The Hong Kong Polytechnic University

School of Optometry

A retrospective survey of orthokeratology on children

By

Chan Lap Kong

A thesis submitted in partial fulfillment of the requirements

for the degree of Master of Philosophy

December 2008

CERTIFICATE OF ORIGINALITY

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

_____ (Signed)

Chan Lap Kong (Name of student)

ABSTRACT

Orthokeratology (Ortho-k) is a contact lens technique mainly used for temporarily reducing myopia. The Optometry Clinic of The Hong Kong Polytechnic University (PolyU) has been providing an ortho-k service since 1997. Much useful information regarding refractive and ocular changes with ortho-k lens wear awaits collation and analysis. This information will be useful to help ortho-k practitioners improve the practice of ortho-k.

The human eye is directly exposed to light and an atmospheric environment containing reactive oxygen species (ROS) which may cause ocular tissue damage and disease. To protect the cornea from ROS, the tear film acts as the first barrier and contains several antioxidants for ocular defense. Ascorbate (vitamin C) is one of the most important antioxidants in human tears. Overnight ortho-k lens wear induces ocular stress which may increase the demand of antioxidants for ocular protection. Contact lens binding, leading to corneal staining, is a commonly observed problem in overnight ortho-k lens wear and artificial tears are commonly prescribed for patients to use before going to sleep with the lenses, and to aid lens removal in the morning. However, artificial tears which do not contain antioxidants would dilute the useful antioxidants in tears,

hence altering the ocular defense/protective system conferred by natural tears on the anterior surface of the eye during sleep. Therefore, there is a need to investigate if it is possible to include antioxidants, such as ascorbate, in the formulation of artificial tears to increase their effectiveness for the promotion of safe overnight ortho-k lens wear and corneal health.

OBJECTIVES

The objectives of this MPhil study were:

1. collect the demographical characteristics of children undergoing ortho-k at the Optometry Clinic, The Hong Kong Polytechnic University (HKPU),
2. conduct a telephone survey of ortho-k wearers to understand the problems encountered and their satisfaction with treatment,
3. evaluate the validity of the Jessen formula in determining the back optic zone radius (BOZR) of ortho-k lenses,
4. investigate the relationship between corneal topographical changes and refractive changes induced by ortho-k,
5. conduct a pilot study to evaluate the stability of standard ascorbate in commercially-available single dosage formulation artificial tears.

METHODS

A clinical survey was conducted by reviewing the records of all patients fitted with ortho-k lenses in the Optometry Clinic, HKPU between April 2000 and November 2003. Only children under the age of 16 years and still continuing with the ortho-k treatment with the same pair of lenses worn for a six month period were included in the analytical study. Demographical and clinical data were retrieved from clinical files, and corneal parameters were retrieved from the corneal topographer. A telephone interview was conducted using a pre-structured list of questions, asking about the visual performance and the satisfaction of the treatment. The validity of the Jessen formula, and the relationship between corneal topographical changes and refractive changes induced by ortho-k was investigated from the same group of patients in the clinical survey.

The stability of ascorbate in artificial tears was studied by measuring the degradation rate of different ascorbate concentrations in three commercially available artificial tears using Ferric Reducing/Antioxidant Power assay.

RESULTS

A total of 257 ortho-k patients were fitted with ortho-k lenses in the Optometry Clinic, HKPU during the study period, and most of the wearers (91%) were children. The group of children who met the study criteria had a median age of nine years when they started treatment. A significant myopic reduction, improvement in unaided vision and corneal topographical changes were observed after a single overnight session of lens wear. An optimum ortho-k effect was achieved by one week. However, the spherical ortho-k lens design was ineffective in reducing the refractive cylindrical power. Corneal staining was the most commonly observed complication with overnight ortho-k, and over 80% of patients were advised to apply artificial tears to aid loosening the lenses before removal. Almost all (97%) of the patients whose files were reviewed were using a suction holder to aid lens removal.

Ortho-k was mainly undertaken for myopic control, and about 90% of the respondents reported good or very good unaided vision after the procedure and ranked the treatment as satisfactory or very good. Lens binding and ocular discharge were the most frequently reported problems during the treatment.

The BOZR of a reverse geometry lens (RGL) determined from the conventional Jessen formula, with a compression factor of 0.75, was found to under-estimate the intended target of myopic reduction. Our study suggests that the original formula *(i.e. BOZR = Flat K – Target – 0.75)* should be revised as *BOZR = Flat K – 1.23Target − 1.27.*

There is a significant correlation between achieved myopic reduction and the change in apical corneal power (ΔACP), and between achieved myopic reduction and maximum corneal power change within the treatment zone (ΔMCP) after ortho-k. However, both ΔACP (under-estimate) and ΔMCP (over-estimate) were unable to reflect the achieved myopic reduction accurately. We also found that initial *Q* was not useful as a predictive factor for the outcome in ortho-k.

The stability of ascorbate solution in artificial tears, except Bion Tears (Alcon Inc, Fort Worth, TX, USA), was good. A higher concentration of ascorbate added to the artificial tears showed a slower degradation of ascorbate, and the stability was further enhanced when the mixture was stored at a low temperature. Among the three artificial tears tested, Vismed (Lab Chemedica AG, Munich,

Germany) showed the greatest potential for the new formulation of artificial tears with ascorbate.

CONCLUSIONS

Overnight ortho-k is a fast and effective way for correcting low to moderate levels of myopia. The spherical reverse geometry lens (RGL) design is not effective in the correction of astigmatism.

The Jessen formula for deriving an approximate BOZR to correct the refractive error is suspect, if the assumption of 0.75 D over-correction is taken into consideration.

The change in apical corneal power determined from the topographical map is not able to reflect the manifest refractive change accurately. However, when compared with retinoscopy and auto-refraction, apical corneal power change is still useful for estimating myopic reduction after the procedure. The initial corneal asphericity Q measured from corneal topography is not a useful predictor for ortho-k success.

Our results showed that ascorbate in artificial tears could be stable, especially under higher concentration and low temperature.

Publications arising from the thesis

Journal Articles

- Chan B, Cho P, Cheung SW. Orthokeratology Practice in a University Clinic in Hong Kong: children population. Clin Exp Optom 2008;91:453-60.
- Chan B, Cho P, Mountford J. The validity of Jessen formula in overnight orthokeratology: A retrospective study. Ophthal Physiol Opt 2008;28:265-8.
- Chan B, Cho P, Mountford J. Relationship between corneal topographical changes and subjective myopic reduction in overnight orthokeratology (Submitted to Clinical and Experimental Optometry)
- Chan B, Choy C, Cho, Benzie, IF. A pilot study on the stability of ascorbate added to commercially available lubricating eyedrops (in preparation)

Conference papers

- Chan B, Cho P, Cheung SW. Orthokeratology Practice in a University Clinic. Poster presentation at the 2004 Global Orthokeratology Symposium. 23-25 July, 2004.
- Chan B, Cho P, Mountford J. Corneal eccentricity and myopic reduction in orthokeratology. Paper presented at the 15th Asia-Pacific Optometric Congress. International Federation of Asia-Pacific Associations of Optometrists, 10-15 October 2005, Tokyo.

- Chan LK, Cho P, Mountford J. Analysis of the relationship between corneal changes and lens parameters on the refractive changes by overnight orthokeratology. Paper presented at the 2nd Asia Cornea and Contact Lens Conference, 14-15 April 2005, Hong Kong.
- Chan LK, Cho P, Cheung SW. Orthokeratology Practice in a University Clinic. Poster presentation at the 2nd Asia Cornea and Contact Lens Conference, 14-15 April 2005, Hong Kong.

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to my chief supervisor, Dr. Pauline Cho, for her patience, guidance and encouragement on the preparation of this thesis and other projects during the past years. Dr. Cho has taught me a lot on how to perform a research study and write a thesis.

I would also like to thank Prof. Iris Benzie, my co-supervisor, for providing much advice on the laboratory work. Dr. Camus Choy is to be thanked for his support and valuable input on laboratory work.

I am very grateful to the Department of Health Technology and Informatics (HTI) for providing access to the laboratory equipment and materials for the laboratory work.

It was a great experience for me to take part in the First International Symposium on Orthokeratology (ISOK) and I would like to thank Mr. John Mountford for giving me inspiring suggestions on topographical analysis when we met at the symposium.

My thanks also go to the orthokeratology group colleagues, Connie, Jessie, Marvit, May May, Peggy, Roy, Tsui Tsui and Yvonne for working as a team and for giving me much support throughout the study period.

Finally, I would like to direct my warmest thanks to my family for their support and encouragement, especially my wife, Stephanie, who persevered with me through every step of the long MPhil study. I am deeply thankful for her love and faithful support.

I give all the glory and thanks to my Lord and saviour Jesus Christ for helping me to start and complete my MPhil study.

Table of contents **Page**

List of tables

Page

List of figures

List of abbreviations

AC	Alignment Curve
ACP	Apical corneal power
AL	Axial length
BOZD	Back Optic Zone Diameter
BOZR	Back Optic Zone Radius
BT	Bion Tears
CRT	Cornreal Refractive Therapy
D	Dioptre
Dk	Oxygen permeability
Dk/t	Oxygen transmissibility
e-value	Eccentricity
FDA	Food and Drug Administration
FRAP assay	Ferric Reducing/Antioxidant Power assay
Fe^{II}	Iron II ion
Fe^{III}	Iron III ion

K_f	Flattest simulated keratometry reading
K_s	Steepest simulated keratometry reading
logMAR	Logarithm of the Minimum angle of resolution
MCP	Maximum corneal power
MK	Microbial keratitis
n	Number of subjects
n	Refractive index
OCT	Optical Coherence Tomography
Ortho-k	Orthokeratology
p	Shape factor
PMMA	Polymethylmethacrylate
PC	Peripheral Curve
PRK	Photorefractive Keratectomy
Q	Asphericity
RC	Reverse Curve
RGL	Reverse geometry lens
RGP	Rigid gas permeable
ROS	Reactive oxygen species
S	Ablation depth

T	Desired refractive change
TNF	Tear Naturale Free
TPTZ	2,4,6-tri-pyridyl-s-triazine
UVA	Unaided visual acuity
VA	Visual acuity
VCD	Vitreous chamber depth
VM	Vismed
ΔM_{ach}	Achieved myopic reduction
ΔM_{att}	Attempted refractive change

CHAPTER 1

Literature review and background of study

1.1 Introduction

Myopia is the refractive condition in which parallel light incident on the eye is focused in front of the retina. A myopic person will usually have blurred vision at distance, but clear vision at near. Spectacles and contact lenses are the most commonly used methods to correct myopia. In the recent years, due to the advent of advanced ophthalmic technology, there is a rising interest in refractive surgery for treating myopia. However, refractive surgery is irreversible, invasive and has a higher risk of post-operative complications including dry eyes (Ambrosio et al., 2008; Quinto et al., 2008) and corneal ectasia (Uceda-Montanes et al., 2008), and is not suitable for children.

Myopia is more prevalent among the ethnic Chinese population, apparently regardless of the variation in the education curriculum (Lam and Goh, 1991; Edwards, 1999; Lin et al., 2001; Junghans and Crewther, 2005; Cheng et al., 2007), and the progression of myopia takes place during childhood (age range from six to 12 years). In Hong Kong, the prevalence of myopia has increased from 11% among seven-year-olds, up to 57% among 12-year-olds, and over 70% among 17-year-olds (Lam and Goh, 1991; Edwards and Lam, 2004). High myopia is associated with the sight threatening problems, such as glaucoma, cataract, retinal detachment and macular degeneration (Perkins, 1960; McCarty et al., 1999; Burton, 1989; Saw et al., 2005). Much research has been undertaken to investigate reliable means, including

spectacles, contact lenses, and pharmaceutical agents, to control the progression of myopia in children. However, none of the interventions has been shown to be effective in achieving that purpose.

Orthokeratology (ortho-k) is a contact lens technique which aims to temporarily reshape the cornea using rigid contact lenses resulting in a reduction in myopia and an improvement in unaided vision. The technique was introduced over 40 years ago, but did not gain popularity. In recent years, with the advent of new lens materials, design and technology, it has gained popularity with several lens designs being currently available in the market. Numerous clinical studies have shown the efficacy and safety of ortho-k for the reduction of myopia (Mountford, 1997a; Nichols et al., 2000; Sima et al., 2000; Rah et al., 2002a; Mika et al., 2007). A previous study also showed a promising result for overnight ortho-k in the retardation of myopia in children (Cho et al., 2005a). Ortho-k was introduced into Hong Kong in the late 1990s', and most of the wearers were children requiring myopic control (Cho et al., 2002a; Cho et al., 2003). However, although over a decade of ortho-k practice in this region has gone by, there is no study reporting the demographical and clinical profile of children undergoing ortho-k.

The tear film is the first defense barrier protecting the eye against ocular oxidative stress from the atmospheric environment including photo-active substances, ultraviolet radiation, toxic chemical pollutants, free radicals and other reactive oxygen species (ROS) (Wolff, 1946; Holly, 1973; Moore and Tiffany, 1979; Paterson and O'Rourke, 1987; Shimmura et al., 1996; Rozanowska et al., 1998; Gogia et al., 1998; Rose et al., 1998; Dontsov et al., 1999; Halliwell and Gutteridge,

1999). Human tears contain several water-soluble antioxidants, with ascorbate (vitamin C) and urate together making up of about 50% of the total antioxidant capacity (Choy et al., 2000; Choy et al., 2001). Ascorbate is a powerful reducing substance which acts as a ROS scavenger to eliminate or inactivate oxidative species which damage ocular tissue (Delamere, 1996; Taylor et al., 1997; Rose et al., 1998), and has been suggested to play an important role in keeping the cornea healthy (Gogia et al., 1998).

Ascorbate is also a major vitamin antioxidant in human tears which has a small molecular weight and is present in the main lacrimal gland secretion of fresh reflex tears (Choy et al., 2003). It is not produced by the body but only obtained from dietary intake, especially fruits and vegetables. Ascorbate has the ability to control corneal inflammation and enhance wound healing (Paterson and O'Rourke, 1987; Vaxman et al., 1995; Kasetsuwan et al., 1999).

Overnight contact lens wear induces stress on ocular tissues and is generally accepted to be associated with a greater risk of ocular complications (Garber, 2001; Hutchinson and Apel, 2002). Lens binding is one of the most frequently reported symptoms by ortho-k wearers (Cho et al., 2003; Chui et al., 2003; Cheung and Cho, 2004) which exaggerates ocular stress. To minimize the effect of lens binding leading to corneal abrasion, some practitioners suggested applying artificial tears before sleeping with the lenses, and on awakening before attempting lens removal (Cho et al., 2003).

Therefore an adequate anti-oxidative mechanism in the tear film is important to maintain an optimal ocular defence and ocular health during overnight ortho-k treatment. The application of lubricating eye-drops containing an adequate level of ascorbate may be beneficial to ortho-k wearers and increase the success rate. However, artificial tears currently available in the market are composed of polyvinyl alcohol, hydroxypropyl methylcellulose (Hypromellose, HPMC) or hyaluronic acid, which only function as (re)wetting agents and lubricants. In addition, the ingredients in artificial tears may affect the stability of tear ascorbate, and the application of artificial tears could dilute tear ascorbate concentration which may weaken the ocular defence ability, especially under a higher ocular stress during overnight ortho-k lens wear.

The main objective of this thesis is to report the demographical and clinical profile of myopic children for whom ortho-k treatment was taken in the Optometry Clinic of The Hong Kong Polytechnic University during the first three years of this century. A secondary objective is to report a pilot study on the stability of ascorbate added to different commercially available artificial tears.

The following sections of this chapter present a review on the development of ortho-k and the clinical efficacy of the technique on refractive error reduction. In addition, different lens fitting assessment methods in modern ortho-k and the principle of the ortho-k effect are discussed, and the safety issue and the usage of ortho-k for myopic control is also reviewed. In the last part of this section, a general overview of the importance of tear ascorbate in protecting the health of the eye is discussed.

1.2 Orthokeratology

The concept of ortho-k apparently originated in ancient China. A recent ortho-k review stated that unconfirmed stories in China suggest that the ancient Chinese placed a small weights or sandbags on the eyelids during sleep in attempt to deform the shape of the cornea resulting in a reduction in myopia (Swarbrick, 2006).

Ortho-k is defined as a procedure using a programmed application of rigid contact lenses leading to the flattening of the central cornea to accomplish a refractive power reduction of the ocular system. Ortho-k has developed from using conventional rigid contact lenses (from PMMA to rigid gas permeable materials) for day wear to a unique reverse geometry design contact lens using hyper-oxygen permeable rigid materials for overnight treatment. The technique is based on the properties of the human cornea which contributes up to two-thirds of the total ocular refractive power (about 43 D) (Duke-Elder, 1970), and is elastic in nature. Small changes to the corneal curvature induced by ortho-k will produce a significant reduction in myopia. After treatment, if the corneal response is good, the wearer can benefit from a temporary reduction in myopia and improved unaided visual acuity without any additional optical aids. However, as the cornea is highly elastic, if lens wear is stopped, the molded cornea will gradually resume its original shape and the myopia will regress after a few days of no lens wear (Barr et al., 2004). Therefore, ortho-k lenses must be worn on a regular basis in order to retain the effect. The procedure is a non-invasive and reversible solution for myopic correction.

Table 1.2.1 Summary of the earlier orthokeratology studies using PMMA lenses for myopic reduction

	Duration of study (months)	Average initial ages (years)	Number of subjects	Baseline refraction (SER)* (SD) (D)	Myopic reduction at the end of the study (SER)* (SD) (D)
Kerns (1976-1978)	24	18.4	18	–2.11	1.06 (0.98)
Binder et al. (1980)	12	23.4	23	–2.50	1.60 (1.54)
Polse et al. (1983)	14	26.2	31	–2.70 (1.10)	1.01
Coon (1984)	20	24.4	14	–2.37 (1.05)	0.58 (0.56)

* *Spherical equivalent refraction (SER)*

1.2.1 Traditional orthokeratology

Traditional ortho-k is based on the concept of "orthofocus" described by Jessen (Jessen, 1962). The treatment used progressively flat-fitting conventional rigid contact lenses. A polymethylmethacrylate (PMMA) lens (Neilson et al., 1964; Grant and May, 1971) was initially used, followed by rigid gas permeable materials. Flat-fitting rigid contact lenses led to the flattening of the anterior corneal surface. Although many clinical studies reported that traditional ortho-k was effective and safe for the temporary reduction in myopia (Table 1.2.1), these studies only reported successful cases (Kerns, 1976c; Binder et al., 1980; Polse et al., 1983; Coon, 1984).

Unsatisfactory lens centration is the major drawback of this flat-fitting method and caused significant corneal distortion and undesirable with-the-rule

astigmatism (Kerns, 1977 a-d; Binder et al., 1980). In addition, traditional ortho-k was only effective in reducing a low level of myopia, approximately 0.50 to 1.50 D, and required multiple lenses changes. Therefore it could take over 20 months to reduce myopia by about 1 D (Kerns, 1976 a-c; Kerns, 1977 a-d; Kerns, 1978). Due to the various disadvantages with this treatment, the procedure did not gain popularity among eye-care practitioners and was abandoned after the 1970s.

1.2.2 Modern orthokeratology

Modern ortho-k emerged in the late 1980s, and is different from traditional ortho-k in lens design and the materials used. The successful reintroduction of modern ortho-k was due to the advance in technology that allows a faster and more predictable treatment effect. Sophisticated instruments, specifically the corneal topographer allowed the cornea to be monitored accurately, and the introduction of CNC lathes enabled special lens designs to be fabricated based on the corneal parameters measured with a topographer.

1.2.2.1 Reverse geometry lens

The introduction of the reverse geometry lens (RGL) design improved the problem of poor lens centration which frequently occurred in the flat-fitting philosophy in traditional ortho-k. The first RGL design was developed by Wlodyga and Bryla (1989) and consisted of three distinct zones. The lens was designed with the central base curve flatter than the corneal curvature (flat meridian), and the mid-peripheral curve (the Reverse Curve (RC)) is fitted steeper than the base curve of the lens. A steeper RC was claimed to allow the central base curve to be fitted much flatter than traditional ortho-k, with better lens centration.

The use of this lens design has been reported to increase the amount of myopic reduction and shorten the time required to achieve optimum refractive change (Wlodyga and Bryla, 1989). Compared to the traditional flat-fitting philosophy, the RGL gives a relatively larger treatment zone and better retention of myopic reduction with minimal daytime regression (Wlodyga and Bryla, 1989; Carkeet et al., 1995; Mountford, 1998; Nichols et al., 2000; Rah et al., 2002a; Soni et al., 2003).

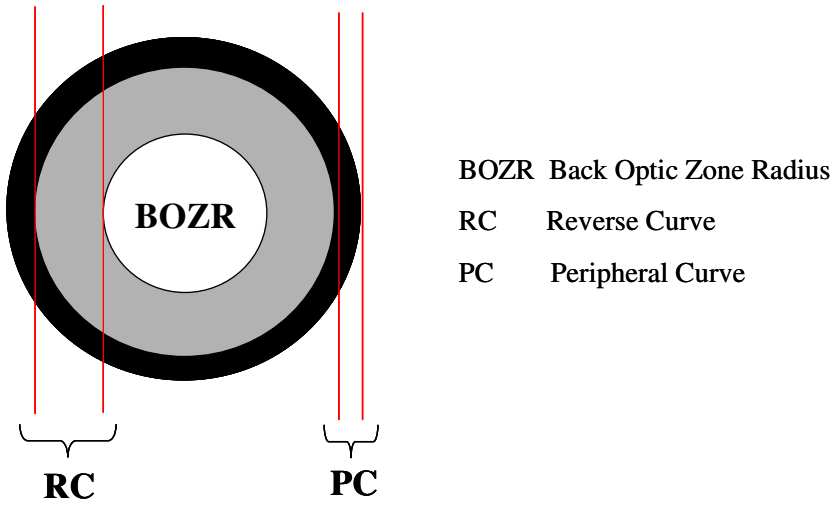


Figure 1.2.1 Basic structure of a three-zone reverse geometry lens

Table 1.2.2 Basic structure of a three-zone reverse geometry lens

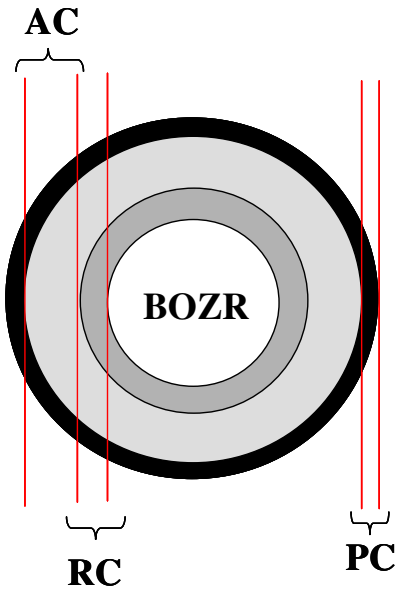
Back Optic Zone Back Optic Zone Radius (BOZR) 	• ~ 6.0 to 8.0 mm (diameter) • BOZR is based on the refractive change required • Tear layer behind lens provides subtle applanation force necessary to re-distribute the tissue • Not a factor affecting lens fitting
Reverse Zone Reverse Curve (RC) 	• ~ 3.0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

1.2.2.1.1 Three-zone design

A three-zone design consists of a Back Optic Zone Radius (BOZR), a Reverse Curve (RC), and a Peripheral Curve (PC). The basic structure of the lens and the functions of each curve are illustrated in Figure 1.2.1 and Table 1.2.2 respectively. The range of Back Optic Zone Diameters (BOZD) is between 6.00 mm and 8.00 mm, and the RC is fitted with the curvature ranging from 1.00 D to 15.00 D steeper than the BOZR (Mountford, 2004).

The Contex OK lens series (Contex Laboratories, Sherman Oaks, CA, USA) is an example of a three-zone design. It is the first RGL design to receive approval from the Food and Drug Administration (FDA) of the United States of America in May

1988 for daywear ortho-k for myopic reduction up to 3.00 D. Although a greater and faster refractive change can be achieved with a three-zone design, the problem of lens decentration persisted.



BOZR Back Optic Zone Radius
RC Reverse Curve
*AC Alignment Curve
PC Peripheral Curve

**For a five-zone lens, AC1 and AC2*

Figure 1.2.2 Basic structure of a four-zone and five-zone reverse geometry lens

Table 1.2.3 Basic structure of a four-zone and five-zone reverse geometry lens

Back Optic Zone Back Optic Zone Radius (BOZR) 	• ~ 6.0 to 8.0 mm (diameter) • BOZR is based on 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) aligning with mid peripheral cornea
	• Controls total lens movement and is responsible for centration
	• Can be spherical, aspherical or a tangential
	• Sagittal height of the lens is controlled by change of the alignment configuration or the tangent angle
	
	For toric design:
	• Sagittal height of the lens is different between the steep and flat meridian
	• Tangents of the lens are calculated from the apical radius of the steep and flat meridian as well as the elevation along each respective meridian

Reverse Zone Reverse Curve (RC) 	• ~ 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 meridian
Peripheral Zone Peripheral Curve (PC) 	• ~ 0.3 to 0.5 mm (width) • Provides the desired edge lift • Facilitates lens movement and tear exchange beneath the lens

1.2.2.1.2 Four- and Five-zone design

A four-zone and a five-zone design were later developed by Reim (1999). They are similar to a three-zone design except for an additional area, called the alignment zone which consists of the Alignment Curve (AC) connecting the reverse and peripheral curves. The AC aligns with the peripheral cornea, and further controls lens centration resulting in a better prediction of the outcome of the treatment and an increase in the rate of refractive change. The basic structure of the lens and the functions of each curve are illustrated in Figure 1.2.2 and Table 1.2.3 respectively. Since the introduction of a four-zone lens, many similar RGL designs with different fitting philosophies were developed. Currently, most ortho-k lenses are of four-zone design. Due to the greater and faster effect of a four-zone design, ortho-k using this design is also known as 'accelerated orthokeratology' to differentiate it from the traditional ortho-k. Similar to a three-zone lens, the BOZD of a four-zone lens is approximately 6.00 mm. The width of the RC ranges from 0.60 to 1.00 mm while the width in the AC is approximately 1.00 to 1.30 mm. In a five-zone lens design, the AC is divided into AC1 and AC2. Both ACs play a major role in the total lens movement and centration. Examples of different lens designs of a four-zone and a five-zone lens are summarized in Table 1.2.4.

Table 1.2.4 Examples of a four-zone and five-zone lens

Trade name	Design	Manufacturer	Fitting philosophy	Lens diameter (mm)	BOZR* (mm)	RC (mm)	1st AC (mm)	2nd AC (mm)	PC (mm)
BE Lens	Four-zone or Five zone	UltraVision Pty. Ltd. Brisbane, Queensland, Australia	Diagnostic or Empirical	10.6 to 11.0	6.0 to 8.0 (diameter) Not base on Jessen formula Depends on Ro and e-value over a specific chord diameter	▪ Tangent periphery determined 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 with each size of 0.2mm, 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 life to the lens
Paragon Corneal Refractive Therapy (CRT)	Four-zone	Paragon Vision Science Mesa, AZ, USA	Diagnostic	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 Landing Zone
Contex OK	Four-zone	Contex Laboratories Sherman Oaks, CA, USA	Diagnostic 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 Macro Vision Group, Taiwan	Diagnostic	10.0 to 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	Diagnostic	10.6 or greater	6.0	0.6 (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	Diagnostic or Empirical	10.2,10.6,11.0, >11.0 10.6 for five-zone	6.0 to 8.0 (diameter) 6.2 for five-zone	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)
Nachtlens 2	Four-zone	NKL Contactlenzen Netherlands	Empirical	10.2, 10.6, 11.0	Not base on Jessen formula Selected with the aid of computer program	1.2 (width) for 10.6	1.1 (width) for 10.6 Tangent periphery		Tangent periphery
Fargo	Four-zone or Five zone	C&E G.P Specialists San Clemente, CA, USA	Diagnostic	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)

1.2.2.2 Lens selection

There are three ways to select the first RGL. They are diagnostic, empirical lens fitting and computer-assisted fitting. Each fitting method has its own advantages and disadvantages, and some designs may use more than one of the three methods.

1.2.2.2.1 Diagnostic fitting

Diagnostic fitting involves fitting a patient with a lens from a trial lens set or from a lens inventory based on the corneal curvature information from the corneal topographer. The first trial lens is selected either by using nomograms or computer software. Some trial lens calculating programs may be incorporated in the corneal topographer or computer to aid selection of the lens to fit. The purpose of trial fitting is to get an AC which provides a good centration on a particular cornea. If the lens fit is good, a lens order will be made according to the best fitted AC of the lens and the desired refractive change. If the lens fit is poor, another trial lens will be used until a lens giving the desired performance is found. When the fitting of the lens and refractive change is satisfactory, it will become the retainer lens which is worn on a regular basis, usually every night, to retain the corneal shape and the corrected myopia. Table 1.2.4 shows some examples of lens designs using the diagnostic fitting philosophy.

The advantages of this fitting method include the ability of the practitioner to evaluate the performance of the fitted lens parameters, and patients can immediately experience the feeling of lens wear. The practitioner can also assess the corneal response to determine if the patient is suitable for the procedure by corneal topographical changes after an overnight trial. However, the disadvantage of such a

fitting method is that the practitioner needs to keep a lens inventory, and a longer chair time is required in a trial lens fitting visit.

1.2.2.2.2 Empirical fitting

Empirical fitting involves ordering custom made trial lenses from the manufacturer by sending data on corneal topographical readings, attempted refractive change, pupil size and corneal diameter to the laboratory, who would then fabricate the lenses for the patient (Mountford, 2004). Alternately, some manufacturers provide software programs that can be incorporated in some corneal topographers to help the practitioner determine required lens parameters for a particular patient (Mountford, 2004). At the delivery visit, if the lens fit and refractive change is satisfactory, it will be dispensed and become the retainer lens. If the lens fit is unsatisfactory, either due to poor lens centration or poor corneal response, the manufacturer is consulted and changes will be made according to the topographical results and a second pair of lenses will be ordered and tried again.

This fitting method can save time as the trial lens which gives a good fitting is likely to become the retainer lens. The practitioner also does not need to keep a lens inventory, saving the space and administration needed for the lens inventory. However, this method does not allow the patient to experience the feeling of the lenses in the eyes before lens ordering. There is also a chance that the patient may not respond well after the first overnight lens wear, an indication that he or she is not a suitable candidate. The practitioner may have to refund fee to such patients. Table 1.2.4 shows some examples of lens designs using an empirical fitting philosophy.

1.2.2.2.3 Back Optic Zone Radius selection

As discussed previously, ortho-k involves corneal flattening by the application of a RGL. During the process, the apex of the cornea is flattened, leading to a reduction in the refractive power of the eye while the mid-peripheral cornea becomes steeper. Similar to traditional ortho-k, BOZR in modern ortho-k is determined from the attempted refractive change. Almost all currently available ortho-k lens designs calculate the desired BOZR based on the Jessen formula. The formula assumes that the amount of myopic reduction can be achieved by fitting the BOZR of the lens flatter than the flattest curvature of the cornea by the same amount. For example, a 2.00 D refractive correction would require the BOZR of the lens to be fitted 2.00 D flatter than the flattest curvature of the cornea. This was the original 'orthofocus' technique as described by Jessen (1962), wherein the tear lens becomes the correcting factor. However, as the formula was incorporated into RGL designs, an additional factor, called the compression factor, has been added. The idea was to compensate for daytime regression of the ortho-k effect during the no lens-wear period, so that the wearer can obtain clear distance vision throughout the day (Mountford, 1998). The recovery rate varies from individual to individual with a mean daytime regression of approximately 0.34 D (Mountford, 1998; Nichols et al., 2000). Therefore, a small amount of overcorrection (0.50 to 0.75 D) is desired to ameliorate daytime regression. The BOZR is, therefore, calculated by subtracting the desired myopic reduction (usually equal to the initial spherical component of the refractive error in the ocular plane) and the corneal compression factor from the flattest keratometry reading, as measured using a corneal topographer. Different compression factors have been used by different manufacturers, ranging between

0.50 and 1.00 D (Mountford, 2004). The equation for determining the BOZR of the lens aiming at correcting myopia lower than 4.00 D is, therefore:

$$BOZR = K_f - T - compression\ factor \qquad Equation\ 1.2.1$$

where *Kf* is the flattest simulated keratometry reading and *T* is the desired refractive change. However, clinical experience always gives a lower manifest refractive change than the attempted change calculated from the formula (Nichols et al., 2000; Sorbara et al., 2005). Mountford (1997a) also reported that the refractive change using this formula shows a large variation and affects the predictability of the ortho-k outcome. He suggested the sag fitting philosophy in which the lens was fitted based on the sagittal height of the cornea over the common chord of the cornea.

1.2.2.2.4 Sag fitting philosophy

The sag fitting philosophy was developed by Mountford and Noack (Capricornia BE). They incorporated the concept of a tangential periphery on the lens as a means of controlling centration. Lens parameters are calculated based on the corneal sagittal height measurement; the lens is fitted to form a tear film layer underneath the lens so as to create a squeeze film force to mold the cornea. This fitting approach does not follow the Jessen formula to determine the BOZR of the lens. The corneal sag height and the base curve of the lens can be determined by computer calculation using the apical radius and shape factor measured from corneal topography (Figure 1.2.3). The sag of a five-zone RGL can be calculated as follow:

$$Total\ sag = X_0 + X_1 + X_2 + X_3 \qquad Equation\ 1.2.2$$

$$= Corneal\ Sag + Apical\ Tear\ Film\ Thickness$$

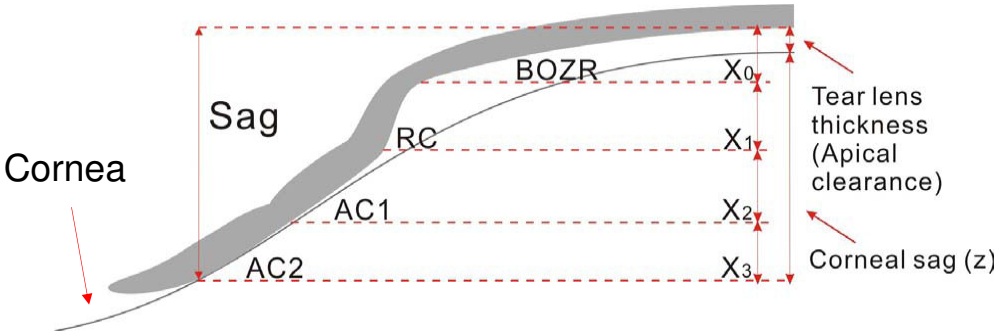


Figure 1.2.3 The sagittal height of a five-zone reverse geometry lens

The calculation of the sag for multi-curve lens is:

$$\text{Sag} = R_1 - \sqrt{R_1^{\,2} - (\frac{D_1}{2})^2} + \left[R_2 - \sqrt{R_2^{\,2} - (\frac{D_2}{2})^2}\right] - \left[R_2 - \sqrt{R_2^{\,2} - (\frac{D_1}{2})^2}\right] + \left[R_3 - \sqrt{R_3^{\,2} - (\frac{D_3}{2})^2}\right] - \left[R_3 - \sqrt{R_3^{\,2} - (\frac{D_2}{2})^2}\right] + \cdots\cdots \left[R_n - \sqrt{R_n^{\,2} - (\frac{D_n}{2})^2}\right] - \left[R_n - \sqrt{R_n^{\,2} - (\frac{D_{n-1}}{2})^2}\right]$$

R_1 = BOZR D_1 = BOZD

R_2 = 2nd Back Peripheral Radius D_2 = 2nd Back Peripheral Diameter

R_3 = 3rd Back Peripheral Radius D_3 = 3rd Back Peripheral Diameter

R_n = nth Back Peripheral Radius D_n = nth Back Peripheral Diameter

After the lens-corneal sag relationship has been determined, the required BOZR can then be calculated to produce the appropriate clearance ratio from the corneal apex and under the RC. The use of a sag fitting philosophy has been claimed to allow a more accurate selection of an initial BOZR, to enhance the predictability of the ortho-k outcome, and to achieve significantly higher refractive change compared to traditional ortho-k (Mountford, 1997a). BE lens (see Table 1.2.4) is an example of a lens design using a sag fitting approach. However, a study comparing four different RGL designs for overnight ortho-k on young adults showed similar efficacy in

myopic reduction using either the Jessen formula or the sag fitting philosophy in determining the BOZR (Tahhan et al., 2003).

1.2.2.3 Gas permeable lens materials

Clinical complications related to contact lens wear is frequently associated with corneal hypoxia (Binder, 1979; Polse et al., 2001). Bacterial binding on the corneal epithelium is more likely to occur under hypoxic conditions and will result in an increased risk of lens-related corneal complications (Cavanagh et al., 2002). To avoid corneal hypoxic complications, traditional ortho-k using oxygen impermeable PMMA material was limited to day wear only. However, even with RGL designs, this contact lens wearing modality has had greater difficulty in gaining general acceptance in terms of comfort and convenience. Therefore, day-wear ortho-k is not attractive as a means for myopic correction.

Holden and Mertz (1984) reported that the minimum oxygen transmissibility (Dk/t) of a soft contact lens required to avoid overnight corneal swelling exceeding 4%, (the amount of normal overnight swelling without lens wear), was 87.0 x 10^{-9} (cm • ml O_2)/ (s • ml • mmHg). However, other studies have shown lower values, ranging from 0.7% to 3.8% of normal overnight swelling (Kiely et al., 1982; Sweeney and Holden, 1987; Fonn et al., 1999; du Toit et al., 2003; Moezzi et al., 2006). More recent studies have confirmed that overnight swelling during sleep (without any lens) is approximately 3% (du Toit et al., 2003; Moezzi et al., 2006). In order to reduce the corneal swelling in overnight contact lens wear, greater Dk/t materials are needed. Harvitt and Bonanno (1999) reported that a Dk/t of a soft lens of 125 x 10^{-9}

(cm • ml O_2)/ (s • ml • mmHg) was needed if the corneal swelling in overnight contact lens wear is to be reduced to 3.2%.

The advent of hyper Dk/t materials (HDS100, Boston XO, and Menicon Z) rigid gas permeable contact lenses have been shown to enhance oxygen transmission to the cornea, and permitting ortho-k treatment to be used safely during sleep (Swarbrick, 2006). Overnight ortho-k is a more convenient and attractive modality as lens wearing discomfort is minimized compared with open-eye lens wear conditions, and allows clear unaided vision during waking hours. In addition, overnight ortho-k is especially attractive to parents who are concerned about myopic progression in their children. It is also attractive to people who have low to moderate myopia and do not want to have refractive surgery, and for unsuccessful contact lens wearers with symptoms of dryness and redness. Overnight ortho-k was first approved in the USA in June 2002 to CRT (see Table 1.2.4) for temporary reduction of up to 6.00 D of myopia and in eyes with up to 1.75 D of astigmatism.

1.2.2.4 Corneal topography

In traditional ortho-k, lenses were fitted according to the corneal curvatures measured with the keratometer. The difference between central and peripheral corneal curvatures was used to determine the flattening rate of the cornea and to predict the outcome of the treatment (Wlodyga and Bryla, 1989). However, only the curvatures of the central 3 mm of the cornea can be measured with the keratometer and such a small measured area is inadequate for the monitoring of ortho-k effects as the treatment involves a larger area of the cornea. The difference between central and peripheral curvatures was also unable to represent the actual flattening rate of the

cornea (Joe et al., 1996). A comprehensive topography of the corneal shape became possible after the introduction of corneal topography in 1980s.

The introduction of corneal topography has pushed ortho-k into a new era, and the corneal topographer is now an essential instrument in ortho-k practice (Mountford, 2004; Swarbrick, 2006; El Hage et al., 2007; Cho et al., 2008). Corneal topography presents a more comprehensive representation of the cornea. This advanced technique helps to rule out poor candidates with an irregular corneal shape and any corneal anomaly such as keratoconus and pellucid marginal degeneration, which are unsuitable for ortho-k. The instrument can also give subtractive maps to aid assessment of the lens-induced corneal shape change. Understanding how the cornea changes with lens wear is useful for refining the lens fit. El Hage and colleagues (1999) were pioneers who described RGL fitting with the aid of a corneal topographer.

Corneal topography provides a useful index quantifying the shape of the anterior cornea by calculating and presenting the shape factor (p) (Figure 1.2.4). The conic section of the cornea can be determined by Baker's equation, as proposed by Baker (1943) as:

$$\textit{Shape factor } (p) = (2r_o z - y^2)/z^2 \qquad \textit{Equation 1.2.3}$$

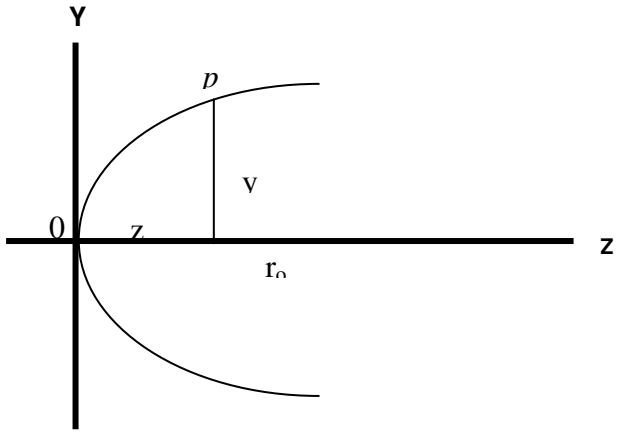


Figure 1.2.4 Shape factor (*p*) in a conic section

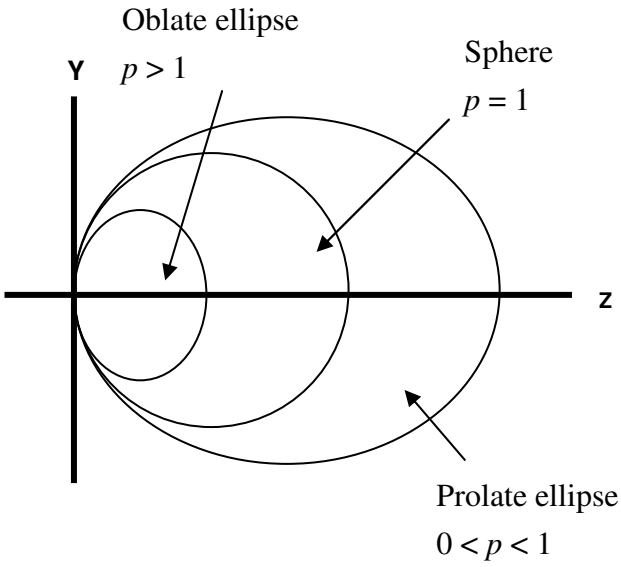


Figure 1.2.5 Schematic diagram showing different corneal shapes

Different corneal shapes described by p are shown in Figure 1.2.5. Apart from p, the corneal topographer also gives other indices to describe the shape of the cornea; the eccentricity (e-value) and asphericity (Q). These indices are inter-related mathematically by the following equations:

$$p = 1 - e^2, \qquad \textit{Equation 1.2.4}$$

$$p = 1 + Q, \qquad \textit{Equation 1.2.5}$$

$$Q = -e^2 \qquad \textit{Equation 1.2.6}$$

The shape of a normal human corneal surface is usually described as a prolate ellipse, indicating a gradual flattening from center to periphery. During ortho-k lens wear, the shape of the cornea becomes more spherical or oblate (steepening towards the periphery from center). Knowing the rate of corneal change with ortho-k lens wear is important for a better understanding of the desired refractive effect. Mountford (2004) reported an approximate myopic reduction of 0.75 D before any change in keratometry values; he suggested that this result may be mainly attributed to the changes in e-value and sagittal height of the cornea rather than only the central corneal curvature.

As described previously, the corneal topographer has a subtractive topographical map function which provides useful information on the amount of change over 80% of the cornea after treatment. The subtractive axial map (sagittal) measures the change of the corneal surface relative to the optical axis, and is best for determining the axial curvature or power change (El Hage and Leach, 1999). Previous studies (Mountford, 1997a; Nichols et al., 2000) have reported a high correlation between

the change in apical corneal power (ACP) and refractive changes using an axial subtractive topographical map (see Section 1.2.2.5.4).

The subtractive tangential map (instantaneous/ true) measures the change of the corneal surface independent of the optical axis. The normal to the measured corneal point does not necessary have to cross the optical axis, but is calculated by referring to its neighboring points. Therefore, the tangential map is more sensitive to sudden changes in corneal curvature, and is best to evaluate lens centration under a closed eye environment. Four typical tangential subtractive topographical patterns can be observed after overnight ortho-k lens wear. These patterns include 'Bull's eye', 'Smiley face', 'Central island' and 'Frowny face', representing good centration, decentered lens and steep fit of the lens during sleep (details will be discussed in Section 1.3.2).

The subtractive refractive map measures the change of the refractive power of the cornea by converting the surface power into refractive power using the Snell's law. It is best to evaluate the change in corneal refractive power and determine the size of the treatment area, since the axial and tangential maps will over- and under-estimate the size of this zone respectively (Mountford, 1997a).

A real key to successful ortho-k fitting is the acquisition of accurate corneal maps at pre-fitting and during every aftercare visit. However, the accuracy and repeatability of any individual reading varies with different topographers due to the different algorithms used to reconstruct different corneal shapes (Tang et al., 2000). Even if the same corneal topographer was used, individual readings may also vary due to

poor tear stability and poor fixation of the patients during measurements. Therefore, repeated measurements, at least two readings, were suggested in order to give more accurate readings (Cho et al., 2002b).

1.2.2.5 Clinical efficacy of modern orthokeratology

With the introduction of RGL design and the advent of corneal topography in the late 1980s, the efficacy of ortho-k significantly improved and clinical interest in using ortho-k for myopic reduction grew considerably (Mountford, 1997a; Nichols et al., 2000; Rah et al., 2002a; Alharbi and Swarbrick, 2003; Soni et al., 2003; Koffler and Smith, 2004; Sorbara et al., 2005). Table 1.2.5 summarizes the previous studies in myopic reduction using RGL designs for overnight treatment (Mountford, 1997a; Nichols et al., 2000; Rah et al., 2002a; Alharbi and Swarbrick, 2003; Cho et al., 2003; Joslin et al., 2003; Soni et al., 2003; Tahhan et al., 2003; Hiraoka et al., 2004; Koffler and Smith, 2004; Owens et al., 2004; Berntsen et al., 2005; Maldonado-Codina et al., 2005; Sorbara et al., 2005; Lu et al., 2007; Kobayashi et al., 2008; Lipson et al., 2008).

Table 1.2.5 Summary of overnight orthokeratology studies using reverse geometry lenses for myopic reduction

Studies (year)	Lens	Dk	Duration of study (months)	Initial age (years)	Number of subjects	Baseline myopia (mean ± SD) (D)	Myopic reduction at the end of the study (mean ± SD) (D)
Mountford (1997a)	Contex OK	–	1	28.0 ± 12.0	60	−2.19 ± 0.79 [a]	2.19 ± 0.57
Nichols et al. (2000)	Contex OK	–	2	25.9 ± 3.9	8	−1.84 ± 0.81 [b]	1.83 ± 1.23
Rah et al. (2002a)	Fargo 6 Paragon CRT	–	3	–	31	−2.14 ± 0.98 (RE) [a] −2.16 ± 1.00 (LE) [a]	2.08 ± 1.11 (RE) 2.16 ± 1.05 (LE)
Alharbi & Swarbrick (2003)	BE	100 x 10^{-11}	3	22 – 29	18	−2.63 ± 0.67 [a]	2.63 ± 0.57
Cho et al. (2003)	Contex OK	–	1 – 12	5 – 46	69	−3.93 ± 2.30 [a]	–
Joslin et al. (2003)	Paragon CRT	100 x 10^{-11}	1	34 ± 10	9	−3.33 ± 1.26 [a]	3.08 ± 0.93
Soni et al. (2003)	Contex OK	–	3	21 – 43	8	−1.76 ± 0.70 [b]	2.12
Tahhan et al. (2003)	Rinehart & Reeves, BE, DreimLens, Contex	–	1	20 – 37	46	−2.24 ± 0.77 (RE) [a] −2.25 ± 0.81 (LE) [a]	2.00 ± 0.34
Hiraoka et al. (2004)	Emerald	85 x 10^{-11}	12	10 – 44	31	−2.49 ± 1.11 [a]	2.40
Koffler & Smith (2004)	Paragon CRT	100 x 10^{-11}	4 – 13	14 – 55	16 (31 eyes)	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
Owen et al. (2004)	BE/ABE	100 x 10^{-11}	1	17 –37	20	−2.28 ± 0.84 [a]	−0.01 ± 0.60
Berntsen et al. (2005)	Paragon CRT	100 x 10^{-11}	1	12 – 37	20	−3.11 ± 0.96 [b]	3.33 ± 0.77
Maldonado-Codina et al. (2005)	BE, No.7	100 x 10^{-11}	7 days	28 ± 10	9	BE : −2.22 ± 0.63 [a] No.7: −2.40 ± 0.59 [a]	BE : 2.89 No.7 : 2.23
Sorbara et al. (2005)	Paragon CRT	100 x 10^{-11}	1	25.8 ± 6.9	23	−3.00 ± 1.03 [b]	2.59 ± 0.77
Lu et al. (2007)	Paragon CRT	100 x 10^{-11}	28 days	26.1 ± 7.6	23	−3.00 ± 0.22 [b]	−0.40 ± 0.16
Kobayashi et al. (2008)	BE	100 x 10^{-11}	12	27.3 ± 5.0	15	−2.54 ± 0.97 [b]	−0.95 ± 0.96
Lipson et al. (2008)	Paragon CRT/custom designed lenses made from Boston	–	51	17.7 ± 13.2	296	−3.40 ±1.50 [b]	−0.20 ± 0.40

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

1.2.2.5.1 Myopic reduction

Overnight ortho-k was initially recommended to reduce low myopia and most attempts aimed at 4.00 D or less. The first clinical report on overnight ortho-k lens wear was by Mountford (1997a). He reported a mean reduction of 2.19 ± 0.80 D myopia for subjects with an initial refractive sphere power of −2.19 ± 0.79 D after one-month of lens wear, with a maximum reduction of 5.00 D. In 2000, Nichols and co-workers (2000) published the first prospective clinical results on overnight ortho-k. Over a period of two months of lens wear, they found a mean reduction of 1.83 ± 1.23 D for subjects with a baseline spherical equivalent power of −1.84 ± 0.81 D.

Overnight ortho-k, compared with traditional ortho-k, increases the amount of myopic reduction by an average of about 3.00 D (Joslin et al., 2003; Koffler and Smith, 2004; Berntsen et al., 2005; Lipson, 2008). The inconsistency in the amount of myopic reduction resulting from an overnight modality (see Table 1.2.5) may be due to the refractive error profile of the participating subjects, most of whom have a baseline myopia of less than 4.00 D. To date, no clinical study has been conducted to investigate the maximum amount of myopic reduction that can be achieved with ortho-k, although one study has indicated an individual myopic reduction of up to 6.00 D (Koffler and Smith, 2004).

1.2.2.5.2 Astigmatic reduction

The inability to correct astigmatism has been one of the major limitations in current ortho-k practice. A few studies have concerned the use of ortho-k for correcting corneal astigmatism (Lu et al., 1999; Mountford and Pesudovs, 2002). Lu and colleagues (1999) reported about a two-thirds astigmatic reduction in a group of

young subjects with a baseline with-the rule astigmatism of up to 3.00 D in day and overnight RGL wear. Mountford and Pesudovs (2002) conducted a retrospective study using power vector analysis to examine both the magnitude and direction of astigmatic change after ortho-k. They analyzed 23 patients with pre-ortho-k corneal astigmatism between 0.50 and 2.00 D using two different vector analysis techniques, – Bailey-Carney (Bailey and Carney, 1970) and Alpins method (Alpin, 1997) and corneal topographical analysis. They found that, on average, there was a reduction of approximately 50% in corneal astigmatism over the central 2 mm of the cornea with spherical RGL, if the lens was located centrally on the cornea.

Apart from Mountford and Pesudovs's study, most other clinical studies showed no significant change in corneal or refractive astigmatism in overnight ortho-k using a spherical RGL design (Rah et al., 2002a; Tahhan et al., 2003; Soni et al., 2003; Koffler and Smith, 2004; Sorbara et al., 2005). Some studies even reported an increase of astigmatism after the procedure (Hiraoka et al., 2004). Due to an ineffective reduction of astigmatism with a spherical ortho-k lens, the procedure is restricted to those with low to moderate corneal toricity (under 1.50 D, with-the-rule). High corneal toricity (over 1.50 D, with-the-rule) is considered to be a contraindication for treatment, at least for the spherical design. Limbus to limbus corneal astigmatism is contraindicated for ortho-k as a stable lens cannot be obtained on the cornea (Mountford and Pesudovs, 2002).

In view of the increased demand for ortho-k in the recent years, some manufacturers have developed toric periphery RGL designs. Different lens sags along two different meridians induce differential corneal flattening and myopic reduction in the two

meridians. At the Global Orthokeratology Symposium in Toronto in August 2002, several scientific papers were presented regarding astigmatic reductions using these lenses. A multi-center retrospective study using toric periphery RGL designs has been evaluated in Switzerland with a reported 82.5% successful fitting rate (Baertschi, 2005). Another study in the Netherlands also reported that toric periphery RGL can successfully correct astigmatism up to 3.50 D, and can also be used for the correction of against-the-rule astigmatism (Beerten et al., 2005). Their report also showed that 70% of their patients achieved unaided visual acuity (UVA) of 6/9 (Snellen VA chart) in both eyes.

1.2.2.5.3 Vision improvement

Overnight ortho-k improves UVA, and the improvement is associated with a change in myopia (Nichols et al., 2000; Rah et al., 2002a; Tahhan et al., 2003; Koffler and Smith, 2004; Walline et al., 2004a; Wang et al., 2005; Cheung et al., 2007). Nichols and colleagues (2000) investigated 10 subjects who had worn RGL for 60 days and reported a mean UVA improvement of 0.55 logMAR (5.5 lines improvement), giving a mean UVA of – 0.03 ± 0.16 logMAR (Snellen equivalent, 20/19). A larger clinical study, with 60 subjects, conducted by Rah and colleagues (2002a) also found that 74% of subjects were able to achieve 20/20 or better UVA, and 96% were able to achieve 20/25 or better UVA after three months of ortho-k treatment.

A study comparing four different ortho-k lens designs (Contex, DriemLens, BE and Reinhart and Reeves) found no significant differences in the subjective rating and UVA improvement among the lens designs. The mean logMAR UVA was 0.02 ± 0.14 (Snellen equivalent, $6/6^{-}$) (Tahhan et al., 2003). Koffler and Smith (2004) fitted

a group of subjects (aged from 14 to 55 years) with the CRT lenses (see Table 1.2.4) for overnight ortho-k. After one month of lens wear, all achieved UVA of 20/40 or better and 55% achieved UVA of 20/20. Walline and co-workers (2004a) used the same lens design on 23 subjects aged eight to 11 years for overnight ortho-k. They reported a mean improvement of the high contrast UVA from 0.67± 0.22 logMAR (Snellen equivalent 20/94) to 0.08 ± 0.15 logMAR (Snellen equivalent 20/24).

1.2.2.5.4 Corneal curvature changes

Ortho-k significantly flattens corneal curvatures and there is a significant relationship between curvature change and refractive change (Mountford, 1997a; Nichols et al., 2000). Mountford (1997a), using the EyeSys topographer (version 3.20), reported a significant relationship between corneal shape and refractive changes in a group of subjects undergoing ortho-k. Interestingly, he found a zero change in corneal curvature with a refractive change of 0.71 D. He also reported a high correlation between change in apical corneal power (ACP) and refractive change with the relationship of

$$\textit{Change in refraction} = 0.92\ (\textit{change in ACP}) + 0.15$$

Nichols and co-workers (2000) also showed significant mean ACP flattening of 1.19 D with 1.40 D refractive change after seven days of overnight ortho-k lens wear on eight young subjects.

1.2.2.5.5 Time course of effect

Modern ortho-k using an RGL design provides a rapid reduction of myopia. Overnight ortho-k can lead to an approximately 70% reduction in refractive error after the first night of lens wear, and most of the refractive change and visual improvement occurs within one week of lens wear (Alharbi and Swarbrick, 2003; Sridharan and Swarbrick, 2003; Soni et al., 2003; Tahhan et al., 2003; Owens et al., 2004; Soni et al., 2004; Sorbara et al., 2005).

A detectable corneal and refractive response can be observed even after a short period of lens wear. Sridharan and Swarbrick (2003) investigated the effect of the BE lens (see Table 1.2.4) on nine young adult subjects over eight hours. They found a statistically significant flattening (mean ± SD: 0.61 ± 0.35 D) in corneal curvatures and improvement in UVA (mean ± SD: logMAR 0.16 ± 0.18) after 10 minutes of open-eye lens wear. Jackson and co-workers (2004) also reported similar results using CRT lenses (see Table 1.2.4). Jayakumar and associates (2005) investigated the short-term ortho-k response in different age groups (age ranged five to 57 years). They found a statistically significant improvement in UVA, topographical changes and central corneal thickness thinning after one hour of open-eye ortho-k lens wear in all age groups.

1.2.2.6 Predictability of orthokeratology effect

Over the 40 years of ortho-k history, several modifications in the technique were proposed to obtain the most effective fitting philosophy with the least side effects. Apart from the knowledge, skill and experience of the ortho-k practitioner, a reliable parameter(s) which can accurately predict the outcomes of ortho-k would be very

useful. It would help ortho-k practitioner to screen and advise potential wearers before commencing treatment. A number of studies have suggested initial ocular parameters – such as e-value (Coon, 1984; Wlodyga and Bryla, 1989; Carkeet et al., 1995; Joe et al., 1996; Mountford, 1997a; Lui and Edwards, 2000a; Lui and Edwards, 2000b; Jayakumar and Swarbrick, 2005), corneal power difference between the central and peripheral area (Freeman, 1978; Wlodyga and Bryla, 1989; Lui and Edwards, 2000a), initial myopia level (Carkeet et al., 1995), central corneal thickness (Lui and Edwards, 2000a), ocular rigidity and intraocular pressure (Kerns, 1978; Joe et al., 1996) – as predictive tools for myopic reduction in ortho-k. However, these parameters had either been rejected (Carkeet et al., 1995; Joe et al., 1996; Cheung and Cho, 2004) or data collected from these studies involved only a small group of subjects (Joe et al., 1996). To date, no specific parameter has been confirmed to be useful for predicting ortho-k outcome.

e-value will decrease and approach zero due to the "sphericalization" effect of ortho-k (Mountford, 1997a). Previous studies have shown that myopic reduction following ortho-k was accompanied by a significant change in e-value (Joe et al., 1996; Mountford, 1997a; Lui and Edwards, 2000a; Lui and Edwards, 2000b). e-value is the most commonly used index to describe the shape of the cornea – the greater the e-value, the faster the rate of corneal flattening from the apex towards the periphery. It ranges from zero to one, with an e-value equal to zero when the cornea is a sphere and an e-value equal to one when the cornea is a parabola (see Figure 1.2.5). In the general Caucasian and Chinese populations, the average e-value in normal corneas was reported to be about 0.5 unit (Guillon et al., 1986; Lam and Loran, 1991; Eghbali et al., 1995; Lam and Douthwaite, 1996; Cheung et al., 2000).

In a retrospective study comparing changes in corneal parameters with refractive changes in a group of ortho-k subjects (overnight wear), Mountford (1997a) found a significant correlation between the change in e-value and the change in ACP, and the refractive change. He concluded that the initial e-value may be useful for predicting the possible amount of refractive change, with about 0.21 unit change in e-value for each dioptre of myopia change. However, the shape of the cornea has been moulded from a prolate ellipse before ortho-k, to an oblate ellipse after the treatment (Coon, 1984; Wlodyga and Bryla, 1989; Lebow, 1996; Day et al., 1997). To describe the oblate corneal shape, p should be greater than one. From the Equation 1.2.4, the e-value is therefore equal to a square root of a negative value, which is nonsense (Swarbrick, 2004). Therefore the e-value given by the corneal topographer after ortho-k is no longer a true e-value which indicates the flattening of the cornea. It is therefore inappropriate to use post-ortho-k e-value to represent the corneal shape. Recent studies (Nichols et al., 2000; Mountford, 2005) have used Q for analysing the shape of the cornea in ortho-k. Nichols and co-workers (2000) reported a mean refractive change of 1.83 D associated with a change of 0.11 unit in Q. Mountford (2005) examined changes in Q (ΔQ) over the central 6.00 mm chord or treatment zone before and after ortho-k in 35 subjects. His results showed a high correlation between ΔQ and achieved myopic reduction ($r^2 = 0.77$, $p = 0.001$) but a poor correlation between initial Q and achieved myopic reduction ($r^2 = 0.09$). This is to be expected as Q can be associated with different levels of myopia.

In addition, changes in corneal thickness induced from ortho-k were reported to be associated with the refractive change (Swarbrick et al., 1998; Nichols et al., 2000). There are some similarities between ortho-k and laser refractive surgery, which uses

the Munnerlyn formula to calculate the ablation depth in PRK (Munnerlyn et al., 1988). The amount of tissue manipulation required for a desired refractive change in refractive surgery can be determined by the following equation (Munnerlyn et al., 1988):

$$t = -S^2 \cdot T/8\,(n-1) \qquad \textit{Equation 1.2.7}$$

where t is ablation depth, S is ablation diameter, T is the desired refractive change, and n is the refractive index of the cornea which is assumed to be 1.377. The formula assumes that the posterior corneal shape remained unchanged throughout the procedure.

Alharbi and Swarbrick (2003) used the Munnerlyn's formula to predict the refractive change induced by overnight ortho-k based on the corneal sagittal height change. In a group of subjects with baseline refractive error of mean of −2.63 ± 0.68 D, they claimed that the formula may be used to predict the manifest refractive change after ortho-k treatment, with the relationship of:

$$\textit{Refractive change} = 1.24\ \textit{Predicted refractive change} + 0.37\ (r = 0.88,\ p < 0.001)$$

1.2.2.7 Recovery and regression

One of the benefits that ortho-k has over refractive surgery for myopic correction is that the former is non-permanent and reversible. Due to the high flexibility of corneal tissue, the cornea will gradually resume its pre-treatment shape after cessation of lens wear (Barr et al., 2004; Soni et al., 2004; Sorbara et al., 2005;

Kobayashi et al., 2008). Therefore, to maintain the induced myopic reduction, regular retainer lens wear is required. Although the recovery process is gradual and begins after lens removal, due to individual differences in corneal viscoelasticity and stromal lamellar responses, the rate of recovery varies among individuals (Soni et al., 2003; Johnson et al., 2007).

Previous researchers have reported both regression and recovery from the ortho-k effect. Regression refers to a reduction in the effect on parameter/s caused by ortho-k lens wear, such as refractive error, visual acuity, corneal curvature and corneal thickness, during the day when ortho-k lenses are not worn. Recovery rate refers to how fast the changed parameters (due to the ortho-k lens wear) return to baseline level/s after ortho-k lens wear has been terminated. In general, in ortho-k, over 90% recovery will be determined as total recovery (Soni et al., 2004; Barr et al., 2004; Kobayashi et al., 2008).

Fast regression will affect vision during the day. Slow regression may allow patients to wear their lenses every second or third night, or even less frequently, while maintaining adequate daytime unaided vision. Regression was reported to be greater for higher refractive changes (Polse et al., 1983) and during the earlier stage of ortho-k lens wear (Mountford, 1998; Soni et al., 2003; Johnson et al., 2007). Once the effect of ortho-k has stabilized, which is usually after about one week of lens wear, the average regression in refractive error would range between 0.25 and 0.75 D (Mountford, 1998; Nichols et al., 2000; Rah et al., 2002a; Sorbara et al., 2005). From the study by Mountford (1998), the amount of change in ACP following overnight ortho-k was not significantly correlated with the regression, and the rate of

regression became slower with the continuation of lens wear. A similar result was reported by Johnson and co-workers (2007). They conducted a clinical study on six subjects wearing BE lenses for overnight ortho-k and compared the stability of the refractive error over nine hours of no lens wear after one day and eight days. Their results showed that the regression of refractive power was slower after eight days of treatment.

Some researchers have investigated the regression of UVA in ortho-k. Similar to the regression of refractive error, the regression of UVA appeared longer with lens wear period (Nichols et al., 2000; Soni et al., 2003; Sorbara et al., 2005). Nichols and colleagues (2000) examined eight subjects after 30 nights of ortho-k lens wear and found a mean regression less than 0.02 logMAR UVA after eight hours from lens removal. Soni and colleagues (2003) measured and monitored a group of eight subjects undergoing ortho-k in a period of three months. They did not find any regression in UVA after 12 hours of lens removal. Sorbara and co-workers (2005), using a computerized logMAR chart, measured the ortho-k effect on myopic reduction after a one month treatment period. They found the improved UVA can be maintained for three to seven hours, and the regression from seven to 14 hours of no lens wear was also slow.

Several studies have investigated the recovery from the ortho-k effect after discontinuation of lens wear (Soni et al., 2004; Barr et al., 2004; Sorbara et al., 2005; Kobayashi et al., 2008). Barr and co-workers (2004) investigated the recovery rate from the ortho-k effect in a group of subjects with baseline refractive error between –1.62 and –3.00 D. After six to nine months of ortho-k lens wear, they reported a

70% recovery towards baseline refractive error after 72 hours of no lens wear. Sorbara and colleagues (2005), measuring a group of subjects with a similar refractive error of mean –2.72 ± 1.06 D after 28 days of overnight ortho-k treatment, reported a 60% recovery of refractive error after ceasing lens wear for 72 hours.

Soni and colleagues (2004) investigated the total recovery in refractive error and corneal topography after one month of overnight ortho-k lens wear. They found that the central corneal thickness showed the fastest rate of recovery, with complete recovery after ceasing lens wear for just one night. Next was the central corneal curvature which recovered fully in one week. The refractive power and UVA showed the slowest recovery rate and they took two weeks to achieve full recovery.

A recent clinical study conducted in Japan (Kobayashi et al., 2008) investigated the recovery of visual acuity, refractive error, corneal topography and contrast sensitivity after one year of overnight ortho-k treatment. Their results showed that all measured parameters had returned to baseline values after discontinuation of lens wear for two months.

1.3 Assessment of lens fit

Assessment of ortho-k lens fitting is initially performed by assessing the fluorescein pattern with lenses in situ under silt-lamp microscope, similar to the assessment in conventional RGP fitting. Since modern ortho-k involves lens wear under closed-eye conditions where the lid pressure may alter the fit of the lens, it is therefore inadequate to determine the lens fit solely by assessing the fluorescein pattern alone. Hence, in addition, ortho-k lens fitting is also determined by the assessment of

corneal topographical change after a few hours or one night of lens wear. Careful assessment of lens fit is essential to ensure that the lens gives a proper cornea-lens relationship and good centration, satisfactory corneal shape and refractive changes without causing ocular complications. In RGP lens fitting, the appearance of the fluorescein pattern provides accurate information when determining the lens fit (Brungardt, 1976; Orsborn et al., 1989).

1.3.1 Fluorescein pattern analysis

1.3.1.1 Static fluorescein pattern analysis

The static fluorescein pattern reflects the relationship between the cornea and the back surface of an RGL. The fitting is assessed with the lens centered on the cornea with the lids pulled wide apart. The ideal tear profile of an RGL is totally different from that of a conventional RGP lens. Since fluorescein underneath the lens can only be seen with the naked eye when the tear layer thickness is over 20 μm (Carney, 1972; Mountford et al., 2004), the assessment criteria for the fluorescein pattern are different in ortho-k lens fitting (Figure 1.3.1)

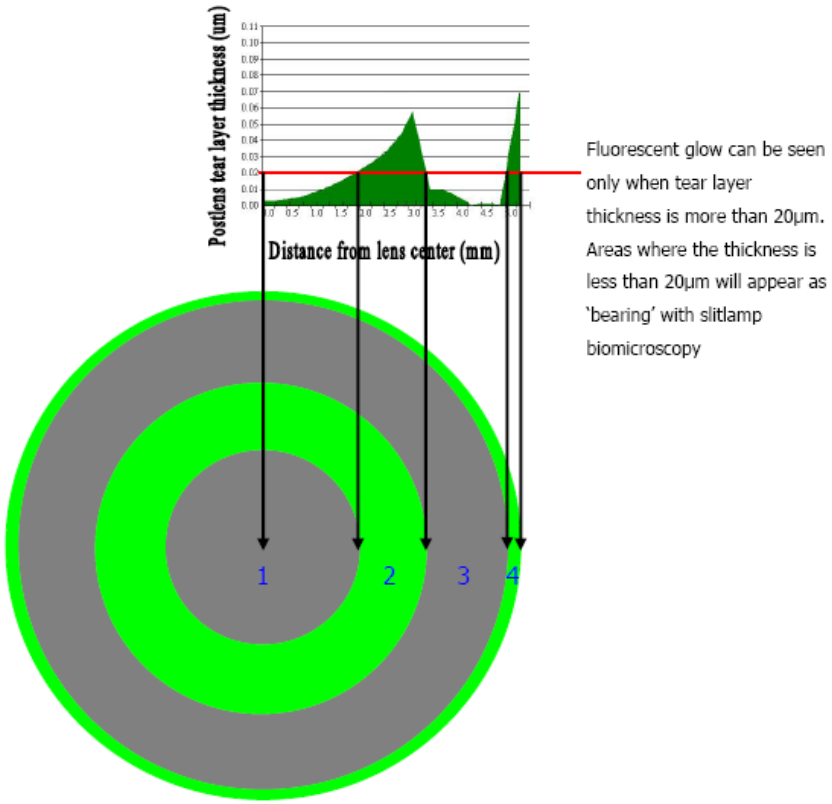


Figure 1.3.1 Fluorescein pattern of an RGL on the eye

A desirable fluorescein pattern of an RGL should demonstrate, from the center of the lens towards the lens edge, the following characteristics:

1. Central bearing

   An apparent non-glowing central area of 3.0 – 5.0 mm diameter, where the tear film is about 5 – 10 µm thick

2. Annulus of tear reservoir

   0.5 – 1.0 mm band of fluorescein annulus under the reverse zone

3. Mid-peripheral bearing

   Around 1.0 – 1.5 mm band of bearing under the alignment zone, where the lens is supposed to align with the peripheral cornea

4. Edge lift

   Around 0.4 mm in width

1.3.1.2 Dynamic fluorescein pattern analysis

Dynamic lens fit reflects the interaction between the eye lid and the RGL, as well as the cornea-lens relationship. The on-eye lens position is assessed after a normal blink. A desirable lens fitting is one where the lens is centered on the cornea or is slightly low-riding, and moves smoothly with each blink to give adequate tear exchange.

However, the appearance of the static and dynamic fluorescein patterns of an RGL is not sensitive enough to determine optimum fitting and the likely effect on corneal shape (Mountford et al., 2005). The major application of assessing a static and dynamic fluorescein pattern is to rule out a gross misfitting lens, to ensure adequate peripheral clearance and ensure that the lens is not impinging on the cornea. In view of the limitations of fluorescein pattern analysis, the post-wear corneal responses (physiological and topographical) must be considered in the determination of the lens fit.

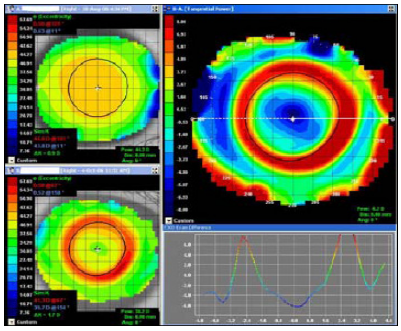
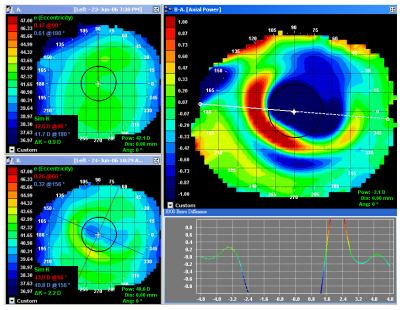
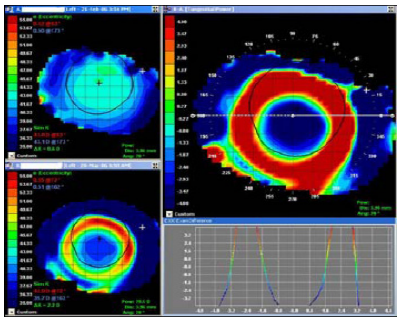
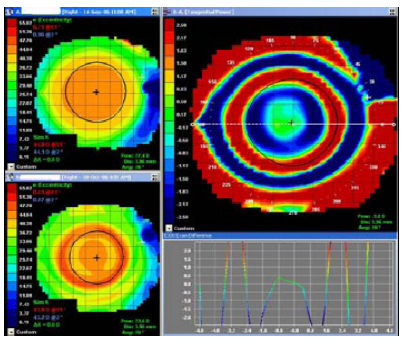
1.3.2 Corneal topographical changes

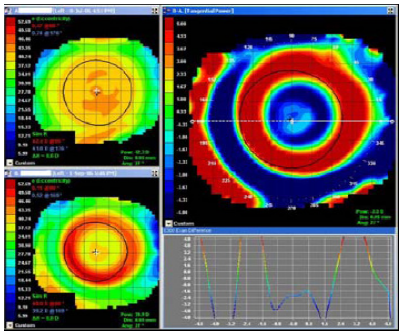
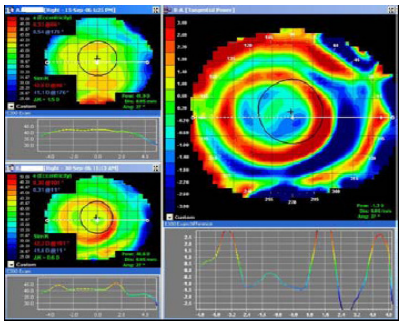
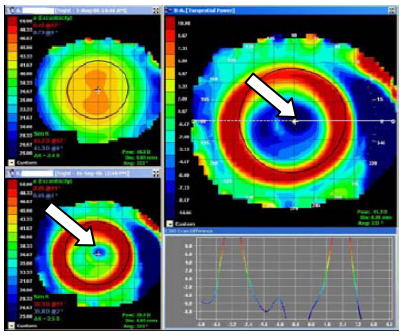
The corneal topographer, as well as the slit-lamp, is an essential instrument in ortho-k practice. The corneal topographer is not only used to assess the corneal response to the ortho-k lens, but also provide invaluable information to the practitioner to decide when or how to refine the lens fit. The subtractive maps between pre- and post-wear are extremely useful to evaluate the fit of the lens and to determine the amount of corneal response. Different topographical scales (Axial, Tangential and Refractive scales) also provide different information on the lens fit (see Section 1.2.2.4).

Generally, there are seven commonly observed subtractive tangential topographical patterns which represent different lens fitting, as shown in Table 1.3.1.

A ‘Bull’s eye’ pattern is present when the subtractive plot shows a central flat corneal curvature area (treatment zone) surrounded by an annulus of steepening (red ring). The treatment zone should be large enough to cover the entire pupil under normal room lighting. This pattern indicates a good lens fit. A ‘Smiley face’ pattern is present when a flat corneal curvature area is displaced superiorly relative to the pupil center with an inferior partial arc-like steep red ring. This pattern indicates a flat lens fit. The third commonly seen subtractive topographical pattern after ortho-k is called a ‘Central island’ pattern where the flat corneal curvature area is within the center of the pupil except for a small area of relative steep curvature, which is steeper than the original curvature, within the optical zone of the eye. This pattern indicates a steep lens fit which will give poor myopic correction or even poor visual acuity. Apart from the appearance of the ‘Central island’ pattern, a steep fitting lens can also show a ‘Frowny face’ pattern where the flat corneal curvature area and the steep ring are displaced inferiorly relative to the pupil.

Table 1.3.1 Tangential topographical changes in orthokeratology lens wear

Patterns	***Descriptions and comment on the lens fit***
Bull's eye 	❑ Ideal lens fit ❑ Good centration with central flat area ❑ Steep mid-peripheral zone (red ring) centered with respect to the pupil
Smiley face 	❑ Flat lens fit ❑ Lens decentered superiorly ❑ Red ring decentered superiorly with respect to the pupil
Frowny face 	❑ Steep lens fit ❑ Lens decentered inferiorly ❑ Red ring decentered inferiorly with respect to the pupil
True central island 	❑ Steep lens fit ❑ Good lens centration (as in Bull's eye) with a small central steep area within the optical zone ❑ Red ring centered perfectly with respect to the pupil ❑ ACP subtraction shows positive value

Fake central island 	❑ Good/flat lens fit ❑ Good lens centration (as in Bull's eye) with apparent central area of steepening ❑ Red ring centered perfectly with respect to the pupil ❑ ACP subtraction shows negative value ❑ Under response or too flat lens fit
Lateral displacement 	❑ Good/ steep/ flat lens fit ❑ Lens diameter too small ❑ Asymmetry nasal and temporal corneal curvatures ❑ Red ring decentered nasally or temporally
Central divot (white arrow) 	❑ Gross localized corneal flattening within the treatment zone ❑ Disruption of corneal tissue

1.4 General principle of orthokeratology

Based on the Jessen orthofocus concept, traditional ortho-k using flat-fitting PMMA lenses assumed that the cornea was moulded toward the back surface shape of the contact lens, resulting in reduced refractive error with the same dioptric amount of base curve flattening. Apart from corneal change, several ocular parameter changes were suggested to be induced from ortho-k, including axial length and crystalline lens power (Erickson and Thorn, 1977; Patterson, 1975). However, these suggestions were not accepted by other researchers (Coon, 1984). Tabb suggested that the 'hydraulic force' created from the post-lens tear film led to the corneal shape change in traditional ortho-k (Coon, 1982). This concept was further developed by Mountford and Noack (1998), and they called the force as the 'squeeze film force'. The tear squeeze film force underneath the lens is the combination of positive pressure at the apex of the cornea and negative 'suction' pressure under the RC.

It is not confirmed whether corneal shape change induced by ortho-k involves the epithelium, stroma, endothelium or the whole cornea. With the advent of corneal topography for monitoring corneal changes, many clinical studies have shown that corneal shape change during ortho-k lens wear was mainly due to the moulding of the anterior corneal surface (Swarbrick et al., 1998; Tsukiyama et al., 2008). However, failure in matching refractive change to the anterior corneal curvature changes suggest that there are other changes in the eye involved in ortho-k (Mountford, 1997a). Some investigators have proposed that changes in the posterior corneal curvature and corneal thickness also contributed to refractive change (Joslin et al., 2003; Owens et al., 2004). Histological studies also showed that ortho-k involves corneal thickness changes, and the changes were mainly due to epithelial

and stromal layers rather than the cornea as a whole (Swarbrick et al., 1998; Alharbi and Swarbrick, 2003; Wang et al., 2003; Haque et al., 2004; Choo et al., 2008).

1.4.1 Overall corneal bending

As yet, there is no conclusive evidence showing that ortho-k involves an overall bending of the cornea. There is a study showing that the changes in the posterior corneal curvature also contributed to refractive change during ortho-k (Owens et al., 2004). The authors concluded that an overall corneal bending is possible in the initial stage of RGL wear, at least before one week of treatment.

However, rather than overall bending of the cornea, most clinical research studies show that flattening of anterior corneal curvatures which resulted in a decrease in corneal sagittal height is the major cause of the ortho-k effect (Swarbrick et al., 1998; Alharbi and Swarbrick, 2003; Tsukiyama et al., 2008). A recent study by Tsukiyama and colleagues (2008), using the Pentacam (Oculus, Inc., Lynwood, WA), measured the changes in anterior and posterior corneal curvatures and anterior chamber depth after overnight ortho-k on nine subjects. They collected seven sets of data over 53 weeks, and found no significant changes in the central posterior corneal curvature or depth of the anterior chamber.

1.4.2 Corneal thickness change

Change in corneal curvatures induced by ortho-k are believed to be associated with corneal tissue redistribution leading to changes in the corneal thickness (Iskeleli et al., 1996; Swarbrick et al., 1998; Nichols et al., 2000; Alharbi and Swarbrick, 2003; Soni et al., 2003; Wang et al., 2003). Iskeleli and colleagues (1996) found a

decrease in corneal thickness of 17 µm in response to overnight ortho-k during a six month lens wear period.

Swarbrick and colleagues (1998) using the Payor-Holden optical micropachometer found a mean of 7.1 ± 7.1 µm central epithelial thinning and 13.0 ± 11.1 µm mid-peripheral corneal thickening after one month of RGL wear. They postulated that the thickness change was due to cellular migration or redistribution from the central region to the mid–periphery, and concluded that ortho-k does not involve overall corneal bending. Nichols and co-workers (2000) also reported a significant thinning of 2.6% in the central cornea as measured with the Orbscan corneal topographer (Bausch & Lomb, Rochester, NY) on 10 subjects over a two-month overnight ortho-k treatment. Alharbi and Swarbrick (2003), using optical pachometry, found a mean of 15.8 ± 3.3 µm central epithelial thinning after one night of ortho-k lens wear in 18 subjects. They found no significant central stromal thickness change during the three-month study period. Using optical coherence tomography (OCT), Wang and colleagues (2003) also reported a central corneal thinning of 5.1%, and mid-peripheral thickening of 1.9% on the temporal side, and 2.4% on the nasal side in subjects wearing CRT lenses. Haque and co-workers (2004) showed that the central corneal epithelium thinned by 7.3% and the mid-peripheral epithelium thickened by 13% after one night CRT lens wear in 23 subjects.

1.4.3 Evidence from animal models

Although there are numerous structural and physiological differences between an animal model and human eye, histological studies on animals can give a general insight into the corneal changes in human eyes (Matsubara et al., 2004; Choo et al.,

2008). Greenberg and Hill (1973) reported that steep-fitting conventional PMMA lenses caused epithelial thinning in rabbits.

Matsubara and associates (2004), using a battery of histological and histochemical tests in the rabbit model, studied the morphologic changes in corneal cell layers after wearing ortho-k lenses. Their results showed that the ortho-k effect was confined to the corneal epithelium with no significant changes in stromal thickness, and the change was consistent with topographical fingdings. The histochemical analysis also indicated no significant change in the epithelial function.

A recent histological study by Choo and colleagues (2008) also indicated that the primary response of the central cornea of cats to ortho-k lens wear was due to cell compression rather than cell movement or a loss of cell layers. They reported involvement of both the epithelium and stroma in response to ortho-k. However, it is unclear if these short term changes in animal models are applicable in humans.

1.5 Safety of orthokeratology

The use of ortho-k lenses, like any other contact lenses, carries an inherent risk of injury to the cornea especially if not used in accordance with the instructions of the optometrist. The occurrence of complications depends on the knowledge and skill of the eye care professional prescribing the lenses and the compliance of the wearer in caring for their lenses and lens accessories (Cho et al., 2002a). Serious corneal complications associated with contact lens wear can lead to vision impairment and potential blindness (Spindel and Perry, 1986; Holden et al., 2003).

Poor lens cleaning procedures will increase deposits on the lens surface over time. Poor lens hygiene not only causes mechanical abrasion to the corneal surface (Goldberg et al., 1997), but also reduces the amount of oxygen transferred though the lens surface, and increases the risk of bacterial binding to the lens surface (Alongi et al., 1998).

1.5.1 Corneal staining

Corneal staining is the most commonly reported complication in ortho-k (Cho et al., 2002a; Rah et al., 2002a; Chui and Cho, 2003; Walline et al., 2004a; Lipson, 2008). Walline and co-workers (2004a) reported that over half of their subjects exhibited corneal staining in the morning immediately after lens removal during six months of ortho-k lens wear. A more recent study by Lipson (2008) reported 32% (90 of 282 patients cases) of corneal staining after the first night of ortho-k lens wear. The incidence of staining dropped to 16% after one-week of lens wear, and to 5.3% after one-month of lens wear. The staining was most often observed in the central corneal region, which indicated that an aggressive compressive force under the central optical area of the lens may cause a certain amount of corneal insult in the initial stage of lens wear. When the corneal response stabilizes, the relative risk of central corneal staining may be lowered. Lipson (2008) also reported that the incidence of corneal staining resulting from ortho-k lens wear increases with an increase in initial refractive errors of the eye. However, the severity of the staining after lens removal was reported to be clinically insignificant, and none of the studies recommended that subjects discontinue lens wear because of corneal staining.

Several risk factors including lens fit, dimple veiling, lens binding and lens deposits are associated with the incidence of corneal staining in ortho-k (Chui and Cho, 2003; Walline et al., 2004a; Stillitano et al., 2007). If the lens is too flat, mechanical abrasion of the central epithelium may result, and if the lens is too steep, excessive apical clearance will lead to lens imprint (Mountford, 1997b). Therefore, lens fitting should be adjusted carefully by increasing the sag of the lens to steepen a flat fit or decreasing the sag to flatten a steep fit.

1.5.2 Dimple veiling

Dimple veiling is another common problem in ortho-k. Small air-bubbles can be trapped underneath the reverse curve in the central area of a steep fitting lens. A flat-fitting lens with heavy fluorescein clearance at the peripheral area of the lens may also trap air bubbles in the clearance region. These bubbles are then mechanically compressed by the lens and they will indent the corneal epithelium causing dimple veiling. The compression produces a transient depression or divot in the cornea. Although a large area of dimple veiling can interfere with vision, it is not a true staining as there is no cell damage involved and the cornea will recover spontaneously within minutes or hours (depending on the severity) after lens removal (Dixon, 1962; Stillitano et al., 2007).

1.5.3 Lens binding

Lens binding is one of the most common problems reported by overnight ortho-k wearers, especially upon awakening (Chui and Cho, 2003; Cho et al., 2003; Cheung and Cho, 2004). An absence of lens movement and blinking lead to reduced tear circulation and increased tear viscosity, and the level of binding is patient-dependent

(Swarbrick and Holden, 1987; Swarbrick and Holden, 1989). In addition to the positive forces exerted by the eyelid during eye closure, this may result in lens adherence to the cornea. Improper removal of a bound lens will disrupt corneal epithelial cells, causing corneal staining (Cho et al., 2003). However, lens binding associated with overnight ortho-k cannot be eliminated or improved by changing the lens fit (Chui and Cho, 2003). Therefore, it is important for the practitioner to advise patients on how to safely remove a bound ortho-k lens (Cho et al., 2008).

1.5.4 Corneal pigmentation arc

Corneal pigmentation has been observed in the mid-peripheral region in many patients undergoing overnight ortho-k (Cho et al., 2002c; Barr et al., 2003; Liang et al., 2003; Hiraoka et al., 2004; Cho et al., 2005b). Corneal pigmentation in ortho-k appears as a brown arc-shaped deposition, similar to Fleischer's ring seen in keratoconic patients. Similar findings have been found in normal patients with no predisposing condition other than age (Hudson-Stahli line), at the anterior head of a pterygium (Stocker's line), near filtering blebs (Ferry's line) and following refractive surgery or penetrating keratoplasty (Koenig et al, 1983; Steinberg et al., 1984; Assil et al., 1993; Probst et al., 1999; Vongthongsri et al., 1999). The pigmented arc in ortho-k is presumed to be iron deposition in the basal layer of the corneal epithelium. The location of the arc corresponds to the mid-peripheral steep area seen in the subtractive topographical map. The reason for the formation of the pigmented arc is unknown, but may be due to an abrupt change in corneal curvature and subsequent tear pooling beneath the steep secondary curve of RGL (Cho et al., 2002c; Rah et al., 2002b; Cho et al., 2005b). Another possibility is that iron accumulates in cells in the area of the tear reservoir where the epithelial cell turnover rate reduced with RGL

wear (Rah et al., 2002b; Barr et al., 2003). Although the occurrence of the corneal pigmentation arc is high among Chinese subjects in ortho-k lens wear (Cho et al., 2002c; Cho et al., 2005b), there does not appear to be any clinical ramification and it is reversible (Cho et al., 2003). However, the long-term effect of the corneal pigmentation arc induced by ortho-k is still unknown and thus careful monitoring is still necessary.

1.5.5 Microbial keratitis

Traditional ortho-k for myopic correction has been reported to be safe for day wear (Binder et al., 1980; Polse et al., 1983). Only one case report in the literature concerns a serious corneal complication with the procedure (Levy, 1982). With the improvement in the oxygen permeability of contact lens materials and better designs and fitting of lenses on the cornea, ortho-k lenses have been accepted as safe for wear during sleep (Mountford, 1997a; Nichols et al., 2000; Rah et al., 2002a). In overnight ortho-k, patients only need to wear the contact lenses while sleeping and clear daytime vision without any optical aid can be achieved. The advantage of having freedom from spectacles or contact lens wear attracts many people with low to moderate myopia to choose this treatment as an alternative to refractive surgery for improving unaided vision during waking hours (Cho et al., 2002a). However, several case reports in the last decade have documented the occurrence of microbial keratitis (MK) associated with overnight ortho-k (Chen et al., 2001; Hutchinson and Apel, 2002; Lau et al., 2003; Poole et al., 2003; Wang and Lim, 2003; Xuguang et al., 2003; Young et al., 2003; Young et al., 2004; Hsiao et al., 2004; Lang and Rah, 2004; Hsiao et al., 2005; Tseng et al., 2005; Sun et al., 2006).

Watt and Swarbrick (2007) summarized all cases of confirmed and presumed MK associated with ortho-k lens wear from case reports published in the literature and from cases presented at the optometric and ophthalmic conferences between 2001 and 2007. They noted a total of 123 reported cases since 2001 with the majority of these being in East Asia, particularly China and Taiwan (69% of the total cases). Female wearers were predominantly affected, and the ages of infected patients ranged from eight to 60 years (mean of 15.8 ± 6.4 years) and the median age was 15 years. In 55% of the cases (58 out of 106 patients with a known lens-wearing period), patients had worn ortho-k lenses for 12 months or less before the occurrence of MK. For all patients with known lens-wearing modality, almost all of them (92%, 73 of 79 cases) wore ortho-k lenses on an overnight basis. *Pseudomonas aeruginosa* (37%) and *Acanthamoeba* (33%) were presumably the most frequently identified microorganisms involved in MK associated with ortho-k. The authors concluded that their results from the review were more likely to reflect the ortho-k lens-wearing population which was predominantly in Asia and also mostly children and adolescents. However, it is uncertain whether children and adolescents are inherently more susceptible to corneal infection, and whether the compliance on lens care and hygiene is poorer in children than in adults in overnight ortho-k.

Since most wearers, particularly in Asia, are children and treatment involves overnight lens wear, extra-care should be taken. The need for strict compliance with the practitioner's instructions on lens use and care cannot be over-emphasized. With careful monitoring and good compliance, complications with overnight ortho-k wear can be minimized.

1.6 Myopic control with orthokeratology

The development of myopia is mainly due to the excessive elongation of the axial length (AL) of the eye, and the longer the AL, the higher the myopia (Adams, 1987; Grosvenor, 1988; Hosaka, 1988; Lam and Goh, 1991; Grosvenor and Scott, 1993; Lin et al., 1996). Grosvenor and Scott (1993) reported that all myopia was axial in origin and that myopia due to an increase in corneal power or lens power without AL elongation was non-existent. Furthermore, AL elongation has been reported to be primarily due to an increase in vitreous chamber depth (VCD) (Adams, 1987; Hosaka, 1988; Goss et al., 1990; Grosvenor and Scott, 1993).

Although the exact aetiology or mechanism behind myopia is still unclear, the development of myopia has been reported to be associated with both environmental and genetic factors (Yap et al., 1993; Zadnik et al., 1994; Zadnik and Mutti, 1995), and there is no conclusive evidence showing the extent of the contribution of the role of nature and nurture in its development (Wallman, 1994; Mutti et al., 1996).

High myopia is associated with retinal detachment, the most prevalent blinding disease among high myopes, and other eye diseases such as retinal degeneration and glaucoma (Perkins, 1960; Burton, 1989; McCarty et al., 1999; Saw et al., 2005). Therefore, the topic of how to control myopia has been and still is of great interest in optometry research due to the increasing prevalence of high myopia, particularly in Asian children.

Many clinical trials, including under-correction of distance refractive error (Chung et al., 2002; Adler and Millodot, 2006), bifocals (Miles, 1962; Oakley and Young,

1975; Goss, 1986; Grosvenor et al., 1987; Parssinen et al., 1989; Jensen, 1991; Fulk et al., 2002) and progressive spectacle lenses (Leung and Brown, 1999; Edwards et al., 2002; Gwiazda et al., 2003), soft (Andreo, 1990; Horner et al., 1999) and rigid contact lenses (Grosvenor et al., 1989; Perrigin et al., 1990; Khoo et al., 1999; Katz et al., 2003; Walline et al., 2004b) and pharmaceutical agents such as cyclopentolate (Ehrlich et al., 1995), atropine (Bedrossian, 1979; Chiang et al., 2001; Shih et al., 2001; Chua et al., 2006) and pirenzipine (Siatkowski et al., 2004; Tan et al., 2005; Siatkowski et al., 2008), have been investigated in retarding the progression of myopia. Although some interventions have shown a positive effect, studies using bifocal and progressive addition lenses (Oakley and Young, 1975; Leung and Brown, 1999; Khoo et al., 1999) suffered from study design weaknesses including small sample size, absence of controls, no cycloplegic refraction under taken, no masking, no AL measurements and no randomization of subjects. There are also safety concerns regarding regular and long-term use of pharmaceutical agents in children for myopic control (Tan et al., 2005; Chua et al., 2006; Siatkowski et al., 2008). To date, there are no practical and reliable interventions mentioned above that can effectively and safely retard the progression of myopia in children.

Since myopic progression often begins during childhood at the age of six years (Lam et al., 1999) and myopia becomes progressively worse through adolescence, myopic control studies are always conducted on children. When choosing treatment options for correcting myopia in children, factors including the efficacy, safety, comfort, and convenience of the methods should be taken into consideration.

In recent years, overnight ortho-k has become increasingly popular for myopic control, particularly in Asian countries (Cho et al., 2008). The first study using ortho-k for myopic control in children was conducted by Cho and co-workers (Cho et al., 2005a). This pilot study consisted of 35 children wearing overnight ortho-k lenses. The AL of the subjects was compared to a control group of children matched for age and initial degree of myopia. After 24 months of ortho-k lens wear, the ortho-k group showed about 50% less increase in AL and VCD compared to the control group wearing single vision spectacles. The mean AL and VCD increases were 0.29 ± 0.27 mm and 0.23 ± 0.25 mm respectively for the ortho-k group, and 0.54 ± 0.27 mm and 0.48 ± 0.26 mm respectively for the control group. However, the study suffered from using spectacle-wearing children as controls, and the protocol for fitting ortho-k lenses was not standardized. There is therefore a need for a randomized study to confirm the myopic control effect of ortho-k. Currently, a number of studies are being conducted in different parts of the world.

It has been speculated that changes in higher-order aberrations and peripheral refraction induced by ortho-k lens wear triggered a slower rate of eye growth (Charman et al., 2006). Recent studies have suggested the possibility of relative peripheral hyperopic defocus in causing myopic progression in children (Choo and Holden, 2007). The fully-corrected myopic eye, either using conventional spectacles or contact lenses, induced a relative hyperopic retinal defocus in the peripheral retinal plane. To match the peripheral image plane, the AL elongated accordingly, thereby resulting in myopic progression. This new concept may promote the development of new optical interventions for myopic control in children.

1.7 Tear ascorbate

The eye is continuously exposed to the atmospheric environment where there is a high level of oxidative stress including photo-active substances, ultraviolet radiation, toxic chemical pollutants, free radicals and other reactive oxygen species (ROS) (Holly, 1973; Shimmura et al., 1996; Rozanowska et al., 1998; Dontsov et al., 1999). It has been reported that there is an increasing risk of age-related ocular diseases including dry-eye syndrome, cataract, glaucoma and age-related macular degeneration, under a high oxidative stress environment (Richer and Rose, 1998; Ahuja et al., 1999; Cai et al., 1999; Carper et al., 1999; Cho et al., 1999; Kayatz et al., 1999; Boscia et al., 2000).

Biochemical processes in the human body are a balance of oxidative and reducing (also called antioxidant) activities. Antioxidant refers to any substance which significantly delays or prevents oxidation of an oxidisable substrate when present at low concentrations compared to that of the oxidisable substrate (Halliwell, 1995). Sufficient antioxidants in the eye are important to suppress ROS formation, scavenge, break chain propagation from active ROS (Paterson and O'Rourke, 1987; Gogia et al., 1998), and therefore maintain the balance of oxidants and antioxidants essential to keep the eye healthy.

Tear fluid bathes the corneal and conjunctival surfaces, and acts as the first ocular defense barrier against ROS, and contains variety of antioxidants including enzymes, protein, and other endogenous molecules and dietary intake vitamins (Fullard and Snyder, 1990; Crouch et al., 1991; Behndig et al., 1998; Gogia et al., 1998; Zigman et al., 1998; Berry and Kohen, 1999; Choy et al., 2000; Bilgihan et al., 2001; Choy et

al., 2001). Disturbances in tear distribution can result in corneal damage. The pre-corneal tear film can be disrupted by contact lens wear leading to various corneal problems (Guillon and Maissa, 2008).

Ascorbate is a reduced form of vitamin C which is known to be an essential water-soluble vitamin to keep the eye healthy, particularly the cornea (Delamere, 1996; Taylor et al., 1997; Gogia et al., 1998; Rose et al., 1998). It is also a major vitamin antioxidant and has been found in high concentration in human tears (Choy et al., 2000; Choy et al., 2001) which is present in the main lacrimal gland secretion in fresh reflex tears (Choy et al., 2003). Choy and co-workers (2000) reported that ascorbate and urate together contribute 50% of the total antioxidant capacity in healthy human tears.

Ascorbate is not produced by the body and only obtained exclusively from the diet (Cadenas and Packer, 1996), especially fruits and vegetables. It has been reported to be important in suppressing inflammatory response and in enhancing wound healing in the cornea (Williams and Paterson, 1986; Vaxman et al., 1995; Yue, 1996; Kasetsuwan et al., 1999; Chaiyotwittayakun et al., 2002; Smirennaia et al., 2002; Jagetia et al., 2003).

Ascorbate is highly unstable and easily oxidized to dehydroascorbic acid (Halliwell and Gutteridge, 1999). It is often stabilized in biological fluids ex vivo by the addition of a strong acid, such as metaphosphoric acid (Margolis and Duewer, 1996). This method of stabilization, however, cannot be used in artificial tears as its formulation should emulate natural tears more closely in neutral pH.

Most contact lens wearers, including day wear and overnight ortho-k, will use artificial tears as lubricants or comfort drops. However, none of these products contain antioxidants but can dilute the concentration of ocular antioxidants when instilled into the eye. Further studies should therefore be conducted to investigate the possibility of including antioxidants in artificial tears or eye-drops.

1.8 Summary

Myopia is the most common refractive error throughout the world, especially in Asian countries. Many myopic control methods have been used to retard its progression, however none of these methods have been confirmed to be effective and/or safe for the purpose. Overnight ortho-k has, however, been shown to have potential for myopic control and its popularity has increased in recent years. Although the introduction of newer lens designs, in combination with an overnight wear modality and accurate monitoring of corneal changes via corneal topography, have improved the accuracy and predictability of the treatment effect, there is still an urgent need for further studies to improve ortho-k practice to ensure the safety of this treatment for children. It is important to monitor the lens-to-cornea fitting relationship, corneal integrity and topographical change during the treatment. It is evident, with the growing consumer interest in overnight ortho-k and the number of lens designs currently submitted for FDA approval, that ortho-k use should increase dramatically in the coming years.

Ascorbate is a major water-soluble vitamin in human tears and it is also important for corneal health because it acts as an antioxidant to protect the eye against ROS. The use of artificial tears is common in contact lens and ortho-k lens wearers. The application of artificial tears with no antioxidants will dilute the tear antioxidant concentration and affect the ocular defense/protective system conferred by natural tears on the anterior surface of the eye. It is necessary to investigate the stability of ascorbate concentration in commercially available artificial tears, and the possibility of developing a new artificial tear formulation with ascorbate.

CHAPTER 2

Aims and methodology

The objectives of this MPhil study were to:

1. collect the demographical characteristics of children undergoing ortho-k at the Optometry Clinic of The Hong Kong Polytechnic University (PolyU) (Chapter 3),
2. conduct a telephone survey of those ortho-k wearers, aiming to understand the problems encountered by wearers and their satisfaction with treatment (Chapter 3),
3. evaluate the validity of the Jessen formula in determining the back optic zone radius (BOZR) of the ortho-k lens (Chapter 4),
4. investigate the relationship between corneal changes and myopic reduction following ortho-k (Chapter 5),
5. conduct a pilot study to evaluate the stability of standard ascorbate in commercially available single dosage formulation artificial tears (Chapter 6).

Except for the laboratory work, all data were retrieved from the same group of patients (n = 108) who started ortho-k treatment between April 2000 and November 2003 at the Optometry Clinic of PolyU. All patients were children under the age of 16 years when starting treatment. Only patients who had a pair of lenses used for at least six months and were still on ortho-k during the surveyed period were included

in the study, and only information from the right eye was used for analysis. Demographical and clinical data were retrieved from patient's clinic files during the six-month treatment period. Corneal topographical data were retrieved from the Medmont E300 corneal topographer (version 3.90, Medmont Pty. Ltd., Camberwell, Australia).

A telephone interview was conducted using a pre-structured series of questions (Appendix). The general questions in the questionnaire were answered by parents, while questions involving visual performance and the satisfaction of the treatment were addressed to the children themselves.

For the laboratory work, ascorbate concentration was measured by the Ferric Reducing/Antioxidant Power (FRAP) assay using a Cobas Fara centrifugal analyzer (Roche Diagnostics Ltd. Basel, Switzerland).

The precision and detection limit was first determined from four standard quantities of aqueous ascorbate (from D-L extra pre crystals, Merck, Darmstadt, Germany), at 20, 40, 80 and 100 μM. The stability of different ascorbate concentrations was assessed in three commercially available artificial tears, Vismed (Lab Chemedica AG, Munich, Germany), Tear Naturale Free (Alcon Inc, Fort Worth, TX, USA) and Bion Tears (Alcon Inc, Fort Worth, TX, USA), by measuring the degradation rate with time and under different temperatures.

CHAPTER 3

Orthokeratology practice in a university clinic in Hong Kong

3.1 Introduction

The effectiveness of overnight ortho-k in flattening the cornea and temporarily reducing myopia has been widely documented (see Section 1.2.2.5). A non-randomized clinical study has shown overnight ortho-k to be effective in slowing the rate of myopic progression (Cho et al., 2005a). Overnight ortho-k was introduced in the late 1990s' into Hong Kong where the prevalence of myopia is high (Lam and Goh, 1991; Edwards and Lam, 2004). The majority of wearers in this region are children aiming for myopic control (Cho et al., 2002a; Cho et al., 2003). The primary aim of the study was to conduct a clinical survey of children undergoing ortho-k in the Optometry Clinic of The Hong Kong Polytechnic University (PolyU) in the first three years of this century. Through a telephone interview, patients'/parents' attitude and satisfaction towards ortho-k, and the most commonly encountered problems during the treatment were also solicited.

Table 3.2.1 Summary of all orthokeratology patients reviewed

		Number of patients	Status
Total files reviewed		257 (*Adult: 31; #Children: 226)	-
Continued the treatment	Adult	15	Still wearing ortho-k lens
	Children	160	In 52 out of 160 patients, no single lens had been worn for over six months. Therefore 108 patients were eligible for data analysis

* Patients aged of 16 years or older

Patients under 16 years

3.2 Methods

All patients (n = 257) who were fitted with ortho-k in the Optometry Clinic in PolyU between April 2000 and November 2003 were reviewed (Table 3.2.1). Only 175 patients continued the treatment and most of them were children (91%, 160 out of the 175 patients) aged under 16 years when enrolled in ortho-k treatment. For all of the 257 patients, a 32% drop out from the treatment was largely due to intolerance to lens wear (> 90%). In this study, only children who had worn a pair of lenses for at least six months and were still on ortho-k during the surveyed period were included in this study. One hundred and eight patients met these inclusion criteria. Demographical and clinical data were retrieved from the clinical files during the six-month treatment period – baseline data before the treatment, after the first night of lens wear, and approximately one week, two

weeks, one month, three months and six months after wearing the lenses (lenses the patient had been wearing for at least six months). Only information from the right eye was used for analysis. A non-cycloplegic subjective refraction (all sphere and cylinder presented in the thesis are in negative forms), and unaided and best-corrected visual acuity recorded at each visit was retrieved. Corneal topographical data, including the flattest and steepest simulated keratometry readings and apical radius of curvature (Ro), were retrieved from the Medmont E300 corneal topographer (version 3.90, Medmont Pty. Ltd., Camberwell, Australia). Asphericity Q at 9.8 mm chord at the flattest meridian will be retrieved at the baseline visit. Corneal staining (with sodium fluorescein) information as recorded by the practitioners (based on Efron's scale) (Efron, 1998) was also retrieved. Information on the brands of lenses used, the recommended lens care system and the number of lenses required to achieve the optimum ortho-k effect was also collected.

A telephone interview was also conducted using a pre-structured series of questions (see Appendix). The general questions in the questionnaire were to be answered by parents, while questions involving visual performance and the satisfaction of the treatment were addressed to the children themselves.

3.3 Treatment of data

As this was a retrospective study where data were collected from clinic files, most of the results were presented in numbers and percentages. In addition, some data may be missing due to omissions in the patient's record at some visits. Data were analyzed to determine the efficacy of overnight ortho-k on refractive change, and the relationship between refractive change and visual and corneal changes.

The distribution of age, refractive sphere, UVA, and topographical parameters were not significantly different from normal (Kolmogorov-Smirnov D tests, $p > 0.05$), so parametric tests were used for statistical analyses. Repeated measures analysis of variance (ANOVA) was used to test for changes over the six-month treatment period; paired t tests with Bonferroni correction were used to test for differences between any two consecutive visits. p-values less than 0.008 (0.05/6) for refractive sphere and topographical parameters (six comparisons), and 0.01 (0.05/5) for UVA (five comparisons) respectively were considered as significant. The distributions of the data for the baseline and six-month refractive cylinder, and six-month residual refractive sphere were significantly different from normal (Kolmogorov-Smirnov D tests, $p < 0.05$). So for these and ordinal

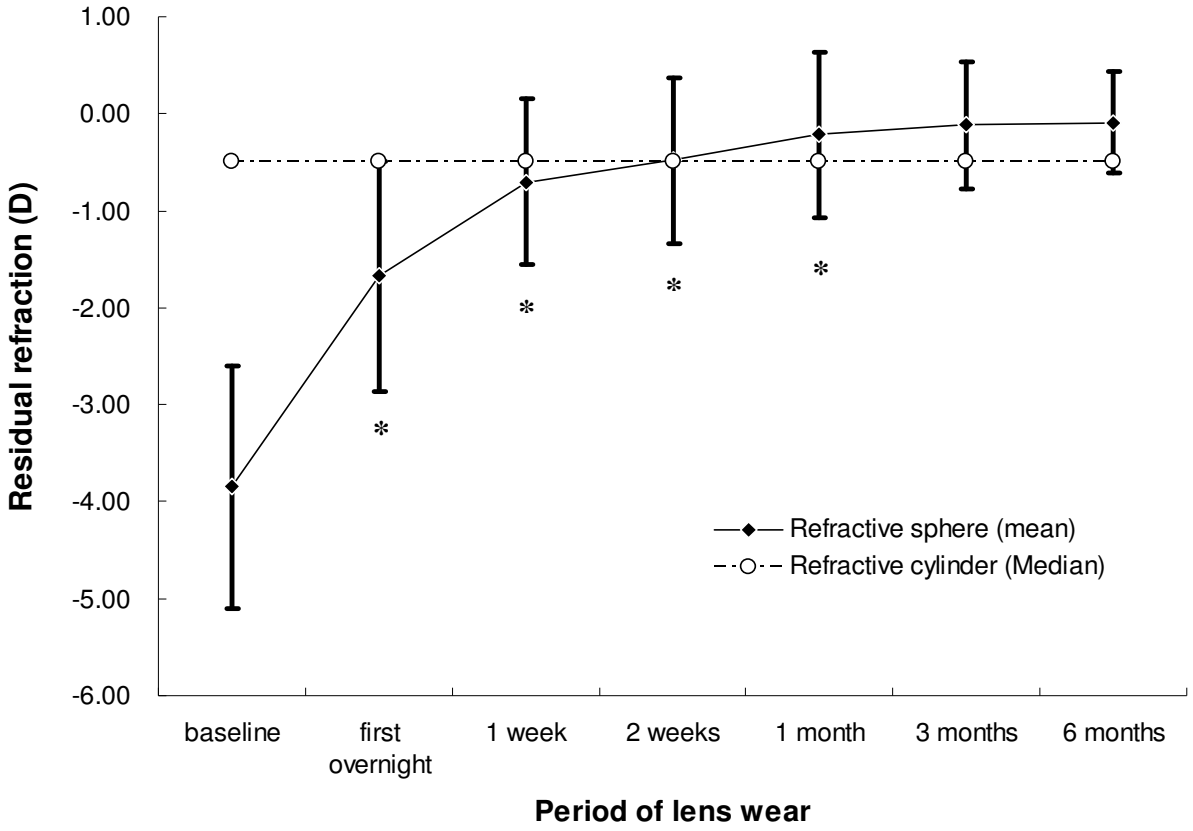
variables (e.g. corneal staining), Friedman test and Spearman's correlation coefficient were used for analysis (Scatter plots are shown in Appendix 1).

3.4 Results

Table 3.4.1 presents the demographical data of the children (n = 108) whose files were reviewed. At the time of lens fitting, the median age of wearers was nine (range six to 15 years), and most of them were female (66%).

Table 3.4.1 Patient demographics (n = 108)

Median age (range)	9 (6 – 15) years
Gender (male/female)	37/71
Mean ± SD pre-treatment refractive sphere	–3.56 ± 1.49 D
Median pre-treatment refractive cylinder range (range)	–0.50 (0 to –4.25) D



*p < 0.001 (the residual spherical refraction is significantly different when compared with previous visit)

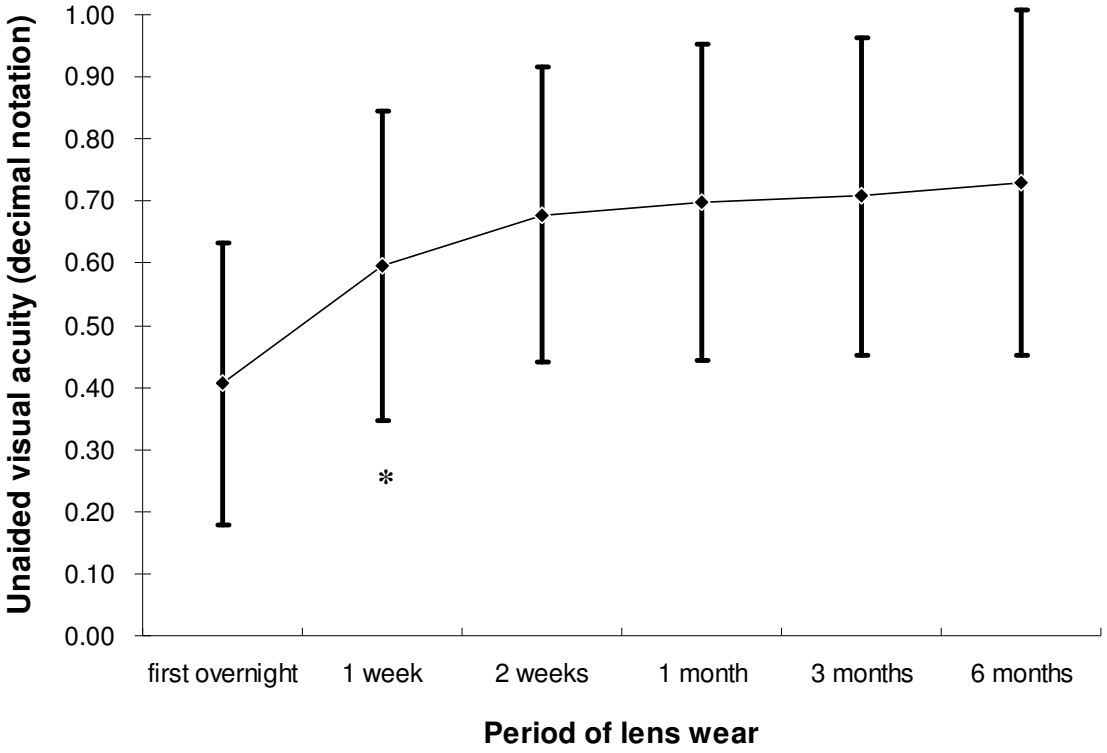
Figure 3.4.1 Residual subjective refractive error at different visits during six months of lens wear (Each error bar indicates one standard deviation) (n = 27).

3.4.1 Refraction and unaided visual acuity

The mean pre-treatment refractive sphere of all surveyed subjects (n = 108) was –3.56 ± 1.49 D and the median refractive cylinder was –0.50 D (range 0 to –4.25 D)(Table 3.4.1). However, only 27 patients had subjective refraction recorded at every data collection visit and their changes in refractive sphere and cylinder during the six-month treatment period are shown in Figure 3.4.1. The refractive sphere after ortho-k treatment was significantly reduced when compared to the

baseline (repeated measures ANOVA, $F(6, 21) = 60.32$, $p < 0.001$), and the amount of reduction increased with the time of treatment. The largest refractive spherical reduction (58%) was observed after the first night of lens wear and appeared to be stabilized by the first month of wear (98%) (paired t tests, $p < 0.008$). No further change was observed among subsequent visits (paired t tests, $p > 0.008$). The mean myopia reduced from –3.88 ± 1.27 D (baseline) to –0.26 ± 0.83 D (one month). At the six-month visit, the mean residual refractive sphere was −0.09 ± 0.53 D. No significant reduction in refractive cylinder was found over the six-month treatment period (Friedman $X^2 = 8.24$, $p = 0.221$) (see Figure 3.4.1).

For all patients with a subjective refraction recorded at the six-month visit (n = 106), the residual refractive sphere and cylinder were significantly associated with the pre-treatment refractive sphere and cylinder, respectively (refractive sphere: Spearman $r^2 = 0.15$, $p < 0.001$; refractive cylinder: Spearman $r^2 = 0.19$, $p < 0.001$).



*p < 0.001 (the unaided visual acuity is significantly different when compared with previous visit)

Figure 3.4.2 Unaided visual acuity at different visits during six months of lens wear (Each error bar indicates 1 standard deviation) (n = 29)

For patients with UVA recorded at all data collection visits (n = 29), the mean UVA after the first night of lens wear was 0.41 ± 0.23 decimal (0.40 logMAR or Snellen 6/15), and continued to improve (repeated measures ANOVA, $F(5, 24) = 13.57$, $p < 0.001$) until after two weeks' of lens wear (paired t test, $p < 0.01$). No further improvement was observed thereafter (i.e. among subsequent visits) ($p > 0.01$). The mean UVA for this group of patients at the two-week and six-

month visits were 0.68 ± 0.24 decimal (0.18 logMAR or Snellen 6/9) and 0.73 ± 0.28 decimal (0.12 logMAR or Snellen 6/7.5), respectively (Figure 3.4.2).

For all patients who had UVA recorded at the six-month visit (n = 103), 58% had UVA of 0.80 decimal (0.10 logMAR or Snellen 6/7.5) or better, and 4% of the patients had UVA worse than 0.20 decimal (0.70 logMAR or Snellen 6/30). This was mainly due to the significant residual refractive error and lens decentration. The mean UVA at the six-month visit was significantly correlated to the residual refractive sphere (Spearman $r^2 = 0.30$, $p < 0.001$) and cylinder (Spearman $r^2 = 0.23$, $p < 0.001$). The mean UVA was also correlated to the pre-treatment refractive sphere and refractive cylinder respectively (refractive sphere: Spearman $r^2 = 0.28$, $p < 0.001$; refractive cylinder: Spearman $r^2 = 0.08$, $p = 0.004$).

Table 3.4.2 Ocular parameters of patients with or without the need for visual aids during the daytime after orthokeratology

	Visual aid required (n = 21)	Visual aid not required (n = 87)	p-value
	mean ± SD	mean ± SD	Unpaired-t-test
Baseline refractive sphere (D)	–5.18 ± 1.30 (range –3.50 to –8.75)	–3.16 ± 1.26 (range –0.75 to –6.25)	< 0.001
Baseline K_f (mm)	7.79 ± 0.15	7.81 ± 0.28	> 0.05
Baseline K_s (mm)	7.48 ± 0.14	7.58 ± 0.24	> 0.05
Baseline Ro (mm)	7.71 ± 0.40	7.73 ± 0.22	> 0.05
Baseline Q	–0.43 ± 0.15	–0.43 ± 0.13	> 0.05
Residual refractive sphere at six month (D)	–1.64 ± 1.43	–0.08 ± 0.48	< 0.001
	Median (range)	**Median (range)**	**Mann-Whitney U test**
Baseline refractive cylinder (D)	–1.00 (0.00 to –4.25)	–0.50 (0.00 to –2.25)	< 0.001

K_f = Flattest simulated keratometry reading; K_s = Steepest simulated keratometry reading; Ro = Apical radius of curvature; Q = Asphericity value

After six months of ortho-k treatment, 21 of the 108 patients (19%), with mean residual refractive sphere of –1.64 ± 1.43 D, required the aid of spectacles in order to obtain acceptable clear distance vision during the daytime. These patients also had, on average, significantly higher pre-treatment refractive sphere and cylinder than patients who did not require visual aids during the daytime (see Table 3.4.2). However, two patients with lower pre-treatment myopia (e.g. 3.50 D) also had significant residual refractive errors and required the aid of spectacles after the procedure.

Table 3.4.3 Summary of mean ± SD corneal changes at different visits over six months of lens wear (n = 73)

	Baseline	First overnight	1 week	2 weeks	1 month	3 months	6 months
K_f (mm)	43.38 ± 1.52	42.18 ± 1.35	42.01 ± 1.42	41.72 ± 1.47	41.71 ± 1.61	41.55 ± 1.56	41.61 ± 1.55
K_s (mm)	44.79 ± 1.65	43.80 ± 1.58	43.40 ± 1.63	43.11 ± 1.67	43.10 ± 1.71	43.09 ± 1.68	43.14 ± 1.67
Ro (mm)	7.70 ± 0.26	8.06 ± 0.37	8.12 ± 0.29	8.14 ± 0.32	8.19 ± 0.33	8.20 ± 0.32	8.20 ± 0.35

K_f = Flattest simulated keratometry reading; K_s = Steepest simulated keratometry reading; Ro = Apical radius of curvature;

3.4.2 Corneal responses

Table 3.4.3 summarizes the corneal topographical changes over the six months of lens wear (n = 73). There was a significant flattening in the simulated keratometry reading and Ro after commencing ortho-k treatment (repeated measured ANOVA: flattest simulated keratometry reading: $F(6, 67) = 72.08$, $p < 0.001$; steepest simulated keratometry reading: $F(6, 67) = 57.89$, $p < 0.001$; Ro: $F(6, 67) = 184.34$, $p < 0.001$). Maximum changes in corneal parameters were observed after the first night of lens wear, with stabilization within two weeks of lens wear (paired t test, $p < 0.008$).

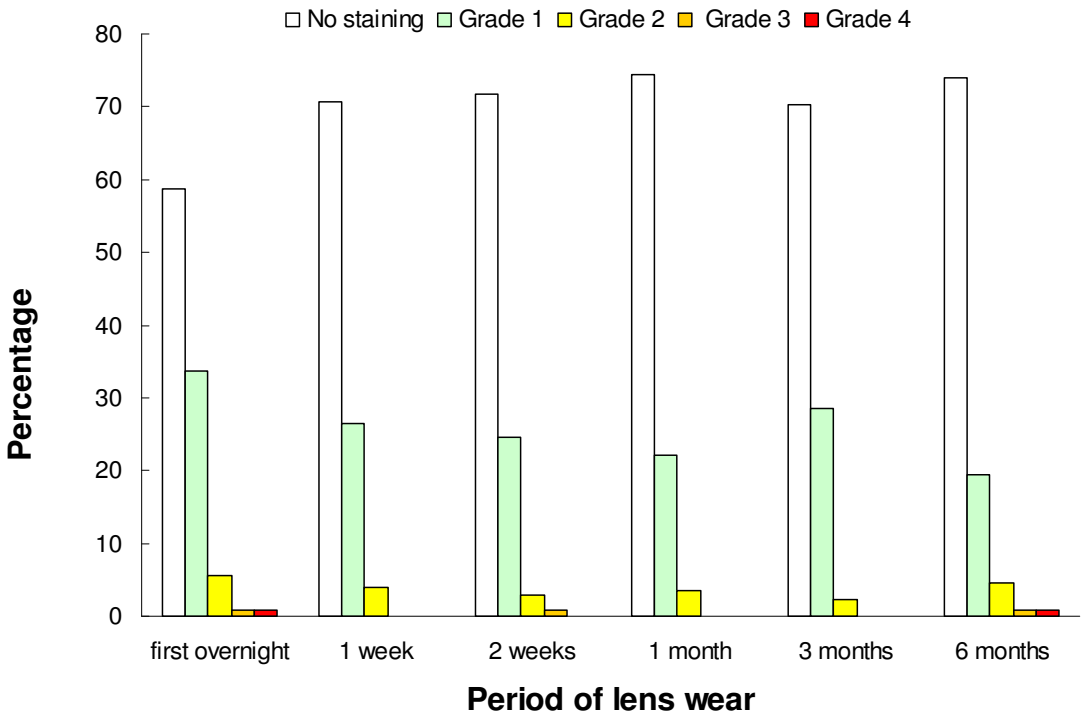


Figure 3.4.3 Corneal staining recorded at different visits during six months of lens wear (First overnight, n = 107; 1 week, n = 102; 2 weeks, n = 106; 1 month, n = 86; 3 months, n = 91; 6 months, n = 108)

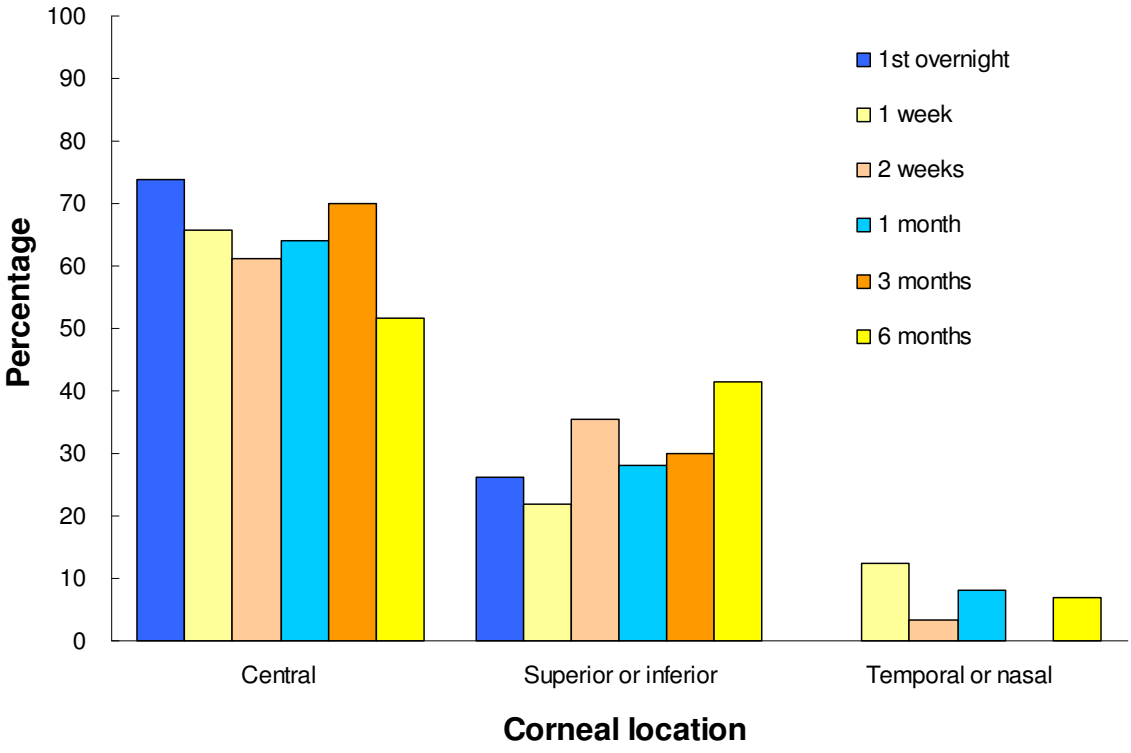


Figure 3.4.4 Corneal staining at different locations at different visits during six months of lens wear (First overnight, n = 107; 1 week, n = 102; 2 weeks, n = 106; 1 month, n = 86; 3 months, n = 91; 6 months, n = 108)

After the first overnight lens wear, corneal staining was observed in 41% of patients (44 out of 108) and 74% of staining recorded was within the central 3 mm of the cornea. The incidence of corneal staining decreased over the course of treatment – from 41% after the first overnight lens wear to 25% at the six-month visit. Most staining (84%) at all visits was graded as mild (Grade 1 or less); 13% were graded as Grade 2 and only 3% were graded as Grade 3 or Grade 4. Patients who had a Grade 2 or higher level of staining in the central cornea were advised to cease lens wear until the condition subsided. Figures 3.4.3 and 3.4.4 summarize the percentages of subjects showing different levels of staining at different corneal locations over the six-month treatment period respectively. None of the patients had corneal staining observed at every data collection visit. At the six-month aftercare visit, the frequency of staining was significantly associated with the increase in pre-treatment spherical refractive error (Spearman $r = -0.25$, $p = 0.01$), though the association was not very strong.

3.4.3 Lens designs and care regimen used

DreimLens (Taiwan Macro Vision Group, Taiwan) was the most commonly used lens design (80%), followed by eLens (E&E Optics Asia Ltd, Hong Kong) (14%) and Fargo 6 (C&E G.P Specialists San Clemente, CA, USA) (4.6%). Only 1.4% of patients used a 'custom made' lens design. The lens material used

for all patients was Boston XO (Polymer Technology Corporation, Rochester, NY, USA).

Most patients (76%) were recommended to use a separate daily cleaner and disinfecting solution. Boston Advance Cleaner and Boston Advance Conditioning Solution (Polymer Technology Corporation, Rochester, NY, USA) were the most commonly recommended care solutions. The remaining patients (24%) were prescribed multipurpose solution — 22.8% used Unique pH (Alcon Laboratories Inc, Fort Worth, TX, USA) and 1% used Boston Simplus (Polymer Technology Corporation, Rochester, NY, USA). All patients were instructed to use normal saline for rinsing the lenses after cleaning.

Over 80% (89 out of 108) of patients were advised to use artificial tears before lens removal in the morning, and about 58% were recommended to use single-dose formulation. The most commonly recommended single-dose ocular lubricant was Tear Naturale Free (Alcon Laboratories Inc, Fort Worth, TX, USA).

Almost all reviewed patients (97%) used a suction holder to aid lens removal. Only 3% of patients removed lenses with their fingers.

3.4.4 Number of lenses

For patients with myopia greater than 4.00 D (n = 40), a 'stepwise' fitting protocol (see Section 3.5.5) was applied, so the number of lenses used was dependent on the amount of pre-treatment myopia. For patients with myopia equal to or lower than 4.00 D (n = 68), the first pair of lenses prescribed aimed for full correction. The majority of these patients (73.5%) achieved optimum ortho-k effect using only one pair of lenses, and all of them also had good lens centration, as shown in their topographical maps, and the mean myopic reduction was within ± 0.25 D of the target. Of the patients with myopia equal to or less than 4.00 D, about 16% of the patients required two pairs of lenses and 7.4% required three pairs of lenses to achieve the optimum ortho-k effect. Two patients (2/68, about 3%) were unable to achieve a satisfactory result with vision even after four pairs of lenses.

The number of lenses required for all patients with myopia equal or lower than 4.00 D to achieve optimum myopic reduction was significantly associated with the increased in baseline refractive sphere (Spearman $r = -0.33$, $p = 0.005$), but was not associated with refractive cylinder, corneal curvature, Ro (Spearman $-0.07 < r < 0.008$, $p > 0.05$) (Scatter plots are shown in Appendix 2).

3.4.5 Telephone survey

Ninety-four patients agreed to a telephone interview. The primary reason for undergoing ortho-k was myopic control (87%). Over 50% heard about ortho-k from their friends and relatives who had children undergoing the treatment, about 30% learned about the treatment from their optometrists, 12% from newspapers and 1% from public seminars.

Almost 90% of those interviewed reported good or very good post-ortho-k unaided distance vision. Fifty-seven percent of the patients reported that the quality of unaided vision could be maintained until the end of the day, and the remainder reported a noticeable deterioration of distance vision at about 12 hours (median) after lens removal (range: four to 16 hours).

The most frequently reported non-visual problems were lens binding (44%) and ocular discharge in the morning (40%), followed by tearing (21%), redness (18%) and discomfort (12%).

Of the respondents, 89% (84 out of 94) ranked the treatment as good or very good, 8.5% (8 out of 94) ranked the treatment as acceptable, and 2% ranked the treatment as poor. The latter two had discontinued lens wear (after more than six

months) due to discomfort and unacceptable post-ortho-k vision even after modifications to the lenses.

3.5 Discussion

3.5.1 Demographics

This retrospective study collected an extensive body of data on children who started ortho-k treatment in The Optometry Clinic of PolyU during the first three years of this century. Our patients included 17 children with high myopia (≥ 6.00 D) and astigmatism (≥ 1.50 D). The parents of these patients however requested ortho-k for myopic control for their children even though they were informed of the necessity of wearing spectacles to correct residual refractive errors to achieve satisfactory distance vision after the procedure.

3.5.2 Refraction and unaided visual acuity

The greatest change in refractive sphere was observed after the first night of lens wear (58%). Similar results have been reported in the literature (Swarbrick et al., 1998; Nichols et al., 2000; Soni et al., 2003; Tahhan et al., 2003; Sorbara et al., 2005). Although there was a continued reduction in refractive sphere after one month of lens wear, optimum visual improvement was reached after two weeks of wear. At the six-month aftercare visit, the average UVA of our patients

improved to the maximum level of 0.73 decimal (equivalent to 0.12 logMAR or Snellen 6/7.5). This finding is relatively worse than the average 0.02 logMAR or better as reported in most studies (Nichols et al., 2000; Soni et al., 2003; Tahhan et al., 2003; Sorbara et al., 2005). Those previous studies involved subjects with a pre-treatment refractive sphere less than −4.00 D, and with a low level of refractive cylinder. Subjects with low refractive powers (sphere and cylinder) would increase their chances of having a full myopic correction and are more likely to have a good UVA from the procedure. On the contrary, among our patients, 42 (38.9%) had pre-treatment refractive sphere of more than 4.00 D, and 11 patients had pre-treatment refractive cylinder of more than 1.50 D. If we excluded these patients, UVA was improved to mean 0.88 decimal (equivalent to 0.06 logMAR or Snellen 6/7), which is still worse than that reported previously. Consistent with previous reports (Nichols et al., 2000; Rah et al., 2002a; Soni et al., 2003; Cheung and Cho, 2004), the UVA of all patients after ortho-k was significantly correlated to the amount of pre-treatment and residual refractive error, including spherical and cylindrical errors. For those subjects with a significant amount of residual refractive error and unacceptable UVA after the procedure, they were recommended to use spectacles in the day time to achieve good distance vision.

Ortho-k has been reported to be ineffective in the reduction of astigmatism (see Section 1.2.2.5.2). The present survey agrees with these reports — no significant astigmatic change was noted during the six-month ortho-k treatment period. However, some researchers have reported changes in with-the-rule corneal astigmatism in their ortho-k subjects (see Section 1.2.2.5.2). In a separate project, we have done a comprehensive analysis of astigmatic changes in ortho-k for this group of subjects using the Thibos vector analysis and a paper has been published (Cheung et al., 2009).

3.5.3 Corneal responses

As with previous studies (Mountford, 1997a; Nichols et al., 2000; Sridharan and Swarbrick, 2003; Tahhan et al., 2003; Maldonado-Codina et al., 2005), we found significant correlations between corneal shape changes, including simulated keratometry readings and apical radius of curvature, and refractive changes. Several authors have reported similar clinical findings in overnight ortho-k (see 1.2.2.5.4).

The safety of overnight ortho-k for myopic reduction is still a controversial issue despite the development of innovative lens designs and hyper-oxygen permeable lens materials which allow greater myopic reduction and more predictable post-

treatment results (see Section 1.2.2). Safety is a major concern since there have been several published case reports of serious corneal complications associated with ortho-k, and most of the cases involved children (see Section 1.5.5). Corneal staining is a common complication in any type of contact lens wear, and the incidence of staining is increased in ortho-k lens wear (Lipson et al., 2005). Possible reasons for corneal staining in ortho-k are thinning of central corneal epithelium, improper lens fitting, corneal hypoxia, hyper-sensitivity to the contact lens solutions, and mechanical abrasion due to the build up of deposits on the back surface of the lens, lens binding and incorrect removal of a bound lens upon awakening (Chui and Cho, 2003; Walline et al., 2004a). Our results show that 41% of patients exhibited corneal staining after the first night of ortho-k lens wear. The incidence of staining decreased to 25% at the six-month visit. Although the incidence of corneal staining decreased with the period of lens wear, most of the staining (74%) was observed in the central cornea. Central (as opposed to peripheral) corneal staining is of greater concern as the disruption of central corneal integrity is more likely to lead to sight-threatening complications if accompanied by improper use and care of lenses and accessories. Hence in ortho-k practice, the level of central corneal staining that is regarded as clinically significant should be more stringent. In the present study, most staining (84%)

was graded as clinically insignificant (i.e. lower than Grade 2) and no clinical action was taken for these patients. For patients who had a Grade 2 or higher level of staining in the central 3 mm of the cornea, they were advised to cease lens wear until the condition subsided and none of them required any medical treatment. A few studies have also reported the incidence of corneal staining after the commencement of overnight ortho-k treatment (Rah et al., 2002a; Walline et al., 2004a). We also noted that the incidence of corneal staining tended to be higher when a higher target of myopic reduction was aimed for.

3.5.4 Lens designs and care regimens used

DreimLens was the most frequently used brand of lenses in our clinic in the early 2000s as it was the first lens design introduced into Hong Kong for overnight ortho-k therapy. However, the trend has changed with time as many different lens designs have since been introduced into this region.

The majority of patients were, as instructed by their optometrists, using a separate lens care system. i.e. daily cleaner for cleaning and rubbing the lenses, saline for rinsing and a disinfecting solution for storing the lenses, instead of a bottle of multi-purpose solution for cleaning, rinsing and disinfecting. Single bottle systems are less complex and more convenient to use, and are believed to facilitate compliance. However, in terms of efficacy, a single bottle solution

serving the functions of cleaning, rinsing and disinfecting is essentially a compromise solution (Stapleton et al., 1997), and some multipurpose solutions can cause irritation when they are in contact with the eye. Ortho-k involves sleeping with high Dk lenses, hence it is desirable to have the lenses as clean as possible and any chance of solution sensitivity should be avoided. Therefore, rubbing lenses with a daily cleaner, and rinsing the lenses with non-preserved saline after cleaning and before insertion are recommended. Several disinfecting solutions are available in the market for rigid gas permeable lenses, and the majority of these solutions are compatible with ortho-k lenses.

It should be noted that the brands of lenses and solutions used in this study do not necessarily reflect the effectiveness of these brands over the others. Which lenses or disinfecting solutions to prescribe for the patient depend on the preferences of the individual practitioner and/or the availability in the stock of a particular brand in our clinic. Our results on the preferred solutions to be prescribed to patients only highlighted the importance placed by ortho-k practitioners in our clinic on the use of daily cleaner and non-preserved saline in the care of ortho-k lenses.

The use of artificial tears is optional in overnight ortho-k treatment as dryness is not a problem during sleep. However, due to the high incidence of lens binding

associated with overnight ortho-k, over 80% of patients were advised to apply artificial tears to aid lens removal in the morning. Patients were instructed to apply artificial tears to mobilize the lens first before removal, thereby ensuring safety. Most patients were advised to use non-preserved single dose formulations, to avoid problems from hypersensitivity to the preservatives present in multi-dosage formulations, and to minimise contamination. However, only about 50% of the patients used single dose artificial tears.

The majority of patients/parents (97%) were taught to use a suction holder to aid lens removal. Lens removal with a suction holder is much easier to learn than using fingers, especially for patients/parents who have no previous experience in rigid lens wear. However, a recent study has shown a high contamination rate of suction holders in ortho-k lens wearers (Boost and Cho, 2005). Dependency on suction holders for removal of ortho-k lenses is also not to be encouraged as patients/parents may not know how to remove the lenses properly should they lose the suction holder. There is the danger of serious corneal damage when a suction holder is used to remove a lens that is not on the cornea. Also, lens binding is common in overnight ortho-k; removing a bound lens forcefully can cause severe injuries to the cornea, and the situation can be more severe if a suction holder was used to aid removal. In order to reduce the risk of microbial

infection in ortho-k lens wear and to increase safety in removal, our clinic has commenced teaching parents/patients to remove ortho-k lenses with their fingers; a suction holder is given for emergency use only. In cases where a suction holder is necessary, daily cleaning, proper storage, weekly disinfection and regular replacement of the suction holder should be emphasized.

3.5.5 Number of lenses used

Many of our patients (73.5%), with pre-treatment myopia equal to or lower than 4.00 D (n = 68), required only one pair of lenses to achieve the optimum ortho-k effect. In our clinic, for patients with myopia greater than 4.00 D, a 'stepwise' fitting protocol was used. That is, the first pair of lenses will target a myopic reduction of 4.00 D; if the corneal health and lens centration are good, the target of reduction is increased progressively (usually in 1.00 D steps) until either the desired refractive change is achieved (usually within one month) or the cornea is no longer responding. Therefore, the greater the amount of myopia, the more lenses are required to achieve optimum myopic reduction. Our clinicians believe that a stepwise protocol for higher myopic reduction is prudent as it is less aggressive and allows monitoring of the cornea with a lower target lens before attempting a higher target.

3.5.6 Telephone Interview

Generally, myopic control is the main reason why parents enrolled their children for ortho-k treatment at our clinic. Most of them learned of the treatment from other parents, friends or relatives whose children had received the treatment, and some of them were recommended by their optometrists.

Most of the interviewed patients reported good post-ortho-k unaided vision and no visual problems during waking hours. Although it has been reported that the daily regression of the ortho-k effect was insignificant (see Section 1.2.2.7), about half of our patients (57%) reported a deterioration of post-ortho-k vision towards the end of the day, mostly after about 12 hours (median) (range: four to 16 hours) of no lens wear. This may reflect the need for a nightly basis of ortho-k retainer lens wear for most of the wearers in order to retain the corrected myopia and good UVA.

Over 40% of the respondents ranked lens binding as the most common non-visual problem they experienced in ortho-k. Lens binding associated with overnight ortho-k has been reported previously (Chui and Cho, 2003; Tahhan et al., 2003), and the suggested cause was the reduction of tear circulation and the increase in tear viscosity during sleep with the lenses on, resulting in a fluid

adhesion force between the lens and the cornea. The level of binding is therefore patient-dependent (Swarbrick and Holden, 1987; Swarbrick and Holden, 1989) and may not be resolved by improving the lens fit (Chui and Cho, 2003). Improper removal of a bound lens can cause serious damage to the cornea, especially, as mentioned earlier, if a suction holder is used to aid removal. Proper patient education on how to free a bound lens before removal is of vital importance, not only at the visit before lens dispensing, but also at each aftercare visit.

About 90% of the interviewed patients ranked the treatment as good or very good. Previous surveys using the National Eye Institute Refractive Error Quality of Life (NEI-RQL 42) instrument to evaluate the levels of patient satisfaction with overnight ortho-k showed either no differences (Ritchey et al., 2005) or better (Lipson et al., 2005) quality-of-life indices in overnight ortho-k compared to 30-day continuous wear silicone hydrogel lenses or daily disposable hydrogel lenses, respectively. This indicates that overnight ortho-k is well accepted as a means for myopic correction.

3.6 Conclusions

This study provides comprehensive information and overview of the characteristics of the children undergoing ortho-k in the Optometry Clinic of PolyU during the first three years of this century. In general, most children were undergoing ortho-k for myopic control. Overnight ortho-k using modern reverse geometry lens designs has been shown to be an effective non-surgical way for the reduction of low to moderate myopia and improvement in unaided vision. However, the procedure, using spherical ortho-k lens designs, is not effective for the reduction of refractive cylinder. Most of the ortho-k effect occurs within the first week of lens wear with the greatest effect observed after the first night of wear. Refractive changes in ortho-k are associated with corneal topographical changes. Apart from occasional corneal staining, we had no records of significant corneal complications in these patients. The majority of patients (73.5%) under 4.00D of myopia, required only one pair of lenses to achieve an optimum effect. Referral from friends was the major source of introduction to ortho-k. Almost 90% of the surveyed wearers reported the post-treatment unaided distance vision as good or very good, and none reported problems at near. Improved unaided vision after ortho-k lens wear was maintained over an average of 12 hours after lens removal. From a safety viewpoint, patients should

be recommended and trained to use finger manipulation instead of a suction holder to remove their lenses. At the delivery of ortho-k lenses, it is essential for all ortho-k practitioners to strongly emphasize proper removal of bound lenses with the use of artificial tears and to reinforce these instructions at each follow-up visit.

The work described in this chapter has been published in "Chan B, Cho P, Cheung SW. Orthokeratology Practice in a University Clinic in Hong Kong: children population. Clin Exp Optom. 2008; 91: 453-60".

CHAPTER 4

Validity of Jessen formula in determining the Back Optic Zone Radius (BOZR) of the orthokeratology lens

4.1 Introduction

In ortho-k, unlike conventional RGP, the BOZR of the lens plays no role in the lens fitting but mainly determines the amount of attempted refractive change. The flatter the BOZR relative to the particular cornea, the greater is the amount of attempted myopic reduction. Several ortho-k lens designs available in the market (see Table 1.2.4) determine the BOZR of the lens using the Jessen formula (see Section 1.2.2.3). However, clinical experience always gives a lower manifest refractive change than the attempted change calculated from the formula (Nichols et al., 2000; Sorbara et al., 2005). There is no study evaluating the accuracy of the formula in determining the BOZR of the ortho-k lens. Understanding the relationship between attempted and manifest refractive change would help practitioners in predicting the possible outcome after the procedure.

4.2 Aim

This part of the study aims to determine the validity of the Jessen formula with a compression factor of 0.75 in calculating the BOZR of ortho-k lenses for myopic reduction.

4.3 Methods

From the 128 clinical files reviewed in the ortho-k survey study, 63 patients fulfilled the following inclusion criteria – (1) first time ortho-k lens wearer fitted with a four- or five-zone reverse geometry lenses in both eyes; (2) two-week morning visit, including non-cycloplegic subjective refraction and bull's eye pattern subtractive topographical result measured by the Medmont E300 corneal topographer (version 4.8.0, Medmont Pty. Ltd., Camberwell, Australia); and (3) the same pair of lenses (at the two-week visit) were used as retainer lenses and worn for at least six months. Clinical data for these patients at the visit before commencement of ortho-k treatment (baseline) and at the visit after two weeks of lens wear were retrieved. Although the ortho-k effect stabilized until the first month of lens wear, only a small number of subjects had subjective refraction taken in the morning at the one-month aftercare visit (n=10). And, the mean difference of the refractive changes between the two-weeks and one-month visit

was only –0.25 D. Therefore, the two-weeks results (n=63) were used in this study. Only the data for the right eye of 58 patients were analysed. The data of five subjects were excluded because at the two-week visit, three of the patients had less than five hours of lens wear the night before, and the other two patients had a very poor corneal topographical response. All five subjects had less than 50% of the attempted myopic change at this visit.

All included patients were either fitted with DreimLens (DreimLens Taiwan, Taiwan Macro Vision group, Taiwan) (81%), or the eLens (E&E Optics Ltd., Hong Kong SAR, China) (19%) design. All lenses were made of Boston XO materials (Polymer Technology Corporation, Rochester, NY, USA) with oxygen permeability (DK) of 100 (ISO/Fatt). Achieved myopic reduction (ΔM_{ach}) was determined by subtracting the subjective refractive spheres between baseline and two-week visits. Visual acuity was assessed using a projector decimal visual acuity chart which was reflected from a mirror at three meters. The fitting philosophies of the two lens designs are similar and both designs use the Jessen formula with a compression factor of 0.75 to calculate the BOZR,

$$BOZR = K_f - T - 0.75 \qquad \textit{Equation 4.3.1}$$

where K_f is the flattest simulated keratometry reading, and T is the desired refractive change. The attempted refractive change (ΔM_{att}) following ortho-k is therefore,

$$\Delta M_{att} = T + 0.75 \qquad \textit{Equation 4.3.2}$$

From Equations 4.3.1 and 4.3.2,

$$\Delta M_{att} = K_f - BOZR \qquad \textit{Equation 4.3.3}$$

In this study, the validity of Jessen formula (Equation 4.3.3) was evaluated by comparing the equation obtained from the plot of K_f – BOZR (i.e. ΔM_{att}) and ΔM_{ach}. As there were no statistically significant changes in refractive cylinder during the two-week lens wear period (results not presented), only the refractive sphere component of the sphero-cylinder correction was used for analysis.

4.4 Treatment of data

Kolmogorov-Smirnov D-tests were performed to assess data normality. The level of significance was set at 0.05. Only data from the right eye were presented. The distributions of ΔM_{att} and ΔM_{ach} were not significantly different from normal ($p > 0.05$); therefore the Pearson correlation coefficient of determination (r^2) was used for analyses. Since the K_f – BOZR is calculated from the flattest corneal meridian and ΔM_{att}, and is relatively more controllable and error free, it was placed on the x-axis in all analyses.

4.5 Results

The median age and mean spherical refractive error of patients whose data were retrieved before the treatment was 10 years (range six to 37) and –3.38 ± 1.38 D (range –1.00 to –7.00 D) respectively. Figure 4.5.1 presents the relationship between ΔM_{ach} and ΔM_{att}. ΔM_{ach} was significantly correlated to ΔM_{att}, i.e. (K_f – BOZR) (Pearson $r^2 = 0.71$, $p < 0.001$).

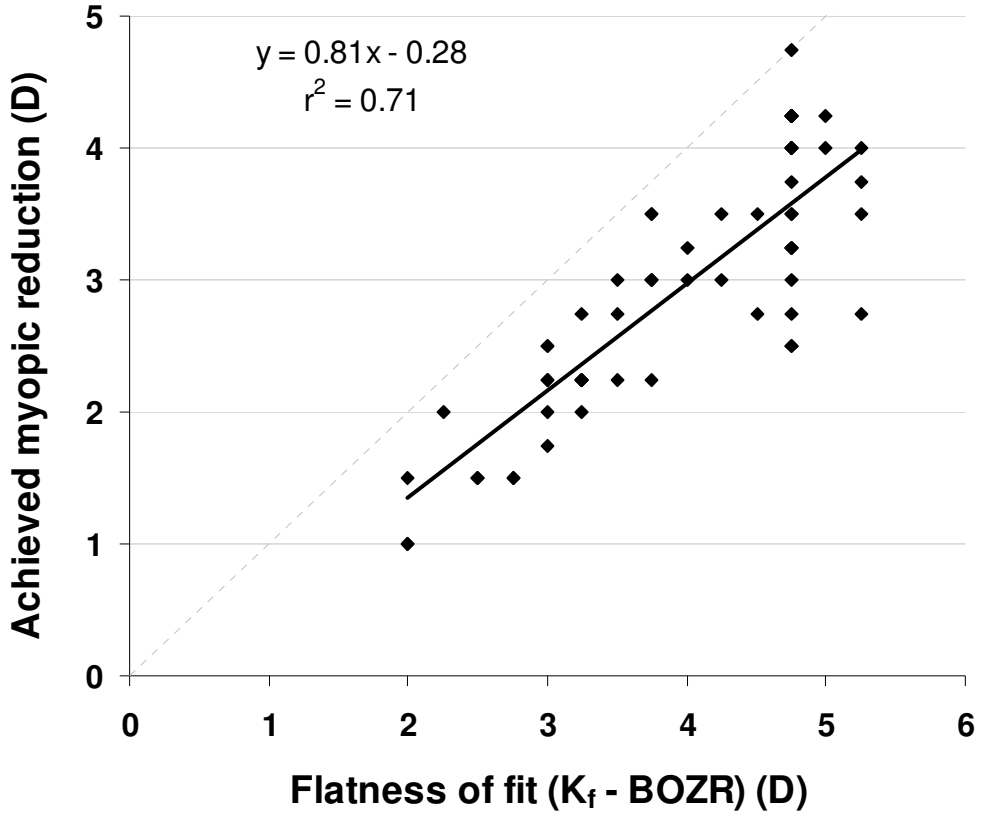


Figure 4.5.1 Relationship between achieved myopic reduction and flatness of lens fit (i.e. attempted myopic reduction) (n = 58)

Linear regression shows that the relationship between these two variables can be described by the linear equation of:

$$\Delta M_{ach} = 0.81(K_f - BOZR) - 0.28 \qquad \textit{Equation 4.5.1}$$

But, according to the Equation 4.3.2, $\Delta M_{att} = T + 0.75$, if the Jessen formula is valid, ΔM_{ach} should be equal to ΔM_{att}; therefore, from Equations 4.3.2 and 4.5.1, we have

$$0.81(K_f - \text{BOZR}) - 0.28 = T + 0.75$$

$$\text{BOZR} = K_f - 1.23\,T - 1.27$$

The results suggested that the BOZR of the lens should be flattened by a factor of $(1.23\,T + 1.27)$ instead of 0.75 if the intention is to overcorrect myopia by 0.75 D with ortho-k. Bland and Altman analysis (Figure 4.5.2) shows that there is no significant relationship between the differences and the means of the two variables ($p > 0.05$).

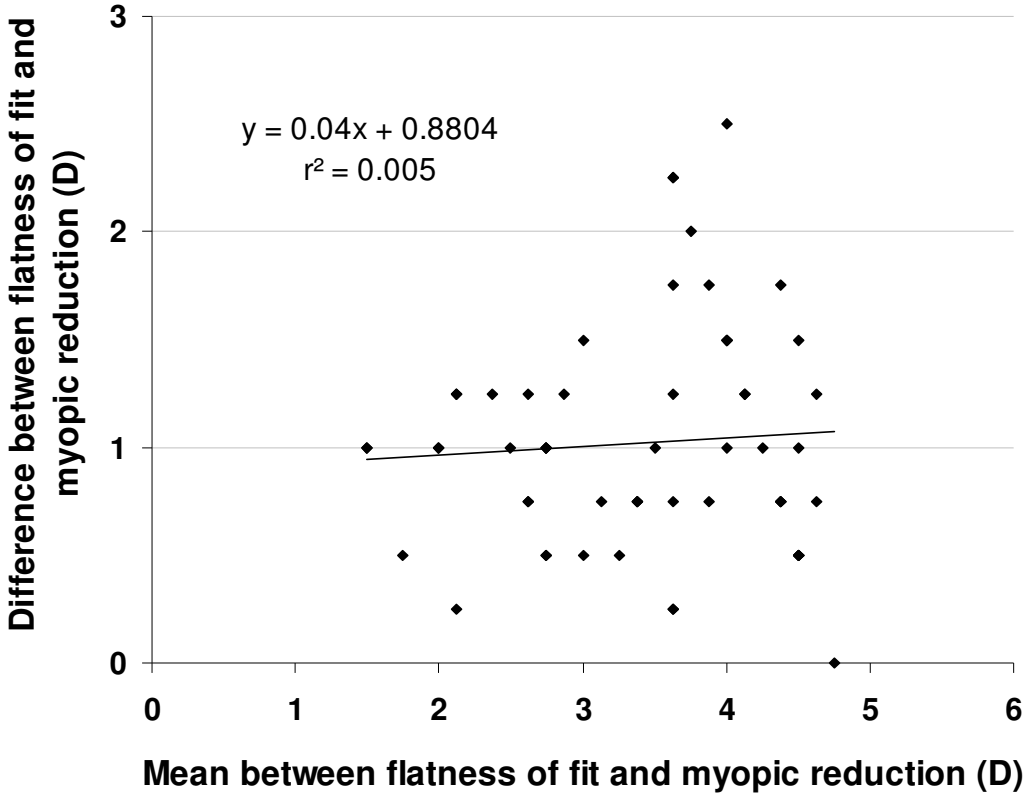


Figure 4.5.2 The Bland and Altman plot between the mean and difference between flatness of fit and myopic reduction

Since there was a lot of scatter for those with higher attempted myopic reduction, the data were re-analysed with the attempted myopic reduction less than 4.75 D (n = 34) and Figure 4.5.3 presents the relationship between ΔM_{ach} and ΔM_{att} for these patients. ΔM_{ach} was significantly correlated to ΔM_{att}, i.e. (K_f – BOZR) (Pearson $r^2 = 0.76$, $p < 0.001$). Linear regression shows that the relationship between these two variables can be described by the linear equation of:

$$\Delta M_{ach} = 0.92(K_f - BOZR) - 0.61 \qquad \textit{Equation 4.5.2}$$

Therefore, from Equations 4.3.2 and 4.5.2, we have

$$0.92(K_f - \text{BOZR}) - 0.61 = T + 0.75$$

$$\text{BOZR} = K_f - 1.09\,T - 1.48 \cong K_f - T - 1.48$$

The results suggest that the BOZR of the lens should be flattened by a factor 1.48 instead of 0.75 if the intention is to overcorrect myopia by 0.75 D with ortho-k for those with attempted myopic reduction less than 4.75 D.

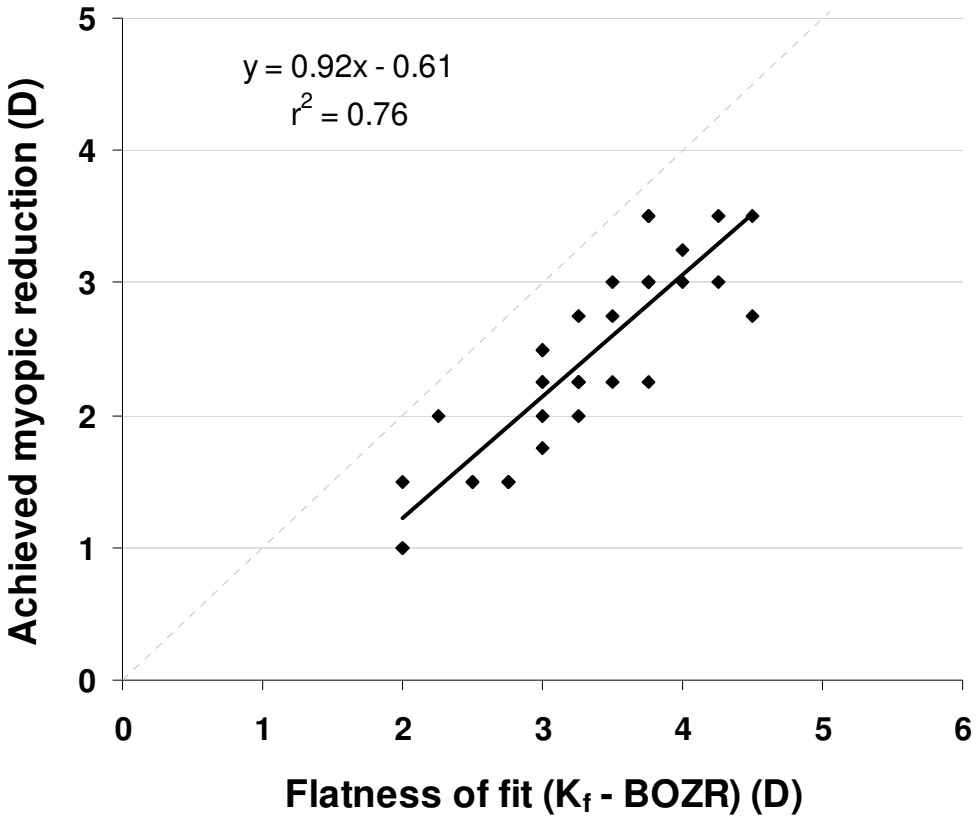


Figure 4.5.3 Relationship between achieved myopic reduction and flatness of lens fit (i.e. attempted myopic reduction) (n = 34), excluding patients with attempted myopic reduction over 4.50 D

4.6 Discussion

Modern ortho-k temporarily induces central corneal flattening through the use of RGL. The pressure and forces developed underneath the RGL during lens wear lead to a myopic reduction (see Section 1.4). The BOZR of the lens is fitted flatter than the flattest curvature of the cornea, depending on the degree of myopic reduction intended. The force created by the BOZR and the reverse curve of the lens moulded and flattened the corneal surface to effect myopic reduction. The mid-peripheral alignment curve(s)/tangent is/are responsible for stabilizing the lens for good centration (see Section 1.2.2.1.2).

The lens designs examined in the current study use the Jessen formula to calculate the BOZR of lenses to order. The result showed the formula to under-estimate the effect of myopic reduction after the procedure. Although the amount of myopic reduction after overnight ortho-k is dependent on the flatness of the lens fit, i.e. the flatter the BOZR fitted, the greater the amount of myopic reduction achieved ($r^2 = 0.71$, $p < 0.001$), the relationship is not 1:1. This is in agreement with the results reported by Rah and co-workers (2002a). Rah and co-workers also found the amount of myopic reduction after one-month of ortho-k

lens wear to be significantly correlated to the flatness of fit of the lens in both eyes of their subjects (right eye, r = 0.70; left eye, r = 0.68).

According to the Jessen formula, taking the compression factor into consideration, to correct a patient with myopia of 1.00 D, the BOZR of the lens should be fitted flatter than the flattest corneal curvature by 1.75 D so as to obtain 1.75 D myopic reduction after the procedure. But from the current study, the amount of achieved myopic reduction after the treatment was significantly lower than that of the attempted reduction as calculated from the Jessen formula. If it is desirable to overcorrect a patient by an amount of 0.75 D, a flattening factor of 1.23 times the desired refractive power reduction plus 1.27 D in the Jessen formula is required to achieve the desired refractive change, i.e., to correct a 1.00 D myope, the BOZR of the lens should be fitted flatter than the flattest curvature by 2.50 D (i.e. BOZR = K_f – (1.23 T + 1.27)) instead of 1.75 D if the original Jessen formula is used. If the data from patients with attempted myopic reduction over 4.50 D (large scattering of data observed for these patients) were excluded, a formula of BOZR = K_f – (T + 1.48) was obtained. Therefore, if patients with refractive error under 4.75 D, an extra flattening

factor of 0.73 (calculated by 1.48 – 0.75) is required to determine the BOZR of a four-zone reverse geometry ortho-k lens.

However, since this formula is generated from analysing data from clinical findings, and has not been tried clinically, it is unclear if the extra flattening of BOZR would actually lead to overcorrection of myopia by 0.75 D in practice. Also, it is not clear if the extra flattening of the BOZR would increase the risk of corneal complications, for example, corneal staining. Obviously, a careful clinical trial is warranted to test these formulae. Also, there is a need to further investigate the effectiveness of ortho-k for the reduction of high myopia since the results in the current study show a large variability in the corneal topographical response to higher attempted myopic reduction.

4.7 Conclusion

This study shows that the Jessen formula with a compression factor of 0.75 in ortho-k for determining the BOZR of some ortho-k lens designs would underestimate the myopic reduction outcome. An extra flattening power may be required to achieve the desired refractive change if the objective is to overcorrect by 0.75 D.

The work described in this chapter has been published in "Chan B, Cho P, Mountford J. The validity of Jessen formula, and the relationship between corneal changes and myopic reduction in overnight orthokeratology. Ophthal Physiol Optics 2008; 28: 265-268".

CHAPTER 5

Relationship between corneal topographical changes and myopic reduction in overnight orthokeratology

5.1 Introduction

Corneal topography is an essential instrument in ortho-k practice as it measures most of the corneal surface and gives a more detailed assessment of the cornea. Different topographical maps allow assessment of the ortho-k lens performance on the cornea during sleep (see Section 1.2.2.4). The difference map feature is specifically useful for monitoring lens centration and patient management during the procedure (see Section 1.3.2). Munnerlyn's formula was originally used to calculate the ablation depth in Photorefractive Keratectomy to determine the refractive change (Munnerlyn et al., 1988). The formula has also been used by some researchers to account for refractive changes in ortho-k (Alharbi and Swarbrick, 2003) (see Section 1.2.2.6). Other researchers have suggested that myopic reduction in ortho-k can also be determined from the change in the apical corneal power (ACP) calculated from the axial difference map (Mountford, 1997a; Nichols et al., 2000) (see Section 1.2.2.4).

Since ortho-k involves corneal shape change, various initial corneal parameters have been suggested as predictors for the outcome of the procedure (Coon, 1984; Wlodyga and Bryla, 1989; Joe et al., 1996; Mountford, 1997a; Lui and Edwards, 2000a) (see Section 1.2.2.6). Any factor that can accurately predict the outcome of the treatment would be most useful, as it would help practitioners to better estimate the level of success in a particular patient before commencing the procedure. However, to date, there has not been any study investigating the usefulness of initial corneal shape index as a predictor of overnight ortho-k outcomes.

The Medmont E-300 (Medmont Pty. Ltd., Camberwell, Australia) corneal topographer has been reported to be an accurate, and precise instrument (Tang et al., 2000), and providing repeatable and reproducible topographical measurements (Cho et al., 2002b; Chui and Cho, 2005). This part of the study aims to investigate the relationship between changes in central corneal power and manifest refractive changes. We also investigated the use of initial meridional Q for predicting the outcome of ortho-k.

5.2 Methods

Of the files reviewed in the survey study in Chapter 3, 63 patients fulfilled the following inclusion criteria – (1) first time ortho-k lens wearer fitted with 4- or 5-zone reverse geometry lenses in both eyes; (2) two-week morning visit, including subjective refraction and bull's eye subtractive topographical pattern measured by the Medmont E300 corneal topographer (version 4.8.0, Medmont Pty. Ltd., Camberwell, Australia); and (3) the same pair of lenses (at two week visit) had been successfully worn for at least six months. Only data for the right eye of the 58 patients were analysed. The data for five subjects were excluded as three of them had less than five hours of lens wear the night before the two-week visit, and the other two patients had a very poor corneal topographical response at that visit. All five subjects had less than 50% of the attempted myopic change at that visit.

The relationship between the achieved myopic reduction (ΔM_{ach}) and ACP (default) changes (ΔACP) was evaluated. Since the maximum change in corneal power may not necessarily be the default ACP given by the topographer, we also investigated the relationship between ΔM_{ach} and maximum corneal power change

within the treatment zone (ΔMCP). The treatment zone is determined by moving the cursor from the center of the cornea to the point on the nasal and temporal side where the difference between the pre- and post-treatment corneal refractive power is zero. Both ΔACP and ΔMCP were determined from the difference topographical map (subtractive axial map) between baseline and the two-week visit. Although the subtractive refractive map is best to determine the corneal power change after ortho-k (see Section 1.2.2.4), this study only analysed the power change in the central corneal area where the ΔACP measured between the axial and refractive map is the same. And the mean ΔMCP measured between the two maps was only 0.03 ± 0.04 D which is not clinically significant. Therefore, in this study, the subtractive axial map was used to compare the findings with previous study (Mountford, 1997a). As there were no statistically significant changes in refractive cylinder during the two-week lens wear period (results not presented), only the refractive sphere was used for analysis.

To investigate whether initial Q can be used for predicting the ortho-k effect, the flattest Q at the 9.80 mm chord was used. Since the same amount of myopia can be associated with a different Q, percentage myopic reduction ($\Delta\%M_{ach}$) was used to investigate the correlation between initial Q and ΔM_{ach}.

5.3 Treatment of data

Statistical analyses were made using the SPSS 15.0 version. Data normality was tested using Kolmogorov-Smirnov D-tests before any statistical analysis. A p-value of 0.05 was set to indicate statistical significance. All data, except $\Delta\%M_{ach}$ were normally distributed; therefore, paired-t-tests were used to test for differences between ΔM_{ach} and ΔACP and ΔMCP; the Pearson correlation coefficient was used to determine the association between topographical data and the reduction in myopia, and the Spearman correlation coefficient was used to determine the relationship between initial Q and $\Delta\%M_{ach}$.

5.4 Results

There was a significant difference between ΔM_{ach} and ΔACP after two weeks of lens wear, with ΔM_{ach} greater than ΔACP by a mean of 0.34 ± 0.57 D (paired-t-test, $p < 0.001$), and there was a significant correlation between the two variables (Pearson $r^2 = 0.61$, $p < 0.001$) (Figure 5.4.1). Their relationship can be described by the equation of $\Delta M_{ach} = 0.91\ \Delta ACP + 0.57$.

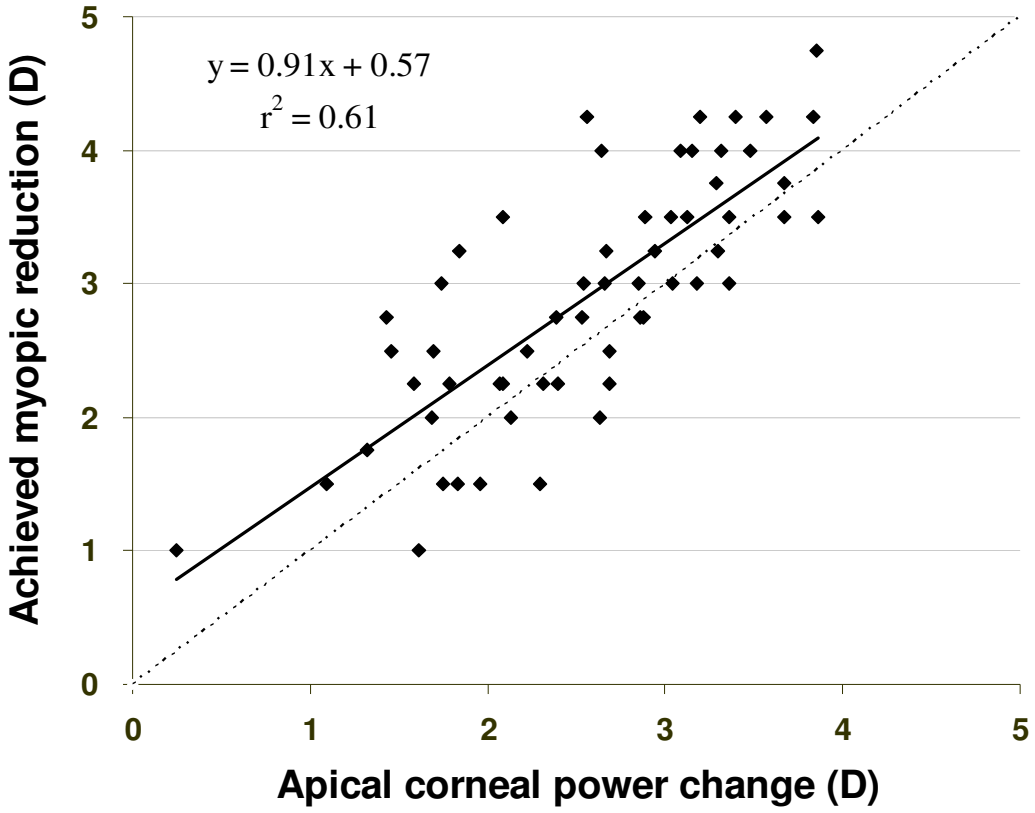


Figure 5.4.1 Relationship between achieved myopic reduction and apical corneal power change (ΔACP) (N = 58)

A significant difference was also found between ΔACP and ΔMCP (paired-t-test, $p < 0.001$), and between ΔM_{ach} and ΔMCP after two weeks of lens wear; however, ΔM_{ach} was smaller than ΔMCP by a mean of 0.23 ± 0.57 D (paired-t-test, $p < 0.001$). The relationship between ΔM_{ach} and ΔMCP was $\Delta M_{ach} = 0.93$ ΔMCP + 0.01 (Pearson $r^2 = 0.62$, $p < 0.001$) (Figure 5.4.2).

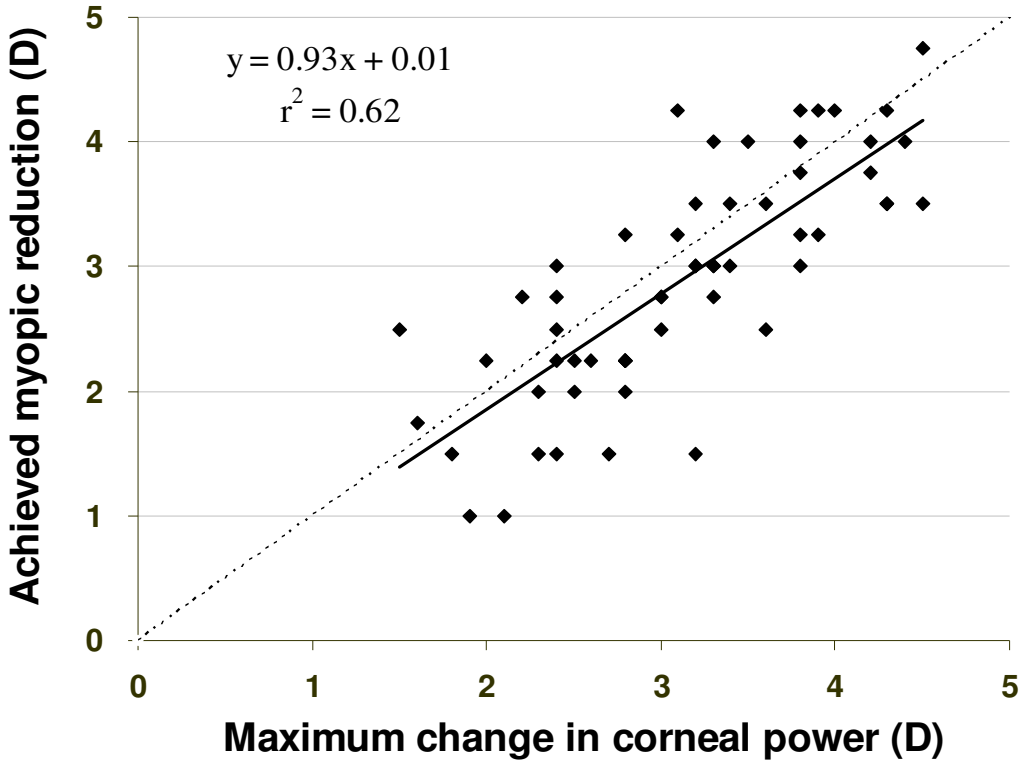


Figure 5.4.2 Relationship between achieved myopic reduction and maximum change in corneal power (ΔMCP) (N = 57)

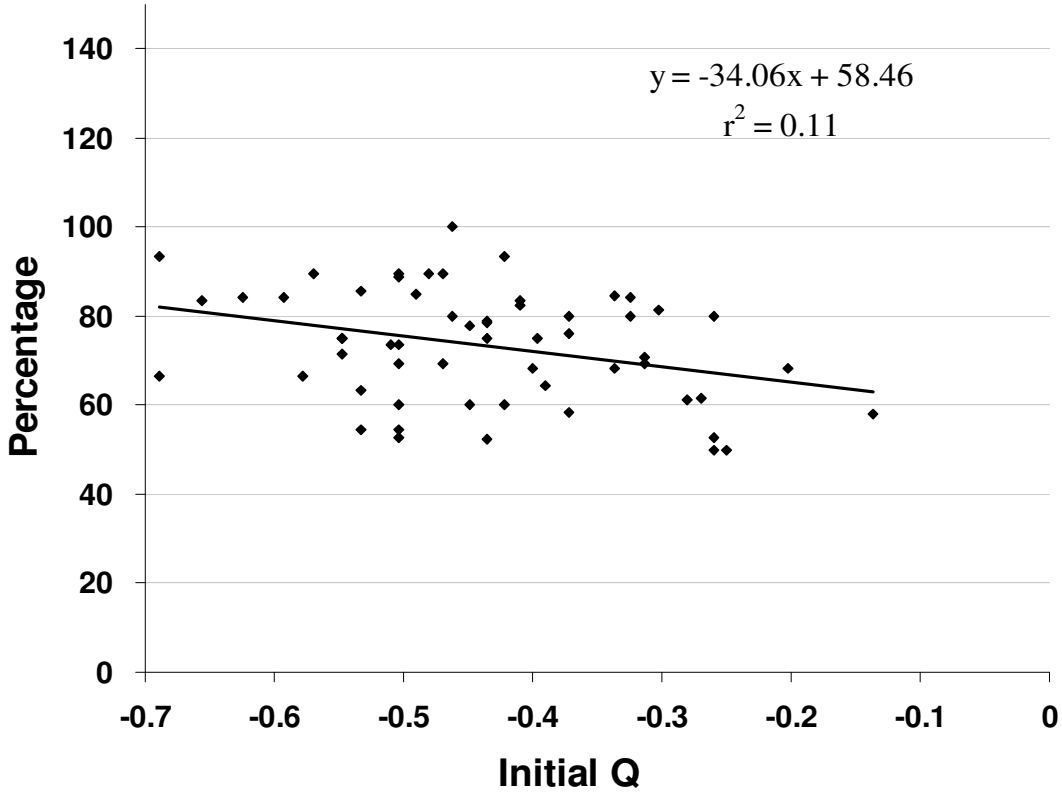


Figure 5.4.3 Relationship between percentage of change in myopic refraction and initial Q

5.5 Discussion

ΔM_{ach} was significantly associated with ΔACP, but ΔACP significantly under-estimated the manifest refractive change by a mean of 0.34 ± 0.57 D. The relationship between the two parameters can be represented by the equation of $\Delta M_{ach} = 0.91\ \Delta ACP + 0.57$ (see Figure 5.4.1). Mountford (1997a), showed a significant correlation (r = 0.95) between ΔACP and ΔM_{ach} with a relationship of $\Delta M_{ach} = 0.92\ \Delta ACP + 0.15$. The discrepancy in results between Mountford's and our study may be due to the different methodologies used. For example, Mountford (1997a) used data from a visit which showed a maximum refractive change within a six-month study period, whereas in the present study, data were collected after two weeks of lens wear irrespective of the refractive errors.

The amount of ΔACP measured with the Medmont E-300 corneal topographer in the current study does not account for the total myopic reduction following ortho-k probably because we do not really know how changes in the corneal shape (Δ asphericity) affects the optics of the eye. A previous study has also shown that objective methods using retinoscopy and auto-refraction under-estimate post-ortho-k refractive error change (Cheung and Cho, 2004). In

addition, ΔACP is a measure of the power change at the apex of the cornea, which is a point, whereas subjective refraction measures the refractive error of the ocular system within the entrance pupil (which involves a certain area of the central corneal surface), depending on the size of the treatment zone after ortho-k as well as the pupil size. The discrepancy between ΔACP results reported in previous papers and those in the current study may be due to the method used for the reconstruction of ACP from different corneal topographers. The EyeSys corneal topographer uses a basic spherical reconstruction algorithm and applies an aspheric best fit to the data to calculate the value of ACP, whereas the Medmont corneal topographer uses the arc-step reconstruction algorithm and then extrapolates into the centre to determine the ACP. The difference in corneal curvature reconstruction algorithm between the two instruments may also cause an inaccurate ACP measurement after ortho-k (Tang et al., 2000).

In the current study, ΔMCP gave a closer estimation (a mean difference (ΔMCP − ΔM_{ach}) of 0.22 D) of the amount of myopic reduction when compared to ΔACP (a mean difference (ΔACP − ΔM_{ach}) of −0.34 D), however, the difference did not reach a clinically significant level. Also, since ΔACP is given by the topographer by default, whereas MCP has to be located manually by the user, there is no

advantage to the use of MCP instead of ACP to estimate ΔM_{ach} after overnight ortho-k.

Although our results showed that the ΔACP was not able to accurately evaluate the ΔM_{ach} after ortho-k lens wear, ΔACP is still recommended to be used as an objective method to reflect a change in myopic reduction, at least better than retinoscopy or auto-refraction which under-estimate the post-ortho-k refractive error change by about 50% (Cheung and Cho, 2004).

In addition to the knowledge, skill and experience of the ortho-k practitioner, a reliable parameter which can accurately predict the amount of myopic reduction after ortho-k would be very useful. Although many studies have suggested initial ocular parameters as predictive tools for myopic reduction in ortho-k, to date, none of the parameters have been confirmed to be useful for predicting the ortho-k outcome (see Section 1.2.2.6).

Significant changes in the e-value following ortho-k have been reported previously (Joe et al., 1996; Mountford, 1997a; Lui and Edwards, 2000b). However, as mentioned earlier, the post-ortho-k corneal shape is no longer a

normal conic section/conicoidal surface. The corneal shape descriptive indices (p, e-value or Q) given by the corneal topographer is invalid to be used to describe such corneal shape. Therefore, we examine the usefulness of initial Q for the prediction of myopic correction in ortho-k. The result showed a significant but weak relationship between initial Q and $\Delta\%M_{ach}$ ($r^2 = 0.11$, $p = 0.01$). Therefore, initial Q is not useful to predict the amount of myopic reduction in ortho-k.

5.6 Conclusions

A change in apical corneal power (ΔACP) under-estimates the achieved myopic reduction in ortho-k ($\Delta M_{ach} = 0.91\ \Delta ACP + 0.57$). However, compared with retinoscopy and auto-refraction, it is still a useful method to provide an estimate of the post-ortho-k refractive change. Although ΔMCP appears to give a closer estimation of ΔM_{ach} than ΔACP, there is no significant difference in the estimations by either parameter. Hence, there is no advantage in using of MCP instead of ACP to estimate ΔM_{ach}. Initial Q is not useful as a predictive factor for the outcome in ortho-k.

The results of this study have been presented at the 2nd Asia Cornea & Contact Lens Conference, April 2005; and the 15th Asia-Pacific Optometric Congress, October 2005.

CHAPTER 6

A pilot study on the stability of ascorbate in artificial tears

6.1 Introduction

Human tears contain several water-soluble antioxidants, with ascorbate (vitamin C) and urate together contributing about 50% of the total antioxidant capacity of tears (Choy et al., 2000; Choy et al., 2001). The human corneal cells are rich in ascorbate (Brubaker et al., 2000), and ascorbate is a powerful reducing substance which acts as a ROS scavenger to eliminate or inactivate potentially damaging oxidative species on ocular tissue (Delamere, 1996; Taylor et al., 1997; Rose et al., 1998; Smirennaia et al., 2002). For the exposed and vulnerable cornea, an adequate and continuous supply of ascorbate may be beneficial to corneal health, and tear fluid may be a dynamic and effective renewable and immediate source of ascorbate.

Contact lens binding to the cornea is commonly reported in overnight ortho-k lens wear (Cho et al., 2003; Cheung and Cho, 2004) (see Section 1.5.3), and the improper removal of a bound lens can cause corneal damage (Cho et al., 2003). To minimize the incidence of lens binding in overnight ortho-k wear, artificial tears are the commonly prescribed treatment for patients to use before going to sleep with the lenses and to aid in lens removal in the morning (Cho et al., 2003). However, most of these products focus on how to prolong the duration of the effect of the artificial

tears after application, and little has been done to determine how the composition and action of artificial tears may be made to emulate natural tears more closely. Indeed, the use of these artificial tears will dilute the useful constituents in tear fluid and may alter the defense/protective system conferred by natural tears on the anterior surface of the eye. The problem would be more pronounced in current ortho-k lens wear, as overnight sleep with lenses in is likely to increase corneal stress and damage (Garber, 2001; Hutchinson and Apel, 2002).

It is possible to include antioxidants, such as ascorbate, in artificial tears and this may be a useful strategy to increase the effectiveness of artificial tears for the promotion of safe ortho-k lens wear. However, ascorbate is highly unstable and easily oxidized to dehydroascorbic acid (Halliwell and Gutteridge, 1999). It was of interest, therefore, to investigate the stability of ascorbate added to commercial artificial tears products, and this was the aim of this part of the study. Results would be useful to evaluate the possibility of including ascorbate in a new formulation of artificial tears.

6.2 Methods

Ascorbate standards (between 0, 20, 40, 80 and 100 μM) were prepared in distilled water using extra pure ascorbic acid crystals (Sigmam, Riedel de Haen). These solutions were used immediately after preparation. Precision was assessed by nine measurements of one set of standards run in parallel (in-run), and on five sets of standards run on separate days (between-run). Different amounts of ascorbate were added to three commercially available artificial tears, Vismed (VM) (Lab Chemedica AG, Munich, Germany), Tear Naturale Free (TNF) (Alcon Inc, Fort Worth, TX, USA), and Bion Tears (BT) (Alcon Inc, Fort Worth, TX, USA) (see Table 6.2.1), to produce artificial tear-based solutions of known ascorbate concentration.

Table 6.2.1 Composition of artificial tears used

Solution	Company	Active ingredients (Or Composition)	Other ingredients
Bion Tears (BT)	Alcon Inc, Fort Worth, TX, USA	0.1% Dextran 70, 0.3% Hydroxypropyl Methylcellulose (HPMC)	Bicarbonate and zinc
Tear Naturale Free (TNF)	Alcon Inc, Fort Worth, TX, USA	0.1% Dextran 70, 0.3% Hydroxypropyl Methylcellulose (HPMC)	Hydrogen chloride, Sodium hydroxide, CO2
Vismed (VM)	Lab Chemedica AG, Munich, Germany	0.18% Sodium hyaluronate	Calcium, magnesium and potassium, sodium chloride, potassium chloride, sodium citrate, disodium hydrogen phosphate

To assess linearity, one set of each artificial tear-based ascorbate standards (0, 20, 40, 80 and 100 μM) were measured in duplicate. To assess stability, two sets of artificial tear-based ascorbate of known concentrations were aliquoted and stored, one set at room temperature and one set at 4ºC, respectively, for 1, 2, 3, 4, 5, 6, 24 and 48 hours after preparation. At each time interval, one aliquot of each set was measured and compared with that of the freshly prepared (at 0 hour) solution.

Table 6.2.2 Program settings for the FRAP assay (Benzie and Strain, 1999)

COBAS FARA test program to determine the FRAP value	
▪ Measurement mode: Abs	▪ Diluent Volume: 30
▪ Reaction mode: R1-1-S-A	▪ First Reading: 0.5s
▪ Reagent Blank: reag/dil	▪ Number of Reading: 25
▪ Wavelength: 593 nm	▪ Reading Interval: 15s
▪ Temperature: 37°C	▪ Reaction Direction: increase
▪ R1: 300	▪ Calculation: endpoint
▪ M1: 1.0s	▪ First Reading for Calculation: M1
▪ Sample Volume: 29	▪ Last Reading for Calculation: 5 (i.e. 1 minute)
▪ Diluent Name: H_2O	

A sample of each artificial tear product was first assessed to confirm no native ascorbate or antioxidant activity (result not shown). The Ferric Reducing/Antioxidant Power (FRAP) assay was used for antioxidant activity, and a modified version, referred to as the FRASC assay was used for measuring ascorbate concentration (Benzie, 1996; Choy et al., 2000). Reagents and equipment used for the FRAP /FRASC assays for ascorbate concentration measurement were as described in detail elsewhere (Benzie and Strain, 1999), and using a Cobas Fara centrifugal analyzer (Roche Diagnostics Ltd, Basel Switzerland). Table 6.2.2

illustrates the settings for the FRAP/FRASC assays. In brief, the FRAP assay utilizes the ability of antioxidants to reduce Iron III ion (Fe^{III}) -TPTZ complex to its blue-coloured Iron II ion (Fe^{II}) form. The change in absorbance at 593 nm ($\Delta\mathbf{A}_{593nm}$) after a reaction time of one minute is due to the ascorbate present in the sample. FRAP/FRASC assay reagents were as follows: 300 mM acetate buffer, pH 3.6 was prepared by dissolving 3.1 g sodium acetate trihydrate (Riedel-de Haen, Germany) in distilled water, with 16 ml glacial acetic acid (BDH Laboratory Supplies, England) added; this was made up to one litre with distilled water; a 10 mM TPTZ (2,4,6 tripyridyl-s-triazine, Fluka Chemicals, Switzerland) solution in 40 mM HCl (BDH), and a 20 mM $FeCl_3 \cdot 6H_2O$ (BDH) solution in distilled water were prepared. Working FRAP assay reagent was freshly prepared as required by mixing 25 ml of acetate buffer in with 2.5 ml of TPTZ solution and 2.5 ml of ferric chloride solution. Freshly prepared aqueous solutions of Fe^{II} (1000 µM from $FeSO_4.7H_2O$; Riedel de Haen) and ascorbate (5, 25, 50, and 100 µM from extra pure crystals; Merck, Germany), were used for calibration of the assay. Calculation of FRAP assay results was performed from absorbance reading as follows.

Using the water-diluted samples, the ascorbate (µM) concentration =

$$\frac{1 \text{ min } \Delta\mathbf{A}_{593nm} \text{ of test sample}}{1 \text{ min } \Delta\mathbf{A}_{593nm} \text{ of standard}} \text{ x [standard] (µM)}$$

For statistical analysis, Pearson's correlation was used to investigate relationships between different ascorbate samples and absorbance at 593 nm, and Repeated

Measures Analysis of Variance (ANOVA) test was used to investigate stability.

6.3 Results

The FRAP /FRASC assay for ascorbate showed good linearity and sensitivity (Figure 6.3.1). Precision was also good: in-run and between-run coefficients of variation were, respectively, less than 3.0% (n = 9) and < 3.0% (n = 6) at between 20 and 100 μM ascorbate. Results showed over 95% recovery of ascorbate from each artificial tear-based ascorbate sample. Significant decreases were seen in ascorbate added to each brand of artificial tears at room temperature (25^{o}C) and low temperature (4^{o}C) up to 48 hours ($p < 0.0001$) (see Figure 6.3.2 and Figure 6.3.3 respectively). The degradation rate was found to be lower in higher concentrations of ascorbate ($p < 0.0001$) and low storage temperature ($p < 0.0001$). Ascorbate was found to be more unstable in Bion Tears. Under room temperature, the ascorbate concentration (at 20 μM) in Vismed, Tears Naturale Free, and Bion Tears decreased by 2.1%, 1.3%, and 14.6% after one hour of storage, compared to an increase of 8.3% in ascorbate in water at room temperature, and decreased by 50.3%, 57.2% and 98.4% for the same tear products after 48 hours of storage, compared to a decrease of 20.9% for ascorbate in water. At low temperature (4^{o}C), the ascorbate concentration (at 20 μM) in Vismed, Tear Naturale Free, and Bion Tears decreased by 17.9%, 17.6% and 78.1%, respectively after 48 hours of storage compared to a 18.3% decline for the pure water-based ascorbate solution.

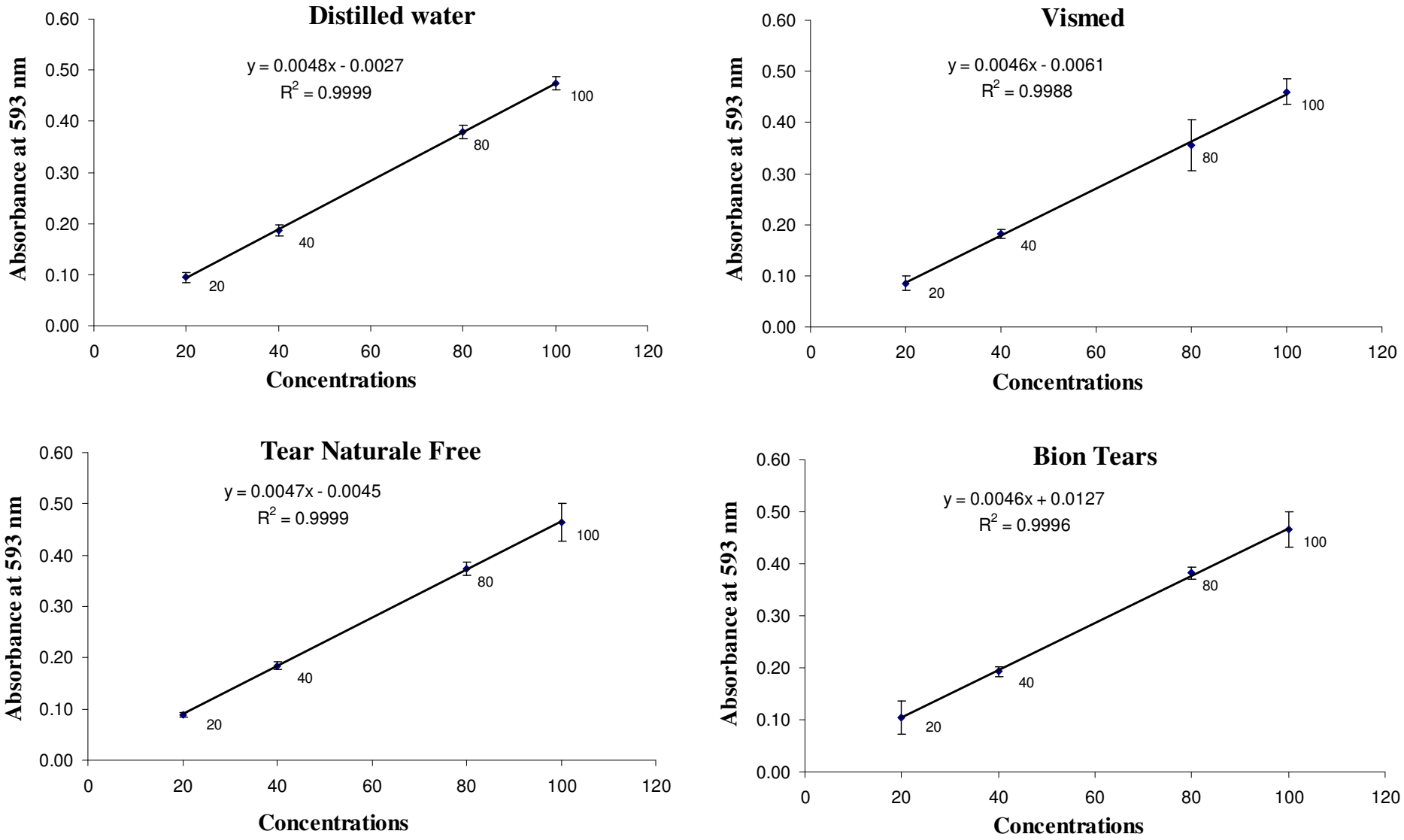


Figure 6.3.1 Linearity of FRAP assay for ascorbate added to different artificial tears. Results are mean ± 1SD of the nine measurements

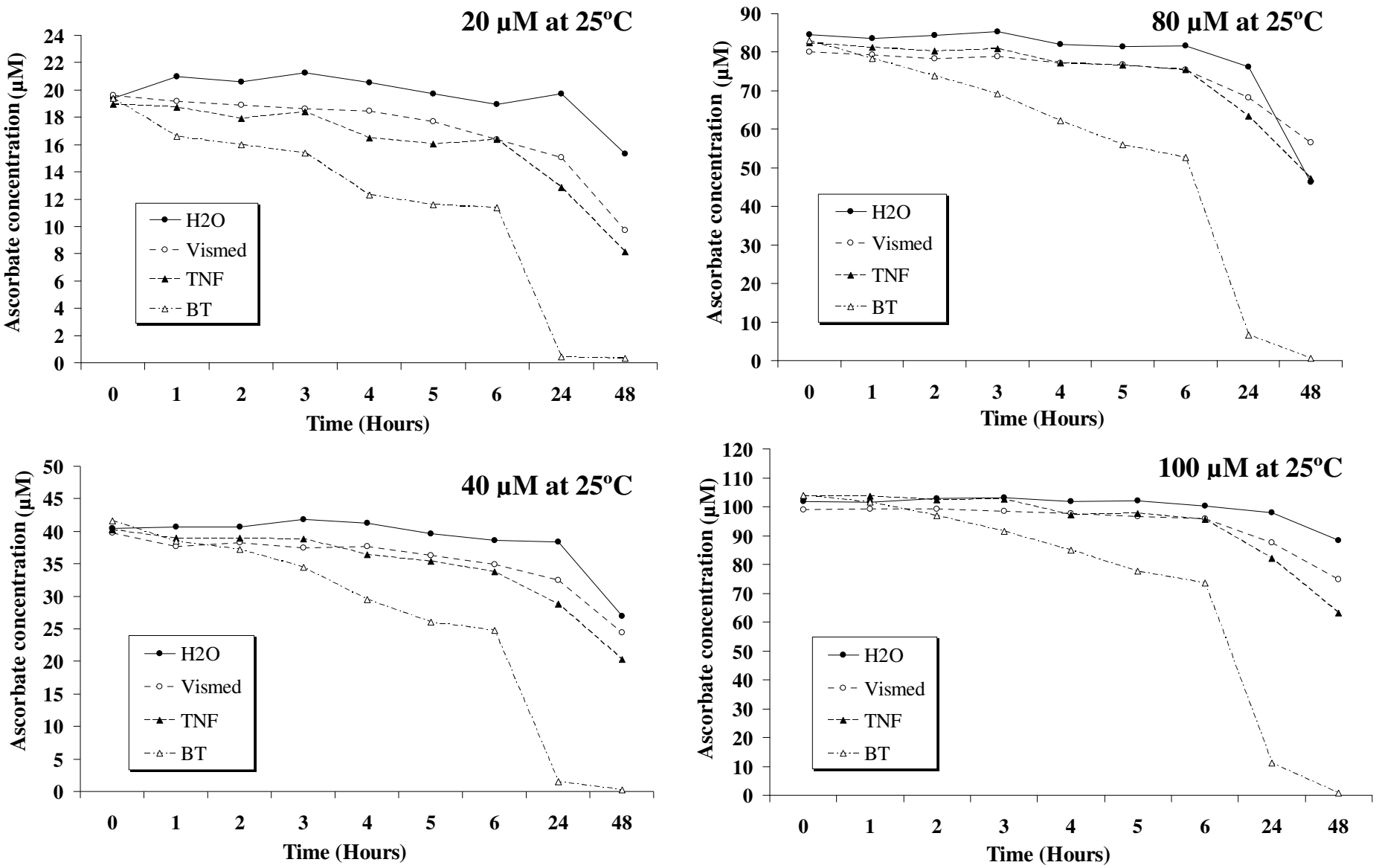


Figure 6.3.2 Stability of ascorbate added to different artificial tear products and to distilled water stored at room temperature for up to 48 hour (n =4).

H_20: Water; TNF: Tear Naturale Free; BT: Bion Tears

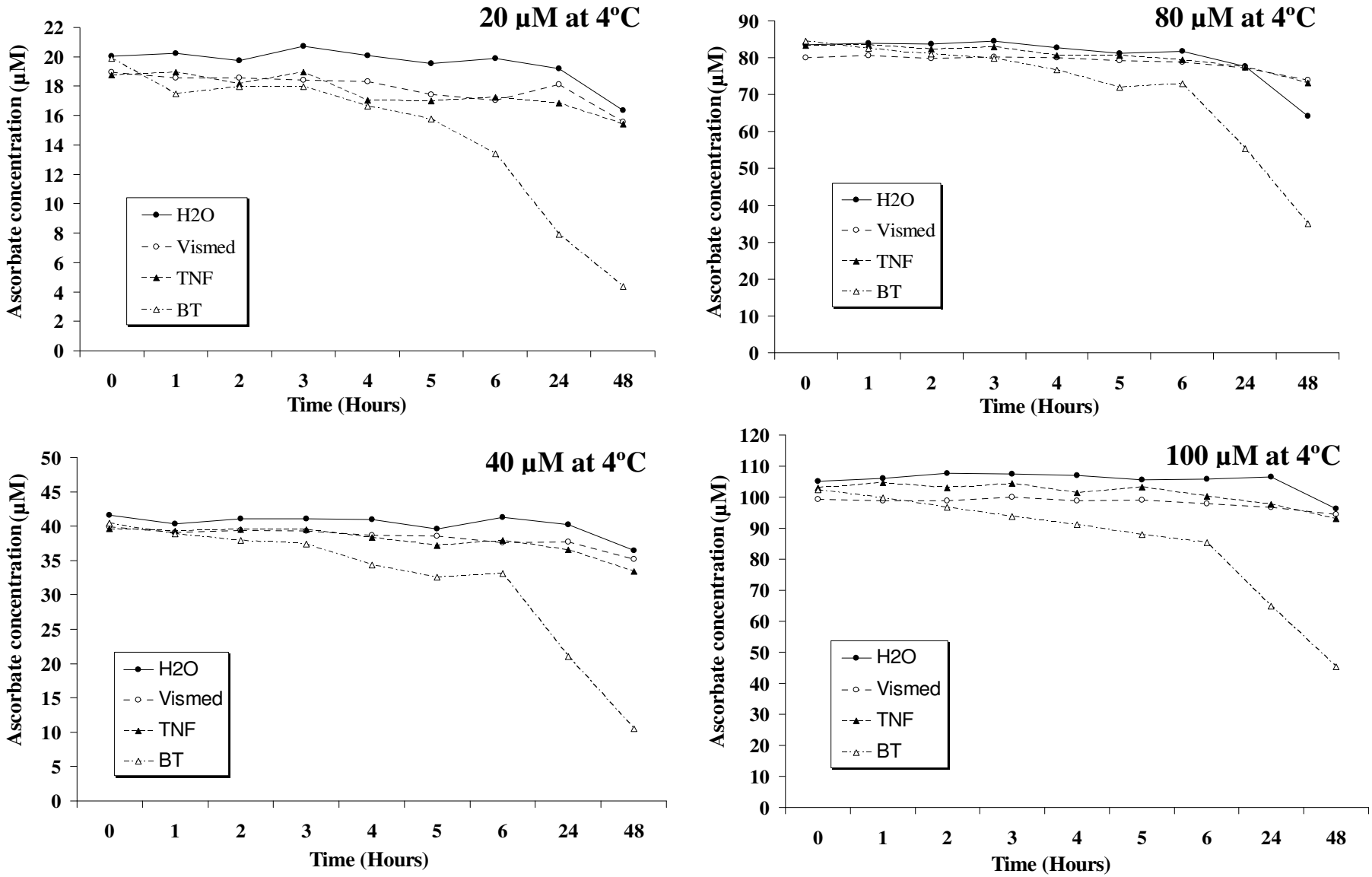


Figure 6.3.3 Stability of ascorbate added to different artificial tear products and to distilled water stored at 4ºC for up to 48 hours (n=4).

H_20: Water; TNF: Tear Naturale Free; BT: Bion Tears

6.4 Discussion

Ascorbate (vitamin C) is an effective water-soluble antioxidant and has been reported to be important in the suppression of inflammatory response and promoting corneal wound healing (Patel et al., 1993; Vaxman et al., 1995; Jagetia et al., 2003). This study has shown that ascorbate solution prepared in artificial tears shows good linearity and recovery, and only a 5% decrease was shown after one hour of storage in Vismed and Tear Naturale Free. This finding suggests that the instillation of Vismed and Tear Naturale Free into the human eye will not affect the tear ascorbate concentration. However, the application of artificial tears (Vismed, Tear Naturale Free, Bion Tears) that do not contain ascorbate will dilute the ascorbate present in tear fluid. A new generation of artificial tears that contain ascorbate may help promote corneal health. However, the issue of stability during storage is clearly one that has to be considered.

In this current study, a high concentration (100 μM) of ascorbate was more stable in Vismed or Tear Naturale Free. However, the use of a high amount of ascorbate may alter the pH of artificial tears (no pH measured in this study) leading to ocular discomfort. Indeed, it is likely to be the lower pH induced by the higher ascorbate concentrations that led to increased stability at higher values. The amount of ascorbate used in artificial tears must be carefully determined to emulate natural tears more closely. Previous studies have demonstrated that tears contain a mean ascorbate concentration of 23 μM, and after four weeks of vitamin C

supplementation, the maximum fasting tear ascorbate concentration attained was 33 μM (Choy et al., 2003). Ascorbate in the order of 40 μM may be the appropriate concentration for the new formulation of artificial tears. In addition, results presented here demonstrate that ascorbate added to artificial tears is more stable if stored at 4^{o}C. Tear formulations with added ascorbate should, therefore, be kept in the refrigerator, but even then it is noted that the matrix is important – it was clearly demonstrated that ascorbate added to Bion tears showed a marked degradation after five hours even at 4^{o}C. More work is warranted to explore the addition of ascorbate in artificial tears and its potential benefits to corneal health.

6.5 Conclusions

Ascorbate added to artificial tears shows different degrees of stability depending on the type of artificial tears and the storage temperature. On the basis of the results shown here, it is recommended that 4^{o}C be used for storage. In relation to the three commercial products tested (Vismed, Tear Naturale Free and Bion Tears), ascorbate was most stable in Vismed and least stable in Bion Tears.

The work described in this chapter is under preparation for submission and the tentative title is "The Change of Tear Ascorbate Concentration and Total Antioxidant Activity after Using Artificial Tears: the stability of ascorbate in artificial tears."

.

CHAPTER 7
Conclusions

7.1 Clinical survey in children undergoing ortho-k

In agreement with previous studies, most ortho-k wearers in the Optometry Clinic of PolyU in the first three years of this century were children. Most of the children enrolled for the treatment mainly for the purpose of myopic control. A spherical reverse geometry lens design can only correct low to moderate myopia and is not effective in correcting astigmatism. Although the parents of some patients (17 out of 108 patients) who had high myopia (greater than 6.00 D) or/and high astigmatism (greater than 1.50 D) understood the necessity of lower powered spectacles to correct residual refractive errors for better daytime distance vision after the treatment, they still requested enrolling their children for ortho-k for myopic control. This reflects the great concern of parents on the progression of myopia in children in Hong Kong.

During the first six months of ortho-k lens wear, with a regular aftercare schedule, no serious clinical complication was found in any of our patients. This may indicate the importance of regular after care visits in minimizing the incidence of serious corneal complications associated with overnight ortho-k. Among all

patients who were interviewed, most of the children were happy with ortho-k for refractive correction although about 29% (66 out of 226 patients) were not able to tolerate lens wear in the initial fitting visit and dropped out from the treatment.

7.2 Using the Jessen formula to determine the Back Optic Zone Radius (BOZR) of the orthokeratology lens

The Jessen formula, with a compression factor of 0.75, for determining the BOZR of reverse geometry lens for ortho-k was found to under-estimate the intended target of myopic reduction. Our findings suggest an extra flattening power is required to achieve the desired refractive change of an over-correction by 0.75 D and the original formula should be revised to BOZR = Flattest K reading – (1.23 Target + 1.27). Clinical trials are necessary to test and confirm the validity of this formula.

7.3 Relationship between corneal topographical changes and subjective myopic reduction in overnight orthokeratology

The apical corneal power changes measured by the Medmont E300 corneal topographer after ortho-k do not accurately reflect the manifest refractive change. However, when compared with retinoscopy and auto-refraction, it is still recommended as an objective method to estimate the ortho-k effect. We also found that initial Q is not useful as a predictor for the ortho-k outcome.

7.4 Stability of ascorbate in artificial tears

Our findings show good linearity and recovery of ascorbate added to three commercially-available (unpreserved, unit dosage) artificial tears. Our results also show a large variation in ascorbate stability in different artificial tears, with the ascorbate in Vismed (Lab Chemedica AG, Munich, Germany) showing the best stability and ascorbate added to Bion Tears (Alcon Inc, Fort Worth, TX, USA) showing the poorest stability. The stability, for all artificial tears, was further enhanced when the mixture was stored at low temperature. Among the three tested artificial tears, Vismed appears to be the best artificial tear for exploring new formulations of artificial tears with ascorbate.

CHAPTER 8
Limitations and further study

8.1 Limitations

In this study, clinical data were retrieved from clinic records (Chapter 3). A retrospective design suffers from collecting data from clinical records and the corneal topographer, in which there is a lot of missing data and no standard protocol on lens fitting and data measurement. In addition, due to the missing data, analytical tests have to be performed on a relatively small group of patients, and this may have introduced bias on the ortho-k effect.

The validity of the Jessen formula (Chapter 4) and the relationship between topographical changes and myopic reduction after ortho-k (Chapter 5) were determined using subjective refraction. The results may also be biased by the non-cycloplegic refractive errors retrieved from clinical files.

8.2 Further studies

Many questions regarding ortho-k are still to be answered. In view of the potential use of the technique for myopic control, the number of children enrolling in the treatment has increased dramatically in the past few years. It is

of importance to investigate the safety of long-term use of overnight ortho-k lenses. A randomized longitudinal myopic control study is currently underway in Hong Kong. The future of overnight ortho-k will greatly depend on the results of the safety issue and the effectiveness for myopic control in children.

New RGL designs now focus on the correction of high myopia, hyperopia and high corneal astigmatism. There is therefore a need to investigate the efficacy of these lens designs.

Although our results show that the conventional Jessen formula under-estimates the manifest refractive change after ortho-k, and a new equation was formulated, clinical trials are necessary to determine if the new formula is applicable for calculating the BOZR of the ortho-k lens. However, such work is beyond the scope of this thesis.

The stability of ascorbate in artificial tears investigated in the current study may not reflect the actual stability of the ascorbate when added to the human eyes where the constituents of tear fluid may decompose the ascorbate. Further studies

on the stability of ascorbate in the mixture of artificial tears and human tears are also warranted.

APPENDIX 1

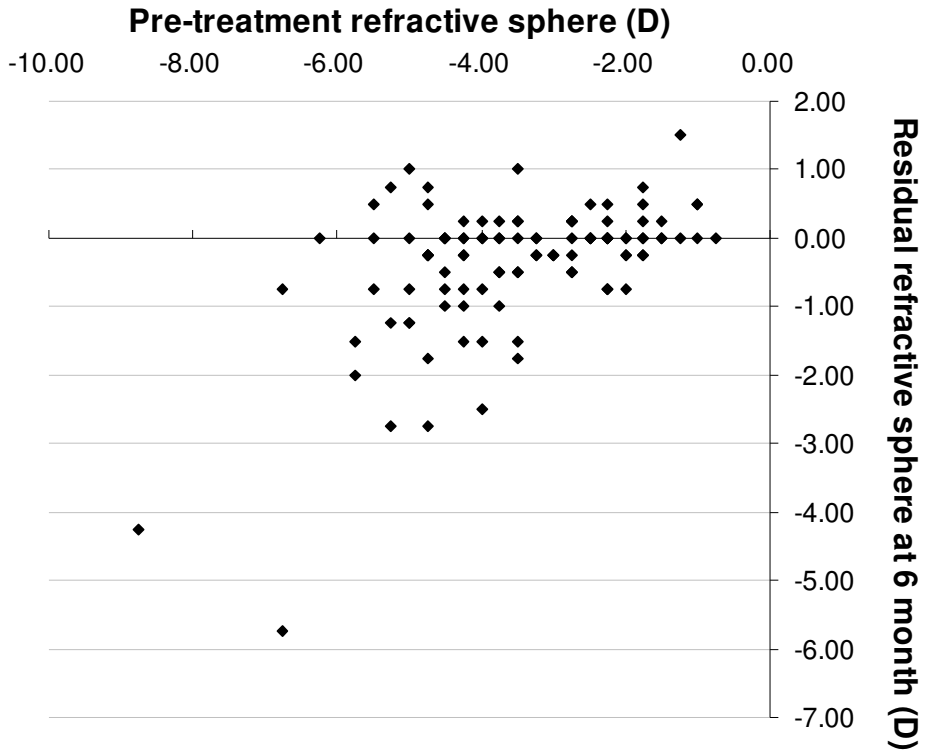


Figure A1.1 Scatter plot between pre-treatment refractive sphere and residual refractive sphere after 6-month lens wear. Spearman $r^2 = 0.13$, $p < 0.001$ (n =104)

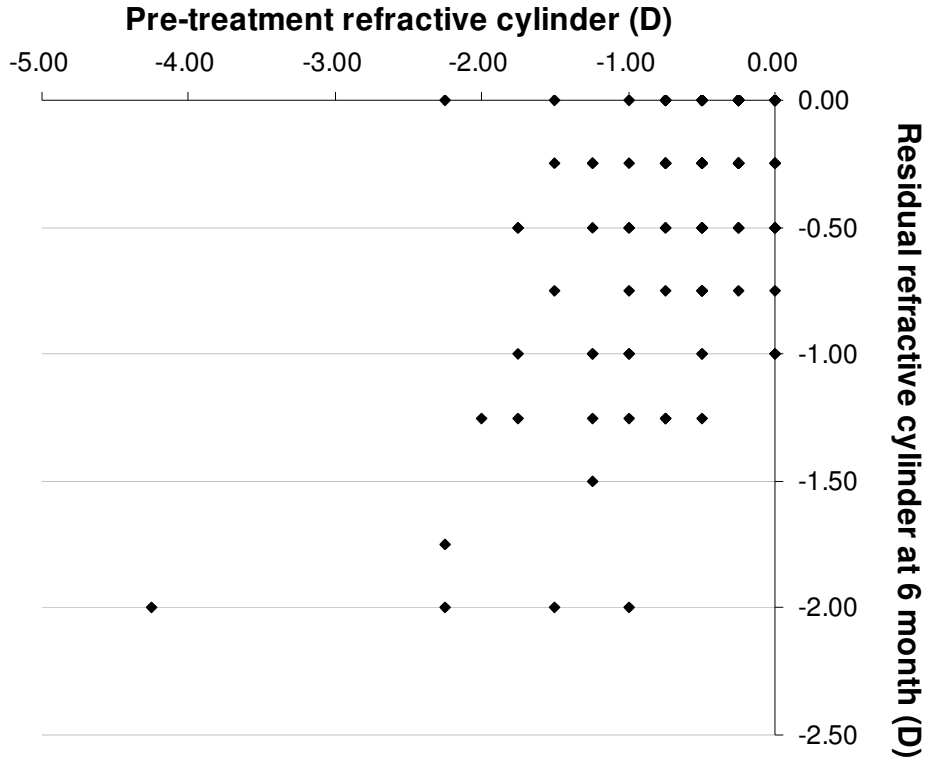


Figure A1.2 Sscatter plot between pre-treatment refractive cylinder and residual refractive cylinder after 6-month lens wear. Spearman $r^2 = 0.19$, $p < 0.001$ (n =106)

.

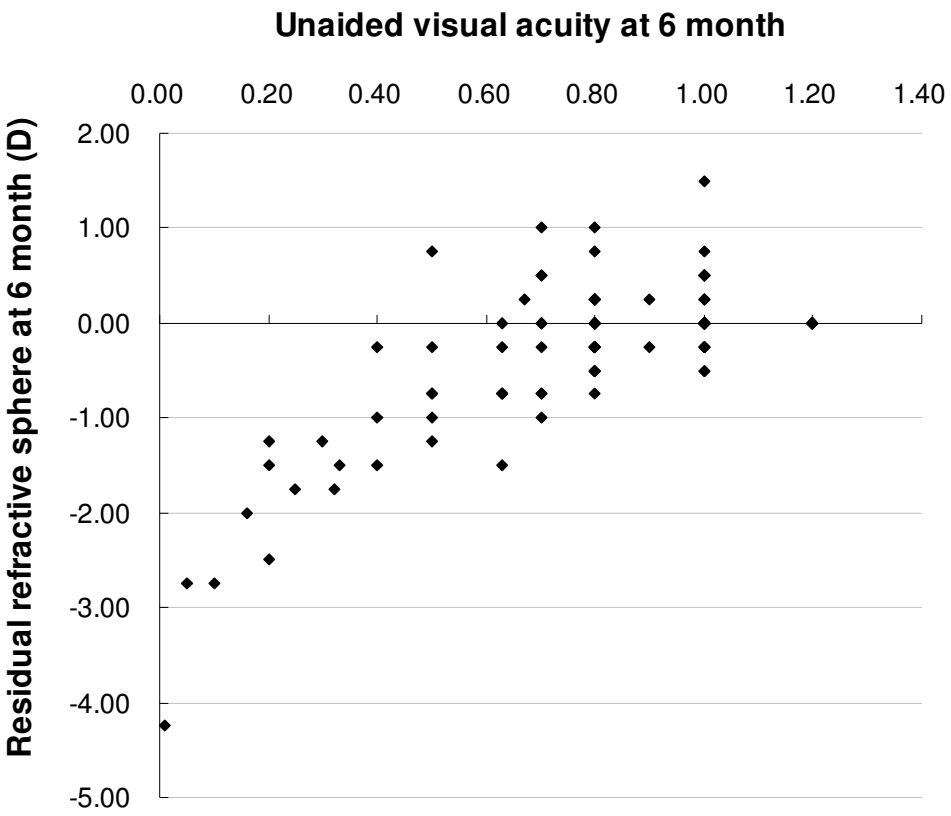


Figure A1.3 Scatter plot between residual refractive sphere and unaided visual acuity after 6-month lens wear. $r^2 = 0.30$, $p < 0.001$ (n =103)

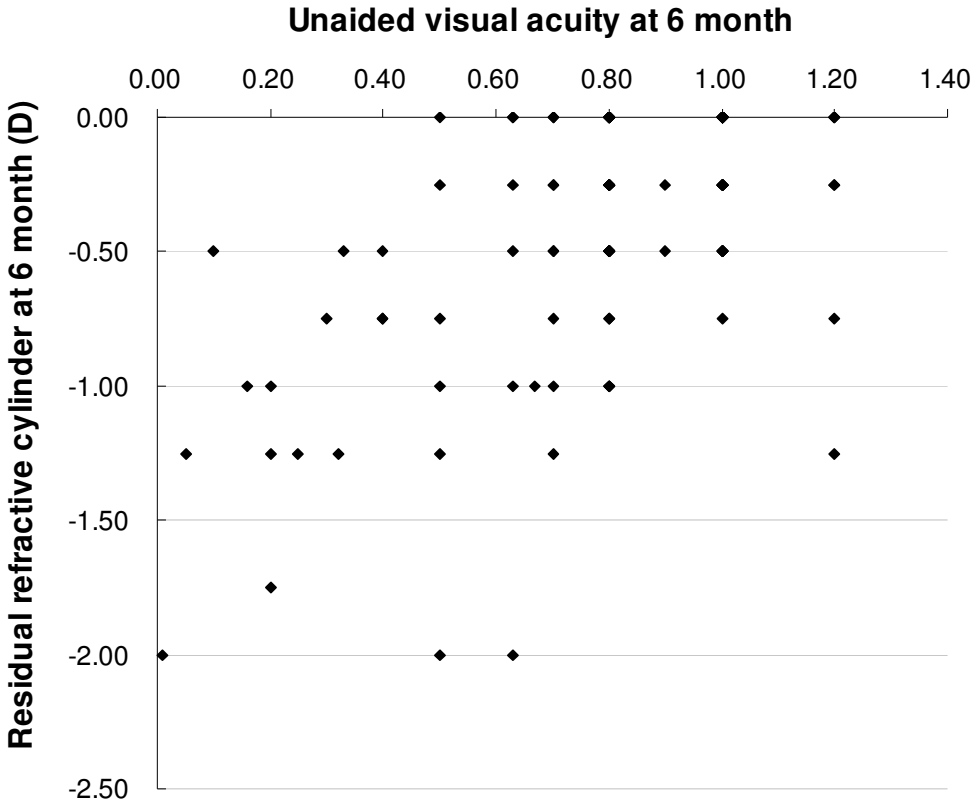


Figure A1.4 Scatter plot between residual refractive cylinder and unaided visual acuity after 6-month lens wear. Spearman $r^2 = 0.23$, $p < 0.001$ (n =103)

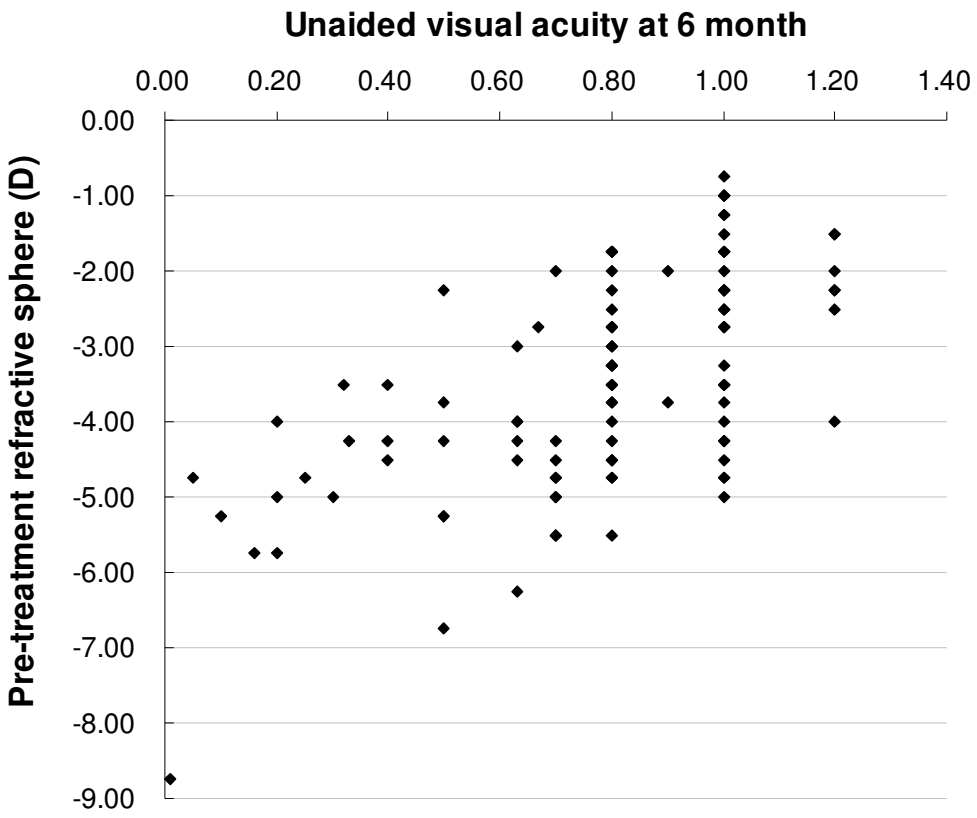


Figure A1.5 Scatter plot between pre-treatment refractive sphere and unaided visual acuity after 6-month lens wear. Spearman $r^2 = 0.28$, $p < 0.001$ (n = 103)

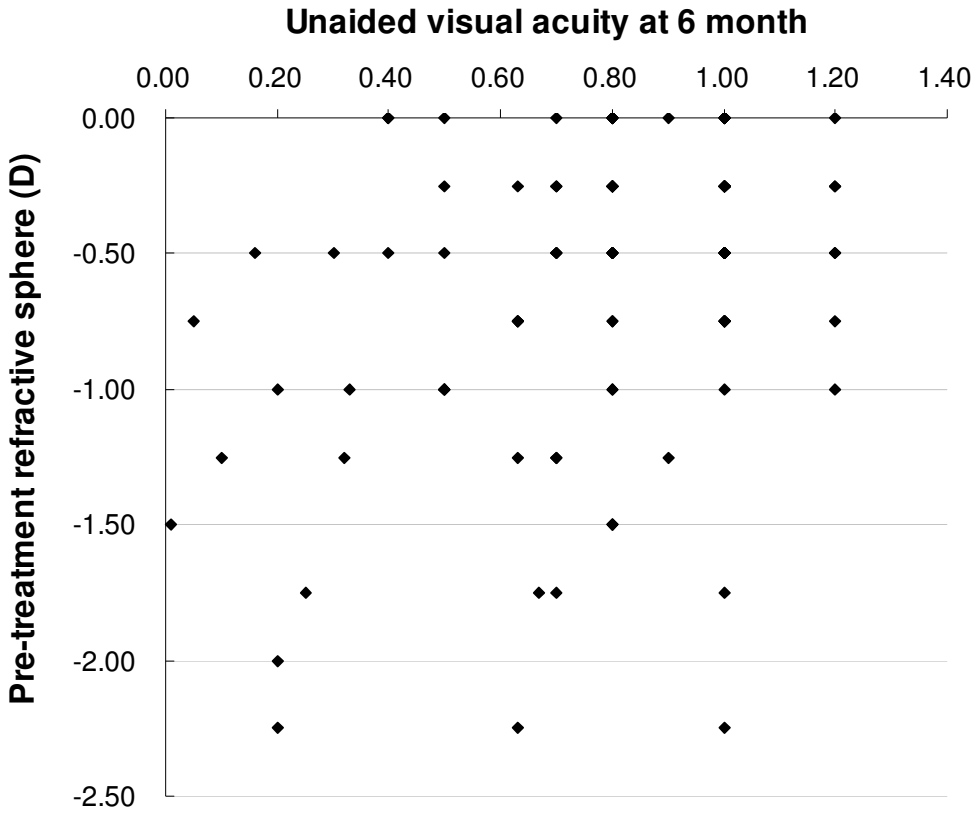


Figure A1.6 Scatter plot between pre-treatment refractive cylinder and unaided visual acuity after 6-month lens wear. Spearman $r^2 = 0.08$, $p = 0.004$ (n = 103)

APPENDIX 2

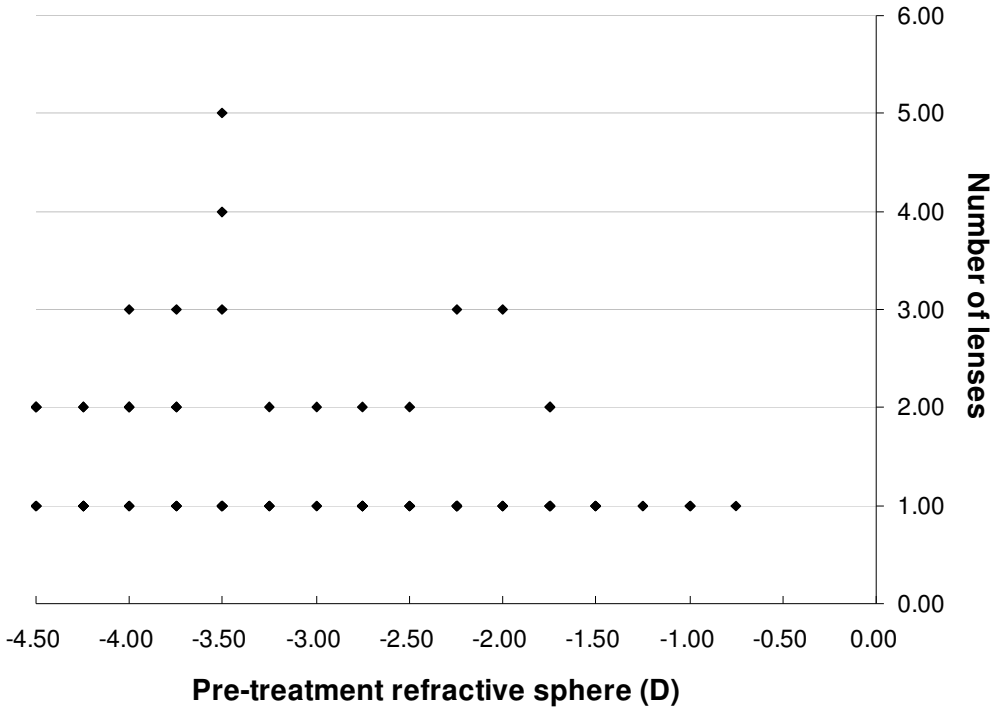


Figure A2.1 Scatter plot between number of lenses used and pre-treatment refractive sphere (≤ –4.00 D). Spearman $r^2 = 0.11$, $p = 0.005$ (n = 68)

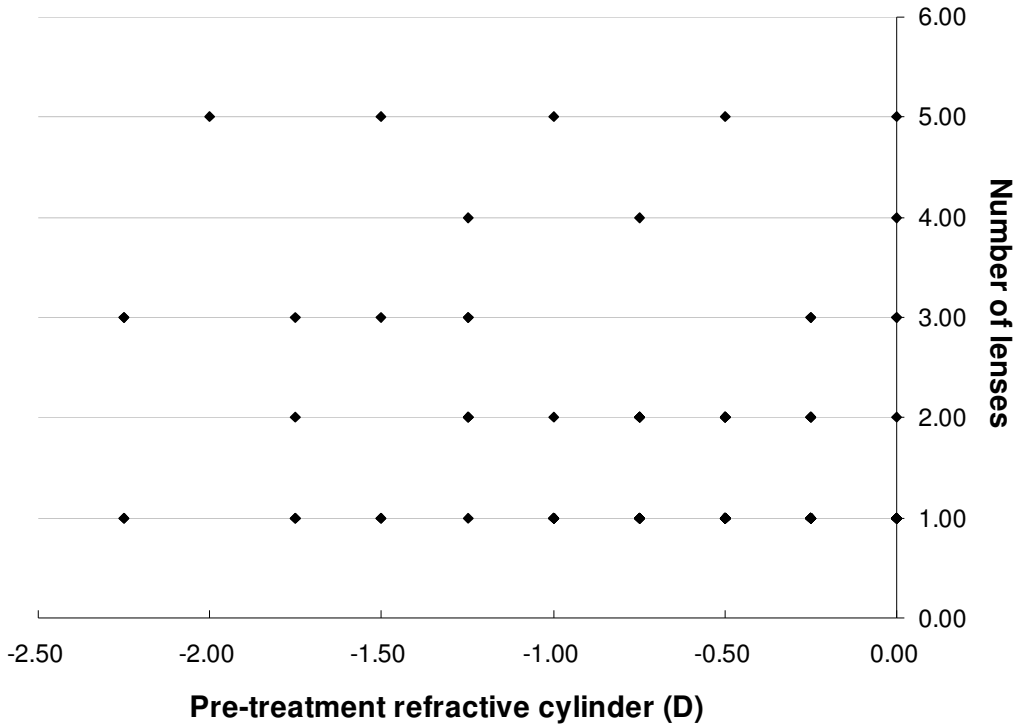


Figure A2.2 Scatter plot between number of lenses used and pre-treatment refractive cylinder. Spearman $r^2 = 0.01$, $p = 0.566$ (n = 68)

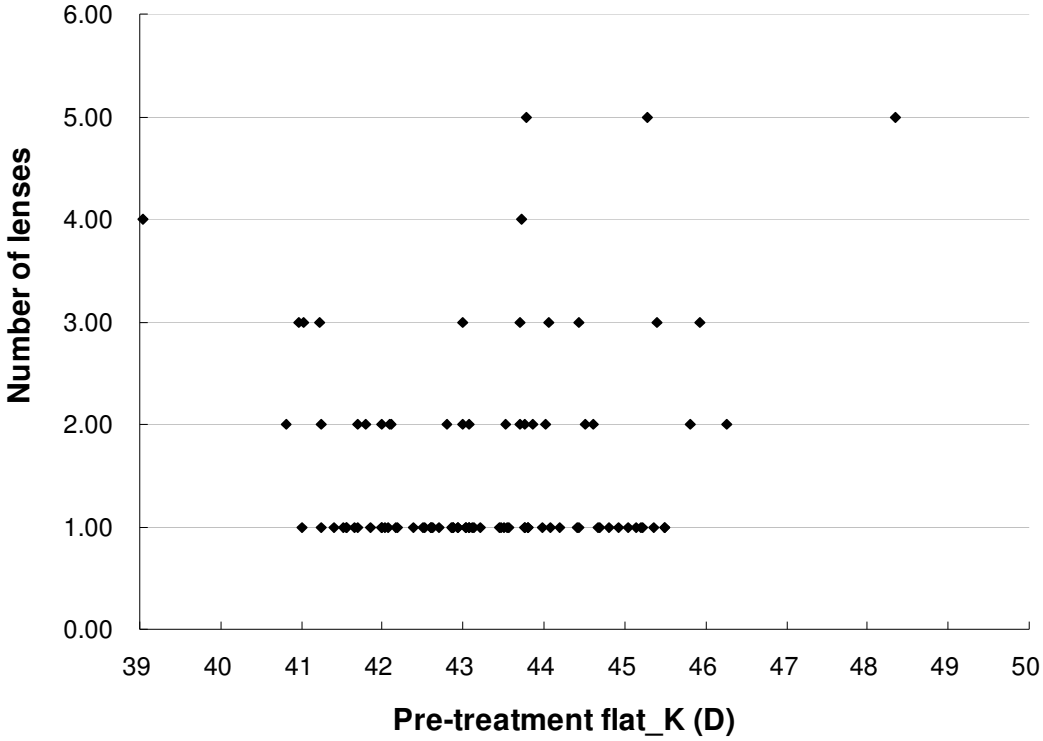


Figure A2.3 Scatter plot between number of lenses used and pre-treatment flat k-reading. Spearman r^2= 0.0002, p = 0.897 (n = 58)

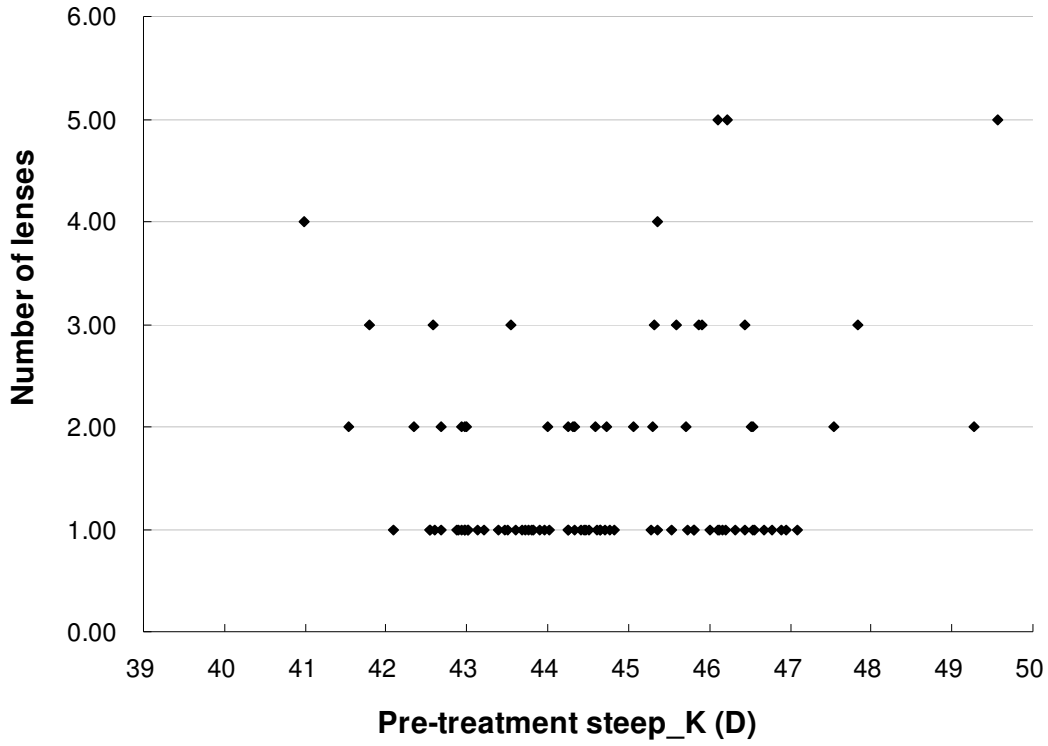


Figure A2.4 Scatter plot between number of lenses used and pre-treatment steep k-reading. Spearman $r^2 = 0.0002$, p = 0.922 (n = 58)

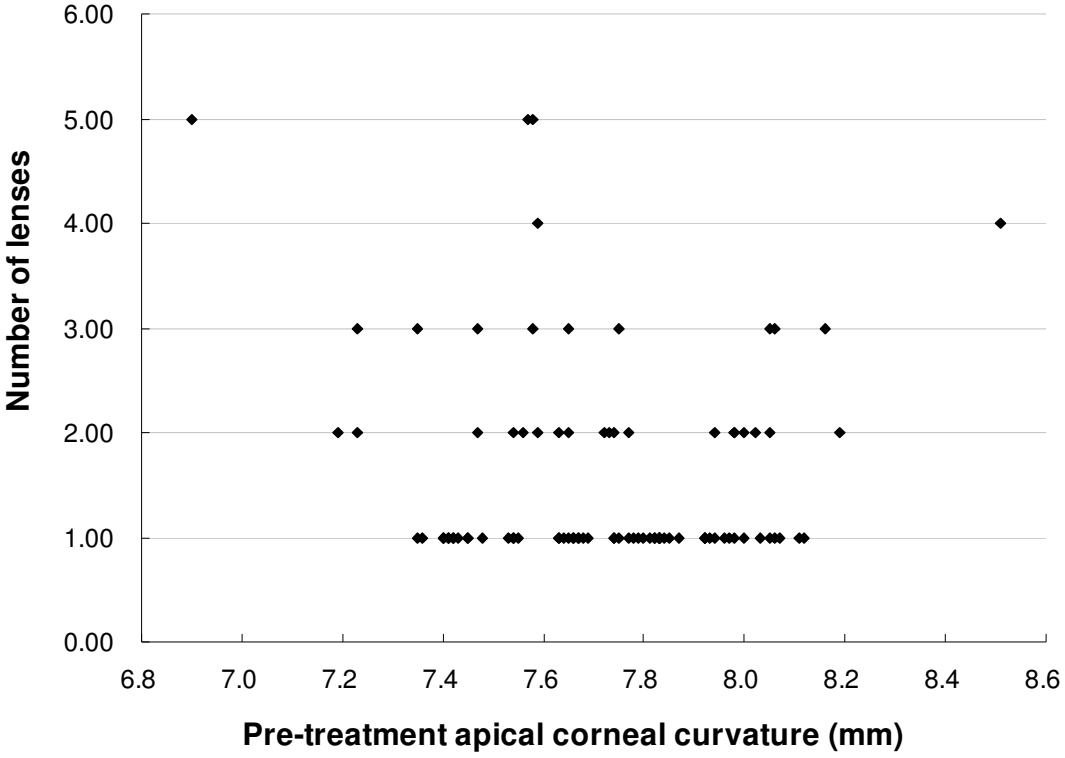


Figure A2.5 Scatter plot between number of lenses used and pre-treatment apical corneal curvature. Spearman $r^2 = 0.0001$, $p = 0.954$ (n = 58)

References

- Adams AJ. Axial length elongation, not corneal curvature, as a basis of adult onset myopia. *Am J Optom Physiol Opt*. 1987; 64: 150-152.
- Adler D, and Millodot M. The possible effect of undercorrection on myopic progression in children. *Clin Exp Optom.* 2006; 89: 315-321.
- Ahuja RP, Borchman D, Dean WL, Paterson CA, Zeng J, Zhang Z, Ferguson-Yankey S, and Yappert MC. Effect of oxidation on Ca2+ -ATPase activity and membrane lipids in lens epithelial microsomes. *Free Radic Biol Med*. 1999; 27: 177-185.
- Alharbi A, and Swarbrick HA. The effects of overnight orthokeratology lens wear on corneal thickness. *Invest Ophthalmol Vis Sci*. 2003; 44: 2518-2523.
- Alongi S, Rolando M, Macri A, Colonna A, Balestra G, Rizzetto R, and Calabria G. Bacterial load and protein deposits on 15-day versus 1-day disposable hydrophilic contact lenses. *Cornea*. 1998; 17: 146-151.
- Alpins NA. New method of targeting vectors to treat astigmatism. *J Cataract Refract Surg*. 1997; 23: 65-75.
- Ambrosio R, Jr., Tervo T, and Wilson SE. LASIK-associated dry eye and neurotrophic epitheliopathy: pathophysiology and strategies for prevention and treatment. *J Refract Surg*. 2008; 24: 396-407.

- Andreo LK. Long-term effects of hydrophilic contact lenses on myopia. *Ann Ophthalmol.* 1990; 22: 224-227, 229.
- Assil KK, Quantock AJ, Barrett AM, and Schanzlin DJ. Corneal iron lines associated with the intrastromal corneal ring. *Am J Ophthalmol.* 1993; 116: 350-356.
- Baertschi M. Short and long term success with correction of high astigmatism in orthokeratolgy. In: Global Orthokeratology Symposium. Chicago: 2005.
- Bailey IL, and Carney LG. Analyzing contact lens induced changes of the corneal curvature. *Am J Optom Arch Am Acad Optom.* 1970; 47: 761-768.
- Baker T. Ray tracing through non-spherical surfaces. *Proc Phys Soc.* 1943; 55: 361-364.
- Barr JT, Rah MJ, Jackson JM, and Jones LA. Orthokeratology and corneal refractive therapy: a review and recent findings. *Eye Contact Lens*. 2003; 29: S49-53.
- Barr JT, Rah MJ, Meyers W, and Legerton J. Recovery of refractive error after corneal refractive therapy. *Eye Contact Lens*. 2004; 30: 247-251.
- Bedrossian RH. The effect of atropine on myopia. *Ophthalmology*. 1979; 86: 713-719.
- Beerten R, Christie C, Sprater N, and Ludwig F. Improving orthokeratology

results in astigmatism. In: Poster Global Orthokeratology Symposium. Chicago: 2005.

- Behndig A, Svensson B, Marklund SL, and Karlsson K. Superoxide dismutase isoenzymes in the human eye. *Invest Ophthalmol Vis Sci.* 1998; 39: 471-475.
- Benzie IF. An automated, specific, spectrophotometric method for measuring ascorbic acid in plasma (EFTSA). *Clinical Biochemistry.* 1996; 29: 111-116.
- Benzie IFF, and Strain JJ. Ferric reducing (antioxidant) power as a measure of antioxidant capacity: the FRAP assay. In: *Oxidants and Antioxidants,* edited by Packer L. Orlando: Academic Press, 1999, p. 15-27.
- Berntsen DA, Barr JT, and Mitchell GL. The effect of overnight contact lens corneal reshaping on higher-order aberrations and best-corrected visual acuity. *Optom Vis Sci.* 2005; 82: 490-497.
- Berry EM, and Kohen R. Is the biological antioxidant system integrated and regulated? *Med Hypotheses.* 1999; 53: 397-401.
- Bilgihan A, Bilgihan K, Toklu Y, Konuk O, Yis O, and Hasanreisoglu B. Ascorbic acid levels in human tears after photorefractive keratectomy, transepithelial photorefractive keratectomy, and laser in situ keratomileusis. J *Cataract Refract Surg.* 2001; 27: 585-588.
- Binder PS. Complications associated with extended wear of soft contact lenses.

Ophthalmology. 1979; 86: 1093-1101.

- Binder PS, May CH, and Grant SC. An evaluation of orthokeratology. *Ophthalmology.* 1980; 87: 729-744.
- Boost MV, and Cho P. Microbial flora of tears of orthokeratology patients, and microbial contamination of contact lenses and contact lens accessories. *Optom Vis Sci.* 2005; 82: 451-458.
- Boscia F, Grattagliano I, Vendemiale G, Micelli-Ferrari T, and Altomare E. Protein oxidation and lens opacity in humans. Invest *Ophthalmol Vis Sci.* 2000; 41: 2461-2465.
- Brubaker RF, Bourne WM, Bachman LA, and McLaren JW. Ascorbic acid content of human corneal epithelium. Invest *Ophthalmol Vis Sci.* 2000; 41: 1681-1683.
- Brungardt TF. Fluorescein: pattern analysis and staining. *J Am Optom Assoc.* 1976; 47: 333.
- Burton TC. The influence of refractive error and lattice degeneration on the incidence of retinal detachment. *Trans Am Ophthalmol Soc.* 1989; 87: 143-155.
- Cadenas E, and Packer L. *Handbook of Antioxidants.* New York: Marcel Dekker, 1996.
- Cai J, Wu M, Nelson KC, Sternberg P, Jr., and Jones DP. Oxidant-induced

apoptosis in cultured human retinal pigment epithelial cells. *Invest Ophthalmol Vis Sci.* 1999; 40: 959-966.

- Carkeet NL, Mountford JA, and Carney LG. Predicting success with orthokeratology lens wear: a retrospective analysis of ocular characteristics. *Optom Vis Sci*. 1995; 72: 892-898.
- Carney LG. Luminance of fluorescein solutions. *Am J Optom Arch Am Acad Optom.* 1972; 49: 200-204.
- Carper DA, Sun JK, Iwata T, Zigler JS, Jr., Ibaraki N, Lin LR, and Reddy V. Oxidative stress induces differential gene expression in a human lens epithelial cell line. *Invest Ophthalmol Vis Sci.* 1999; 40: 400-406.
- Cavanagh HD, Ladage PM, Li SL, Yamamoto K, Molai M, Ren DH, Petroll WM, and Jester JV. Effects of daily and overnight wear of a novel hyper oxygen-transmissible soft contact lens on bacterial binding and corneal epithelium: a 13-month clinical trial. *Ophthalmology.* 2002; 109: 1957-1969.
- Chaiyotwittayakun A, Erskine RJ, Bartlett PC, Herd TH, Sears PM, and Harmont RJ. The effect of ascorbic acid and L-histidine therapy on acute mammary inflammation in dairy cattle. *J dairy Sci.* 2002; 85: 60-67.
- Charman WN, Mountford J, Atchison DA, and Markwell EL. Peripheral Refraction in Orthokeratology Patients. *Optom Vis Sci.* 2006; 83: 641-648.

- Chen KH, Kuang TM, and Hsu WM. Serratia Marcescens corneal ulcer as a complication of orthokeratology. *Am J Ophthalmol.* 2001; 132: 257-258.
- Cheng D, Schmid KL, and Woo GC. Myopia prevalence in Chinese-Canadian children in an optometric practice. *Optom Vis Sci.* 2007; 84: 21-32.
- Cheung SW, and Cho P. Subjective and objective assessments of the effect of orthokeratology--a cross-sectional study. *Curr Eye Res.* 2004; 28: 121-127.
- Cheung SW, Cho P, Chui WS, and Woo GC. Refractive error and visual acuity changes in orthokeratology patients. *Optom Vis Sci.* 2007; 84: 410-416.
- Cheung SW, Cho P, and Douthwaite W. Corneal shape of Hong Kong-Chinese. *Ophthalmic Physiol Opt*. 2000; 20: 119-125.
- Cheung SW, Cho P, Chan B. Astigmatic changes in orthokeratology. *Optom Vis Sci.* 2009; 86: 1352-1358.
- Chiang MF, Kouzis A, Pointer RW, and Repka MX. Treatment of childhood myopia with atropine eyedrops and bifocal spectacles. *Binocul Vis Strabismus Q*. 2001; 16: 209-215.
- Cho KS, Lee EH, Choi JS, and Joo CK. Reactive oxygen species-induced apoptosis and necrosis in bovine corneal endothelial cells. *Invest Ophthalmol Vis Sci.* 1999; 40: 911-919.
- Cho P, Cheung SW, and Edwards MH. Practice of orthokeratology by a group

of contact lens practitioners in Hong Kong--Part 1. General overview. *Clin Exp Optom*. 2002a; 85: 365-371.

- Cho P, Lam AK, Mountford J, and Ng L. The performance of four different corneal topographers on normal human corneas and its impact on orthokeratology lens fitting. *Optom Vis Sci.* 2002b; 79: 175-183.
- Cho P, Chui WS, Mountford J, and Cheung SW. Corneal iron ring associated with orthokeratology lens wear. *Optom Vis Sci.* 2002c; 79: 565-568.
- Cho P, Cheung SW, Edwards MH, and Fung J. An assessment of consecutively presenting orthokeratology patients in a Hong Kong based private practice. *Clin Exp Optom.* 2003; 86: 331-338.
- Cho P, Cheung SW, and Edwards MH. Longitudinal Orthokeratology Research In Children (LORIC) in Hong Kong: a pilot study on refractive changes and myopic control. *Curr Eye Res*. 2005a; 30: 71-80.
- Cho P, Cheung SW, Mountford J, and Chui WS. Incidence of corneal pigmented arc and factors associated with its appearance in orthokeratology. *Ophthalmic Physiol Opt*. 2005b; 25: 478-484.
- Cho P, Cheung SW, Mountford J, and White P. Good clinical practice in orthokeratology. *Cont Lens Anterior Eye*. 2008; 31: 17-28.
- Choo JD, and Holden BA. The prevention of myopia with contact lenses. *Eye*

Contact Lens. 2007; 33: 371-372.

- Choo JD, Caroline PJ, Harlin DD, Papas EB, and Holden BA. Morphologic changes in cat epithelium following continuous wear of orthokeratology lenses: A pilot study. *Cont Lens Anterior Eye.* 2008; 31: 29-37.
- Choy CK, Benzie IF, and Cho P. Ascorbic acid concentration and total antioxidant activity of human tear fluid measured using the FRASC assay. *Invest Ophthalmol Vis Sci*. 2000; 41: 3293-3298.
- Choy CK, Cho P, Chung WY, and Benzie IF. Water-soluble antioxidants in human tears: effect of the collection method. *Invest Ophthalmol Vis Sci.* 2001; 42: 3130-3134.
- Choy C, Benzie IF, and Cho P. Antioxidants in tears and plasma: Inter-relationships and effect of vitamin C supplementation. *Curr Eye Res.* 2003; 27: 55-60.
- Chua WH, Balakrishnan V, Chan YH, Tong L, Ling Y, Quah BL, and Tan D. Atropine for the treatment of childhood myopia. *Ophthalmology.* 2006; 113: 2285-2291.
- Chui WS, and Cho P. Recurrent lens binding and central island formations in a fast-responding orthokeratology lens wearer. *Optom Vis Sci.* 2003; 80: 490-494.
- Chui WS, Cho P. A comparative study of the performance of different corneal

topographers on children with respect to orthokeratology practice. *Optom Vis Sci.* 2005; 82: 420-427.

- Chung K, Mohidin N, and O'Leary DJ. Undercorrection of myopia enhances rather than inhibits myopia progression. *Vision Res*. 2002; 42: 2555-2559.
- Coon LJ. Orthokeratology. Part II: Evaluating the Tabb method. *J Am Optom Assoc*. 1984; 55: 409-418.
- Coon LJ. Orthokeratology: part I historical perspective. *J Am Optom Assoc.* 1982; 53: 187-195.
- Crouch RK, Goletz P, Snyder A, and Coles WH. Antioxidant enzymes in human tears. *J Ocul Pharmacol Ther.* 1991; 7: 253-258.
- Day J, Reim T, Bard RD, McGonagill P, and Gambino MJ. Advanced orthokeratology using custom lens designs. *Contact Lens Spectrum*. 1997; 12: 34-40.
- Delamere NA. Ascorbic acid and the eye. *Subcell Biochem.* 1996; 25: 313-329.
- Dixon JM, and Lawaczeck E. Corneal dimples and bubbles under corneal contact lenses. *Am J Ophthalmol.* 1962; 54: 827-831.
- Dontsov AE, Glickman RD, and Ostrovsky MA. Retinal pigment epithelium pigment granules stimulate the photo-oxidation of unsaturated fatty acids. *Free Radic Biol Med.* 1999; 26: 1436-1446.

- du Toit R, Vega JA, Fonn D, and Simpson T. Diurnal variation of corneal sensitivity and thickness. *Cornea.* 2003; 22: 205-209.
- Duke-Elder S. The dioptric imagery of the eye. In: *Ophthalmic optics and refraction system of ophthalmology.* Kimpton, London: Mosby, 1970.
- Edwards MH. The development of myopia in Hong Kong children between the ages of 7 and 12 years: a five-year longitudinal study. *Ophthalmic Physiol Opt.* 1999; 19: 286-294.
- Edwards MH, Li RW, Lam CS, Lew JK, and Yu BS. The Hong Kong progressive lens myopia control study: study design and main findings. *Invest Ophthalmol Vis Sci.* 2002; 43: 2852-2858.
- Edwards MH, and Lam CS. The epidemiology of myopia in Hong Kong. *Ann Acad Med Singapore.* 2004; 33: 34-38.
- Efron N. Grading scales for contact lens complications. *Ophthalmic Physiol Opt.* 1998; 18: 182-186.
- Eghbali F, Yeung KK, and Maloney RK. Topographic determination of corneal asphericity and its lack of effect on the refractive outcome of radial keratotomy. *Am J Ophthalmol.* 1995; 119: 275-280.
- Ehrlich DL, Atkinson J, Braddick O, Bobier W, and Durden K. Reduction of infant myopia: a longitudinal cycloplegic study. *Vision Res.* 1995; 35:

1313-1324.

- El Hage S, Leach NE, Miller W, Prager TC, Marsack J, Parker K, Minavi A, and Gaume A. Empirical advanced orthokeratology through corneal topography: the University of Houston clinical study. *Eye Contact Lens*. 2007; 33: 224-235.
- El Hage SG, and Leach NE. Tangential or saggital dioptric plots: is there a difference? *ICLC*. 1999; 26: 39-45.
- El Hage SG, Leach NE, and Shahin R. Controlled kerato-reformation (CKR): an alternative to refractive surgery. *Practical Optometry*. 1999; 10: 230-235.
- Erickson P, and Thorn F. Dose refractive error change twice as fast as corneal power in orthokeratology? *Am J Optom Physiol Opt.* 1977; 54: 581-587.
- Fonn D, du Toit R, Simpson TL, Vega JA, Situ P, and Chalmers RL. Sympathetic swelling response of the control eye to soft lenses in the other eye. *Invest Ophthalmol Vis Sci.* 1999; 40: 3116-3121.
- Freeman RA. Predicting stable changes in orthokeratology. *Contact Lens Forum.* 1978; 3: 21-31.
- Fulk GW, Cyert LA, and Parker DE. A randomized clinical trial of bifocal glasses for myopic children with esophoria: results after 54 months. *Optometry*. 2002; 73: 470-476.
- Fullard RJ, and Snyder C. Protein levels in nonstimulated and stimulated tears

of normal human subjects. *Invest Ophthalmol Vis Sci*. 1990; 31: 1119-1126.

- Garber JM. Overnight orthokeratology. *Optom Vis Sci.* 2001; 78: 480.
- Gogia R, Richer SP, and Rose RC. Tear fluid content of electrochemically active components including water soluble antioxidants. *Curr Eye Res.* 1998; 17: 257-263.
- Goldberg EP, Bhatia S, and Enns JB. Hydrogel contact lens-corneal interactions: a new mechanism for deposit formation and corneal injury. *CLAO J.* 1997; 23: 243-248.
- Goss DA. Effect of bifocal lenses on the rate of childhood myopia progression. *Am J Optom Physiol Opt.* 1986; 63: 135-141.
- Goss DA, Cox VD, Herrin-Lawson GA, Nielsen ED, and Dolton WA. Refractive error, axial length, and height as a function of age in young myopes. *Optom Vis Sci.* 1990; 67: 332-338.
- Grant SC, and May CH. Orthokeratology control of refractive errors through contact lenses. *J Am Optom Assoc.* 1971; 42: 1277-1283.
- Greenberg MH, and Hill RM. The physiology of contact lens imprints. *Am J Optom Arch Am Acad Optom*. 1973; 50: 699-702.
- Grosvenor T, Perrigin DM, Perrigin J, and Maslovitz B. Houston Myopia Control Study: a randomized clinical trial. Part II. Final report by the patient care team.

Am J Optom Physiol Opt. 1987; 64: 482-498.

- Grosvenor T. High axial length/corneal radius ratio as a risk factor in the development of myopia. *Am J Optom Physiol Opt.* 1988; 65: 689-696.
- Grosvenor T, Perrigin J, Perrigin D, and Quintero S. Use of silicone-acrylate contact lenses for the control of myopia: results after two years of lens wear. *Optom Vis Sci.* 1989; 66: 41-47.
- Grosvenor T, and Scott R. Three-year changes in refraction and its components in youth-onset and early adult-onset myopia. *Optom Vis Sci.* 1993; 70: 677-683.
- Guillon M, Lydon DP, and Wilson C. Corneal topography: a clinical model. *Ophthalmic Physiol Opt.* 1986; 6: 47-56.
- Guillon M, and Maissa C. Contact lens wear affects tear film evaporation. *Eye Contact Lens.* 2008; 34: 326-330.
- Gwiazda J, Hyman L, Hussein M, Everett D, Norton TT, Kurtz D, Leske MC, Manny R, Marsh-Tootle W, and Scheiman M. A randomized clinical trial of progressive addition lenses versus single vision lenses on the progression of myopia in children. *Invest Ophthalmol Vis Sci.* 2003; 44: 1492-1500.
- Halliwell B. How to characterize an antioxidant: an update. *Biochem Soc Symp.* 1995; 61: 73-101.
- Halliwell B, and Gutteridge JMC. *Free Radicals in Biology and Medicine.*

Oxford: Oxford Univeristy Press, 1999.

- Haque S, Fonn D, Simpson T, and Jones L. Corneal and epithelial thickness changes after 4 weeks of overnight corneal refractive therapy lens wear, measured with optical coherence tomography. *Eye Contact Lens.* 2004; 30: 189-193; discussion 205-186.
- Harvitt DM, and Bonanno JA. Re-evaluation of the oxygen diffusion model for predicting minimum contact lens Dk/t values needed to avoid corneal anoxia. *Optom Vis Sci.* 1999; 76: 712-719.
- Hiraoka T, Furuya A, Matsumoto Y, Okamoto F, Sakata N, Hiratsuka K, Kakita T, and Oshika T. Quantitative evaluation of regular and irregular corneal astigmatism in patients having overnight orthokeratology. *J Cataract Refract Surg.* 2004; 30: 1425-1429.
- Holden BA, and Mertz GW. Critical oxygen levels to avoid corneal edema for daily and extended wear contact lenses. *Invest Ophthalmol Vis Sci.* 1984; 25: 1161-1167.
- Holden BA, Sweeney DF, Sankaridurg PR, Carnt N, Edwards K, Stretton S, and Stapleton F. Microbial keratitis and vision loss with contact lenses. *Eye Contact Lens.* 2003; 29: S131-134.
- Holly FJ. Formation and rupture of the tear film. *Exp Eye Res.* 1973; 15:

515-525.

- Horner DG, Soni PS, Salmon TO, and Swartz TS. Myopia progression in adolescent wearers of soft contact lenses and spectacles. *Optom Vis Sci*. 1999; 76: 474-479.
- Hosaka A. Myopia prevention and therapy. The role of pharmaceutical agents. Japanese studies. *Acta Ophthalmol Suppl.* 1988; 185: 130-131.
- Hsiao CH, Yeh LK, Chao AN, Chen YF, and Lin KK. Pseudomonas aeruginosa corneal ulcer related to overnight orthokeratology. *Chang Gung Med J*. 2004; 27: 182-187.
- Hsiao CH, Lin HC, Chen YF, Ma DH, Yeh LK, Tan HY, Huang SC, and Lin KK. Infectious keratitis related to overnight orthokeratology. *Cornea*. 2005; 24: 783-788.
- Hutchinson K, and Apel A. Infectious keratitis in orthokeratology. *Clin Experiment Ophthalmol.* 2002; 30: 49-51.
- Iskeleli G, Oral AY, and Celikkol L. Changes in corneal radius and thickness in response to extended wear of rigid gas permeable contact lenses. *CLAO J.* 1996; 22: 133-135.
- Jackson JM, Bildstein T, Anderson J, Leak B, and Buresh K. Short-term corneal changes with corneal refractive therapy (CRT). *Invest Ophthalmol Vis Sci*. 2004;

45: ARVO E-Abstract 1574.

- Jagetia GC, Rajanikant GK, and Rao SK. Evaluation of the effect of ascorbic acid treatment on wound healing in mice exposed to different doses of fractionated gamma radiation. *Radiat Res*. 2003; 159: 371-380.
- Jayakumar J, and Swarbrick HA. The effect of age on short-term orthokeratology. *Optom Vis Sci.* 2005; 82: 505-511.
- Jensen H. Myopia progression in young school children. A prospective study of myopia progression and the effect of a trial with bifocal lenses and beta blocker eye drops. *Acta Ophthalmol Suppl.* 1991; 200:1-79.
- Jessen GN. Orthofocus techniques. *Contacto.* 1962; 6: 200-204.
- Joe JJ, Marsden HJ, and Edrington TB. The relationship between corneal eccentricity and improvement in visual acuity with orthokeratology. *J Am Optom Assoc.* 1996; 67: 87-97.
- Johnson KL, Carney LG, Mountford JA, Collins MJ, Cluff S, and Collins PK. Visual performance after overnight orthokeratology. *Cont Lens Anterior Eye.* 2007; 30: 29-36.
- Joslin CE, Wu SM, McMahon TT, and Shahidi M. Higher-order wavefront aberrations in corneal refractive therapy. *Optom Vis Sci.* 2003; 80: 805-811.
- Junghans BM, and Crewther SG. Little evidence for an epidemic of myopia in

Australian primary school children over the last 30 years. *BMC ophthalmol.* 2005; 5: 1.

- Kasetsuwan N, Wu FM, Hsieh F, Sanchez D, and McDonnell PJ. Effect of topical ascorbic acid on free radical tissue damage and inflammatory cell influx in the cornea after excimer laser corneal surgery. *Arch Ophthalmol*. 1999; 117: 649-652.
- Katz J, Schein OD, Levy B, Cruiscullo T, Saw SM, Rajan U, Chan TK, Yew Khoo C, and Chew SJ. A randomized trial of rigid gas permeable contact lenses to reduce progression of children's myopia. *Am J Ophthalmol*. 2003; 136: 82-90.
- Kayatz P, Heimann K, and Schraermeyer U. Ultrastructural localization of light-induced lipid peroxides in the rat retina. *Invest Ophthalmol Vis Sci.* 1999; 40: 2314-2321.
- Kerns RL. Research in orthokeratology. Part I: Introduction and background. *J Am Optom Assoc.* 1976a; 47: 1047-1051.
- Kerns RL. Research in orthokeratology. Part II: Experimental design, protocol and method. *J Am Optom Assoc*. 1976b; 47: 1275-1285.
- Kerns RL. Research in orthokeratology. Part III: results and observations. *J Am Optom Assoc.* 1976c; 47: 1505-1515.
- Kerns RL. Research in orthokeratology. Part IV: Results and observations. *J Am*

Optom Assoc. 1977a; 48: 227-238.

- Kerns RL. Research in orthokeratology. Part V: Results and observations--recovery aspects. *J Am Optom Assoc*. 1977b; 48: 345-359.
- Kerns RL. Research in orthokeratology. Part VI: statistical and clinical analyses. *J Am Optom Assoc*. 1977c; 48: 1134-1147.
- Kerns RL. Research in orthokeratology. Part VII: examination of techniques, procedures and control. *J Am Optom Assoc.* 1977d; 48: 1541-1553.
- Kerns RL. Research in orthokeratology. Part VIII: results, conclusions and discussion of techniques. *J Am Optom Assoc*. 1978; 49: 308-314.
- Khoo CY, Chong J, and Rajan U. A 3-year study on the effect of RGP contact lenses on myopic children. *Singapore Med J*. 1999; 40: 230-237.
- Kiely PM, Carney LG, and Smith G. Diurnal variations of corneal topography and thickness. Am J Optom Physiol Opt. 1982; 59: 976-982.
- Kobayashi Y, Yanai R, Chikamoto N, Chikama T, Ueda K, and Nishida T. Reversibility of effects of orthokeratology on visual acuity, refractive error, corneal topography, and contrast sensitivity. *Eye Contact Lens.* 2008; 34: 224-228.
- Koenig SB, McDonald MB, Yamaguchi T, Friedlander M, and Ishii Y. Corneal iron lines after refractive keratoplasty. *Arch Ophthalmol*. 1983; 101: 1862-1865.

- Koffler BH, and Smith VM. Myopia reduction using corneal refractive therapy contact lenses. *Eye Contact Lens.* 2004; 30: 223-226.
- Lam AK, and Douthwaite WA. Application of a modified keratometer in the study of corneal topography on Chinese subjects. *Ophthalmic Physiol Opt.* 1996; 16: 130-134.
- Lam CS, and Goh WS. The incidence of refractive errors among school children in Hong Kong and its relationship with the optical components. *Clin Exp Optom.* 1991; 74: 97-103.
- Lam CSY, and Loran DFC. Designing contact lenses for oriental eyes. *J Br Contact Lens Assoc.* 1991; 14: 109-114.
- Lam CS, Edwards M, Millodot M, and Goh WS. A 2-year longitudinal study of myopia progression and optical component changes among Hong Kong schoolchildren. *Optom Vis Sci.* 1999; 76: 370-380.
- Lang J, and Rah MJ. Adverse corneal events associated with corneal reshaping: a case series. *Eye Contact Lens.* 2004; 30: 231-233.
- Lau LI, Wu CC, Lee SM, and Hsu WM. Pseudomonas corneal ulcer related to overnight orthokeratology. *Cornea*. 2003; 22: 262-264.
- Lebow KA. Using corneal topography to evaluate the efficacy of orthokeratology fitting. *Contacto.* 1996; 39: 20-26.

- Leung JT, and Brown B. Progression of myopia in Hong Kong Chinese schoolchildren is slowed by wearing progressive lenses. *Optom Vis Sci.* 1999; 76: 346-354.
- Levy B. Permanent corneal damage in a patient undergoing orthokeratology. Am *J Optom Physiol Opt.* 1982; 59: 697-699.
- Liang JB, Chou PI, Wu R, and Lee YM. Corneal iron ring associated with orthokeratology. *J Cataract Refract Surg*. 2003; 29: 624-626.
- Lin LL, Shih YF, Lee YC, Hung PT, and Hou PK. Changes in ocular refraction and its components among medical students--a 5-year longitudinal study. *Optom Vis Sci.* 1996; 73: 495-498.
- Lin LL, Shih YF, Hsiao CK, Chen CJ, Lee LA, and Hung PT. Epidemiologic study of the prevalence and severity of myopia among schoolchildren in Taiwan in 2000. *J Formos Med Assoc*. 2001; 100: 684-691.
- Lipson MJ. Long-term clinical outcomes for overnight corneal reshaping in children and adults. *Eye Contact Lens.* 2008; 34: 94-99.
- Lipson MJ, Sugar A, Musch DC. Overnight corneal reshaping versus soft disposable contact lenses: vision-related quality-of-life differences from a randomized clinical trial. *Optom Vis Sci.* 2005; 82: 886-891.
- Lu F, Jiang J, Qu J, Jin W, Mao X, and Shen Y. Clinical study of orthokeratology

in young myopic adolescents. *ICLC.* 1999; 26: 113-116.

- Lu F, Simpson T, Sorbara L, and Fonn D. The relationship between the treatment zone diameter and visual, optical and subjective performance in Corneal Refractive Therapy lens wearers. *Ophthalmic Physiol Opt*. 2007; 27: 568-578.
- Lui WO, and Edwards MH. Orthokeratology in low myopia. Part 1: efficacy and predictability. *Cont Lens Anterior Eye.* 2000a; 23: 77-89.
- Lui WO, and Edwards MH. Orthokeratology in low myopia. Part 2: corneal topographic changes and safety over 100 days. *Cont Lens Anterior Eye.* 2000b; 23: 90-99.
- Maldonado-Codina C, Efron S, Morgan P, Hough T, and Efron N. Empirical versus trial set fitting systems for accelerated orthokeratology. *Eye Contact Lens.* 2005; 31: 137-147.
- Margolis SA, and Duewer DL. Measurement of ascorbic acid in human plasma and serum: stability, intralaboratory repeatability, and interlaboratory reproducibility. *Clin Chem*. 1996; 42: 1257-1262.
- Matsubara M, Kamei Y, Takeda S, Mukai K, Ishii Y, and Ito S. Histologic and Histochemical Changes in Rabbit Cornea Produced by an Orthokeratology Lens. *Eye Contact Lens*. 2004; 30: 198-204.
- McCarty CA, Mukesh BN, Fu CL, and Taylor HR. The epidemiology of cataract

in Australia. *Am J Ophthalmol.* 1999; 128: 446-465.

- Mika R, Morgan B, Cron M, Lotoczky J, and Pole J. Safety and efficacy of overnight orthokeratology in myopic children. *Optometry.* 2007; 78: 225-231.
- Miles PW. A study of heterophoria and myopia in children. Some of whom wore bifocal lenses. *Am J Ophthalmol.* 1962; 54: 111-114.
- Moezzi AM, Fonn D, and Simpson TL. Overnight corneal swelling with silicone hydrogel contact lenses with high oxygen transmissibility. *Eye Contact Lens.* 2006; 32: 277-280.
- Moore JC, and Tiffany JM. Human ocular mucus. Origins and preliminary characterisation. *Exp Eye Res*. 1979; 29: 291-301.
- Mountford J. An analysis of the changes in corneal shape and refractive error induced by accelerated orthokeratology. *ICLC.* 1997a; 24: 128-144.
- Mountford J. Orthokeratology. In: *Contact Lenses*, edited by Philips AJ, Speedwell L, Stone J, and Hough TBoston: Butterworth-Heinemann, 1997b, p. 653-692.
- Mountford J. *Orthokeratology: principles and practice*. London ; Philadelphia: Butterworth-Heinemann, 2004.
- Mountford J. Retention and regression of orthokeratology with time. *ICLC.* 1998; 25: 59-64.

- Mountford J. Spherical aberration, corneal shape and orthokeratology. In: Lecture presented at the 3rd Global Orthokeratology Symposium. Chicago, USA: 2005.
- Mountford J, Cho P, and Chui WS. Is fluorescein pattern analysis a valid method of assessing the accuracy of reverse geometry lenses for orthokeratology? *Clin Exp Optom.* 2005; 88: 33-38.
- Mountford J, and Noack D. A mathematical model for corneal shape changes associated with ortho-k. *Contact Lens Spectrum*. 1998; 13: 39-45.
- Mountford J, and Pesudovs K. An analysis of the astigmatic changes induced by accelerated orthokeratology. *Clin Exp Optom*. 2002; 85: 284-293.
- Munnerlyn CR, Koons SJ, and Marshall J. Photorefractive keratectomy: a technique for laser refractive surgery. *J Cataract Refract Surg*. 1988; 14: 46-52.
- Mutti DO, Zadnik K, and Adams AJ. Myopia. The nature versus nurture debate goes on. *Invest Ophthalmol Vis Sci*. 1996; 37: 952-957.
- Neilson R, May C, and Grant SC. Emmetropization through contact lenses. *Contacto.* 1964; 8: 20-21.
- Nichols JJ, Marsich MM, Nguyen M, Barr JT, and Bullimore MA. Overnight orthokeratology. *Optom Vis Sci.* 2000; 77: 252-259.
- Oakley KH, and Young FA. Bifocal control of myopia. *Am J Optom Physiol Opt.*

1975; 52: 758-764.

- Orsborn GN, Zantos SG, Godio LB, Jones WF, and Barr JT. Aspheric rigid gas permeable contact lenses: practitioner discrimination of base curve increments using fluorescein pattern evaluation. *Optom Vis Sci.* 1989; 66: 209-213.
- Owens H, Garner LF, Craig JP, and Gamble G. Posterior corneal changes with orthokeratology. *Optom Vis Sci.* 2004; 81: 421-426.
- Parssinen O, Hemminki E, and Klemetti A. Effect of spectacle use and accommodation on myopic progression: final results of a three-year randomised clinical trial among schoolchildren. *Br J Ophthalmol.* 1989; 73: 547-551.
- Patel S, Plaskow J, and Ferrier C. The influence of vitamins and trace element supplements on the stability of the pre-corneal tear film. *Acta Ophthalmol.* 1993; 71: 825-829.
- Paterson CA, and O'Rourke MC. Vitamin C levels in human tears. *Arch Ophthalmol*. 1987; 105: 376-377.
- Patterson TC. Orthokeratology: changes to the corneal curvature and the effect on refractive power due to the sagittal length change. *J Am Optom Assoc.* 1975; 46: 719-729.
- Perkins ES. Glaucoma in the younger age groups. *Arch Ophthalmol.* 1960; 64: 882-891.

- Perrigin J, Perrigin D, Quintero S, and Grosvenor T. Silicone-acrylate contact lenses for myopia control: 3-year results. *Optom Vis Sci.* 1990; 67: 764-769.
- Polse KA, Brand RJ, Schwalbe JS, Vastine DW, and Keener RJ. The Berkeley Orthokeratology Study, Part II: Efficacy and duration. *Am J Optom Physiol Opt.* 1983; 60: 187-198.
- Polse KA, Graham AD, Fusaro RE, Gan CM, Rivera RK, Lin MC, Sanders TL, McNamara NA, and Chan JS. The Berkeley Contact Lens Extended Wear Study. Part II : Clinical results. *Ophthalmology*. 2001; 108: 1389-1399.
- Poole TR, Frangouli O, and Ionides AC. Microbial keratitis following orthokeratology. *Eye*. 2003; 17: 440-441.
- Probst LE, Almasswary MA, and Bell J. Pseudo-Fleischer ring after hyperopic laser in situ keratomileusis. *J Cataract Refract Surg.* 1999; 25: 868-870.
- Quinto GG, Camacho W, and Behrens A. Postrefractive surgery dry eye. *Curr Opin Ophthalmol.* 2008; 19: 335-341.
- Rah MJ, Jackson JM, Jones LA, Marsden HJ, Bailey MD, and Barr JT. Overnight orthokeratology: preliminary results of the Lenses and Overnight Orthokeratology (LOOK) study. *Optom Vis Sci*. 2002a; 79: 598-605.
- Rah MJ, Barr JT, and Bailey MD. Corneal pigmentation in overnight orthokeratology: a case series. *Optometry.* 2002b; 73: 425-434.

- Reim T. US Patent and Trademark Office. USA: 1999.
- Richer SP, and Rose RC. Water soluble antioxidants in mammalian aqueous humor: interaction with UV B and hydrogen peroxide. *Vision Res*. 1998; 38: 2881-2888.
- Ritchey ER, Barr JT, and Mitchell GL. The Comparison of Overnight Lens Modalities (COLM) study. *Eye Contact Lens.* 2005; 31: 70-75.
- Rose RC, Richer SP, and Bode AM. Ocular oxidants and antioxidant protection. *Proc Soc Exp Biol Med*. 1998; 217: 397-407.
- Rozanowska M, Wessels J, Boulton M, Burke JM, Rodgers MA, Truscott TG, and Sarna T. Blue light-induced singlet oxygen generation by retinal lipofuscin in non-polar media. *Free Radic Biol Med*. 1998; 24: 1107-1112.
- Saw SM, Gazzard G, Shih-Yen EC, and Chua WH. Myopia and associated pathological complications. *Ophthalmic Physiol Opt.* 2005; 25: 381-391.
- Shih YF, Hsiao CK, Chen CJ, Chang CW, Hung PT, and Lin LL. An intervention trial on efficacy of atropine and multi-focal glasses in controlling myopic progression. *Acta Ophthalmol Scand*. 2001; 79: 233-236.
- Shimmura S, Suematsu M, Shimoyama M, Tsubota K, Oguchi Y, and Ishimura Y. Subthreshold UV radiation-induced peroxide formation in cultured corneal epithelial cells: the protective effects of lactoferrin. *Exp Eye Res.* 1996; 63:

519-526.

- Siatkowski RM, Cotter S, Miller JM, Scher CA, Crockett RS, and Novack GD. Safety and efficacy of 2% pirenzepine ophthalmic gel in children with myopia: a 1-year, multicenter, double-masked, placebo-controlled parallel study. *Arch Ophthalmol.* 2004; 122: 1667-1674.
- Siatkowski RM, Cotter SA, Crockett RS, Miller JM, Novack GD, and Zadnik K. Two-year multicenter, randomized, double-masked, placebo-controlled, parallel safety and efficacy study of 2% pirenzepine ophthalmic gel in children with myopia. *J Aapos.* 2008.
- Sima J, Zhou J, Luo Z, and Chen R. Result of orthokeratology for treatment of young people with myopia. *Yan Ke Xue Bao.* 2000; 16: 149-152.
- Smirennaia E, Kourenkov V, Chesnokova NB, and Kuznetsova TR. Antioxidant activity of tear fluid and antioxidant therapy in myopic patients after laser in situ keratomileusis. *J Refract Surg.* 2002; 18: S364-365.
- Soni PS, Nguyen TT, and Bonanno JA. Overnight orthokeratology: refractive and corneal recovery after discontinuation of reverse-geometry lenses. *Eye Contact Lens.* 2004; 30: 254-262.
- Soni PS, Nguyen TT, and Bonanno JA. Overnight orthokeratology: visual and corneal changes. *Eye Contact Lens*. 2003; 29: 137-145.

- Sorbara L, Fonn D, Simpson T, Lu F, and Kort R. Reduction of myopia from corneal refractive therapy. *Optom Vis Sci.* 2005; 82: 512-518.
- Spindel GP, and Perry HD. Serious corneal complications associated with extended-wear soft contact lenses for myopia. *Ann Ophthalmol.* 1986; 18: 141-143.
- Sridharan R, and Swarbrick H. Corneal response to short-term orthokeratology lens wear. *Optom Vis Sci.* 2003; 80: 200-206.
- Stapleton F, Phillips AJ, and Hopkins GA. Drugs and solutions in contact lens practice and related microbiology. In: *Contact Lenses*, edited by Phillips AJ, and Speedwell L. London: Butterworth-Heinemann, 1997.
- Steinberg EB, Wilson LA, Waring GO, Lynn MJ, and Coles WH. Stellate iron lines in the corneal epithelium after radial keratotomy. *Am J Ophthalmol.* 1984; 98: 416-421.
- Stillitano I, Maidana E, Lui M, Lipener C, and Hofling-Lima AL. Bubble and corneal dimple formation after the first overnight wear of an orthokeratology lens: a case series. *Eye Contact Lens*. 2007; 33: 253-258.
- Sun X, Zhao H, Deng S, Zhang Y, Wang Z, Li R, Luo S, and Jin X. Infectious keratitis related to orthokeratology. *Ophthalmic Physiol Opt.* 2006; 26: 133-136.
- Swarbrick H. Mind your p's and Q's! (or describing corneal shape). In: Lecture

presented at the 2nd Global Orthokeratology Symposium. Toronto, Canada: 2004.

- Swarbrick HA. Orthokeratology review and update. *Clin Exp Optom*. 2006; 89: 124-143.
- Swarbrick HA, and Holden BA. Rigid gas permeable lens binding: significance and contributing factors. *Am J Optom Physiol Opt.* 1987; 64: 815-823.
- Swarbrick HA, and Holden BA. Rigid gas-permeable lens adherence: a patient-dependent phenomenon. *Optom Vis Sci*. 1989; 66: 269-275.
- Swarbrick HA, Wong G, and O'Leary DJ. Corneal response to orthokeratology. *Optom Vis Sci.* 1998; 75: 791-799.
- Sweeney DF, and Holden BA. Silicone elastomer lens wear induces less overnight corneal edema than sleep without lens wear. *Curr Eye Res.* 1987; 6: 1391-1394.
- Tahhan N, Du Toit R, Papas E, Chung H, La Hood D, and Holden AB. Comparison of reverse-geometry lens designs for overnight orthokeratology. *Optom Vis Sci*. 2003; 80: 796-804.
- Tan DT, Lam DS, Chua WH, Shu-Ping DF, and Crockett RS. One-year multicenter, double-masked, placebo-controlled, parallel safety and efficacy study of 2% pirenzepine ophthalmic gel in children with myopia. *Ophthalmology.*

2005; 112: 84-91.

- Tang W, Collins MJ, Carney L, and Davis B. The accuracy and precision performance of four videokeratoscopes in measuring test surfaces. *Optom Vis Sci.* 2000; 77: 483-491.
- Taylor A, Jacques PF, Nowell T, Perrone G, Blumberg J, Handelman G, Jozwiak B, and Nadler D. Vitamin C in human and guinea pig aqueous, lens and plasma in relation to intake. *Curr Eye Res.* 1997; 16: 857-864.
- Tseng CH, Fong CF, Chen WL, Hou YC, Wang IJ, and Hu FR. Overnight orthokeratology-associated microbial keratitis. *Cornea.* 2005; 24: 778-782.
- Tsukiyama J, Miyamoto Y, Higaki S, Fukuda M, and Shimomura Y. Changes in the anterior and posterior radii of the corneal curvature and anterior chamber depth by orthokeratology. *Eye Contact Lens.* 2008; 34: 17-20.
- Uceda-Montanes A, Tomas JD, and Alio JL. Correction of severe ectasia after LASIK with intracorneal ring segments. *J Refract Surg.* 2008; 24: 408-411.
- Vaxman F, Olender S, Lambert A, Nisand G, Aprahamian M, Bruch JF, Didier E, Volkmar P, and Grenier JF. Effect of pantothenic acid and ascorbic acid supplementation on human skin wound healing process. A double-blind, prospective and randomized trial. *Eur Surg Res.* 1995; 27: 158-166.
- Vongthongsri A, Chuck RS, and Pepose JS. Corneal iron deposits after laser in

situ keratomileusis. *Am J Ophthalmol.* 1999; 127: 85-86.

- Walline JJ, Rah MJ, and Jones LA. The Children's Overnight Orthokeratology Investigation (COOKI) pilot study. *Optom Vis Sci.* 2004a; 81: 407-413.
- Walline JJ, Jones LA, Mutti DO, and Zadnik K. A randomized trial of the effects of rigid contact lenses on myopia progression. *Arch Ophthalmol.* 2004b; 122: 1760-1766.
- Wallman J. Nature and nurture of myopia. *Nature. 1*994; 371: 201-202.
- Wang IJ, Chiou CJ, Fung JF, Chu JM, and Hu FR. One-year outcome of overnight orhtokeratology in Taiwanese children and adolescents. *Tzu Chi Med J.* 2005; 17: 27-33.
- Wang J, Fonn D, Simpson TL, Sorbara L, Kort R, and Jones L. Topographical thickness of the epithelium and total cornea after overnight wear of reverse-geometry rigid contact lenses for myopia reduction. *Invest Ophthalmol Vis Sci*. 2003; 44: 4742-4746.
- Wang JC, and Lim L. Unusual morphology in orthokeratology contact lens-related cornea ulcer. *Eye Contact Lens*. 2003; 29: 190-192.
- Watt KG, and Swarbrick HA. Trends in microbial keratitis associated with orthokeratology. *Eye Contact Lens*. 2007; 33: 373-377.
- Williams RN, and Paterson CA. A protective role for ascorbic acid during

inflammatory episodes in the eye. *Exp Eye Res.* 1986; 42: 211-218.

- Wlodyga RJ, and Bryla C. Corneal molding: the easy way. *Contact Lens Spectrum.* 1989; 4: 58-65.
- Wolff E. The muco-cutaneous junction of the lid-margin and the distribution of the tear fluid. *Trans Ophthalmol Soc UK*. 1946; 66: 291-308.
- Xuguang S, Lin C, Yan Z, Zhiqun W, Ran L, Shiyun L, and Xiuying J. Acanthamoeba keratitis as a complication of orthokeratology. *Am J Ophthalmol.* 2003; 136: 1159-1161.
- Yap M, Wu M, Liu ZM, Lee FL, and Wang SH. Role of heredity in the genesis of myopia. *Ophthalmic Physiol Opt.* 1993; 13: 316-319.
- Young AL, Leung AT, Cheung EY, Cheng LL, Wong AK, and Lam DS. Orthokeratology lens-related Pseudomonas aeruginosa infectious keratitis. *Cornea.* 2003; 22: 265-266.
- Young AL, Leung AT, Cheng LL, Law RW, Wong AK, and Lam DS. Orthokeratology lens-related corneal ulcers in children: a case series. *Ophthalmology.* 2004; 111: 590-595.
- Yue BY. The extracellular matrix and its modulation in the trabecular meshwork. Surv Ophthalmol. 1996; 40: 379-390.
- Zadnik K, Satariano WA, Mutti DO, Sholtz RI, and Adams AJ. The effect of

parental history of myopia on children's eye size. *JAMA*. 1994; 271: 1323-1327.

- Zadnik K, and Mutti DO. Myopia--a challenge to optometric research. *J Am Optom Assoc.* 1995; 66: 145-146.
- Zigman S, Schultz JB, and Schultz M. Measurement of oxygen production by in vitro human and animal lenses with an oxygen electrode. *Curr Eye Res.* 1998; 17: 115-119.