TORIC ORTHOKERATOLOGY FOR SLOWING EYE ELONGATION (TO-SEE) IN MYOPIC AND ASTIGMATIC CHILDREN

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Toric Orthokeratology for Slowing Eye Elongation (TO-SEE) in Myopic and Astigmatic Children

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CERTIFICATE OF ORIGINALITY

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Publications arising from the thesis

Journal Articles

- Chen C, Cheung SW, Cho P. Myopia control using toric orthokeratology (TO-SEE study). Invest Ophthalmol Vis Sci. 2013; 54: 6510-17.
- Chen C, Cheung SW, Cho P. Toric orthokeratology for highly astigmatic children. Optom Vis Sci. 2012; 89: 849-55.
- Chen C, Cho P. Toric orthokeratology for high myopic and astigmatic subjects for myopic control. Clin Exp Optom. 2012; 95: 103-8.

Conference papers

- Chen C and Cho P. Toric orthokeratology for slowing eye elongation (TO-SEE) study. Presented at the 9th Asia Cornea and Contact Lens Conference, 22-23 April 2014, Taiwan. (Programme & Abstract Book, pp 44)
- Chen C and Cho P. Toric orthokeratology for slowing eye elongation (TO-SEE) study. Presented at the British Contact Lens Association 37th Clinical Conference and Exhibition, 6-9 June, 2013, Birmingham, United Kingdom. (Conference Manual, pp 59)
- Chen C, Cheung SW, Cho P. One year results of the toric orthokeratology: slowing eyeball elongation study. Poster presented at the 8th Asia Cornea and Contact Lens Conference, 26-27 April 2012, Hong Kong. (Programme & Abstract Book, pp 33, Poster #2)
- Chen C, Cheung SW, Cho P. Corneal biomechanical changes in long-term orthokeratology wear on myopic and astigmatic children.

Presented at the 3rd Asia Orthokeratology and Specialty Lens Conference, 30-31 March 2012, Hangzhou China. (Abstract Book, pp 221)

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ABSTRACT

The prevalence of myopia is high in East Asian countries, such as Hong Kong, China, Taiwan, Japan and Korea, and has also been reported to be increasing gradually in the western countries. Preventing or slowing myopic progression has attracted the interest of many clinicians and researchers. Spherical design ortho-k has been shown to be effective for reducing myopia and for myopic control but they are not effective in reducing astigmatism. With higher corneal astigmatism (> 1.50 D), lens decentration is the most common problem which can lead to induced astigmatism and poor vision. Hence spherical design ortho-k lenses are only recommended for children with low astigmatism. However, many myopic children also have significant astigmatism and considering the high prevalence of astigmatism in myopic children, there is a need for a myopic control treatment for myopic children with astigmatism. Toric reverse geometry design lenses have therefore been developed and introduced to improve lens centration as well as for astigmatic correction. However, except for a few case reports or conference presentations, there was no published study on the use of toric design ortho-k for myopic control in children with moderate to high amount of astigmatism. There was therefore a need to investigate the effectiveness of a toric design ortho-k for myopic and astigmatic reduction as well as for myopic control in this group of children.

OBJECTIVES

The objectives of this PhD study were:

1. To determine the clinical performance of a toric design ortho-k lens and the safety of ortho-k lens wear in terms of corneal staining and corneal binding
2. To determine the effectiveness of the toric design ortho-k lenses for myopic and astigmatic reduction and control
3. To investigate long-term ortho-k lens wear on anterior and posterior corneal curvatures, and corneal thickness
4. To determine the treatment zone sizes and their correlations with the refractive changes in the ortho-k subjects
5. To investigate long-term ortho-k effects on corneal biomechanics in terms of corneal hysteresis (CH) and corneal resistance factor (CRF)

METHODS

Eighty subjects (6 - 12 years old) (ortho-k: 43; control: 37), with myopia of -0.50 to -5.00 D and with-the-rule astigmatism of -1.25 to -3.50 D and unremarkable ocular and general conditions were enrolled. Data collection, including visual acuity, subjective and objective refraction, axial length, corneal topography, biomicroscopy examination, and corneal biomechanical properties were performed every six months during the 2-year study period. Axial length (AL) was monitored with the IOLMaster and the anterior and posterior corneal curvatures, central corneal thickness (CCT), CH, and CRF were performed with the Pentacam and

Ocular Response Analyser (ORA), respectively. Results from the right eye or the eye with higher astigmatism were reported.

RESULTS

A total of 35 ortho-k and 23 control subjects successfully completed the study. The mean ± SD myopia was -2.53 ± 1.31 D at baseline. Myopia was significantly reduced to -1.33 ± 0.80 D (42% reduction) at the 1-overnight visit and to -0.41 ± 0.43 D (81% reduction) at the 1-month visit. The mean ± SD refractive (with-the-rule) astigmatism reduced from -1.86 ± 0.64 D at baseline to -0.88 ± 0.59 D (54% reduction) and -0.40 ± 0.39 D (79% reduction) at the 1-overnight and 1-month visits, respectively. Corneal toricity reduced from -2.28 ± 0.53 D at baseline to -2.01 ± 0.61 (13%) at the 1-overnight visit and -1.28 ± 0.52 D (44%) at the 1-month visit. Subjects in both ortho-k and control groups demonstrated axial elongation.

At the end of study, the average axial elongation was 0.31 ± 0.27 mm in the ortho-k group and 0.64 ± 0.31 mm in the control group.
Axial elongation was significantly slower in the ortho-k group than in the control group at every 6-month visit. The levels of reduction of myopia progression compared to the spectacle-wearing control group were 61%, 58%, 53%, and 52% (cumulative elongations) after 6, 12, 18 and 24 months of ortho-k lens wear. Axial elongation was significantly correlated with the initial age of the subjects and treatment assigned. ANCOVA analysis was conducted to test the effect of ortho-k treatment on axial

length increase adjusted for age and the small difference in age did not bias the effect of the treatment. Moreover, axial length elongation was not affected by gender, initial myopia, initial refractive cylinder or initial corneal toricity.

Significant changes in the anterior Sim K_{flat} and Sim K_{steep} were observed in the ortho-k group, but only at the 1-month visit. No significant changes were observed in the subsequent visits with ortho-k lens wear. In the control group, no significant changes in anterior Sim K_{flat} and Sim K_{steep} were observed during the study period. There were no significant changes in the posterior Sim K_{flat} and Sim K_{steep} at all visits in both ortho-k and control groups.

In the ortho-k group, significant CCT thinning of 7 ± 9 μm was observed at the 1-month visit ($p = 0.004$). No significant differences in CCT were observed in the subsequent visits. No significant differences in CCT were observed at any visit during the 2-year study period in the control group.

No significant changes were observed in CH at any visit for both groups of subjects. In the ortho-k group, CRF significantly reduced from an average of 10.7 ± 1.4 mmHg at baseline to 10.0 ± 1.4 mmHg after 1-month of lens wear ($p = 0.003$). Again, no significant differences were found in the subsequent visits with continued ortho-k lens wear. In the control group, no significant change in CRF was found during the study.

CONCLUSIONS

The toric design ortho-k lenses used were effective for myopic reduction

and astigmatic reduction. The results also demonstrated the strong potential for the toric ortho-k lenses to control myopic progression by about 50%. Myopia reduction from ortho-k treatment involved flattening of the anterior corneal curvatures with no involvement of the posterior curvatures. Corneal biomechanical properties, in terms of CH and CRF, were not useful parameters to predict the ortho-k response.

Keywords: toric design, orthokeratology, astigmatism, myopia, myopic control

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Abbreviations

AC	Alignment Curve
AL	Axial Length
AVA	Aided visual acuity
BCVA	Best corrected visual acuity
BOZD	Back Optic Zone Diameter
BOZR	Back Optic Zone Radius
CCT	Central Corneal Thickness
CFZ	Central Flattened Zone
CH	Corneal hysteresis
CT	Corneal thickness
CRF	Corneal resistance factor
CRT	Corneal refractive therapy
D	Diopter
Dk	Oxygen permeability
Dk/t	Oxygen transmissibility
e-value	Eccentricity
FDA	Food and Drug Administration
HVID	Horizontal visible iris diameter
IOP	Intraocular pressure
JCC	Jackson crosscylinder
K_{flat}	Flattest simulated keratometry reading
K_{steep}	Steepest simulated keratometry reading
logMAR	Logarithm of the minimum angle of resolution
n	Number of subjects
Ortho-k	Orthokeratology
PMMA	Polymethylmethacrylate
PC	Peripheral Curve
RC	Reverse Curve
RGL	Reverse geometry lens
RGP	Rigid gas permeable

S	Ablation Diameter
SCL	Soft contact lenses
SD	Standard Deviation
SER	Spherical Equivalent Refraction
t	Ablation depth
TRC	Toric peripheral radius
TxZ	Treatment zone
UVA	Unaided visual acuity
VA	Visual acuity
VST	Vision shaping treatment
WTR	With-the-rule

CHAPTER 1

Literature review and background of the study

1.1 Introduction

Myopia is a refractive defect of the eye in which a parallel light produces images focused in front of the retina when accommodation is relaxed. In this situation, distance objects cannot be perceived distinctly. A myopic person will see blurred images at distance, but clear at near. Myopia is a very common condition and it has been widely studied. Although the etiology of myopia is not well understood, the characteristics of myopia are well known. In the clinical management of myopia, spectacles and contact lenses are the most commonly used to correct myopia to bring the image back to the retina (Goss, 1987; Grosvenor, 1987). Many factors affect the prevalence of myopia and a major factor is age. Prevalence of myopia at different ages has been reported in different studies (Mantyjarvi, 1985; Grosvenor, 1987; Lam and Goh, 1991; Lam et al., 1999; Mutti and Zadnik, 2000; Saw et al., 2000; Fan et al., 2004a; Lam et al., 2012). Mantyjarvi (1985) indicated that myopia was greater for earlier onset of myopia in both boys and girls among 214 myopic children (7 - 15 years old). When myopia started before at ten years old or younger, 70% of the children ended up with myopia of -3.00 to -5.75 D, only 12.5% remained under -3.00 D, and 17.5% had myopia -6.00 D or more. They reported that the early onset of myopia maybe associated with a higher rate of myopia progression.

Myopia is a common ocular disorder, the prevalence of which is high especially in Asian countries such as Hong Kong, Singapore, Korea, Taiwan and China (Lam and Goh, 1991; Zhao et al., 2000; Lin et al., 2001; Zhao et al., 2002; Lam et al., 2004; Lin et al., 2004; Lam et al., 2012). In Hong Kong, the prevalence of myopia increased from 11% in seven-year old children to 57% in 12-year old children, and to more than 70% in 17-year old teens (Lam and Goh, 1991; Edwards and Lam, 2004). The prevalence of myopia for children in Singapore was 8.6% (3 - 7 years old) (Saw et al., 2000) while Lam and Goh (1991) reported it was 30% in Hong Kong children (6 - 7 years old). Lam and colleagues (1999) reported a 2-year longitudinal study in Hong Kong children (6 - 17 years old) in which the prevalence of myopia increased from 52% to 62% over 2 years. Fan et al. (2004a) reported that the prevalence of myopia increased from 17% at age seven to 53% at age 11 in Hong Kong children in a cross-sectional study. A more recent studyhas reported that the prevalence of myopia in Hong Kong in six- and 12-year old children was 18.3% and 61.5%, respectively (Lam et al., 2012).

The myopic progression in children is of great concern in Asian countries as the prevalence of myopia is high in Asia and may be increasing (Fan et al., 2004a; Cheng et al., 2007). In Hong Kong, the myopia progression rate per year in myopic children (6 - 17 years old) in 1999 was reported to be -0.46 D (Lam et al., 1999), but was -0.63 D (5 - 16 years old) in 2004 (Fan et al., 2004a). In the Singapore longitudinal study (Saw et al., 2005c), the rate of myopic progression decreased with time, it was -0.95 D, -0.69,

and -0.47 D at the first, second, and third year. In the Taiwan study (Shih et al., 2010), the mean rate of myopic progression in myopic eyes was -0.60 D (7 - 18 years old) per year. The mean rate of myopic progression is similar in these previous studies.

Some other factors affecting the myopic prevalence include educational attainment, occupation, near work, gender, genetic factor, and ethnicity. Several longitudinal studies (Parssinen and Lyyra, 1993; Goss and Rainey, 1998; Saw et al., 2005a) have suggested that near work may be a contributing factor to the fast progression of myopia. Higher progression rates are associated with earlier onset of myopia (Mantyjarvi, 1985; Grosvenor, 1987; Goss et al., 1990). Saw et al. (2000) reported that 153 Singapore children (6 - 12 years old) who were more myopic at baseline had a more rapid myopic progression rate.

High myopia is associated with sight-threatening problems, such as cataract, glaucoma, retinal detachment, and macular degeneration (Perkins, 1960; Curtin et al., 1979; Burton, 1989; Fong et al., 1990; McCarty et al., 1999; Mitchell et al., 1999; Grodum et al., 2001; Saw et al., 2005b; Cheng et al., 2013; Muller and Joussen, 2013; Pan et al., 2013), which can contribute to loss of vision as well as ultimately blindness. Pan et al. (2013) reported that myopia was associated with an increased prevalence of both nuclear and posterior subcapsular cataract and the prevalence of posterior subcapsular cataract increased dramatically when myopia is less than -5.00 D (higher myopia). Previous studies have

suggested that myopic individuals have abnormal connective tissue that could predispose for glaucoma (Curtin et al., 1979; Fong et al., 1990). Other studies have shown that the peripheral retinal degenerative changes and optic nerve crescent in high myopic teenage subjects (Cheng et al., 2013) and foveal retinal detachment and retinoschisis are common features in high myopic eyes with posterior staphyloma (Muller and Joussen, 2013).

Table 1.1 Studies of myopic control treatment using different treatment methods

	Cho et al. (2005)	Chua et al. (2005)	Siatkowski et al. (2008)	Walline et al. (2009)	Kakita et al. (2011)	Hiraoka et al. (2012)	Cho and Cheung (2012)
Age (years)	7-12	6-12	8-12	8-11	8-16	8-12	7-10
Duration of study (years)	2	2	2	2	2	2	2
Intervention	Ortho-k	Atropine	Pirenzepine	Ortho-k	Ortho-k	Ortho-k	Ortho-k
Control treatment	Spectacles	Placebo	Placebo	Soft lenses	Spectacles	Spectacles	Spectacles
Initial myopia (study group) (mean±SD) (D)	-2.27±1.09 (SER)	-3.36±1.38	-2.10±0.90 (SER)	--	-2.55±1.82 (SER)	-1.89±0.82 (SER)	-2.16±0.77
Initial myopia (control group) (mean±SD) (D)	-2.55±0.98 (SER)	-3.58±1.17	-1.93±0.83	--	-2.59±1.66 (SER)	-1.83±1.06 (SER)	-2.36±0.86
Increase in AL (study group) (mean±SD) (mm)	0.29±0.27	-0.02±0.35	0.28	0.25±0.27	0.39±0.27	0.45±0.21	0.36±0.24
Increase in AL (control group) (mean±SD) (mm)	0.54±0.27	0.38±0.38	0.40	0.57±0.27	0.61±0.24	0.71±0.40	0.63±0.26
Increase in myopia (study group) (mean±SD) (D)	--	-0.28±0.92	0.58	--	--	--	--
Increase in myopia (control group) (mean±SD) (D)	--	-1.20±0.69	0.99	--	--	--	--
Myopic control effect	46%	--	--	55%	36%	37%	43%

AL: axial length

Previous studies have investigated various myopic control methods, including spectacles, contact lenses, and pharmaceutical agents in children (Table 1.1). However, most of these interventions have not been satisfactory as a method for controlling myopia. Complications such as cycloplegia, photophobia, near-vision problems and some systemic difficulties have been reported with the use of these antimuscarinic drugs (Tan et al., 2005; Chua et al., 2006; Siatkowski et al., 2008). Hence, in spite of the success, clinicians are reluctant to subject children to a long term application of these ocular drugs (Brodstein et al., 1984).

Although some studies have reported a positive effect of different optical interventions, such as bifocal and progressive addition lenses (Oakley and Young, 1975; Khoo et al., 1999; Leung and Brown, 1999), most studies suffered from serious limitations such as a small sample size, non cycloplegic refraction, no masking, no AL measurements or no randomization. Subsequent studies using more stringent methodologies have failed to show significant myopic control (Edwards et al., 2002; Gwiazda et al., 2003). Orthokeratology (also called OK, ortho-k, corneal reshaping, corneal refractive therapy (CRT), and vision shaping treatment (VST)), is a clinical technique which temporarily reshapes the cornea using rigid contact lenses to reduce myopia and improve vision. The concept of ortho-k was introduced in the early 1960s but did not gain popularity at that time. In the last decade, ortho-k has rekindled clinical and research interest because the advancement of technology has given birth to better lens materials and designs. Sophisticated equipment also allows accurate monitoring of

the cornea. Various clinical studies have investigated the efficacy and the safety of ortho-k for myopic reduction (Mountford, 1997b; Nichols et al., 2000; Sima et al., 2000; Rah et al., 2002b; Mika et al., 2007) and a number of studies have shown the potential of ortho-k for myopic control (Cho et al., 2005a; Walline et al., 2009; Kakita et al., 2011; Cho and Cheung, 2012).

Astigmatism is a common refractive condition that affects both normal and diseased eyes. The curvature of astigmatic eye has steepest and flattest meridians in the corneal front surface (Figure 1.1). In an eye with astigmatism, the image fails to come to a single focus on the retina to produce clear vision. Instead, two focal planes occur, either in front of or behind the retina (or both) (Figure 1.2). Previous studies have reported that infants have a high incidence of clinically significant astigmatism (Howland et al., 1978; Fulton et al., 1980) but it is greatly reduced or eliminated during the first two years of life (Atkinson et al., 1980; Gwiazda et al., 1984; Gwiazda et al., 1993). Table 1.2 shows the prevalence of astigmatism in subjects with myopia.

Table 1.2 Prevalence of astigmatism in subjects with myopia

Studies (year)	Number of subjects	Age (years)	Astigmatism (D)	Prevalence of astigmatism (%)
Kleinstein et al. 2003	2523 491 (Asian)	10.05±2.28 (5-17)	At least -1.00 or above	28.4 (all) 33.6 (Asian)
Fan et al. 2004	697	55.7±10.9 (months)	-0.65±0.58	55.8 (>0.50D) 21.1 (>1.00D)
He et al. 2004	4364	5-15	≥0.75	33.6
Shih et al. 2004	11175 (1995) 10878 (2000)	7-18	≥1.00	27.9 (1995) 32.6 (2000)
Saw et al. 2006	1962 (Singapore) 1752 (Malaysia)	7-9	≥0.75	Singapore: 44.3 (Malay) 42.5 (Chinese) 41.3 (Indian) 33.3 (Others) Malaysia: 18.7 (Malay) 34 (Chinese) 22.4 (Indian) 35.7 (Others)
Leung et al. 2012	2759	3-84	At least -1.00	Age 3-10: 17.8 Age 11-20: 31.4 Age 31-30: 38.1 Age 31-40: 29 Age 41-50: 25.8 Age 51-60: 26.7 Age >60: 41.8

ATR: against the rule; WTR: with the rule

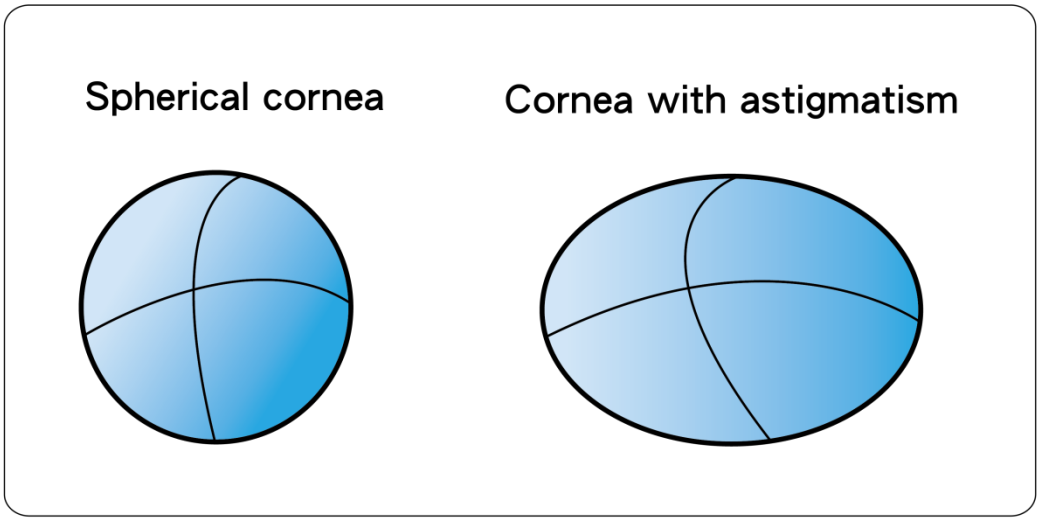


Figure 1.1 Cornea with and without astigmatism. Cornea without astigmatism is curved like a basketball, with the same degree of roundness in all areas. The astigmatic cornea is more oval than round and has steepest and flattest meridians in the front surface

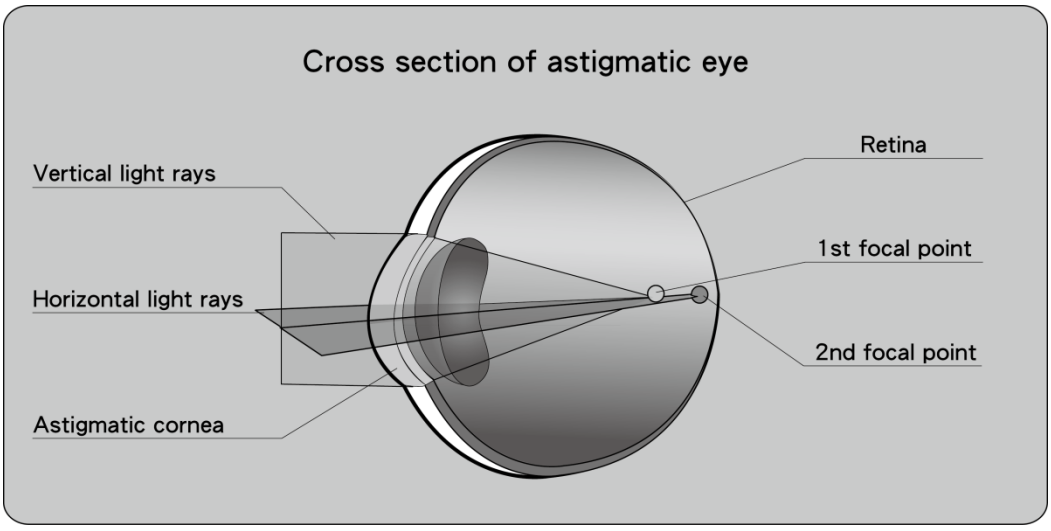


Figure 1.2 Cross section of astigmatic eye. In the illustration, the cornea has a different curvature in the veritcal and horizontal meridians. Vertical light rays and the horizontal light rays can be seen to focus in front of the retina. The difference in light focusing power between the vertical and horizontal is equal to the amount of the eye's astigmatism

A review of the prevalence of astigmatism and changes with age has been presented by Read et al. (2007). Changes in corneal shape and degree of astigmatism can be classified by four stages: birth to four years (early childhood), four to 18 years (children), 18 to 40 years (adulthood), and 40+ years (older adulthood).

Gwiazda et al. (2000) reported that about 50% of 0 - 6 months old infants have significant astigmatism (one or more diopters), but that the prevalence was less than 5% at age six to 10 years old, slowly rising again after that. Parssinen (1991) reported that the prevalence of with-the-rule astigmatism increased from 10 to 18% in myopic children (starting at mean age 11 years old) in a 3-year study. The prevalence of astigmatism was 28% in school-age children (age 5 - 17 years old) in the United States (Kleinstein et al., 2003). Astigmatism, particularly high amounts of astigmatism, is frequently associated with significant spherical ametropia in human (Guggenheim and Farbrother, 2004) and in animal models (Kee et al., 2005; Kee and Deng, 2008). In addition, astigmatism has been reported to be associated with the development of amblyopia (Fulton et al., 1982; Alward et al., 1985), and progression of myopia (Fulton et al., 1982; Howland, 1982; Goss and Erickson, 1987; Gwiazda et al., 2000; Fan et al., 2004b).

However, there appears to have been no longitudinal study on the changes in astigmatism among preschool children in a Chinese population. In Asian countries, the prevalence of astigmatism was reported to range

from 23% to 58% in urban areas (Fan et al., 2004b; He et al., 2004; Shih et al., 2004; Saw et al., 2006). Fan et al. (2004b) reported that the prevalence of astigmatism was 55.8% (> 0.50 D) and 21.1% (> 1.00 D) in 697 children (mean age 55.7 ± 10.9 months). He et al. (2004) reported that the prevalence of astigmatism was 33.6% (> 0.75 D) in 4364 children (5 - 15 years) in southern china. Shih and colleagues (2004) reported that the prevalence of astigmatism (less than 1.00 D) in Taiwan schoolchildren was 27.9% and 32.6% in 1995 and 2000 years, respectively. Most myopic children are also astigmatic (Kleinstein et al., 2003; Fan et al., 2004b). Kleinstein and coworkers (2003) reported that the prevalence of astigmatism was 33.6% in Asian children (5 - 17 years old). They defined astigmatism as at least a 1.00 D difference between the two principal meridians. Recently, Leung and colleagues (2012) reported that the prevalence of astigmatism of more than 1.00 D among three- to 10-year old children was 17.8% and that the prevalence increased to 31.4% among teenagers aged 11 to 20 in Hong Kong.

Unlike hyperopic or myopic refractive errors, astigmatism constantly degrades the eye’s image quality and uncorrected astigmatism could significantly affect quality of life (Harle and Evans, 2006; Wolffsohn et al., 2011). Methods for correcting astigmatism include spectacles, contact lenses, ortho-k lenses or refractive surgery to bring the image back to the retina (Goss and West, 1948; Yang et al., 2001; Kastl, 2003; Russell and Slonim, 2003; Baertschi, 2005; Beerten et al., 2005; Shah et al., 2012).

Ortho-k has been confirmed to correct mild to moderate myopia, however, there is limited information about the safety and success rate on correcting high myopia. Clinically, use of ortho-k at high myopic correction could result in corneal staining, heavy lens binding, and lens decentration (Chan et al., 2008). Effectiveness of ortho-k for partially corrected refractive errors and for myopic control on high myopes has been reported (Charm, 2012). Full correction was not obtained in their study and these subjects needed to wear spectacles to correct residual refractive error to obtain clear daytime vision.

Although it has been shown that spherical design ortho-k lenses are effective in correcting low to moderate myopia, they cannot reduce refractive astigmatism (Rah et al., 2002b; Soni et al., 2003; Tahhan et al., 2003; Cheung and Cho, 2004; Sorbara et al., 2005; Chan et al., 2008; Cheung et al., 2009). Hence, such lenses are not indicated for children with refractive or corneal astigmatismof more than 1.50 D. Spherical ortho-k lenses on toric cornea can lead to poor lens centration, induced astigmatism, and poor vision (Mountford and Pesudovs, 2002; Chan et al., 2008). However, apart from some case reports (Chan et al., 2009), and some conference abstracts (Baertschi, 2005; Beerten et al., 2005), there are no published reports of ortho-k for myopic control in moderate to high astigmatic children.

The ortho-k effect has also been reported to be affected by corneal biomechanical properties. However, whilst changes in corneal

biomechanics with short-term ortho-k lens wear have been reported (Gonzalez-Meijome et al., 2008; Chen et al., 2009), to date, there are no reports on corneal biomechanical properties with long term ortho-k lens wear.

1.2 Orthokeratology

The concept of ortho-k supposedly originated in ancient China. A number of papers on ortho-k have reported the unconfirmed story that the ancient Chinese put small sandbags on the eyes during sleep to help them see better in the morning (Swarbrick, 2006).

Ortho-k originally describes a process using a programmed application of rigid contact lenses to flatten the central cornea to accomplish refractive power changes. It then developed from using conventional rigid contact lenses (made of PMMA and later, rigid gas permeable materials) for day wear modality to reverse geometry design contact lenses (modern ortho-k) using hyper oxygen permeable materials to allow overnight treatment. If the corneal response is good, the ortho-k wearer may have good unaided visual acuity (UVA) without the need to wear spectacles or contact lenses during the daytime. However, the lenses must be worn regularly to retain the ortho-k effect. Ortho-k is a non-invasive and reversible option for myopic correction. Once lens wear is stopped, the cornea will gradually rebound and the myopia will return after a few days of ceased lens wear (Barr et al., 2004).

1.2.1 Traditional orthokeratology

Traditional ortho-k used conventional lens designs fitted much flatter than flat K to effect myopic reduction (Kerns, 1976c; Binder et al., 1980; Polse et al., 1983a; Coon, 1984). Originally, PMMA lenses were used (Neilson et al., 1964; Grant and May, 1971; Kerns, 1976b; Kerns, 1976a; Kerns, 1976c; Kerns, 1977b; Kerns, 1977d; Kerns, 1977a; Kerns, 1977c; Binder et al., 1980; Brand et al., 1983; Polse et al., 1983a) which was replaced bya low to moderate DK RGP lens material when these were introduced (Wlodyga and Bryla, 1989; Harris and Stoyan, 1992; Wlodyga and Harris, 1993). The keratometer was used to monitor the contact lens effects (e.g. corneal curvature changes) on the cornea (Wlodyga and Bryla, 1989). Wlodyga and Bryla (1989) used the difference between central and peripheral keratometric readings to establish the corneal shape factor and to predict the amount of myopic reduction. However, since the keratometer only measures the central 3 mm of the cornea, it is not adequate for monitoring corneal changes effected by ortho-k treatment. Keratometric readings cannot present the actual changes or flattening rate of the cornea (Joe et al., 1996).

There are a number of problems and disadvantages associated with traditional ortho-k. Fitting flatter than K using conventional rigid lens designs and low DK materials led to problems with lens decentration (Kerns, 1976b), corneal edema (Kerns, 1977a; Coon, 1984), corneal distortion (Kerns, 1977a; O'Neal et al., 1984), and hypoxia (O'Neal et al., 1984; Wang et al., 2003). It was only effective in reducing low level myopia

via multiple lenses (Kerns, 1976b; Binder et al., 1980; Polse et al., 1983a; Coon, 1984), and the effect on myopic reduction usually lasted for only a few hours (Polse et al., 1983a). Patients were required to regularly wear the lenses for some hours during the daytime to retain the short period of time of ortho-k effect and many reported discomfort with open-eye lens wear (Schlanger, 1993).

Earlier studies and lens designs allowed an average of 1.00 D of spherical equivalent change after 2 to 10 months of daily lens wear (Kerns, 1976b; Kerns, 1977c; Polse et al., 1983a; Lui and Edwards, 2000). Results were also unpredictable and unreliable due to lens decentration and unwanted corneal cylinder (Binder et al., 1980; Polse et al., 1983a).

These ocular and lens problems finally led to an abandonment of ortho-k until the late 1990s when, with the development of newer and better lens materials and designs, and the introduction of corneal topographers, interest in ortho-k was rekindled.

1.2.2 Modern orthokeratology

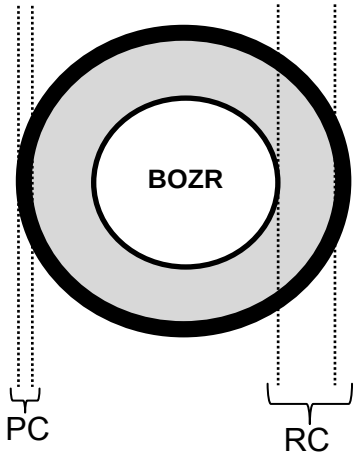
Modern ortho-k was introduced in the early 1990's (Grant, 1992; Harris and Stoyan, 1992; Mountford, 1997b). The development of sophisticated computerized corneal topography allowed careful and accurate screening of patients, monitoring of corneal effects, and fabrication of novel lens designs and fitting modalities to effect faster results (Mountford, 1997b; Nichols et al., 2000; Rah et al., 2002b; Alharbi and Swarbrick, 2003; Cho

et al., 2003a; Joslin et al., 2003; Soni et al., 2003; Tahhan et al., 2003; Hiraoka et al., 2004c; Koffler and Smith, 2004; Owens et al., 2004; Berntsen et al., 2005; Cho et al., 2005a; Maldonado-Codina et al., 2005; Sorbara et al., 2005; Cheung et al., 2007; Lu et al., 2007a; Chan et al., 2008; Kobayashi et al., 2008; Lipson, 2008; Walline et al., 2009; Kakita et al., 2011; Chan et al., 2012; Cho and Cheung, 2012).

1.2.2.1 Reserve geometry lens

The first reverse geometry lens (RGL) design, developed by Wlodyga and Bryla (1989), was a three-zone design. The three-zone lens (Cho et al., 2012a) (Table 1.3) consists of a central base curve (the back optic zone radius (BOZR)) flatter than the corneal curvature (flat meridian), a mid-peripheral curve (the Reverse Curve (RC)) fitted steeper than the BOZR of the lens, and a peripheral curve. The optical zone is typically 6.0 to 8.0 mm in diameter and the BOZR is based on the refractive change requirement. In the OK-60 lens, the initial BOZR is fitted 1.00 D flatter than the flat K reading or half of the difference between the central and temporal horizontal K reading, and subsequent lenses 1.00 D flatter than the last lens. The fitting relationship of this lens changes as a result of flattening the central cornea. However, a new lens with a flatter BOZR has to be dispensed promptly to prevent distortion and other physiological problems of the cornea. The purpose of the steeper RC is to allow better lens centration with the central base curve fitted flatter than flat K. The peripheral curve (PC) is approximately 0.4 to 0.5 mm wide with a radius of

Table 1.3 Structure of the three-zone reverse geometry lens

	
Back Optic Zone Back Optic Zone Radius (BOZR)	● 6.0 to 8.0 mm (diameter) ● BOZR is based on the refractive change required ● Tear layer behind lens provides subtle applanation force necessary to re-distribute the tissue ● Not a factor affecting lens fitting
Reverse Zone Reverse Curve (RC)	● About 3.0 mm (width) ● Steeper secondary curve ● Maximizes control of centration ● Available in both spherical and aspheric forms
Peripheral Zone Peripheral Curve (PC)	● About 0.5 mm (width) ● Provides the desired peripheral corneal clearance ● Facilitates lens movement and tear exchange beneath the lens

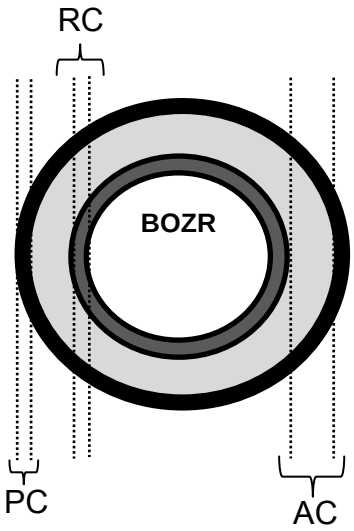
(Cho et al., 2012b)

10.5 to 12.25 mm. The PC provides the desired peripheral corneal clearance and it facilitates lens movement and tear exchange beneath the lens (Ramkisson, 2004). Compared to traditional ortho-k, the amount of myopic reduction is significantly improved and the time required to achieve the ideal refractive change is much reduced with this lens design (Wlodyga and Bryla, 1989).

Contex OK lens series (Contex Laboratories, Sherman Oaks, CA, USA) was the first approved RGL for a daytime wear modality for myopic reduction by the Food and Drug Administration (FDA) of USA in May 1988. However, a major problem with the three-zone RGL is lens decentration. This led to the introduction of four-zone designs to improve lens centration and hence the myopic reduction effect.

In the four-zone and five-zone designs, an alignment curve (AC) is introduced and it connects the RC and PC.

Table 1.4 Structures of the four-zone and five-zone reverse geometry lenses

	
Back Optic Zone Back Optic Zone Radius (BOZR)	● 6.0 to 8.0 mm (diameter) ● BOZR is based on the refractive change required ● Tear layer formed behind lens provides subtle applanation force necessary to re-distribute the tissue ● Does not affect lens fit ● Always spherical

Alignment/Fitting Zone
Alignment Curve (AC)
Four-zone design
 	
Five-zone design
	● Four-zone lens: AC ~ 1.0 to 1.5 mm (width)
	● Five-zone lens:
	  ● AC1 ~ 0.5 to 0.7 mm (width)
	  ● AC2 ~ 0.5 to 0.6 mm (width)
	● Mid-peripheral curve(s) aligns with mild peripheral cornea
	● Control total lens movement and is responsible for centration
	● Can be spherical, aspherical or a tangent
	● Sagittal height of the lens is controlled by changing the alignment configuration or the tangent angle
	For toric design:
	● Sagittal height of the lens is different between the steep and flat meridians
	● Tangents of the lens are calculated from the apical radius of the steep and flat meridians as well as the elevation along each respective meridian

Reverse Zone Reverse Curve (RC)	● About 0.6 to 1.0 mm (width) ● 6 to 12 D steeper than BOZR ● Joining AC with BOZR ● Completes the construction of tear reservoir ● Provides a relief area for tissue distribution ● Aspheric peripheral curve **For toric design:** ● Either toric or spherical with a differential width between the steep and flat meridians
Peripheral Zone Peripheral Curve (PC)	● About 0.3 to 0.5 mm(width) ● Provides desired edge lift ● Facilitates lens movement and tear exchange beneath the lens

(Cho et al., 2012b)

Table 1.5 Characteristics of four-zone and five-zone reverse geometry lenses

Trade name	Design	Manufacturer	Fitting method	Lens diameter (mm)	BOZR (mm)	RC (mm)	1st AC (mm) 2nd AC (mm)	PC (mm)
Z Night lens	Four-zone	NKL Contactlenzen Netherlands	Empirical	10.2, 10.6, 11.0	6.0	1.0 to 1.5 (width)	1.0 (width) Tangent periphery	0.1 to 0.5 (width) Tangent periphery
BE lens	Four-zone or Five-zone	Ultra Vision Pty. Ltd. Brisbane, Queensland, Asutralia	Trial lens or Empirical	10.6 or 11.0	• 6.0 to 8.0 (diameter) Not based on Jessen formula • Depends on R0 and e-value over a specific chord diameter	• Tangent periphery determine by calculating the cone angle according to individual eye • 1/4 tangent (for standard design) • Produce the required tear reservoir/tear layer thickness • 3 fenestrations of size 0.2 mm, at 120˚ intervals, between the reverse and alignment zones		A peropitc curve that converts the last section of the tangent into a curve that imparts a constant axial edge lift
Paragon Corneal Refractive Therapy (CRT)	Four-zone	Paragon Vision Science Mesa, AZ, USA	Trial lens or Empirical	10.5	(Treatment zone) 6.0; selected with the Lens Selector Slide Rule	(Return Zone) 1.0 (width) Sigmoid curve ~ 525 to 575 µm	(Landing zone) Tangent periphery	(Edge lift) Controlled by the angle of the Landing Zone
Contex OK	Four-zone	Contex Laboratories Sherman Oak, CA, USA	Trial lens or Empirical	10.6	6.0 to 8.0 (diameter)	0.6 to 1.0 (width) Usually 3 to 5 D steeper than BOZR	1.0 to 1.5 (width)	Aspheric curve
DriemLens	Four-zone or Five-zone	Taiwan Marco Vision Group, Taiwan	Trial lens	10.0 or 10.6	6.0 to 8.0	0.6 to 1.0 (width) Usually 3 to 5 D steeper than BOZR	1.0 to 1.5 (width)	0.4 (width)
eLens	Four-zone or Five-zone	E&E Optics Asia Ltd. Hong Kong SAR, China	Trial lens	10.6 or greater	6.0	0.6 to (width) Usually 3 to 5 D steeper than BOZR	1.30 (width)	0.4 (width)
Emerald Euclid	Four-zone or Five-zone	Euclid Systems Co. Herndon, VA, USA	Trial lens or Empirical	10.2, 10.6, 11.0 >11.0 10.6 for five-zone	6.0 to 8.0 (diameter)	0.6 to 1.0 (width)	1.0 to 1.5 (width) for four-zone; 1.2 (width) for five-zone	0.4 (width) 11.5 (radius)
Fargo	Four-zone or Five-zone	C&E G.P Specialists San Clemente, CA, USA	Trial lens	10.6, 11.2	6.0	0.6 to 1.0 (width) Usually 3 to 5 D steeper than BOZR	1.0 to 1.5 (width)	0.4 (width)

The AC, parallel to the peripheral cornea, mainly controls the lens centration to produce a better ortho-k outcome. The five-zone design has two AC (AC1 and AC2) and both play a major role in the total lens movement and lens centration. The basic structure of the lens and functions of each curve are shown in Table 1.3. Examples of different four-zone and five-zone lenses are shown in Table 1.5.

Previous studies have reported that spherical design ortho-k lenses cannot adequately reduce moderate refractive astigmatism (Rah et al., 2002b; Tahhan et al., 2003; Cheung and Cho, 2004; Sorbara et al., 2005; Chan et al., 2008; Cheung et al., 2009). Although Rah et al. (2002b) reported, that the spherical design ortho-k could reduce moderate myopia, they did not limit the baseline eccentricity or keratometry measurements and recruited subjects with astigmatism up to 2.00 D at any orientation. In their study, some subjects discontinued ortho-k treatment at different visits because of significant residual astigmatism. Tahhan et al. (2003) reported no astigmatic reduction using spherical design lenses and no significant changes in subjective refractive astigmatism between visits over a 3-month period in 60 subjects (18 - 35 years old). Cheung and Cho (2004) reported good UVA in subjects (8 - 19 years old) with low to moderate myopia wearing spherical ortho-k lenses, but astigmatism was not reduced. Sobrara et al. (2005) reported that in 23 subjects (mean ± SD age 25.8 ± 6.9 years) who wore ortho-k lenses for four weeks, myopic

reduction was 2.59 ± 0.77 D after 28 days of lens wear. Slight increases of 0.25 D at the 1-overnight visit were observed in both corneal and refractive astigmatism, but the change was not clinically significant.

Chan and colleagues (2008) reported a 98% myopic reduction after 1-month of ortho-k treatment but no significant reduction in refractive cylinder was observed over a 6-month period in their subjects (6 - 15 years old). Cheung et al. (2009) compared changes in refractive astigmatism and corneal toricity among 74 patients (7 - 16 years old) who had worn ortho-k lenses for at least six months. They found no significant changes in corneal toricity and no correlations between the changes in refractive astigmatism and changes in corneal toricity.

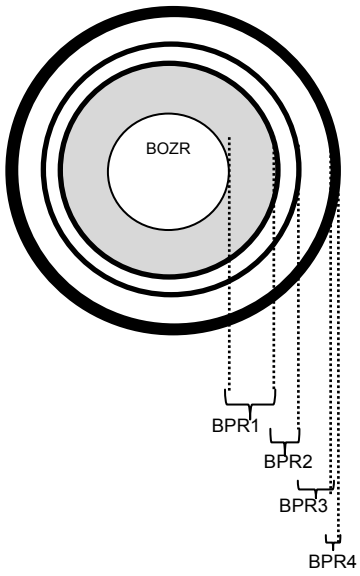
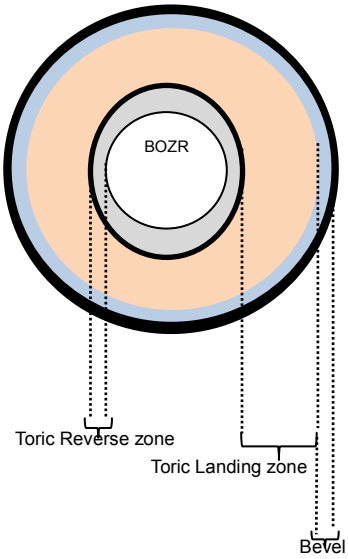
Mountford and Pesudovs (2002) investigated the efficacy of ortho-k lenses for astigmatic reduction in 23 eyes with with-the-rule (WTR) astigmatism of 0.50 D to 1.75 D. They reported that patients with astigmatism between 0.50 D to 0.75 D could achieve a satisfactory outcome. Chan et al. (2008) conducted a retrospective study on 108 patients (median age nine years old) and they reported no significant change in astigmatism with spherical ortho-k lens wear.

In summary, spherical ortho-k has been widely used and reported. The treatment using spherical ortho-k lenses is indicated for low to moderate myopia with WTR astigmatism of not more than 1.50 D.

Toric RGL designs have been developed to improve lens centration as well as for astigmatic correction. The basic structure and information on the toric RGL used in the previous studies for astigmatic correction is shown in Table 1.6. The Toric double reservoir lens (Precilens, Creteil, France) is a new toric design RGL. The posterior surface of the lens is toric consisting of five distinct zones: a toric BOZR, first and second toric peripheral radius (TRC_1), third toric peripheral radius (TRC_2), and fourth toric peripheral radius (Table 1.6). The toric design lens described as the toric landing zone in the FOKX (Falco Kontaktlinsen, Switzerland) study (Baertschi, 2005) (Table 1.6).

The structure of the Z Night Toric reverse geometry lens is shown in Figure 1.3. This lens has a spherical BOZR with toric sagittal height and tangent angle between the two meridians to flatten the flattest meridian and transform the steeper meridian of the cornea. The tangent is calculated based on the apical radii of the steep and flat meridians, as well as the elevation along each meridian (NKL Contactlenzen Netherlands). The toric alignment curve is similar to that of a conventional toric rigid gas permeable lens, which facilitates lens stabilization and centration on the toric cornea.

Table 1.6 Basic structure and characteristics of the toric design reverse geometry lens

Full Toric Double Reservoir Lens		FOKX	
Lens diameter	● 10.80 mm	Lens diameter	● 10.60 mm
Back Optic Zone Back Optic Zone Radius (BOZR)	● 6.6 mm (diameter) ● BOZR with both curvatures determined through Jessen Factor (flatter than the corneal curvature by 0.20 mm for each 1.00 D of aimed refractive change, with an additional flattening of 0.20 mm as a compression factor)	Back Optic Zone Back Optic Zone Radius (BOZR)	● 8.95 mm ● Power +1.00 D
First toric peripheral radius (BPR_1)	● Steeper than BOZR and matching the sagittal depth at each meridian ● As first toric reverse curve (TRC_1)	Toric Reverse Zone	● Confidential
Second toric peripheral radius (BPR_2)	● Flatter than BPR_1	Toric Landing Zone	● Confidential
Third toric peripheral radius (BPR_3)	● Steeper than BPR_2 ● As second toric reverse curve (TRC_2)	Lens material	● Boston XO
Fourth toric peripheral radius (BPR_4)	● With an appropriate curvature to ensure edge lift and adequate tear exchange		

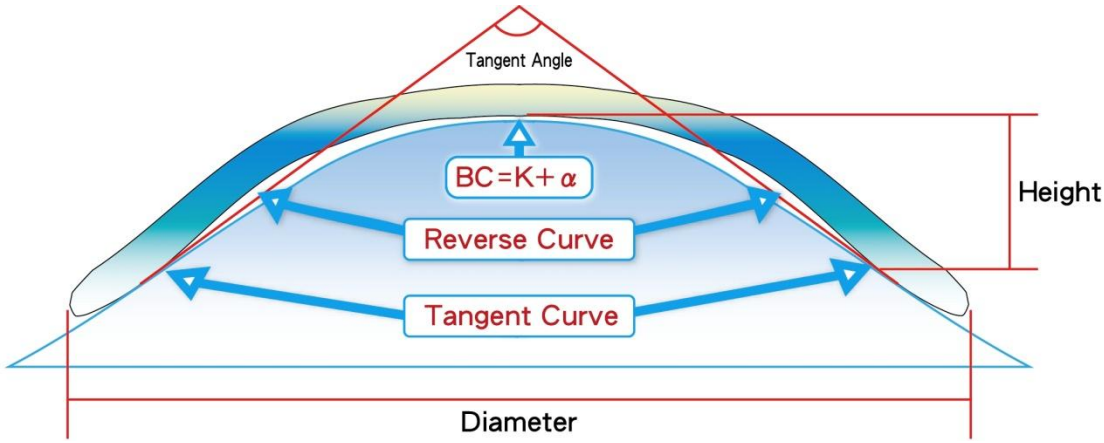


Figure 1.3 Z Night Toric reverse geometry lens (The tangent curves or alignment curves give rise to different lens sagittal heights at the horizontal and vertical meridians, creating different tear profiles and compression forces along the two principle meridians)

1.2.2.2 Gas permeable lens materials

Both daily and overnight wear ortho-k lenses have been used in several studies (Grant, 1992; Mountford, 1997b; Mountford, 1998; Swarbrick et al., 1998; Lui and Edwards, 2000). Corneal hypoxia is a common clinical complication associated with contact lens wear (Binder, 1979; Polse et al., 2001). To minimize corneal hypoxia, a traditional ortho-k lens using a PMMA material was limited to a daily wear modality only. Even with RGL designs, a daily wear modality was not popular due to inconvenience and discomfort associated with lens wear (Schlanger, 1993).

Harvitt and Bonanno (1999) reported that if the corneal swelling in overnight lens wear was to be reduced to 3.2%, DK/t of soft lens of 125 x 10^{-9} (cm x ml O_2)/ (sml x mmHg) was required. The introduction of high DK (≥ 100) RGP lens materials allowed ortho-k lenses to be worn overnight. Hyper DK materials e.g.Boston XO (Polymer Technology), Paragon HDS 100 (Paragon Vision Sciences, Mesa, AZ, USA), and Menicon Z (Menicon), rigid gas permeable contact lenses were introduced to improve oxygen transmission to the cornea to allow ortho-k treatment to be used during sleep (Swarbrick, 2006). Boston XO material has the same oxygen permeability (DK) as HDS and both have a DK of 100 x 10^{-11} (cm^2 /sec) [(ml O_2 / (ml x mmHg)]. Menicon Z has a DKof 163 x 10^{-11} (cm^2 /sec) [mlO_2 / (ml x mmHg)]. Hyper DK material reduces clinical complications such as corneal oedema and hypoxia (Woods and Efron, 1999). In overnight wear

modality, modern ortho-k lenses are removed promptly after awakening. This modality has gained popularity as it is more convenient compared to day wear (Walline et al., 2004b; Cho et al., 2005a; Swarbrick, 2006; Cho et al., 2008). Patients only need to wear the lenses during sleep and there is no discomfort or irritation associated with open-eye lens wear. With successful myopic reduction, patients can achieve good UVA during all waking hours (Nichols et al., 2000; Rah et al., 2002b; Cho et al., 2003a; Joslin et al., 2003; Soni et al., 2003; Tahhan et al., 2003; Hiraoka et al., 2004a; Walline et al., 2004b; Maldonado-Codina et al., 2005; Sorbara et al., 2005; Cheung et al., 2007; Lipson, 2008).

In June 2002, the FDA granted approval to Paragon Vision Sciences for overnight corneal reshaping for Corneal Refractive Therapy (CRT) lenses (http://www.paragoncrt.com/consumers/faqs.asp), to be used for temporary reduction of myopia up to 6.00 D and astigmatism up to 1.75 D. The hyper DK materials used (HDS 100, Paragon Vision Sciences) allowed significant transmission of oxygen to the cornea during closed-eye lens wear (Rah et al., 2002b; Wang et al., 2003; Walline et al., 2004b; Swarbrick, 2006).

1.2.2.3 Corneal topography

In the 1970s and 1980s, the keratometer and the keratoscope were the only instruments available for measuring the corneal curvature in traditional ortho-k. These instruments provided limited information on

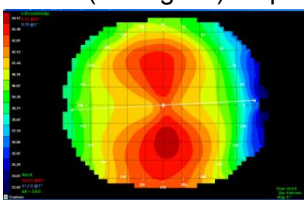
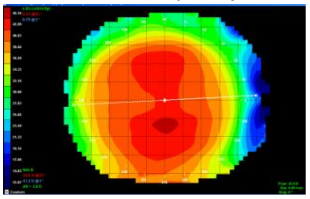
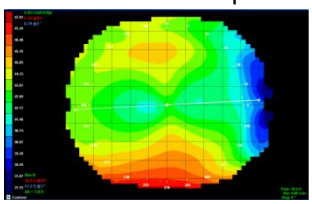
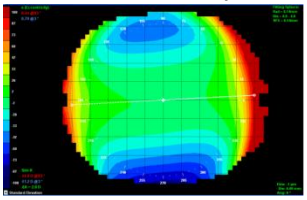
corneal curvatures and also it was difficult to predict the ortho-k outcome (Wlodyga and Bryla, 1989). The keratometer only can measure the central 3 mm of corneal curvature and it is insufficient for the monitoring of ortho-k effect as the treatment involves a wide area of the cornea.

In the late1980s, computer-assisted keratography was introduced and this technique provided comprehensive corneal information, including overall corneal curvatures, apical radius, and eccentricity. The corneal topographer is an essential instrument in ortho-k practice (Mountford, 2004; Swarbrick, 2006; El Hage et al., 2007; Cho et al., 2008). It helps practitioners screen out unsuitable ortho-k candidates, e.g. those with corneal abnormalities, such as keratoconus and irregular corneal shape, and also provides refractive, curvature, and elevation data. In ortho-k lens fitting, it is important to understand how the cornea changes during lens wear. The corneal topographer provides subtractive maps to allow comparison of corneal changes pre- and post-ortho-k lens wear. RGL fitting using the corneal topography was first described by El and Leach (1999). One of the main advantages of corneal topography is the colour display which provides accurate and repeatable measurements of the corneal radius of curvature. Data from baseline corneal curvature can be stored and be compared with post-ortho-k lens wear data. There are three main maps representing different information about the cornea, including curvature, elevation, and pachymetry maps (Wilson and Klyce, 1991; Mountford et al., 2004b).

In the curvature map, the red colour (warm) represents a steeper area and the blue colour (cool) represents a flatter area. In an elevation map, the red colour represents the area above the reference sphere and the blue colour represents the area below the reference sphere.

This table provides a summary of the types of corneal topographical maps and their functions (Table 1.7).

Table 1.7 Corneal topographical maps and displays of the same eye at the same visit

Map	Characteristics/Functions
Axial (or Sagittal) map 	● Describes the surface of the cornea relative to the optical axis ● Gives a general view of the cornea contour ● Relates to the optical power of the cornea ● Can be displayed in millimeters (curvature map) or diopters (power map) ● Highly dependent on patient's fixation and corneal asymmetry ● Can be used to check centration after ortho-k treatment or refractive surgery
Tangential (or true curvature) map 	● Describes the surface of the cornea independent of the optical axis ● Shows small localized changes on the cornea ● Can be displayed in millimeters (curvature) or diopters (power map) ● Shows the location of the apex of the cone in keratoconus ● Shows lens centration after ortho-k treatment or refractive surgery
Refractive map 	● Describes the refractive powers of the cornea by converting the surface power into refractive power using Snell's law ● Compensates for spherical aberrations as well as the aspheric contour of the cornea ● Useful for identifying central island and treatment zone size after ortho-k treatment or refractive surgery
Elevation map 	● Shows heights relative to a reference sphere

Two functional scales (normalized and absolute) can be used to interpret the maps. Normalized (or relative) scale is the default scale used by the topographer and it gives a general idea of the corneal shape and can be used to check the quality of the maps. Absolute (or customized) scale can be selected by the examiner and used for more detailed analysis.

The corneal topographer has a subtractive topographical map function which can provide useful information about the cornea before and after ortho-k treatment, (Table 1.8).

Table 1.8 Subtractive (or differential) maps of two captures, pre- and post-orthokeratology treatment

Map	Functions
Axial subtractive map	● Determines the treatment zone size and the maximum refractive change using profile map
Tangential subtractive map	● Determines lens centration ● Determines localized change by observing for any local steeping or flattening
Refractive subtractive map	● Determines refractive change ● Determines the treatment zone size

A subtractive axial map (sagittal) provides the radius of curvature at each point of the cornea, (Figure 1.4). The change in curvature is directly related to the prescription change in dioptric power and is best for determining the refractive change in ortho-k (El Hage and Leach, 1999).

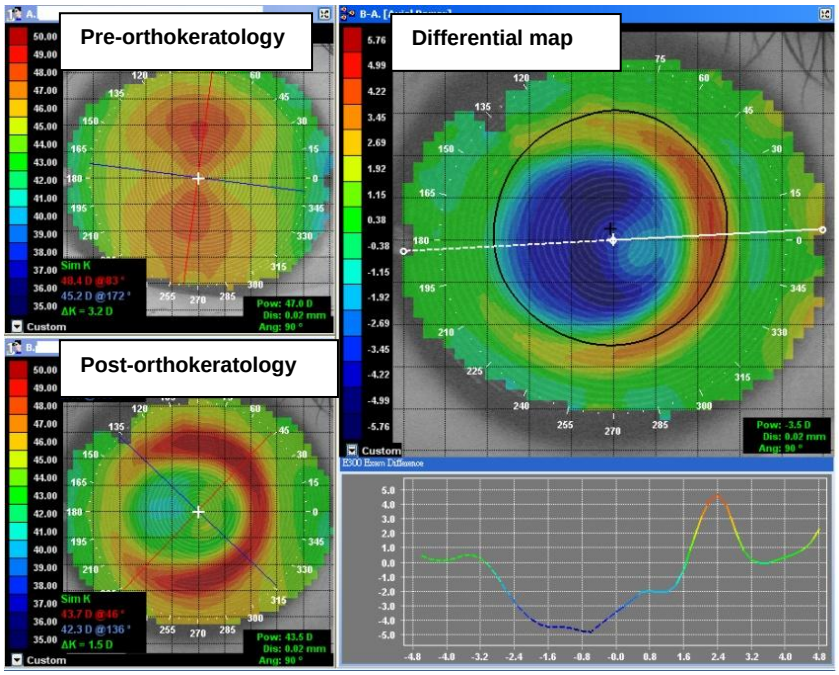


Figure 1.4 Axial subtractive map of the right eye of an orthokeratology subject. Graph on the top left is pre-orthokeratology and bottom left is the post-orthokeratology cornea, with the subtractive difference map shown on the right-hand side

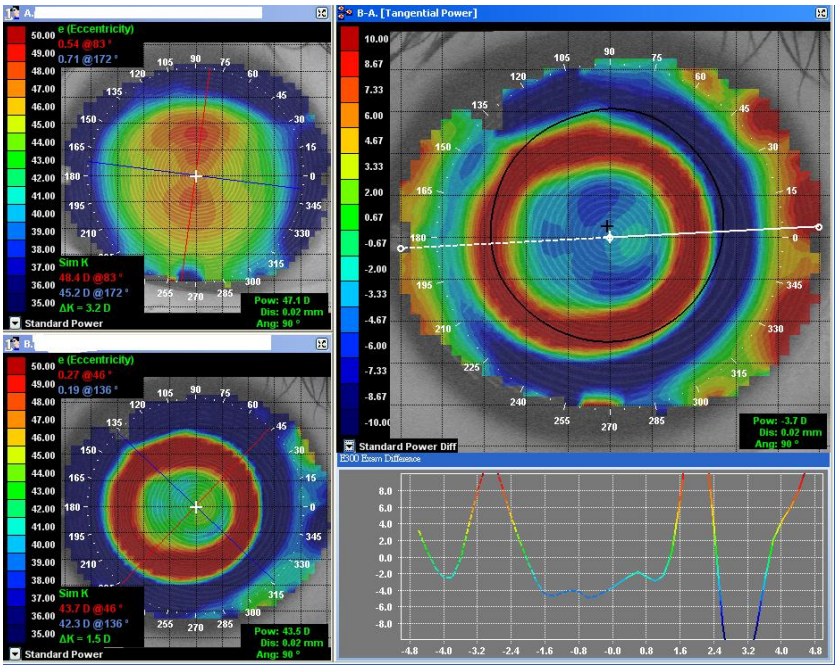


Figure 1.5 Bull's eye topographical pattern after overnight orthokeratology lens wear. Graph on the top left is pre-orthokeratology and the bottom left is post-orthokeratology cornea, with the subtractive difference map shown on the right-hand side

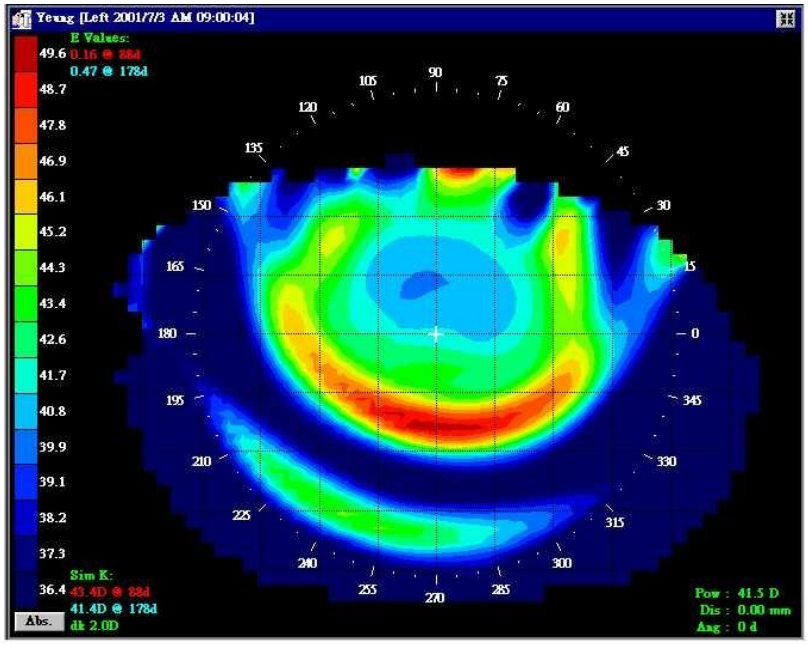


Figure 1.6 Smiley face topographical pattern due to a flat-fitting orthokeratology lens. This graph noted the inferior crescent of steepening, and the off-centre position of the flattened zone

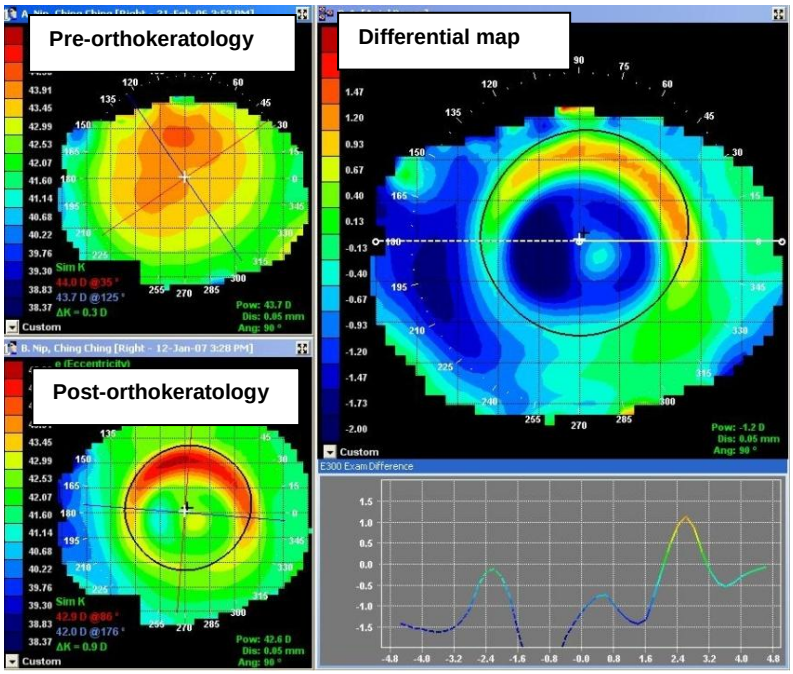


Figure 1.7 Frowny face topographical pattern due to a steep-fitting orthokeratology lens. Graph on the top left is pre-orthokeratology and the bottom left is post-orthokeratology cornea, with the subtractive difference map shown on the right-hand side

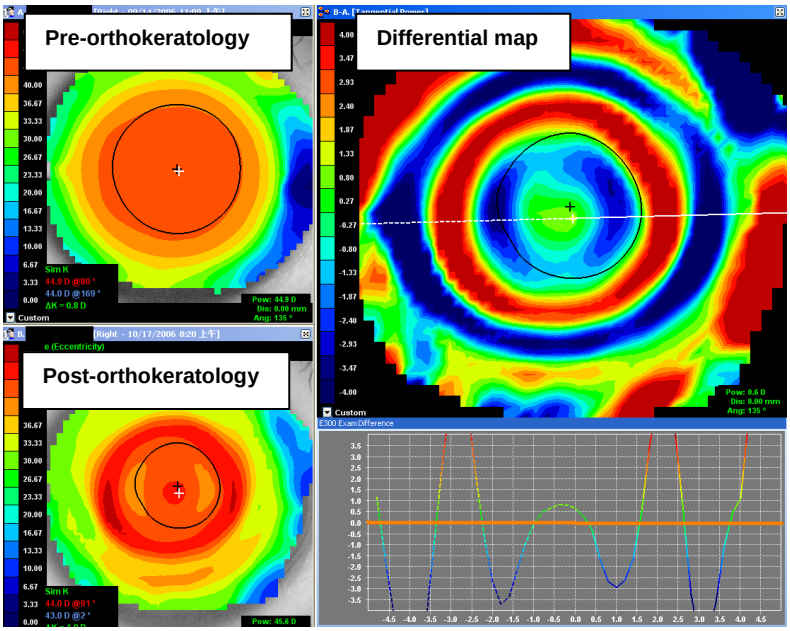


Figure 1.8 Central island topographical pattern due to a steep-fitting orthokeratology lens. Graph on the top left is pre-orthokeratology and the bottom left is post-orthokeratology cornea, with the subtractive difference map shown on the right-hand side. The difference map shows a good centration with a central corneal steepening and surrounded by a trench of marked flattening

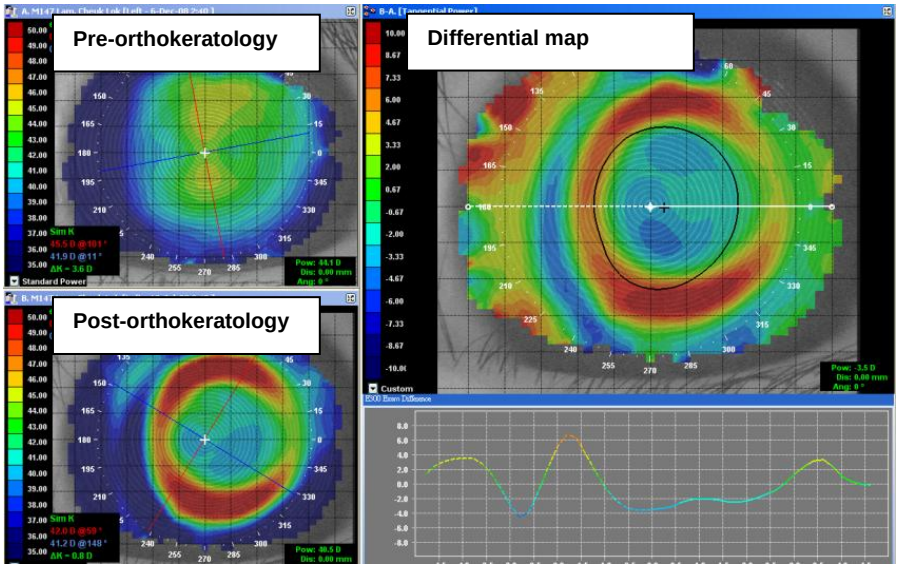


Figure 1.9 Lateral displacement may due to an asymmetrical cornea (pre-orthokeratology). Graph on thetop left is pre-orthokeratology and the bottom left is post-orthokeratology cornea, with the subtractive difference map shown on the right-hand side. Lens in the left eye decenters temporally with reference to the pupil. The flattened area decenters out with respect to the pupil

A subtractive tangential map (instantaneous/true) defines points of corneal curvature change. A tangential subtractive topographical map can be described as “Bull’s eye, “Smiley face”, and “Frowny face” and these represent good lens centration, decentered lens flat, and steep fit of the lens during sleep, respectively, (Figures 1.5 to 1.9). A “Central island” pattern (Figure 1.8) also indicates a steep fit. Figure 1.9 shows an asymmetrical cornea with lateral lens decentration.

A refractive map can derive dioptric power based on Snell’s law to present the refractive power of the cornea, (Figure 1.8) and be used to determine the treatment zone size. As tangential and axial maps can over- or under-estimate the effect of an ortho-k treatment, the refractive map is the preferred map used to determine the treatment zone after ortho-k treatment.

An elevation map can be used to evaluate the height from which the corneal curvature varies (above or below) from a computer-generated reference surface. Warm colours represent the area higher than the reference surface and cool colours represent the lower points of cornea. (Table 1.7)

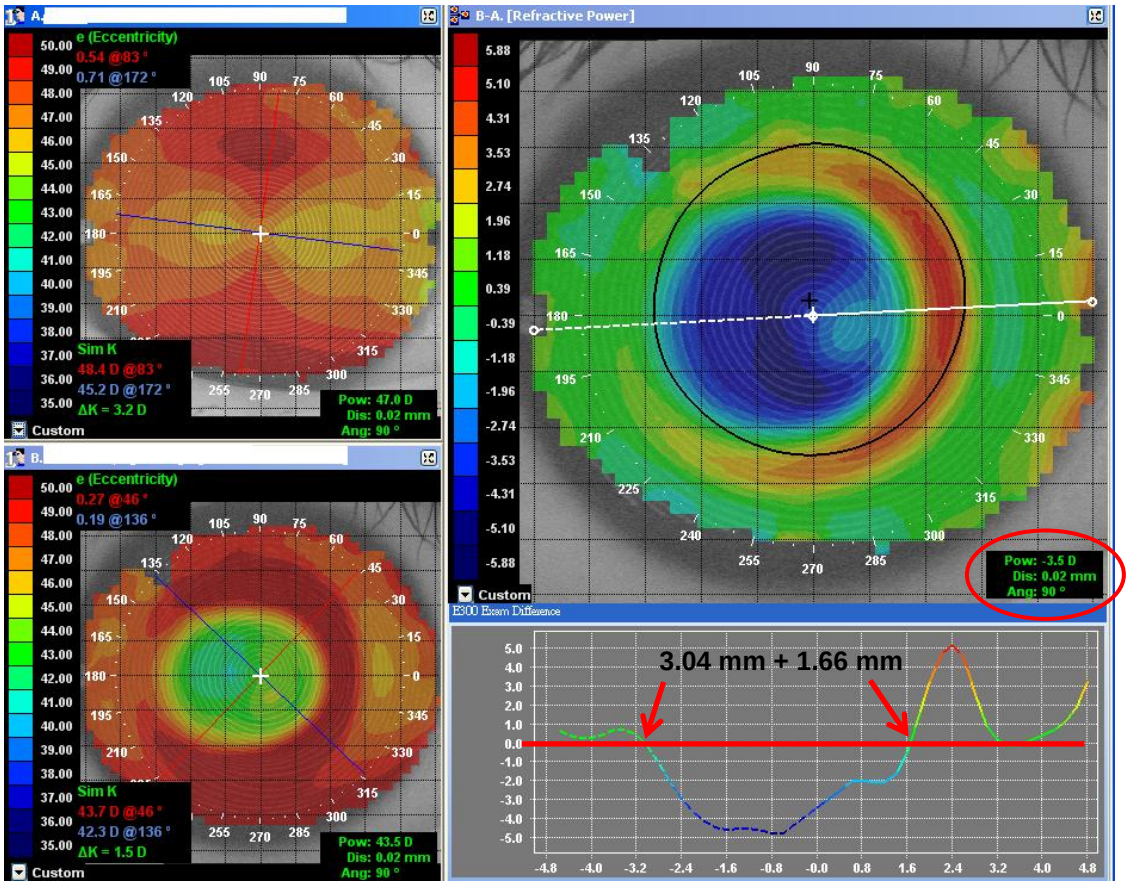


Figure 1.10 Refractive subtractive map showing a 4.70 mm treatment zone and 3.50 D change in corneal power after orthokeratology treatment. Graph on the top left is pre-orthokeratology and the bottom left is post-orthokeratology cornea, with the subtractive difference map shown on the right-hand side

1.2.2.4 Fitting methodology

Different methods may be used to determine the RGL parameters to order for an eye, including trial lens fitting, empirical fitting, and each fitting method has its own advantages and disadvantages.

1.2.2.4.1 Trial lens fitting

Based on the topographical data of an eye, a trial lens is selected from a trial lens set provided by the manufacturer. Simulated K values (flat), taking into account the amount of myopic reduction desired, is used to determine the BOZR. The corneal e-value is used to decide the AC or tangent angle selection. The total lens diameter is based on the horizontal visible iris diameter (HVID). Trial lens fitting is commonly used by practitioners because it allows practitioners to evaluate initial lens performance and patients can experience the feeling of the lenses in their eyes. However, the disadvantages of trial lens fitting method are a longer chair time and the need to store and maintain a large set of trial lenses in the practices.

1.2.2.4.2 Empirical and computer-assisted fitting

Practitioners may also order ortho-k lenses by sending the corneal topographical data to the laboratory and the lens parameters will be determined by the lab (Mountford et al., 2004a). Some contact lens manufacturers provide computer software to assist practitioners to

determine lens parameters required for the desired effect (Mountford et al., 2004a). Both empirical and computer-assisted fitting eliminate the need for trial lens fitting and reduce chair time. If the lens fitting is unsuitable due to a poor lens centration or poor corneal response, practitioners can consult with the manufacturer and lens parameters will be revised based on the topographical results.

For computer-assisted fitting, pertinent data, including the manifest refractive error, the horizontal visible iris diameter (HVID) and corneal topographical maps are required for the computer program to calculate the initial lens parameters for the eye. The software calculates the BOZR according to the refractive power (target reduction) and simulated K reading. HVID is used to determine the lens diameter (about 90% of the HVID) and the software also determines the tangent angle and the lens height based on the corneal topography. If an ordered lens produces an undesirable response (Mountford, 1997a) e.g. central island, lateral displacement, smiley face and frowny face (Figure1.4 to Figure 1.7) after one night of lens wear, a new lens can be ordered for the eye using the software to revise the lens parameters.

The advantage of this method is that the practitioner does not need to keep a large number of trial lenses, which would require storage space, and time and effort for regular maintenance. Also, this is ideal for

practitioners who are concerned about cross-contamination or transmission of prion disease from trial lenses (Boost and Cho, 2005). However, the disadvantage of this method is that the patient will not have any prior experience of lenses in the eyes before lens ordering.

1.3 Clinical efficacy of modern orthokeratology

With the availability of corneal topographers and the introduction of better lens materials and RGL designs, modern ortho-k can now achieve a significant amount of myopic reduction within a relatively short period of time, compared to traditional ortho-k and is increasing in popularity (Mountford, 1997b; Nichols et al., 2000; Rah et al., 2002b; Alharbi and Swarbrick, 2003; Soni et al., 2003; Koffler and Smith, 2004; Sorbara et al., 2005; Kakita et al., 2011; Cho and Cheung, 2012). Studies have shown that subjects could achieve a maximum reduction of myopia within three weeks of lens wear (Mountford, 1997b). Studies on the clinical efficacy of myopic reduction with modern ortho-k are summarized in Table 1.9.

1.3.1 Myopic reduction

Many studies have shown modern overnight ortho-k to be effective in reducing myopia up to 4.00 D (Nichols et al., 2000; Rah et al., 2002b; Cheung and Cho, 2004). Mountford (1997b) reported a mean ± SD myopia reduction of 2.19 ± 0.80 D after one month of overnight ortho-k lens wear in 60 subjects (mean ± SD age 28 ± 12 years).

Table 1.9 List of overnight orthokeratology studies using reverse geometry lenses for myopic reduction *(Adapted from Ben Chan's thesis)*

Studies (year)	Lens	Dk	Duration of study (months)	Number of subjects	Initial age (years)	Baseline myopia (mean±SD) (D)	Myopic reduction at the end of the study (mean±SD) (D)	Final unaided vision (mean±SD)
Mountford (1997a)	Contex OK	-	1	60	28.0±12.0	-2.19±0.79[a]	2.19±0.57	-
Nichols et al. (2000)	Contex OK	-	2	8	25.9±3.9	-1.84±0.81[b]	1.830±1.23	-0.03±0.16 logMAR
Rah et al. (2002a)	Fargo 6 Paragon CRT	-	3	31	-	-2.14±0.98 (RE)[a] -2.16±1.00 (LE)[b]	2.08±1.11 (RE) 2.16±1.05 (LE)	R: 74% 6/6 L: 61% 6/6
Alharbi & Swarbrick (2003)	BE	$100x10^{-11}$	3	18	22-29	-2.63±0.67[a]	2.63±0.57	-
Cho et al. (2003)	Contex OK	-	1-12	69	5-46	-3.93±2.30[a]	-	-
Joslin et al. (2003)	Paragon CRT	$100x10^{-11}$	1	9	34±10	-3.33±1.26[a]	3.08±0.93	-0.07±0.18 logMAR
Soni et al. (2003)	Contex OK	-	3	8	21-43	-1.76±0.70[b]	2.12	Mean -0.13 logMAR; 100% 6/6 or better
Tahhan et al. (2003)	Rinehart & Reeves, BE, DreimLens, Contex	-	1	46	30-37	-2.24±0.77 (RE)[a] -2.25±0.81 (LE)[b]	2.00±0.34	+0.02±0.14 logMAR
Hiraoka et al. (2004)	Emerald	$85x10^{-11}$	12	31	10-44	-2.49±1.11[a]	2.40	-0.07±0.10 logMAR
Koffler & Smith (2004)	Paragon CRT	$100x10^{-11}$	4-13	16 (31 eyes)	14-55	Initial -1.00 to -3.00[a] Initial -3.25 to -6.00[a] Initial Rx over -6.00[a]	1.50±0.80 2.90±0.60 5.80±1.80	100% 20/40 55% 20/20
Owen et al. (2004)	BE/ABE	$100x10^{-11}$	1	20	17-37	-2.28±0.84[a]	-0.01±0.60	-

[a] spherical power; [b] Spherical equivalent refraction

Studies (year)	Lens	Dk	Duration of study (months)	Number of subjects	Initial age (years)	Baseline myopia (mean±SD) (D)	Myopic reduction at the end of the study (mean±SD) (D)	Final unaided vision (mean±SD)
Berntsen et al. (2005)	Paragon CRT	$100x10^{-11}$	1	20	12-37	-3.11±0.96[b]	3.33±0.77	-
Maldonado-Codina et al. (2005)	BE; No.7	$100x10^{-11}$	7 days	9	28±10	BE: -2.22±0.63[a] No.7: -2.40±0.59[a]	BE: 2.89 No.7: 2.23	BE: -0.04±0.10 No.7: +0.06±0.15 logMAR
Sorbara et al. (2005)	Paragon CRT	$100x10^{-11}$	1	23	25.8±6.9	-3.00±1.03[b]	2.59±0.77	83% ≤ 6/6
Cho et al. (2005)	-	-	-	35	9.6±1.5	-2.27±1.09	2.09±1.34	-
Lu et al. (2007)	Paragon CRT	$100x10^{-11}$	28 days	23	26.1±7.6	-3.00±0.22[b]	-0.40±0.16	-
Cheung et al. (2007)	-	-	-	31	18.3±7.6	3.45±1.39	-0.32±0.37 (better eye) -0.55±0.48 (worse eye)	0.00±0.11 (better eye) 0.13±0.14 (worse eye)
Chan et al. (2008)	-	-	≥ 6	27	6-15	-3.56±1.49	-0.09±0.53 (residual)	0.12 logMAR
Kobayashi et al. (2008)	BE	$100x10^{-11}$	12	15	27.3±5.0	-2.54±0.97[b]	-0.95±0.96	-
Lipson et al. (2008)	Paragon CRT	-	51	396	17.7±13.2	-3.40±1.50[b]	-0.20±0.40	R & L: +0.08±0.10 Both: +0.03±0.07 logMAR
Kakita et al. (2011)	Emerald	$100x10^{-11}$	24	42 (84 eyes)	12.0±2.6	-2.55±1.82	-0.68±1.02 (residual myopia)	
Cheung and Cho (2012)	Z Night	$163x10^{-11}$	24	78	9.23±1.06 (ortho-k, n=37) 9.39±1.00 (control, n=41)	-2.05±0.72 (ortho-k) 2.23±0.84 (control)	-	0.02±0.10 (ortho-k)

[a] spherical power; [b] Spherical equivalent refraction

Nichols et al. (2000) conducted a prospective clinical study on overnight ortho-k. They reported a mean ± SD myopic reduction of 1.83 ± 1.23 D for eight subjects with residual subjective refraction of -0.02 ± 0.81 at day 60 of lens wear. Rah et al. (2002b) conducted a pilot study of overnight orthokeratology, described as: preliminary results of the Lenses and Overnight Orthokeratology (LOOK) study to evaluate the success and safety of ortho-k treatment. Sixty subjects were monitored for three months. Only 31 subjects completed the three-month visit and a mean ± SD myopic reduction of 2.08 ± 1.11 D in the right eye and 2.16 ± 1.05 D in the left eye was reported. In 2005, Cho and co-workers (2005a) published the first longitudinal ortho-k results on children in Hong Kong. They found a mean ± SD myopic reduction in spherical equivalent refraction (SER) of 2.09 ± 1.34 D with residual SER of -0.18 ± 0.69 D at the end of the two-year study. Berntsen et al. (2005) reported a mean ± SD myopic reduction of 3.33 ± 0.96 D in their 20 subjects (mean ± SD age 27 ± 5 years) after one month of lens wear.

Chan and colleagues (2008) reported a mean ± SD myopic reduction from -3.88 ± 1.27 D at baseline to -0.26 ± 0.83 D after one month of lens wear. Chen et al. (2010) reported a mean ± SD myopic reduction from -2.95 ± 0.88 D at baseline to -0.23 ± 0.63 D after one month of lens wear in 28 subjects (mean ± SD age 23.1 ± 2.9 years).

The discrepancy on the amount of myopic reduction between different studies may due to the differences in subject criteria though most of subjects had baseline myopia of less than 4.00 D. The average myopic reduction was about 3.00 D in previous reports (Joslin et al., 2003; Koffler and Smith, 2004; Berntsen et al., 2005; Lipson, 2008; Kakita et al., 2011). Only one study reported a myopic reduction of 7.00 D and only in one subject (Koffler and Smith, 2004).

In all overnight ortho-k studies reported, the refractive errors could be reduced and UVA improved rapidly with lens wear. Maximum target reduction required 1 - 3 weeks depending on the brand of lens used and the individual cornea (Cheung and Cho, 2004; Walline et al., 2004b; Cho et al., 2005a; Johnson et al., 2007; Kang et al., 2007; Chan et al., 2008; Stillitano et al., 2008).

1.3.2 Astigmatic reduction

As mentioned in Section 1.1, the most common problem with spherical ortho-k lenses on patients with a significant amount of corneal astigmatism is poor lens centration which can lead to induced astigmatism and poor vision (Mountford and Pesudovs, 2002; Chan et al., 2008). Clinically, corneal toricity greater than 1.50 D (WTR) is regarded as unsuitable for spherical ortho-k although some authors (Mountford and Pesudovs, 2002)

have reported a limited correction of astigmatism using spherical ortho-k lenses.

Mountford and Pesudovs (2002) conducted a retrospective study using power vector analysis to examine both the amount and direction of astigmatic change after ortho-k treatment.
Pre-ortho-k corneal astigmatism between 0.50 to 2.00 D of 23 subjects was analyzed using two different vector analysis methods. Bailey and Carney (1970) and Alpins method (Alpins, 1997) reported a 50% reduction in WTR corneal astigmatism of not more than 1.50 D with a spherical design ortho-k lens if only the central 2-mm chord was considered.

Other clinical studies have reported no significant changes in both refractive and corneal astigmatism using spherical ortho-k (Rah et al., 2002b; Soni et al., 2003; Tahhan et al., 2003; Koffler and Smith, 2004; Sorbara et al., 2005; Cheung et al., 2009). A few studies have reported increased astigmatism after using spherical ortho-k lenses (Hiraoka et al., 2004c; Hiraoka et al., 2006). Because of the inability of spherical design ortho-k lenses to reduce astigmatism, these lenses are limited to subjects with low to moderate corneal astigmatism under 1.50 D (Walline et al., 2004b; Sorbara et al., 2005). High corneal toricity (above 1.50 D) is considered to be a contraindication for spherical design ortho-k treatment.

Toric design ortho-k lenses have been developed to improve lens centration as well as for astigmatic correction (Baertschi, 2005; Beerten et al., 2005; Paune et al., 2012). However, reports on toric designs are scarce and mainly include case reports (Chan et al., 2009), and conference abstracts. One retrospective study on 102 subjects using toric periphery RGL reported an 82.5% successful fitting rate (Baertschi, 2005), whilst another reported that toric peripheral RGL can correct astigmatism up 3.50 D and can be used for the correction of against-the-rule astigmatism (Beerten et al., 2005). No information on the subjects in these studies was available. Recently, Paune and colleagues (2012) conducted a retrospective study using a double tear reservoir toric RGL and reported a mean ± SD astigmatic reduction of -1.80 ± 1.06 D, a change of 85% from the initial astigmatism in 32 patients (26 - 35 years old). To date, no toric ortho-k lenses have been used in studies on myopic control.

1.3.3 Vision improvement

Several clinical studies have reported the effect of ortho-k on vision. Post ortho-k UVA reported by different clinical studies on overnight ortho-k were good as most of the subjects could achieve good UVA. The improvement in UVA was dependent on the reduction of myopia and the pre-ortho-k myopia in most of these studies was less than 4.00 D (Joslin et al., 2003; Tahhan et al., 2003; Koffler and Smith, 2004; Berntsen et al., 2005; Wang et al., 2005; Cheung et al., 2007). A list of more recent overnight ortho-k

studies is presented in Table 1.9.

A clinical study of 60 subjects was conducted by Rah et al. (2002b) who reported that 74% and 61% of the right and left eyes respectively were able to achieve UVA of 20/20 after three months of lens wear.
Tahhan et al. (2003) investigated four different brands of ortho-k lenses, including Contex, DriemLens, BE, and Reinhart and Reeves, and compared the vision outcome . After one month of lens wear, the numbers of subjects (18-35 years old) wearing lenses of each design were 18, 13, 16, and 45, respectively. They reported no significant differences in UVA between lens types and the mean ± SD logMAR UVA in each group was -0.07 ± 0.07, -0.09 ± 0.05, -0.10 ± 0.08, and -0.07 ± 0.07, respectively. Koffler and Smith (2004) conducteda clinical study among 14 subjects (14-55 years old) using the CRT lenses for one month and the result showed that all subjects achieved a UVA of 20/40 or better and 55% subjects achieved a UVA of 20/20 . Walline et al. (2004b) conducted a pilot study using the same lens design as Koffler et al. (2004) on 29 children (8 - 11 years old) and they reported a mean ± SD logMAR UVA of 0.08 ± 0.15 after six months of ortho-k treatment. Johnson and colleagues (2007) investigated a group of subjects with myopia less than 3.00 D and fitted BE ortho-k lenses for eight nights. They reported a mean improvement of in logMAR UVA from 0.24 ± 0.31 at day one to -0.09 ± 0.07 at day eight. Cheung et al. (2007) conducted a retrospective study on 31 subjects (7 - 35

years old) and reported a mean ± SD logMAR UVA of 0.00 ± 0.11 and 0.13 ± 0.14 in the better and worse eye, respectively. In 2008, Chan and colleagues (2008) conducted a prospective study in Hong Kong and reported a mean decimal UVA of 0.73 ± 0.28 (0.12 logMAR) at the 6-month visit among 29 patients (6 - 15 years old). Recently, Cho and Cheung (2012) reported a randomized and longitudinal myopic control study on children aged seven to 10 years old. They reported a mean ± SD logMAR UVA of 0.02 ± 0.10 on 37 subjects (mean ± SD age 9.23 ±1.06 years) in the ortho-k group.

1.4 Myopic control with orthokeratology

Myopia is due to excessive eyeball elongation and it is well established that the higher the myopia, the longer the axial length (AL) of the eye ball (Figure 1.11) (Adams, 1987; Grosvenor, 1988; Lam and Goh, 1991; Grosvenor and Scott, 1993; Lin et al., 1996). Elongation of AL in high myopia can lead to serious complications such as retinal degeneration, retinal detachment, and glaucoma (Perkins, 1960; Burton, 1989; McCarty et al., 1999; Saw et al., 2005b) . Myopia is a common refractive problem, especially in East Asia where the prevalence of myopia can be as high as 50% to 68.6% among 12 year-old children (Lin et al., 1995; Lin et al., 2001; Fan et al., 2004a; Lam et al., 2012). In the United States, Sperduto and colleagues (1983) reported that the prevalence of myopia was 25% in subjects aged 12 to 54 years old between 1971 and 1972. Vitale et al. (2009) conducted a vision examination

on participants aged 12 years old and older in 1999 to 2004.

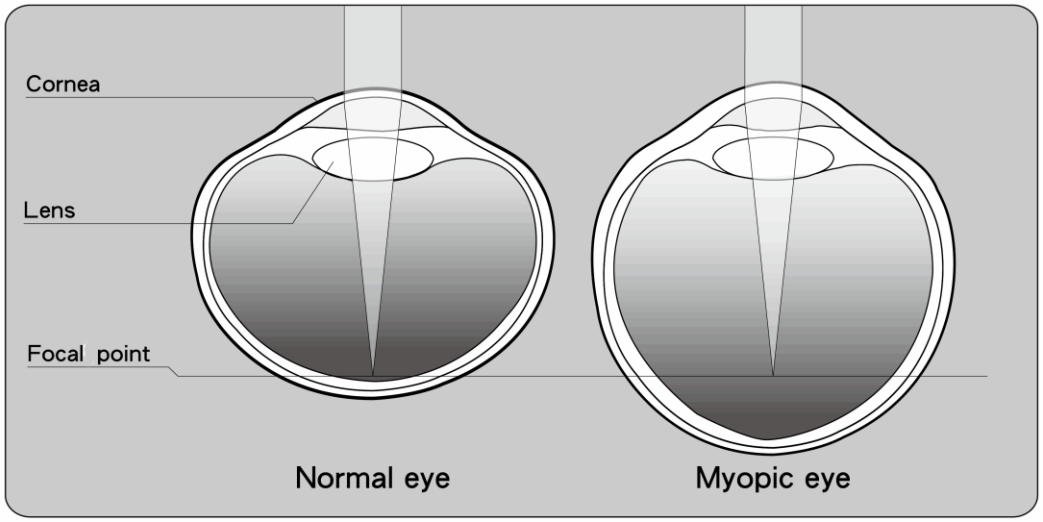


Figure 1.11 The myopic eye shows longer axial length of the eye ball

They reported that the prevalence of myopia among 615 participants of ages 20 to 39, 40 to 59 and 60 or more was 50.2%, 50.1%, and 26.5%, respectively. The prevalence of myopia was higher than the 25% reported in the previous two studies in the United State (Sperduto et al., 1983; Kempen et al., 2004) and the prevalence was similar to that of 40 year-old or older Asian populations in Singapore (Wong et al., 2000). They reported that the prevalence of myopia might be over-estimated as their results were based on non-cycloplegic refraction using the autorefractor. Although the mechanism of myopia development is yet to be confirmed, it is generally agreed that myopia is associated with two main factors, environmental and genetic (Garner et al., 1985; Yap et al., 1993; Zadnik et al., 1994; Zadnik and Mutti, 1995; Mutti et al., 2002; Grosvenor, 2003; Shih et al., 2010; Cui et al., 2013; Wu et al., 2013; Yip et al., 2013). Shih et al.

(2010) reported that the average myopic progression in urban areas was greater than that in rural areas in Taiwan. Environmental factors such as urban development and academic grade level may be the main factor to myopic progression. Recently, Cui et al. (2013) reported that with increasing daylight hours, the axial eye growth and myopia progression decreased in 235 children (8 - 14 years). Yap et al. (1993) reported that children with myopic parents are more likely to be myopic. Yip and colleagues (2013) recently reported that the gene mutations may be considered as one of the rare genetic risk factors for high myopia. However, the mechanism of myopia development is still uncertain.

For many years, researchers have investigated various clinical methods for the retardation of myopic progression (Kelly et al., 1975; Oakley and Young, 1975; Goss, 1986; Grosvenor et al., 1989). When choosing treatment options for correcting myopia in children, factors including the efficacy, safety, comfort, and convenience of the methods must be taken into consideration.

Many studies have explored the scope and effectiveness of myopic control treatments (Grosvenor et al., 1987; Horner et al., 1999; Khoo et al., 1999; Leung and Brown, 1999; Chiang et al., 2001; Siatkowski et al., 2004; Walline et al., 2004b; Cho et al., 2005a; Tan et al., 2005; Chua et al., 2006; Siatkowski et al., 2008; Tong et al., 2009; Walline et al., 2009; Kakita et al.,

2011; Cho and Cheung, 2012). For many years it was widely believed that atropine control myopic progression by paralysing accommodation but the findings from a number of animal studies have refuted this belief. Although yet to be confirmed, recent findings favour a retinal based mechanism via muscarinic receptor signalling (McBrien et al., 1993). However, complications such as cycloplegia, photophobia, near-vision problems and some systemic difficulties have been reported with the use of these drugs (Tan et al., 2005; Chua et al., 2006; Siatkowski et al., 2008). Hence, in spite of the success, clinicians are reluctant to subject children to a long term application of these ocular drugs (Brodstein et al., 1984).

Although some studies have reported a positive effect of different optical interventions, such as bifocal and progressive addition lenses (Oakley and Young, 1975; Khoo et al., 1999; Leung and Brown, 1999), most of these studies suffered from serious limitations such as a small sample size, non cycloplegic refraction, no masking, no AL measurements or no randomization. Subsequent studies using more stringent methodologies have failed to show significant myopic control (Edwards et al., 2002; Gwiazda et al., 2003). Several studies have reported on the use of rigid contact lenses for myopic control (Grosvenor et al., 1989; Andreo, 1990; Perrigin et al., 1990; Horner et al., 1999; Khoo et al., 1999; Katz et al., 2003; Walline et al., 2004a).

Grosvenor et al. (1989) recruited 100 subjects (8 - 13 years) and fitted them with Paraperm O2 plus silicone-acrylate contact lenses for three years. At the end of two years, 60 subjects remained. They reported that the mean increase in AL during the 2-year with conventional RGP lenses was 0.1 mm for regular wearers (n = 53), and 0.4 mm for the irregular wearers (n = 7). A group of age-matched subjects (n = 31) wore single vision spectacles and AL was increased by 0.6 mm in this group. Perrigin et al. (1990) recruited 100 subjects (8 - 13 years old) and fitted them with Paraperm O2 plus silicone-arcylate contact lenses. They reported the mean ± SD myopic increase was 0.48 ± 0.70 D among the remaining 56 subjects (mean age 11.7 ± 1.2 years) after three years of Paraperm O2 plus silicone-acrylate contact lens wear compared with 20 subjects (mean age 11.2 ± 1.2 years), with an initial refractive error match, wearing spectacles, In whom the progression of myopia was 1.53 ± 0.81 D. Khoo and colleagues (1999) also reported that the progression of myopia was slower in children who wore RGP lenses compared to those who wore single vision spectacles. The mean increase in AL per year for the RGP lens wearers was 0.22 mm, while for the spectacle wearers, it was 0.31 mm.

Katz et al. (2003) conducted a randomized clinical trial study on 564 subjects aged six to 12 years old. The subjects were randomized to wear RGP lenses (n = 281) on spectacles (n = 283) for two years. At the 2-year visit, there were 105 subjects and 192 subjects remaining in RGP lens and

spectacles groups, respectively. They reported that RGP lens wear did not slow myopic progression. The mean ± SD AL increases were 0.84 ± 0.47 mm and 0.79 ± 0.45 mm after 2 years in the RGP lens and spectacles groups, respectively.

Walline and colleagues (2004a) conducted the first randomized clinical trial in the United States to examine the effects of rigid contact lenses on myopic progression among young children. Children enrolled in their study (8 - 11 years old) were randomly assigned to wear RGP and soft contact lenses (SCL). They found no significant difference in AL between the groups over the 3-year study period.

Although some studies (Grosvenor et al., 1989; Perrigin et al., 1990) have shown a positive effect of myopic control used SCL, the limitations of these studies include an inadequate control group, no AL measurement and incomplete data on the control subjects. However, randomized studies (Katz et al., 2003; Walline et al., 2004a) have shown no statistically significant differences in the rate of myopic progression between a rigid contact lens group and the group using single vision spectacles.
In recent years, new SCL designs have been introduced for myopic control. Antice and Phillips (2011) conducted a randomized study on 40 children aged between 11 and 14 years. The treatment eyes (n = 20 eyes) wore Dual-Focus (DF) SCL and the control eyes (n = 20 eyes) single

vision distance (conventional design) SCL for 10 months (period one) and the two eyes swapped lens types and lenses were worn for a further 10 months (period two). The DF SCL design consists of a central correction zone and correction zones encompassing a series of treatment and correction zones. They reported that the increase in AL was less in eyes wearing the DF SCL (0.11 ± 0.09 mm) compared to those wearing single vision SCL (0.22 ± 0.10 mm). The AL elongation was reduced by 49% in eyes wearing DF SCL in the first 10 months (period one) and the eyes wearing DF SCL also showed significantly less increase in AL than the eyes wearing single vision SCL in period two.

When overnight ortho-k was introduced, it quickly gained popularity as a potential for myopic control in children, especially in East Asia (Reim et al., 2003; Cheung et al., 2004; Cho et al., 2005a; Jacobson, 2005). A number of studies on the use of ortho-k for myopic control have been reported. Results from previous studies confirm that ortho-k lenses have the potential to slow the myopic progression in children (Reim et al., 2003; Cheung et al., 2004; Cho et al., 2005a; Walline et al., 2009; Kakita et al., 2011; Cho and Cheung, 2012).

Cho and colleagues (2005a) conducted a pilot study on 35 children (7 - 12 years old), with SER of -0.25 D to -4.50 D, astigmatism less than -2.00 D. These children were fitted with overnight ortho-k lenses; AL was measured using A-scan ultrasound and their AL were compared to those

of a historical group of controls (wearing single vision glasses) matched for age and the initial amount of myopia. They reported that AL increased by 0.29 ± 0.27 mm and 0.54 ± 0.27 mm in children wearing ortho-k lenses and in the control group after two years of monitoring. Walline et al. (2009) recruited 40 subjects (8 - 11 years old) and fitted them with ortho-k lenses and they reported similar findings, a mean increase in AL after two years was 0.25 ± 0.27 mm in the ortho-k group and 0.57 ± 0.27 mm in the control group. Their control subjects were age-matched SCL wearers from a previous myopic control study (Walline et al., 2004a).

Kakita et al. (2011) recruited 105 subjects (45 and 60 in the ortho-k and control groups, respectively) and 92 subjects (42 and 50 in the ortho-k and control groups, respectively) completed the 2-year follow-up examinations. The ortho-k subjects wore four-zone RGL lenses and the control subjects wore single vision spectacles. They reported an increase in AL of 0.39 ± 0.27 mm and 0.61 ± 0.24 mm, in the ortho-k and control groups respectively during the 2-year study period.

Hiraoka et al. (2012) conducted a 5-year myopic control study on 43 subjects (22 and 21 in the OK and control groups, respectively) (mean ± SD age 10.4 ± 1.43 and 9.95 ± 1.59 in the ortho-k and control groups, respectively). Significant differences in the annual increase in AL between ortho-k and control groups were found in the first, second and third year of monitoring, but no significant differences in the fourth and fifth years.

During the 5-year study period, the increase in AL in the ortho-k group was 0.19 ± 0.09 mm (first year), 0.26 ± 0.13 mm (second year), 0.19 ± 0.15 mm (third year), 0.18 ± 0.17 mm (fourth year), and 0.16 ± 0.13 mm (fifth year), respectively. The increase in AL in the control group was 0.38 ± 0.20 mm (first year), 0.33 ± 0.18 mm (second year), 0.29 ± 0.16 mm (third year), 0.24 ± 0.18 mm (fourth year), and 0.17 ± 0.14 mm (fifth year), respectively.

Swarbrick et al. (2010) conducted a study on 14 subjects aged between 10 to 17 years with a baseline AL of 24.96 ± 1.00 mm and 24.97 ± 0.95 mm in the ortho-k and RGP lens wearing eyes, respectively. The subjects wore an ortho-k lens in one eye and an RGP lens in the other eye during daytime for a period of six months and then the lenses were swapped over to the other eye after six months. They reported that the AL elongation was increased significantly by 0.06 ± 0.09 mm in the RGP eye with no significant change (-0.02 ± 0.08 mm) in the ortho-k eye. During the second six months period, AL was increased by 0.11 ± 0.11 mm in the RGP eye with no significant change in the ortho-k eye (-0.02 ± 0.12 mm).

Cho and Cheung (2012) published the first long term randomized study on ortho-k for myopic control. In their study, 37 and 41 subjects completed the study. Subjects were aged six to 10 years and had myopia between 0.50 to 4.00 D and astigmatism not more than 1.25 D. They were assigned

to an ortho-k group and a control group (single vision glasses). They reported that AL increased by 0.36 ± 0.24 mm and 0.63 ± 0.26 mm in subjects wearing ortho-k lenses and single vision glasses respectively after two years of study. They concluded that subjects wearing ortho-k lenses had a slower increase in AL by 43% compared to subjects wearing single-vision spectacles. Their study confirmed the effectiveness of ortho-k for myopic control in children aged six to 10 years old.

All these published studies used spherical design ortho-k lenses and subjects' refractive errors were restricted to low-moderate myopia (usually not more than 5.00D) and with-the-rule astigmatism (not more than 1.50D). With the availability of toric ortho-k lenses which, in principle, can give better lens centration and hence better myopic reduction results, a myopic control study using toric ortho-k lenses for children with higher astigmatism is warranted.

1.5 Changes in corneal biomechanics in orthokeratology

Clinical measurement of corneal biomechanics in vivo can be difficult due to the complicated calculations required. These difficulties have meant that few studies have reported work on corneal biomechanics in the past. It is well recognized that, due to its elastic properties, the cornea, could return to its original shape after cessation of ortho-k lens wear (Polse et al., 1983b). Polse et al. (1983b) was perhaps the first report the corneal

biomechanical properties in traditional ortho-k treatment. Carkeet et al., (1995) investigated the correlation between ocular rigidity and the efficacy of ortho-k in nine subjects (mean ± SD age 33.7 ± 11.2 years) but did not find any relationship. In their study, they used the Friedenwald's formula to calculate the elastic properties of whole eyeball instead of corneal biomechanics (Carkeet et al., 1995).

1.5.1 Corneal biomechanics

Corneal biomechanics includes parameters such as central corneal thickness, corneal viscosity, elasticity, hydration and regional corneal thickness (Liu and Roberts, 2005). A device that can measure the corneal biomechanical response of the cornea is now available (Luce, 2005).

1.5.1.1 Corneal hysteresis (CH) and corneal resistance factor (CRF)

The Ocular Response Analyzer (ORA, Reichert Inc., US) is a non-contact tonometer which provides in vivo measurements of corneal biomechanical properties in terms of corneal hysteresis (CH) and corneal resistance factor (CRF) and their correlation with intraocular pressure (IOP) (Luce, 2005). Figure 1.10 shows an image from the ORA presenting the two applanation pressure readings. When the non-contact probe releases an air pulse onto the cornea, a double peak graph is generated as shown in Figure 1.12. The reading may be accepted or rejected based on the recommendation of the manufacturer. The two peaks shown in the graph are caused by the optical

signal received during the inward and outward applanation phases of the cornea. Three coloured curves are depicted on the graph. The strength of the air pulse applanating on the cornea is represented by the green curve while the raw signal of the applanation detection system is represented by the red curve shows. A filtered version of the red curve, designed to determine the “optimum point of applanation” in less than ideal signals, is represented by the blue curve. The applanation pressures are determined by dropping a vertical line from the peaks of the blue curve to the green pressure curve and these points are indicated by the blue squares and are termed as P1 and P2 as shown in Figure 1.12. The difference (P1 – P2) is defined as CH. CRF is derived from the same two data points as the CH and calculated from the formula P1 - (k * P2), where k is a constant. It is suggested that CRF can represent overall cornea resistance (Luce, 2005). The higher the differences between P1 and P2 readings, the higher the CH and CRF values.

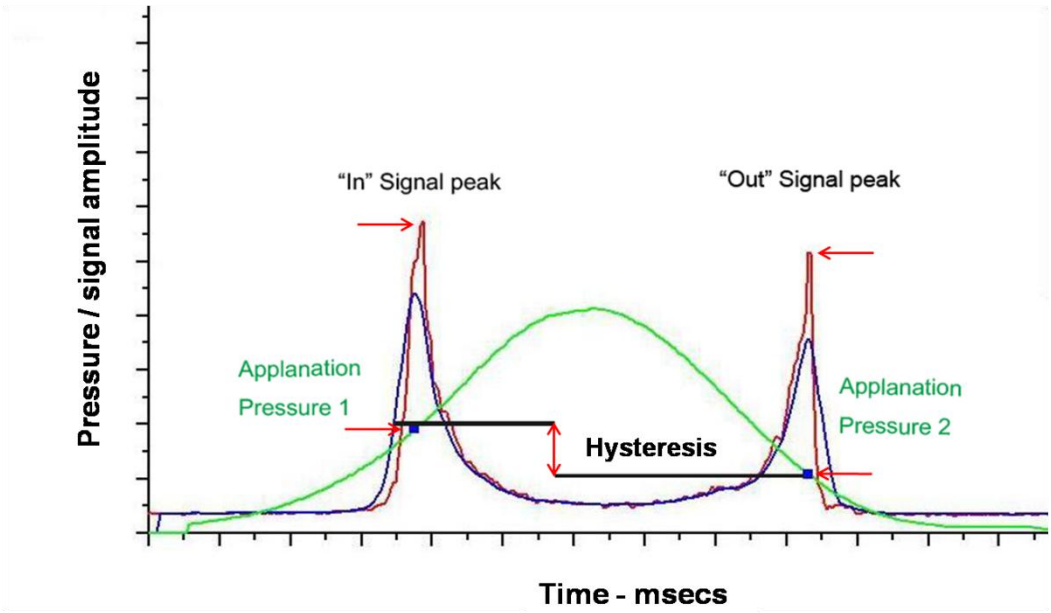


Figure 1.12 Ocular response analyzer process signals. The double-peak featured graph (suggested by manufacturer) and description of corneal hysteresis are shown on the graph (manually illustrated by the author)

Use of ORA is becoming increasingly popular in corneal biomechanics studies because of its ease of use and rapid measurements. Many recent studies have investigated CH and CRF in adult subjects (Kotecha et al., 2006; Kida et al., 2008), CT (Kida et al., 2006; Kotecha et al., 2006; Shah et al., 2006; Lam et al., 2007; Lu et al., 2007b; Kida et al., 2008; Abitbol et al., 2010), and the relationship between CH and CRF and AL (Lim et al., 2008; Shen et al., 2008; Wells et al., 2008; Avetisov et al., 2009). In addition, changes in CH and CRF with contact lens wear (Lu et al., 2007b; Gonzalez-Meijome et al., 2008; Chen et al., 2009) and after refractive surgery (Luce, 2005; Ortiz et al., 2007; Kirwan and O'Keefe, 2008; Shah and Laiquzzaman, 2009; Shah et al., 2009) have also been reported. Other studies also investigated corneal biomechanics changes in pathological

ocular status such as in patients with keratoconus (Ortiz et al., 2007; Shah et al., 2007; Mollan et al., 2008; Goldich et al., 2009; Schweitzer et al., 2010; Wolffsohn et al., 2012), glaucoma (Kotecha et al., 2009; Mangouritsas et al., 2009; Abitbol et al., 2010), and Fuchs' dystrophy (Luce, 2005) (Table 1.10).

Gonzalez-Meijome et al. (2008) evaluated the correlation between corneal biomechanics properties in terms of CH and CRF and the changes in keratometry readings after the short-term ortho-k effect. They reported on eight subjects (mean ± SD age 21.9 ± 1.1 years) who were targeted for a 4.00 D reduction with ortho-k. Corneas with higher CH have a slower rate of corneal response in short-term ortho-k treatment ($P < 0.05$). Chen and colleagues (2009) conducted a pilot study on corneal biomechanical changes in short-term ortho-k treatment. They recruited 20 subjects (mean ± SD age 24.1 ± 2.6 years) with baseline SER of -2.74 ± 0.85 D and -2.73 ± 1.03 D in the right and left eyes, respectively.

Table 1.10 Summary [mean±SD] of age, corneal hysteresis (CH) and corneal resistance factor (CRF) reported in published studies

Studies	Age (years) (range)	CH (mmHg)	CRF (mmHg)
Abitbol et al., 2010	61.4±10.9 (45-85)	10.46±1.6	--
Franco and Lira, 2009	--	10.8±1.53	10.6±1.71
Chen et al., 2009	(19-30)	11.1±1.0	10.7±1.3
Song et al., 2008	14.7±0.8	10.7±1.5	--
Lim et al., 2008	14.0±0.9	11.8±1.6	11.9±1.7
Kirwan et al., 2008	35.0±8.1	9.6±1.5	9.4±1.6
Shah et al., 2007	62.1±18.1 (18-87)	10.7±2.0	--
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., 2007	19.7±1.1	11.5±1.4	9.6±1.9
Lam and Chen, 2007	(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	10.3±2.0
Kirwan et al., 2006	(4-18)	12.5±1.4	--
Luce, 2005	28.0 (23-38)	9.6	--

They reported that CH did not show any change with short-term (15, 30, and 60 minutes and overnight) ortho-k lens wear, while CRF showed a reduction with increasing duration of lens wear. Glavine's (2009) conducted a study on the relationship between corneal characteristics and ortho-k treatment. They recruited 41 subjects (mean age 24 years) with baseline myopia of the right eye and left eye of -2.96 and -2.91 D, respectively. They reported a significant decrease in CRF after 3-week of ortho-k lens wear. However, in Glavine's study (2009), different results were obtained from the two eyes. Only the right eyes showed a significant decrease in CRF at the 1-week and 3-week visit. To date, there is no

report of changes in corneal biomechanics with long-term ortho-k treatment and the relationship between corneal biomechanics and ortho-k effect is yet to be determined.

1.5.1.2 Corneal thickness

In 1998, Swarbrick et al. (1998) investigated CT changes in six subjects (21 - 27 years old) wearing OK-74 ortho-k lenses (Contex Inc., Sherman Oaks, CA) of high Dk material (AirPerm; Dk = 88) for 28 days. They used the Payor-Holden optical micropachometer to measure CT and reported central epithelium thinning of mean ± SD 7.1 ± 7.1 μm and mid-peripheral corneal thickening of 13.0 ± 11.1 μm. Nichols et al. (2000) confirmed occurrence of central corneal thinning of 12 ± 11 μm, measured with the Orbscan Slit-Scan corneal topographer/Pachometry system analyzer (Orbtek, Salt Lake City, UT) on eight subjects (mean ± SD age 25.9 ± 3.9 years) who had worn ortho-k lenses for two months. Alharbi and Swarbrick (2003), using the Payor-Holden optical micropachometer to measure CT also reported a mean ± SD of 15.8 ± 3.3 μm central epithelium thinning after one-month of overnight ortho-k lens wear in 18 adult subjects and no significant changes in central stromal thickness. Haque et al. (2004) and Wang et al. (2003) also reported central corneal thinning of 7.3% and 5.1%, respectively, but they did not specify if the thinning was restricted to the epithelium.

Choo et al. (2004) reported compression and thickening of epithelium cells

at different corneal regions with ortho-k lens wear on cats. Their report provided evidence of redistribution of the anterior corneal tissues in ortho-k treatment. In 2007, Stillitano et al. (2007) reported CCT changes from 527.84 ± 27.09 μm at baseline to 531 ± 28.93 μm and 530.12 ± 24.24 μm after one and eight nights of ortho-k lens wear, respectively in 14 subjects (mean ± SD age 30 ± 8.43 years). No significant changes were observed in central and nasal corneal thicknesses between baseline and 1-overnight, baseline and eight nights, 1-overnight and eight nights of ortho-k lens wear. Reinstein et al. (2009) published a case report (22 year-old male) who displayed central epithelium thinning of 14 μm (right eye) and 18 μm (left eye) and mid-peripheral epithelium thickening of 6 μm (right eye) and 16 μm (left eye) after 30 days of ortho-k lens wear. Choo et al. (2008) conducted a pilot animal study on cats and observed central epithelial thinning and mid-peripheral epithelial thickening in the myopia corrected eye and central stroma thickness of the myopic eye was thinner relative to the hyperopic eye after 14 days of continuous ortho-k lens wear.

Read and Collins (2009) reported a small but significant diurnal thinning on CCT among 15 subjects (mean age 22 years) with no contact lens wear. Chen et al. (2011) reported significant corneal thinning at the corneal apex in 20 subjects (mean ± SD age 24.1 ± 2.6 years). CT decreased from 575.6 ± 29.5 μm at baseline to 563.2 ± 28.3 μm after 6 months of ortho-k lens wear. Gonzalez-Perez et al. (2012) reported a

mean ± SD of 22.25 ± 12.13 μm central corneal thinning in 32 subjects (mean ± SD age 27 ± 7.4 years) after 12-month of ortho-k lens wear.

1.5.1.3 Treatment zone size

Munnerlyn's formula is used for calculating the depth of corneal ablation for photorefractive surgery to produce a certain refractive error change over a defined ablation zone diameter. It assumes that the posterior surface is unaffected during refractive surgery and the change in the anterior corneal curvature can be related to the change in sagittal of the front surface (Munnerlyn et al., 1988; Owens et al., 2004). The formula can be expressed as $t = -S^2x\ D/8(n - 1)$, where t is ablation depth, S is ablation diameter (both inmeters), and D is the desired refractive change in diopters. A refractive index n for the cornea of 1.377 is usually assumed. Swarbrick et al. (1998) and Alharbi and Swarbrick (2003) suggested that changes in corneal thickness can explain the refractive changes induced by ortho-k treatment. They used Munnerlyn's formula (1988) to calculate the expected change in refractive error based on measured changes in corneal thickness or corneal sagittal height in ortho-k treatment (Figure 1.13). To apply this formula in ortho-k, t was taken as the change in corneal sagittal height or change in corneal thickness (epithelial thinning), S was taken as the ortho-k treatment zone diameter, and the equation will resolve D, the refractive change predicted solely on the basis of corneal thickness changes.

Table 1.11 Treatment zone diameter reported in published studies

Studies	Age (years) (range, mean±SD)	Duration of lens wear	Lenses used and treatment zone diameter (mm)	Subtractive map used
Tahhan et al. 2003	20-37 (27±4)	1 month	Contex: 4.9±0.6 [a] DreimLens: 5.1±0.7 [a] BE: 5.7±0.7 [a] R&R: 5.0±0.9 [a]	Axial difference map
Sridharan and Swarbrick, 2003	18-35	8 hours	BE: 5.59±0.83	NA
Owen et al. 2004	17-37	4 weeks	BE: 4.66±0.56 (vertical meridian)	NA
Lu et al. 2007	19-51 (26.1±7.6)	4 weeks	CRT: 3.61±0.07	Tangential difference map

[a] subjects wore the Rinehart Reeves (R&R) lens in one random eye and either a Contex, DreimLens, or BE lens in the contralateral eye. (Contex: Contex Laboratories, Sherman Oaks, CA, USA; DreimLens: DreimLens, Melbourne, Florida; BE: Ultravision Capricornia, QLD, Australia; R&R: Danker Laboratories, Sarasota, FL; CRT: Paragon Vision Sciences, mesa, AZ, USA)

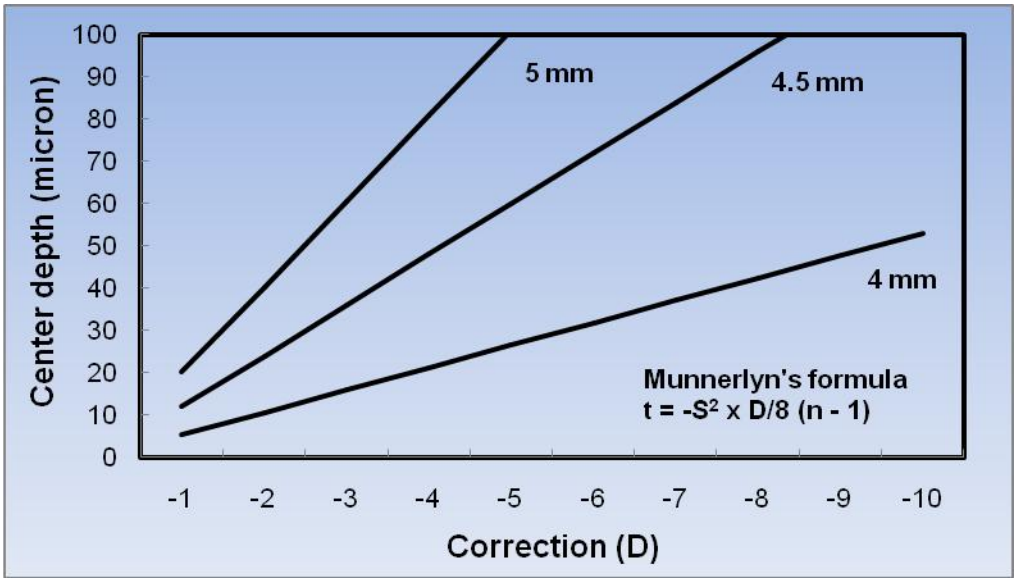


Figure 1.13 Munnerlyn's formula to calculate the expected change in refractive error based on measured changes in corneal thickness or corneal sagittal height. The ablation has to be deeper or the treatment zone has to be smaller for larger amounts of myopic correction

The concept of treatment zone (TxZ) is important in corneal refractive surgery (Munnerlyn et al., 1988; Chang et al., 2003; Macsai et al., 2004) and ortho-k treatment (Alharbi and Swarbrick, 2003) as the success of the treatment may be associated with the treatment area. Only a few studies have reported the TxZ diameter in ortho-k lens wear (Sridharan and Swarbrick, 2003; Tahhan et al., 2003; Owens et al., 2004; Lu et al., 2007a) (Table 1.11). It is unclear how Tahhan et al. (2002) and Owens et al. (2004) defined TxZ diameter in their studies. Sridharan and Swarbrick (2003) defined the TxZ diameter as the horizontal distance from inner edge to inner edge of the “zero diopter change” zone inside the ring of mid-peripheral steepening on the difference map. Lu et al. (2007a) defined TxZ diameteras the change in corneal curvature from negative to positive (ideally zero) along the horizontal meridian through the center of the central flattened zone (CFZ), using the tangential difference map. Sridharan and Swarbrick (2003) reported a TxZ diameter of 3.86 ± 0.88 mm after 10 minutes of lens wear and 5.59 ± 0.83 mm after eight hours of open eye ortho-k lens wear in nine young adult subjects. Tahhan et al. (2003) recruited 60 subjects (mean ± SD age 27 ± 4 years) and reported TxZ diameters ranging from 4.9 ± 0.6 mm to 5.7 ± 0.7 mm after 1-month of ortho-k lens wear using four different types of lenses. They reported no correlation between the TxZ and the visual acuity measurements. The TxZ diameters in the eyes wearing BE lenses were significantly larger than those in the eyes wearing both DreimLens and R&R lenses after

1-overnight of lens wear and also larger than those in the eyes wearing both Contex and R&R lenses at 1-month visit (Table 1.11). Owen et al. (2004) reported that an increasing TxZ diameter was apparent over time, from 3.32 ± 1.08 mm after 1-overnight to 4.66 ± 0.56 mm (vertical meridian) after 4-weeks lens wear in 19 young myopic subjects (17 - 37 years old). They reported that the TxZ diameter was difficult to measure after 1-overnight of lens wear because of the frequently undefined edge of the TxZ. Lu et al. (2007a) recruited 23 myopic subjects (mean ± SD age 26.1 ± 7.6 years) to wear ortho-k lenses for 28 days. They reported that the CFZ diameter increased from 3.41 ± 0.09 mm to 3.61 ± 0.07 mm after 1-overnight and 28 days of ortho-k lens wear, respectively. They reported that TxZ diameter was associated with the residual refractive error, aberrations, subjective vision, higher order aberrations, and spherical aberration. However, CFZ diameter was not associated with both high and low contrast VA and coma and the larger the CFZ, the lower the residual refractive error in the 4-week study.

1.5.1.4 Anterior and posterior corneal curvature changes

With modern ortho-k lens wear, anterior corneal curvatures can change rapidly within 10 minutes (Sridharan and Swarbrick, 2003). The cornea reshapes during lens wear overnight and the ortho-k effect can usually be sustained for at least eight hours after lens removal in the morning, after stabilization of ortho-k treatment (Cheung et al., 2007; Chan et al., 2008).

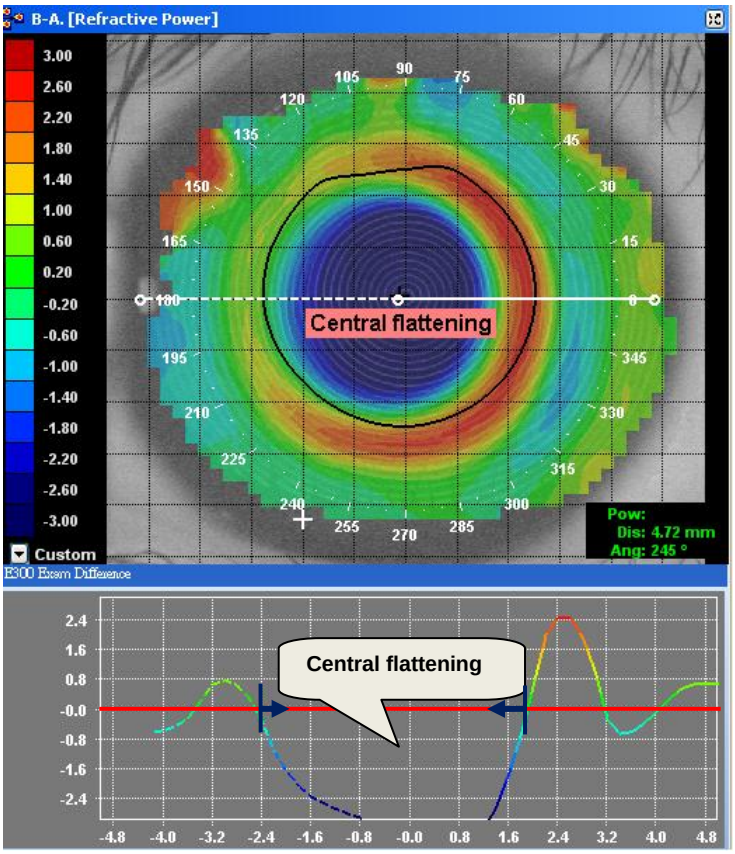


Figure 1.14 Central flattening of the corneal curvature after orthokeratology treatment

Myopic reduction in ortho-k treatment is mainly due to the flattening of the anterior corneal curvature to redirect the image to the retina (Alharbi et al., 2005; Cho et al., 2005a; Jayakumar and Swarbrick, 2005; Kang et al., 2007; Chan et al., 2008; Stillitano et al., 2008) (Figure 1.14).

Some researchers however, have suggested that the posterior corneal curvatures also contribute to the myopic reduction (Owens et al., 2004). The first investigation of posterior corneal curvature changes in ortho-k treatment was conducted by Owens et al. (2004). In their study, they

recruited 19 subjects (17 - 37 years old) and all subjects were fitted with Ultravision's BE/ABE (Ultravision Pty, Ltd, Brisbane, Australia) RGL and wore the lenses for one month. They reported flattening of the posterior corneal curvatures at the one week visit after commencing ortho-k treatment. The measurements were made in the morning within two hours after lens removal. Although the posterior corneal curvatures were significantly different at the one week visit, the difference became less with additional lens wear. However, subsequent studies have reported no effect of ortho-k lens wear on the posterior corneal curvatures in short (e.g. one week) and longer (e.g.one year) of ortho-k treatment. Stillitano et al. (2007) recruited 14 myopic subjects (mean ± SD age 31 ± 8.43 years) and fitted them with BE ortho-k lenses (Ultravision Pty, Ltd, Brisbane, Australia). They found no significant changes in the posterior corneal curvatures after one week of ortho-k lens wear. Tsukiyama et al. (2008) also reported no significant changes in the posterior corneal curvatures. In their study, nine subjects (mean ± SD age 29.6 ± 3.8 years) were recruited and wore the lenses for one year. Read and Collins (2009) investigated the diurnal variation of the posterior corneal curvatures using Scheimpflug image-based corneal topography. They recruited 15 subjects (mean age 22 years) who were non-contact lens wearers. The measurements included six sessions over 24 hours (Session 1 at 9:40 AM to Session 6 at 9:20 AM). In Session five, the subjects were asked to sit for five minutes with their eye closed before the measurement to minimize postural

variations. They reported steepening of the posterior corneal curvatures immediately after sleep and the curvatures returned to their original values two to three hours after waking up (Read and Collins, 2009). More studies are needed to confirm posterior corneal curvature changes with modern ortho-k treatment. Chen et al. (2010) investigated the changes in posterior corneal curvatures in 28 subjects of (mean age 23.1 ± 3.0 years) and reported steepening of the posterior corneal curvatures after the 1-overnight lens wear. However, these curvatures steepened immediately after lens removal and flattened two hours after lens removal after 6 months of lens wear. The posterior corneal curvatures were similar to the baseline value after cessation of lens wear at the follow up visits including one week, two weeks, one month, and two months.

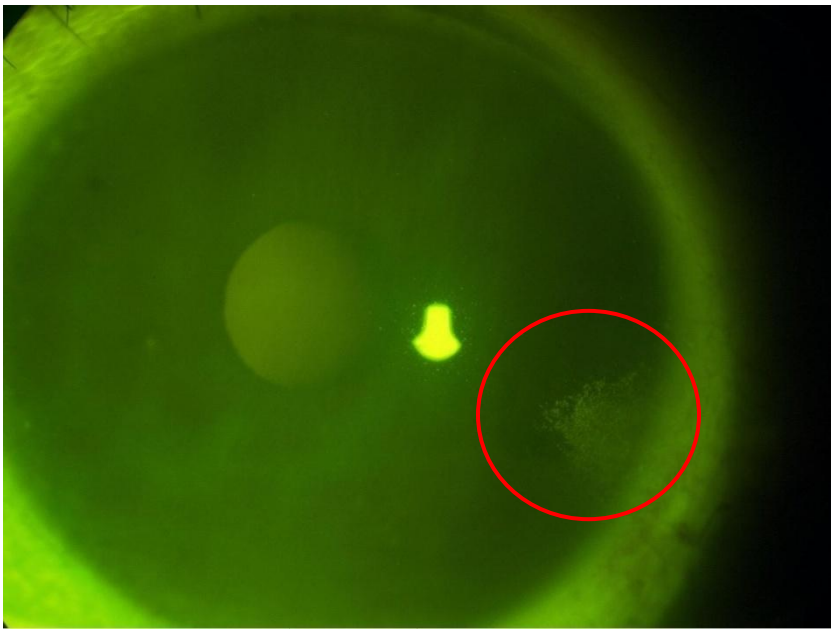


Figure 1.15 Temporal corneal staining (red circle) observed after orthokeratology lens wear

1.5.2 Corneal staining

Corneal staining is one of the most common complications in ortho-k lens wear (Fan et al., 1999; Cho et al., 2002a; Chui and Cho, 2003; Cheung and Cho, 2004; Walline et al., 2004b; Mika et al., 2007; Chan et al., 2008; Lipson, 2008) (Figure 1.15). Most staining reported was in the early stages of the treatment and the incidence of staining decreased with duration of ortho-k treatment (Cho et al., 2003a; Walline et al., 2004b; Mika et al., 2007; Chan et al., 2008; Lipson, 2008; Chan et al., 2012).

Fan et al. (1999) reported that corneal staining occurred in 45% of eyes after wearing ortho-k lens for six months in 54 young adolescents (11 - 15 years old). Staining was observed mainly in subjects with tear problems. Cho et al. (2003a) reported that the incidence of corneal staining was not related to refractive error and UVA or the age of their subjects. They also reported that the increase in incidence of corneal staining could be related to increase with incorrect lens removal of a bound lens. Walline and colleagues (2004b) monitored 23 subjects (mean ± SD age 10.3 ± 1.0 years) over a period of six months. All subjects were fitted with CRT contact lenses of HDS-100 material (Paragon Vision Sciences). Over 50% of the subjects showed corneal staining in the morning aftercare visits but only about 35% showed corneal staining in the afternoon visits. Most subjects displayed punctate staining. Of this punctate staining, 77.8% was presenting the central cornea atthe morning visit whereas 47.5% central

and 45% inferior cornea staining was present at the afternoon visit. The mean severity was grade 1.6 in the morning, which reduced to grade 1.3 in the afternoon. The staining was graded from 1.0 (trace) to 4.0 (severe) in 0.5 steps, based on their clinical guidelines and was not correlated with a standardized grading scale.

Cheung and Cho (2004) conducted a cross-sectional study among 30 subjects (8 - 19 years) who underwent ortho-k treatment for over 12 months. At the morning visit, they reported only two subjects with central corneal staining and seven subjects showing peripheral punctuate staining. Chan and colleagues (2008) conducted a prospective study to review and analyse the ortho-k effects in a university clinic in Hong Kong. Corneal staining was observed in 41% (44 out of 108) patients (6 - 15 years old) after the 1-overnight of lens wear. Of this, 74% was in the central cornea, but most of the staining was not clinically significant. The staining rate decreased to 25% at the 6-month visit.

Lipson (2008) conducted a retrospective study on 296 subjects (mean ± SD age 17.7 ± 13.2 years) who were on ortho-k treatment for 21.6 ± 18.1 months. Among the 282 subjects with available baseline to one-month results, they reported that corneal staining was observed in 32% (90/282) of the subjects after the 1-overnight ortho-k lens wear. The incidence of staining dropped to 16% and 5.3% at the one-week and one-month visits

respectively. Corneal staining was most frequently observed in the central cornea (26.6% after the 1-overnight, 2.1% after one month of lens wear). In the study, younger children (aged ≤ 12 years) also showed more staining than older (aged >12 years) children. However, none of the corneal staining observed was of clinical significance and the visual acuity was not affected by the staining at any visit. They also reported that corneal staining was not significantly different from the previous reports on soft lens wearers (daily-wear) and that younger children showed a trend towards more frequent staining than older children.

1.5.3 Lens binding

Lens binding is a commonly seen complication in ortho-k lens wear and lens binding has been reported in 41% to 83% of subjects in different studies (Cho et al., 2003a; Chui and Cho, 2003; Tahhan et al., 2003; Cheung and Cho, 2004; Chan et al., 2008). Cheung and Cho (2004) investigated the subjective and objective characteristics of 30 subjects (8 - 19 years old) who had been wearing ortho-k lenses for more than 12 months. They reported that lens binding (73%) was the most common problem/symptom experienced by these subjects. Forcefully removing a bound lens can cause serious complications to the cornea especially if the patients used a suction holder to aid removal. Boost and Cho (2005) have shown the suction holder to be the most heavily contaminated item used by ortho-k patients, most probably due to improper care. Increased

corneal staining from lens handling and inappropriate removal may lead to increased risk of corneal infection. It is therefore important for ortho-k patients to learn how to remove their lenses safely, without the use of a suction holder (Cho et al., 2008). Chan et al. (2008) conducted a retrospective study on 108 subjects (6 - 15 years old). They reported that lens binding (44%) was the most frequently reported problem during the ortho-k treatment period.

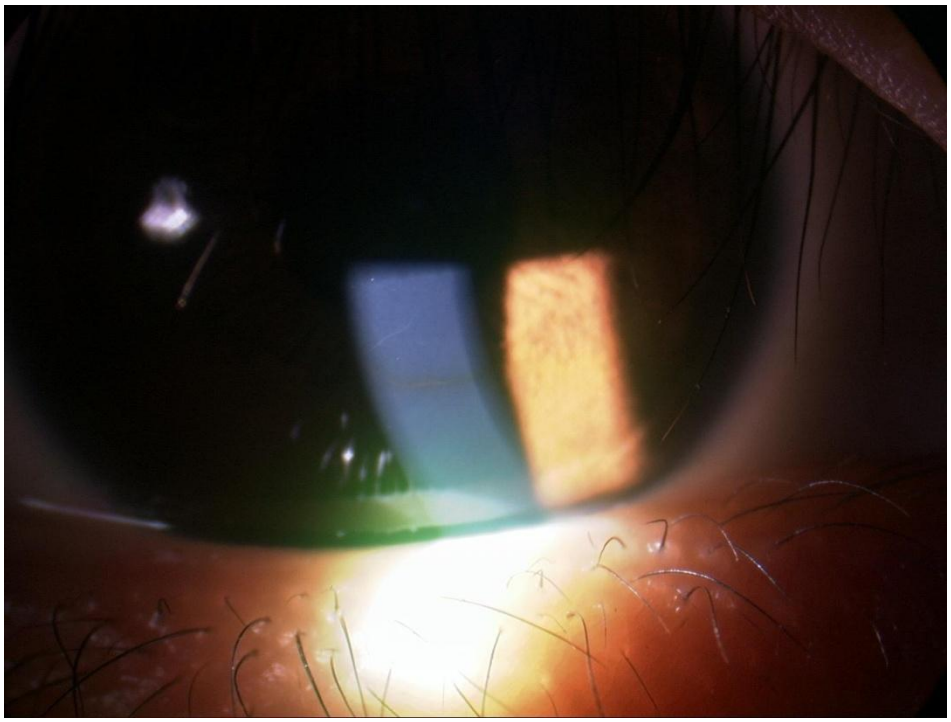


Figure 1.16 Corneal pigmented arc observed after six months of orthokeratology lens wear

1.5.4 Corneal pigmentation arc

Corneal pigmentation has been reported to be associated with overnight ortho-k lens wear (Cho et al., 2002b; Rah et al., 2002b; Liang et al., 2003; Hiraoka et al., 2004b; Cho et al., 2005b). Cho et al. (2005b) monitored 35 subjects (9 - 35 years old) who had undergone ortho-k treatment for over 12 months. The incidences of a corneal pigmented arc in the left (right) eyes were 17% (27%), 49% (49%) and 90% (93%) after three, six and 12 months lens wear, respectively (Cho et al., 2005b). The arc appeared in the mid-peripheral cornea which coincided with the tear reservoir in the reverse curve of RGL lensand the appearance is similar to Fleischer's ring observed in keratoconic patients (Figure 1.16). The pigmented arc is presumed to be iron deposition at the basal epithelial layer of the cornea and is apparently related to the period of lens wear. It may not appear at the same time in both eyes even when the target reductions in the two eyes are the same (Cho et al., 2005b). The reason for development of the pigmented arc is still unknown, but it has been proposed that arc formation may be due to the drastic curvature changes in the mid peripheral cornea due to RGL lens design (Cho et al., 2002b; Rah et al., 2002a; Cho et al., 2005b). It has also been suggested that the arc was due to the accumulation of iron in the epithelium behind the tear reservoir (reverse curve) where turnover of the epithelial cells is minimal (Rah et al., 2002a; Barr et al., 2003). The pigmented arc has been shown to be reversible after the cessation of lens wear. Cho and colleagues (2003b) reported the

regression of the arc in two patients within two-months after cessation of ortho-k lens wear.

1.6 Conclusion

The prevalence of myopia is high, particularly in East Asia (e.g. Hong Kong, China, Taiwan, Japan, Korea) (Lam and Goh, 1991; Zhao et al., 2000; Lin et al., 2001; Zhao et al., 2002; Lam et al., 2004; Lin et al., 2004; Lam et al., 2012). However, an increase in the prevalence of myopia is also being observed in the United States and elsewhere. Hence, there is an increased interest to find an effective treatment for slowing myopic progression. The prevalence of myopia is increasing and many children whose myopia increases over the year end up with high myopia as an adult. There are risks associated with high myopia. High myopia can lead to serious complications such as cataracts, retina detachment or other serious ocular problems. Modern ortho-k has been shown to be effective in correcting myopia in children with low to moderate myopia. Although most of studies demonstrated a certain degree of corneal complications using ortho-k lens, but most of these complications did not result in any impact on vision. A recent randomized clinical trial has confirmed that ortho-k can slow myopic progression in children (Cho and Cheung, 2012). However, published myopic control studies only recruited children with low-moderate (<1.50D) astigmatism. Since most myopic children are also

astigmatic and spherical ortho-k lenses tend to decentre on toric corneas which may lead to poor lens centration and hence ortho-k effects. A toric design ortho-k lenses would be desirable. A few toric design ortho-k lenses have been developed but studies on such lens designs are scarce. There was therefore a need to investigative the effectiveness of a toric design ortho-k for myopic and astigmatic reduction as well as for myopic control in children with moderate to high astigmatism. While a number of studies have published effects of ortho-k on corneal curvatures, staining and thickness, the long-term effect of ortho-k on corneal biomechanics is still unclear.

CHAPTER 2

Aims and study design

2.1 Aims

The objectives of this PhD study were:

1. to determine the clinical performance of a toric design ortho-k lens and the safety of ortho-k lens wear in terms of corneal staining and corneal binding (Chapter 3)
2. to determine the efficacy of ortho-k lenses for myopic and astigmatic reduction and control (Chapter 4)
3. to investigate long-term ortho-k effects on corneal thickness, anterior and posterior corneal curvatures (Chapter 5)
4. to investigate long-term ortho-k effects on corneal biomechanics in terms of corneal hysteresis (CH) and corneal resistance factor (CRF) (Chapter 6)

2.2 Subject recruitment

Subject recruitment was conducted via advertisements in magazines and newspapers, targeting children studying in primary schools.

The study consisted of two parts: Part one was to investigate the efficacy of toric ortho-k lenses for myopic and astigmatic correction and myopic control in children with moderate to high with-the-rule astigmatism. The primary outcomes were improvements in unaided visual acuity, reduction in subjective refraction, and a reduced rate axial elongation. The secondary outcome concerned the incidence of complications in ortho-k lens wear.

Part two of this study was to compare changes in central corneal thickness (CCT), anterior and posterior corneal curvatures, corneal hysteresis (CH), and corneal resistance factor (CRF) in ortho-k and control group subjects to determine if ortho-k affected these parameters.

Recruitment of subjects for the ortho-k group started in April 2008, whereas subjects for the control group were recruited one year later to expand the scope of the study. Subjects in the two groups were matched for age and refractive error. This was a single-mask experiment. Examiner 1 was responsible for lens fitting and most of the measurements of the project except the axial length measurement. To maintain the single-masking in the measurement of axial length, a masked examiner,

examiner 2 was involved in the data collection visits (every six month visit) for axial length measurement only.

2.2.1 Sample size

This study was designed to achieve 80% power to detect a minimum difference 0.18 mm (0.50 D) difference in AL in two years at a 5% level of statistical significance, using the within-group standard deviation of 0.27 mm (Cho et al., 2005a). A sample size of 20 subjects was required for each group. Allowing for 50% dropouts, at least 80 subjects were recruited.

2.2.2 Inclusion and exclusion criteria

All subjects were required to satisfy the inclusion and exclusion criteria (Table 2.1), with myopia 0.50 to 5.00 D (inclusive) and with-the-rule astigmatism of 1.25 to 3.50 D. Only subjects with unremarkable ocular and general health with best-corrected visual acuity (BCVA) of 0.10 logMAR or better in either eye were recruited. All subjects had to be available for follow-up for at least two years.

All procedures followed the Declaration of Helsinki and ethics approval was obtained from the Departmental Research Committee of the School of Optometry of The Hong Kong Polytechnic University prior to commencement of study. Written informed consent was obtained from the

parents of each subject before commencement of the study.

Table 2.1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Age: 6-12 years • Chinese • Myopia: 0.50-5.00 D • With-the-rule astigmatism: 1.25-3.50 D (axis 180±20) (lens design used is recommended for WTR astigmatism only) • Anisometropia: not more than 1.50 D in myopia • Best-corrected monocular visual acuity: equal to or better than 0.10 logMAR • Available for follow-up for at least 2 years	• Strabismus at distance or near • Contraindication for contact lens wear and orthokeratology (e.g. limbus to limbus corneal cylinder, dislocated corneal apex) • Prior experience with the use of soft or rigid lenses (including orthokeratology) or with myopic control • Systemic or ocular conditions which may affect contact lens wear (e.g. allergy and medication) or affect refractive development (e.g. Down syndrome, ptosis)

2.2.3 Subjects

An information sheet (Appendix A1 (English version) and A2 (Chinese version)), a written consent form (Appendix B1 (English version) and B2 (Chinese version)), and a complete disclosure of the effects of the eye drops used were given to each parent after a detailed explanation of the examination procedures.The parents had to sign the consent form on behalf of their child before commencement of the study. A total of 80 eligible subjects (6 - 12 years old) were enrolled. Cycloplegic eye examination was performed at the baseline visit (before the commencement of ortho-k lens wear) and biannually for a period of two

years. Subjects were either assigned to the ortho-k (n = 43) or the control (single-vision spectacles) group (n = 37), without randomization.

There was little data on the performance of toric ortho-k when this study was planned. The success rate (e.g. refractive correction for both spherical and astigmatic components and its safety) of toric ortho-k in children was unknown. At the time, ortho-k lenses were spherical in design and toric ortho-k lenses were only just being introduced in selected markets, with limited or unknown success (e.g. no published reports). Hence conventionally, children with high astigmatism were considered contraindicated for ortho-k. The effectiveness and acceptance of using toric ortho-k treatment for myopic correction was therefore unknown. Considering these issues, we could not plan for a randomized trial.

2.2.3.1 Orthokeratology subjects

Eligible subjects were fitted with toric ortho-k lenses (see Section 2.2.4) and followed up for two years as scheduled (see Section 2.2.3 and Table 2.2). Subjects were required to record their lens insertion and removal times, as well as the occurrence and severity of lens binding in the ortho-k diary provided (Appendix D).

2.2.3.2 Control subjects

Subjects were fitted with single vision spectacles (see Section 2.2.4) and

followed up for two years.

2.2.3.3 Withdrawal of subjects in orthokeratology and control groups

Any subject who presented with significant adverse events or who failed to comply with the prescribed procedures despite reminders was required to withdraw from the study. Upon completion or withdrawal from the study, the prescribed lenses, solutions, and all other accessories provided had to be returned to the examiner.

2.2.4 Data collection visits

All subjects were required to attend the data collection visits (Table 2.8). The following examinations/measurements were conducted at different types of visit.

(a) Non-cycloplegic visits

- subjective refraction
- AVA
- UVA
- ocular health
- corneal topography
- intraocular pressure
- CH and CRF

Table 2.2 Summary of baseline and aftercare visits of orthokeratology subjects

Visit	Time	Duration	Purposes
Baseline	Daytime	Approximately 2.5 to 3 hours	• Obtain informed consent from the parents • Determine if the subject satisfied the inclusion criteria • Explain procedures to the subject and the parents • Baseline study measurements (cycloplegic examination) • Arrange next follow-up visit
1-overnight, 1-week, 1-month, 3-month	Morning	Approximately 1 hour	• Determine the refractive changes and corneal response • If the cornea showed poor response (e.g. Smiley face or central island, residual myopia or astigmatism more than 0.50D), a new lens would be ordered for the eye
6-, 12-, 18-, 24-month	Daytime	Approximately 2 hours	• Same as baseline measurements • If the cornea showed poor refractive changes, a new lens with a higher target would be ordered for the eye where indicated
9-, 15-, 21-month	Daytime	Approximately 1 hour	• Determine refractive changes and corneal response • If the cornea showed poor refractive changes, a new lens with a higher target would be ordered for the eye where indicated
Unscheduled	--	--	• Unscheduled visits would be arranged where necessary or indicated

(b) Cycloplegic visits

- subjective refraction
- AVA
- UVA
- ocular health
- corneal topography
- intraocular pressure
- AL

Table 2.3 Grading scale for lens binding (Chan et al., 2012)

Grade	Definition
0	No binding observed. Lens moving freely
1	Lens bound and loosens up spontaneously after less than five forced blinks
2	Lens bound and loosens up after one episode of pressure on the upper lid, then repeated on the lower lid and less than five forced blinks
3	As Grade 2, but two pressure pushes on the lids and less than five forced blinks
4	As Grade 2, but with three pressure pushes and less than five forced blinks

Table 2.4 Procedures for subjects on how to loosen a bound lens in the morning (Cho et al., 2012b)

1. Wash hands with liquid soap, rinse thoroughly with water, and dry hands with a clean paper towel
2. Instill 1-2 drops of artificial tears into the eye and blink gently before checking, by looking into a mirror to determine, if the lens is on the cornea and is moving on blink
3. If the lens is not moving (bound to the cornea), blink (forcefully) 5 times to try to loosen the lens. If you can feel the lens moving on your cornea if it is mobile. Check, by looking into a mirror, that the lens is still on the cornea and is moving on blink
4. If the lens is still bound to the cornea, look slightly upward. Gently but firmly press the lower eyelid margin against the inferior limbus three times without touching the lens
5. Then look slightly downward. Gently but firmly press the upper eyelid margin against the superior limbus three times without touching the lens
6. Blink forcefully 5 times to try to loosen the lens
7. If the lens is still bound to the cornea, instill 1-2 drops of artificial tears and repeat 4-6 until you can see/feel the lens moving before lens removal
8. Repeat step 7 as necessary

2.2.4.1 Orthokeratology group

Table 2.2 summarizes the baseline and aftercare visit schedule for the subjects in the ortho-k group. After the baseline visit, lens insertion and removal training sessions were arranged. Trial lenses (E&E Optics Ltd., Hong Kong SAR, China) from our clinic, based on the subject's corneal curvature, were selected for practising insertion and removal. Any subject who failed the insertion and removal training (three sessions) was excluded from the study. Table 2.3 shows the grading scale of lens binding given to the subjects. The subjects were required to wear the lenses for eight to 10 hours every night unless instructed otherwise by the examiner. Subjects and parents were informed about possible lens binding and were taught how to remove a bound lens safely (Table 2.4).

After the subject had passed the insertion and removal training, lenses were ordered for subjects based on their ocular parameters and calculated using the NKL Easy Fit software (version VIP 2006, NKL Contactlenzen B.V., Emmen, The Netherlands).

For each ortho-k subject, a delivery visit was arranged after the arrival of the lenses. At this visit, lens fitting in each eye was evaluated and the subject and parents were given written and oral instructions on lens usage and care. The subject was required to return for an aftercare visit after the 1-overnight lens wear with lenses in situ, within two hours after waking up

the next morning. The purpose for subjects to return with their lenses in situ was to allow evaluation of significant lens binding and more accurate assessment of any corneal staining caused by lens binding.

Routine aftercare visits were arranged at one week, one month, and every three months after commencement of lens wear. Unscheduled visits were also arranged where necessary (e.g. poor UVA). Any subject who presented undesirable corneal topographic response was required to stop lens wear and another visit arranged after one week of ceased lens wear to allow the cornea to return to baseline before reordering new lenses (see lens ordering and replacement procedures).

Only subjects who presented with a bull's eye corneal topographic pattern were allowed to continue lens wear. If another corneal response (e.g. central island, smiley face and frowny face) was observed, the subject was required to stop lens wear and lens adjustment was determined using the NKL Easy Fit software (see Section 2.2.4.1a).

2.2.4.1a Z Night Toric RGL fitting technique

Z Night Toric RGL was ordered using the Easy Fit software. Pertinent data, including the manifest refractive error, HVID and one corneal topographic map were required for the computer program to calculate the initial lens parameters for the eye. The Easy Fit software calculates the BOZR

according to the refractive power and simulated keratometry reading (Figure 2.1). If an ordered lens produces an adverse response, such as lens displacement, smiley face, or frowny face topographic pattern after one night of lens wear, a new lens was ordered for the eye using the Easy Fit software, as described in Section 2.2.4.1.

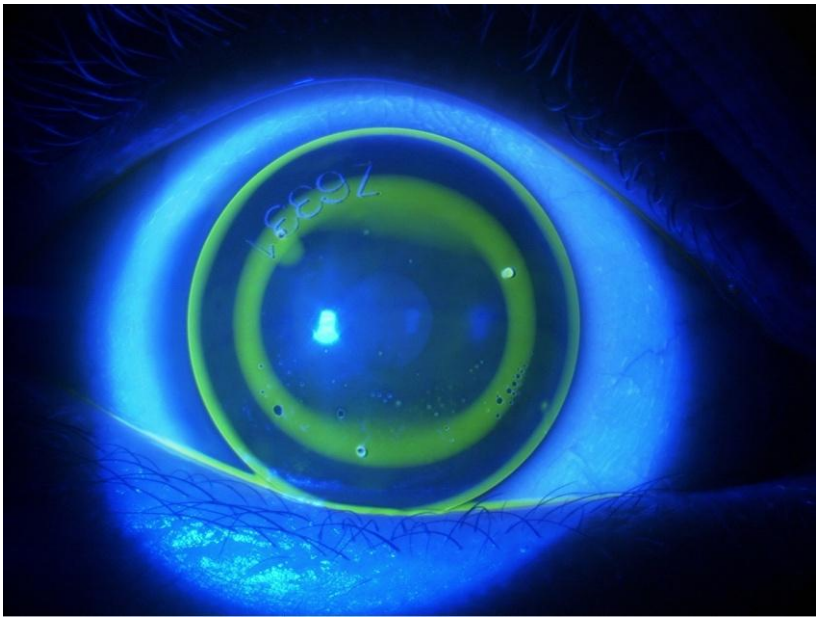


Figure 2.1 Fluorescein pattern of lens fitting at lens delivery visit

Ortho-k lens fitting was first performed by examining the fluorescein pattern was with the lens in situ using the slit lamp. The ideal fluorescein pattern was characterized by a central zone of light touch (3.0 to 3.5 mm diameter), surrounded by a wide deep doughnut-shape tear reservoir, a zone of peripheral light touch, and peripheral clearance, with lens

movement of 1 - 2 mm on blink. Lenses demonstrating the described fluorescein pattern for an acceptable fit were delivered and the subject was instructed to wear them overnight (Figure 2.1). Subjects who could not achieve a satisfactory lens fitting or target reduction, despite repeated modifications of lens parameters (three pairs of lenses) were terminated from the study.

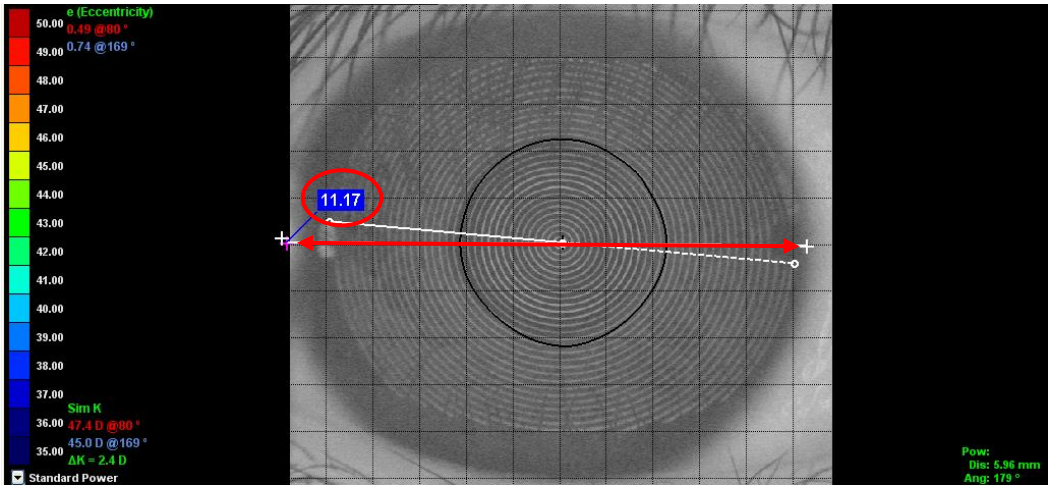


Figure 2.2 The horizontal visible iris diameter (red line) is determined by drawing a line from limbus to limbus passing through the apex

HVID (Horizontal visible iris diameter) (Figure 2.2) was used to determine the lens diameter (about 90% of the HVID) and this software also determines the tangent angle and the lens height based on the corneal topography. For an eye with myopia not more than 4.00 D, the target reduction would be the full amount of myopia. For an eye with myopia of 4.25 to 5.00 D, the first pair of lenses ordered targeted at a 4.00 D reduction. Figure 2.3 shows the lens order diagram and it also shows the

required initial parameters to order for subjects based on their ocular parameters and calculated using the NKL Easy Fit software.

The second pair of lenses would be ordered according to the corneal responses to an ortho-k lens on a cornea and the residual myopic power, up to a maximum of 1.00 D, and a third pair ordered if there was any significant residual myopia left follow use of the second pair (Figure 2.3 (a)).

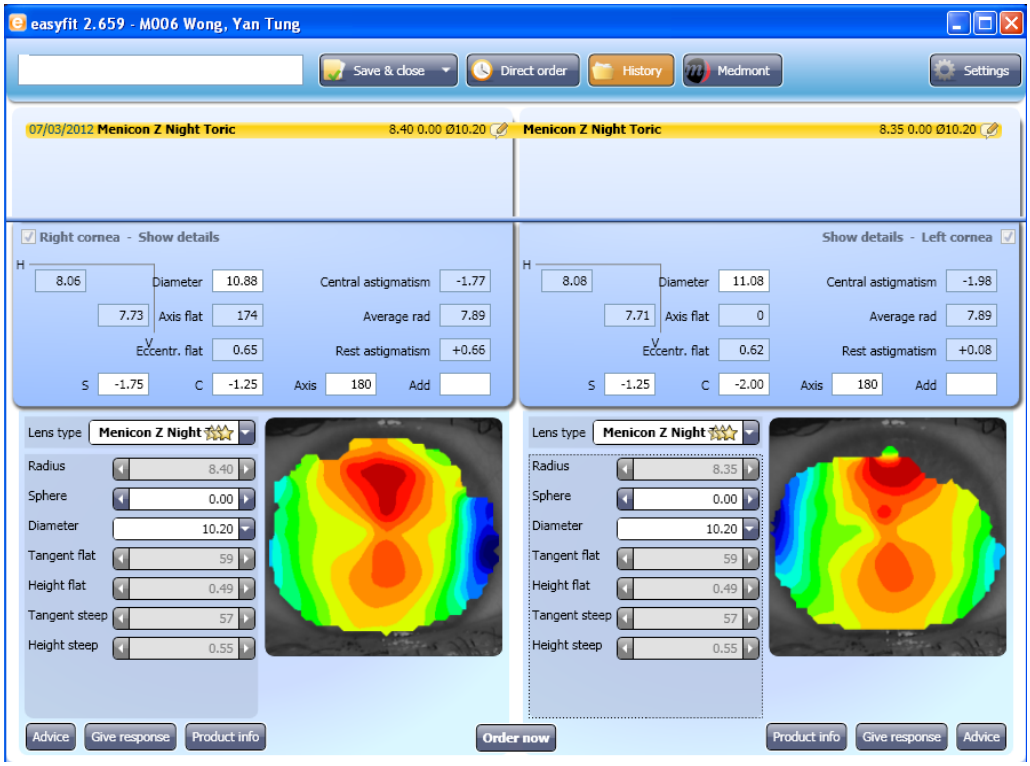


Figure 2.3 Easy Fit software interface showing the required initial parameters to order for the eyes with the information shown. Graph on the left hand side shows the details of right cornea parameters and graph on right had side shows the details of left cornea parameters. The practitioner needs to enter the refractive error and horizontal visible iris diameter. Based on these parameters, a lens will be calculated by the software

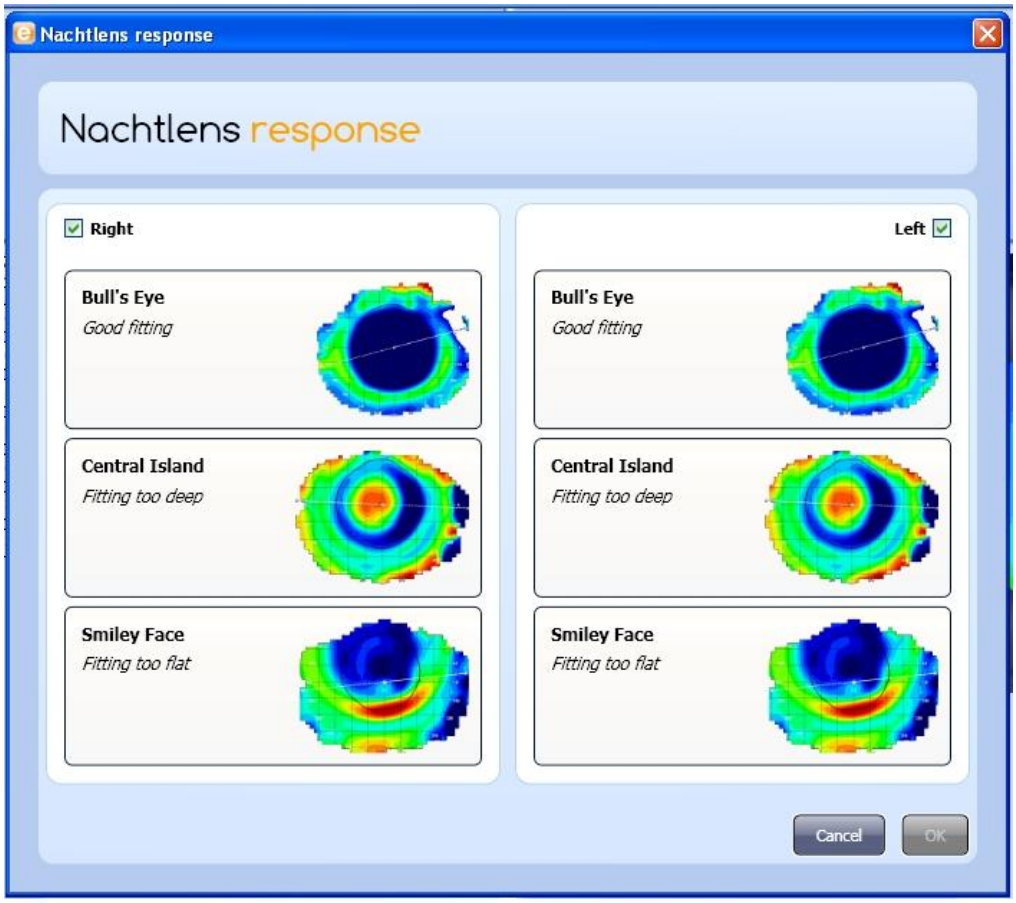


Figure 2.3 (a) Possible corneal responses to an orthokeratology lens on a cornea (printout from NKL's Easy Fit software)

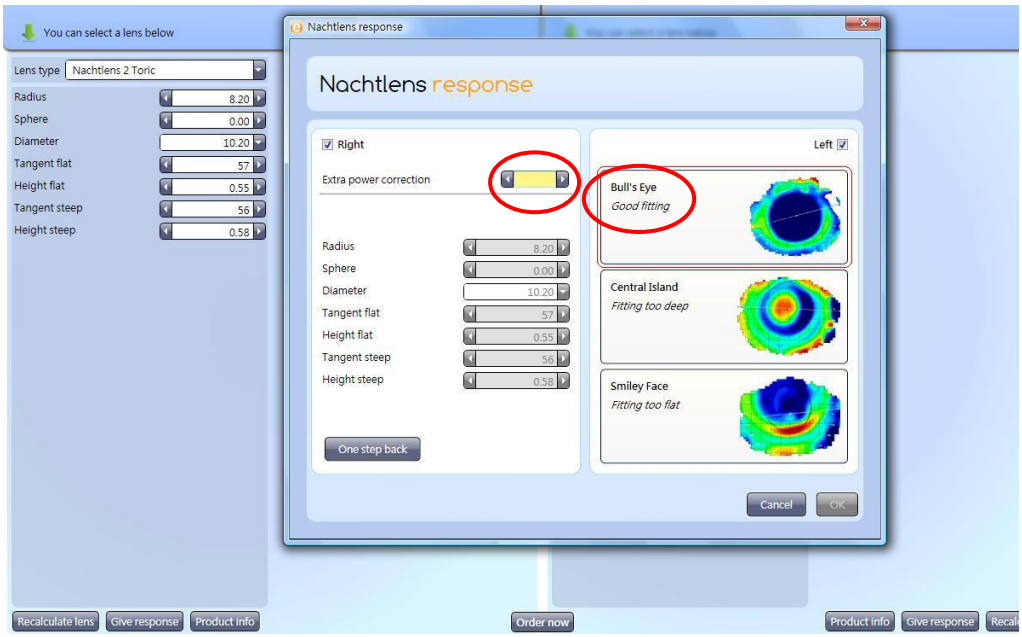


Figure 2.3 (b) Increased lens target by adjusting lens radius using NKL's Easy Fit software (calculation of new lens parameters)

When the post-ortho-k topographic map shows bull's eye pattern, it means an ideal response to the wear of lens and the map shows well-centered area of central flattening. When the target myopic reduction was not achieved by the former lens, new lens with an increased target was attempted to try to achieve a further reduction (Figure 2.3 (b)).

When the post-ortho-k topographic map shows a Central Island, it means the lens fitting is too steep and reorder of the lens is required. Lens adjustment was using the NKL Easy Fit software (Figure 2.3 (c)); decreased lens sagittal height on horizontal and vertical meridian was attempted. As shown in the red circle on Figure 2.3 (c), the height flat and steep of the lens needs to decrease from the values of 0.54 and 0.57 to 0.53 and 0.56 (values suggested by the software).

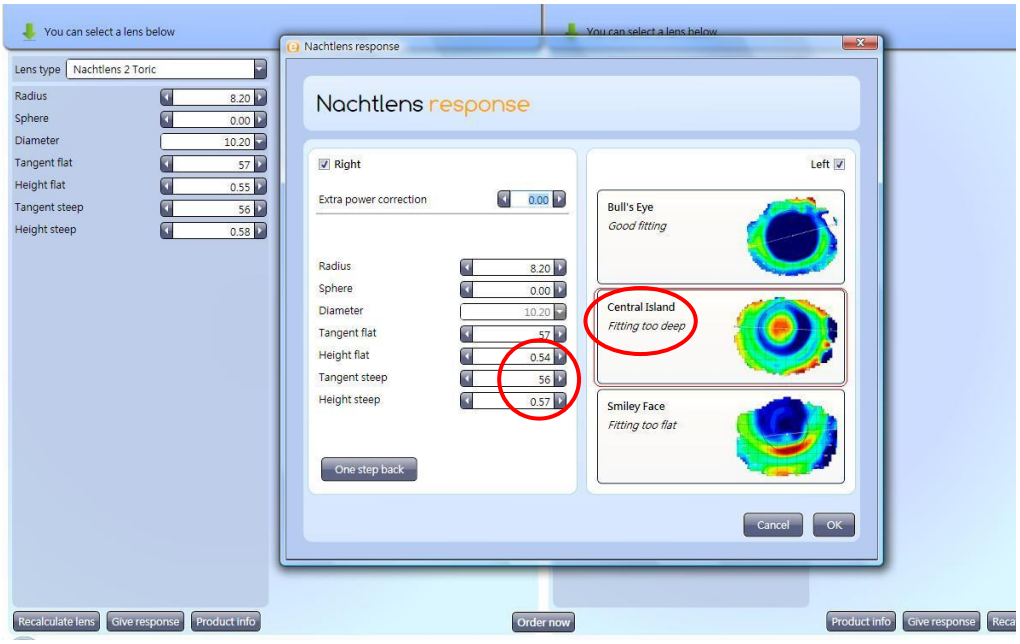


Figure 2.3 (c) If a Central Island was obtained, and then a new lens with decreased lens height should be ordered as shown in this NKL's Easy Fit software

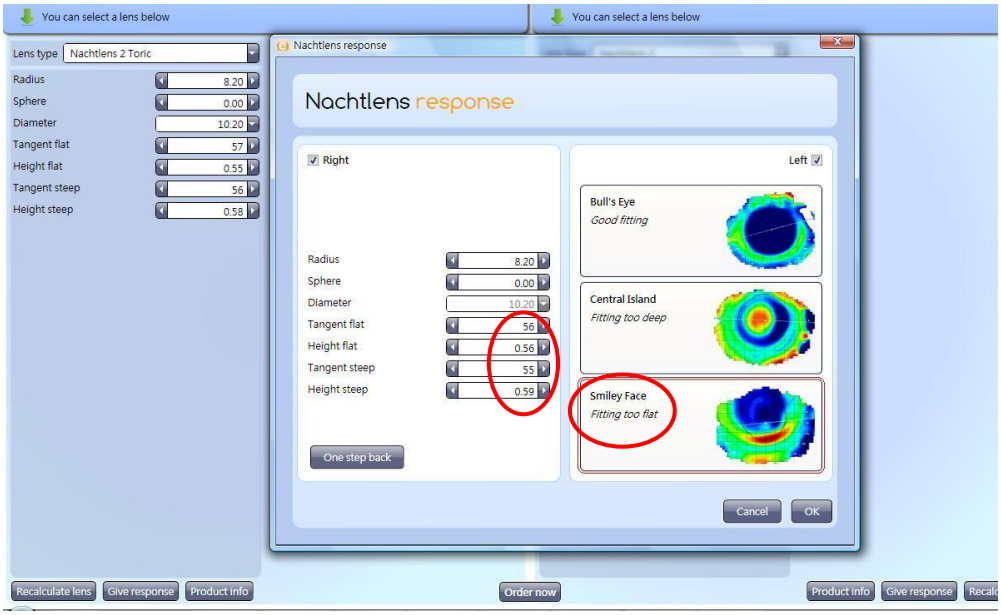


Figure 2.3 (d) If a Smiley Face was obtained, then a new lens with decreased lens tangent and increased lens height should be ordered as shown

When the post-ortho-k topographic map shows smiley face, it means the lens fitting is too flat. Lens adjustment was using the NKL Easy Fit software (Figure 2.3(d)), decreased lens tangent and increased sagittal height on both horizontal and vertical meridian was attempted. As shown in the red circle on Figure 2.3 (d), the tangent flat and steep of the lens needs to decrease from the values of 56 and 55 to to 55 and 54, and the height flat and steep of the lens was increased from 0.56 and 0.59 to 0.57 and 0.60 (values suggested by the software).

Table 2.5 Lens adjustment of Z Night Lens

Corneal response	Cause	Lens adjustment/Management
Central island	• Excessive lens sag	• Decrease the lens height
Smiley face	• Under-estimated lens sag	• Increase the lens height
Frowny face	• Over-estimated lens sag	• Decrease the lens height

If the target myopic reduction was not achieved by the former lens, a lens with an increased target was attempted to try to achieve a further reduction. If no significant reduction was achieved with the higher target lens in any eye despite repeated modifications (three pairs of lenses), the subject was terminated from the study.

If the corneal response showed a bull's eye pattern at the 1-overnight visit, the subject would continue lens wear. If an ordered lens produced an adverse response such as lens displacement, smiley face, or frowny face

topographic pattern after one night of lens wear, lens wear was ceased and a new lens with adjusted parameters was ordered, as suggested by the Easy Fit software (based on topographic response of first lens). Adjustments to lens parameters are summarized in Table 2.5 and Figures 2.3 (a) to (d).

At any visit after stabilization, lenses with an increased target were reordered if UVA was worse than 0.18 logMAR or if the residual refractive errors (either myopia or astigmatism) were less than -0.50 D. If there was no improvement despite modifications, such subjects would be discontinued from the study.

2.2.4.2 Control group

All subjects were prescribed single vision spectacles for day time use and were required to return for data collection every six months. If the subject's habitual visual acuity (VA) was found to be worse than 0.18 logMAR or if the refractive errors (either myopia or astigmatism) increased by 0.50 D or more at any data collection visit, the prescription would be updated. All lenses used were complimentary to the subjects.

Table 2.6 Parameters of Z Night Toric contact lenses

Manufacturer	NKL
Material name	Siloxanylstyrene fluoromethacrylate (tisifilcon A)
Design	Parallel reverse geometry
Dk (Barrer)	163
Back Optic zone radius (mm)	7.2-9.50 (0.05 mm step)
Back Optic Zone Diameter (mm)	6
Overall lens diameter (mm)	10.2/10.6/11.0
Reverse curve (width) (mm)	1.2 mm for 10.6 mm lens
Alignment curve (width) (mm)	1.1 mm for 10.6 mm lens (peripheral curve that meets the corneal surface tangentially)
Peripheral Curve	Tangential periphery
Tangential angle (degree)	50-65 (1^0 step)
Sagittal depth (mm)	0.50-0.99 (0.01 mm step)
Central thickness (mm)	0.24

2.2.5 Materials

2.2.5.1 Orthokeratology lenses

Subjects in the ortho-k group were fitted with the Z Night Toric RGL (NKL Contactlenzen B.V., Emmen, The Netherlands) (Table 2.6). The Z Night Toric lens is a peripheral toric ortho-k lens design with two different tangent angles and lens heights and with a spherical back optic zone. The back optic zone diameter is 6.0 mm, central thickness is 0.24 mm, and lens diameters are 10.2, 10.6, and 11.0 mm. The back vertex power of the lens is plano. Each lens has three fenestrations at 120 degree intervals in the area of the reverse curve. All lenses are made of Menicon Z material [ISO Dk 163 x 10^{-11} (cm2 /sec) [mlO2 / (ml.mmHg)] ISO 9913-1]. All lenses used in this study were replaced at least yearly.

Table 2.7 Contact lens solutions and lens care accessories

Solutions and accessories	Name of products	Manufacturer's Instructions
Cleaner	O2 Daily Cleaner	• Rub each lens surface for 10 seconds
Soaking	MeniCare Plus	• Replace every month
Rinsing	Bausch and Lomb Saline	• Rub and rinse lens before insertion • Replace solution every 2 weeks
Lens case for daily storage	Menicon cylindrical case	• Daily clean: rinse the case with tap water after lens insertion, then air dry without closing the caps • Weekly: soaked in boiled water for 10 minutes • Replace case with every new bottle of MeniCare Plus solution
Enzymatic cleaner	MeniconProgent	• Once a week
Lens case for enzymatic cleaner	Menicon SP vial	• Replace every 3 months
Artificial tears	Alcon Tears natural Free (unit dose)	• One drop to be applied to each eye before lens insertion and removal • Dispose immediately after use

2.2.5.2 Lens solutions

The lens care system prescribed included Menicon O2 CareCleaner, Menicare Plus, and Progent A+B (Menicon Co., Ltd, Nagoya, Japan), Alcon Tears Naturale Free (Alcon Lab., Fort Worth, TX, USA) and Bausch & Lomb Sensitive Eye Saline (Bausch & Lomb, Inc. Rochester, NY, USA)(Table 2.7). Subjects were required to rinse the lenses thoroughly with saline after rubbing with Menicon O2 daily cleaner, followed by

disinfecting their lenses in MeniCare Plus during the day, and to rinse their lenses again with saline before lens insertion. Artificial tears were used before lens insertion to minimize the formation of air bubbles and before lens removal to loosen the lenses. Protein removal was performed weekly using Progent A and B. The subject had to mix A and B doses in the Progent vial and soak the lenses for 30 minutes. After soaking, the lenses were cleaned again using Menicon O2 daily cleaner, rinsed throughly with saline, and disinfected in MeniCare Plus. The lens case was soaked in just-boiled water for 10 minutes weekly and all solutions and lens cases were replaced every month except for saline (a bottle of saline would last for about one to two weeks). Tap water and a suction holder were not allowed for lens handling to minimize the risk of infection. All lenses and solutions used were complimentary to ensure that all subjects used the same solutions and complied with the replacement schedules. All ortho-k subjects are required to bring back the used solutions and accessories for replacement at the ortho-k aftercare visits. They were required to follow the instructions (written and oral) given on lens handling (including insertion and removal, cleaning and disinfection, and replacement of solutions and accessories) (Appendix E). An emergency contact number for all parents was provided (Appendix D).

2.2.5.3 Spectacles

Subjects in the control group were fitted with single vision spectacles. Single vision lenses were made of plastic lens material (CR-39), with refractive index of 1.56 (Hong Kong Optical Lens Co., Hong Kong, China). All lenses were complimentary to ensure that all subjects wore the same type of lenses (eg. spherical design) and complied with regularly updating of their prescriptions during the study period.

2.2.6 Measurement procedures

Subjective refraction, UVA, AVA, ocular health, anterior and posterior corneal curvatures, intraocular pressure, CCT, CH, CRF, and AL were evaluated at different data collection visits as shown in Table 2.8. For cycloplegic examination (Table 2.8), cycloplegia was first achieved by the instillation of one drop of alcaine (proparacaine hydrochloride 0.5%), followed by one drop of tropicamide 1.0% and one drop of cyclopentolate 1.0% administered 5 minutes apart. Measurements were performed at least 30 minutes after the instillation of eye drops. Amplitude of accommodation was checked with an RAF rule and needed to have been less than 2.00 D to ensure that accommodation had been paralyzed.

Table 2.8 Data collection visits and aftercare visits of all subjects

Data collection: non-cycloplegic examination	**Orthokeratology aftercare visits (OK) / Both group (B)**												
	Baseline	Delivery	1-overnight	1-week	1-month	3-month	6-month	9-month	12-month	15-month	18-month	21-month	24-month
Unaided/Habitual high contrast logMAR VA (EDTRS)	OK	OK	OK	OK	OK	OK		OK		OK		OK	
Best corrected high contrast logMAR VA (EDTRS)		OK	OK	OK	OK	OK		OK		OK		OK	
Slit-lamp examination and photo-documentation		OK	OK	OK	OK	OK		OK		OK		OK	
Corneal topography	B	OK	OK	OK	OK	OK	B	OK	B	OK	B	OK	B
Non-contact tonometry		OK	OK	OK	OK	OK		OK		OK		OK	
Corneal pachymetry		-	-	-	-	-		OK		OK		OK	
Corneal biomechanics (CH and CRF)		-	-	-	OK	-		OK		OK		OK	
Data collection: Cycloplegic examination													
Subjective refraction and best corrected high contrast logMAR VA (EDTRS)													
Axial length (AL) measurement	B	--					B	-	B	-	B	-	B
Dilated fundal examination													

2.2.6.1 Visual acuity and subjective refraction

At each visit, the LCD logMAR VA chart in the same examination room was used to assess the entrance VA and subjective refraction. Distance subjective monocular refractive error for each eye was determined using trial frame and trial lenses. All subjects were asked to attempt the best corrected VA with high (100%) contrast ETDRS charts (Precision Vision, IL, USA) (Table 2.8). Each subject was first asked to read the middle letter of the line with the largest letters down to the smallest letter that could be read correctly and record how many letters they could read. When the subject reached the line where they could not read the middle letter (the subject was encouraged to make a guess), he or she was asked to go back and read the letters on the previous line. If the subject correctly read all the letters on this line, he or she was encouraged to attempt the next line down.

If the subject read any of the letters incorrectly, he or she was asked to go back and attempt reading these letters again and the VA was then noted. The total error scores were added to the logMAR VA of that line. These procedures were carried out to ensure consistency of the threshold criterion across subjects. In ortho-k group subjects, both unaided vision and best corrected VA (BCVA) with high (100%) contrast ETDRS charts were obtained, whereas for subjects in the control group, only BCVA with high (100%) contrast ETDRS charts was assessed. All BCVA were

obtained through the subjective refraction results in a trial frame.
The amount of myopic reduction at each subsequent visit was determined by subtracting the residual myopia from baseline myopia. Changes in astigmatism were determined by comparing changes in refractive astigmatism as well as power vector: J_0= (-C/2) cos (2θ) and J_{45} = (-C/2) sin (2θ), where C denotes the amount of astigmatism at axis θ, and J_0 and J_{45} are the horizontal or vertical and oblique components of astigmatism, respectively (Thibos et al., 1997). Changes in corneal toricity were also analyzed and presented (see Section 2.2.6.4).

2.2.6.2 Anterior ocular health

Anterior ocular health assessment was performed at each visit using a TOPCON TRC-NW6S photo slit lamp (Topcon, Tokyo, Japan) (Figure 2.4) after visual acuity assessment. Corneal staining, taking into account the type, depth and extent, was graded from 0 (absent) to 4 (severe) using Efron grading scales (Efron et al., 2001). The Efron grading scale is one of the most commonly used clinical scales used for the assessment of the anterior surface of the eye and it has been published. The location (superior, inferior, nasal, temporal, and central) of the corneal staining was also recorded. The presence of lens binding and corneal pigmented arc were also determined at every visit after commencement of lens wear in ortho-k subjects.

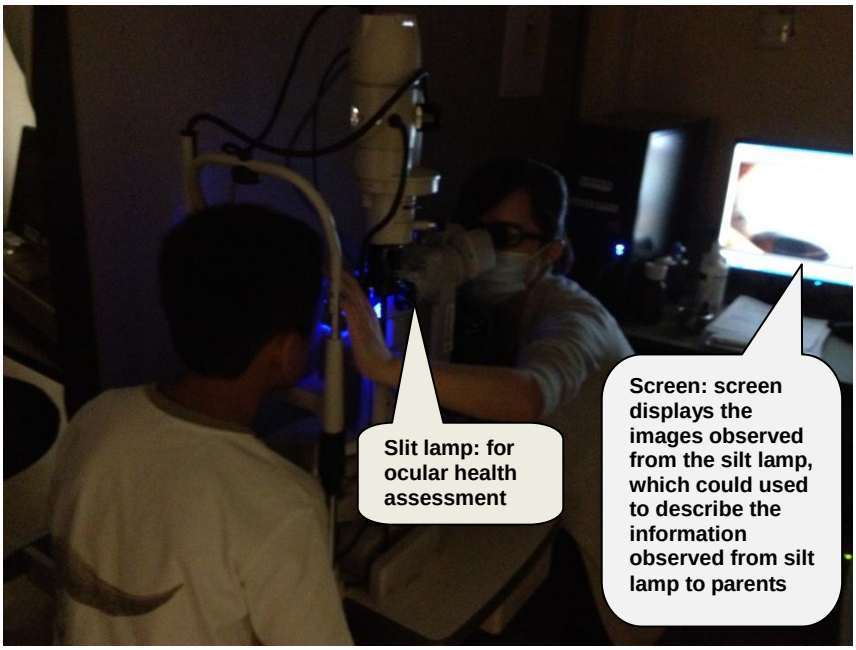


Figure 2.4 TOPCON TRC-NW6S slit lamp. Slit lamp was used to evaluate the anterior ocular health and detect any changes caused by orthokeratology lens wear at each visit. The screen displays the image taken by the examiner such as lens fitting and ocular health assessment, and parents can observed the examination from the screen at each visit

2.2.6.3 Corneal topography

Corneal topography was measured using a Medmont E300 corneal topographer (version 3.9.3, Medmont Pty. Ltd., Camberwell, Australia) (Figure 2.5) at every data collection visit without cycloplegia (Table 2.8). Measurements were taken on both eyes with the right eye always measured first. The subject was asked to blink normally to avoid the disruption of the tear film, open the eyes wide after the last blink, and fixate on the internal target during the image acquisitions. Images were automatically captured and four images, each with score higher than 98, were accepted and used for analyses.

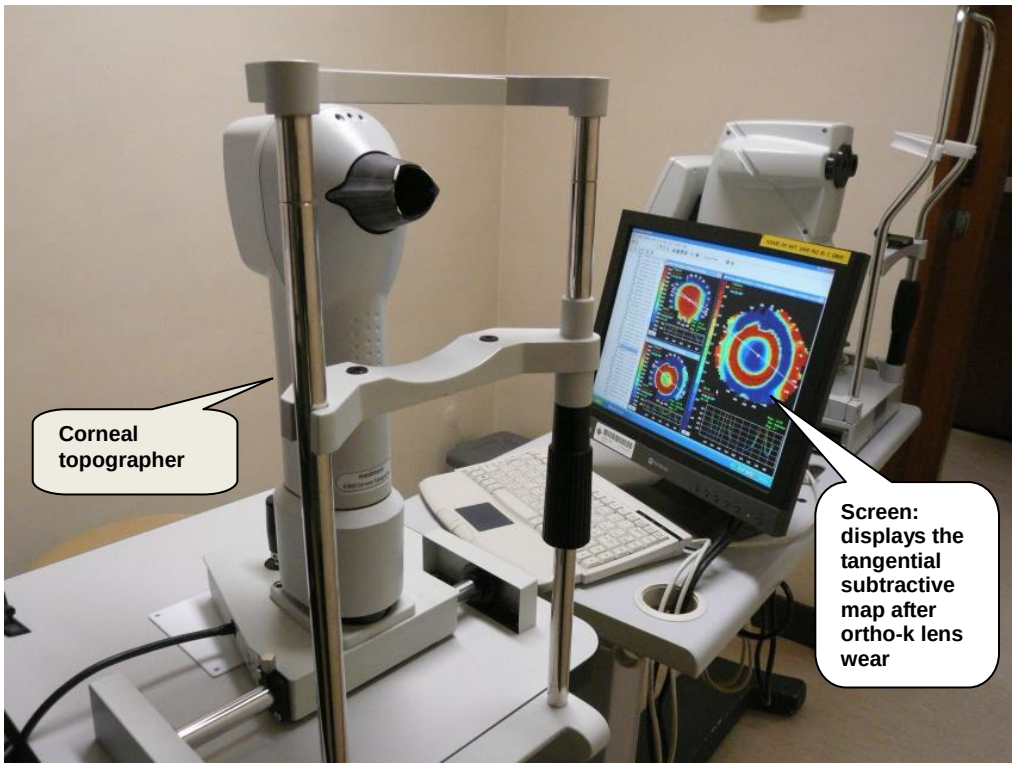


Figure 2.5 Medmont E300 corneal topographer. The screen displays the tangential subtractive map and it shows a well-centered treatment zone after orthokeratology lens wear

For ortho-k subjects, corneal curvatures were also measured at every aftercare visit. Corneal topographic maps taken at each visit were compared with those taken at baseline visit to assess changes over time with ortho-k lens wear and to determine lens centration. The subtractive (refractive) maps between pre- and post-lens wear were used to determine lens centration and the amount of corneal flattening. The tangential map was used to evaluate the centration after ortho-k treatment and the axial map was used to evaluate changes in dioptric power.

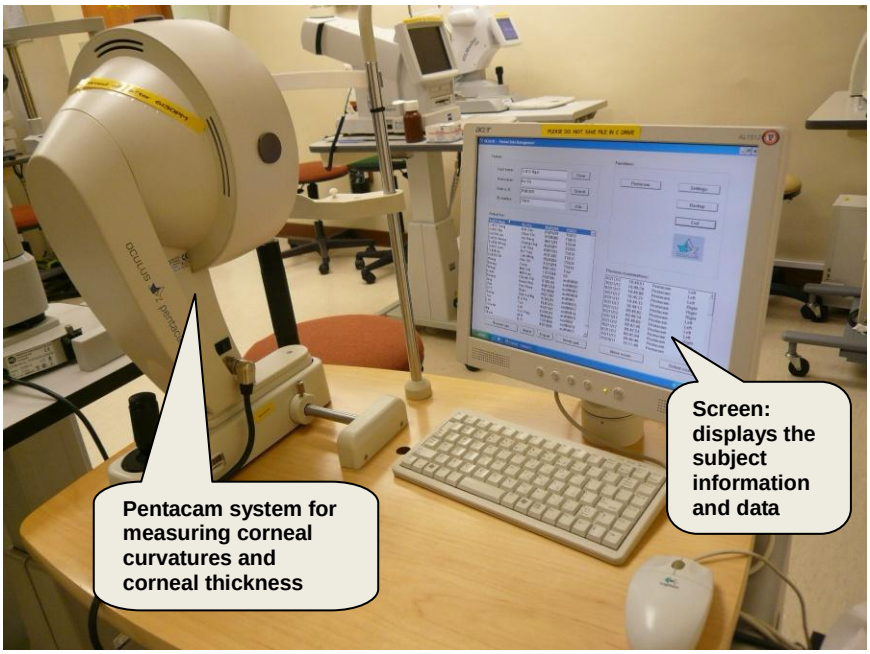


Figure 2.6 Pentacam system. The screen displays the subject's information and data

2.2.6.4 Anterior and posterior corneal curvatures

Anterior and posterior corneal curvatures were measured using the Pentacam system (software version 1.12, Oculus, Germany). The Pentacam system is a rotating Scheimpflug imaging-based corneal topographer. Figure 2.6 shows the Pentacam instrument used in the current study. The system can capture 25 or 50 slit images per scan with each image containing 500 data points. In this study, the original system with the "25 image mode" was used. The subject was asked to fixate an internal target inside the instrument. The instrument automatically took one scan by rotating the camera 360 degrees to rapidly acquire multiple images of the anterior segment. Twenty five Scheimpflug images were

captured within two seconds between scans. The corneal parameters were automatically generated and three Scheimpflug images were saved. Only scans registered as an “OK” indication on the Examination Quality Specifications of the Pentacam were stored and used for data analysis.

Power vector analysis was used to determine changes in astigmatism (Thibos et al., 1997; Thibos and Horner, 2001). Refractive and corneal astigmatism was converted to rectangular vector coordinates (Thibos et al., 1997; Thibos and Horner, 2001). Power vectors are a geometrical represention of spherocylindrical refractive errors in three fundamental dioptric components, which is mathematically independent of the others (Thibos et al., 1997). A spherical lens cannot be produced by any combination of JCC lenses, a JCC lens with axis 0 degree cannot be produced by any combination of spherical lenses with JCCs at axis 45 degrees, and a JCC lens with axis 45 degrees cannot be produced by any combination of spherical lenses with JCCs at axis 0 degree. The manifest refractions in conventional script notation: S, C, and θ were converted to power vector coordinates and overall blurring strength by the following formulas.

$M = S + C/2$

$J_0 = (-C/2) \cos (2\theta)$

$J_{45} = (-C/2) \sin (2\theta)$

Where M is the spherical equivalent, C denotes the amount of astigmatism

at axis θ, and J_0 and J_{45} are the horizontal or vertical and oblique components of astigmatism, respectively. In this study, the refractive astigmatic components were denoted as RJ_0 and $RJ_{45,}$ whereas the corneal astigmatic components were denoted as CJ_0 and $CJ_{45.}$ Changes in astigmatism were evaluated by comparing refractive astigmatism, corneal toricity as well as J_0 and J_{45} before and after ortho-k treatment.

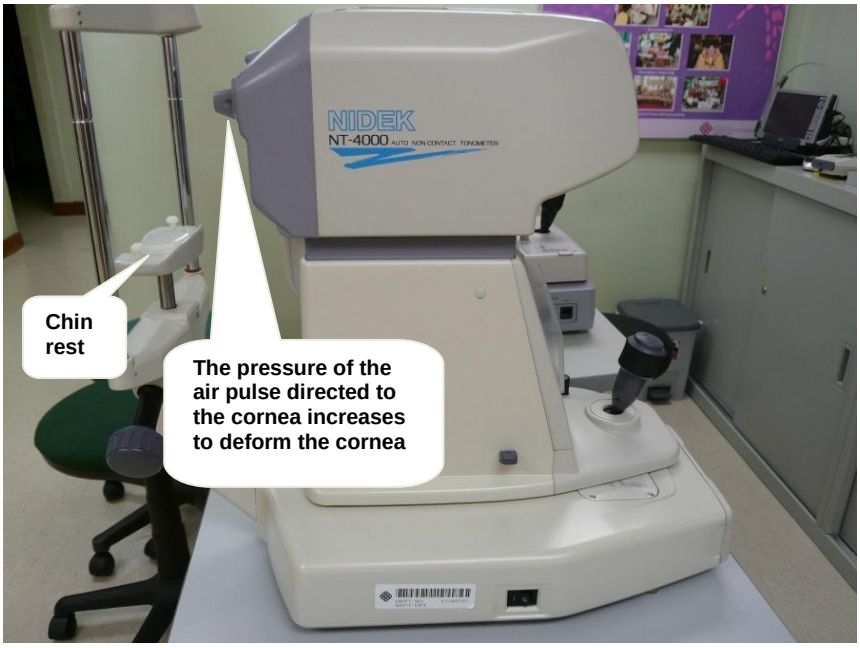


Figure 2.7 NIDEK NT-4000 non-contact tonometer

2.2.6.5 Intraocular pressure

The NIDEK NT-4000 (Nidek Co.Ltd., Gamagori, Japan) non-contact tonometer (Figure 2.7) was used to measure intraocular pressure. Measurements were made on the right eye first, then the left eye. Automatic intraocular pressure readings were given by the tonometer

once alignment was achieved. Three measurements were taken for each eye at every data collection visit for all subjects without cycloplegia.

Figure 2.8 Zeiss IOLMaster™ instrument. Subject information was entered and the mode was switched to measure the axial length. The subject was asked to put the chin on the chin rest and the forehead against the forehead rest. The right eye was examined first and subject was instructed to look at the red light and align the instrument

2.2.6.6 Axial length (AL)

The Zeiss IOLMaster™ (Zeiss Humphrey, Dublin, CA, USA) (Figure 2.8) was used to monitor AL elongation. Measurements were determined for all subjects at every data collection visit after cycloplegia. The first five

consecutive AL readings (signal-to-noise ratio greater than 5.0 and the difference between the greatest and smallest readings in each set of five readings was less than 0.02 mm of one another, as recommended by the manufacturer) were averaged and recorded.

2.2.6.7 Corneal thickness

Central corneal thickness (CCT) was measured using the Pentacam topographic system (Figure 2.6). Three CCT readings at the corneal apex were recorded for each eye (right eye first) of all subjects at every data collection visit before cycloplegia (Table 2.8).

2.2.6.8 Corneal biomechanical properties

The Reichert Ocular Response Analyzer (ORA) (version 1.2, Reichert Ophthalmic Instruments, Buffalo, NY, USA) (Figure 2.9) was used for measurements of corneal biomechanical properties, in terms of CH and CRF. Four readings on each eye were made for all subjects at each data collection visit before cycloplegia. Measurements were always made on the right eye first.

Subjects were asked to fixate the internal target and the electro-optical monitoring system automatically triggered the non-contact probe to release an air pulse onto the cornea. A double-peak of graph was generated. The air pulse causes an inward deformation of the cornea to a

predominately applanated state (pressure 1, P1) and pushes it into a concave state. Then, the air pulse reduces until the cornea returns to the

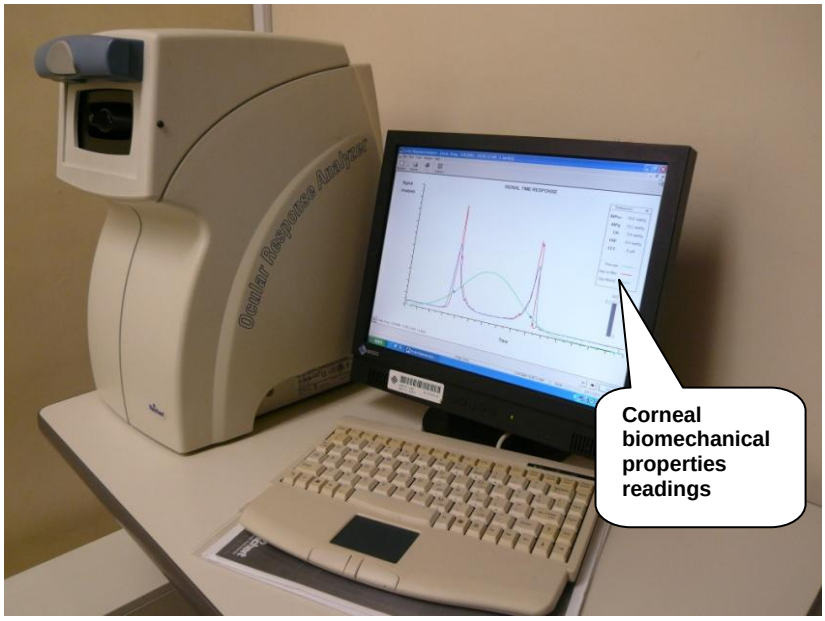


Figure 2.9 Reichert Ocular Response Analyzer (ORA). On the screen, a distinctive double-peak graph is presented and in the top right box shows the readings of the corneal biomechanical properties

predominantly applanated state again (pressure 2, P2). CH is the difference between P1 and P2, which represents the viscous damping response of the cornea. The CRF is another parameter that is derived from P1 and P2 (P1 – k*P2, where k is a constant) (Kotecha, 2007).

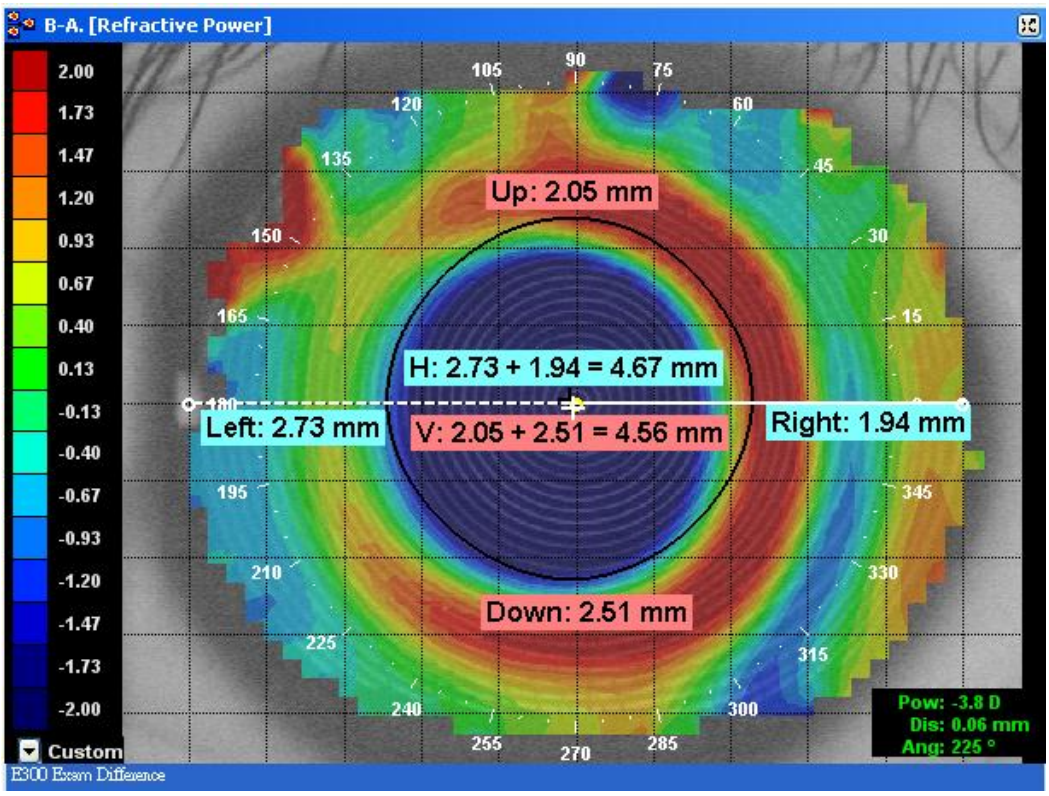


Figure 2.10 Medmont E300 corneal topographer (for treatment zone size measurement)

2.2.6.9 Treatment zone size

Treatment zone (TxZ) size was measured using a Medmont E300 corneal topographer (version 3.9.3, Medmont Pty. Ltd., Camberwell, Australia) (Figure 2.5) at the 1-month visit without cycloplegia. On the corneal topography map, ortho-k lens creates a central circular zone of corneal flattening, termed the “TxZ”, which was surrounded by a ring of midperipheral corneal steeping. The TxZ size was measured from the refractive subtractive map between baseline and 1-month visit. The criterion for determining the TxZ size on horizontal (H) and vertical (V) was

from the inner edge of the zero diopter change zone inside the ring of midperipheral steepening on the refractive subtractive map (Figure 2.10). The sizes of TxZ (H) and TxZ (V) are the sum of the diameter of the horizontal width of the zone, and the vertical height of the zone, respectively (Figure 2.10).

2.3 Treatment of data

The statistical package used was SPSS version 18 (SPSS Inc., Chicago, IL, USA). Since the distributions of data were not significantly different from normal (Kolmogorov-Smirnov tests, $p > 0.05$), parametric tests were used to compare myopia, astigmatism, J_0 and J_{45}, and VA data between baseline and the subsequent visits. Repeated Measures ANOVA were used to study the change in the parameters after ortho-k lens wear and paired t-test with Bonferroni correction were used for post-hoc analysis. Paired t-tests were used to compare the changes in CCT, CH and CRF values between baseline and subsequent visits. Data from the right eye, if the two eyes had the same amount of refractive astigmatism, or the eye with higher refractive astigmatism were analyzed and reported. For comparison of baseline data between the two groups, an unpaired t-test was used. Pearson correlations were also performed to study the relationship between the myopic and astigmatic reduction and changes in corneal curvature, changes in CCT, and between baseline CH and CRF and myopic and astigmatic reduction.

CHAPTER 3

Clinical performance of toric design orthokeratology lenses in children with moderate to high astigmatism

3.1 Introduction

Ortho-k has been shown to be effective for myopic reduction leading to improved unaided vision in low myopes with low astigmatism. Many myopic children are also astigmatic (Kleinstein et al., 2003; Fan et al., 2004b). While spherical design ortho-k lenses are effective in correcting low-moderate myopia, they do not adequately reduce astigmatism (Cheung and Cho, 2004; Chan et al., 2008; Cheung et al., 2009). The most common problem with spherical ortho-k lenses on a patient with a significant amount of corneal astigmatism is poor lens centration, which can lead to induced astigmatism and poor vision (Mountford and Pesudovs, 2002; Chan et al., 2008).

Toric reverse geometry lens designs have therefore been developed to improve lens centration as well as for astigmatic correction. High DK lens materials allow overnight treatment and minimize corneal hypoxia.
In this chapter, the clinical performance of a toric design ortho-k lens in terms of lens fitting success rate, visual acuity, changes in myopia and astigmatism and ocular health in children in an ortho-k group is reported.

First fit success rate was determined by the percentage of subjects who achieved satisfactory fitting and continued lens wear with the first pair of lenses after the 1-overnight visit.

Table 3.1 Baseline data (Mean ± SD) of subjects recruited (n=43) (Right eye or the eye with higher astigmatism)

Age (years)	9.4±1.4
Myopia (D)	2.46±1.31
Astigmatism (D)	1.86±0.64
Flat K (D)	43.32±1.54
Steep K (D)	45.47±1.31
High contrast BCVA (logMAR)	0.00±0.05

BCVA: best corrected visual acuity

3.2 Results

3.2.1 Subjects

A total of 43 subjects (22 male, 21 female), who satisfied the recruitment criteria were enrolled and fitted with the toric ortho-k lenses. The mean ± SD age was 9.4 ± 1.4 years (Table 3.1). Figure 3.1 describes of subject recruitment and progress of the subjects. This flow chart shows the subject recruitment, clinical performance of the lenses. Forty-five subjects were eligible and all of them were fitted with toric ortho-k lenses using Easy Fit Software. After 1-overnight of lens wear, re-order lenses was necessary for two subjects due to lens decentration and inadequate

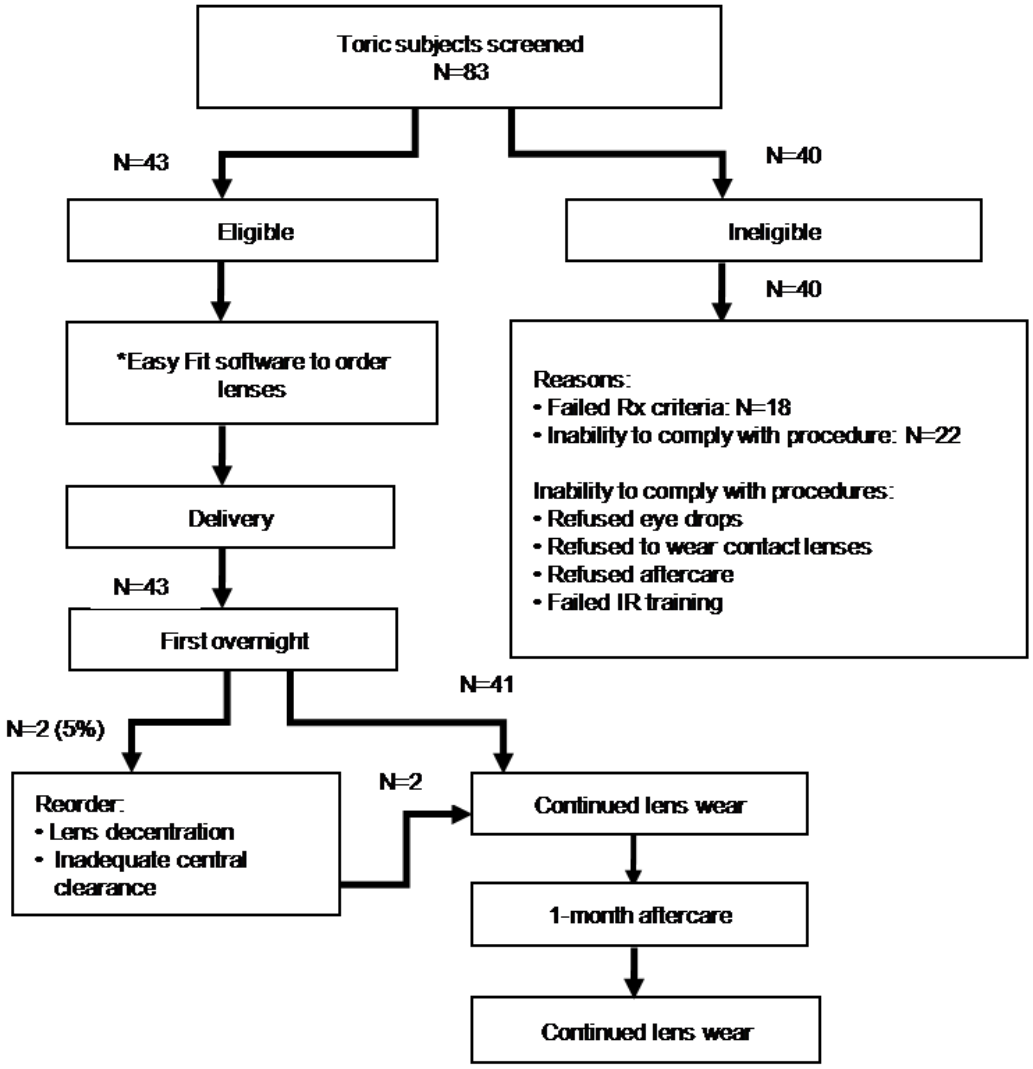


Figure 3.1 Subject recruitment and clinical performance of the lenses at 1-month visit (*NKL Easy Fit Software (version VIP 2006, NKL Contactlenzen B.V., Emmen, The Netherlands)) (IR: insertion and removal)

central clearance. After re-ordering of lenses for these two subjects, all subjects continued lens wear. Forty subjects were ineligible for this study

because they did not satisfy the inclusion criteria and because of their inability to comply with the required procedures.

3.2.2 First fit success rate

Lens fittings with the first pair of lenses were satisfactory for all subjects at the delivery visit. At the 1-overnight visit, only two subjects were refitted with a second pair of lenses due to poor lens centration and inadequate central clearance. The first lens fit success rate without the use of trial lenses was 95%.

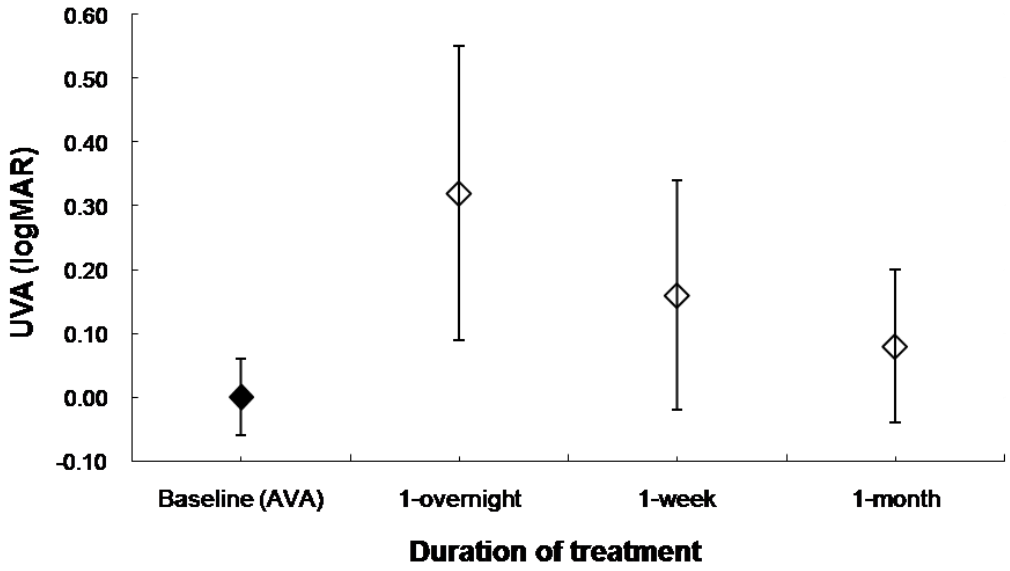


Figure 3.2 LogMAR visual acuity of subjects wearing orthokeratology lens at baseline (◆aided VA) and at different visits during one month of lens wear (◇unaided VA) (Each error bar indicates one standard deviation) (n=43)

3.2.3 Visual acuity (VA)

The mean ± SD unaided VA was 0.37 ± 0.24 logMAR at the 1-overnight visit and improved to 0.11 ± 0.13 logMAR after 1-month of lens wear (paired t test, $p < 0.001$) (Figure 3.2). Unaided VA at 1-month was significantly different from baseline best-corrected VA (BCVA) (0.00 ± 0.05 logMAR) (paired t test, $p < 0.001$). BCVA at the 1-month visit (-0.01 ± 0.05 logMAR) was not significantly different from that at baseline (paired t test, $p=0.628$).

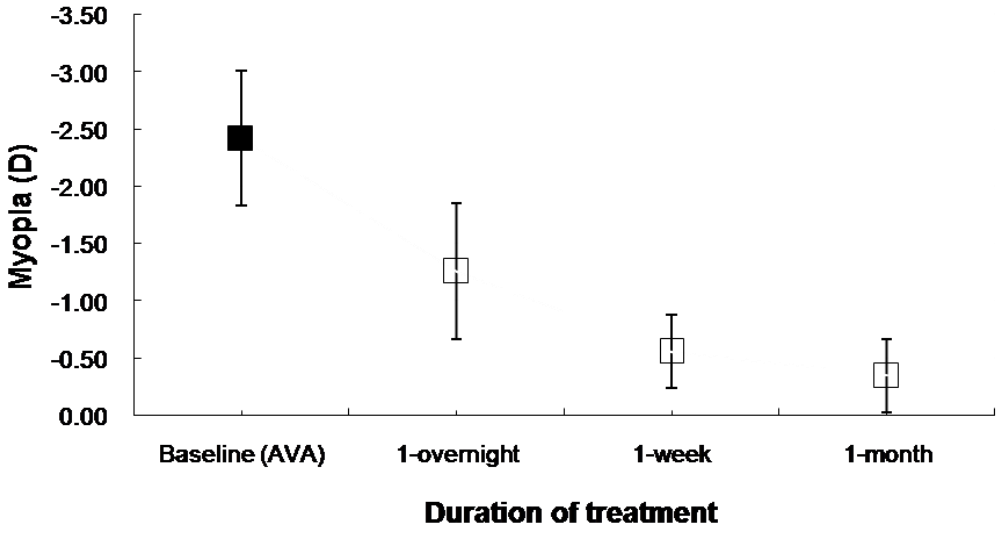


Figure 3.3 Refractive error (myopia) at baseline (■ manifest myopia) and at different visits (□ residual myopia) after commencing orthokeratology lens wear (Each error bar indicates one standard deviation) (n=43)

3.2.4 Changes in myopia and astigmatism

There were significant changes in myopia and refractive astigmatism after 1-month lens wear (repeated Measures ANOVA, $p<0.05$). Mean ± SD myopia of 2.46 ± 1.31 D at baseline was significantly reduced to 1.30 ± 0.82 D (42% reduction) at the 1-overnight visit, and to 0.37 ± 0.43 D (81% reduction) at the 1-month visit (paired t tests, $p< 0.001$) (Figure 3.3).

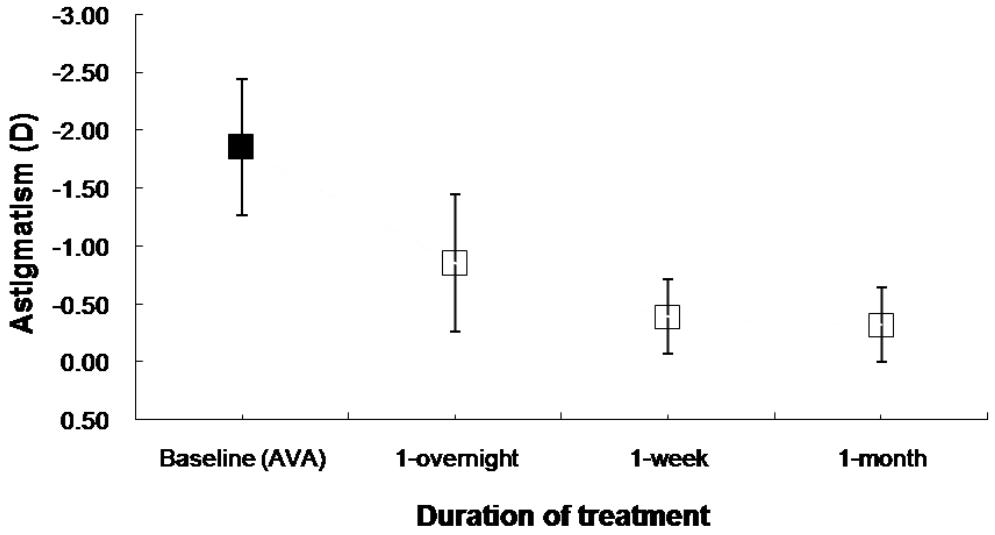


Figure 3.4 Refractive error (astigmatism) at baseline (■ manifest astigmatism) and at different visits (□ residual astigmatism) after commencing orthokeratology lens wear (Each error bar indicates one standard deviation) (n=43)

The mean ± SD refractive astigmatism reduced from 1.86 ± 0.64 D at baseline to 0.87 ± 0.60 D (54% reduction) and to 0.32 ± 0.34 D (79% reduction) at the 1-overnight and 1-month visits, respectively (paired t tests, $p< 0.001$) (Figure 3.4). Corneal toricity reduced from 2.28 ± 0.53 D

at baseline to1.95 ± 0.60 (13%) at the 1-overnight visit and 1.28 ± 0.52 D (44%) at 1-month visit (repeated Measures ANOVA, p<0.001).

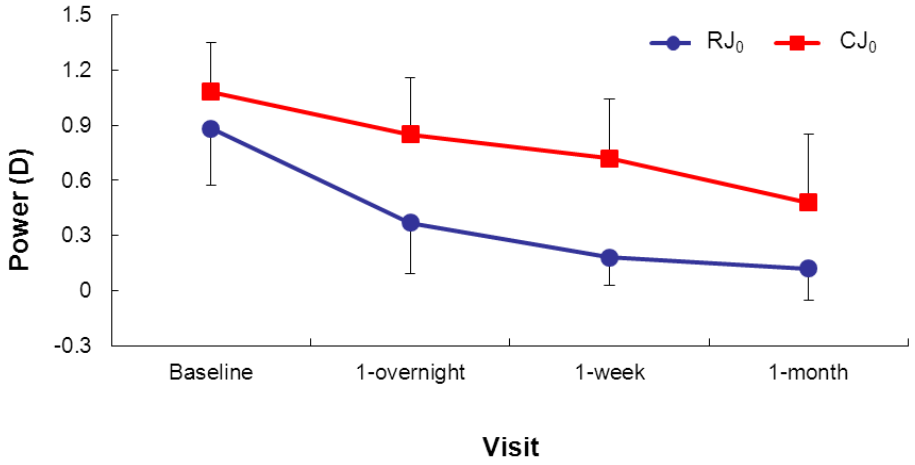


Figure 3.5 Refractive astigmatic (● RJ_0) and corneal toricity (■ CJ_0) at baseline and at different visits after commencing lens wear (Each error bar indicates one standard deviation) (n=43)

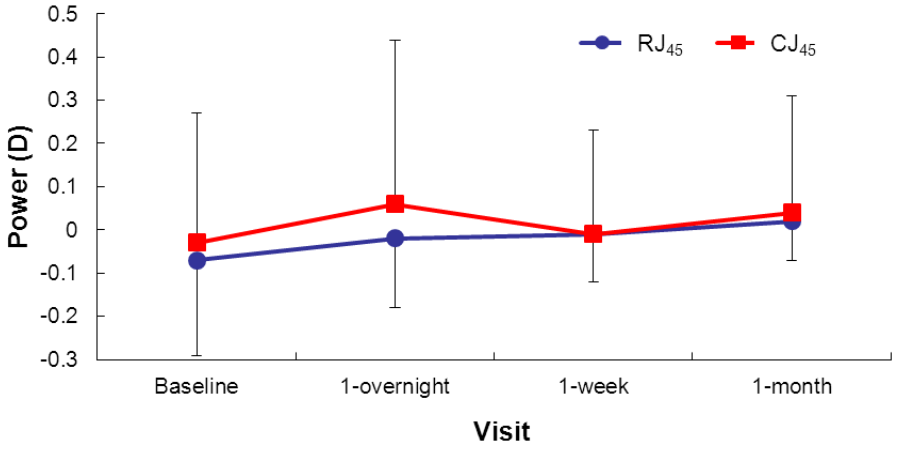


Figure 3.6 Refractive astigmatism (● RJ_{45}) and corneal toricity (■ CJ_{45}) at baseline and at different visits after commencing lens wear (Each error bar indicates one standard deviation) (n=43)

Figures 3.5 and 3.6 show the refractive astigmatism and corneal toricity, J_0 and J_{45}, respectively before and after ortho-k treatment using the power vector analysis (see Section 2.2.6.4). Significant reductions at subsequent visits were observed for J_0 of both refractive astigmatism (repeated measures ANOVA, $p < 0.001$) and corneal toricity (repeated measures ANOVA, $p < 0.001$). No significant changes were observed for J_{45} of both refractive astigmatism and corneal toricity over the 1-month period (repeated measures MANOVA, p=0.238).

Table 3.2 Percentage of mild corneal staining (Efron's Grading Scale) at different locations in subjects wearing orthokeratology lenses over the 1-month study period

Corneal staining	Baseline	1-overnight	1-week	1-month
Grade 1	C: 0 I: 20 S: 3 N: 0 T: 0	C: 29 I: 11 S: 6 N: 6 T: 6	C: 11 I: 14 S: 3 N: 9 T: 6	C: 9 I: 34 S: 14 N: 6 T: 9
Grade 2	C: 0 I: 3 S: 0 N: 0 T: 0	C: 0 I: 0 S: 0 N: 0 T: 0	C: 0 I: 3 S: 0 N: 0 T: 0	C: 0 I: 0 S: 0 N: 0 T: 0
Grade 3	NA	NA	NA	NA
Grade 4	NA	NA	NA	NA

(C: central; I: inferior; S: superior; N: nasal; T: temporal)

3.2.5 Anterior ocular health

At the 1-overnight visit, mild corneal staining was observed at different corneal zones of some subjects (central (29%), inferior (11%), superior (6%), nasal (6%), and temporal (6%)) (Table 3.2). Apart from one grade 2 corneal staining in an ortho-k subject at the 1-week visit, no significant corneal staining (most staining were < Grade 2) was observed in the subsequent visits during the 1-month of lens wear. As observed at the 1-overnight visit, only mild (Grade 1) staining was observed at different corneal locations in some subjects at different visits.

Dimple veiling was observed in 70% of the subjects (30/43) at the 1-overnight visit (Figure 3.7). No dimple veiling was observed at subsequent visits. During the 1-month lens wear, no pigmented arc was observed and no adverse events were noted in any subject.

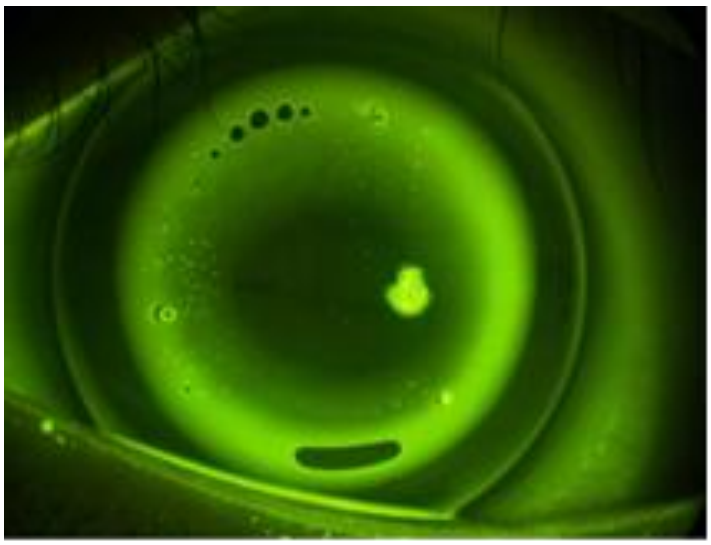


Figure 3.7 Dimple veiling with lens in situ, after the instillation of fluorescein

3.3 Discussion

Toric design ortho-k was effective for correcting refractive astigmatism. The toric design lenses also improved lens centration. In this study, no subject was excluded because of poor lens centration. No trial lenses were used in the current study. The NKL Easy Fit Software (NKL Contactlenzen B.V., Emmen, The Netherlands) allows empirical lens ordering, hence reducing chair time which would otherwise be needed for trial lens fitting. This is ideal for those who are concerned with cross-contamination or transmission of prion disease from trial lenses (Hogan, 2003).

The results of this study show that the first lens fit success rate with Z Night Toric RGL was 95%, which was better than the rate reported with trial lens fitting (Chan et al., 2008) in the Optometry Clinic of The Hong Kong Polytechnic University (73.5%). The Easy Fit Software also allows practitioners to modify parameters during the treatment period, which is an added advantage for experienced practitioners.

Results from the current study show that toric ortho-k could reduce myopia by 81% and refractive astigmatism by 79% after 1-month of lens wear with one pair of lenses. The mean ± SD myopic reduction after one month of lens wear in our subjects was 2.03 ± 1.26 D (81%) whereas previous studies have reported a reduction in spherical equivalent of 1.50 D to 3.50 D (Alharbi and Swarbrick, 2003; Cho et al., 2005a; Sorbara et al., 2005), depending on the baseline refractive errors of the subjects recruited.

These previous studies have reported no significant change in refractive astigmatism with spherical ortho-k lens wear. In the current study, ortho-k subjects achieved 79% reduction in refractive astigmatism with the toric design lenses after 1-month of lens wear. All subjects reported satisfactory vision, although unaided VA (mean ± SD 0.11 ± 0.13 logMAR) was significantly poorer compared to baseline BCVA due to residual myopia (0.41 ± 0.43 D) and/or refractive astigmatism (0.40 ± 0.39 D). Uncorrected myopia or astigmatism of -0.25 D is possible in ortho-k group. Lenses with higher targets were ordered for 12 subjects who under-responded at the 1-month visit as they had not achieve the endpoint criteria (i.e. myopia < 0.75 D or unaided VA better than 0.18 logMAR), to allow them to continue in the myopic control study.

Corneal staining associated with ortho-k lens wear is a common finding and mechanical trauma and hypoxia have been proposed to be likely causes (Rah et al., 2002b; Tahhan et al., 2003; Chan et al., 2008). Mild corneal staining of about 40% had been reported after 1-overnight wear of ortho-k lenses (Tahhan et al., 2003; Chan et al., 2008). In the current study, the incidence of corneal staining observed in central cornea at the 1-overnight visit was about 29%. In agreement with previous reports (Rah et al., 2002b; Walline et al., 2004b), none of the subjects presented any adverse events that required them to cease lens wear or seek medical intervention. The low incidence of staining observed in the current study

compared to previous reports, may be due to improved lens centration with the toric design ortho-k, the hyper DK lens material used, and the lower incidence of lens binding associated with the use of lens fenestrations (see Section 1.5.3).

Dimple veiling occurs when air bubbles are trapped between the lens and the cornea. The lens mechanically compresses the bubbles leading to corneal epithelial indentations, producing transient depressions on the corneal surface which are observed as dimple veiling in the fluorescein-stained eye (McMahon, 2002). Most of the staining usually recovers one to two hours after lens removal (Dave, 2002). In the current study, dimple veiling was observed in 70% of the subjects at the 1-overnight visit. This was likely to be because of the requirement for subjects to return for this visit without removing their lenses. Air bubbles may have been trapped during blinking, with the lenses in situ, on the way to our clinic.

To conclude, the findings of this 1-month study showed that Night Toric RGL can be used safely, with stringent aftercare and instructions, and effectively for myopic and astigmatic reduction in myopic children with moderate to high astigmatism.

Publications:

1. Chen C, Cheung SW and Cho P. Toric orthokeratology for highly astigmatic children. Optom Vis Sci. 2012; 89: 849-55.

Conference presentations:

1. Chen C, Cheung SW, Cho P. Toric design reverse geometry lenses for myopic astigmatism, clinical performance and preliminary results. 34th British Contact Lens Association Clinical Conference and Exhibition, Birmingham, 27 -30 May 2010. (Poster) #65) (Conference Manual, pp 121)
2. Chen CC, Cheung SW, Cho P. Toric design reverse geometry lenses for myopic astigmats – preliminary results. Abstracts of Scientific Program of The 17th Asia Pacific Optometric Congress 5-7 November, 2009. Hong Kong. Pp 41

Chapter 4

Orthokeratology for correcting myopia and astigmatism and for myopic control

4.1 Introduction

The prevalence of myopia is high in East Asia e.g. Hong Kong, China, Taiwan, Japan and Korea (see Section 1.1). Vitale and co-workers (2009) have also reported increasing prevalence of myopia in the United States in recent decades. Hence, preventing or slowing myopic progression has attracted the interest of many clinicians and researchers. For years, researchers have been trying to find an effective method to retard or control the progression of myopia in children (see Section1.1). These myopic control treatments include bifocal spectacle lenses, progressive spectacle lenses, under-correction of myopia, rigid contact lenses, soft bifocal contact lenses, and pharmaceutical agents such as atropine and pirenzepine (see Section 1.1).

The potential of modern ortho-k, which uses reverse geometry rigid contact lenses worn overnight to reshape the cornea thus temporarily reducing myopia (see Section 1.3.1), for myopic control (see Section 1.4) has recently been confirmed via a 2-year randomized clinical trial (Cho and Cheung, 2012). The rate of axial elongation of the eyeball in children wearing ortho-k lenses has been reported to be 32% to 55% slower

compared to those wearing single-vision spectacles or soft contact lenses (see Section 1.5). All of these studies used ortho-k lenses of spherical design on low myopes (< 6.00 D) with low astigmatism. Clinically, corneal astigmatism greater than 1.50 D (with-the-rule) is regarded as unsuitable for spherical ortho-k lenses because of problems with poor lens centration and limited or no correction of astigmatism using spherical lens design (Cheung and Cho, 2004; Chan et al., 2008; Cheung et al., 2009). In patients with high corneal astigmatism (> 1.50 D), lens decentration is the most common problem with spherical ortho-k lenses and it can lead to induced astigmatism and poor vision (see Section 1.1). Hence, spherical ortho-k is not indicated for children with refractive (corneal) astigmatism more than 1.50 D. However, most myopic children are also astigmatic and the prevalence of astigmatism has been reported to be about 21% and 34% in Asian children aged 15 - 17 years, respectively (see Section 1.1). Previous myopic control studies utilizing various methods mainly focused on myopic children with no or low amount of astigmatism. Considering the high prevalence of astigmatism in myopic children, there is a need for a myopic control treatment for myopic children with astigmatism to control progression of myopia while providing clear unaided vision in the daytime. Toric reverse geometry designs have therefore been developed and introduced to improve lens centration as well as for astigmatic correction. While there are a number of reports on the effectiveness of toric design ortho-k lenses for astigmatic correction (see Section 1.3.2), there is no

published study on the use of toric ortho-k for myopic control in children with moderate to high amount of astigmatism.

This chapter reports the results of the investigation of toric ortho-k for correcting myopia and astigmatism and for myopic control in terms of axial elongation in myopic children with moderate to high astigmatism.

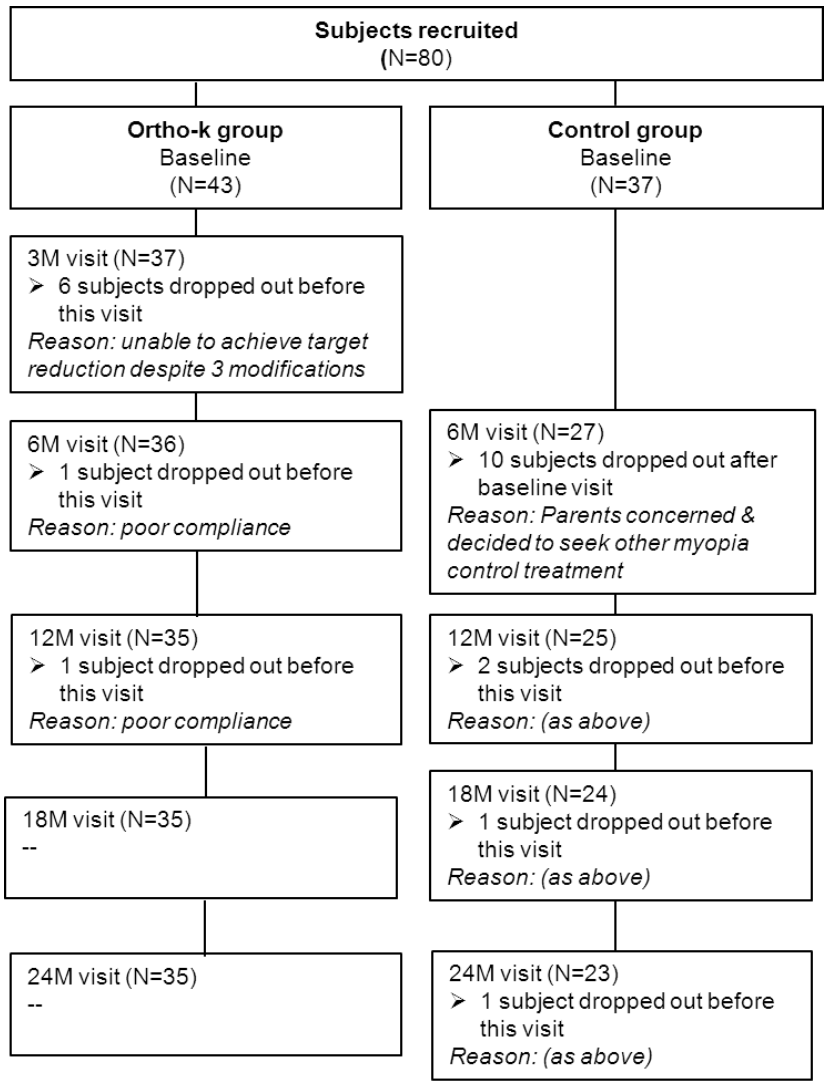


Figure 4.1 Number of subjects dropping out at different visits (M = month)

4.2 Results

Forty-three subjects were fitted with ortho-k lenses and 37 control subjects were fitted with single-vision spectacles. Only 35 subjects (18 males and 17 females) in the ortho-k group successfully completed the 2-year study (Figure 4.1).

Table 4.1 Reasons of subject withdrawal from study

Subjects in ortho-k group:
● 6 subjects could not achieved the target reduction after 1-month of lens wear and no improvement despite lens modifications
● 2 subjects showed poor compliance (e.g. no lens wear without notification)

Of the eight subjects who dropped out, six could not achieve the target reduction in HVA after 3-month lens wear despite lens modifications (three times) and two subjects showed poor compliance during the study period, one before 6-month visit and one before 12-month visit (Table 4.1).

Only 23 subjects (8 males and 15 females) in the control group completed the study; 10 subjects dropped out after the baseline visit, two after the 6-month visit, one after 12-month visit, and one after 18-month visit (Figure 4.1). The main reason for dropout was parental anxiety about the myopic progression in their children. None of the dropouts in either group of subjects was due to ocular adverse events.

Table 4.2 Baseline characteristics of subjects who completed the 2-year study period

	Ortho-k group (n=35, 18 male/17 female) (Mean±SD)	Control group (n=23, 8 male/15 female) (Mean±SD)	P value
Age (years)	9.4±1.4	8.9±1.6	0.22
Myopia (D)	-2.46±1.32	-2.04±1.09	0.21
Refractive astigmatism (D)	-1.86±0.64	-2.07±0.56	0.22
Corneal astigmatism (D)	-2.28±0.53	-2.43±0.62	0.35
Best-corrected VA (logMAR)	0.00±0.05	-0.02±0.03	0.10
Axial length (AL) (mm)	24.37±0.88	24.18±1.00	0.43

No statistically significant differences in baseline values (age, myopia, astigmatism, corneal astigmatism, BCVA and axial length) were found between those who completed and those who dropped out of the study (unpaired t-tests, $0.10 < p < 0.43$). The mean ± SD age of the ortho-k and control subjects who completed the study were 9.4 ± 1.4 and 8.9 ± 1.6 years, respectively when they commenced this study and their baseline data are shown in Table 4.2.

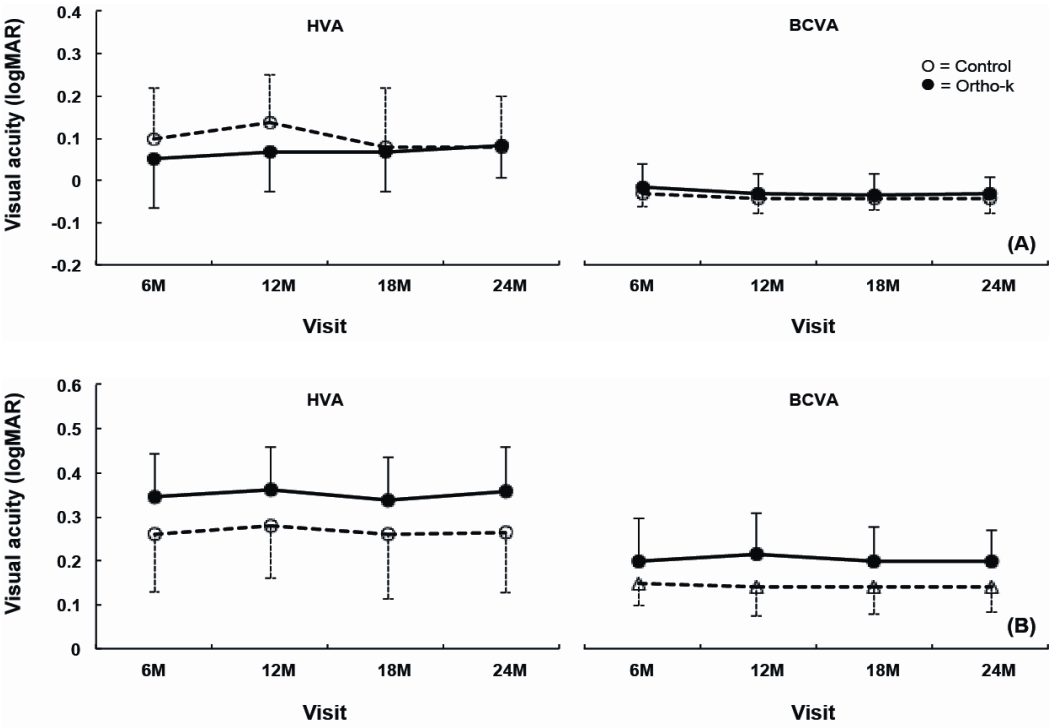


Figure 4.2 High contrast (A) and low contrast (B) habitual (HVA) and best corrected (BCVA) logMAR visual acuities at different visits during the study period (Habitual logMAR visual acuity in orthokeratology subjects = unaided visual acuity) (Each error bar represents one standard deviation) (M = month)

4.2.1 Visual acuity

Figures 4.2 (A) and (B) show the high and low contrast HVA and BCVA of the subjects, respectively. There were no significant differences in the high and low contrast HVA and BCVA during the study period in both groups of subjects (repeated measures ANOVAs, $p > 0.05$). Changes in high and low contrast HVA and BCVA were not significantly different between the two groups of subjects at any visits during the study period (unpaired

t-tests (Bonferroni correction applied), $p > 0.01$). At the 2-year visit, in the ortho-k and control groups, the mean ± SD high contrast logMAR HVA were 0.08 ± 0.11 and 0.08 ± 0.13, respectively and high contrast logMAR BCVA were -0.03 ± 0.05 and -0.04 ± 0.03, respectively. Mean ± SD low contrast HVA for the ortho-k and control groups were 0.36 ± 0.15 and 0.27 ± 0.14, respectively and low contrast BCVA were 0.20 ± 0.08 and 0.14 ± 0.05, respectively.

Table 4.3 High and low contrast habitual and best corrected visual acuities (mean±SD) in both groups during the 2-year visit

	Baseline	6-month	12-month	18-month	24-month
High contrast					
Habitual VA (logMAR)					
Ortho-k group	0.10±0.12	0.05±0.09	0.07±0.10	0.07±0.08	0.08±0.11
Control group	0.12±0.12	0.11±0.10	0.15±0.14	0.08±0.13	0.08±0.13
Best corrected VA (logMAR)					
Ortho-k group	0.00±0.07	-0.01±0.05	-0.03 ± 0.05	-0.04±0.04	-0.03±0.05
Control group	-0.03±0.03	-0.03±0.03	-0.04±0.03	-0.04±0.04	-0.04±0.03
Low contrast					
Habitual VA (logMAR)					
Ortho-k group	--	0.35±0.13	0.36±0.12	0.34±0.12	0.36±0.15
Control group	--	0.26±0.13	0.28±0.12	0.26±0.15	0.27±0.14
Best corrected VA (logMAR)					
Ortho-k group	--	0.20±0.09	0.22±0.08	0.20±0.07	0.20±0.08
Control group	--	0.15±0.07	0.14±0.06	0.14±0.08	0.14±0.05

Table 4.3 shows the details of high and low contrast habitual and best corrected visual acuities in both groups of subjects during the study period.

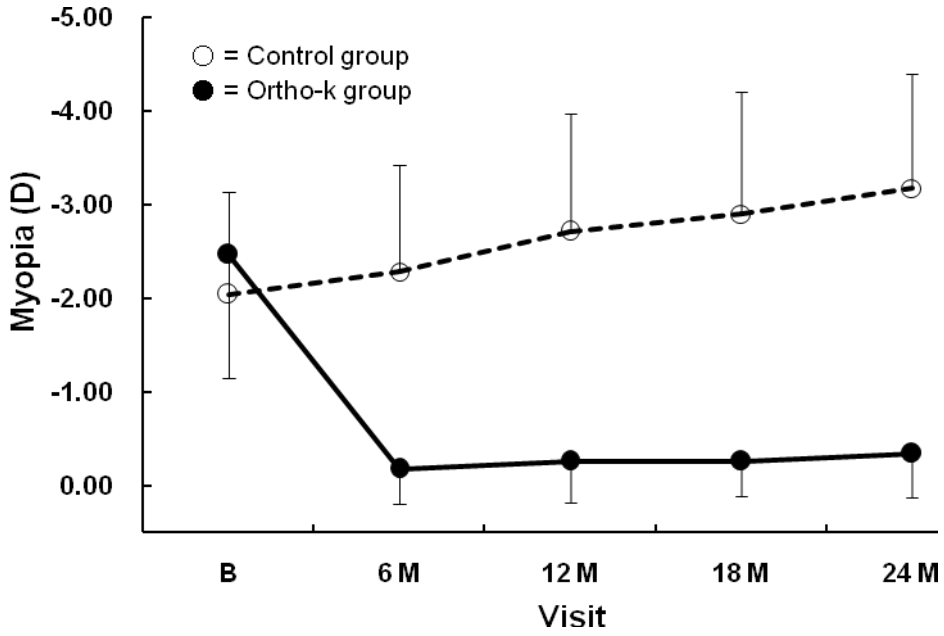


Figure 4.3 Changes in myopia of all subjects at different visits (Each error bar represents one standard deviation) (B = baseline; M = month)

4.2.2 Changes in myopia

Figure 4.3 shows the myopic changes (spherical refraction) of subjects in both groups at different visits during the study period. Myopia reduced from -2.46 ± 1.32 D at baseline to -0.39 ± 0.53 D at the end of 2-year visit in ortho-k group (repeated measures ANOVA, $p < 0.001$). For control subjects, the amount of myopia increased with time (repeated measure ANOVA, $p < 0.001$): myopia increased from -2.04 ± 1.09 D at baseline to -3.17 ± 1.22 D at the 2-year visit.

Table 4.4 Myopia and astigmatism (mean±SD) of all subjects in orthokeratology and control group at different visits

	Baseline	6-month	12-month	18-month	24-month
Myopia (D)					
Ortho-k group	-2.46±1.32	-0.18±0.37	-0.26±0.44	-0.26±0.38	-0.39±0.53
Control group	-2.04±1.09	-2.28±1.14	-2.71±1.26	-2.90±1.30	-3.17±1.22
Astigmatism (D)					
Ortho-k group	-1.86±0.64	-0.37±0.39	-0.38±0.29	-0.43±0.36	-0.41±0.39
Control group	-2.07±0.56	-2.00±0.53	-1.87±0.56	-2.03±0.47	-2.10±0.51
Corneal toricity (D)					
Ortho-k group	-2.28±0.53	-1.22±0.68	-1.30±0.53	-1.33±0.61	-1.49±0.58
Control group	-2.42±0.62	-2.44±0.55	-2.36±0.53	-2.46±0.67	-2.48±0.66

Table 4.4 shows the characteristic of myopia, astigmatism, and axial length changes during the study period of all subjects who completed the 2-year study.

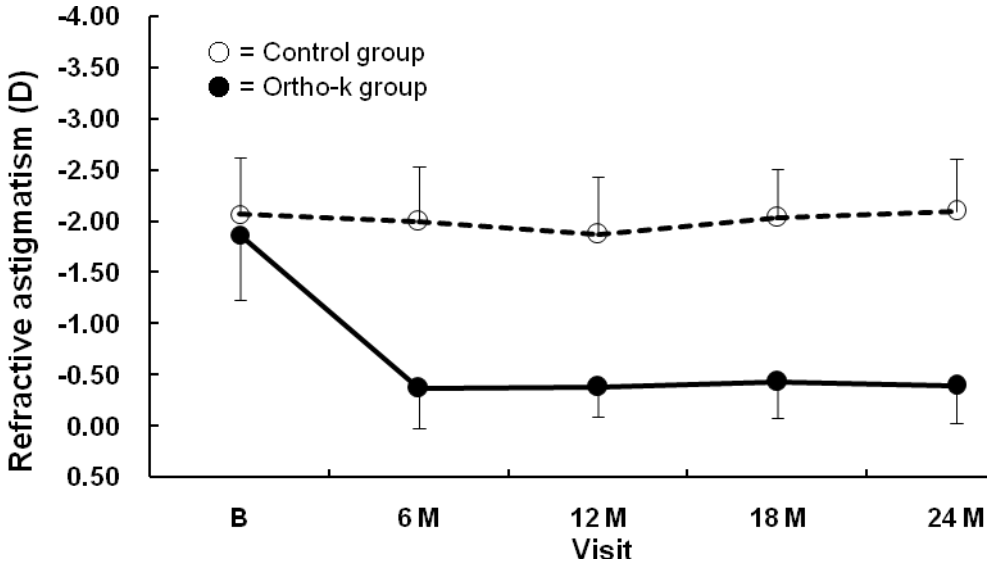


Figure 4.4 Changes in refractive astigmatism of all subjects at different visits (Each error bar represents one standard deviation) (B = baseline; M = month)

4.2.3 Changes in astigmatism

In ortho-k group, refractive astigmatism reduced from -1.86 ± 0.64 D at baseline to -0.41± 0.39 D at the 2-year visit (repeated measure ANOVA, $p < 0.001$) (Figure 4.4). For the control group, refractive astigmatism remained unchanged (repeated measure ANOVA, $p = 0.07$) (Table 4.4).

The mean ± SD of corneal toricity reduced from -2.28 ± 0.53 D at baseline and to -1.28 ± 0.52 D at 1-month visit in ortho-k group (paired t tests, $p < 0.001$). After 2-year of ortho-k lens wear, the mean ± SD corneal toricity was -1.49 ± 0.58 D. Corneal toricity shows significant changes after 1-month of lens wear (paired t test, $p=0.04$). No significant differences in corneal toricity in the control group were observed during the study period (repeated measures ANOVA, $p = 0.70$) (Table 4.4).

Table 4.5 Summary of changes (mean±SD) in refractive astigmatism and corneal toricity in orthokeratology and control groups during the 2-year study period

	Baseline	6-month	12-month	18-month	24-month
Refractive astigmatism (D)					
Ortho-k group					
M	-3.40±1.40	-0.37±0.39	-0.45±0.50	-0.47±0.38	-0.59±0.51
J_0	0.89±0.32	0.16±0.19	0.16±0.12	0.19±0.18	0.17±0.19
J_{45}	-0.07±0.28	-0.01±0.09	0.00±0.13	0.01±0.09	0.02±0.12
Control group					
M	-3.08±1.06	-3.28±1.17	-3.65±1.25	-3.92±1.34	-4.22±1.25
J_0	1.00±0.27	0.98±0.25	0.90±0.26	0.99±0.22	1.02±0.24
J_{45}	-0.15±0.17	-0.07±0.21	-0.14±0.23	-0.07±0.23	-0.03±0.28
Corneal toricity (D)					
Ortho-k group					
M	-1.14±0.27	-0.61±0.34	-0.64±0.26	-0.66±0.30	-0.72±0.32
J_0	1.08±0.28	0.54±0.34	0.58±0.23	0.63±0.32	0.67±0.34
J_{45}	-0.02±0.41	-0.03±0.33	-0.10±0.36	0.0±0.31	-0.09±0.33
Control group					
M	-1.21±0.31	-1.21±0.27	-1.18±0.26	-1.23±0.33	-1.24±0.33
J_0	1.19±0.30	1.18±0.26	1.14±0.26	1.20±0.32	1.20±0.32
J_{45}	-0.18±0.20	-0.11±0.25	-0.17±0.26	-0.11±0.26	-0.05±0.31

Summary of the refractive and cornea power vectors of both ortho-k and control groups are shown in Table 4.5. After ortho-k lens wear, mean changes in RJ_0 was significantly different compared with baseline values (paired t-tests, $p < 0.001$) and no significant differences were observed at the subsequent visits (repeated measures ANOVA, $p = 0.38$). No significant difference in RJ_{45} were observed in both ortho-k (repeated measures ANOVA, $p = 0.07$) and control (repeated measures ANOVA, $p = 0.22$) subjects throughout the study period.

For corneal toricity, significant changes in CJ_0 were observed at the 1-month

visit in ortho-k group (paired t-test, $p < 0.001$) and no significant changes were observed at the subsequent visits (repeated measures ANOVA, $p = 0.19$). No significant changes in CJ_0 were observed in the control group (repeated measures ANOVA, $p = 0.62$). There were no significant changes in CJ_{45} in both ortho-k and control groups throughout the study period (repeated measures ANOVA, ortho-k: $p = 0.36$; control: $p = 0.26$).

Table 4.6 Percentages of mild corneal staining (not more than grade 2 (Efron, 1998)) at different corneal locations in orthokeratology and control subjects at different visits

	Location	Baseline	6-month	12-month	18-month	24-month
Ortho-k (n=35)	Central	0	0	2.9	5.7	5.7
	Inferior	22.9	17.2*	17.2*	17.1	17.1
	Superior	2.9	5.7	8.6	14.3	8.6
	Nasal	0	5.7	0	2.9	5.7
	Temporal	0	2.9	5.7	2.9	0
Control (n=23)	Central	2.9	0	0	2.9	0
	Inferior	20.0	20.0	14.3#	17.1	8.6
	Superior	2.9	0	0	5.7	2.9
	Nasal	0	2.9	0	0	0
	Temporal	0	0	0	0	0

* One subject showed grade 2 corneal staining
# Two subjects showed grade 2 corneal staining

4.2.4 Anterior ocular health

There was no significant adverse event observed in either group of subjects (Fisher's Exact Tests, $p > 0.05$). Only mild corneal staining (Grade 1) was observed in both groups of subjectsat different visits (Table 4.6) and most were in the inferior cornea. There were no changes in the incidences of inferior corneal staining over time in ortho-k group (17 -

23%). Incidence of mild central corneal staining was not common in either group of subjects; two observations in the control group and five observations in the ortho-k group at different visits over the 2-year study period. Superior and nasal corneal staining in the control group was rare and no corneal staining was observed in the temporal cornea of the control subjects. Incidence of mild corneal staining in the peripheral corneal regions appeared to increase after ortho-k lens wear, especially in the inferior cornea. No lens binding was reported after one month of lens wear.

Pigmented arc were observed in 29 (83%) of 35 ortho-k subjects at 6-month visit, in 34 (97%) of subjects at the 12-month visit, and were observed in all subjects (100%) thereafter at the subsequent visits.

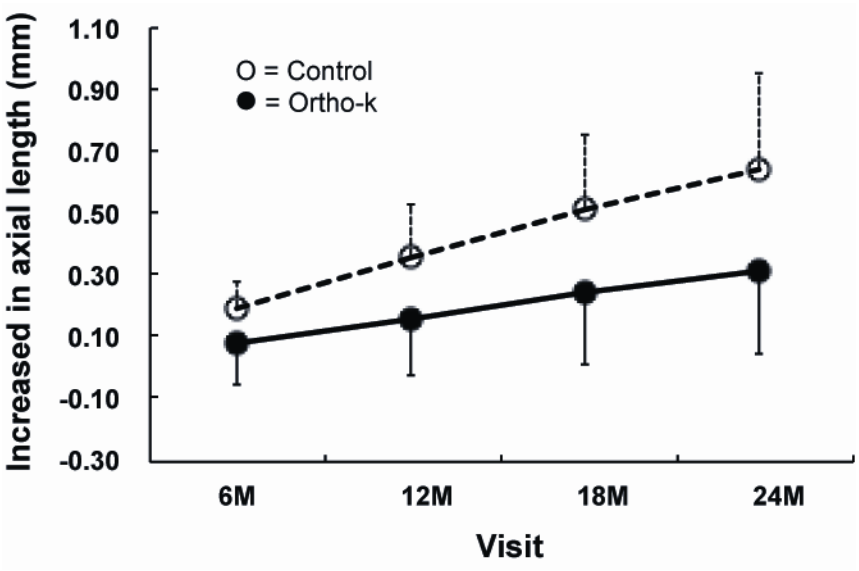


Figure 4.5 Changes in axial length in orthokeratology and control group after the 2-year study period (M = month)

Table 4.7 Increases in axial length in orthokeratology and control subjects at different visits during the study period

	Orthokeratology (n=35) (Mean±SD) (mm)	Control(n=23) (Mean±SD) (mm)
6-month	0.10±0.14	0.19±0.08
12-month	0.18±0.19	0.36±0.16
18-month	0.27±0.24	0.51±0.24
24-month	0.33±0.28	0.64±0.31

4.2.5 Axial length changes

Changes in axial length during the study period are shown in Figure 4.5. Subjects in both groups demonstrated significant axial elongation (repeated measures ANOVA, ortho-k: $p < 0.001$; control: $p < 0.001$). Axial

elongation was significantly slower in the ortho-k group than in the control group at every 6-month visit (unpaired t-tests, $0.01 < p < 0.001$). The mean ± SD increase in axial length in ortho-k subjects was 0.33 ± 0.05 mm less than the control subjects at the end of the 2-year study period (Table 4.7). The levels of reduction of myopic progression compared to the spectacle-wearing control group were 61%, 58%, 53%, and 52% (culumative elongations) after 6, 12, 18 and 24 months of ortho-k lens wear.

At the end of the 2-year monitoring period, seven subjects in the control group demonstrated fast myopic progression (myopic progression exceeding 1.00 D per year or axial elongation > 0.36 mm per year) while only one subject in the ortho-k group had fast myopic progression. The odds of becoming fast progressors was 14.9 times greater in children wearing single-vision spectacles than those wearing ortho-k lenses (95% CI: 1.7, 131.3; Fisher's Exact Test: $p = 0.005$). Stepwise multiple linear regression analysis showed that among the predicting factors, axial elongation was significantly correlated with the initial age of the subjects (standardized beta = -0.30, $p = 0.02$) and treatment assigned (standardized beta = -0.36, $p = 0.04$). However, axial length elongation was not affected by gender, initial myopia, initial refractive cylinder or initial corneal toricity (partial r: -0.36 to 0.22, $p > 0.08$).

4.3 Discussion

This study is the first longitudinal clinical study to investigate the effectiveness of toric design ortho-k for controlling myopic progression in myopic children with moderate to high amounts of astigmatism. Our results showed that toric design ortho-k effectively correct myopia and astigmatism, providing the ortho-k subjects with high and low contrast unaided visual acuity comparable to the HVA of the control subjects after stabilization of ortho-k treatment. Previous studies have reported reductions in low contrast visual acuity after ortho-k treatment (Tahhan et al., 2003; Berntsen et al., 2005). Tahhan et al. (2003) compared low contrast VA with four lens types after one month of lens wear and reported some variations among the lens types, from 1/2 to three letters which may not be clinically significant for low contrast acuity. Their subjects only wore ortho-k lens for about one month. Our results consistently showed no changes in low contrast VA over time (see Figure 4.2 (B)). Toric design ortho-k lenses can also slow myopic progression in children with myopia and moderate to high astigmatism.

Reports discussing the relationship between myopia and astigmatism are scarce (Saw et al., 2000; Fan et al., 2004b). Saw and co-workers (2000) reported no difference in the increase in myopia between astigmats (astigmatism > 0.50D) and non-astigmats in children six to 11 years old, but they did not investigate the association between initial astigmatism

and myopic progression. Fan et al. (2004b) reported an association between astigmatism and myopic progression among Asian children aged three to six years old but it appeared that their subjects were mostly hyperopes. Unfortunately, they did not provide further information about the myopic and astigmatic progression in their subjects.

The relationship between the baseline astigmatism and axial elongation of our subjects was analyzed and our result showed no correlation between these two factors. Since the current study did not include children with low astigmatism, in order to have better understanding of the effect of the astigmatism on myopic progression in children, we compared our results with those obtained from the ROMIO study (Cho and Cheung, 2012) which was a randomized clinical trial on the use of ortho-k for myopic control in myopic children with no or low astigmatism. TO-SEE and ROMIO studies were conducted concurrently at the same location by the same research group. The inclusion criteria of the two studies differed in age (up to 10 years old in ROMIO and up to 12 years old in TO-SEE) and refractive astigmatism ('low astigmats': refractive astigmatism of less than 1.25 D in ROMIO study; 'moderate-high astigmats': refractive (corneal) astigmatism 1.25 D or more in TO-SEE study). There were no significant differences in the initial myopia among the four groups of subjects (low or moderate-high astigmates fitted with ortho-k or spectacles (One-way ANOVA, $F_{3,132} = 1.30$, $p = 0.28$). We used analysis of covariance to adjust the effect of age and initial myopia and to test for differences between low

astigmats and moderate-high astigmats wearing ortho-k lenses or single-vision spectacles. There were no differences in the axial elongation between the low and moderate-high astigmats wearing single-vision spectacles (One-way ANCOVA, $F_{1,60} = 0.20$, $p = 0.66$) or ortho-k lenses (One-way ANCOVA, $F_{1,68} = 0.28$, $p = 0.60$). The 2-year axial elongations were 0.63 ± 0.26 mm and 0.65 ± 0.31 mm in low astigmats and moderate-high astigmats, respectively, wearing single-vision spectacles, and were 0.36 ± 0.24 mm and 0.33 ± 0.28 mm in low astigmats and moderate-high astigmats, respectively, wearing ortho-k lenses. That is, myopic progression was not affected by the initial refractive astigmatism of the eye but by the method of vision correction given to the subjects. Some investigators have queried if the use of axial lenth measurement is valid for monitoring myopic progression in children wearing ortho-k lenses since the treatment leads to corneal flattening and central corneal thinning. However, Cheung and Cho (2013) have shown that the anterior segment length (i.e. central corneal thickness + anterior chamber depth + crystalline lens thickness) was unaffected by ortho-k treatment when compared with children wearing glasses and confirmed that axial length is a valid parameter for monitoring myopic progression in ortho-k treated eyes.

Corneal complications associated with any contact lens wear can lead to vision impairment and potential blindness (Holden et al., 2003). Many

clinicians/researcher are concerned with the potentially increased risk involving overnight wear in ortho-k treatment (Tseng et al., 2005; Watt and Swarbrick, 2005; Santodomingo-Rubido et al., 2012b). Microbial keratitis in ortho-k lens wear has been reported in case studies (Watt and Swarbrick, 2007; Shehadeh-Masha'our et al., 2009), but not in clinical studies which usually require a higher standard of care being given to the subjects. Clinical studies on ortho-k for myopic control published to date, including the current study, have shown no severe adverse events which left permanent damage to the eye or vision (Walline et al., 2009; Swarbrick et al., 2010; Kakita et al., 2011; Cho and Cheung, 2012; Hiraoka et al., 2012). That is, with stringent management protocol (e.g. proper education and review on lens handling, and lens care products and procedures, frequent aftercare visits, education and re-education of patients and parents, and delivery of both written and verbal instructions), complications associated with ortho-k lens wear can be minimized. Santodomingo and co-workers (2012b) reported adverse events such as contact lens-induced peripheral ulcer and conjunctivitis but they also reported that these conditions “are not considered to be serious, are similar to those reported with other contact lens types, and can be managed easily in clinical practice”.

In the current study, we found no significant adverse events in both groups of subjects. Although ortho-k lens wear tended to increase the incidence of corneal staining in the peripheral cornea, the staining observed was

considered to be mild as depth of staining was mostly superficial (Grade 1) and the average incidence was less than 10%. The situation was similar to wearing any other types of daily wear soft contact lenses (Nichols et al., 2002). Such minor ocular problems can be monitored and easily managed by early detection and treatment such as use of artificial tears for lubrication.

Poor lens cleaning procedure and poor lens hygiene may increase the risk for infection in ortho-k patients as lenses are worn overnight (McLaughlin-Borlace et al., 1998; Watt and Swarbrick, 2007). Therefore, providing careful and specific education in the care of ortho-k lenses to both parents and children is important to minimize complications in ortho-k lens wear.

Lens binding has been reported to be the most common non-visual problem in ortho-k lens wear (Cho et al., 2003a; Chui and Cho, 2003; Cheung and Cho, 2004) and is a risk factor for corneal staining. However, in the current study, no lens binding was reported after 1-month lens wear nor at the subsequent visits. The low incidence of lens binding may be due to the use of fenestrated lenses (Cho et al., 2012a) and application of artificial tears to the eye prior to lens removal. All ortho-k subjects were required to remove the lens from each eye with fingers instead of lens remover. These steps may have aided lens mobility after waking up and minimized lens binding.

In ortho-k, the reshaped cornea changed relative peripheral refraction of the myopic eyes from relative hyperopia to relative myopia and this appears to be consistent with the suggestion that relative peripheral hyperopia drives myopic progression (Kang and Swarbrick, 2011). However, further evidence is required before any firm conclusion can be made on the mechanism of myopic control in ortho-k. The effectiveness of ortho-k for myopic control, in terms of axial elongation, using ortho-k has been reported to range from 32% to 55% (Cho et al., 2005a; Walline et al., 2009; Cho and Cheung, 2012; Hiraoka et al., 2012; Santodomingo-Rubido et al., 2012a). The only randomized longitudinal clinical trial published to date was 43% (Cho and Cheung, 2012). Axial elongation of subjects wearing toric ortho-k lenses was 52% slower compared to subjects wearing spectacles in the current study. However, as this was a non-randomized study, systematic bias cannot be ruled out. In the current study, the odds of children having fast progression in myopia (more than 1.00 D per year) were reduced with the use of ortho-k lenses. However, no conclusive evidence can be drawn on this issue from this study as there were only eight subjects demonstrating fast progression.

A randomized clinical trial would have provided better evidence on the effectiveness of using toric ortho-k for myopic control in myopic children with significant astigmatism. When we first planned this study, there was little report or clinical evidence of the effectiveness of toric ortho-k for

correcting astigmatism since toric design lenses were not commercially available in Hong Kong then. So, ethically, we could not conduct a randomised study on toric ortho-k for myopic control. In a non-randomized study, the observed differences may be attributed to pre-treatment differences between the test and control subjects, that is, there may be self-selection bias as subjects were allowed to choose which group they preferred to be. However, in this study, ortho-k subjects were recruited first as the original study (for a MPhil project) did not plan to have a control group. Control subjects were recruited later, after recruitment for ortho-k subjects had been completed. Self-selection bias was also minimised by making sure that there were no significant differences in baseline data between the control and the ortho-k groups and axial length measurements, the primary outcome, were made by a masked examiner who did not know the subjects' baseline data or which study they were participating in. However, in this study there were more subjects dropping out from the control group due to concerns about myopic progression at during the study (see next paragraph) and randomization would not have helped to reduce selection bias. Our result (ie. the rate of myopic control with ortho-k) may therefore have been underestimated as the control group may have less fast progressors than the ortho-k group.

Another potential limitation of this study is that it is unknown if the treatment effect continues after year two. We believe that a randomized clinical trial, with larger sample sizes to account for the potentially high

dropouts, particularly in the control group, is now warranted, in light of the evidence from this study, to confirm the effectiveness of toric ortho-k for myopic control.

Apart from being effective and safe, a good myopic control treatment should also provide convenience for children's daily activities. If the treatment is causing inconvenience or problems, a high dropout rate would be expected. The dropout rates with ortho-k lens wear ranged from 6% (Santodomingo-Rubido et al., 2012a) to 30% (Walline et al., 2009) in previous studies. In the current study, the dropout rates were 19% (8/43) and 38% (14/37) in the ortho-k and control groups, respectively.
All the dropouts in the control group were initiated by the parents. For the control subjects, any increase in myopia of 0.50 D or above at each subsequent visit required redispensing of spectacles. The four subjects who dropped out of the study at different visits during the study required an update in spectacles at each of the subsequent visit and this may have initiated parental anxiety. Concerned and worried about the myopic progression in their children, the parents decided to withdraw their children from the study and seek myopic control treatment elsewhere. On the other hand, dropouts in the ortho-k group were initiated by the investigators, either because of the unsatisfactory ortho-k lens wear which affected the daytime vision (six out of eight subjects) or noncompliance to the study protocol (stopped lens wear from time to time without notifying the

investigator) which affected the daytime vision and therefore the results of myopic control (two subjects).

Although we did not find any significant differences in the baseline data of those who dropped out and those who completed the study, nevertheless, the higher drop-out rate in the control group could lead to potential bias as explained in previous paragraph. It should be noted that the dropout results may be an indication that parents in Hong Kong are very concerned about myopic progression in their children and are eager to seek for an effective treatment to slow myopia. However, not all children are suitable to wear ortho-k lenses and even those who had good response in the beginning may not continue to show good or satisfactory responses with continued lens wear. Good ocular and visual responses require combined efforts from the practitioners, the children and their parents. Subjects wearing ortho-k lenses who completed the study had comparable visual quality to those wearing single-vision spectacles but enjoyed the additional benefit of convenience from spectacle-free vision in the daytime.

4.4 Conclusion

This non-randomized study has provided evidence that toric ortho-k lenses can provide clear unaided vision for myopic children with moderate to high astigmatism and effectively slows axial elongation in these children.

Chapter 4. Orthokeratology for correcting myopia and astigmatism and for myopic control

Publications:

1. Chen C, Cheung SW and Cho P. Myopia control using toric orthokeratology (TO-SEE study). Invest Ophthalmol Vis Sci. 2013; 54: 6510-17.
2. Chen C and Cho P. Toric orthokeratology for high myopic and astigmatic subjects for myopic control. Clin Exp Optom. 2012; 95: 103-8.

Conference presentations:

1. Chen C and Cho P. Toric orthokeratology for slowing eye elongation (TO-SEE) study. Presented at the 9th Asia Cornea and Contact Lens Conference, 22-23 April 2014, Taiwan. (Programme & Abstract Book, pp 44)
2. Chen C and Cho P. Toric orthokeratology for slowing eye elongation (TO-SEE) study. Presented at the British Contact Lens Association 37th Clinical Conference and Exhibition, 6-9 June 2013, Birmingham, United Kingdom. (Conference Manual, pp 59)
3. Chen C, Cheung SW, Cho P. One year results of the toric orthokeratology: slowing eyeball elongation study. Poster presented at the 8th Asia Cornea and Contact Lens Conference, 26-27 April 2012, Hong Kong. (Programme & Abstract Book, pp 33, Poster #2)

CHAPTER 5

Longitudinal changes in anterior and posterior corneal curvaturesand corneal thickness and effect of treatment zone size in myopic astigmatic children undergoing ortho-k treatment

5.1 Introduction

The clinical efficacy of ortho-k lenses for the reduction of low to moderate myopia is well reported. Ortho-k lenses are fitted with a base curve flatter than flat K to apply pressure to the central cornea to change the shape of the cornea. Ortho-k has been reported to reshape the anterior corneal curvatures, however changes to the posterior corneal curvatures in ortho-k has also received attention. The changes in corneal thickness and corneal curvatures with RGL, have focused mainly on anterior corneal shape (Swarbrick et al., 1998; Nichols et al., 2000; Alharbi and Swarbrick, 2003; Sridharan and Swarbrick, 2003; Haque et al., 2004; Cheung et al., 2007; Stillitano et al., 2007; Chan et al., 2008; Chen, 2011). Only a limited number of reports have included data on posterior curvatures (Owens et al., 2004; Stillitano et al., 2007; Tsukiyama et al., 2008; Chen et al., 2010; Chen, 2011) (see Sections 1.5.1.2 and 1.5.1.4). As both anterior and posterior corneal curvatures and corneal thickness can now be easily assessed using the Pentacam (see Sections 2.2.6.4 and 2.2.6.7), more

comprehensive data can now be obtained. The Pentacam calculated both anterior and posterior corneal power values by taking the average radius of axial (sagittal) curvature within the central 3.0 mm.

The system calculated total corneal power using the following formula:

$P_a = (n_2 - n_1) / R_a$

$P_p = (n_3 - n_2) / R_p$

$P_t = P_a + P_p - (2_t / _n) \times P_a \times P_p$

P_a = anterior corneal power; R_a = anterior corneal radius; P_p= posterior corneal power; R_p = posterior corneal radius; P_t = total corneal power; t = corneal thickness; and n_1, n_2, and n_3 are the refractive indices of air (1.000), cornea (1.376), and aqueous humor (1.336), respectively.

This chapter reports an investigation of longitudinal changes in anterior and posterior corneal curvatures and central corneal thickness (CCT) induced by ortho-k treatment and the comparison of these parameters with those from a control group wearing single vision spectacles. The validity of Munnerlyn's formula to explain refractive changes in ortho-k and the effect of treatment zone size (TxZ) on ortho-k refractive effect are alsoreported. Since the size of the TxZ is different along the horizontal (H) and vertical (V) meridians in toric ortho-k, for comparison of the astigmatic reduction with TxZ (V) size, the reduction in astigmatism was converted to reduction of refractive power along the vertical meridian (ie. myopia plus astigmatic reduction).

5.2 Results

5.2.1 Anterior and posterior corneal curvatures

There were no significant differences in baseline anterior and posterior Sim K_{flat} and Sim K_{steep} between two groups of subjects (unpaired t-tests, anterior at baseline: Sim K_{flat}, $p = 0.52$; Sim K_{steep}, $p = 0.21$); (posterior: Sim K_{flat}, $p = 0.25$; Sim K_{steep}, $p = 0.42$).

Table 5.1 Anterior and posterior Sim K_{flat} and Sim K_{steep} with orthokeratology lens wear

	Baseline	1-month	6-month	12-month	18-month	24-month
Anterior*						
Sim K_{flat}	43.32±1.34	42.04±1.31*	41.92±1.29*	41.93±1.39*	41.80±1.44*	41.89±1.37*
Sim K_{steep}	45.47±1.50	43.54±1.46*	43.40±1.43*	43.43±1.40*	43.46±1.48*	43.54±1.48*
Posterior						
Sim K_{flat}	-6.07±0.24	-6.07±0.21	-6.08±0.20	-6.09±0.20	-6.09±0.19	-6.09±0.22
Sim K_{steep}	-6.67±0.23	-6.66±0.24	-6.65±0.25	-6.69±0.23	-6.70±0.24	-6.69±0.23

*Significant changes from baseline were observed with the commencement of orthokeratology lens wear (repeated measures ANOVA (all visits), $p < 0.05$) but changes among subsequent visits (1-24-month visits)were not significant (repeated measures ANOVA, $p > 0.05$).

In the ortho-k group, significant changes in the anterior Sim K_{flat} and Sim K_{steep} were observed during the study period (repeated measures ANOVA (all visits), Sim K_{flat}, $p < 0.001$; Sim K_{steep}, $p < 0.001$). However, this was entirely due to differences in curvature from the baseline visit, as no changes were observed in subsequent visits (repeated measures ANOVA

(1- 24-month visits), Sim K_{flat}, p = 0.10; Sim K_{steep}, p = 0.53) (Table 5.1).

In the control group, no significant changes in anterior Sim K_{flat} and Sim K_{steep} were observed over the study period (repeated measures ANOVA, Sim K_{flat}, p = 0.33; Sim K_{steep}, p = 0.43) (Table 5.2).

In both ortho-k and control groups, there were no significant changes in the posterior Sim K_{flat} and Sim K_{steep} at all visits (repeated measures ANOVA, ortho-k group: Sim $K_{flat,}$ p = 0.92; Sim K_{steep}, p = 0.06; control group: Sim K_{flat}, p = 0.19; Sim K_{steep}, p = 0.96).

Table 5.2 Anterior and posterior Sim K_{flat} and Sim K_{steep} in the control subjects at different visits

	Baseline	6-month	12-month	18-month	24-month
Anterior					
Sim K_{flat}	43.54±1.17	43.37±1.37	43.38±1.29	43.35±1.34	43.38±1.27
Sim K_{steep}	45.95±1.27	45.75±1.59	45.83±1.48	45.83±1.58	45.87±1.57
Posterior					
Sim K_{flat}	-6.15±0.25	-6.07±0.25	-6.09±0.21	-6.09±0.22	-6.09±0.21
Sim K_{steep}	-6.73±0.25	-6.72±0.28	-6.73±0.25	-6.74±0.27	-6.72±0.26

Significant correlation between myopic reduction and changes in anterior Sim K_{flat} was observed at the 1-month visit (r = 0.49, p = 0.003) but no such correlation was observed with anterior Sim K_{steep} (r = 0.25, p = 0.15). No correlations between changes of anterior Sim K_{flat} and Sim K_{steep} and astigmatic reduction were observed after 1-month of lens wear (Sim K_{flat}: r = -0.14, p = 0.43; Sim K_{steep}: r = -0.20, p = 0.24).

Table 5.3 Central corneal thicknesses in orthokeratology and control group at different visits

Visit	Orthokeratology (n=35) (Mean±SD) (μm)	Control(n=23) (Mean±D) (μm)	P value
Baseline	566±30	577±35	
1-month	558±33	--	--
6-month	559±31	576±32	0.04
12-month	558±32	576±32	0.05
18-month	562±32	582±32	0.02
24-month	561±30	583±31	0.01*

*probability values for differences between groups using independent t-testwith Bonferroni correction (adjusted $p < 0.01$)

5.2.2 Corneal thickness

Table 5.3 shows the CCT values (mean ± SD) obtained at different visits in both ortho-k and control subjects. For the ortho-k subjects, CCT was significantly thinned by 7 ± 9 μm at the 1-month visit (paired t-test, $p = 0.004$). As had been observed with anterior curvature, no significant differences in CCT were observed atthe subsequent visits after the 1-month visit (repeated measures ANOVA (1 - 24 month visits), $p = 0.41$). In the control group, no significant differences in CCT were observed at any visits during the 24-month study period (repeated measures ANOVA, $p = 0.09$). Comparing the ortho-k and control groups, no significant differences in the CCT were observed at all visits (unpaired t-tests (with Bonferroni correction), $p > 0.01$), except at the 24-month visit (Table 5.3). In the ortho-k group, after 1-month of lens wear, no correlation between

changes in CCT and myopic and astigmatic reductions were observed (Myopic reduction: r = 0.23, p = 0.18; astigmatic reduction: r = 0.01, p = 0.95).

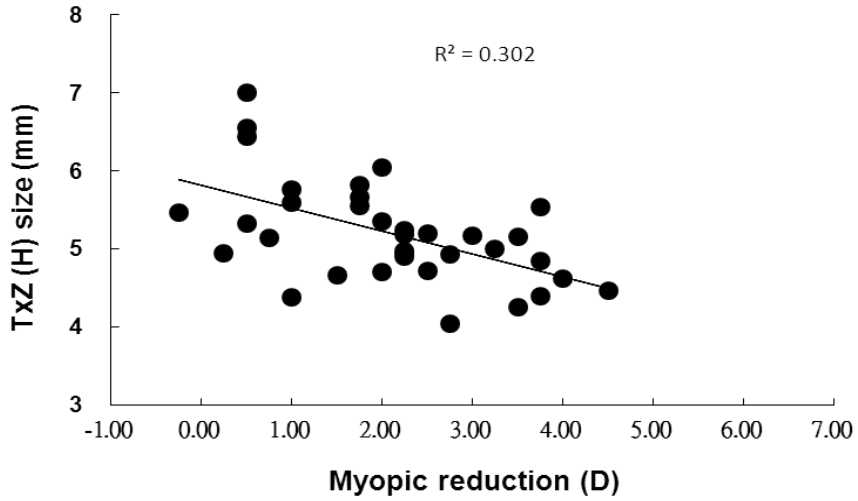


Figure 5.1 Relationship between horizontal treatment zone size and myopic reduction

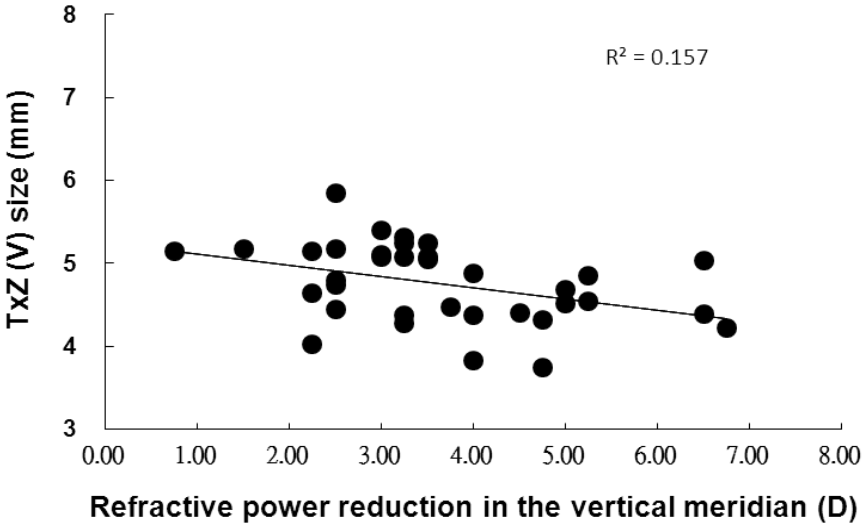


Figure 5.2 Relationship between vertical treatment zone size and the refractive power reduction in the vertical meridian

5.2.3 Treatment zone size diameter

Mean ± SD TxZ (H) and TxZ (V) sizes were 5.20 ± 0.65 mm and 4.76 ± 0.47 mm after 1-month of ortho-k lens wear, respectively. The difference between TxZ (H) and TxZ (V) size was not correlated to the astigmatic reduction ($r = -0.24$, $p = 0.16$).

TxZ (H) and TxZ (V) sizes along the horizontal and vertical meridians were compared with the myopic reduction and refractive power reduction in the vertical meridian, respectively at 1-month visit. TxZ (H) size was significantly associated with myopic reduction ($r = -0.55$, $p < 0.001$) (Figure 5.1) and TxZ (V) was significant correlated with the refractive power reduction in the vertical meridian ($r = -0.40$, $p = 0.02$) (Figure 5.2) after 1-month of lens wear.

Both TxZ (H) TxZ (V) sizes were not correlated with any of the following factors: high contrast UVA and BCVA (UVA: $-0.17 < r < -0.002$, $0.32 < p < 0.99$; BCVA: $-0.09 < r < 0.07$, $0.62 < p < 0.68$) and low contrast UVA and BCVA (UVA: $r = -0.27 < r < -0.10$, $0.12 < p < 0.56$; BCVA: $-0.24 < r < -0.19$, $0.16 < p < 0.28$).

5.3 Discussion

Two main hypotheses on the mechanism of refractive correction in ortho-k treatment have been proposed. The first proposes that overall corneal bending causes the effect, whereas the second suggests that the effect is caused by changes in the anterior segment of the cornea (Swarbrick et al.,

1998; Alharbi and Swarbrick, 2003; Stillitano et al., 2007; Chen et al., 2010). In this long-term study, significant changes in anterior Sim K_{flat} and Sim K_{steep} were observed in the ortho-k group at the 1-month visit but no further changes were observed in the subsequent visits. This may be explained by the stabilization of the ortho-k effect after about one month of lens wear.

Our results showed no significant change in the posterior corneal curvatures in both ortho-k and control groups over time. Owens et al. (2004) reported a transient change (statistically significant) in the posterior corneal curvatures after one week of ortho-k lens wear (see Section 1.4.1.3). They suggested the possibility of overall corneal bending during the early adaptive stage of ortho-k treatment. Read and Collins (2009) reported posterior corneal steepening immediately after sleep without wearing lenses and Chen et al. (2010) reported that the posterior corneal curvatures steepened after 60 minutes and overnight ortho-k lens wear. Although these two studies both showed posterior corneal steepening, the curvatures returned to their original values two to three hours after awakening in Chen and colleagues' report (2010). Read and Collins (2009) suggested that the steepening of posterior corneal curvatures was due to uneven corneal oedema between the central and peripheral corneal regionsafter sleep. Read and Collins (2009) reported that the mean amplitude of change in the posterior corneal best sphere was 0.05 ± 0.03 D and 0.04 ± 0.02 D for the central 3.5 and 7.0 mm diameters after sleep

without wearing lenses. Chen et al. (2010) reported that the change in posterior SimK_{flat} and Sim K_{steep} steepening of 0.06 D and 0.07 D (from baseline values of -6.09 to -6.15 D (SimK_{flat}) and -6.48 to -6.55 D (Sim K_{steep})) (central 3 mm zone) after lens removal within two hours of eye opening after overnight ortho-k lens wear, and no corneal steepening was observed at the other visits. Hence, the corneal steepening observed is unlikely to be related to ortho-k lens wear. Results from subsequent studies (Stillitano et al., 2007; Tsukiyama et al., 2008) also showed no significant changes in posterior corneal curvatures with ortho-k lens wear in short (one week) and longer (one year) term ortho-k treatment. In the current study, the data were taken within two hours after awakening at the 1-month visit and within six to 12 hours after lens removal in the subsequent visits. Any posterior corneal steepening induced by wearing overnight ortho-k lens may have recovered when the measurements were taken. After one month of lens wear, the treatment was considered to have stabilized, so measurements taken after this period could reflect the ortho-keffect more accurately. The refractive error changes in ortho-k treatment is mainly due to the flattening of the anterior corneal curvature and the treatment was stabilized after 1-month of lens wear, which was in agreement with the findings of previous studies (Alharbi et al., 2005; Cho et al., 2005a; Jayakumar and Swarbrick, 2005; Kang et al., 2007; Chan et al., 2008; Stillitano et al., 2008). On the other hand, our results confirmed that the posterior corneal curvatures did not play a role in effecting

refractive changes in ortho-k treatment (Stillitano et al., 2007).

Swarbrick et al. (1998) reported central epithelium thinning of 7.1 ± 7.1 μm after 28 days of day wear ortho-k treatment. Alharbi and Swarbrick (2003) reported epithelium thinning of 15.8 ± 3.3 μm after 1-month of overnight ortho-k treatment (see Section 1.4.1.2). They concluded that ortho-k led to a rapid thinning and thickening of the epithelium and mid-peripheral stroma respectively. Using Munnerlyn's formula, they showed that the changes in corneal thickness led to a change in corneal sagittal height which could account for the refractive change observed in ortho-k. In their case report, Reinstein et al. (2009) reported a central epithelium thinning of 14 μm (right eye) and 18 μm (left eye) after 30 days of ortho-k lens wear and they concluded that the refractive changes during ortho-k treatment was mainly induced by changes in epithelium thickness. Gonzalez-Perez et al. (2012) reported a mean ± SD of 22.25 ± 12.13 μm central corneal thinning after 12-month of ortho-k lens wear.

In the current study, significant differences in CCT were observed between ortho-k and control groups (see Section 5.2.2), but CCT thinning observed in ortho-k group (3 to 7 μm) was substantially less than those reported in previous studies (see Section1.5.1.2). The mean ± SD of myopic and astigmatic reduction were 2.09 ± 1.22 D and 1.32 ± 0.93 D respectively after 1-month of ortho-k lens wear (see Section 3.2.4). Our results also showed no correlation between changes in CCT and myopic and

astigmatic reductions.

If we applied Munnerlyn's formula using the 1-month data of myopic reduction, with an average TxZ (H) diameter of 5.20 ± 0.65 mm, the CCT thinning should be 18 ± 9 μm instead of 7 ± 9 μm. However, the CCT thinning at 1-month visit was only 7 ± 9 μm. We therefore concluded that corneal thickness changes alone could not explain the change in refractive error of the ortho-k treated eye and there may be other factors such as aberration or refractive index. Variations in magnitudes of corneal thinning reported between studies could be due to the use of different instruments in different studies (see Section 1.5.1.2). Optical pachometry was used in the studies of Swarbrick (1998), Alharbi and Swarbrick (2003) and Stillitano et al. (2007) whereas other reports (Chen, 2011; Charm and Cho, 2013b) used the Pentacam system. Different lens design and duration of lens wear were also used in different studies which may also affect the results. It appears likely that there are other mechanisms underlying the ortho-k effect. It would be interesting to perform further studies investigating epithelial, stromal, and total corneal thickness profile changes using different ortho-k lens designs.

Only a few papers have reported the TxZ size after ortho-k treatment (Sridharan and Swarbrick, 2003; Tahhan et al., 2003; Owens et al., 2004; Lu et al., 2007a), and most of them only measured, either the horizontal or the vertical TxZ diameters. None of them reported both horizontal and

vertical treatment zone sizes, this study being the first to investigate both horizontal and vertical TxZ sizes in toric ortho-k treated eyes. The difference between TxZ (H) and TxZ (V) was due to the use of toric ortho-k lens design which allowed astigmatic correction. The correlation between myopic reduction and TxZ (H) size was 0.55 so only 30% of the variance of the myopic reduction was accounted for by linear relationship with TxZ (H) size. A weak but statistically significant correlation in the TxZ (V) size and refractive power reduction in the vertical meridian was found. Only 16% of the variance of the TxZ (V) size was accounted for by linear relationship with refractive power reduction in the vertical meridian. In the current study, the TxZ (H) was associated with myopic reduction and TxZ (V) was associated with the refractive power reduction in the vertical meridian. As shown in Figures 5.1 and 5.2, the lower the power reduction, the larger the treatment zone and this was true for both horizontal and vertical meridians. The TxZ (H) size was similar to those reported in previous studies (4.66 to 5.59 mm) (Table 1.11) and the average myopic reduction was similar to the previous studies (Table 1.9). Other possible factors may affect the TxZ size such as the initial corneal shape, corneal eccentricity, or lens diameter and this remains an area for further study. The back optical zone and reverse zone of thelens design used in the current study is of spherical design (see Section 1.2.2.1). To initiate the ortho-k effect for myopic reduction, forces under the lens called “squeeze film force” are increased (Mountford and Noack, 1998). The tear squeeze

film force underneath the lens is the combination of positive compressive (+ve) at the apex of the cornea and negative tension (-ve) under the RC. Compression force acts in the central region and tension force acts at the junction between the BOZR and RC. The lens heights and tangent angles at the alignment zone of the lens are different with respect to the two principal meridians, which can provide an optimal fitting and centration on a toric cornea (see Section 1.2.2.1). The peripheral toric ortho-k design means the tangents to align the lens on the peripheral cornea. Changing the tangent angles alters the sagittal height of the lens. The tangent angles are calculated from the apical radius values of the steep and flat meridians, as well as the elevation along each meridian.

When a spherical ortho-k lens is fitted on a spherical cornea, a complete 360 degrees alignment compression is created as the lens sagittal height is the same at each meridian, effecting a myopic reduction. As mentioned in Section 1.1, centration of spherical ortho-k lens on a toric cornea is poor. The toric lens used in this study has a spherical BOZR (for myopic reduction) and toric alignment curves which give rise to different lens sagittal heights at the horizontal and vertical meridians, creating different tear profiles and compression forces along the two principal meridians. The greater seal off at the vertical meridian, because of larger compression force, leads to larger power reduction, effecting astigmatic reduction.

Spherical ortho-k lenses have been shown to be ineffective for the

correction of astigmatism. Lens decentration is the most common problem with spherical ortho-k lenses on patients with high corneal astigmatism and poor lens centration can lead to induced astigmatism, glare and poor vision.

Differential changes in corneal curvature in the horizontal and vertical meridians would be reflected in changes in refractive astigmatism, which may cause the difference of treatment zone size in horizontal and vertical meridians.

Our results confirmed that TxZ (H) and TxZ (V) were associated with myopic reduction and the refractive power reduction in the vertical meridian, respectively. Hence, for toric design lenses for correcting astigmatism, any studies on TxZ would require determination and analysis of the treatment zone size along the two principal meridians.

5.4 Conclusion

Results from current study confirmed that ortho-k treatment led to a flattening of anterior corneal curvatures which stabilized after 1-month of lens wear with no changes to the posterior corneal curvatures. Myopic and astigmatic reduction induced by ortho-k could not be explained by changes in anterior corneal curvatures or CCT alone, and Munnerlyn’s formula cannot be used for explaining refractive changes. TxZ (H) and (V) sizes were associated with refractive changes in horizontal and vertical

meridians respectively.

Chapter 5. Longitudinal changes in cornealcurvaturesand corneal thickness and effect of treatment zone size

Publication:

Conference presentation:

1. Chen C, Cheung SW, Cho P. Corneal biomechanical changes in long-term orthokeratology wear on myopic and astigmatic children. Presented at the British Contact Lens Association 35th Clinical Conference and Exhibition, 26-29 May 2011, Manchester, United Kingdom. (Conference Manual, pp 22)

CHAPTER 6

Longitudinal changes in corneal biomechanics in terms of corneal hysteresis (CH) and corneal resistance factor (CRF) in myopic astigmatic children undergoing ortho-k treatment

6.1 Introduction

The Reichert Ocular Response Analyzer (ORA; Reichert, Depew, NY) can be used to assess the corneal biomechanical response of the cornea and its ability to differentiate the biomechanical characteristics of keratoconus, glaucoma, and post-LASIK corneas from normal corneas has been demonstrated (see Section 1.5.1.1). Corneal biomechanics include parameters such as central corneal thickness, corneal viscosity, elasticity, hydration and regional corneal thickness (Liu and Roberts, 2005). Both CH and CRF have been shown to be significantly reduced after refractive surgery (Pepose et al., 2007; Chen et al., 2008; Franco and Lira, 2009; Shah et al., 2009) and could influence the measurements of IOP (Liu and Roberts, 2005; Hager et al., 2007). Several recent studies have reported CH and CRF in adults and the mean values ranged from 9.6 to 12.5 mmHg and 9.4 to 11.9 mmHg, respectively (see Section 1.5.1.1) (Table 1.10). However, there is limited data on the corneal biomechanical properties of children, although the CH values in children have been reported to be similar to values in adults (Kirwan et al., 2006). With the

increasing popularity of ortho-k for myopic control in children, there is a need to understand how the biomechanical properties of the corneas in children wearing ortho-k lenses may affect the treatment, or if ortho-k can change the corneal biomechanics. To date, there is no study on the effect of long-term ortho-k lens wear on biomechanical properties of the cornea.

The purpose of this study was therefore to investigate CH and CRF changes in myopic astigmatic children undergoing ortho-k treatment and compare them with those wearing single vision spectacles in a 2-year longitudinal study.

6.2 Results

Fifty-eight subjects (ortho-k: 35; control: 23) completed the 2-year study (See Table 4.2 for demographical data of the two groups). Myopic and astigmatic reductions were stabilized after 1-month lens wear with no significant changes observed in the subsequent visits (repeated measures ANOVA, myopia: $p = 0.05$; astigmatism: $p = 0.64$) (See Table 4. 4).

Baseline CH and CRF were 10.8 ± 1.3 mmHg and 10.7 ± 1.4 mmHg in the ortho-k group and 11.4 ± 1.9 mmHg and 11.1 ± 1.5 mmHg in the control group, respectively. There were no significant differences in baseline CH and CRF between the two groups of subjects (unpaired t-test, CH: $p = 0.19$; CRF: $p = 0.34$).

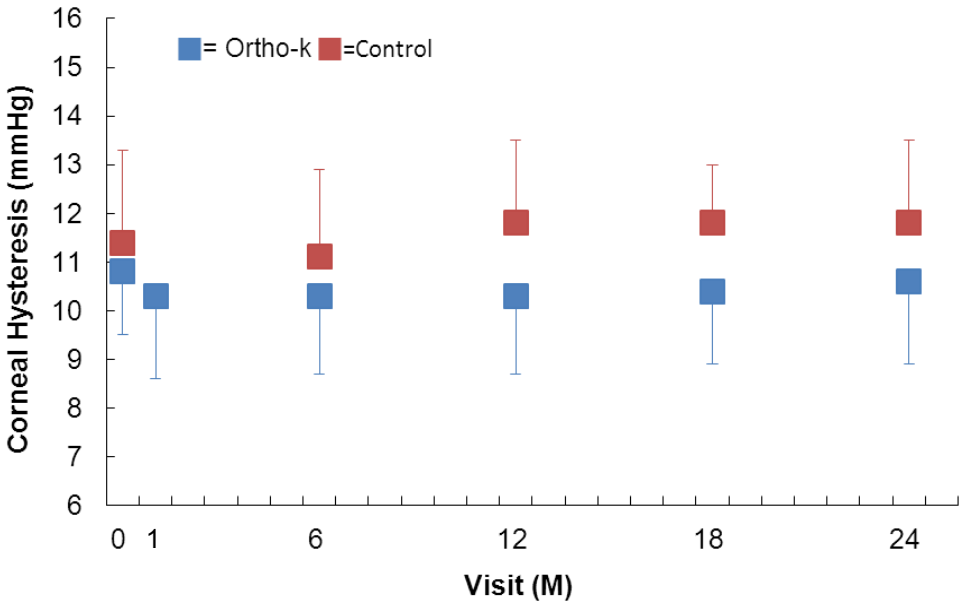


Figure 6.1 Corneal hysteresis values in the orthokeratology and control subjects at different visits during the study period (Each error bar indicates one standard deviation) (M = month)

6.2.1 Corneal hysteresis (CH)

Figure 6.1 shows the CH measurements in the two groups of subjects at baseline and at different visits during the study period. No significant changes were observed in CH at all visits for either group of subjects (repeated measures ANOVA, Ortho-k: $p = 0.08$; Control: $p = 0.19$).

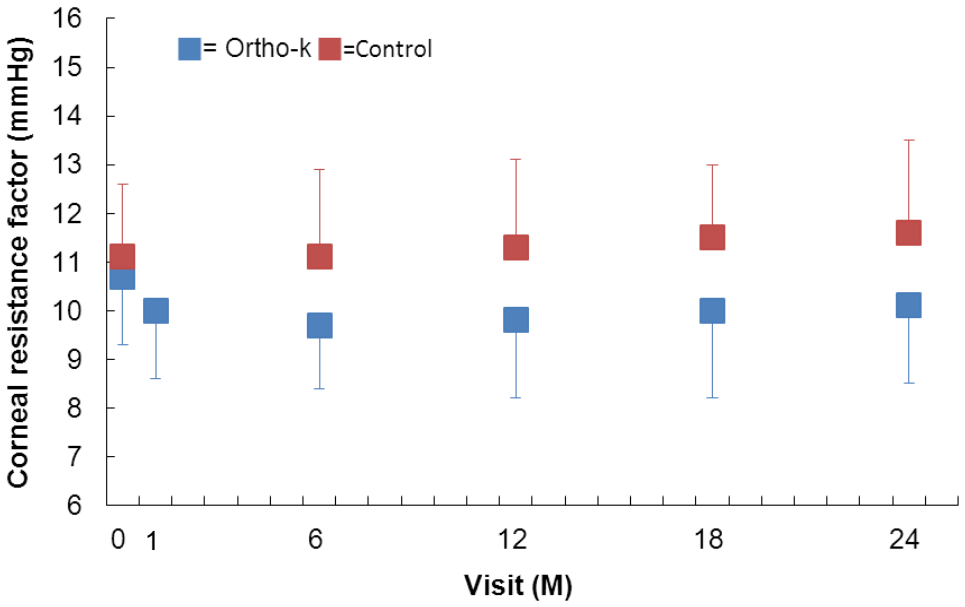


Figure 6.2 Corneal resistance factor values in orthokeratology and control groups at different visits during the study period (Each error bar indicates one standard deviation) (M = month)

6.2.2 Corneal resistance factor (CRF)

Figure 6.2 shows the CRF values in both ortho-k and control subjects. In the ortho-k group, CRF significantly reduced from an average of 10.7 ± 1.4 mmHg at baseline to 10.0 ± 1.4 mmHg after 1-month of lens wear (paired t-test, $p = 0.003$) and no significant difference were found in the subsequent visits (1-24 months: repeated measures ANOVA, $p = 0.36$). In the control group, no significant changes in CRF was found throughout the study (repeated measures ANOVA, $p = 0.27$).

6.2.3 Correlation between changes in CH and CRF and myopic and astigmatic reduction in orthokeratology subjects

There was no correlation between baseline CH and baseline CRF and

myopic and astigmatic reduction after 1-month of lens wear (i.e. after stabilization of treatment) (myopic reduction: CH: r = -0.10, p = 0.57; CRF: r = -0.12, p = 0.51; astigmatic reduction: CH: r = 0.16, p = 0.36; CRF: r = 0.23, p = 0.19).

No correlation was found between changes in CRF and myopic reduction (r = 0.06, p = 0.75) and no correlation between changes in CRF and astigmatism reduction (r = 0.31, p = 0.07) after 1-month of lens wear were found.

6.2.4 Correlation between CH and CRF and changes of Sim K_{flat} and Sim K_{steep}

No significant correlations between baseline CH and changes of Sim K_{flat} and Sim K_{steep} were observed (Sim K_{flat}: r =0.31, p = 0.07; Sim K_{steep}: r = 0.26, p = 0.13). Similarly, there were no significant correlations between changes of CRF and changes of Sim K_{flat} and Sim K_{steep}. However, after 1-month of lens wear, correlations between baseline CRF and Sim K_{flat} (r = 0.40, p = 0.02) and Sim K_{steep} reached significance (r = 0.38, p = 0.02) although observed. However, the relationships were very weak. No significant correlations between baseline CH and baseline CRF and reduction in corneal toricity were observed (Bonferroni correction applied), p > 0.01).

6.3 Discussion

For corneal biomechanics, the baseline results of our subjects were similar to those reported in previous studies (Luce, 2005; Kirwan et al., 2006; Shah et al., 2006; Lam et al., 2007; Lu et al., 2007b; Ortiz et al., 2007; Pepose et al., 2007; Shah et al., 2007; Kirwan et al., 2008; Lim et al., 2008; Song et al., 2008; Chen et al., 2009; Franco and Lira, 2009; Abitbol et al., 2010) (Table 1.10)

To date, only a few studies have reported the effect of ortho-k treatment on CH and CRF (Gonzalez-Meijome et al., 2008; Chen et al., 2009; Glavine, 2009). Gonzalez-Meijomeand colleagues (2008) reported a significant correlation between CH and changes in steep keratometry. They also reported that corneas with higher CH values showed slower ortho-k effect and no correlation was found between ortho-k effect and CRF values. However, in their study, they had a small sample size and ortho-k effect was observed after only three hours of lens wear. Chen et al. (2009) investigated the corneal biomechanical property changes after four different durations of ortho-k lens wear (15, 30, 60 minutes and overnight). They reported no significant changes in CH throughout the study, while CRF significantly reduced from an average of 10.7 mmHg at baseline to 10.1 mmHg after overnight lens wear (repeated measures ANOVA, $p < 0.05$).

Glavine (2009) reported a significant decrease in CRF after 3-week of lens wear and but this may be because the ortho-k effect had not stabilized.

Also, Glavine reported different results in two eyes of ortho-k subjects. Only the right eye showed a significant decrease in CRF at 1-week and 3-week visits.

In the current study, a similar result was obtained compared with previous studies (Chen et al., 2009; Glavine, 2009). No significant correlations between baseline CH and CRF and myopic and astigmatic reduction were found at the 1-month visit. There was no correlation between the changes in CRF and both myopic and astigmatic reductions after the 1-month visit, that is, after stabilization of ortho-k treatment.

Results suggested that the parameters stabilized with the stabilization of ortho-k treatment after one month of lens wear. The change in CRF may be effected by the initial change in the corneal shape/tissue from ortho-k lens wear. The change in CRF was noted in two previous studies (Chen et al., 2009; Glavine, 2009) and it is still unclear whether or not the CRF change represents an overall reduction in corneal rigidity brought about by ortho-k treatment. There was no strong evidence in the data indicating that a significant relationship exists between corneal properties and corneal curvature change with ortho-k treatment. Although (Gonzalez-Meijome et al., 2008) suggested that CH and CRF were predictive of rates of corneal change over short term lens wear, the results of this study which had a larger sample size and longer term ortho-k lens wear, did not support their susggestion.

Myopia reduction is achieved by significant flattening of the anterior corneal curvature and reduction in the central corneal thickness, which prompted interest in investigating corneal biomechanical properties in ortho-k treatment. Many ortho-k researchers are interested in the predictability of the ortho-k effect. However, our results showed that CH and CRF were not useful parameters for predicting myopic reduction by ortho-k treatment. More studies are needed to investigate changes in the in vivo measurement of corneal biomechanics, other than CH and CRF.

6.4 Conclusion

This study confirmed no significant changes in CH with long-term ortho-k lens wear. CRF initially decreased but stabilized after one month of lens wear. No significant correlation was found between CRF values and myopic reduction. Therefore, neither CH nor CRF are therefore useful parameters for predicting ortho-k response.

Publications:

Conference presentations:

1. Chen C, CheungSW, Cho P. Corneal biomechanical changes in long-term orthokeratology wear on myopic and astigmatic children. Presented at the 3rd Asia Orthokeratology and Specialty Lens Conference, 30-31 March 2012, Hangzhou China. (Abstract Book, pp 221)
2. Chen C, Cheung SW, Cho P. Corneal biomechanical changes in long-term orthokeratology wear on myopic and astigmatic children. Presented at the British Contact Lens Association 35th Clinical Conference and Exhibition, 26-29 May 2011, Manchester, United Kingdom. (Conference Manual, pp 22)

CHAPTER 7

Summary and conclusion

7.1 Summary and conclusion

The prevalence of myopia is high especially in Asian countries. Most myopic children are also astigmatic but spherical design ortho-k lenses cannot significantly reduce astigmatism and may not be used to successfully reduce myopia. There is therefore a need for a toric design ortho-k lens that can be used for children with myopia and moderate-to-high astigmatism.

This study was a single masked, non-randomized longitudinal study to evaluate the effectiveness of a toric design ortho-k lens for correcting myopia and astigmatism and for myopic control. The long term effects and changes on corneal curvatures and biomechanics were investigated over a 2-year period. At the end of the 2-year study period, 35 ortho-k and 23 control subjects completed the study (Chapter 4). No statistically significant differences in baseline values (age, myopia, astigmatism, corneal astigmatism, BCVA and axial length) were found between the two groups of subjects who completed and those who dropped out of the study (see Section 4.2).

Significant reductions in myopia and astigmatism were observed with toric design ortho-k lens wear over the 2-year study period. The maximum

myopic and astigmatic reductions were 81% and 79%, respectively after 1-month of lens wear. No significant changes in myopia and astigmatism were observed after the 1-month visit (Chapter 3).

The use of toric design ortho-k lenses gave better lens centration which probably led to better astigmatic reduction. Changes in both subjective and objective refractive astigmatism (corneal plane) were not reflected by changes in corneal toricity. The maximum reduction in corneal toricity (and J_0) was only about 45% in ortho-k subjects. Slight and clinically insignificant changes were observed in J_{45}. These results suggested that the normal relationship between refractive astigmatism and corneal toricity in non-ortho-k treated eyes may not apply in ortho-k, and some other factors may be effecting the change in refractive astigmatism in post-ortho-k subjects.

Although subjects reported a satisfactory vision, UVA was poorer compared to baseline BCVA. UVA was 0.11 ± 0.13 logMAR at 1-month visit whereas baseline BCVA was 0.00 ± 0.07. For subjects with residual myopia or astigmatism more than 0.75 D or UVA worse than 0.18 logMAR after 4 weeks of lens wear, lenses with higher targets were ordered and fitted to attempt higher reductions to achieve our endpoint criteria, that is myopia < 0.75 D or unaided VA better than 0.18 logMAR. All of these subjects achieved the endpoint criteria with the replacement lenses.

Our results showed mean ± SD axial elongation of 0.36 ± 0.16 and 0.28 ± 0.22 mm in the first year and second year, respectively, in the control subjects, and 0.15 ± 0.18 and 0.16 ± 0.12 mm, respectively, in the ortho-k subjects (Chapter 4). The levels of reduction of myopic progression compared to the spectacle-wearing control group were 61%, 58%, 53%, and 52% (cumulative elongations) after 6, 12, 18 and 24 months of ortho-k lens wear (see Section 4.2.5). No significant adverse event was observed in either the ortho-k or control subjects during the study period.

The drop-out rates in the current study were 19% and 38% in the ortho-k and control groups, respectively. Drop-outs from the ortho-k group were all initiated by the investigators, due of unsatisfactory myopic and astigmatic reduction which may affect the daytime vision and due to non-compliance to the study protocol. For the control subjects, all the drop-outs were initiated by the parents. The main reason for the drop-outs in the control group was that parents were worried about the myopic progression in their children. Our results demonstrated the strong potential for toric design ortho-k to slow the development of myopia in children.

Results from the current study confirmed that toric design ortho-k treatment led to a flattening of anterior corneal curvatures and with no changes to the posterior corneal curvatures in both ortho-k and control groups during the study period (see Section 5.2.1). A significant change in CCT was observed after 1-month of lens wear in ortho-k subjects but no

significant changes were observed in the subsequent visits after the 1-month visit. No significant differences in CCT were observed at any visits during the 2-year study period in the control subjects (see Section 5.2.2).

The results also showed no correlation between changes in CCT and myopic and astigmatic reductions. Myopic and astigmatic reductions induced by ortho-k could not be explained by changes in anterior corneal curvatures or CCT alone, and Munnerlyn's formula cannot be used for explaining refractive changes. Further investigations may be warranted to ascertain the changes in corneal thickness and the role it plays in myopic reduction in ortho-k treated eyes.

The treatment zone on a toric cornea after wearing a toric design ortho-k lens tended to be oval in shape. Not unexpectedly, the horizontal treatment zone size was significantly correlated with myopic reduction andvertical treatment zone size with the refractive power reduction in the vertical meridian.

CH values did not change significantly with ortho-k lens wear during the study period (Chapter 6). A significant change in CRF value was observed, and it stabilized after 1-month visit and remained stable with continued lens wear (see Section 6.2). The change in CRF may be due to the initial change in the corneal shape/tissue from ortho-k lens wear.

No significant correlations between baseline CH and CRF and myopic and astigmatic reduction were found at 1-month visit (Chapter 6).

We also found no evidence to indicate any significant relationship between corneal properties and corneal curvature change in ortho-k treatment. Our results showed that CH and CRF were not useful parameters for predicting myopic reduction by ortho-k treatment.

7.2 Limitations and further studies

Similar to other studies, there are some limitations in this study. Arandomized clinical trial would be the gold standard design for evaluating the effect of myopic control and/or astigmatism improvement for any treatment.

If this was a randomized clinical trial, our results would have provided confirmation on the effectiveness of toric design ortho-k for myopic control in myopic children with significant astigmatism.

When this study was planned there was little data on the performance of toric ortho-k. The success rate (e.g. refractive correction for both spherical and astigmatic components and its safety) of toric ortho-k in children was not known. At the time, ortho-k lenses were spherical in design and the toric ortho-k lenses was only just being introduced in selected markets, with limited or unknown success (i.e. no published reports). Hence conventionally, children with high astigmatism were considered contraindicated for ortho-k. The effectiveness and acceptance of using

toric ortho-k treatment for myopic correction was therefore unknown. Considering these issues, we could not plan for a randomized trial.
So as non-randomized clinical study was performed systematic bias cannot be ruled out. Another potential limitation is that it is unknown if the treatment effect continues after year two. Given the results of the study, a randomized clinical trial is now warranted, to confirm the effectiveness of toric design ortho-k for myopic control.

A 2-year randomized study which assessed the clinical performance of partial reduction using ortho-k lens and myopic progression in high myopic children (8-11 years) with SER -5.75 D or abovehas recently been completed (Charm and Cho, 2013a). These researchers confirmed that retarding of myopic progressionby using ortho-k lens for partial reduction is safe and effective option for high myopic children. The prevalence of high myopia (> 6.00 D) in Hong Kong was recently estimated as 3.8% in 12 years old children (Lam et al., 2012), but the prevalence of high astigmatism in high myopic children is unknown. Further studies could be conducted to investigate the toric design ortho-k for partial correction on high myopic and astigmatic children for myopic control.
The myopic progression in children is of great concern in Asian countries as the prevalence of myopia is high in Asia and may be increasing (Fan et al., 2004a; He et al., 2004; Cheng et al., 2007; Shih et al., 2010; Lam et al., 2012) and the prevalence of astigmatism was reported to range from 23 to 58% in Asian countries (Fan et al., 2004b; He et al., 2004; Shih et al.,

2004; Saw et al., 2006; Leung et al., 2012). However, this study was limited to only Hong Kong children. The effectiveness of toric design ortho-k for myopic and astigmatic correction and myopic control of different ethnicity is still uncertain, so further studies are warranted to confirm the current results.

Leung et al. (2012) reported that higher myopia was associated with astigmatism in young Chinese adults, who noted that the prevalence of astigmatism increased from 17.8% in the three to ten years old group to 31.4% in the 11 to 20 years old group. They also mentioned that the young adult population (21-30 years) not only had the highest magnitude of myopia (84.7%) but also a higher prevalence of manifest astigmatism (38.1%) (Leung et al., 2012). Follow up studies could be conducted to investigative the effects of toric design ortho-k for myopic and astigmatic correction on adults with moderate to high astigmatism.

Axial length is the gold standard to monitor the myopic progression in myopic control studies. Read et al. (2008) reported axial length has a diurnal variation (0.046 ± 0.022 mm) in young adults.However, it is very difficult in Hong Kong to arrange all the data collection visits in the morning because children need to attend school. Although the amplitude was small, we assumed that as it was subjected to the same variations the differences in effect would be similar for both the ortho-k and control groups. Further study may take into consideration the time for axial length

measurement.

This study has answered some questions about the short- and long-term ortho-k effects on posterior corneal curvatures, corneal biomechanics and corneal thickness. However, more investigations are required to explore the association of other corneal parameters with the ortho-k response. Many questions about ortho-k treatment for myopic control are still unanswered. Previous studies reported that ortho-k lens induced relative myopic defocus in the peripheral retina (Mathur and Atchison, 2009; Smith et al., 2009; Kang and Swarbrick, 2011) and this was the main reason for retardation of myopic progression. However, peripheral refraction was not measured in the current study asthe suggestion that relative peripheral hyperopia caused myopic progression did not happen until after the commencement of this study. With a randomized clinical trial, peripheral refraction before and after ortho-k treatment could be measured to investigate the idea that relative peripheral hyperopia may be a cause of myopic progression. Nevertheless this study has provided strong evidence on the use of ortho-k can lead to improvement in myopic control in children with astigmatism and may offer an effective and acceptable treatment modality for this subject group.

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APPENDIX A1: INFORMATION SHEET (ENGLISH)

Research Study Information Sheet

Title of Project:

Orthokeratology in Chinese Children with Astigmatism

Project Leader:
Dr Pauline Cho, SO (Tel: 2766 6100)

Project member:
Ms Connie Chen, SO (Tel: 2766 4467)
Ms Peggy Cheung, SO (Tel: 2766 4462)
Dr Chea-Su Kee, SO (Tel: 2766 7941)

Why is the study being performed?

This study aims at investigating the efficacy in correcting myopia and astigmatism using toric orthokeratology lenses as well as monitoring the myopic progression in children.

What do parents and volunteers for the study have to do?

1. If youwould like to volunteer your child for the study, and your child is willing, you will be asked to sign an informed consent form on behalf of your child that you understand the information presented on this sheet.
2. Your child will be required to wear a pair of orthokeratology lenses. We will provide the orthokeratology lenses and contact lens solutions while you are required to provide spectacles for your child during the study period.
3. You or your representative will be required to come with your child to the Optometry Clinic at The Hong Kong Polytechnic University for a baseline visit at one week, two week, three monthes, and every six months for a period of two years.
4. Refraction, vision, noncontact tonometry, corneal topography, aberrometry, corneal health and axial length measurement will be performed at the baseline visit and six, 12, 18 and 24 months after commencement of the study. Topical anesthetics, mydriatic and cycloplegic drugs will be applied to the eyes to assist the measurement of refraction and corneal health. The examination at each of these visits will take 3-4 hours.
5. If your child is assigned to wear orthokeratology lenses, in addition to the biannual visits, s/he will be required to come back regularly, accompanied by you or your respresentative, for the orthokeratology after-care visits:
    - Your child will be required to come in early in the morning (within two hours after awakening) for the orthokeratology after-care visits in which refraction, vision, corneal topography and corneal health will be assessed. Afternoon after-care visits may be arranged to check the regression of refraction.
    - Unless otherwise instructed, your child will wear the lenses every night, following the instruction given by the research personnel and use the solutions provided in this study. You / your child will be required to fill in the ortho-k lens wear checklist every day.
    - Your child will bring the used contact lens solutions and the checklist, which will be collected and replaced upon presenting the used ones at each visit.
    - The orthokeratology after-care visits last for about 60-90 minutes.
6. If your child is assigned to wear orthokeratology lenses, if indicated, s/he may need a pair of spectacles with lower power to correct the residual refractive error for distance.
7. You can keep the orthokeratology lenses after the completion of the study if you and your child wish to continue orthokeratology treatment, provided you sign an agreement that your child will be followed up at our clinic as paid patients.

Is there any benefit or risk if my child participates in the study?

Risk: Risks associated with overnight orthokeratology such as poor unaided vision, allergic reaction to contact lens solutions and possible corneal infection can be minimized by careful patient selection, provision of high standard professional services to the patients and good compliance from the patients. Local anaesthetics, mydriatic and cycloplegia may produce stinging sensation and eye redness right after instillation, the effect is only transient and will not cause any harm to the eyes. Some children may have allergic reaction to the eyedrops. Should any problem be detected, appropriate clinical action (e.g. medical referral) will be taken. Parents will be required to bare the medical expenses if referral is indicated. After-office contact number will be provided for emergency.
Benefit: Subjects will have good unaided vision in the daytime if the treatment results are good and their ocular conditions will be regularly and carefully reviewed by professional optometrist. Children in the spectacle group will received free eye examination to monitor the refractive and ocular condition provided by a professional optometrist.

Can a volunteer withdraw from the study?
Yes, you can stop your child from participating in the study at any time with no penalty or any prejudice to the orthokeratology treatment. The deposit will be refunded but the orthokeratology lenses, contact lens solutions and lens accessories must be returned to the research personnel.

Can I get more information on the study?
Yes, contact *Dr Pauline Cho / Ms Peggy Cheung / Ms Connie Chen* and s/he will try to answer any questions you may have.
This study has been approved by the Departmental Research Committee of the School of Optometry of The Hong Kong Polytechnic University. If you have any complaints about the conduct of this research study, please do not hesitate to contact the Secretary of the Human Subjects Ethics Sub-Committee of The Hong Kong Polytechnic University in person or in writing (c/o Human Resources Office of the University).

Drug Effects

The following drugs will be used in this study:

Drug name	**Alcaine 0.5%**	**Tropicamide 1.0%**	**Cyclopentolate 1.0%**
Drug effects	* Topical anesthetic – numb the corneal sensation temporarily	* Pupil dilation * Cycloplegia - paralysis of focusing muscles temporarily	* Cycloplegia - paralysis of focusing muscles temporarily * Pupil dilation
Indication	* Facilitate the measurement of the length of the eyeball	* Better examination of the retina, optic nerve and ocular blood vessels	* Help to yield more accurate assessment of the length of the eyeball, especially in far-sightedness, pseudo nearsightedness and squint
Recovery time	* 15-20 mins	* 4-6 hrs, maximum of 24 hrs	* 24 hrs
Possible side effects	* Blur vision * Mild eye pain * Swollen eyes	* Foggy vision * Eye pain	* Foggy vision, Eye pain * Incoherent speech * Hallucination * Imbalance
Cautions	* DO NOT rub eyes or put on contact lenses within 2 hours of eyedrop instillation, and avoid the windy and dusty conditions if possible.	* Blur vision at near within the first few hours of eyedrop instillation * Light sensitivity, sunglasses and a wide brimmed hat/cap may help to provide better comfort * AVOID outdoor activities in open daylight and vigorous activities which require the use of near vision within 12 hours of eyedrop instillation	

APPENDIX A2: INFORMATION SHEET (CHINESE)
研究章程

研究名稱

角膜矯形術矯正散光的成效 -- 華裔兒童的應用

研究負責人

曹黃惠華博士　　電話：2766 6100

研究成員

陳佳琪小姐　　電話：2766-4467

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爲何舉行這項研究?

這項研究的目的爲測試散光角膜矯形鏡矯正近視和散光的成效，以及跟進深試兒童近視度數加深的幅度。

自願者需要做甚麼?

8. 如果您願意代表您的孩子同意參加這項研究計劃，您需要簽署同意書，表明您已閱讀本研究章程和明白這項研究的內容。
9. 您和您的孩子需要在參加研究計劃起一週、兩週、一個月、三個月及六個月到香港理工大學眼科視光學診所接受定時眼睛檢查，整個研究爲期二十四個月。
10. 在每次定時檢查，我們會爲您的孩子檢查屈光度數、視力、角膜地形、像差、角膜健康及眼球軸長，量度屈光度和眼球軸長期間會使用局部麻醉藥水、擴瞳劑及睫狀肌麻痺眼藥水放鬆睫狀肌，整個過程需時約 3-4 小時。
11. 如您的孩子被分派到角膜矯形鏡片組，除了每半年一次的定時檢查外，您和您的孩子需要按角膜矯形鏡的程序經常回理大視光學診所覆檢：
    - 您和您的孩子需要早上起床後兩小時內回來檢查屈光度數、視力、角膜地形和角膜健康。您們可能需要下午回來做屈光度復原檢查。
    - 在一般的情況下，您的孩子需要依從研究員的指示，使用我們提供的藥水，每天晚上佩戴鏡片睡覺，並需要每天填寫＜戴鏡日記＞。
    - 每次回理大眼科視光學診所覆檢時，請携帶已經用過的隱形眼鏡護理藥水、護理配件和＜戴鏡日記＞，方便研究員更換。
    - 角膜矯形鏡的覆檢需時約 60-90 分鐘。
6. 如您的孩子被分派到角膜矯形鏡片組，您需繳付港幣五千元支票作爲保證金，支票需每六個月更新。請保留收據，在研究結束或決定退出參與研究時，出示收據以取回支票。
7. 角膜矯形鏡片組的孩子日間可能需要佩戴框架眼鏡看遠景物。
8. 如果您和您的孩子在研究結束後想繼續使用我們提供的角膜矯形鏡片，您需要簽署一份同意書，表明您們同意日後會在理大視光學診所按當時的收費，定時覆檢眼睛健康。

自願者的得益與潛在危險

潛在危險：角膜矯形術引起的視力不佳、敏感反應和角膜發炎等問題可由選擇合適病人、眼科視光師對治療的專業知識和操守以及佩戴者良好的衞生習慣和依循性能，把風險減至最低。局部麻醉藥水、擴瞳劑和睫狀肌麻痹眼藥水在使用後或會引起刺激感和紅眼，但這只是暫時性的，不會損害眼睛。如發現孩子對眼藥水的成份有過敏反應，我們會即時提供適當的處理（如：醫護轉介，醫療開支需由家長負責），也會留下緊急電話號碼，方便家長聯絡。

得益：使用角膜矯形鏡的兒童，如果矯視結果理想，日間將不需使用眼鏡亦可有理想裸視力。所有孩童會得到定期眼睛檢查，監察近視增長和眼睛健康。

自願者可否退出?

可以，您可以隨時退出而無須作出任何賠償。您需交還角膜矯形鏡片、隱形眼鏡藥水和配件。

我可否取得更多關於此項研究的資料?

可以，請聯絡曹黃惠華博士、陳佳琪小姐、張倩雲小姐、或紀家樹博士，我們會盡力解答您的問題。

保密

所有資料均會保密處理，研究結果或會於日後刊登於有關文獻內，但所有個人資料將不會被公開。

此研究項目已經由眼科視光學院研究委員會批准進行， 如有投訴，請親身或以書面方式與香港理工大學人力資源處人類實驗操守委員會屬會秘書長聯絡。

藥性

我們會使用以下藥物進行眼睛檢查：

藥物名稱	**丙對卡因氧化物 0.5%**	**托品酰胺溶液 1.0%**	**環戊酯氫氧化物溶液 1.0%**
藥性	* 局部麻醉藥	* 擴瞳劑 * 睫狀肌麻醉劑	* 擴瞳劑 * 睫狀肌麻醉劑
作用	* 麻醉角膜的神經感覺協助測量眼球軸長	* 擴大瞳孔檢查視網膜、視神經及血管等	* 麻痺睫狀肌，能更準確地檢查遠視、假性近視及斜視等眼睛問題
復原時間	* 15-20 分鐘	* 4-6 小時，最長約 24 小時	* 24 小時
副作用	* 視力模糊 * 眼痛 * 眼腫	* 視力模糊 * 眼痛	* 視力模糊、眼痛 * 說話含糊 * 幻覺、身體不平衡
注意事項	* 避免使用藥物後 24 小時內揉眼	* 看近物件時視力模糊不清 * 瞳孔擴張後較爲畏光，外出時佩戴太陽眼鏡或寬邊帽子可減低畏光感 * 使用藥物後 12 內避免進行戶外或需要近視力的活動	

APPENDIX B1: CONSENT FORM (ENGLISH)

Title of Study

Orthokeratology in Chinese Children with Astigmatism

Informed Consent Form

Have you read the information sheet provided? Yes / No

Have you had an opportunity to ask questions and discuss this study? Yes / No

Have your received satisfactory answers to all of your questions? Yes / No

Have you received enough information about the study? Yes / No

Who provided the information / answered your questions

- ☐ Dr. Pauline Cho, SO, 2766 6100
- ☐ Ms Connie Chen, SO , 2766 4467
- ☐ Ms Peggy Cheung, SO, 2766 4462

Do you understand that participation is entirely voluntary? Yes / No

Do you understand that your child is free to withdraw from the study

- at any time **Yes / No**
- without having to give a reason **Yes / No**
- without affecting your future care **Yes / No**

Do you agree to take part in this study Yes / No

.....	.....
Signature of Child	**Signature of * Parent / Guardian**
.....	.....
Name of Child	**Name of * Parent / Guardian :**
.....	.....
Date	**Date**

* Delete as appropriate

APPENDIX B2: CONSENT FORM (CHINESE)

同意書

研究名稱：華裔兒童近視及散光的矯正 --臨床試驗

您是否已細閱及明白研究章程的內容?	是 / 否
您是否有機會向研究員提出問題和討論此項研究?	是 / 否
對於不明白之處您是否已得到完滿的答案?	是 / 否
您是否對此項研究已得到足夠的資料?	是 / 否

誰向您講解此項研究計劃和回答您的問題?

☐ 曹黃惠華博士	電話：2766 6100
☐ 陳 佳 琪 小 姐	電 話 ：2766 4467
☐ 張 倩 雲 小 姐	電話：2766 4462
☐ 紀家樹博士	電話：2766-7941

您是否明白參與此項研究計劃完全是自願性的?	是 / 否
您是否明白您隨時可退出此項研究?	是 / 否
您是否明白您可退出此項研究而不需給予任何理由?	是 / 否
您是否明白如您退出此項研究，並不會影響您日後所接受的服務水平?	是 / 否
您同意您的孩子參與此項研究計劃嗎?	同意 / 不同意

.....	.....
孩子簽署	*** 家長 / 監護人簽署**
.....	.....
孩子姓名	*** 家長 / 監護人姓名**
.....	.....
日期	日期

* *請刪除不適用者*

APPENDIX C: ETHICS APPROVAL LETTER

THE HONG KONG
POLYTECHNIC UNIVERSITY
香港理工大學

MEMO

To : WONG Hie Hua, School of Optometry
From : YAP Keng Hung Maurice, Chairman, Departmental Research Committee, School of Optometry

Ethical Review of Research Project Involving Human Subjects

I write to inform you that approval has been given to your application for human subjects ethics review of the following research project for a period from 16/03/2010 to 28/04/2012:

Project Title : Corenal biomechanics in astigmatic children and the effects of orthokeratology (ortho-k)

Department : School of Optometry

Principal Investigator : WONG Hie Hua

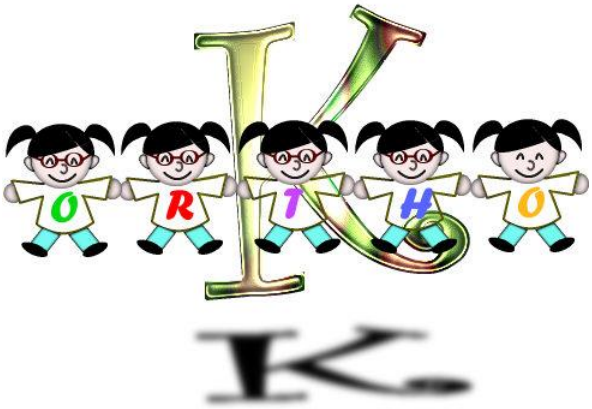
Please note that you will be held responsible for the ethical approval granted for the project and the ethical conduct of the research personnel involved in the project. In the case the Co-PI has also obtained ethical approval for the project, the Co-PI will also assume the responsibility in respect of the ethical approval (in relation to the areas of expertise of respective Co-PI in accordance with the stipulations given by the approving authority).

You are responsible for informing the Departmental Research Committee School of Optometry in advance of any changes in the research proposal or procedures which may affect the validity of this ethical approval.

You will receive separate notification should you be required to obtain fresh approval.

YAP Keng Hung Maurice
Chairman
Departmental Research Committee
School of Optometry

APPENDIX D: ORTHOKERATOLOGY DIARY (Example)



我的戴鏡日記

(20__年__月)

我的姓名　　：_____
眼科視光師姓名　：_____
日間聯絡電話　　：_____
夜間聯絡電話　　：_____

你的名字

(　　)的戴鏡日記 – 2008 年 1 月

1	除鏡時間: _____ 人工淚液: R □ L □ 鏡片鬆動: R □ L □ 鏡片黏著程度: R 0 1 2 3 4 5 L 0 1 2 3 4 5 除蛋白: □	日間視力清晰度: 0 1 2 3 4 5 晚間視力清晰度: 0 1 2 3 4 5 其他不適: _____ _____ 戴鏡時間: _____ 人工淚液: R □ L □
2	除鏡時間: _____ 人工淚液: R □ L □ 鏡片鬆動: R □ L □ 鏡片黏著程度: R 0 1 2 3 4 5 L 0 1 2 3 4 5 除蛋白: □	日間視力清晰度: 0 1 2 3 4 5 晚間視力清晰度: 0 1 2 3 4 5 其他不適: _____ _____ 戴鏡時間: _____ 人工淚液: R □ L □
3	除鏡時間: _____ 人工淚液: R □ L □ 鏡片鬆動: R □ L □ 鏡片黏著程度: R 0 1 2 3 4 5 L 0 1 2 3 4 5 除蛋白: □	日間視力清晰度: 0 1 2 3 4 5 晚間視力清晰度: 0 1 2 3 4 5 其他不適: _____ _____ 戴鏡時間: _____ 人工淚液: R □ L □
4	除鏡時間: _____ 人工淚液: R □ L □ 鏡片鬆動: R □ L □ 鏡片黏著程度: R 0 1 2 3 4 5 L 0 1 2 3 4 5 除蛋白: □	日間視力清晰度: 0 1 2 3 4 5 晚間視力清晰度: 0 1 2 3 4 5 其他不適: _____ _____ 戴鏡時間: _____ 人工淚液: R □ L □
5	除鏡時間: _____ 人工淚液: R □ L □ 鏡片鬆動: R □ L □ 鏡片黏著程度: R 0 1 2 3 4 5 L 0 1 2 3 4 5 除蛋白: □	日間視力清晰度: 0 1 2 3 4 5 晚間視力清晰度: 0 1 2 3 4 5 其他不適: _____ _____ 戴鏡時間: _____ 人工淚液: R □ L □
6	除鏡時間: _____ 人工淚液: R □ L □ 鏡片鬆動: R □ L □ 鏡片黏著程度: R 0 1 2 3 4 5 L 0 1 2 3 4 5 除蛋白: □	日間視力清晰度: 0 1 2 3 4 5 晚間視力清晰度: 0 1 2 3 4 5 其他不適: _____ _____ 戴鏡時間: _____ 人工淚液: R □ L □

APPENDIX E: Procedures for lens insertion, removal, cleaning and loosening a bound lens in the morning

角膜矯形隱形鏡的護理步驟

除下角膜矯形鏡：

1. 凡接觸隱形眼鏡或眼睛前必須先用梘液徹底洗淨雙手。
2. 按照視光師的指示使用手指或塑料吸盤除下角膜矯形鏡片，除下鏡片前先檢查鏡片有没有黏緊在角膜上的情況，並使用人工淚液潤滑鏡片。

清洗角膜矯形鏡：

3. 除下鏡片後，使用隱形眼鏡清潔劑徹底清洗鏡片的正面及底面，然後用蒸餾水或生理鹽水沖洗鏡片，再將鏡片置於盛滿消毒藥水(須每天更換)的鏡盒中並旋緊盒蓋，直至下一次戴鏡。(鏡片的消毒過程不能少於四小時)。
4. 除每日除鏡後清洗鏡片外，還須定期進行除蛋白程序(一般爲每星期一次)，以減輕鏡片表面積聚垢物的情況。此外，所有隱形眼鏡的配件(包括吸盤及鏡片儲存盒)都要徹底清潔、適當消毒及定時更換，並且不要存放在潮濕的地方(如洗手間內)。

戴上角膜矯形鏡：

5. 凡接觸隱形眼鏡或眼睛前必須先用梘液徹底洗淨雙手。
6. 使用人工淚液濕潤眼睛表面。
7. 從鏡盒中取出消毒過的鏡片，然後用生理鹽水沖洗乾淨。
8. 戴鏡前滴一滴人工淚液或生理鹽水在鏡片底面，然後將鏡片戴上眼睛，眨眨眼，確定鏡片没有偏移及眼睛没有不適便可睡覺。
9. 切記戴鏡後不可揉眼睛。

鏡片黏著的處理方法

除鏡前如鏡片出現黏著角膜的情況，***請勿強行除下鏡片！***

請跟隨以下步驟處理：

1. 先滴一至兩滴生理鹽水或人工淚液在眼上，用力眨眼數次。
2. 看著鏡子檢查鏡片是否能移動，如不，再用力眨眼數次(如有需要可再一至兩滴生理鹽水或人工淚液)，用食指按著下眼瞼輕輕往上推動鏡片的底部；重覆以上步驟數次，直至鏡片不再黏緊在角膜上，此時可以除下鏡片。

** 其他有關配戴角膜矯形鏡的須知或緊急情況處理方法、隱形眼鏡藥水的運用等事項，請向您的視光師查詢。*

APPENDIX F: RECORD FORM

Aftercare form (MC/ Toric Project) **Check in time : _____**

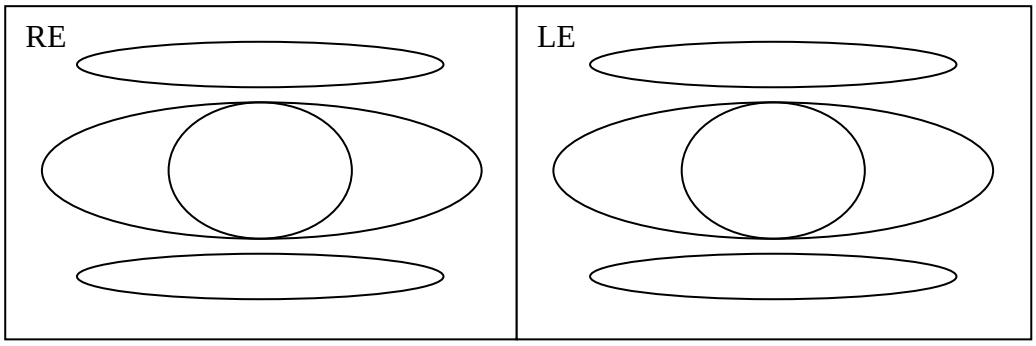
Record no.:_____ Date: _____
Name: _____ (_____)
Visit: 1st ON / 1 wk / 1 mth / 3 mth / 6 mth / others _____
1) Chief Complain, if any

Wearing Schedule: _____ nights per week; _____ hrs per night
Insertion time last night: _____; Removal time this morning: _____
Insertion : Self / Guardian/Others : _____ (Good / Average / Poor)
Removal : Self /Guardian/ Others : _____ (Good / Average / Poor)
Cleaning : Self /Guardian/ Others : _____ (Good / Average / Poor)
☐ Lens binding: G0 / G1 / G2 / G3 / G4

Unaided/Aided LogMAR (High)	OD	OS	OU
Unaided/ Aided LogMAR (Low)	OD	OS	OU

Retinoscopy (RE) _____
(LE) _____
Subjective Rx (RE) _____ ( )
(LE) _____ ( )

2) Slit lamp Microscopy - ☐ Photodocumentation



Pigmented Arc: G0 / G1 / G2 /. G3 **Pigmented Arc: G0 / G1 / G2 / G3**

3) Topography (1-2 per eye)

RE ☐ Bull's eye ☐ Central Island ☐ Smiley Face
☐ Frowny Face ☐ Lateral displacement ☐ Others _____
LE ☐ Bull's eye ☐ Central Island ☐ Smiley Face
☐ Frowny Face ☐ Lateral displacement ☐ Others _____

4) Lens Fitting (1st pair / 2nd pair / _____)

RE	Lens Parameter	LE
	Centration	
	Movement	
	Fluorescein Pattern	
( )	O/Rx (VA)	( )
	Lens Inspection	

5) Other examinations

	OD	OS
ORA(4 per eye)	Yes / No	Yes / No
Pentacam(3 per eye)	Yes / No	Yes / No
IOL Master (AL/K/ACD)	_____	_____
SP2000 (Central x 3)	_____	_____
Auto Rx (Nidek)	Yes / No	Yes / No
Shin Nippon (Central / Auto)	Yes / No	Yes / No
IOP	_____	_____

6) Comments / Management

7) Lens ordering (Re-order / Spare-lens)

RE	
LE	

8) Solution and LogBook Given / Returned

Given	Items	Returned
☐ bottle(s) X _____	MeniCare Plus	☐ bottle(s) X _____
☐ bottle(s) X _____	O2 Care	☐ bottle(s) X _____
☐ bottle(s) X _____	Saline	☐ bottle(s) X _____
☐ box(es) X _____	AT	☐ box(es) X _____
☐ box(es) X _____	Progent	☐ box(es) X _____
☐ X _____	Progent Case	☐ X _____
☐ X _____	Lens Case	☐ X _____
☐ X _____	LogBook	☐ X _____
☐ X _____	Others	☐ X _____

Next Visit: _____ Practitioner:_____Check out time :_____