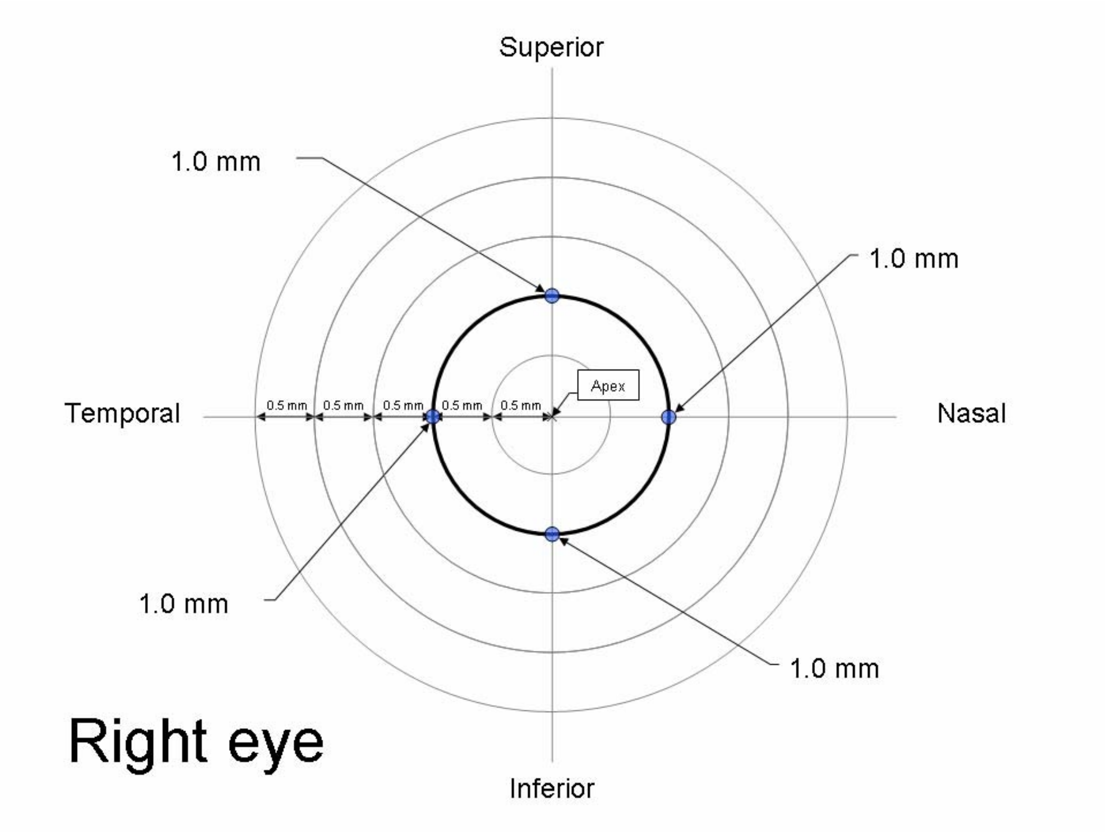


Figure 4.2. An example of corneal thickness extraction from four positions, each at 1.0 mm from apex. This is the 1.0 mm annulus.

4.2.2.4 Corneal biomechanics

The changes in corneal biomechanics in terms of corneal hysteresis and corneal resistance factor, with ortho-k treatment were measured. Subjects were required to be seated comfortably in front of the ORA (Version 1.2. Reichert Ophthalmic Instruments, Buffalo, NY, USA). The subject was asked to fixate the internal target. After the desirable mire was found, the electro-optical monitoring system automatically triggered the non-contact probe to release an air pulse onto the cornea. A double-peak graph was subsequently generated. The reading was accepted or rejected according to the suggestions of the manufacturer. Figure 4.3 shows a distinctive double-peak graph. There are three coloured curves on the graph. According to the ORA user's manual, the green curve represents the strength of the air pulse pressure applanated on the cornea. The red curve shows the raw signal of the applanation detection system. The blue curve is a filtered version of the red curve, designed to determine the "optimum point of applanation" in less than ideal signals. The optical signal received during the inward and outward applanation phases causes the two peaks on both sides of the pressure curve. The applanation pressures are determined by drawing lines down from the peaks of the blue curve to the intersections of the green pressure curve. These points are indicated on the graph by the blue squares. The inward (first or higher) and outward (second or lower) applanation pressures are termed as P1 and P2, respectively. Since the P2 will always occur at a lower position on the pressure curve than the P1, so the difference (P1 – P2) is defined as CH. Corneas with a higher CH will cause a greater discrepancy in the vertical offset of these two pressure points. CH and CRF were automatically generated by the computer software. A previous study reported good inter-session repeatability in the measurements of both parameters (Lam and Chen, 2007a). Comparisons were made between data obtained at the baseline and after different wearing periods.

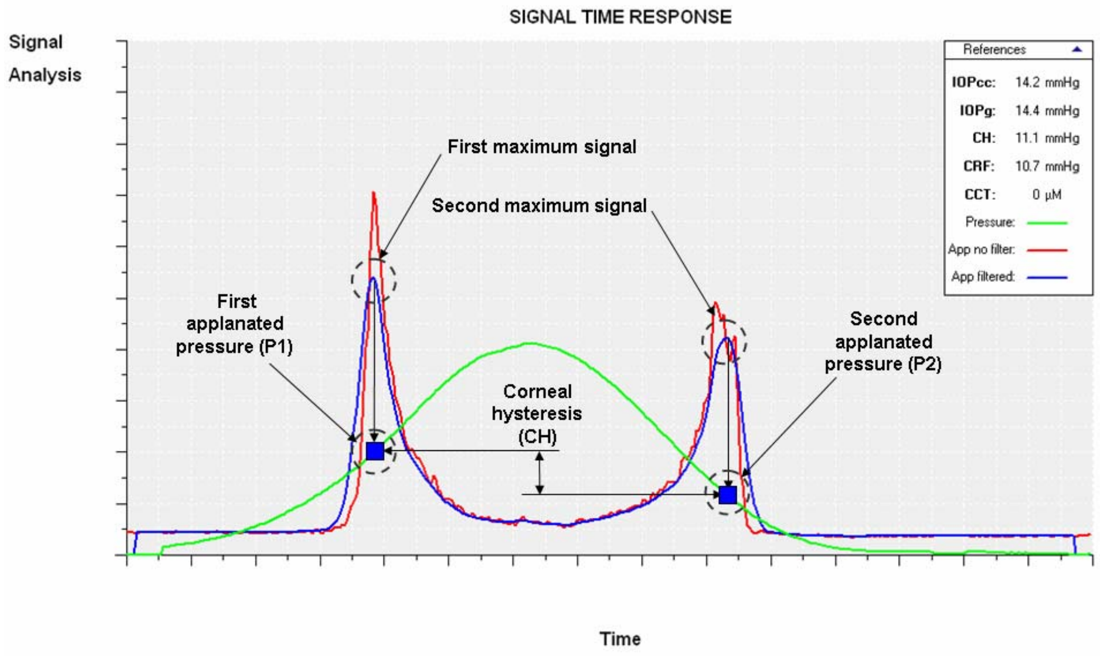


Figure 4.3. The double-peak featured graph (suggested by the manufacturer) and description of corneal hysteresis on the graph (manually illustrated by author).

4.3 Lenses

4.3.1 Lens Designs

4.3.1.1 Ortho-k lens design (Studies I, II and III)

The reverse geometry rigid contact lenses used were of a 5-curve design (eLENS from E & E Optics Ltd., Hong Kong SAR China). The total diameter of the lens was 10.6 mm and the central thickness was 0.22 mm. The lens was constructed with base curve (6.0 mm wide), reverse curve (0.6 mm wide), two alignment curves (AC1, 0.7 mm wide; and AC2, 0.6 mm wide) and peripheral curve (PC, 0.4 mm wide), respectively (Figure 4.4). The total lens size was structured as follow:

$$\text{TD} = \text{width of BC} + \text{width of RC} \times 2 + (\text{widths of AC1} + \text{AC2}) \times 2 + \text{width of PC} \times 2$$

$$10.6\text{ mm} = 6.0\text{ mm} + 0.6\text{ mm} \times 2 + (0.7 + 0.6)\text{ mm} \times 2 + 0.4\text{ mm} \times 2$$

where TD is the total diameter, BC is the base curve, RC is the reverse curve, AC1 and AC2 are the first and second alignment curves respectively, and PC is the peripheral curve.

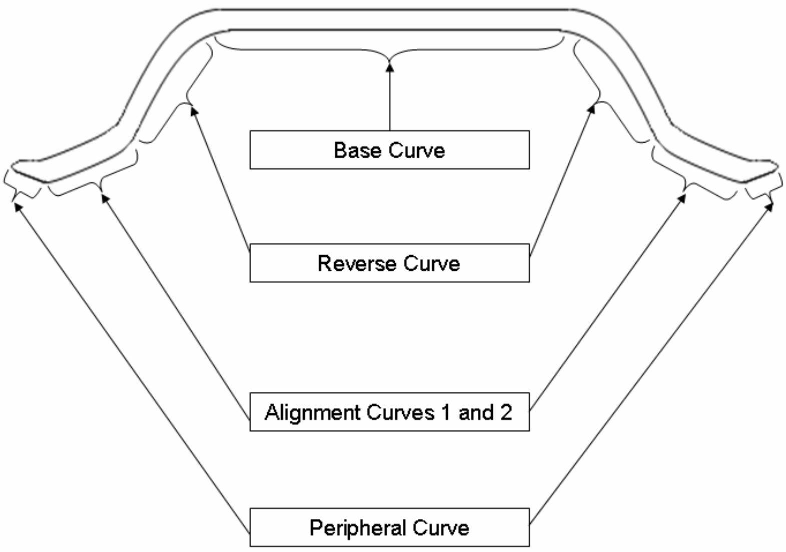


Figure 4.4. A schematic diagram of an orthokeratology lens used in the current study.

4.3.1.2 Conventional alignment fitted lens design (Study II only)

The conventional alignment fitted lens was a bi-aspheric design (E & E optics Ltd., Hong Kong SAR China). The lens was 10.6 mm in overall diameter and the central thickness was 0.22 mm. The lens was constructed with base curve (6.0 mm wide), aspheric secondary curve (1.9 mm wide) and peripheral curve (0.4 mm wide). This lens was used in Study II only and the reason of using a different lens design will be explained in Section 4.6.

4.3.2 Lens material

All lenses, including both the ortho-k and alignment fitted lenses, were manufactured using the Boston XO (Material name: Hexafocon A, Bausch and Lomb, USA). The material type was siloxy-flurometHac copolymer with an oxygen permeability of Dk 100 (ISO/Fatt). The detailed material properties are shown in Table 4.1.

Table 4.1. Detailed properties of the lens material used in all 3 studies.

Proprietary Name	Boston XO
Material Name	Hexafocon A
Manufacturer	Bausch and Lomb, USA
Oxygen Permeability (ISO/FATT)	Dk 100
Wetting Angle (Captive Bubble)	49 degree
Hardness (Rockwell)	112 R
Refractive Index	1.415
Specific Gravity	1.27

4.3.3 Lens fitting philosophy and assessment

4.3.3.1 Ortho-k lens

The choice of an initial diagnostic lens was based on the Sim K_{flat} and the eccentricity value along the flattest meridian, measured with the Medmont topographer (described in Section 4.2.2.3). The base and alignment curves were parameters used to determine the initial lens. The BC was selected according to the measured Sim K_{flat}. The AC was selected by the eccentricity value, which indicated the rate of corneal flattening. A “Standard AC” was selected, if the measured eccentricity value was 0.50. To modify the lens fitting, AC was generally adjusted by steepening or flattening “10 μm” with every 0.10 change of eccentricity value deviated from 0.50. There was no need to specify the actual curvature of the AC and “AC +10” or “AC −10” were relative values compared with the “Standard AC”. If a higher eccentricity value (e = 0.60) was obtained, a flatter AC, “AC −10”, was then required. This indicated that the AC was flattened in order to provide a 10 micron increment in sag height and it was therefore flatter than the “Standard AC”. On the other hand, a lower eccentricity value, for example when e = 0.30 was found, a steeper AC (AC +20) was chosen. This was the general rule of lens selection suggested by the manufacturer. Nevertheless, a thorough fitting assessment using biomicroscopy and sodium fluorescein was required. After the assessment, further modification of AC, as small as 5 μm, could be adjusted during the ordering process.

An initial diagnostic lens was inserted onto the subject’s eye to assess the lens fitting. An ideal lens fitting was determined with good lens centration, 1 to 2 mm of smooth lens movement on blinking at primary gaze and a “bull’s eye” fluorescein pattern. The pattern should show a 4 to 4.5 mm central bearing zone surrounded by a 1 mm wide annulus of mid-peripheral tear reservoir, a 1.5 to 2 mm wide peripheral bearing zone, and a 0.5 to 1 mm wide edge lift (Figure 4.5). After wearing the trial lenses for 30 minutes, the lens performance was evaluated. An ideal lens performance included adequate lens movement during blinking and no sign of lens binding. After lens removal, corneal topography was captured again to generate a difference map from the pre- and post-wear plots (Figure 4.6). A centrally flattened treatment zone surrounded by a steepened annulus indicated an acceptable lens fitting. If the lens performance was not acceptable, lens parameters were modified to improve the lens fit in another trial wearing session after a 1-week washout period. For the short-term studies (Studies I and II), once an acceptable fit was achieved after the trial wear, the same lens was used throughout the experiment. Lens wear started with one week lapsing between the trial wearing session and the beginning of data collection to ensure that any ortho-k effect induced in the trial wearing session had abated. For the long-term study (Study III), the experimental lenses were ordered from the manufacturer based on the parameters of the trial lenses, which gave the best fit. The lenses were delivered to the subjects one week later. The same lenses were used throughout the treatment period. The ortho-k effect was observed at every follow-up visit. In case of any unacceptable lens performance found during follow-up visits, a lens with appropriately modified parameters was ordered and the whole treatment started again with the new lens from the first day of wearing.

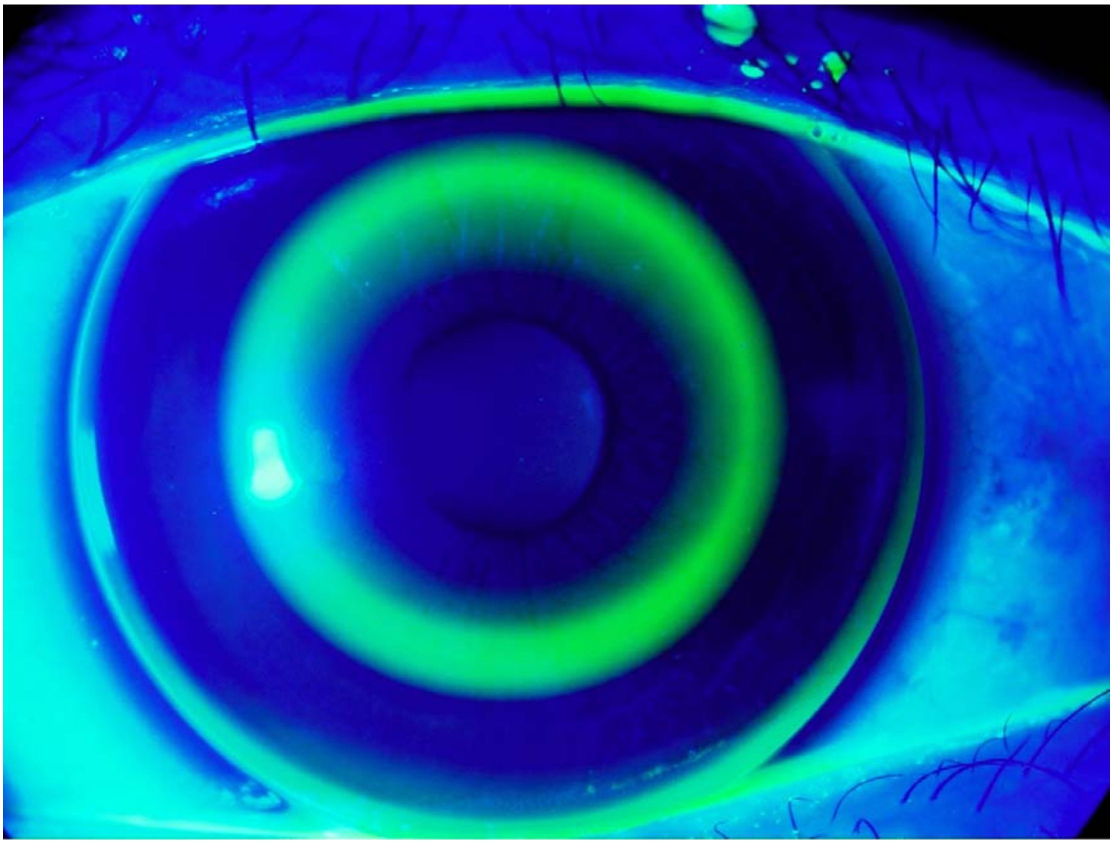


Figure 4.5. An ideal fluorescein pattern of the orthokeratology lens fitting.

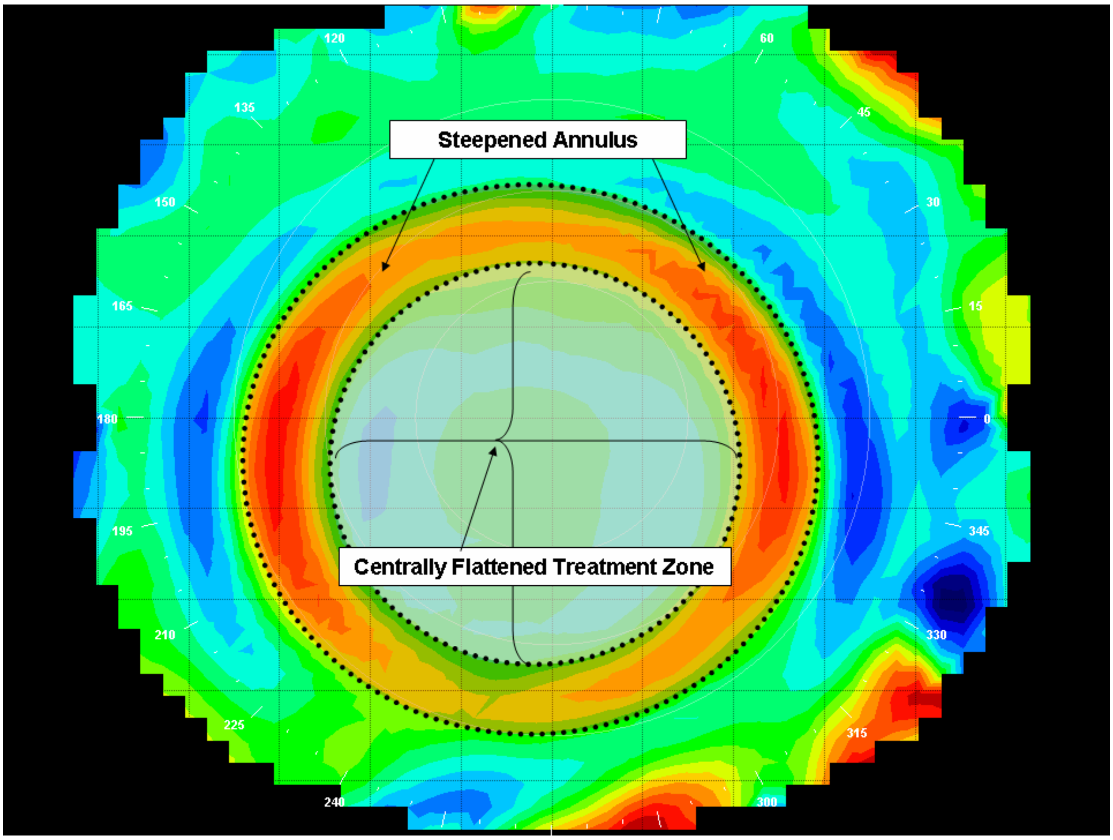


Figure 4.6. The figure shows a difference map in tangential power, compared between the corneal topography of pre- and 30 minutes post-trial lens wearing.

4.3.3.2 Conventional alignment fitted lens design (Study II only)

The bi-aspheric lenses were fitted based on the Sim K_{flat}. The lens fitting was assessed with sodium fluorescein. A conventional alignment-fitted fluorescein pattern was expected. If necessary, modification of the lens parameters was carried out to achieve a standard alignment fit.

4.4 Study I

4.4.1 Introduction

This study aimed to investigate the changes in posterior corneal curvatures, corneal biomechanics, and topographic corneal thickness with short-term (from 15 minutes up to one night) ortho-k treatment.

4.4.2 Experimental protocol

Each subject was required to wear the ortho-k lenses for four different sessions. The lens design of the ortho-k lens used in this study has been described in Section 4.3. The durations of lens wear were 15 minutes, 30 minutes, 60 minutes and one night. Each subsequent session was arranged after at least a one-week rest. This served to avoid any carry-over effects (Machat, 1996). The first three wearing sessions, 15 minutes, 30 minutes, 60 minutes, were randomly assigned while the overnight wear was always the last session. The first three sessions were carried out at approximately the same time during the day to minimize possible diurnal variations in corneal curvatures and thickness (Read and Collins, 2009). For overnight wear, subjects were required to sleep with the lenses for 7 to 10 hours. They were required to return to the Optometry Clinic of The Hong

Kong Polytechnic University the following morning within two hours of waking with the lenses in situ.

4.4.3 Statistical analysis

The Kolmogorov-Smirnov test was used to check the data normality ($p > 0.05$). Parametric and non-parametric statistical tests were then used to analyse the data, as appropriate. In the comparison of baseline data between the two eyes, paired t-tests were used. Repeated measures analysis of variance (ANOVA) was used to compare the changes between baseline and different wearing sessions. Whenever significant differences were found, post-hoc tests (Bonferroni multiple comparisons test) were performed. For non-parametric data, the Friedman test with post-tests (Dunn's procedures) was used in a similar way. Post hoc analyses were performed to minimize any Type I error during multiple comparisons.

4.4.4 Results

This experiment contained 20 subjects (12 males and 8 females). The mean ± SD age of the subjects was 24.1 ± 2.6 years. Their spherical refraction ranged from −0.75 D to −4.25 D. The mean ± SD baseline SERs of the right and left eyes were −2.74 ± 0.85 D and −2.73 ± 1.03 D, respectively. Table 4.2 summarizes their demographic data at the baseline visit. Only data from the right eyes were analysed since no significant differences were found between the two eyes in the SER, UCV, VA, Sim K_{flat} or Sim K_{steep} (Paired t-tests, $p > 0.05$).

Table 4.2. Summary (mean ± one standard deviation) of demographic data of both eyes at the baseline visit.

Age (years)	24.1 ± 2.6	
Gender	12 males and 8 females	
Eye	Right	Left
SER (D)	−2.74 ± 0.85	−2.73 ± 1.03
UCV	0.84 ± 0.23	0.77 ± 0.30
VA	−0.06 ± 0.05	−0.07 ± 0.05
Sim K_{flat} (D)	42.44 ± 1.06	42.46 ± 1.11
Sim K_{steep} (D)	43.33 ± 1.17	43.43 ± 1.22

SER: spherical equivalent refraction.
UCV: uncorrected vision; VA: visual acuity; both in logMAR units.
Sim K_{flat} and Sim K_{steep}: Flattest and steepest simulated keratometric readings (Medmont), respectively.

Table 4.3 shows the detailed results of SER, UCV and VA at different time points. SER was reduced significantly with increasing duration of lens wear, from an average of −2.74 D at baseline to −1.11 D after one overnight wear (Repeated measures ANOVA, $p < 0.01$). The difference was significant after 15 minutes of lens wear (post-hoc test, $p < 0.01$). The UCV improved correspondingly from an average of logMAR 0.84 to logMAR 0.20 after the overnight wear (Friedman test, $p < 0.01$); there was a significant improvement after 15 minutes of lens wear (Dunn's test, $p < 0.01$). No significant change was observed in VA throughout the experiment (Friedman test, $p > 0.05$).

Table 4.3. The results (mean ± one standard deviation) of SER, UCV and VA at different time points, for the right eye only.

	Baseline	15 mins	30 mins	60 mins	Overnight
SER (D)	−2.74 ± 0.85	^−2.31 ± 0.89	^−2.11 ± 0.82	^−1.86 ± 0.90	^−1.11 ± 0.86
UCV	0.84 ± 0.23	^0.53 ± 0.30	^0.49 ± 0.29	^0.43 ± 0.27	^0.20 ± 0.25
VA	−0.06 ± 0.05	−0.08 ± 0.05	−0.08 ± 0.06	−0.06 ± 0.06	−0.05 ± 0.06

SER: spherical equivalent refraction.
UCV: uncorrected vision; VA: visual acuity; both in logMAR units.
^ indicates significance of $p < 0.01$, compared with the baseline result.

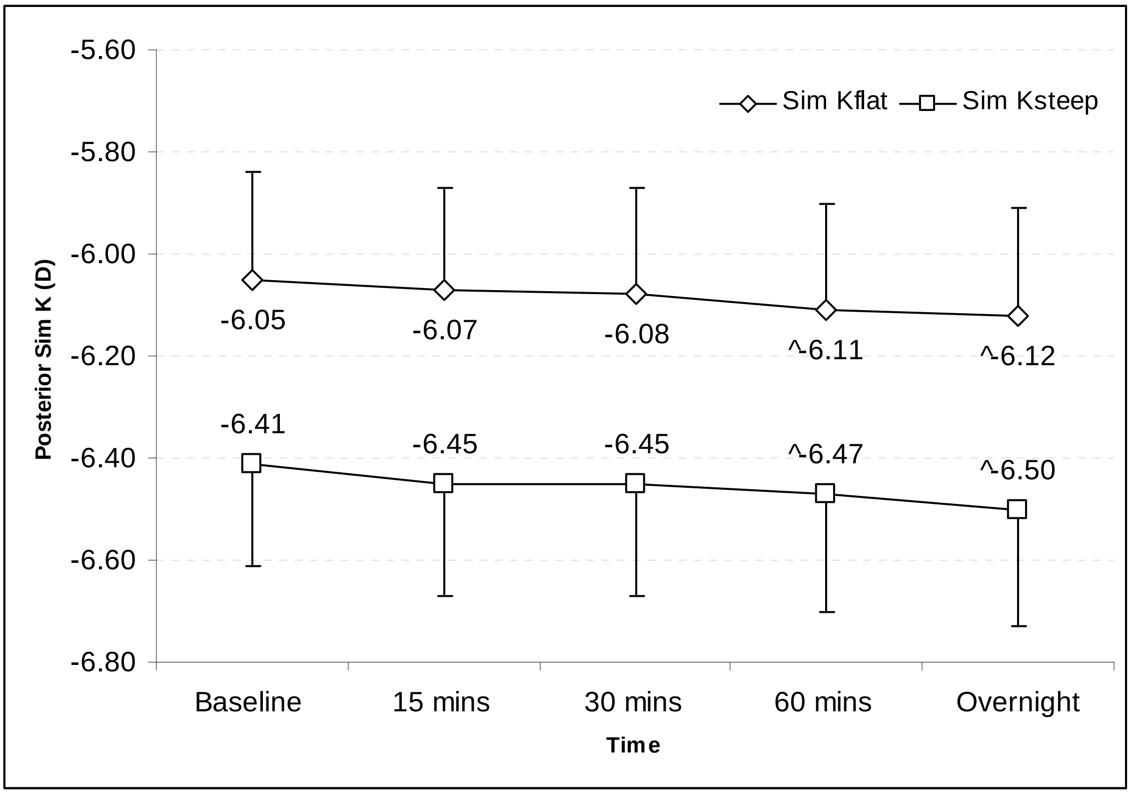
Prompt changes in the anterior Sim K readings (Pentacam) were also demonstrated, which were flattened significantly (Repeated measures ANOVA, Sim K_{steep} and Sim K_{flat}, $p < 0.01$). Significant changes were obtained after as short as 15 minutes of lens wear (post-hoc test, $p < 0.01$). Additionally, the changes in posterior Sim K readings were significant (Repeated measures ANOVA, Sim K_{steep} and Sim K_{flat}, $p < 0.01$). A steepening trend in posterior Sim K readings with longer wearing time was shown (Table 4.4). The significant changes were found in both Sim K_{steep} and Sim K_{flat} after 60 minutes and overnight lens wear (post-hoc tests, $p < 0.01$). Figure 4.7 shows the trend of posterior Sim K changes with ortho-k treatment after different wearing periods.

Table 4.4. The results (mean ± one standard deviation) of Sim K_{flat} and Sim K_{steep} (Pentacam) at different time points, for the right eye only.

Sim K (D)	Baseline	15 mins	30 mins	60 mins	Overnight
Anterior					
Sim K_{flat}	42.54 ± 1.14	*42.26 ± 1.06	^42.17 ± 1.11	^41.91 ± 1.00	^41.61 ± 0.94
Sim K_{steep}	43.42 ± 1.28	*43.14 ± 1.26	^43.07 ± 1.28	^42.86 ± 1.18	^42.59 ± 1.20
Posterior					
Sim K_{flat}	−6.05 ± 0.21	−6.07 ± 0.20	−6.08 ± 0.21	^−6.11 ± 0.21	^−6.12 ± 0.21
Sim K_{steep}	−6.41 ± 0.20	−6.45 ± 0.22	−6.45 ± 0.22	^−6.47 ± 0.23	^−6.50 ± 0.23

Sim K_{flat} and Sim K_{steep}: Flattest and steepest simulated keratometric readings, respectively.
* and ^ indicate significance of $p < 0.05$ and $p < 0.01$, respectively, compared with the baseline result.

Figure 4.7. The trend of posterior Sim K changes after different wearing periods of orthokeratology lens, for the right eye only.



Sim K_{flat} and Sim K_{steep}: Flattest and steepest simulated keratometric readings, respectively.
^ indicates significance of $p < 0.01$, compared with the baseline result.

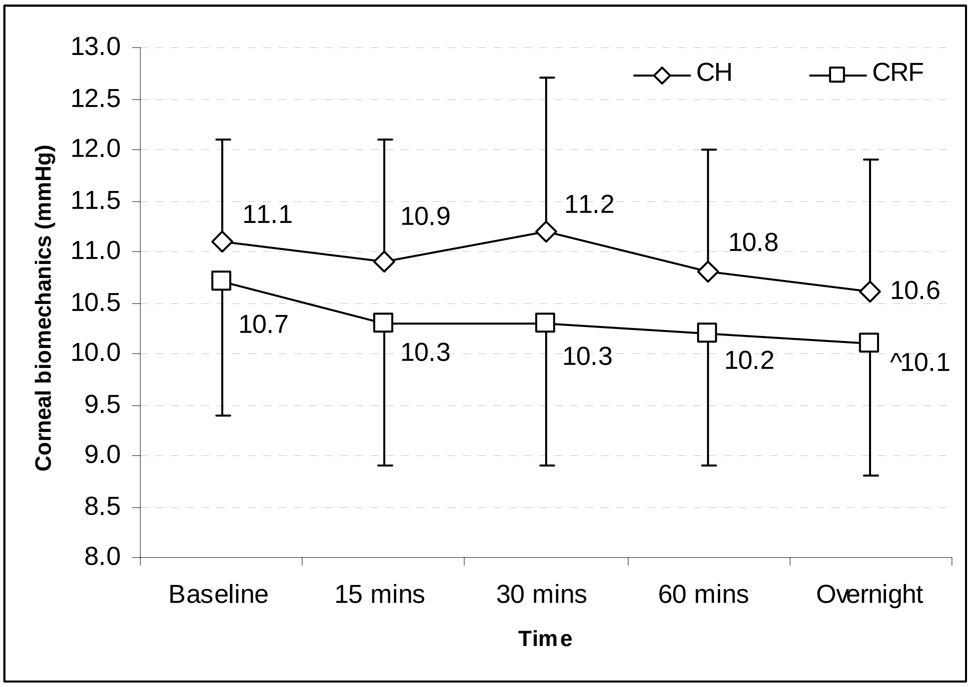
For the corneal biomechanical properties, there were no significant changes in CH throughout the study (Repeated measures ANOVA, $p > 0.05$), while CRF reduced from an average of 10.7 mmHg at baseline to 10.1 mmHg after overnight lens wear (Repeated measures ANOVA, $p < 0.05$). The CRF after overnight wear was significantly lower than the baseline data (post-hoc test, $p < 0.01$) (Table 4.5; Figure 4.8).

Table 4.5. The results (mean ± one standard deviation) of CH and CRF at different time points, for the right eye only.

Corneal biomechanics (mmHg)	Baseline	15 mins	30 mins	60 mins	Overnight
CH	11.1 ± 1.0	10.9 ± 1.2	11.2 ± 1.5	10.8 ± 1.2	10.6 ± 1.3
CRF	10.7 ± 1.3	10.3 ± 1.4	10.3 ± 1.4	10.2 ± 1.3	^10.1 ± 1.3

CH and CRF: corneal hysteresis and corneal resistance factor, respectively.
^ indicates significance of $p < 0.01$, compared with the baseline result.

Figure 4.8. The trend of CH and CRF changes after different wearing periods of orthokeratology lens, for the right eye only.



CH and CRF: corneal hysteresis and corneal resistance factor, respectively.
^ indicates significance of $p < 0.01$, compared with the baseline result

Changes of anterior Sim K_{flat} and Sim K_{steep} after overnight wear were plotted against corneal biomechanics at baseline but no significant correlation was found (Table 4.6).

Table 4.6. Regression analyses between baseline corneal biomechanics and the change of simulated keratometry readings after overnight orthokeratology treatment.

	Change of Anterior Sim K_{flat}		**Change of Anterior Sim K_{steep}**	
	R^2	***p* value**	**R^2**	***p* value**
CH	0.12	0.14	0.11	0.16
CRF	0.13	0.11	<0.01	0.91

CH and CRF: corneal hysteresis and corneal resistance factor, respectively.

Other corneal parameters were analysed against corneal biomechanical changes after overnight wear. The correlations were not significant between CH changes and anterior Sim K readings (Sim K_{steep}, $R^2 < 0.01$, $p > 0.05$; Sim K_{flat}, $R^2 = 0.09$, $p > 0.05$). Changes in CRF were significantly correlated with the changes of Sim K_{steep} ($R^2 = 0.22$, $p < 0.05$) and Sim K_{flat} ($R^2 = 0.42$, $p < 0.01$), respectively (Figure 4.9a and 4.9b).

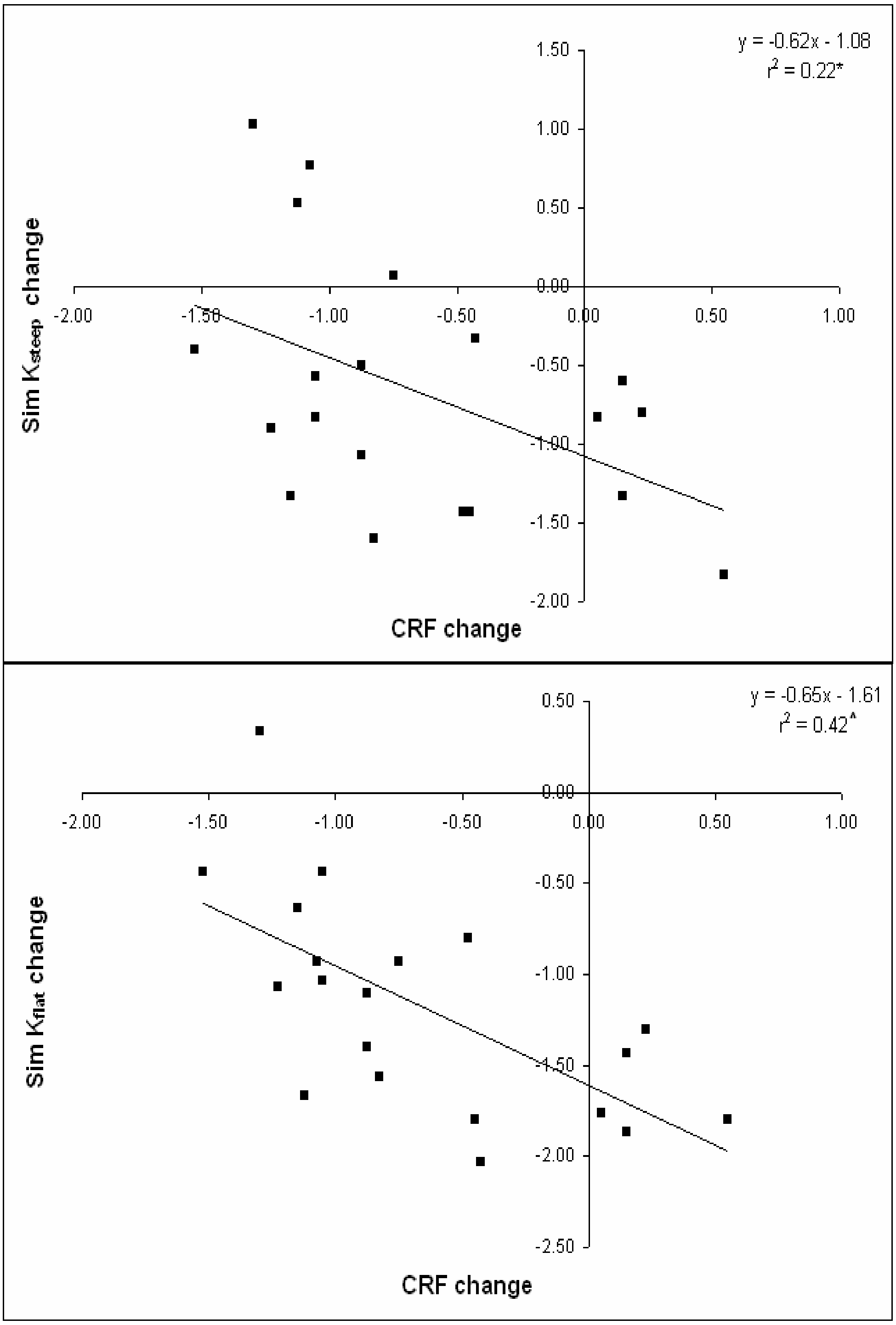


Figure 4.9 (a) Correlation of the change of steepest simulated keratometric (Sim K_{steep}) and the change of corneal resistance factor (CRF). *Significance of $p < 0.05$.
(b) Correlation of the change of flattest simulated keratometric (Sim K_{flat}) and the change of corneal resistance factor (CRF). ^Significance of $p < 0.01$.

For corneal thickness, significant thinning at the apex and the 0.5 mm annulus were found after 60 minutes of lens wear (Repeated measures ANOVA, $p < 0.01$; post-hoc tests, $p < 0.01$) but not at other visits (post-hoc tests, $p > 0.05$). There were no significant changes at the 1.0 mm annulus throughout the study (Repeated measures ANOVA, $p > 0.05$). The 1.5 mm, 2.0 mm and 2.5 mm annuli all showed no significant differences in the daytime wearing sessions but significant thickening was obtained after overnight lens wear (Repeated measures ANOVA, $p < 0.01$; post-hoc test, $p < 0.05$; Table 4.7).

Table 4.7 The results (mean ± one standard deviation) of the central and mid-peripheral corneal thicknesses at different time points, for the right eye only.

	Baseline	**15 mins**	**30 mins**	**60 mins**	**Overnight**
Apex (µm)	579.2 ± 37.1	575.7 ± 32.8	575.0 ± 30.8	^570.4 ± 34.8	581.2 ± 34.4
Mid-peripheral annuli					
0.5 mm (µm)	581.0 ± 37.0	577.8 ± 33.7	577.1 ± 30.6	*572.7 ± 34.6	583.8 ± 34.3
1.0 mm (µm)	586.8 ± 36.6	584.6 ± 33.4	584.1 ± 30.0	580.3 ± 34.0	592.2 ± 33.9
1.5 mm (µm)	597.1 ± 36.0	596.0 ± 33.1	595.9 ± 29.5	592.8 ± 33.4	*605.6 ± 33.4
2.0 mm (µm)	613.3 ± 35.7	613.2 ± 33.3	612.6 ± 29.7	610.7 ± 33.2	^623.6 ± 33.1
2.5 mm (µm)	636.3 ± 34.9	637.7 ± 33.3	637.8 ± 29.7	636.8 ± 32.7	^650.1 ± 32.3

Mid-peripheral annuli represent the average of superior, temporal, inferior and nasal corneal thicknesses with the distance (radius) from apex.
* and ^ indicate significance of $p < 0.05$ and $p < 0.01$, respectively, compared with the baseline result.

4.4.5 Discussion

The mechanism of refractive correction from ortho-k is mainly contributed by flattening the anterior corneal curvatures. Different researchers have also suggested different mechanism including overall corneal bending, redistribution of corneal epithelium, or a combination of both (Swarbrick et al., 1998, Owens et al., 2004a, Stillitano et al., 2007, Gonzalez-Meijome et al., 2008b, Tsukiyama et al., 2008). On the other hand, this technique is one of the popular ways purporting to slow down myopic progression in children (Cho et al., 2005, Walline et al., 2009, Kakita et al., 2011), although the mechanism of myopia control by ortho-k treatment is still not fully understood. In this short-term study, the design is similar to that used by Sridharan and Swarbrick (2003). Three new parameters were introduced including posterior corneal curvatures, topographic CT and corneal biomechanics.

Posterior corneal curvatures steepened after 60 minutes and overnight ortho-k lens wear. Read and Collins (2009) recently reported posterior corneal steepening immediately after sleep. Similar posterior corneal steepening was found in the current study after 60 minutes and overnight lens wear. Could posterior corneal steepening be a normal diurnal variation as reported by Read and Collins (2009)? Interestingly, the posterior cornea was steepened after 60 minutes wear of an ortho-k lens without sleeping. There is also a trend towards posterior corneal steepening from increased wearing time (Table 4.4). This indicates that the ortho-k treatment has some steepening effect on the posterior cornea, although the magnitude was small. Read and Collins (2009) also demonstrated the recovery of posterior corneal steepening back to baseline level within 2 to 3 hours after eye opening. However, this part of the study was limited since the recovery of the changes after lens wear was not monitored and no control eyes were involved. Moezzi et al. (2004) demonstrated a greater oedematous response in the central than in the peripheral cornea resulting in posterior corneal flattening with PMMA lens wear. The difference between their results and these from the current study might be accounted for by the pressure difference under conventional and ortho-k lenses. The relatively positive and negative pressures at the central and mid-peripheral regions were induced by the modern ortho-k lens. The positive pressure inhibits the central corneal oedematous response, while the negative pressure allows thickening in the mid-peripheral cornea. These might consequently result in greater backward movement of the posterior corneal regions at the mid-periphery than the corneal centre. The results here from the topographic CT after overnight ortho-k lens wear demonstrate inhibition of central corneal swelling (apex, and 0.5 mm and 1.0 mm annuli) while thickening of the mid-peripheral CT (1.5 mm) was shown. These changes agree with the suggestion that ortho-k lenses inhibit central swelling (Alharbi et al., 2005). The ortho-k lens might limit central corneal oedema but not in the mid-peripheral cornea. A greater backward movement of the mid-peripheral cornea could be the reason for posterior corneal steepening by the uneven corneal oedema. The measuring protocol used here is different from that of Read and Collins (2009), in that the measurements here were not taken immediately after eye opening following sleep. Apart from the lack of control eyes in this study, the recovery of the ortho-k effect after lens removal was not monitored. It could be difficult to conclude whether these posterior corneal changes resolve when the overnight corneal oedema recovers during the day 2 to 3 hours after lens removal in the current study. Diurnal changes after lens removal were investigated in Study III, which are discussed in a later section (Section 4.6).

For the corneal biomechanics, CH was not significantly changed with short-term ortho-k lens wear, while CRF showed a reduction especially after overnight lens wear. The changes of CRF after overnight lens wear were also significantly correlated with changes to Sim K readings (Figure 4.9). ORA provides an in vivo measurement of corneal biomechanical properties. Table 4.8 tabulates the CH and CRF of normal subjects reported in the literature. All studies found similar CH and CRF (within 1.0 mmHg) except Lu et al. (2007c), who reported a large difference of 1.9 mmHg between the two parameters.

Table 4.8. Summary of previous studies of corneal hysteresis (CH) and corneal resistance factor (CRF) in normal subjects.

Studies	Age (years)	CH (mmHg)	CRF (mmHg)
(Touboul et al., 2008)	48.0 (17 – 80)	10.3	11.1
(Song et al., 2008)	14.7 ± 0.8	10.7 ± 1.5	-
(Lim et al., 2008)	14.0 ± 0.9 (12 – 15)	11.8 ± 1.6 (6.9 – 16.5)	11.9 ± 1.7 (7.8 – 16.8)
(Kirwan et al., 2008)	35 ± 8.1	9.6 ± 1.5 (6.3 – 12.7)	9.4 ± 1.6 (6.2 – 13.9)
(Kirwan and Okeefe, 2008)	36.0 ± 10.0 (21 – 62)	10.8 ± 1.5 (6.9 – 13.7)	-
(Shah et al., 2007)	62.1 ± 18.1 (18 – 87)	10.7 ± 2.0 (6.1 – 17.6)	-
(Pepose et al., 2007)	39.6 ± 11.4	9.7 ± 1.8	9.5 ± 1.9
(Ortiz et al., 2007)	37.0 (9 – 80)	10.8 ± 1.5	11.0 ± 1.6
(Lu et al., 2007c)	19.7 ± 1.1	11.5 ± 1.4	9.6 ± 1.9
(Lam and Chen, 2007a)	- (20 – 31)	11.2 ± 1.4	11.0 ± 1.6
(Lam et al., 2007)	23.1 ± 3.3 (19 – 40)	10.9 ± 1.5	11.0 ± 1.7
(Shah et al., 2006)	62.1 ± 18.1 (18 – 87)	10.7 ± 2.0 (6.1 – 17.6)	10.3 ± 2.0 (5.7 – 17.1)
(Kirwan et al., 2006)	- (4 – 18)	12.5 ± 1.4 (8.2 – 15.7)	-
(Luce, 2005)	28.0 (23 – 38)	9.6	-
Current study (baseline values)	24.1 ± 2.6 (19 – 30)	11.1 ± 1.1 (8.9 – 13.1)	10.7 ± 1.3 (8.8 – 13.1)

Data presented as mean ± standard deviation (range of values given in parentheses).

To date, there has been only one study of the effect of ortho-k on CH and CRF (Gonzalez-Meijome et al., 2008b). This aroused the author’s interest in investigating the corneal biomechanical changes with ortho-k treatment. Previous studies documented a positive association between CRF and central corneal thickness (Shah et al., 2006, Touboul et al., 2008). In addition, reductions of CH and CRF were obtained in cornea received refractive surgery

(Luce, 2005, Ortiz et al., 2007, Pepose et al., 2007, Kirwan and Okeefe, 2008). The extent of CRF reduction is greater than CH with the same amount of stromal tissue ablation. It might indicate that CRF is more sensitive to the change of stromal layer. Lu et al. (2007c) demonstrated that CH is not affected by induced corneal swelling (up to 60 μm) but CRF increased by 0.6 mmHg. In contrast, a decrease in CRF, without a significant change in central corneal thickness, was found in the current study after one overnight lens wear. This opposite effect might be attributed to the thinning of corneal epithelium and stroma produced by the ortho-k treatment. Choo et al. (2008) demonstrated a thinning of epithelial and stromal layer with continuous wear of ortho-k lens in an animal model. Latest technology, such as the spectral domain anterior OCT might help to further understand the corneal changes with ortho-k treatment and its association with CRF reduction.

Could corneal biomechanics be used to predict the effect of ortho-k? Gonzalez-Meijome et al. (2008b) appear to be the first to demonstrate a greater corneal response to corneal refractive therapy from eyes with lower CH and CRF. However, no correlations could be obtained between ortho-k changes after overnight wear and baseline corneal biomechanics in the current study. The discrepancy might be explained by the fact that a stable ortho-k effect has not been achieved after short-term wear, namely, either 3-hours (Gonzalez-Meijome et al., 2008b) or one overnight wear (current study). Also, the sample size was different while only 8 subjects were involved in their study. The relationships between the changes of Sim K_{flat} and Sim K_{steep} and the corneal biomechanical changes are further explored in Section 4.6. Only the associations between the change of CRF and the changes of both Sim K_{steep} and Sim K_{flat} were found to be significant (Figure 4.9a and 4.9b). These results showed that the CRF change was related to the changes in corneal curvatures. The reduction of CRF did not simply follow the degree of flattening of Sim K readings. The negative correlations indicated greater reductions of CRF in corneas with lesser flattening of Sim K. It was difficult to understand the relationship demonstrated. On the other hand, it seems more logical if greater CRF reduction was followed with a higher degree of flattening, which might indicate that the cornea became softer with a higher degree of flattening after overnight ortho-k lens wear. This was not the case in the current study. So, for a cornea with greater flattening magnitude, the cornea resistance remained and could rebound back after treatment, which might implicate that the flattening could only be temporary but not permanent. However, the validity of the CRF measurement is still questionable and not yet fully known. Although Luce (2005) suggested CRF measures the overall resistance of the cornea, it was derived from the difference of P1 and a fraction of P2. Hence, the actual meaning or logic behind the derivation of CRF was not fully understood. It is debatable whether CRF is measuring the overall corneal resistance. More studies are required to evaluate the validity and meaning of this parameter.

The changes in myopia, UCV and anterior Sim K results are comparable to similar studies in the literature (Sridharan and Swarbrick, 2003). Sridharan and Swarbrick (2003) found that UCV improved after as short as 10 minutes of lens wear. Although they did not measure the associated change in refractive error, their estimated refractive error changes (0.52 D) according to the UCV were close to the current findings (Table 4.3). Nevertheless, VA was unaffected by short-term ortho-k treatment. The results here are in agreement with the data of some earlier studies (Berntsen et al., 2006, Johnson et al., 2007).

4.4.6 Conclusions

This study showed changes in posterior corneal curvature, corneal biomechanics and corneal thickness from short-term ortho-k treatment. The posterior corneal curvature steepened and the CRF decreased, especially when wearing the lenses overnight. The change in CH was not significant. The corneal thickness remained unchanged at central but thickened at mid-peripheral regions after overnight ortho-k treatment. However, this study was limited to only one overnight wear. Whether changes in the posterior cornea, corneal biomechanics and corneal thickness would be greater with a longer treatment period is still uncertain. A study with a longer treatment period is warranted and the recovery should also be monitored. In addition, there was no control group in this study. The next section (Study II) mainly addresses this last drawback with the introduction of an alignment-fitted lens wearing group as control. The null hypothesis that no change in the posterior corneal curvature, corneal biomechanical properties, and topographical corneal thickness after short-term ortho-k treatment was rejected.

Paper published:

Chen D, Lam AK, Cho P. A pilot study on the corneal biomechanical changes in short-term orthokeratology. Ophthalmic Physiol Opt. 2009;29:464-471.

Conference presentation:

Chen D, Lam AK, Cho P. The effect of short-term orthokeratology treatment on corneal biomechanics and posterior corneal shape. Presented at The 16th Asia Pacific Optometric Congress, 2007. Goa, India.

4.5 Study II

4.5.1 Introduction

This study was a repeat of the short-term study (Study I) with the addition of a conventional alignment fitted lens on the fellow eye as control. It aimed to compare the changes in posterior corneal curvature, corneal biomechanics and topographic corneal thickness from wearing two types of lenses for a short-term period.

4.5.2 Experimental protocol

Each subject was required to wear the ortho-k lens on one eye (the right eye) and a conventional alignment fitted lens on the other eye. The right eye was the treatment eye and categorised into Group “OK”. The left eye wore the conventional alignment fitted lens and served as the control Group “C”. Lens designs of both types of lens have been described in Section 4.3. The control eye (Group C) still had a contact lens in situ, so possible sympathetic effect from one eye affecting the other could be minimized. For example, the foreign body sensation of rigid lens in lens wearing eye will induce reflex tears and also sympathetically affect the other eye without any lens wearing. This kind of induced tears might introduce a variable in the experiment, so the conventional alignment fitted lens could not only act as a control for comparison, but also help to minimize the sympathetic effect induced.

This study consisted of four different wearing sessions similar to Study I (Section 4.4). The durations of lens wear for each of the four sessions were 15 minutes, 30 minutes, 60 minutes and overnight respectively. To avoid carry-over effects, each subsequent session was scheduled at least one week after the previous visit. The first three wearing sessions, 15 minutes, 30 minutes and 60 minutes, were randomly assigned while the overnight wear was always the last session. The first three sessions were carried out at approximately the same time during the day to minimize possible diurnal variations in corneal parameters. For the overnight wear, subjects were required to wear the lenses for 7 to 10 hours. They were required to return to the Optometry Clinic of The Hong Kong Polytechnic University the following morning within two hours of waking with the lenses in situ.

4.5.3 Statistical analysis

All the data were tabulated into two groups, Group OK and Group C and tested with the Kolmogorov-Smirnov test for normality ($p > 0.05$). Parametric and non-parametric statistical tests were then used to analyse the data, as appropriate. In the comparison of baseline data between the two eyes, paired t-tests were used. Repeated measures ANOVA was used to compare the findings between baseline and different wearing sessions. Whenever significant differences were found, post-hoc tests (Bonferroni Multiple Comparisons Test) were performed. For non-parametric data, the Friedman test with post-tests (Dunn's procedures) was used in a similar way. Bonferroni's and Dunn's procedures were performed to minimize any Type I error. To detect an expected difference of 0.65 mmHg and SD of 0.6 mmHg in CRF (Table 4.5), the number of subjects should be at least 8 for 80% power with alpha 0.05.

4.5.4 Results

There were 9 subjects (4 males and 5 females) involved and their mean age was 21.6 ± 1.8 years. The mean ± SD baseline SER of the Group OK and Group C were −2.63 ± 1.34 D and −2.96 ± 1.31 D, respectively. Table 4.9 shows the summary of demographic results of both groups at baseline. No significant differences were found between the two eyes in the SER, UCV, VA, anterior Sim K_{flat} and Sim K_{steep} (Paired t-test, $p > 0.05$).

Table 4.9. Summary (mean ± one standard deviation) of demographic data of both eyes at the baseline visit.

Age (years)	21.6 ± 1.8	
Gender	4 males and 5 females	
Group	Group OK (Right eye)	Group C (Left eye)
SER (D)	−2.63 ± 1.34	−2.96 ± 1.31
UCV	0.84 ± 0.24	0.90 ± 0.20
VA	−0.07 ± 0.04	−0.07 ± 0.03
Sim K_{flat} (D)	42.53 ± 1.45	42.40 ± 1.31
Sim K_{steep} (D)	43.63 ± 1.43	43.54 ± 1.48

Group OK and Group C: Group of orthokeratology lens wearing eyes and Group of conventional alignment fitted lens wearing eyes (control), respectively.
SER: spherical equivalent refraction.
UCV: uncorrected vision; VA: visual acuity; both in logMAR units.
Sim K_{flat} and Sim K_{steep}: flattest and steepest simulated keratometric reading respectively, measured by the Medmont system.

In Group OK, SER reduced significantly after 30 minutes wear (Repeated measures ANOVA, $p < 0.01$; post-hoc test, $p < 0.05$). After overnight wear, SER reduced to −1.15 D. There were no significant changes in SER in Group C with the conventional alignment fit (Repeated measures ANOVA, $p > 0.05$). The SER remained statistically the same throughout the study. UCV was significantly improved after as short as 15 minutes of ortho-k lens wear (Repeated measures ANOVA, $p < 0.01$; post-hoc test, $p < 0.05$). It further improved to logMAR 0.21 after overnight wear (post-hoc tests, $p < 0.01$). In contrast, no significant change of UCV was observed in the control eyes (Repeated measures ANOVA, $p > 0.05$). For VA, no significant change was observed from ortho-k treatment (Friedman test, $p > 0.05$). Although a significant change was found in the control eyes throughout the experiment (Friedman test, $p < 0.05$), no significant difference could be found in any post hoc analyses (Dunn's procedure, $p > 0.05$).

Table 4.10 shows the detailed results of SER, UCV and VA in both eyes at different time points.

Table 4.10. The results (mean ± one standard deviation) of SER, UCV and VA of both eyes at different time points.

	Group	Baseline	15 mins	30 mins	60 mins	Overnight
SER (D)	**OK**	−2.63 ± 1.34	−2.15 ± 1.35	*−2.07 ± 1.37	^−1.76 ± 1.33	^−1.15 ± 1.21
	C	−2.96 ± 1.31	−3.00 ± 1.21	−2.96 ± 1.34	−2.89 ± 1.36	−2.92 ± 1.30
UCV	**OK**	0.84 ± 0.24	*0.61 ± 0.32	^0.44 ± 0.36	^0.37 ± 0.35	^0.21 ± 0.28
	C	0.90 ± 0.20	0.87 ± 0.25	0.88 ± 0.23	0.87 ± 0.20	0.81 ± 0.28
VA	**OK**	−0.07 ± 0.04	−0.04 ± 0.06	−0.06 ± 0.04	−0.06 ± 0.03	−0.05 ± 0.04
	C	−0.07 ± 0.03	−0.07 ± 0.04	−0.06 ± 0.03	−0.07 ± 0.03	−0.04 ± 0.05

Group OK and Group C: Group of orthokeratology lens wearing eyes and Group of conventional alignment fitted lens wearing eyes (control), respectively.
SER: spherical equivalent refraction.
UCV: uncorrected vision; VA: visual acuity; both in logMAR units.
R and L: Right and left eyes, respectively.
* and ^ indicate significance of $p < 0.05$ and $p < 0.01$, respectively, compared with the baseline result.

For the corneal biomechanical properties, no significant changes were obtained either in CH or CRF throughout the study in both groups (Repeated measures ANOVA, $p > 0.05$) (Table 4.11).

Table 4.11. The results (mean ± one standard deviation) of CRF and CH of both eyes at different time points.

Corneal biomechanics (mmHg)	Group	Baseline	15 mins	30 mins	60 mins	Overnight
CH	**OK**	11.2 ± 0.9	11.0 ± 1.3	10.9 ± 1.1	11.0 ± 1.2	10.7 ± 1.0
	C	10.8 ± 1.0	10.9 ± 1.1	10.6 ± 1.0	10.7 ± 1.3	10.5 ± 1.3
CRF	**OK**	10.9 ± 1.5	10.6 ± 1.6	10.4 ± 1.5	10.5 ± 1.5	10.4 ± 1.7
	C	10.8 ± 1.2	10.7 ± 1.4	10.5 ± 1.3	10.4 ± 1.4	10.4 ± 1.6

Group OK and Group C: Group of orthokeratology lens wearing eyes and Group of conventional alignment fitted lens wearing eyes (control), respectively.

CH and CRF: corneal hysteresis and corneal resistance factor, respectively.

A significant anterior corneal flattening was demonstrated with a longer duration of ortho-k lens wear (Repeated measures ANOVA, $p < 0.01$). The changes were significant after 30 minutes of lens wear for both the Sim K_{flat} and Sim K_{steep} (post-hoc tests, $p < 0.01$). The control eyes remained statistically the same in all the wearing sessions (Repeated measures ANOVA, $p > 0.05$). Regarding the posterior cornea, the treatment eyes demonstrated significant steepening along the Sim K_{steep} after 60 minutes and overnight lens wear (Repeated measures ANOVA, $p < 0.01$; post-hoc tests, $p < 0.05$). For posterior Sim K_{flat}, a significant change was obtained throughout the study (Repeated measures ANOVA, $p < 0.01$) but no significant difference was found comparing different wearing sessions with the baseline visit (post-hoc tests, $p > 0.05$). No significant changes of Sim K readings in the control eyes were obtained (Repeated measures ANOVA, $p > 0.05$) (Table 4.12).

Table 4.12. The results (mean ± one standard deviation) of anterior and posterior simulated keratometric readings (Sim K) at different time points.

Sim K (D)	**Group**	**Baseline**	**15 mins**	**30 mins**	**60 mins**	**Overnight**
Anterior						
Sim K_{flat}	**OK**	42.38 ± 1.39	42.13 ± 1.47	^41.90 ± 1.34	^41.69 ± 1.37	^41.40 ± 1.37
	C	42.21 ± 1.41	42.26 ± 1.42	42.33 ± 1.41	42.24 ± 1.42	42.29 ± 1.38
Sim K_{steep}	**OK**	43.43 ± 1.48	43.19 ± 1.48	^42.93 ± 1.47	^42.61 ± 1.48	^42.44 ± 1.60
	C	43.27 ± 1.54	43.29 ± 1.57	43.37 ± 1.54	43.27 ± 1.51	43.35 ± 1.48
Posterior						
Sim K_{flat}	**OK**	−6.04 ± 0.24	−6.00 ± 0.23	−6.05 ± 0.24	−6.07 ± 0.27	−6.08 ± 0.26
	C	−5.95 ± 0.27	−5.93 ± 0.26	−5.93 ± 0.26	−5.94 ± 0.28	−5.94 ± 0.27
Sim K_{steep}	**OK**	−6.44 ± 0.23	−6.43 ± 0.19	−6.49 ± 0.23	^−6.52 ± 0.21	*−6.50 ± 0.21
	C	−6.41 ± 0.22	−6.41 ± 0.20	−6.39 ± 0.23	−6.41 ± 0.20	−6.44 ± 0.22

Group OK and Group C: Group of orthokeratology lens wearing eyes and Group of conventional alignment fitted lens wearing eyes (control), respectively.
Sim K_{flat} and Sim K_{steep}: Flattest and steepest simulated keratometric readings, respectively.
* and ^ indicate significance of $p < 0.05$ and $p < 0.01$, respectively, compared with the baseline result.

For the topographic corneal thickness, both the treatment eyes and control eyes showed similar findings at the corneal apex, 0.5 mm and 1.0 mm annuli in all wearing sessions (Repeated measures ANOVA, $p > 0.05$). The treatment eyes demonstrated significant thickening at the 1.5 mm, 2.0 mm and 2.5 mm annuli after overnight wear (Repeated measures ANOVA, $p < 0.01$; post-hoc tests, $p < 0.05$). There were no significant changes in the control eyes (Repeated measures ANOVA, $p > 0.05$) (Table 4.13).

Table 4.13. The results (mean ± one standard deviation) of central and mid-peripheral corneal thickness at different time points.

		Baseline	**15 mins**	**30 mins**	**60 mins**	**Overnight**
	Group					
Apex (µm)	**OK**	573.6 ± 29.1	569.5 ± 31.0	573.5 ± 35.5	570.1 ± 32.1	579.3 ± 35.4
	C	560.8 ± 26.8	565.7 ± 30.3	567.1 ± 31.6	564.0 ± 29.1	569.0 ± 30.6
Mid-peripheral annuli						
0.5 mm (µm)	**OK**	575.5 ± 29.0	571.6 ± 30.9	575.8 ± 35.3	572.8 ± 31.9	582.0 ± 35.3
	C	562.5 ± 26.9	567.2 ± 30.2	568.8 ± 31.6	565.7 ± 29.1	570.8 ± 30.5
1.0 mm (µm)	**OK**	581.5 ± 28.6	577.9 ± 30.4	583.0 ± 34.8	580.8 ± 31.4	590.1 ± 34.9
	C	568.1 ± 27.0	572.6 ± 30.2	573.9 ± 31.6	571.0 ± 29.1	576.4 ± 30.0
1.5 mm (µm)	**OK**	592.3 ± 27.9	588.9 ± 30.0	595.1 ± 34.1	594.2 ± 30.7	^603.6 ± 34.4
	C	578.2 ± 27.2	582.5 ± 30.2	583.7 ± 31.3	581.1 ± 29.0	586.7 ± 29.5
2.0 mm (µm)	**OK**	608.5 ± 27.1	605.4 ± 29.7	612.7 ± 33.4	613.0 ± 29.8	^622.4 ± 33.9
	C	594.0 ± 27.3	598.3 ± 30.2	599.1 ± 30.9	597.3 ± 28.5	602.5 ± 29.0
2.5 mm (µm)	**OK**	631.1 ± 26.3	628.0 ± 29.6	636.0 ± 32.7	637.4 ± 28.8	^646.6 ± 33.3
	C	616.3 ± 27.3	620.6 ± 30.1	621.4 ± 30.2	620.1 ± 27.9	624.9 ± 28.7

Mid-peripheral annuli represent the average of superior, temporal, inferior and nasal corneal thicknesses with the distance (radius) from apex.

^ indicates significance of $p < 0.01$, compared with the baseline result.

4.5.5 Discussion

This study was similar to Study I (Section 4.4) with only one difference. The left eye served as the control eye by fitting a lens with conventional alignment fit. The two lenses shared the same overall diameter, lens material and central thickness. Posterior corneal steepening was found with ortho-k lens wear, while the control eyes demonstrated no change. These current results further supported the findings of posterior corneal steepening with ortho-k lens wear in Study I (Section 4.4).

Read and Collins (2009) found posterior corneal steepening immediately after normal sleep. These changes returned to a baseline level within 2 to 3 hours after eye opening. They suggested an uneven corneal oedema after sleep between the central and peripheral corneal regions. The current results after ortho-k lens wearing for 60 minutes (−6.52 D) and one overnight (−6.50 D) demonstrated similar posterior corneal steepening. There was a significant increase in corneal thickness at the mid-peripheral regions (1.5 mm, 2.0 mm and 2.5 mm annuli) in the treatment eyes but no significant changes were obtained in the control eyes. This supports the view that the changes (both posterior corneal steepening and corneal thickness changes) were due to the ortho-k effect. Wang et al. (2003) used a time domain OCT to demonstrate epithelial thinning at the central cornea and mid-peripheral thickening after overnight wear of ortho-k lenses. Although the instrument had a resolution of 6 μm which could help to identify the corneal layers (Maldonado et al., 2000), the latest technology, such as spectral domain OCT, could monitor the epithelial changes in a more precise way. The corneal topographer used here was unable to measure corneal epithelial changes. Nevertheless, the increase in corneal thickness from the centre towards the mid-periphery after overnight ortho-k treatment was in agreement with previous studies (Swarbrick et al., 1998, Wang et al., 2003). The difference in CT in the treatment eyes between overnight and baseline was 5.7 μm at the apex and 15.5 μm at the 2.5 mm mid-peripheral region (Table 4.13). The difference in CT between overnight and baseline in the control eyes was approximately the same (~8 μm) in different regions. Current results regarding topographic corneal thickness after overnight ortho-k lens wear also demonstrated inhibition of central swelling (apex, 0.5 mm and 1.0 mm), while thickening of mid-peripheral CT (1.5 mm, 2.0 mm and 2.5 mm) was shown. If the difference in corneal oedema at various regions originates solely from the corneal epithelium (Wang et al., 2003), it is interesting to note the posterior corneal steepening in the current study. No posterior steepening was found in the control eyes. Read and Collins (2009) demonstrated that normal eyes had posterior corneal steepening induced by sleep. The posterior cornea returned to normal within 2 hours after eye opening. The current study measured corneal thickness immediately after lens removal within 2 hours of waking but not immediately after eye opening with the lenses removed. Therefore, it is not surprising that there was no significant posterior corneal change in the control eyes. Any posterior corneal steepening induced by sleep in the treatment and the control eyes might have recovered before the measurements. The steepening effects were found only in the treatment eyes but not in control eyes, which might further suggest that ortho-k treatment has some steepening effects on the posterior cornea. However, the results in this study were not identical to the results in Study I, where only significant steepening of Sim K_{steep} was obtained. Here, both Sim K readings were steepened significantly. This may be attributed to the smaller number of subjects who participated in this study. It should be acknowledged that the subject recruitment was not easy because of the poor lens comfort with the rigid lens wear. Also, the vision of the subjects became very different (significantly improved in the treatment eye but remain the same in the control eye) after the experiment. Although the visual changes were temporary, the subjects could not wear their own spectacles for a short period of time.

There were no significant changes in corneal biomechanics in either the treatment or the control eyes. Similar to Study I, there was no effect on CH with short-term ortho-k lens wear. For CRF, it dropped 0.5 mmHg for the treatment eyes after overnight wear. The extent of reduction was close to the changes found in Study I (0.6 mmHg, Table 4.5), even though not significant. This might be due to the small sample size. To detect an expected difference of 0.6 mmHg and SD of 1.7 mmHg in CRF (Lam et al., 2007), the number of subjects should be over 165 for 90% power with alpha 0.05. The changes in anterior Sim K readings, UCV and VA were similar to the results reported in Study I and in the literature (Sridharan and Swarbrick, 2003).

4.5.6 Conclusions

The current study replicated Study I in order to address the lack of control eyes. With the conventional alignment fitted lens wearing eyes as controls, current results have demonstrated that ortho-k lens wear has some steepening effects on the posterior corneal shape. Although the samples size is 9 only, this is adequate to detect a difference of 0.06 D and SD of 0.04 D in posterior corneal curvature change (Table 4.12) with 90% statistical power. Smaller subject number involved in the current study comparing with Study I. Different vision between eyes was resulted after removal of ortho-k and conventional lenses. Although the wearing duration was short, it was difficult to recruit subjects because vision was very different between the two eyes from wearing different lens types.

4.6 Study III

4.6.1 Introduction

This study aimed to investigate the changes in posterior corneal curvature, corneal biomechanics, and topographic corneal thicknesses with long-term (6 months) ortho-k treatment. After a 6-month treatment period, these parameters were monitored throughout one day and over a 2-month period after cessation of lens wear.

4.6.2 Experimental protocol

Each subject was required to wear the ortho-k lenses only at night time for 6 months. In the treatment period (Phase I), follow-up visits were scheduled after the first overnight wear and then after 1 week and after 1, 2, 3 and 6 months of lens wear. The design of the ortho-k lens used in this study has been described in Section 4.3. The subjects were required to sleep with the lenses for 7 to 10 hours. After the first overnight wear, subjects were required to return to the Optometry Clinic of The Hong Kong Polytechnic University within 2 hours of waking with the lenses in situ to investigate for any adverse signs such as, lens binding or associated undesirable responses. Data were collected immediately after lens removal in the clinic following the first overnight wear. Measurements were done between 2 to 8 hours after lens removal in all the other follow-up visits. On the day after 6 months of successful lens wear, subjects were required to attend the clinic to monitor any diurnal corneal changes (Phase II). Data were collected at four different times, i.e. immediately, then 2, 4 and 8 hours after lens removal. Ortho-k treatment was ceased after Phase II. Recovery from treatment was monitored for the next 2 months (Phase III), which included follow-up visits scheduled at 1 and 2 weeks, and 1 and 2 months after the cessation of treatment.

4.6.3 Statistical analysis

All data were tested with the Kolmogorov-Smirnov test for normality ($p > 0.05$). Parametric and non-parametric statistical tests were then used to analyse the data, as appropriate. In the comparison of baseline data between the two eyes, paired t-tests (for parametric data) and Wilcoxon matched pairs tests (for non-parametric data) were used. Repeated measures ANOVA was used to compare the changes between baseline and different wearing sessions (Phase I), and recovery visits after cessation of lens wear (Phase III). It was also used to compare the changes between immediate and after lens removal up to 8 hours in Phase II. Whenever significant differences were found, post-hoc tests (Bonferroni Multiple Comparisons Test) were performed. For non-parametric data, the Friedman test with post-tests (Dunn's procedures) was used in a similar way. Post hoc analyses were performed to minimize any Type I errors during multiple comparisons.

4.6.4 Results

Forty-five subjects (17 males and 28 females) completed Phases I and II of this study while 43 subjects (16 males and 27 females) completed Phase III and details were described later (Section 4.6.4.3). Their mean ± SD age was 22.6 ± 2.7 years. The mean ± SD baseline SER of the right and left eyes were −2.74 ± 0.85 D and −2.73 ± 1.03 D, respectively. Table 4.14 shows the demographic results at the baseline visit. Only data from the right eyes were analysed and presented for different phases, as there were no significant differences between the two eyes in SER, UCV, VA, anterior Sim K_{flat}, and Sim K_{steep} (Paired t-tests, SER, VA, anterior Sim K_{flat}, and Sim K_{steep} respectively, $p > 0.05$; UCV, Wilcoxon matched pairs tests, $p > 0.05$).

Table 4.14. Summary (mean ± one standard deviation) of demographic data of both eyes at the baseline visit.

Age (years)	22.6 ± 2.7	
Gender	17 males and 28 females	
Eye	Right	Left
SER (D)	−2.74 ± 0.85	−2.73 ± 1.03
UCV	0.84 ± 0.24	0.83 ± 0.26
VA	−0.06 ± 0.05	−0.08 ± 0.04
Sim K_{flat} (D)	42.84 ± 1.26	42.77 ± 1.25
Sim K_{steep} (D)	43.80 ± 1.32	43.68 ± 1.30

SER: spherical equivalent refraction.
UCV: uncorrected vision; VA: visual acuity; both in logMAR units; Sim K_{flat} and Sim K_{steep}: Flattest and steepest simulated keratometric readings (Pentacam), respectively.

4.6.4.1 Phase I: Six-month treatment period

Significant changes were found in SER and UCV after one overnight wear and throughout the study (Repeated measures ANOVA, $p < 0.01$; post-hoc tests, $p < 0.05$). Statistically, VA significantly improved at the 3-month visit, while no changes were observed at other visits (Repeated measures ANOVA, $p < 0.01$; post-hoc tests, $p < 0.05$) (Table 4.15).

Table 4.15. The results (mean ± one standard deviation) of SER, UCV and VA at different time points, for the right eye only.

	Baseline	**Overnight**	**1-week**	**1-month**	**2-month**	**3-month**	**6-month**
SER (D)	−2.86 ± 0.97	^−1.18 ± 0.79	^−0.29 ± 0.46	^−0.19 ± 0.57	^−0.19 ± 0.47	^−0.05 ± 0.38	^0.04 ± 0.37
UCV	0.84 ± 0.24	*0.22 ± 0.24	^−0.02 ± 0.09	^−0.01 ± 0.12	^−0.01 ± 0.11	^−0.04 ± 0.08	^−0.04 ± 0.09
VA	−0.06 ± 0.05	−0.05 ± 0.06	−0.08 ± 0.06	−0.08 ± 0.05	−0.09 ± 0.04	*−0.09 ± 0.05	−0.08 ± 0.06

SER: spherical equivalent refraction.

UCV: uncorrected vision; VA: visual acuity; both in logMAR units.

***** and **^** indicate significance of $p < 0.05$ *and* $p < 0.01$, respectively, compared with the baseline result.

For the anterior Sim K, significant differences were found during the treatment period (Repeated measures ANOVA, $p < 0.01$). Post tests showed significant flattening of both Sim K_{flat} and Sim K_{steep} throughout the lens wearing period (post-hoc tests, $p < 0.05$). For the posterior Sim K, significant differences were found during the treatment period (Repeated measures ANOVA, $p < 0.01$). Post hoc analyses showed that Sim K_{flat} and Sim K_{steep} steepened from baseline values of −6.12 D to −6.17 D and −6.47 D to −6.55 D, respectively (post-hoc tests, $p < 0.01$) after the first overnight wear. The differences were not significant at other visits (post-hoc tests, $p > 0.05$). Detailed changes of anterior and posterior Sim K readings during the treatment period are given in Table 4.16. The trend of posterior Sim K changes after different wearing periods is shown in Figure 4.10.

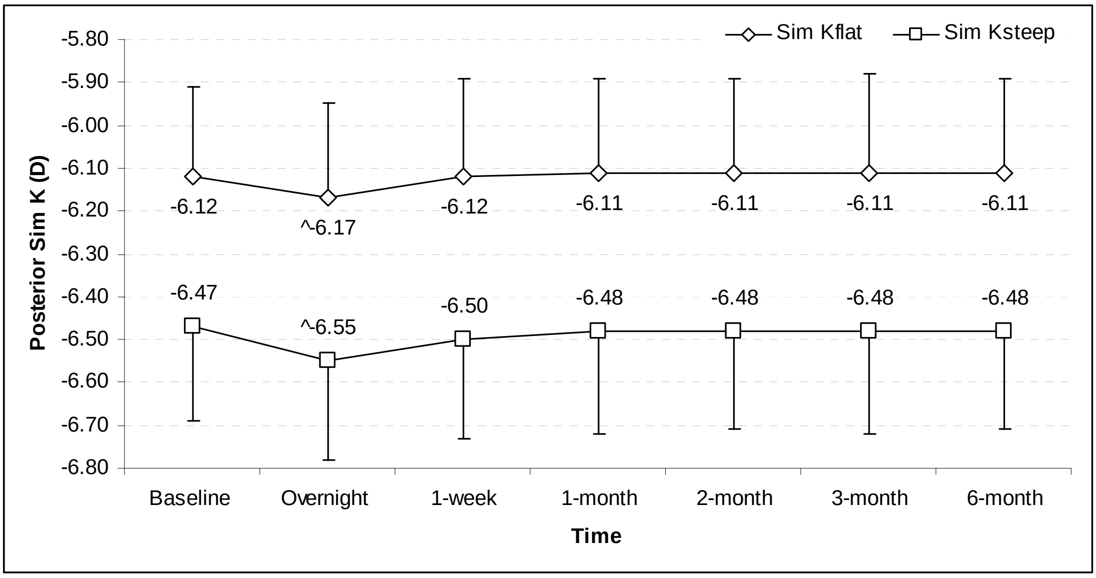
Table 4.16. The results (mean ± one standard deviation) of Sim K_{flat} and Sim K_{steep} (Pentacam) at different time points, for the right eye only.

Sim K	**Baseline**	**Overnight**	**1-week**	**1-month**	**2-month**	**3-month**	**6-month**
Anterior							
Sim K_{flat}	42.84 ± 1.26	^41.86 ± 1.12	^41.45 ± 1.16	^41.45 ± 1.24	^41.42 ± 1.24	^41.44 ± 1.26	^41.37 ± 1.22
Sim K_{steep}	43.80 ± 1.32	^42.96 ± 1.39	^42.37 ± 1.22	^42.37 ± 1.27	^42.26 ± 1.26	^42.36 ± 1.34	^42.39 ± 1.38
Posterior							
Sim K_{flat}	−6.12 ± 0.21	^−6.17 ± 0.22	−6.12 ± 0.23	−6.11 ± 0.22	−6.11 ± 0.22	−6.11 ± 0.23	−6.11 ± 0.22
Sim K_{steep}	−6.47 ± 0.22	^−6.55 ± 0.23	−6.50 ± 0.23	−6.48 ± 0.24	−6.48 ± 0.23	−6.48 ± 0.24	−6.48 ± 0.23

Sim K_{flat} and Sim K_{steep}: Flattest and steepest simulated keratometric readings, respectively.

^ indicates significance of $p < 0.01$, compared with the baseline result.

Figure 4.10. The trend of posterior Sim K changes after different wearing periods of orthokeratology lens, for the right eye only.



Sim K_{flat} and Sim K_{steep}: Flattest and steepest simulated keratometric readings, respectively.
^ indicates significance of $p < 0.01$, compared with the baseline result.

No significant changes in CH were found throughout the study (Repeated measures ANOVA, $p > 0.05$). However, a decreasing trend of CRF was observed with longer duration of treatment (Figure 4.11). Significant reductions of CRF were found after 1 week of lens wear , with further reduction with longer wearing time (Repeated measures ANOVA, $p < 0.01$; post-hoc tests, $p < 0.01$) (Table 4.17).

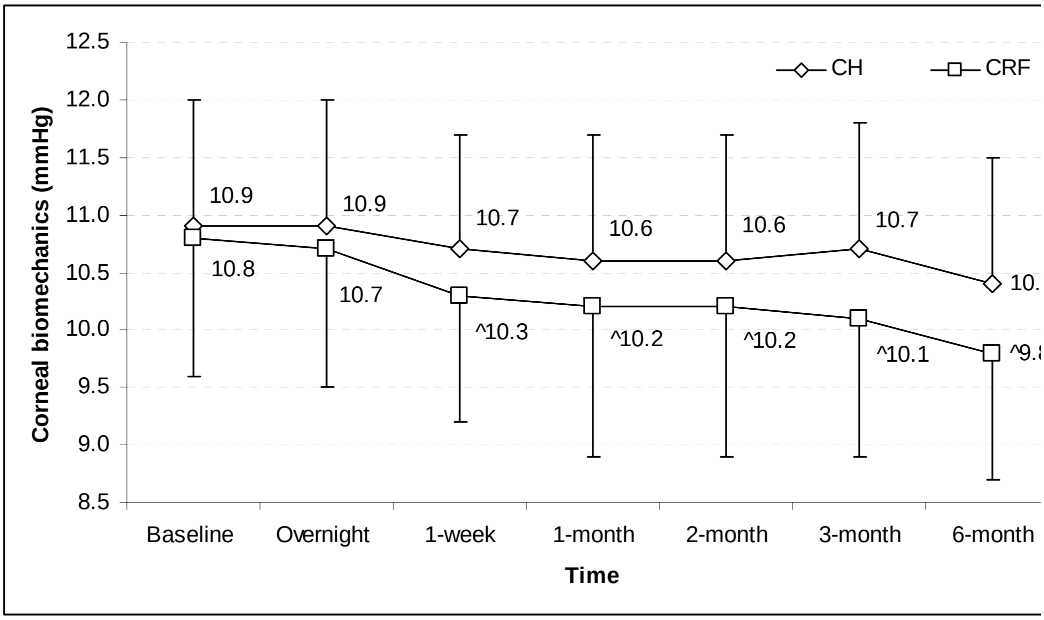
Table 4.17. The results (mean ± one standard deviation) of CH and CRF at different time points, for the right eye only.

Corneal biomechanics (mmHg)	**Baseline**	**Overnight**	**1-week**	**1-month**	**2-month**	**3-month**	**6-month**
CH	10.9 ± 1.1	10.9 ± 1.1	10.7 ± 1.0	10.6 ± 1.1	10.6 ± 1.1	10.7 ± 1.1	10.4 ± 1.1
CRF	10.8 ± 1.2	10.7 ± 1.2	^10.3 ± 1.1	^10.2 ± 1.3	^10.2 ±1.3	^10.1 ± 1.2	^9.8 ± 1.1

CH and CRF: corneal hysteresis and corneal resistance factor, respectively.

^ indicates significance of $p < 0.01$, compared with the baseline result.

Figure 4.11. The trend of CH and CRF changes after different wearing periods of orthokeratology lens, for the right eye only.



CH and CRF: corneal hysteresis and corneal resistance factor, respectively.
^ indicates significance of $p < 0.01$, compared with the baseline result.

The correlations of the changes of anterior Sim K readings after overnight and 1 week of lens wear with the baseline corneal biomechanical properties, both CH and CRF, were explored. The reasons why only the results from these two sessions were analysed are discussed in Section 4.6.5. No significant correlations could be found (All $R^2 \leq 0.03$, $p > 0.05$) (Table 4.18).

Table 4.18. Regression analyses between baseline corneal biomechanics and the efficacy of orthokeratology treatment after overnight and 1-week lens wear.

	Anterior Sim K_{flat}				**Anterior Sim K_{steep}**			
	Wearing time				**Wearing time**			
	Overnight		**1-week**		**Overnight**		**1-week**	
	R^2	***p* value**	**R^2**	***p* value**	**R^2**	***p* value**	**R^2**	***p* value**
CH	0.03	0.29	0.00	0.87	0.02	0.36	0.00	0.99
CRF	0.01	0.42	0.00	0.64	0.00	0.73	0.01	0.56

CH and CRF: corneal hysteresis and corneal resistance factor, respectively.

There was significant corneal thinning at the apex, 0.5 mm and 1.0 mm annuli after 1 month of lens wear (Repeated measures ANOVA, $p < 0.01$; post-hoc tests, $p < 0.05$). The central corneal thickness further decreased with a longer treatment period. For the mid-peripheral region, significant thinning at the 1.5 mm annulus was found at the 6-month visit (Repeated measures ANOVA, $p < 0.01$; post-hoc tests, $p < 0.01$) but this was not shown in other visits (post-hoc tests, $p > 0.05$). Significant thickening of the cornea at the 2.0 mm and 2.5 mm annuli was found initially, after overnight and 1 week of lens wear (Repeated measures ANOVA, $p < 0.01$; post-hoc tests, $p < 0.05$). The mid-peripheral corneal thickness was similar to the baseline values at the subsequent visits (post-hoc tests, $p > 0.05$). Detailed changes in topographic CT are shown in Table 4.19.

Table 4.19. The results (mean ± one standard deviation) of central and mid-peripheral corneal thicknesses at different time points, for the right eye only. (Phase I)

	Baseline	**Overnight**	**1-week**	**1-month**	**2-month**	**3-month**	**6-month**
Apex (µm)	575.6 ± 29.5	577.9 ± 29.0	571.3 ± 29.9	^567.1 ± 31.3	*567.4 ± 29.5	^565.1 ± 28.8	^563.2 ± 28.3
Mid-peripheral annuli							
0.5 mm (µm)	577.4 ± 29.4	580.6 ± 29.0	574.1 ± 29.7	^569.8 ± 31.2	^570.2 ± 29.3	^567.8 ± 28.6	^565.8 ± 28.1
1.0 mm (µm)	583.3 ± 29.3	588.6 ± 28.7	582.4 ± 28.9	*577.8 ± 30.9	*578.4 ± 28.8	^575.9 ± 28.2	^573.8 ± 27.6
1.5 mm (µm)	593.9 ± 29.2	602.2 ± 28.4	596.2 ± 28.1	591.5 ± 30.6	592.2 ± 28.3	589.5 ± 27.8	^587.5 ± 27.1
2.0 mm (µm)	610.2 ± 29.2	^621.5 ± 28.1	*615.8 ± 27.5	610.9 ± 30.5	611.6 ± 28.0	608.9 ± 27.4	607.1 ± 26.9
2.5 mm (µm)	633.1 ± 29.1	^646.6 ± 27.8	^641.2 ± 27.3	636.3 ± 30.5	637.0 ± 27.8	634.3 ± 27.2	632.9 ± 26.9

Mid-peripheral annuli represent the average of superior, temporal, inferior and nasal corneal thicknesses with the distance (radius) from apex.

* and ^ indicate significance of $p < 0.05$ and $p < 0.01$, respectively, compared with the baseline result.

4.6.4.2 Phase II: Diurnal changes after 6 months of ortho-k lens treatment

In this phase after 6 months of lens wear, the diurnal changes of the corneal parameters were studied immediately after and 2, 4 and 8 hours after lens removal. Data obtained immediately after lens removal were treated as the baseline for comparison. Data obtained 2 hours after lens removal in this phase were presented and compared as 6-month results in the Phase I analysis. Therefore, all results under "2 hours after lens removal", shown in the following tables (Tables 4.20, 4.21, 4.22 and 4.23), were the same as the 6-month results reported in Phase I.

Significant differences were obtained for spherical equivalent refraction (Repeated measures ANOVA, $p < 0.05$) between immediate and 4 hours after lens removal (post-hoc tests, $p < 0.05$). No significant difference was found in UCV (Repeated measures ANOVA, $p > 0.05$). VA demonstrated significant improvement 4 hours and 8 hours after lens removal (Repeated measures ANOVA, $p < 0.01$, post-hoc tests, $p < 0.05$). Table 4.20 shows the detailed changes of UCV, SER, and VA.

Table 4.20. The results (mean ± one standard deviation) of SER, UCV and VA at different time points, for the right eye only.

	Immediately after lens removal	**2 hours after lens removal**	**4 hours after lens removal**	**8 hours after lens removal**
SER (D)	0.09 ± 0.43	0.04 ± 0.37	*−0.05 ± 0.39	*−0.07 ± 0.35
UCV	−0.02 ± 0.09	−0.04 ± 0.09	−0.02 ± 0.12	−0.03 ± 0.12
VA	−0.07 ± 0.06	−0.08 ± 0.06	*−0.09 ± 0.06	^−0.10 ± 0.05

SER: spherical equivalent refraction.
UCV: uncorrected vision; VA: visual acuity; both in logMAR units.
* and ^ indicate significance of $p < 0.05$ *and* $p < 0.01$, respectively, compared with the baseline result.

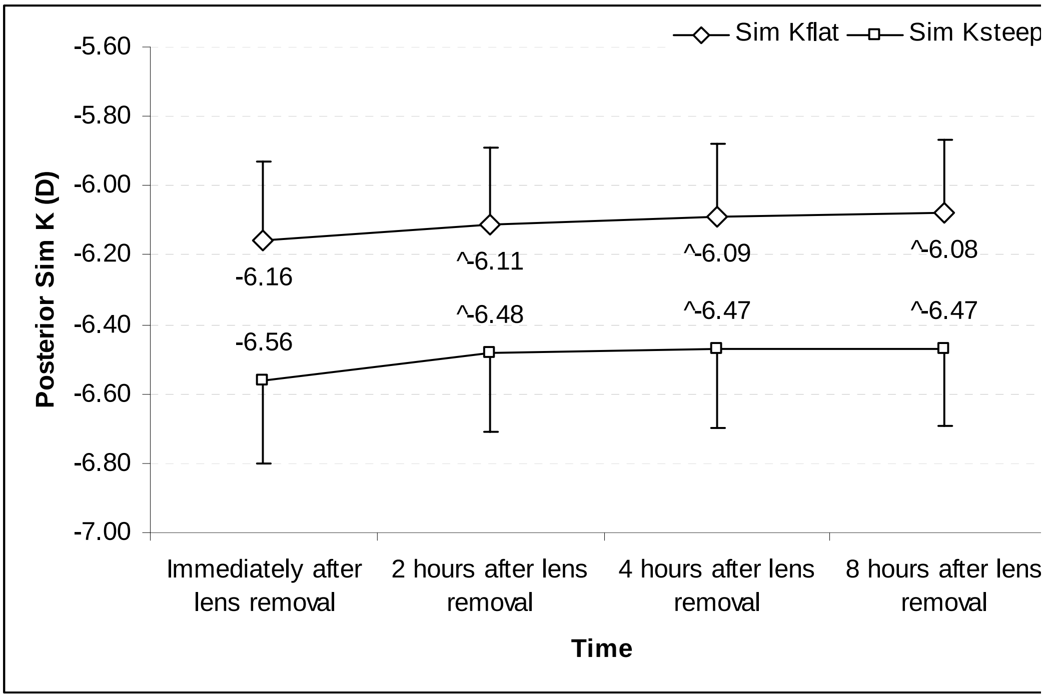
The anterior Sim K_{flat} steepened significantly 2 hours after lens removal (Repeated measures ANOVA, $p < 0.01$, post-hoc tests, $p < 0.01$). This steepening effect continued until 8 hours after lens removal. The Sim K_{steep} remained stable statistically (Repeated measures ANOVA, $p > 0.05$). In contrast, posterior Sim K readings were flattened significantly 2 hours after lens removal and this flattening still existed 8 hours after lens removal (Repeated measures ANOVA, $p < 0.01$; post-hoc tests, $p < 0.01$). Table 4.21 shows the diurnal changes of the anterior and posterior Sim K readings. Figure 4.12 shows the diurnal changes of posterior Sim K readings.

Table 4.21. The results (mean ± one standard deviation) of Sim K_{flat} and Sim K_{steep} at different time points, for the right eye only.

Sim K (D)	**Immediately after lens removal**	**2 hours after lens removal**	**4 hours after lens removal**	**8 hours after lens removal**
Anterior				
Sim K_{flat}	41.19 ± 1.34	^41.37 ± 1.22	^41.42 ± 1.23	^41.45 ± 1.22
Sim K_{steep}	42.30 ± 1.44	42.39 ± 1.38	42.42 ± 1.34	42.38 ±1.32
Posterior				
Sim K_{flat}	−6.16 ± 0.23	^−6.11 ± 0.22	^−6.09 ± 0.21	^−6.08 ± 0.21
Sim K_{steep}	−6.56 ± 0.24	^−6.48 ± 0.23	^−6.47 ± 0.23	^−6.47 ± 0.22

Sim K_{flat} and Sim K_{steep}: Flattest and steepest simulated keratometric readings, respectively.
^ indicates significance of $p < 0.01$, compared with the baseline result.

Figure 4.12. The diurnal changes of posterior Sim K after immediately lens removal and different time periods after lens removal, for the right eye only.



Sim K_{flat} and Sim K_{steep}: Flattest and steepest simulated keratometric readings, respectively.
^ indicates significance of $p < 0.01$, compared with the baseline result.

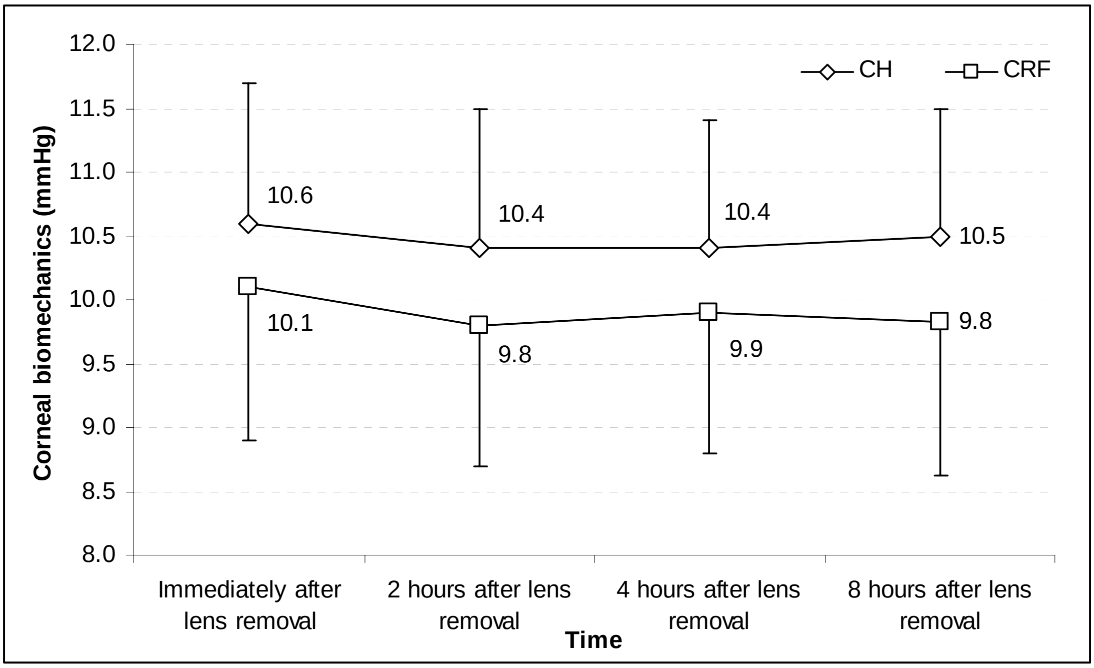
There were no significant diurnal variations in CH or CRF (Repeated measures ANOVA, $p > 0.05$) (Table 4.22; Figure 4.13).

Table 4.23. The results (mean ± one standard deviation) of CH and CRF at different time points, for the right eye only

Corneal biomechanics (mmHg)	Immediately after lens removal	2 hours after lens removal	4 hours after lens removal	8 hours after lens removal
CH	10.6 ± 1.1	10.4 ± 1.1	10.4 ± 1.0	10.5 ± 1.0
CRF	10.1 ± 1.2	9.8 ± 1.1	9.9 ± 1.1	9.8 ± 1.2

CH and CRF: corneal hysteresis and corneal resistance factor, respectively.

Figure 4.13. The diurnal changes of CH and CRF changes after different wearing periods of orthokeratology lens, for the right eye only.



CH and CRF: corneal hysteresis and corneal resistance factor, respectively.

Table 4.23 shows the detailed diurnal changes in corneal thickness at different regions. Corneal thickness at all annuli were the thickest immediately after lens removal and significant thinning was shown in all corneal regions throughout the day after lens removal (Repeated measures ANOVA, $p < 0.01$, post-hoc tests, $p < 0.01$)

Table 4.23. Diurnal changes (mean ± one standard deviation) of central and mid-peripheral corneal thicknesses at different time periods after lens removal, for the right eye only. (Phase II)

	Immediately after lens removal	**2 hours after lens removal**	**4 hours after lens removal**	**8 hours after lens removal**
Apex (μm)	572.9 ± 30.9	^563.2 ± 28.3	^563.3 ± 27.5	^562.9 ± 27.7
Mid-peripheral annuli				
0.5 mm (μm)	575.8 ± 30.6	^565.8 ± 28.1	^565.9 ± 27.4	^565.6 ± 27.6
1.0 mm (μm)	584.6 ± 30.1	^573.8 ± 27.6	^573.8 ± 27.1	^573.5 ± 27.2
1.5 mm (μm)	599.4 ± 29.5	^587.5 ± 27.1	^587.3 ± 26.8	^587.0 ± 26.9
2.0 mm (μm)	620.3 ± 29.2	^607.1 ± 26.9	^606.5 ± 26.6	^606.1 ± 26.7
2.5 mm (μm)	647.4 ± 29.1	^632.9 ± 26.9	^631.7 ± 26.5	^631.3 ± 26.7

Mid-peripheral annuli represent the average of superior, temporal, inferior and nasal corneal thicknesses with the distance (radius) from apex.

^ indicates significance of $p < 0.01$, compared with the baseline result.

4.6.4.3 Phase III: Recovery period after cessation of treatment

All results were compared with the baseline data (before ortho-k treatment) in this recovery study. Two subjects (one male and female) were unable to return to the clinic for all the follow-up visits. Analyses were made from 43 subjects only (16 males and 27 females). Significant changes were obtained in all recovery visits for both SER and VA (SER: Repeated measures ANOVA, $p < 0.01$, post-hoc tests, $p < 0.01$; VA: Friedman test, $p < 0.01$, Dunn's tests, $p < 0.01$). UCV was significantly better than baseline in the 1-week and 2-week recovery visits (Friedman test, $p < 0.01$, Dunn's tests, $p < 0.01$). It returned to the baseline level one month after cessation of treatment (Dunn's tests, $p > 0.05$) (Table 4.24).

Table 4.24. The results (mean ± one standard deviation) of SER, UCV and VA at different time points, for the right eye only.

	Baseline	**1-week recovery visit**	**2-week recovery visit**	**1-month recovery visit**	**2-month recovery visit**
SER (D)	–2.84 ± 0.97	^–2.13 ± 0.92	^–2.45 ± 0.94	^–2.58 ± 0.95	^–2.62 ± 0.97
UCV	0.83 ± 0.24	^0.59 ± 0.28	^0.68 ± 0.24	0.73 ± 0.23	0.76 ± 0.22
VA	–0.07 ± 0.04	^–0.11 ± 0.04	^–0.11 ± 0.06	^–0.11 ± 0.05	^–0.11 ± 0.05

SER: spherical equivalent refraction.
UCV: uncorrected vision; VA: visual acuity; both in logMAR units.
^ indicates significance of $p < 0.01$, compared with the baseline result.

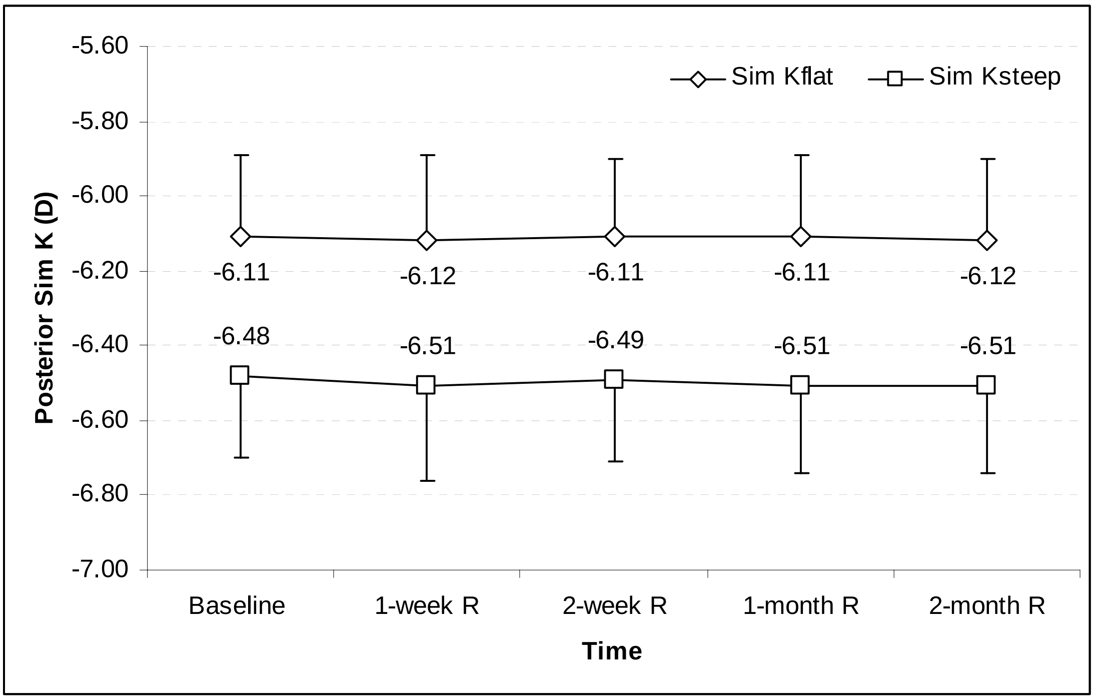
Anterior Sim K_{steep} returned to the baseline level after cessation of lens wear for one month (Repeated measures ANOVA, $p < 0.01$, post-hoc test, $p > 0.05$), while Sim K_{flat} was still statistically flatter even 2 months after lens removal (post-hoc test, $p < 0.05$). The posterior Sim K was similar to baseline values throughout the entire recovery period (Repeated measures ANOVA, $p > 0.05$) (Table 4.25; Figure 4.14).

Table 4.25. The results (mean ± one standard deviation) of Sim K_{flat} and Sim K_{steep} (Pentacam) at different time points, for the right eye only.

Sim K (D)	**Baseline**	**1-week recovery visit**	**2-week recovery visit**	**1-month recovery visit**	**2-month recovery visit**
Anterior					
Sim K_{flat}	42.86 ± 1.27	^42.46 ± 1.19	^42.51 ± 1.14	^42.62 ± 1.20	*42.69 ± 1.25
Sim K_{steep}	43.81 ± 1.34	^43.46 ± 1.33	^43.50 ± 1.24	43.64 ± 1.29	43.71 ± 1.34
Posterior					
Sim K_{flat}	−6.11 ± 0.22	−6.12 ± 0.23	−6.11 ± 0.21	−6.11 ± 0.22	−6.12 ± 0.22
Sim K_{steep}	−6.48 ± 0.22	−6.51 ± 0.25	−6.49 ± 0.22	−6.51 ± 0.23	−6.51 ± 0.23

Sim K_{flat} and Sim K_{steep}: Flattest and steepest simulated keratometric readings, respectively.
* and ^ indicate significance of $p < 0.05$ and $p < 0.01$, respectively, compared with the baseline result.

Figure 4.14. The recovery of posterior Sim K after cessation of treatment, for the right eye only.



Sim K_{flat} and Sim K_{steep}: Flattest and steepest simulated keratometric readings, respectively.

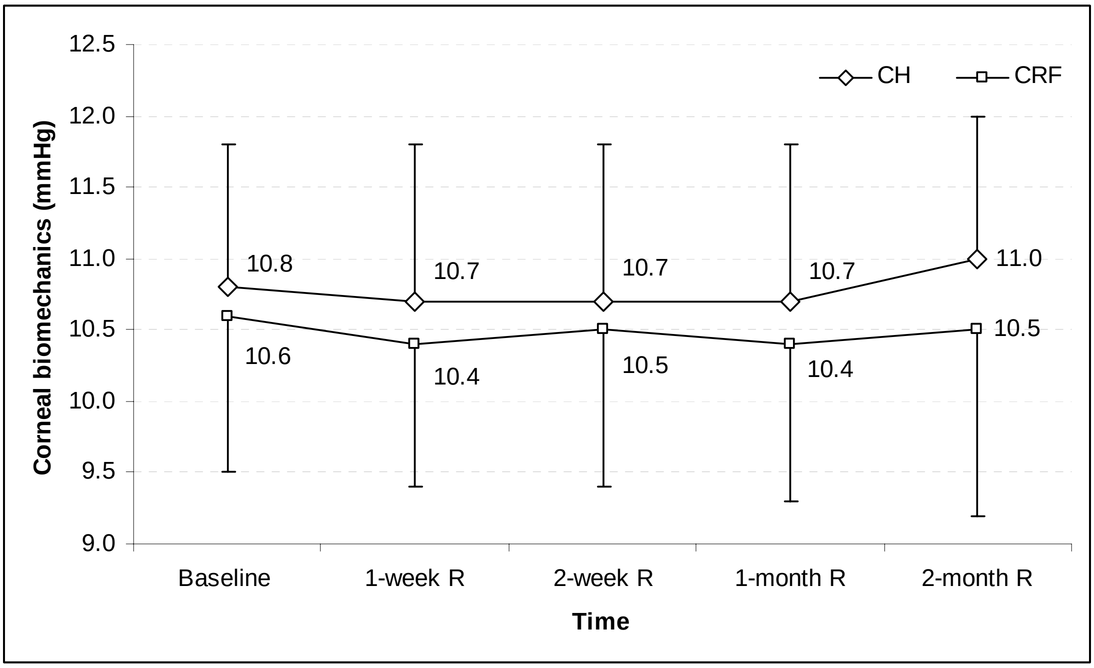
No significant differences were obtained in corneal biomechanical properties in the recovery visits (Repeated measures ANOVA, $p > 0.05$) (Table 4.26).

Table 4.26. The results (mean ± one standard deviation) of CH and CRF at different time points, for the right eye only.

Corneal biomechanics (mmHg)	Baseline	1-week recovery visit	2-week recovery visit	1-month recovery visit	2-month recovery visit
CH	10.8 ± 1.0	10.7 ± 1.1	10.7 ± 1.1	10.7 ± 1.1	10.9 ± 1.3
CRF	10.6 ± 1.1	10.4 ± 1.0	10.5 ± 1.1	10.4 ± 1.1	10.5 ± 1.3

CH and CRF: corneal hysteresis and corneal resistance factor, respectively.

Figure 4.15. The recovery of posterior CH and CRF after cessation of treatment, for the right eye only.



CH and CRF: corneal hysteresis and corneal resistance factor, respectively.

The corneal thicknesses returned to the baseline level in all the central and mid-peripheral regions after cessation of ortho-k treatment for 1 week (Repeated measures ANOVA, $p > 0.05$) (Table 4.27).

Table 4.27. The results (mean ± one standard deviation) of central and mid-peripheral corneal thicknesses at different time points, for the right eye only. (Phase III)

	Baseline	**1-week recovery visit**	**2-week recovery visit**	**1-month recovery visit**	**2-month recovery visit**
Apex (μm)	573.2 ± 27.2	570.6 ± 25.5	571.6 ± 25.6	569.9 ± 25.1	572.3 ± 26.8
Mid-peripheral annuli					
0.5 mm (μm)	575.1 ± 27.2	572.7 ± 25.4	573.6 ± 25.6	571.9 ± 25.0	574.3 ± 26.7
1.0 mm (μm)	580.9 ± 27.1	579.1 ± 25.3	579.9 ± 25.5	578.1 ± 24.9	580.5 ± 26.6
1.5 mm (μm)	591.6 ± 27.0	590.5 ± 25.2	591.3 ± 25.4	591.7 ± 26.5	591.7 ± 26.5
2.0 mm (μm)	607.9 ± 27.0	608.1 ± 25.2	608.7 ± 25.3	606.7 ± 24.6	608.9 ± 26.4
2.5 mm (μm)	630.9 ± 27.1	632.5 ± 25.5	632.8 ± 25.4	630.8 ± 24.7	632.8 ± 26.6

Mid-peripheral annuli represent the average of superior, temporal, inferior and nasal corneal thicknesses with the distance (radius) from apex.

4.6.5 Discussion

This is the first study evaluating the posterior cornea and corneal biomechanics after 6 months of ortho-k treatment. The diurnal changes in these parameters immediately after lens removal and their recoveries were also monitored.

In Phase I, significant posterior corneal steepening was found after overnight ortho-k lens wear. These results were comparable to the findings in Study I. It is likely that such a steepening effect was induced by wearing the ortho-k lenses for sleeping overnight, which has been discussed in Section 4.4.5. Although the steepening was found after overnight wear, such changes were not obtained at other visits (Table 4.16). In this phase, except after the first overnight wear where measurements were made immediately after lens removal in the early morning, subjects returned to the clinic within 8 hours after lens removal at the 1-week, and 1, 2 and 3-month visits. On the day after 6 months of treatment, the measurements were taken immediately after lens removal and throughout the day. However, results measured from 2 hours after lens removal on this day were used for Phase I data analysis.

The posterior corneal steepening was probably transient since it appeared only immediately after lens removal. Phase II results might further help to explain these changes. After a 6-month treatment period, the diurnal changes were monitored immediately and up to 8 hours after lens removal. Subjects were required to attend the clinic with the lenses in situ (similar to Study I) and measurements were obtained immediately after lens removal. The posterior corneal curvatures in Phase II (Sim K_{flat}: −6.16 D; Sim K_{steep}: −6.56 D, Table 4.21) were comparable to the findings after the first overnight wear in Phase I (Sim K_{flat}: −6.17 D; Sim K_{steep}: −6.55 D, Table 4.16). The posterior corneal steepening observed in Phase II was similar to results after 60 minutes and overnight lens wear in Study I and Study II. The steepened posterior cornea then flattened gradually after lens removal (8 hours after lens removal: Sim K_{flat} = −6.08 D and Sim K_{steep} = −6.47 D; Table 4.21) and returned to the baseline level (Baseline: Sim K_{flat} = −6.12 D and Sim K_{steep} = −6.47 D; Table 4.16). It might be associated with the thinning of the cornea after lens removal during the day. Corneal thickness was the highest at all regions immediately after lens removal, and gradually became thinner during the day (Table 4.23). This suggested that mid-peripheral corneal oedema induced by sleeping with the ortho-k lenses was the greatest immediately after lens removal. Corneal thickness significantly regressed 2 hours after lens removal. The magnitude of thinning was slightly greater in the mid-periphery (14.5 μm or 2.2% at the 2.5 mm annulus) compared with the central cornea (9.7 μm or 1.7% at the apex). The uneven thinning of the central and mid-peripheral cornea might result in the recovery of posterior corneal steepening 2 hours after lens removal (that means the posterior cornea becomes flatter as shown in Table 4.21). Although the difference between central and mid-peripheral thinning was small (0.5%), it might be sufficient to support the suggestion that the steepened posterior cornea (immediately after lens removal) flattened to the baseline level throughout the day.

It is likely that the changes can be attributed to the different corneal thickness profile found with ortho-k lens wear. These were discussed in Sections 4.4.5 and 4.5.5. Ortho-k lens fitting exerted relative positive and negative pressures on the central and mid-peripheral corneal regions, respectively (Alharbi et al., 2005). These pressures might allow the mid-peripheral cornea to swell and move the anterior cornea forward and posterior cornea backward, which would result in the anterior Sim K being flattened and the posterior Sim K steepened. This latter would alter the posterior corneal shape. Current corneal thickness results demonstrated no difference in the central cornea but significant thickening at the 2.0 mm and 2.5 mm annuli after overnight wear in Phase I (Table 4.19). These results were comparable to the findings in Study I and Study II. The control eyes fitted with conventional alignment fitted lens in Study II did not demonstrate any change in corneal thickness. The pressure from an alignment fitted lens could be evenly distributed on the cornea, which may exhibit similar changes in the central and mid-peripheral regions, resulting in an insignificant change in the anterior and posterior corneal shape (Table 4.12). This might further suggest that ortho-k has some effects on the posterior cornea.

Although some steepening effects of an ortho-k lens on the posterior cornea have been demonstrated in all three studies (Studies I, II and III), these changes might not be clinically significant or contribute to the optical change. The refractive indices of air, cornea and aqueous humour are 1.000, 1.376 and 1.336

respectively (Tunnacliffe, 1993). The differences of refractive indices at the air/cornea and cornea/aqueous humour interfaces, are 0.376 and –0.04, respectively. The negative sign for the latter indicates that a steepening of the curvature reduces the total corneal power. Although the steepening change favours the reduction of myopia in ortho-k treatment, the corneal refraction principally depends on the air/cornea interface owing to the greater refractive index difference. Its contribution was approximately nine times greater ($\lvert 0.376 / -0.04 \rvert = 9.4$) compared with the cornea/aqueous humour interface. Also, the changes after overnight wear in posterior Sim K_{flat} and Sim K_{steep} are –0.05 D and –0.08 D only {Sim K_{flat}: [–6.17 – (–6.12)] D; Sim K_{steep}: [–6.55 – (–6.47)] D} (Table 4.16). The percentage changes in contributing the SER change by Sim K_{flat} and Sim K_{steep} were 0.8% and 1.2% respectively {Sim K_{flat}: [(–0.05/–6.12)*100] %; Sim K_{steep}: [(–0.08/–6.47)*100] %}. Such a small change suggests that ortho-k lens wear has some effects on the posterior corneal curvature but are not sufficient to explain the optical effects of reduction of myopia.

Current findings support the notion that the mechanism of myopic reduction from ortho-k treatment is mainly achieved by flattening the anterior corneal curvatures instead of an overall corneal bending (Swarbrick et al., 1998). The contribution of the posterior corneal curvatures was minimal. However, current findings were different from the study by Owens et al. (2004), who first reported flattening of the posterior corneal curvature after 1 week of lens wear. The significant changes disappeared after 2 and 4 weeks of overnight lens wear. Therefore, they suggested that the change was adaptive in the early stage of ortho-k treatment. Their measurements were taken approximately 1 hour after lens removal while the posterior corneal steepening shown in the current study was measured immediately after lens removal and the significant change disappeared in the following measurements at 2 hours after lens removal. In addition, they measured the posterior corneal curvatures along the vertical meridian with an indirect method based on Purkinje images, while Sim K readings along the steepest and flattest meridians were monitored in the current study. The different measuring protocols and instruments might explain the difference between the current results and those of the other studies.

Stillitano et al. (2007) found no effect on the highest and lowest elevation heights at the posterior corneal surface after one night and 1 week of ortho-k lens wear. Although they measured the corneal changes immediately after lens removal, the difference between their results and the current studies might be attributed to the use of the Orbscan in their study. Although Maldonado et al. (2006) demonstrated good intra- and inter-session repeatability of the Orbscan on the posterior corneal measurement (except eccentricity values), the Pentacam system has been shown to be even more repeatable (see Chapter 3). Although the accuracy of measurements on the posterior corneal shape by the Pentacam system was acknowledged to be difficult to validate, it is important to use a repeatable instrument to monitor and warrant the changes in a longitudinal study. Tsukiyama et al. (2008) recently used the Pentacam system and reported an insignificant influence on the posterior corneal curvatures following 1-year of ortho-k treatment. They monitored the corneal change 2 weeks after commencing the ortho-k treatment and the corneal measurement was performed between 6 to 12 hours after lens removal. The current results are in agreement with their results, which showed no effect on the posterior corneal surface by ortho-k treatment when measurements were taken hours after lens removal. Although there was no posterior corneal change shown in their measurements, similar posterior corneal steepening may have existed in their subjects, if measurements were obtained immediately after lens removal.

Changes of corneal biomechanics with ortho-k treatment were another emphasis in the current study. The baseline CH and CRF were 10.9 ± 1.1 mmHg and 10.8 ± 1.2 mmHg, respectively and were similar to those reported in other studies (Table 4.8). CH was stable in all three studies reported here. No significant effects on CH were observed with the ortho-k lens wear. In contrast, CRF reduced after 1 week of ortho-k and demonstrated a clear trend towards reduction with longer wearing periods (Table 4.17). CRF dropped from 10.8 mmHg at baseline to 9.8 mmHg at the 6-month visit. Lu et al. (2007c) revealed that CH is not affected by induced corneal swelling but CRF increased by 0.6 mmHg after 3 hours of lens patching. CRF is a new parameter determined by the difference in the first and second applanated pressures multiplied by a constant, which was derived by increasing the association of corneal biomechanical properties with the corneal thickness (Kotecha et al., 2006). Previous studies documented a positive association between CRF and central corneal thickness (Shah et al., 2006, Touboul et al., 2008). CRF has been suggested as a measure of the "overall corneal resistance" (Luce, 2005). Reductions of CRF were demonstrated after one night and 1 week of lens wear in Study I (Table 4.5) and Study III (Table 4.17), respectively. This indicated that the overall corneal resistance was reduced by the treatment. Some other factors might also contribute to the reduction. The positive pressure exerted by the ortho-k lens at the central cornea may have a “clamping” effect, which inhibits central stromal oedema (Alharbi et al., 2005). This effect might influence the modification of corneal hydration and corneal elasticity. It might also alter the rate of recovery from ortho-k treatment after lens removal.

In Phase II, no significant variations in CH or CRF were observed throughout the day immediately after lens removal (Table 4.22). Kida et al. (2006) demonstrated stable CH throughout a 24-hour cycle, while central CT and intra-ocular pressure are thicker and higher, respectively during the nocturnal period. Gonzalez-Meijome et al. (2008a) further revealed that not only CH, but also CRF is stable within a day. CH and CRF were monitored in the current study up to 8 hours after lens removal (Phase II). Although there was corneal thinning in all regions throughout the day (Table 4.23), no corresponding changes in corneal biomechanics were detected. The reduced CRF was not significantly different from the baseline data 1 week after cessation of ortho-k treatment (Table 4.26). This showed that CRF could return to its original level 1 week after lens wearing was stopped. Both CH (Ortiz et al., 2007, Pepose et al., 2007, Kirwan and O’Keefe, 2008) and CRF (Ortiz et al., 2007, Pepose et al., 2007, Chen et al., 2010) are reduced after LASIK surgery. The reduction persists even three months after the procedure (Kirwan and O'Keefe, 2008, Chen et al., 2010). CRF has a greater drop than CH and their reduction is associated with the amount of corneal tissue being ablated (Ortiz et al., 2007, Pepose et al., 2007, Chen et al., 2010). Changes in corneal biomechanical properties are not simply due to changes in central corneal thickness (Lu et al., 2007c). The reduction in CH and CRF from LASIK is due to permanent damage to the corneal tissue from the creation of a flap and the removal of corneal tissue. Ortho-k treatment is unlikely to produce permanent corneal alterations. In a rabbit model, Matsubara et al. (2004) found that the cornea recovered to its original configuration 7 days after discontinuation of ortho-k lens wear. Nowadays, research on corneal biomechanical changes due to ortho-k is still limited and these changes are not fully understood. Although both CH and CRF are derived from P1 and P2, they behaved differently in ortho-k. It could be due to the way these parameters are derived. Apart from analyzing P1 and P2, perhaps the raw data should be analyzed in terms of time for the cornea to first applanate and time for the outward applanation. The time for first and second applanations might provide more information in understanding corneal properties rather than only CH or CRF studied here (Franco and Lira, 2009).

Also, the updated version of the ORA software could provide more parameters and analyses from the deformation of cornea induced by the air puff.

Many ortho-k researchers are interested in the predictability of ortho-k efficacy. Could corneal biomechanical properties be of any use? The reduction of myopia with ortho-k treatment is mainly achieved by flattening of anterior Sim K readings (reducing corneal refractive power). Most of the reduction happens overnight and after one week of lens wear (Alharbi and Swarbrick, 2003, Hiraoka et al., 2004 Owens et al, 2004). Approximately 60% of the myopic reduction {Table 4.15: [–1.18 D – (–2.86) D] / –2.86 D × 100% = –58.7%}, was achieved after one overnight lens wear and further reduction, around another 30% {Table 4.15: [–0.29 D – (–2.86) D] / –2.86 D × 100% = –89.9%; –89.9% – (–58.7%) = –31.2%}, was obtained after the first week of lens wear. To predict the ortho-k efficacy, the relationships between the baseline CH and CRF and the respective differences in anterior Sim K readings after overnight and one week lens wear were evaluated in the current study. However, no significant correlations could be obtained (Table 4.18). Current results suggested that neither CH nor CRF were the predicting factors of ortho-k efficacy. Gonzalez-Meijome et al. (2008b) first demonstrated a relationship between 3 hours of ortho-k lens wear and corneal biomechanical properties. They studied the changes in apical curvature, Sim K_{flat} and Sim K_{steep} with CH and CRF. The Sim K_{steep} changed significantly faster with a lower baseline CH. Similar correlations were not found in the current study. Neither CH nor CRF were likely to play a role in the prediction of ortho-k efficacy in long-term ortho-k wear. No significant relationships were found between baseline corneal biomechanics and Sim K readings in Study I. These results were comparable to the current long-term study. The discrepancy between the current results and those from Gonzalez-Meijome et al. (2008b) might be explained by the fact that their subjects had not reached a stable ortho-k effect from wearing lenses for just 3 hours.

To the best of our knowledge, this is the first report on the long-term (6 months) effect of ortho-k lens wear on corneal biomechanical properties (Phase I), diurnal changes of corneal biomechanics after long-term successful ortho-k treatment (Phase II), and recovery after cessation of lens wear (Phase III). ORA provides a simple and quick assessment of other corneal properties, which could not be explained by corneal thickness. However, it has been suggested that CRF is a measure of the overall resistance of the cornea. It is derived from the difference between P1 and fraction of P2 (P1 − 0.7 × P2). The actual use of CRF is not yet fully understood and validated. The changes in CRF with ortho-k treatment might not be conclusive. More analyses on the raw data of P1 and P2, the signal curves and the time for applanations might provide more information rather than the sole parameter investigated by Franco and Lira (2009). In summary, this study has shown some changes in CRF from long-term ortho-k treatment. The CRF shows a decreasing trend with increasing duration of lens wear but returns to baseline within 1 week after cessation of lens wear. Neither CH nor CRF plays a significant role in the prediction of ortho-k efficacy. Further studies are anticipated to investigate what other corneal parameters could be factors for predicting the efficacy in ortho-k treatment. A previous study found a stronger association between the first applanation time and some other parameters, including corneal elastic properties, age and CRF (Franco and Lira, 2009). Therefore, the first applanation time might help to determine efficacy but more studies are required to confirm this.

The reduction in spherical equivalent refraction and the associated improvement in UCV could be achieved after overnight wear and became stable after 1 week of ortho-k treatment. These rapid changes are similar to those reported in the literature (Sridharan and Swarbrick, 2003, Soni et al., 2004, Owens et al., 2004). The flattening of the anterior corneal curvature was associated with rapid changes of SER and UCV with a similar time course, which supports the fact that the reduction of myopia can be mainly accounted for by flattening of the anterior cornea.

Although myopia significantly regressed 4 hours after lens removal, the mean difference was less than 0.25 D, and ranged from −1.25 D to +1.38 D, and the UCV was not statistically significant. This further supports good sustainability of ortho-k after 6 months of lens wear (Kang et al., 2007). Following successful long-term ortho-k treatment, the anterior cornea steepened again 2 hours after lens removal. However, significant steepening was obtained in Sim K_{flat} but not in Sim K_{steep} (Table 4.21). This steepening could be attributed to the combined effects of both the regressions of ortho-k and the normal diurnal variation in anterior corneal curvatures. Read and Collins (2009) recently demonstrated a flatter anterior corneal curvature immediately on waking, which recovered (that means steepened) to the original level 2 to 3 hours after waking in non-contact lens wearers. In the current study, both Sim K readings steepened, although statistical significance was not present in Sim K_{steep}. Read and Collins (2009) took corneal measurements immediately on waking, while subjects in the current study wore the ortho-k lenses for some time (2 hours the maximum) after eye-opening. Kang et al. (2007) also reported a similar recovery or steepening (0.35 D) in the anterior Sim K readings 8 hours after lens removal in a 12-week treatment period. This small degree of change is close to what has been found in Phase II of this study (Table 4.21).

After cessation of lens wear, SER had not completely returned to the baseline level even 2 months after cessation of lens wear. The difference was within 0.25 D (Table 4.24). In terms of UCV, the ortho-k effect could be statistically maintained for at least 2 weeks after cessation of treatment and its effect faded out after one month of lens cessation. However, the UCV had already regressed to logMAR 0.59 after 1 week cessation of treatment, which could be clinically unacceptable for most subjects. The reported duration of recovery from effects of ortho-k varies in the literature (Soni et al., 2004, Kobayashi et al., 2008). In the current study, the ranges of SER at baseline and 2-month recovery visits were −0.75 D to −5.38 D and −1.13 to −5.38 D, respectively. Around 70% of subjects had their SER returned to baseline level after 2 months cessation of lens wear. The faster recovery in the previous studies might be due to a slightly lower baseline SER (Soni et al., 2004: –2.21 D; Kobayashi et al., 2008: –2.54 D) compared with baseline SER at the current study (Table 4.24: –2.84 D). Table 4.15 and Table 4.24 show different baseline SER from Phases I and III, respectively since two subjects were not able to complete the measurements in the recovery study. The corresponding corneal changes support the partial recovery of SER in the current study. Sim K_{flat} had not fully returned to the original level after 2 months cessation of lens wear. Sim K_{steep} exhibited a faster recovery and the treatment effect disappeared at the 1-month recovery visit. Wu et al. (2009) recently reported that the residual flattening from ortho-k treatment in terms of mean keratometric readings was 0.27 D and did not return to baseline after 2 weeks treatment discontinuation. Their baseline SER was –3.30 D and they found a significant relationship between baseline SER and residual corneal flattening. The higher the baseline SER, the higher the residual corneal flattening was found. In the current study, the residual SER and Sim K_{flat} after 2 months cessation of lens wear were 0.17 D and 0.22 D, respectively (Table 4.24 and 4.25). Therefore, a longer recovery period might be expected from a higher baseline SER. Close monitoring (e.g. monthly) of SER after cessation of ortho-k treatment is suggested.

4.6.6 Conclusions

This long-term study found some changes to the posterior cornea and the CRF. The posterior corneal steepening was a transient effect and it returned to baseline within 2 hours of lens removal. The reduction in myopia was mainly achieved by flattening of the anterior corneal curvatures. The reduction of CRF with a longer wearing period indicated that corneal resistance decreased with ortho-k treatment. Neither CH nor CRF plays a role in predicting the ortho-k effect. By considering that CRF is derived from the difference of P1 and a fraction of P2, further study is required to investigate other factors, e.g. P1, P2, signal curves and times for P1 and P2, which may predict the ortho-k effect. Most of the corneal parameters fully returned to baseline level after 2 months cessation of treatment. The null hypothesis that no change in the posterior corneal curvature, corneal biomechanical properties and topographical corneal thickness within 6 months after ortho-k treatment was rejected.

Paper published:

Chen D, Lam AK, Cho P. Posterior corneal curvature change and recovery after 6 months overnight orthokeratology treatment. Ophthalmic Physiol Opt. 2010;30:274-280.

Conference presentations:

Chen D, Lam AK, Cho P. Posterior corneal shape and corneal biomechanics changes with orthokeratology lens wear and their recovery Presented at American Academy of Optometry Meeting, 2008. Anaheim, United States.

Chen D, Lam AK, Cho P. Posterior corneal shape changes with orthokeratology lens wear and its recovery. Presented at 33rd Clinical Conference & Exhibition by British Contact Lens Association, 2009. Manchester, United Kingdom.

Chapter 5

Summary and the way forward

The mechanism of ortho-k is still not fully understood, though it has become one of the popular ways to attempt to slow down progression of myopia in children (Cho et al., 2005, Walline et al., 2009, Kakita et al., 2011). Overall corneal bending, redistribution of corneal epithelium, or a combination of both have been suggested as the main mechanism by different researchers (Swarbrick et al., 1998, Owens et al., 2004a, Stillitano et al., 2007, Gonzalez-Meijome et al., 2008b, Tsukiyama et al., 2008).

This project contained three studies of which two were short-term and one long-term. For the short-term studies (Study I and Study II), the designs were similar to those used in a previous study (Sridharan and Swarbrick, 2003). The protocol was almost identical between the two short-term studies except for the addition of a control, where the fellow eye wore a conventional alignment fitting lens in Study II (Section 4.5). The long-term study (Study III) monitored corneal parameters during the treatment and recovery periods. It consisted of three phases including a 6-month treatment period, diurnal monitoring immediately after lens removal on the first day of the recovery period, and a 2-

month recovery period. Three new parameters including posterior corneal curvatures, topographic corneal thickness and corneal biomechanics were monitored. The ortho-k effects on these parameters were evaluated in all three studies.

The posterior corneal curvatures steepened after 60 minutes and after overnight ortho-k lens wear in Studies I and II. Similar steepening was found after overnight ortho-k lens wear in Phase I of Study III. The order of changes in all three studies was comparable. The steepening effect was significant after 60 minutes of lens wear. Sleeping with these lenses did not produce a greater posterior corneal steepening. Since this steepening effect could only be found in the morning within 2 hours of lens wear after awakening (Phase II), ortho-k lens wear has a transient effect on the posterior corneal curvatures. Bearing in mind that the posterior corneal changes were measured within two hours after eye opening, the steepening effect might be even greater if the measurement was conducted immediately after eye opening (Read and Collins, 2009). An experiment in a "sleep" laboratory might be required to confirm the magnitude of the posterior corneal steepening after awakening and immediate lens removal. After a 6-month treatment period, the posterior cornea was the steepest immediately after lens removal and the extent of steepening was comparable to the results in Studies I and II. It then flattened and gradually returned to the baseline level 2 hours after lens removal. The regression of posterior corneal steepening might be accounted for by greater thinning at the mid-peripheral cornea. The cornea was the thickest in all regions immediately after lens removal, compared with measurements during the rest of the day. The cornea became thinner throughout the first day in Phase II, slightly more in the mid-periphery (2.5 mm annulus) compared with the central cornea. This thinning effect might help to explain further the flattening of the steepened posterior cornea. Positive pressures might limit central corneal oedema and flatten the corneal curvatures, but the negative pressures in the mid-periphery allow an oedematous response around the mid-peripheral corneal regions, which therefore, altered the posterior corneal shape. However, the optical contribution by the posterior corneal curvatures was limited due to the small difference in refractive index between aqueous humour and cornea. It could only provide approximately one ninth of the refractive power compared with the interface between air and cornea. The changes to the posterior corneal shape suggest that ortho-k lens wear has some effects on the posterior corneal curvature, while its effects are insufficient to explain the optical effects of myopic reduction. Current studies support the notion that the mechanism of reduction of myopia from ortho-k treatment is achieved mainly by flattening of the anterior corneal curvatures instead of an overall corneal bending.

Corneal biomechanical changes with the ortho-k treatment were also emphasised in the current project. Corneal hysteresis and corneal resistance factor are new parameters to quantify the corneal biomechanical properties using a non-contact bi-directional tonometer, the ORA. In this project, CH was unaffected by the ortho-k treatment in all studies, while some reductions in CRF were found in Study I and Study III. The change in CRF during Study II was insignificant, possibly due to the limited number of subjects who participated. A decrease in CRF without a significant change in corneal thickness was found. Future studies assessing changes at a cellular level might help to explain the reduction of CRF with ortho-k treatment.

Whether the corneal biomechanics can determine the efficacy of ortho-k is another concern in the current project. The relationships between CRF, the reduction of spherical equivalent refraction after overnight and one week of lens wear in Study III were explored, however, no significant relationships could be ascertained. This might suggest that CH and CRF in their current derivations are not capable of predicting ortho-k efficacy. Although CRF shows a decreasing trend with increasing duration of lens wear, neither CH nor CRF plays a significant role in the prediction of ortho-k efficacy. Further studies are anticipated to investigate raw data from ORA including P1, P2, and time for applanations to determine the efficacy of ortho-k.

The changes in SER, uncorrected vision and anterior Sim K results were also evaluated and compared to the literature. The ortho-k effects on these parameters were rapid and seen from as short as 15 minutes of lens wear. It takes one week to achieve most of the refractive corrections in long-term treatment. However, the subjects involved had a moderate amount of myopia before treatment (within −5.0 D). A longer period might be required for the correction of higher myopia. The current study supports good sustainability of the ortho-k effect after 6 months of lens wear. In the recovery period, improved UCV could last for at least 2 weeks after cessation of treatment. SER and Sim K_{flat} did not completely return to baseline levels even 2 months after cessation of lens wear. Therefore, a longer recovery period might be required and close monitoring of SER after cessation of ortho-k treatment is suggested.

This project has answered some questions about short- and long-term ortho-k effects on posterior corneal curvatures, corneal biomechanics, and topographic corneal thickness, however, more investigations are required to find out which corneal layers are involved in the posterior corneal curvature changes. Although confocal microscopy could help to monitor the morphological changes with ortho-k treatment, cautious assessment is required because of its relatively invasive nature. The latest technology, such as spectral-domain anterior OCT, could be applied to find out which corneal layers contribute to the posterior corneal steepening. Further studies are required to explore the association of other corneal parameter with the ortho-k efficacy, for example, the actual meaning of the corneal biomechanical changes.

References

Alharbi A, La Hood D, Swarbrick H. Overnight orthokeratology lens wear can inhibit the central stromal edema response. Invest Ophthalmol Vis Sci. 2005; 46: 2334-2340.

Alharbi A, Swarbrick H. The effects of overnight orthokeratology lens wear on corneal thickness. Invest Ophthalmol Vis Sci. 2003; 44: 2518-2523.

Baek T, Lee K, Kagaya F, Tomidokoro A, Amano S, Oshika T. Factors affecting the forward shift of posterior corneal surface after laser in situ keratomileusis. Ophthalmology. 2001; 108: 317-320.

Barkana Y, Gerber Y, Elbaz U, Schwartz S, Ken-Dror G, Avni I, Zadok D. Central corneal thickness measurement with the Pentacam Scheimpflug system, optical low-coherence reflectometry pachymeter and ultrasound pachymetry. J Cataract Refract Surg. 2005; 31: 1729-1735.

Berntsen DA, Barr JT, Mitchell GL. The effect of overnight contact lens corneal reshaping on higher-order aberrations and best-corrected visual acuity. Optom Vis Sci. 2005; 82: 490-497.

Berntsen DA, Mitchell GL, Barr JT. The effect of overnight contact lens corneal reshaping on refractive error-specific quality of life. Optom Vis Sci. 2006; 83: 354-359.

Binder PS, May CH, Grant SC. An evaluation of orthokeratology. Ophthalmology. 1980; 87: 729-744.

Bland JM, Altman DG. Cronbach's alpha BMJ. 1997; 314: 572.

Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet. 1986; 1: 307-310.

Buehren T, Collins MJ, Iskander DR, Davis B, Lingelbach B. The stability of corneal topography in the post-blink interval. Cornea. 2001; 20: 826-833.

Burns-LeGros, D, Wagner, H. Paragon corneal refractive therapy lens prescribed for daily wear in post-radial keratometry patient. Eye Contact Lens. 2007; 33: 50-55.

Carkeet NL, Mountford JA, Carney LG. Predicting success with orthokeratology lens wear: a retrospective analysis of ocular characteristics. Optom Vis Sci. 1995; 72: 892-898.

Caroline PJ. Contemporary orthokeratology. Cont Lens Anterior Eye. 2001; 24: 41-46.

Chan B, Cho P, Mountford J. The validity of the Jessen formula in overnight orthokeratology: a retrospective study. Ophthalmic Physiol Opt. 2008; 28: 265-268.

Chan B, Cho P, de Vecht A. Toric orthokeratology: a case report. Clin Exp Optom. 2009; 92: 387-391.

Charman WN, Mountford J, Atchison DA, Markwell EL. Peripheral refraction in orthokeratology patients. Optom Vis Sci. 2006; 83: 641-648.

Chen S, Chen D, Wang J, Lu F, Wang Q, Qu J. Changes in ocular response analyzer parameters after LASIK. J Refract Surg. 2010; 26: 279-288.

Cheung SW, Cho P, Chan B. Astigmatic changes in orthokeratology. Optom Vis Sci. 2009; 86: 1352-1358.

Cho P, Cheung SW. Repeatability of corneal thickness measurements made by a scanning-slit topography system. Ophthalmic Physiol Opt. 2002; 22: 505-510.

Cho P, Cheung SW. Central and peripheral corneal thickness measured with the TOPCON specular microscope SP-2000P. Curr Eye Res. 2000; 21: 799-807.

Cho P, Cheung S, Edwards M. The longitudinal orthokeratology research in children (LORIC) in Hong Kong: A pilot study on refractive changes and myopic control. Curr Eye Res. 2005; 30: 71-80.

Cho P, Cheung S, Edwards MH. Practice of orthokeratology by a group of contact lens practitioners in Hong Kong--Part 1. General overview. Clin Exp Optom. 2002a; 85: 365-371.

Cho P, Cheung S, Edwards MH. Practice of orthokeratology by a group of contact lens practitioners in Hong Kong. Part 2: orthokeratology lenses. Clin Exp Optom. 2003; 86: 42-46.

Cho P, Lam AK, Mountford J, Ng L. The performance of four different corneal topographers on normal human corneas and its impact on orthokeratology lens fitting. Optom Vis Sci. 2002b; 79: 175-183.

Choo J, Caroline P, Harlin D. How does the cornea change under corneal reshaping contact lenses? Eye Contact Lens. 2004; 30: 211-213.

Choo J, Caroline P, Harlin D, Papas E, Holden B. Morphologic changes in cat epithelium following continuous wear of orthokeratology lenses: A pilot study. Cont Lens Anterior Eye. 2008; 31: 29-37.

Chui WS, Cho P. A comparative study of the performance of different corneal topographers on children with respect to orthokeratology practice. Optom Vis Sci. 2005; 82: 420-427.

Ciolino JB, Belin MW. Changes in the posterior cornea after laser in situ keratomileusis and photorefractive keratectomy. J Cataract Refract Surg. 2006; 32: 1426-1431.

Ciolino JB, Khachikian SS, Cortes MJ, Belin MW. Long-term stability of the posterior cornea after laser in situ keratomileusis. J Cataract Refract Surg. 2007; 33: 1366-1370.

Coon LJ. Orthokeratology. Part II: Evaluating the Tabb method. J Am Optom Assoc. 1984; 55: 409-418.

Dave T, Ruston D. Current trends in modern orthokeratology. Ophthalmic Physiol Opt. 1998; 18: 224-233.

Fan L, Jun J, Jia Q, Wangqing J, Xinjie M, Yi S. Clinical study of orthokeratology in young myopic adolescents. Int Contact Lens Clin. 1999; 26: 113-116.

Franco S, Lira M. Biomechanical properties of the cornea measured by the Ocular Response Analyzer and their association with intraocular pressure and the central corneal curvature. Clin Exp Optom. 2009; 92: 469-475.

Franklin RJ, Morelande MR, Iskander DR, Collins MJ, Davis BA. Combining central and peripheral videokeratoscope maps to investigate total corneal topography. Eye Contact Lens. 2006; 32: 27-32.

Fontana AA. Orthokeratology using the one piece bifocal. Contacto. 1972; 16: 45-47.

Gao L, Fan H, Cheng AC, Wang Z, Lam DS. The effects of eye drops on corneal thickness in adult myopia. Cornea. 2006; 25: 404-407

Gifford P, Au V, Hon B, Siu A, Xu P, Swarbrick H. Mechanism for corneal reshaping in hyperopic orthokeratology. Optom Vis Sci. 2009; 86: 306-311.

Gifford P, Swarbrick HA. Time course of corneal topographic changes in the first week of overnight hyperopic orthokeratology. Optom Vis Sci. 2008; 85: 1165-1171.

Gifford P, Swarbrick HA. The effect of treatment zone diameter in hyperopic orthokeratology. Ophthalmic Physiol Opt. 2009; 29: 584-592.

Goldich Y, Barkana Y, Morad Y, Hartstein M, Avni I, Zadok D. Can we measure corneal biomechanical changes after collagen cross-linking in eyes with keratoconus?-a pilot study. Cornea. 2009; 28: 498-502.

Gonzalez-Meijome JM, Cervino A, Yebra-Pimentel E, Parafita MA. Central and peripheral corneal thickness measurement with Orbscan II and topographic ultrasound pachymetry. J Cataract Refract Surg. 2003; 29: 125-132.

Gonzalez-Meijome JM, Jorge J, Queiros A, Almeida JB, Parafita MA. A comparison of the ARK-700A autokeratometer and Medmont E300 corneal topographer when measuring peripheral corneal curvature. Ophthalmic Physiol Opt. 2004; 24: 391-398.

Gonzalez-Meijome JM, Queiros A, Jorge J, Fernandes P, Cervino A, de Almeida JB. External factors affecting data acquisition during corneal topography examination. Eye Contact Lens. 2007; 33: 91-97.

Gonzalez-Meijome JM, Queiros A, Jorge J, Diaz-Rey A, Parafita MA. Intraoffice variability of corneal biomechanical parameters and intraocular pressure (IOP). Optom Vis Sci. 2008a; 85: 457-462.

Gonzalez-Meijome JM, Villa-Collar C, Queiros A, Jorge J, Parafita MA. Pilot study on the influence of corneal biomechanical properties over the short term in response to corneal refractive therapy for myopia. Cornea. 2008b; 27: 421-426.

Grant SC. Philosophy of orthokeratology. Optom Weekly. 1975; 66: 811-813.

Haque S, Fonn D, Simpson T, Jones L. Epithelial thickness changes from the induction of myopia with CRTH RGP contact lenses. Invest Ophthalmol Vis Sci. 2008; 49: 3345-3350.

Harris DH, Stoyan N. A new approach to orthokeratology. Contact Lens Spectrum. 1992; 7: 37-39.

Harvitt DM, Bonanno JA. Re-evaluation of the oxygen diffusion model for predicting minimum contact lens Dk/t values needed to avoid corneal anoxia. Optom Vis Sci. 1999; 76: 712-719.

Hiraoka T, Furuya A, Matsumoto Y, Okamoto F, Kakita T, Oshika T. Influence of overnight orthokeratology on corneal endothelium. Cornea. 2004; 23: S82-86.

Hiraoka T, Okamoto C, Ishii Y, Kakita T, Okamoto F, Oshika T. Time course of changes in ocular higher-order aberrations and contrast sensitivity after overnight orthokeratology. Invest Ophthalmol Vis Sci. 2008; 49: 4314-4320.

Hiraoka T, Okamoto F, Kaji Y, Oshika T. Optical quality of the cornea after overnight orthokeratology. Cornea. 2006; 25: S59-S63.

Holden BA, Mertz GW. Critical oxygen levels to avoid corneal edema for daily and extended wear contact lenses. Invest Ophthalmol Vis Sci. 1984; 25: 1161-1167.

Huang RY, Lam AK. The effect of mydriasis from phenylephrine on corneal shape. Clin Exp Optom. 2007; 90: 44-48.

Iskander DR, Collins MJ, Read SA. Extrapolation of central corneal topography into the periphery. Eye Contact Lens. 2007; 33: 293-299.

Jayakumar J, Swarbrick H. The effect of age on short-term orthokeratology. Optom Vis Sci. 2005; 82: 505-511.

Jessen GN. Orthofocus technique. Contacto. 1962; 6: 200-204.

Jessen GN. Contact lenses as a therapeutic device. Am J Optom Arch Am Acad Optom. 1964; 41: 429-435.

Johnson K, Carney L, Mountford J, Collins M, Cluff S, Collins P. Visual performance after overnight orthokeratology. Cont Lens Anterior Eye. 2007; 30: 29-36.

Jonsson M, Behndig A. Pachymetric evaluation prior to laser in situ keratomileusis. J Cataract Refract Surg. 2005; 31: 701-706.

Kakita T, Hiraoka T, Oshika T. Influence of overnight orthokeratology on axial length elongation in childhood myopia. Invest Ophthalmol Vis Sci. In press.

Kamiya K, Oshika T. Corneal forward shift after excimer laser keratorefractive surgery. Semin Ophthalmol. 2003; 18: 17-22.

Kamiya K, Oshika T, Amano S, Takahashi T, Tokunaga T, Miyata K. Influence of excimer laser photorefractive keratectomy on the posterior corneal surface. J Cataract Refract Surg. 2000; 26: 867-871.

Kang SY, Kim BK, Byun YJ. Sustainability of orthokeratology as demonstrated by corneal topography. Korean J Ophthalmol. 2007; 21: 74-78.

Kerns RL. Research in orthokeratology. Part III: results and observations. J Am Optom Assoc. 1976; 16: 31-37.

Kida T, Liu JH, Weinreb RN. Effect of 24-hour corneal biomechanical changes on intraocular pressure measurement. Invest Ophthalmol Vis Sci. 2006; 47: 4422-4426.

Kida T, Liu JH, Weinreb RN. Effects of aging on corneal biomechanical properties and their impact on 24-hour measurement of intraocular pressure. Am J Ophthalmol. 2008; 146: 567-572.

Kikkawa Y, Hirayama K. Uneven swelling of the corneal stroma. Invest Ophthalmol. 1970; 9: 735-741.

Kirwan C, Okeefe M. Corneal hysteresis using the Reichert ocular response analyser: findings pre- and post-LASIK and LASEK. Acta Ophthalmol. 2008; 86: 215-218.

Kirwan C, Okeefe M, Lanigan B. Corneal hysteresis and intraocular pressure measurement in children using the Reichert ocular response analyzer. Am J Ophthalmol. 2006; 142: 990-992.

Kirwan C, Rsquo, Malley D, Rsquo, Keefe M. Corneal hysteresis and corneal resistance factor in keratoectasia: findings using the Reichert ocular response analyzer. Ophthalmologica. 2008; 222: 334-337.

Kobayashi Y, Yanai R, Chikamoto N, Chikama T, Ueda K, Nishida T. Reversibility of effects of orthokeratology on visual acuity, refractive error, corneal topography, and contrast sensitivity. Eye Contact Lens. 2008; 34: 224-228.

Kotecha A, Crabb DP, Spratt A, Garway-Heath DF. The relationship between diurnal variations in intraocular pressure measurements and central corneal thickness and corneal hysteresis. Invest Ophthalmol Vis Sci. 2009; 50: 4229-4236.

Kotecha A, Elsheikh A, Roberts CR, Zhu H, Garway-Heath DF. Corneal thickness- and age-related biomechanical properties of the cornea measured with the ocular response analyzer. Invest Ophthalmol Vis Sci. 2006; 47: 5337-5347.

Lackner B, Schmidinger G, Skorpik C. Validity and repeatability of anterior chamber depth measurements with Pentacam and Orbscan. Optom Vis Sci. 2005; 82: 858-861.

Lam AK, Chan JS. Corneal thickness at different reference points from Orbscan II system. Clin Exp Optom. 2003; 86: 230-234.

Lam AK, Chen D. Effect of ocular massage on intraocular pressure and corneal biomechanics. Eye. 2007a; 21: 1245-1246.

Lam AK, Chen D. Effect of proparacaine on central corneal thickness values: an evaluation using noncontact specular microscopy and pentacam. Cornea. 2007b; 26: 55-58.

Lam AK, Chen D, Chiu R, Chui W. Comparison of IOP measurements between ORA and GAT in normal Chinese. Optom Vis Sci. 2007; 84: 909-914.

Lam AK, Lam CH. Effect of warm compress therapy from hard-boiled eggs on corneal shape. Cornea. 2007; 26: 163-167.

Lee D, Wilson G. Non-uniform swelling properties of the corneal stroma. Current Eye Research. 1981; 1: 457-461.

Lim L, Gazzard G, Chan YH, Fong A, Kotecha A, Sim EL, Tan D, Tong L, Saw SM. Cornea biomechanical characteristics and their correlates with refractive error in Singaporean children. Invest Ophthalmol Vis Sci. 2008; 49: 3852-3857.

Liu Z, Huang AJ, Pflugfelder SC. Evaluation of corneal thickness and topography in normal eyes using the Orbscan corneal topography system. Br J Ophthalmol. 1999; 83: 774-778.

Liu J, Roberts C. Influence of corneal biomechanical properties on intraocular pressure measurement: quantitative analysis. J Cataract Refract Surg. 2005; 31: 146-155.

Lu F, Simpson T, Sorbara L, Fonn D. Malleability of the ocular surface in response to mechanical stress induced by orthokeratology contact lenses. Cornea. 2008; 27: 133-141.

Lu F, Simpson T, Sorbara L, Fonn D. The relationship between the treatment zone diameter and visual, optical and subjective performance in Corneal Refractive Therapy lens wearers. Ophthalmic Physiol Opt. 2007a; 27: 568-578.

Lu F, Sorbara L, Simpson T, Fonn D. Corneal shape and optical performance after one night of corneal refractive therapy for hyperopia. Optom Vis Sci. 2007b; 84: 357-364.

Lu F, Xu S, Qu J, Shen M, Wang X, Fang H, Wang J. Central corneal thickness and corneal hysteresis during corneal swelling induced by contact lens wear with eye closure. Am J Ophthalmol. 2007c; 143: 616-622.e612.

Luce D. Determining in vivo biomechanical properties of the cornea with an ocular response analyzer. J Cataract Refract Surg. 2005; 31: 156-162.

Lui WO, Edwards MH. Orthokeratology in low myopia. Part 1: efficacy and predictability. Cont Lens Anterior Eye. 2000; 23: 77-89.

Lui WO, Edwards MH, Cho P. Contact lenses in myopia reduction - from orthofocus to accelerated orthokeratology. Cont Lens Anterior Eye. 2000; 23: 68-76.

Machat JJ. Excimer Laser Refractive Surgery; Practice and Principles. Thorofare, NJ, Slack 1996; pp 67.

Maldonado MJ, Nieto JC, Diez-Cuenca M, Pinero DP. Repeatability and reproducibility of posterior corneal curvature measurements by combined scanning-slit and Placido-disc topography after LASIK. Ophthalmology. 2006; 113: 1918-1926.

Maldonado MJ, Ruiz-Oblitas L, Munuera JM, Aliseda D, Garcia-Layana A, Moreno-Montanes J. Optical coherence tomography evaluation of the corneal cap and stromal bed features after laser in situ keratomileusis for high myopia and astigmatism. Ophthalmology. 2000; 107: 81-87.

Mangouritsas G, Morphis G, Mourtzoukos S, Feretis E. Association between corneal hysteresis and central corneal thickness in glaucomatous and non-glaucomatous eyes. Acta Ophthalmol. 2009; 87: 901-905.

Mathur A, Atchison DA. Effect of orthokeratology on peripheral aberrations of the eye. Optom Vis Sci. 2009; 86: 476-484.

Matsubara M, Kamei Y, Takeda S, Mukai K, Ishii Y, Ito S. Histologic and histochemical changes in rabbit cornea produced by an orthokeratology lens. Eye Contact Lens. 2004; 30: 198-204.

Maloney RK. Discussion of article by Wang Z, Chen J, Yang B. Ophthalmology. 1999; 106: 409-410.

May CH. Computers, photo-electronic keratoscopy, and orthokeratology. Contacto. 1974; 18: 13-14.

Miyata K, Kamiya K, Takahashi T, Tanabe T, Tokunaga T, Amano S, Oshika T. Time course of changes in corneal forward shift after excimer laser photorefractive keratectomy. Arch of Ophthalmol. 2002; 120: 896-900.

Modis L Jr, Langenbucher A, Seitz B. Evaluation of normal corneas using the scanning-slit topography/pachymetry system. Cornea. 2004; 23: 689-694.

Moezzi AM, Fonn D, Simpson TL, Sorbara L. Contact lens-induced corneal swelling and surface changes measured with the Orbscan II corneal topographer. Optom Vis Sci. 2004; 81: 189-193.

Mountford J. An analysis of the changes in corneal shape and refractive error induced by accelerated orthokeratology. Int Contact Lens Clin. 1997; 24: 128-143.

Mountford J, Cho P, Chui WS. Is fluorescein pattern analysis a valid method of assessing the accuracy of reverse geometry lenses for orthokeratology? Clin Exp Optom. 2005; 88: 33-38.

Mountford J, Ruston D, Dave T. Orthokeratology: Principles and Practice, London, Butterworth Heinemann. 2004:pp 1-13.

Munnerlyn CR, Koons SJ, Marshall J. Photorefractive keratectomy: a technique for laser refractive surgery. J Cataract Refract Surg. 1988; 14: 46-52.

Naroo SA, Charman WN. Changes in posterior corneal curvature after photorefractive keratectomy. J Cataract Refract Surg. 2000; 26: 872-878.

Nichols JJ, Marsich MM, Nguyen M, Barr JT, Bullimore MA. Overnight orthokeratology. Optom Vis Sci. 2000; 77: 252-259.

Nolan JA. Approach to orthokeratology. J Am Optom Assoc. 1969; 40: 303-305.

Ortiz D, Pinero D, Shabayek M, Arnalichmontiel F, Alio J. Corneal biomechanical properties in normal, post-laser in situ keratomileusis, and keratoconic eyes. J Cataract Refract Surg. 2007; 33: 1371-1375.

Owens H, Garner LF, Craig JP, Gamble G. Posterior corneal changes with orthokeratology. Optom Vis Sci. 2004; 81: 421-426.

O'Donnell C, Maldonado-Codina C. Agreement and repeatability of central thickness measurement in normal corneas using ultrasound pachymetry and the OCULUS Pentacam. Cornea. 2005; 24: 920-924.

Patterson TC. Orthokeratology: changes to the corneal curvature and the effect on refractive power due to the sagittal length change. J Am Optom Assoc. 1975; 46: 719-729.

Pepose J, Feigenbaum S, Qazi M, Sanderson J, Roberts C. Changes in corneal biomechanics and intraocular pressure following LASIK using static, dynamic, and noncontact tonometry. Am J Ophthalmol. 2007; 143: 39-47.

Polse KA, Brand RJ, Keener RJ, Schwalbe JS, Vastine DW. The Berkeley orthokeratology study, Part III: Efficacy and duration. Am J Optom Phys Opt. 1983a; 60: 321-328.

Polse KA, Brand RJ, Schwalbe JS, Vastine DW, Keener RJ. The Berkeley orthokeratology study, Part II: Efficacy and duration. Am J Optom Phys Opt. 1983b; 60: 187-198.

Portney LG, Watkins MP. Foundations of clinical research; Applications to practice (2nd ed.), Prentice-Hall, Upper Saddle River, NJ. 2000; 557–584.

Rah M, Jackson JM, Jones L, Marsden HJ, Bailey MD, Barr J. Overnight orthokeratology: preliminary results of the Lenses and Overnight Orthokeratology (LOOK) study. Optom Vis Sci. 2002; 79: 598-605.

Read SA, Collins MJ, Carney LG, Franklin RJ. The topography of the central and peripheral cornea. Invest Ophthalmol Vis Sci. 2006; 47: 1404-1415.

Read SA, Collins M. Diurnal variation of corneal shape and thickness. Optom Vis Sci. 2009; 86: 170-180.

Rufer F, Schroder A, Erb C. White-to-white corneal diameter: normal values in healthy humans obtained with the Orbscan II topography system. Cornea. 2005; 24: 259-261.

Sanchis-Gimeno JA, Lleo-Perez A, Casanova J, Alonso L, Rahhal SM. Inter-observer variability of central corneal thickness measurements using non-contact specular microscopy after laser in situ keratomileusis. Clin Exp Optom. 2004; 87: 15-18.

Seitz B, Torres F, Langenbucher A, Behrens A, Suarez E. Posterior corneal curvature changes after myopic laser in situ keratomileusis. Ophthalmology. 2001; 108: 666-672; discussion 673.

Shah S, Laiquzzaman M, Bhojwani R, Mantry S, Cunliffe I. Assessment of the biomechanical properties of the cornea with the ocular response analyzer in normal and keratoconic eyes. Invest Ophthalmol Vis Sci. 2007; 48: 3026-3031.

Shah S, Laiquzzaman M, Cunliffe I, Mantry S. The use of the Reichert ocular response analyser to establish the relationship between ocular hysteresis, corneal resistance factor and central corneal thickness in normal eyes. Cont Lens Anterior Eye. 2006; 29: 257-262.

Shankar H, Taranath D, Santhirathelagan CT, Pesudovs K. Anterior segment biometry with the Pentacam: comprehensive assessment of repeatability of automated measurements J Cataract Refract Surg. 2008; 34: 103-113.

Shen M, Fan F, Xue A, Wang J, Zhou X, Lu F. Biomechanical properties of the cornea in high myopia. Vision Res. 2008; 48: 2167-2171.

Smith EL III, Kee CS, Ramamirtham R, Qiao-Grider Y, Hung LF. Peripheral vision can influence eye growth and refractive development in infant monkeys. Invest Ophthalmol Vis Sci 2005;46:3965-3972.

Smith EL III, Ramamirtham R, Qiao-Grider Y, Hung LF, Huang J, Kee CS, Coats D, Paysse E. Effects of foveal ablation on emmetropization and form-deprivation myopia. Invest Ophthalmol Vis Sci 2007;48:3914-3922.

Smith EL III, Hung LF, Huang J. Relative peripheral hyperopic defocus alters central refractive development in infant monkeys. Vision Res 2009;49:2386-2392.

Song Y, Congdon N, Li L, Zhou Z, Choi K, Lam DS, Pang CP, Xie Z, Liu X, Sharma A, Chen W, Zhang M. Corneal hysteresis and axial length among Chinese secondary school children: the Xichang Pediatric Refractive Error Study (X-PRES) report no. 4. Am J Ophthalmol. 2008; 145: 819-826.

Soni P, Nguyen T. Overnight orthokeratology experience with XO material. Eye Contact Lens. 2006; 32: 39-45.

Soni P, Nguyen T, Bonanno J. Overnight orthokeratology: refractive and corneal recovery after discontinuation of reverse-geometry lenses. Eye Contact Lens. 2004; 30: 254-262.

Sridharan R, Swarbrick H. Corneal response to short-term orthokeratology lens wear. Optom Vis Sci. 2003; 80: 200-206.

Stillitano I, Chalita M, Schor P, Maidana E, Lui M, Lipener C, Hoflinglima A. Corneal changes and wavefront analysis after orthokeratology fitting test. Am J Ophthalmol. 2007; 144: 378-386.

Stillitano I, Schor P, Lipener C, Hofling-Lima A. Long-term follow-up of orthokeratology corneal reshaping using wavefront aberrometry and contrast sensitivity. Eye Contact Lens. 2008; 34: 140-145.

Sun L, Shen M, Wang J, Fang A, Xu A, Fang H, Lu F. Recovery of corneal hysteresis after reduction of intraocular pressure in chronic primary angle-closure glaucoma. Am J Ophthalmol. 2009; 147: 1061-1066.

Swarbrick, HA, Lum E. Lens Dk/t influences the clinical response in overnight orthokeratology. Invest Ophthalmol Vis Sci. 2006; 47, E-abstract 110.

Swarbrick HA, Wong G, O'Leary DJ. Corneal response to orthokeratology. Optom Vis Sci. 1998; 75: 791-799.

Tahhan N, Du Toit R, Papas E, Chung H, La Hood D, Holden AB. Comparison of reverse-geometry lens designs for overnight orthokeratology. Optom Vis Sci. 2003; 80: 796-804.

Tan G, Chen X, Xie RZ, He H, Liu Q, Guo Y, Liao A, Zhong X. Reverse geometry rigid gas permeable contact lens wear reduces high-order aberrations and the associated symptoms in post-LASIK patients. Curr Eye Res. 2010; 35: 9-16.

Tang W, Collins MJ, Carney L, Davis B. The accuracy and precision performance of four videokeratoscopes in measuring test surfaces. Optom Vis Sci. 2000; 77: 483-491.

Thibos LN, Wheeler W, Horner D. Power vectors: an application of Fourier analysis to the description and statistical analysis of refractive error. Optom Vis Sci. 1997; 74: 367-375.

Topuz H, Ozdemir M, Cinal A, Gumusalan Y. Age-related differences in normal corneal topography. Ophthalmic Surg Lasers Imaging. 2004; 35: 298-303.

Touboul D, Roberts C, Kerautret J, Garra C, Mauricetison S, Saubusse E, Colin J. Correlations between corneal hysteresis, intraocular pressure, and corneal central pachymetry. J Cataract Refract Surg. 2008; 34: 616-622.

Tsukiyama J, Miyamoto Y, Higaki S, Fukuda M, Shimomura Y. Changes in the anterior and posterior radii of the corneal curvature and anterior chamber depth by orthokeratology. Eye Contact Lens. 2008; 34: 17-20.

Tunnacliffe AH. Introduction to visual optics. London, Association of British Dispensing Opticians, 1993; 4th edition: pp 33.

Ucakhan OO, Ozkan M, Kanpolat A. Corneal thickness measurements in normal and keratoconic eyes: Pentacam comprehensive eye scanner versus noncontact specular microscopy and ultrasound pachymetry. J Cataract Refract Surg. 2006; 32: 970-977.

Walline J, Rah M, Jones L. The Children's Overnight Orthokeratology Investigation (COOKI) pilot study. Optom Vis Sci. 2004; 81: 407-413.

Walline JJ, Jones LA, Sinnott LT. Corneal reshaping and myopia progression. Br J Ophthalmol. 2009; 93: 1181-1185.

Wang J, Desmond F, Simpson TL, Sorbara L, Kort K, Jones L. Topographical thickness of the epithelium and total cornea after overnight wear of reverse-geometry rigid contact lenses for myopia reduction. Invest Ophthalmol Vis Sci. 2003; 44: 4742-4746.

Wang Z, Chen J, Yang B. Posterior corneal surface topographic changes after laser in situ keratomileusis are related to residual corneal bed thickness. Ophthalmology. 1999; 106: 406-410.

Wells A, Garway-Heath D, Poostchi A, Wong T, Chan K, Sachdev N. Corneal hysteresis but not corneal thickness correlates with optic nerve surface compliance in glaucoma patients. Invest Ophthalmol Vis Sci. 2008; 49: 3262-3268.

Wlodyga RJ, Bryla C. Corneal molding: the easy way. Contact Lens Spectrum. 1989; 4: 58-65.

Wu R, Stapleton F, Swarbrick HA. Residual corneal flattening after discontinuation of long-term orthokeratology lens wear in asian children. Eye Contact Lens. 2009; 35: 333-337.

Ziff SL. Orthokeratology. 1. J. Am. Optom Assoc. 1968a; 39: 143-147 contd.

Ziff SL. Orthokeratology. II. J. Am. Optom Assoc. 1968b; 39: 243-254.

Ziff SL. Orthokeratology. J. Am. Optom. Assoc. 1976; 47: 376.