# COMBINED ATROPINE WITH ORTHOKERATOLOGY IN CHILDHOOD MYOPIA CONTROL (AOK) – A RANDOMIZED CONTROLLED TRIAL

QI TAN

PhD

THE HONG KONG POLYTECHNIC UNIVERSITY

2021

The Hong Kong Polytechnic University

School of Optometry

# Combined Atropine with OrthoKeratology in Childhood Myopia Control (AOK) – A Randomized Controlled Trial

Qi Tan

A thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy

March 2021

# CERTIFICATE OF ORIGINALITY

I hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, it produces 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.

Qi Tan

# Abstract

The mechanism underlying the control effect of atropine or orthokeratology (ortho-k) in retarding myopia progression in children is unclear. The former treatment is believed to act via muscarinic receptors in the eye (e.g. retina, choroid, and sclera) and the latter via an optical mechanism. There may be an additive effect in controlling myopia progression if atropine is combined with ortho-k. A 2-year randomized controlled trial was performed to explore whether combining 0.01% atropine with ortho-k (AOK) would result in less axial elongation than ortho-k alone (OK). As it has been well-documented in previous randomized studies that 0.01% atropine has negligible side-effects compared to those at higher concentrations, this concentration of atropine was used in the current study. To gain a better understanding of the mechanism underlying a possible additive effect if 0.01% atropine was used together with ortho-k, measurements of mesopic and photopic pupil sizes, the amplitude of accommodation, choroidal thickness, and ocular aberrations, which include lower-order (LOA) and higher-order aberrations (HOA) were performed.

After two years, significantly less axial elongation was observed in AOK than in OK subjects (mean ± SD, 0.17 ± 0.20 mm vs 0.31 ± 0.19 mm), indicating that an additive effect exists when 0.01% atropine is used in conjunction with ortho-k for myopia control. Also, the combined treatment was well tolerated by subjects, with no difference in the percentages of occurrence of adverse events, although more symptoms of photophobia (12% vs zero) and haloes (12% vs 6%) were reported by

AOK subjects. However, these symptoms were transient and/or well-tolerated, and no inconvenience was reported by subjects.

Comparison of choroidal thickness changes over two years between subjects undergoing AOK and those receiving OK revealed greater choroidal thickening in the former group at all visits (e.g. 24-month visit, 20.9 ± 21.5 μm vs -4.9 ± 15.6 μm). Furthermore, choroidal thickening was associated with slower axial elongation in both treatment groups over two years, suggesting that the magnitude of choroidal thickening, seemingly a treatment response, may play a role in the treatment effect of either combined 0.01% atropine and ortho-k or ortho-k alone.

After commencement of the treatments, no difference in retinal image quality was observed between the two groups, despite a significant reduction in LOA and an increase in HOA for a 3-mm pupil in both groups. The key findings were that slower axial eye growth was associated with a greater increase in the RMS values of total HOA and Coma, a greater decrease in the RMS value of LOA, a higher level of some HOA terms (e.g. vertical coma) for a photopic pupil in the AOK group, whereas no associations were observed between axial eye growth and any of the aberration metrics in the OK group. This suggests that an optical mechanism involving the changes in the profile of ocular aberrations may underly an additive effect of the combined treatment of 0.01% atropine and ortho-k when compared with ortho-k alone.

# Acknowledgments

I would like to express my special thanks of gratitude to my chief supervisor Prof Pauline Cho, who allowed me this golden opportunity to perform research on myopia control in children. Her principled stance on conducting research impacted me profoundly, and the training from her has changed my way of work and completely reshaped my perspective of viewing the world.

Secondly, I would like to thank Dr Alex Ng and Dr Bonnie Choy, who followed subjects undergoing treatment of atropine eye drops in the research project. I appreciated the time they squeezed out of their busy work schedule, and that they attended subjects with great tenderness and care. I am grateful for the help of Dr George Cheng and Dr Victor Woo in help finishing this research project. I am also grateful to Dr Maureen Boost and Dr Stephen Vincent who provided help in revising this thesis and corresponding manuscripts.

Many thanks to Dr Peggy Cheung and Dr Jason Lau for their precious advice and assistance concerning research work and working attitudes, which resulted in a more efficient output from my PhD study. I would like to thank Mr Ken Wan, Miss Ella Guo, and Miss Grace Yang for their interactions during this research journey.

I would like to thank all the subjects and their parents for devoting their valuable time in participating in and cooperating with our research schedule that finally contributed to a research of quality.

Also, I would like to thank the organizers of the Teaching Postgraduate

Studentship (TPS) Scheme provided by The Hong Kong Polytechnic University. Thanks also to Precision Technology Services (Vancouver, B.C., Canada) that sponsored the contact lenses, Ophtecs Corporation (Japan) that supported the contact lens solutions used, and Aseptic Innovative Medicine Co., Ltd. (Taiwan) that partially sponsored Atropine eye drops used in the research project.

Lastly, I would like to express my sincere gratitude to my husband Hongliang Yuan (袁红亮) and my son Congshu Yuan (袁从舒), who provided full support to my study in Hong Kong. Our separation due to distance caused great sadness, but there was never a single word of complaint and they always firmly supported me to accomplish my work.

Thank you all from the bottom of my heart.

# Table of contents

# List of figures

# List of tables

# List of abbreviations

| | |
|---|---|
| AOK | Atropine with Orthokeratology |
| ATOM | Atropine Treatment Of childhood Myopia |
| BID | Bis in die (Twice daily) |
| BOZD | Back optic zone diameters |
| BS | Bifocal Spectacles |
| CI | Confidence Interval |
| CLAMP | Contact Lens And Myopia Progression |
| CR | Coefficient(s) of repeatability |
| COAS | Complete ophthalmic analysis system |
| Coma | Coma-like aberrations |
| COMET | Correction Of Myopia Evaluation Trial |
| D | Diopter |
| GWAS | Genome-Wide Association Studies |
| HOA | Higher-order aberration(s) |
| HM-PRO | High myopia – Partial Reduction Orthokeratology |
| ICC | Intraclass Correlation Coefficient |
| IR | Insertion and Removal |
| LAMP | Low-concentration Atropine for Myopia Progression |
| LoA | Limits of Agreement |
| LOA | Lower-Order Aberration(s) |
| logMAR | logarithm of the Minimum Angle of Resolution |

| | |
|---|---|
| OCT | Optical Coherence Tomography |
| OK | Orthokeratology alone |
| Ortho-k | Orthokeratology |
| PAS | Progressive Addition Spectacles |
| PD | Pupillary Distance |
| RGP | Rigid Gas Permeable |
| RM ANOVA | Repeated Measures Analyses of Variance |
| RMS | Root-Mean-Square |
| ROC | Recess Outside the Classroom program |
| ROMIO | Retardation of Myopia in Orthokeratology |
| SA | Spherical-like Aberrations |
| SCL | Soft Contact Lens(es) |
| SD | Standard Deviation |
| SD-OCT | Spectral Domain Optical Coherence Tomography |
| SER | Spherical Equivalent Refraction (negative power, unless otherwise specified) |
| SRRG | Soft Radial Refractive Gradient |
| SVS | Single Vision Spectacles |
| TID | Ter In Die (three times daily) |
| TO-SEE | Toric Orthokeratology – Slowing Eyeball Elongation |
| VA | Visual Acuity |
| VOLTZ | Orthokeratology Lens Treatment Zone |
| VST | Visual Strehl Ratio |
| UVA | Unaided Visual Acuity |

# Chapter 1 Literature review

## 1.1 Introduction to myopia

### 1.1.1 Myopia: a threat to ocular health

Regardless of the various classifications used for myopia (Table 1.1), over 95% of human myopia is characterized by a longer than normal axial length (McBrien & Gentle 2003). The threshold for myopia in terms of spherical equivalent refraction (SER) is not universal, with values of at least 0.25, 0.50, or 0.75 diopters (D) used as cut-off points in epidemiological studies (Negrel et al. 2000, Fan et al. 2004, Lin et al. 2004, Dirani et al. 2010, Mutti et al. 2011, French et al. 2013), and no accepted threshold for myopia has been established in terms of axial length (Meng et al. 2011).

In 2020, it was estimated that 34.0% and 5.2% of the world population were affected by myopia and high myopia (at least 5.00 D), respectively (Holden et al. 2016). Myopia has become a major threat to ocular health, as a dose-dependent relationship has been well-documented between myopia and sight-threatening ocular diseases, including myopic maculopathy (Vongphanit et al. 2002, Liu et al. 2010, Gao et al. 2011, Asakuma et al. 2012), open-angle glaucoma (Mitchell et al. 1999, Xu et al. 2007, Marcus et al. 2011, Shen et al. 2016), posterior subcapsular cataract (Lim et al. 1999, Chang et al. 2005), and idiopathic rhegmatogenous retinal detachment (Huang et al. 2019, Tsai et al. 2019). The major goal of controlling myopia progression in children is to reduce the risk of myopia-related sight-threatening ocular diseases in adulthood.

Table 1.1 Classification of myopia

| Criteria | Category | Definition |
|---|---|---|
| Age of onset (Grosvenor 1987) | Congenital myopia | Present at birth |
| | Youth-onset myopia | Onset between 6 and 20 years old |
| | Early adult-onset myopia | Onset between 20 and 40 years old |
| | Late adult-onset myopia | Onset over 40 years old |
| Presence of elongation of axial length (Emsley 1955) | Axial myopia | Due to axial elongation |
| | Refractive myopia | Due to abnormal index/curvature of ocular component/anomalies in anterior chamber depth |
| Severity of refractive error (Cline et al. 1997) | Mild myopia | Up to 3.00 D |
| | Moderate myopia | Between 3.00 D and 6.00 D |
| | High myopia | Over 6.00 D* |
| Clinical entity (Goss et al. 1997) | Simple myopia | Less than 6.00 D and without pathology |
| | Nocturnal myopia | Due to increased accommodative response in dim illumination |
| | Pseudomyopia | Due to overstimulation of ocular accommodation |
| | Pathologic myopia | With posterior eye degeneration |
| | Acquired myopia | Reversible (e.g. exposure to pharmaceutical agents) |

* The definition of high myopia is different among studies, as it can be defined as having equivalent refraction of at least 5.00 D or 6.00 D or 8.00 D, or axial length of greater than 25.5 mm, 26.0 mm, or 26.5 mm (Shih et al. 2006, Hayashi et al. 2010, Gao et al. 2011, Asakuma et al. 2012). However, equivalent refraction of at least 6.00 D was commonly accepted as the threshold value to define high myopia in peer-reviewed literature (Flitcroft et al. 2019).

## 1.1.2 Etiology of myopia

### 1.1.2.1 Hyperopic peripheral defocus

In contrast to the situation in hyperopic children, myopic unaided eyes tend to show hyperopic defocus in the periphery (Mutti et al. 2000, Chen et al. 2010, Lee & Cho 2013). Hyperopic peripheral defocus has been suggested to be a causative factor for myopic progression, after the observation that young adult pilots with hyperopic

peripheral defocus were more likely to become myopic (Hoogerheide et al. 1971). In addition, a longitudinal study has shown that emmetropes, who eventually became myopic, started to exhibit hyperopic relative peripheral defocus (SER in primary gaze subtracted from SER in temporal gaze) two years before myopia onset (Mutti et al. 2007), suggesting that hyperopic peripheral defocus may act as a stimulus to myopia onset. However, a subsequent study reported no significant association between the amount of hyperopic relative peripheral defocus and the onset of childhood myopia, suggesting that peripheral refraction cannot predict onset of myopia (Mutti et al. 2011). In existing myopes, insignificant association between baseline hyperopic relative peripheral defocus and myopia progression was found in studies conducted solely in Asian children (Sng et al. 2011, Lee & Cho 2013). However, these studies were limited to assessing the peripheral defocus by subtracting axial refraction from that at the temporal retina with eccentricity of 30 degrees (Mutti et al. 2011, Sng et al. 2011, Lee & Cho 2013), which may not be accurate to outline the defocus imposed on the peripheral retina. Although there was no solid evidence to support hyperopic peripheral defocus as an etiology of myopia onset in humans, future studies are warranted to further the understanding of the role of hyperopic peripheral defocus in axial eye growth.

#### 1.1.2.2 Accommodative lag

Accommodative lag has been commonly observed in myopic children, particularly fully corrected myopic children, who accommodate significantly less

during near work than their emmetropic peers (Gwiazda et al. 1993, Gwiazda et al. 2005). By extrapolating from the findings of animal studies on hyperopic defocus, it was hypothesized that this lag in accommodation while performing near work, which produces prolonged periods of foveal hyperopic defocus, may potentially result in axial elongation and myopia progression (Gwiazda et al. 1993, Charman 1999).

However, a longitudinal observational study demonstrated that accommodative lag in pre-school children was not elevated before or during the onset of myopia and that an increase was observed only after the onset of myopia (Mutti et al. 2006). A subsequent analysis was performed on the same ethnically diverse study sample, which showed that neither lag at the beginning nor the end of a yearly progression interval was associated with annual myopia progression (Berntsen et al. 2011). Thus, accommodative lag is suggested to be a product rather than a cause of myopia (Mutti et al. 2006, Berntsen et al. 2011). This conclusion was supported by other longitudinal studies, which found a non-significant association between accommodative lag and myopia progression (Weizhong et al. 2008, Koomson et al. 2016).

#### 1.1.2.3 Ocular higher-order aberrations

Unlike ocular lower-order aberrations (LOA), which mainly consist of astigmatism and defocus and can be corrected optically (i.e. sphero-cylindrical correction), higher-order aberrations (HOA) cannot be corrected using conventional optical methods (Charman 2005). HOA, optical imperfections that can lead to a decrease in image quality on the retina, have been proposed to account for myopia progression (Charman 2005). To date, only four longitudinal studies have investigated

the relationship between ocular HOA and myopia progression in myopic children with no anti-myopia treatment. Zhang et al. found more HOA was associated with greater myopia progression, in terms of averaged annual change in cycloplegic refractive errors, in a cohort of myopic children with a mean age of 12.1 years, and also noted that slower myopia progression was associated with more coma and trefoil (Zhang et al. 2013). Conversely, a negative association between axial elongation and ocular HOA was reported by Hiraoka et al., along with slower axial growth associated with positively shifted spherical aberration, in a younger cohort with a mean age of 9.2 years (Hiraoka et al. 2017).

A retrospective study by Lau et al., demonstrated that individual HOA terms, such as spherical aberration and vertical and oblique trefoil, were associated with slower axial elongation (Lau et al. 2018). However, Philip et al. failed to find an association between HOA and axial elongation for myopic children, who were emmetropes at enrollment five years before their final visit (Philip et al. 2014).

In summary, three retrospective, non-interventional studies, although differing in their findings of certain HOA being significantly associated with slower axial elongation or myopia progression, do lend support to the potential role of specific components of HOA influencing axial elongation in myopic children.

## 1.1.3 Risk factors for childhood myopia

### 1.1.3.1 Genetic factors

Several longitudinal studies have shown that the prevalence of myopia in

children increases with the number of their myopic parents (Mutti et al. 2002, Ip et al. 2007, Xiang et al. 2012), suggesting a dose-response relationship between parental myopia and myopia in children. However, it was found that, even before myopia onset, rather than having a longer axial length, children with two myopic parents only demonstrated more rapid eye growth rate than those with no history of parental myopia (Lam et al. 2008). Thus, it seems that myopic parents do not predispose their children's myopic development by passing on longer axial lengths. Considering the etiologically heterologous nature of childhood myopia, parental myopia may affect myopia progression in children through an environmentally-involved mechanism, given that family members experience the same environment and tend to have similar lifestyles.

Several studies on twins concluded that genes contribute significantly to the variation of myopia development, with estimated heritability ranging from 50% to 93% (Hammond et al. 2001, Lee et al. 2001, Lyhne et al. 2001, Dirani et al. 2006, Lopes et al. 2009, Kim et al. 2013). However, studies on twins are inherently flawed by their assumption of equal environment and inevitably lead to overestimation of heritability (Boomsma et al. 2002). In contrast, although familial linkage studies identified two dozen myopic susceptibility loci that were significantly associated with myopia progression in humans (Paluru et al. 2005, Chen et al. 2007, Li et al. 2009), these results cannot be generalized, due to distinct phenotype definition and ascertainment criteria adopted among these studies (Wojciechowski 2011).

As a well-accepted scientific approach to identify genetic risk factors for myopia

(Bush and Moore 2012), genome-wide association studies (GWAS) identified more than 30 distinct susceptibility loci for refractive error and myopia (Kiefer et al. 2013, Verhoeven et al. 2013). However, it was concluded that less than 12% of observed myopia can be attributed to genetic variants, indicating a limited contribution of genetic mutations, as independent risk factors for myopia development (Kiefer et al. 2013, Verhoeven et al. 2013).

1.1.3.2 Environmental factors for myopia

a. Excessive near work

The Sydney Myopia Study (SMS), involving 2353 children aged 12 – 13 years, demonstrated that children who read at close distance (< 30 cm) and those who read continuously for more than 30 min had a 2.5-fold (95% confidence interval (CI) 0.74 – 4.0) and 1.5-fold (95% CI 1.05 – 2.10) higher risk, respectively, to become myopic than those who did not (Ip et al. 2008). In contrast, several other studies failed to establish an association between near work activities and myopia prevalence (Rose et al. 2008, Lu et al. 2009, Wu et al. 2010).

In summary, not all findings from cross-sectional studies support excessive near work as a risk factor for myopia development and progression.

b. Outdoor exposure

Since it was first suggested that there may be a protective effect from outdoor exposure against myopia progression in children (Jones et al. 2007, Rose et al. 2008), three clinical trials have been conducted in Chinese children to investigate the

influence of increasing outdoor activities on the incidence of myopia.

He et al. (2015) recruited over 1000 non-myopic schoolchildren aged six and randomized them into two groups: the intervention group attended an additional 40-min class of outdoor activities on five days each week, while those in the control group followed the regular school curriculum. Over three years, the incidence of myopia in the intervention group was significantly slower than in the control group (30.4% vs 39.5%), but no between-group difference in axial elongation was observed (He et al. 2015).

A second randomized clinical trial was performed by Jin et al. (2015), who revealed a significantly lower incidence rate of myopia in children receiving two additional 20-min recess on five days each week over one year than those who did not (3.70 % vs 8.50 %). Although axial elongation in the intervention group was significantly slower than that in the control group (0.16 ± 0.30 mm/year vs. 0.21 ± 0.21 mm/year), these results were less reliable, as cycloplegic data from only 15% of children recruited in the study was obtained and analyzed (Jin et al. 2015).

The third intervention trial, the Recess Outside the Classroom (ROC) program, was non-randomized and conducted in Taiwan on children aged seven to 11 years. The children were allowed to perform discontinuous outdoor activities in school for up to 80 min daily. One year later, the percentage of children that had new onset of myopia was significantly lower in the ROC group than in the control group (8.4% vs. 17.7%) (Wu et al. 2013). This study did not include measurement of changes in axial length, only documenting that the increase in myopia was 0.13 D slower in the ROC

group compared with the control group (0.25 D/year vs. 0.38 D/year). However, the amount, although statistically significant, did not reach clinical significance.

In summary, based on the results of three clinical trials which included hyperopes, emmetropes, and myopes, it can only be concluded that more outdoor activity may be protective against myopia onset.

## 1.2 Spectacles for myopia control

SER and axial length changes are the two main outcomes adopted in clinical trials to evaluate the control effect of various interventions for myopia control. In this review, axial length change is used as the primary outcome over SER, to present the efficacy of interventions, with changes in SER used where necessary (e.g. when no axial length is available).

### 1.2.1 Under-correction of single vision spectacles

There was a hypothesis that, when myopes are under-corrected, a ‘zero-point error’ could be achieved (i.e. the eye balances itself in terms of reducing axial elongation to achieve zero refractive error), thus slowing or stopping myopia progression (Medina 1987). Compared with full correction when wearing single-vision spectacles (SVS), a 2-year randomized study in Malaysia, using a sample of 94 myopic children aged nine to 14, showed that under-correction of 0.75 D enhanced, rather than inhibited, myopia progression in children by a statistically significantly greater rate of 0.23 D over two years (Chung et al. 2002). Subsequently, a smaller

study involving 48 Israeli myopic children, who were randomized into groups of under-correction of 0.50 D and full correction, was conducted (Adler & Millodot 2006). After 18 months, it was shown that, compared with full correction, under-correction led to an insignificant increase (0.17 D) in myopic progression, indicating that under-correction of myopia did not slow myopia progression in children.

### 1.2.2 Bifocal spectacles

Myopic children with esophoria present a greater accommodative lag in response to near targets than other myopic children (Gwiazda et al. 1999). In a 30-month randomized trial on the effect of bifocal spectacles (BS) with +1.50 D Add in retarding myopia progression, Fulk et al. (2000) enrolled 82 esophoric myopic children of age between six to 13 years and randomized them into the SVS or BS group. The statistically significant difference of 0.25 D increase over 30-month between the two groups did not justify the recommendation of BS as an effective method for myopia control in esophoric myopic children (Fulk et al. 2000). However, the myopia progression rate of enrolled childen before treatment was unknown in this study. There is a possibility that the treatment effect of BS may not be evident in children with slow myopia progression.

In myopic children with orthophoria and exophoria, it was suggested that the treatment effect of BS (if any) may be compromised by a significant exophoric shift and a higher demand for positive fusional vergence (Cheng et al. 2008). Hence, incorporation of near base-in prism into BS may potentially minimize the

compromising effect resulting from positive Add (Cheng et al. 2008). To investigate if the treatment effect of BS could be improved by incorporating base-in prism, Cheng and his colleagues incorporated 3 Δ base-in prism into BS (+1.50 D Add) and compared the retardation effect of regular BS and SVS on myopia progression in a randomized trial. They included children with fast myopia progression (≥ 0.50 D in the preceding year) and all types of phoria at near viewing (i.e. orthophoria, esophoria, and exophoria) (Cheng et al. 2014). The results revealed an accumulative progression rate of 1.01 D in terms of SER and 0.54 mm in axial elongation over three years in the prismatic BS group, which was not significantly different from the 1.25 D and 0.57 mm observed in the regular BS group, but significantly lower than the increase of 2.06 D and 0.82 mm, respectively in the SVS group. The comparative treatment effect observed in the two BS groups suggested that the vergence response was unlikely to affect the treatment effect of BS. It was the lag of accommodation which interacted with the treatment effect, not the type of near phoria. Further analyses showed that, despite a similar treatment effect in the high-lag subgroup demonstrated by both BS groups, prismatic BS appeared to be the most effective design for children in the low-lag subgroup, with a treatment effect of 0.99 D (0.26 mm in retarding axial elongation), compared to 0.50 D (0.16 mm in retarding axial elongation) in the regular BS group (Cheng et al. 2014).

In summary, studies on the myopia retardation effect of BS show that these lenses are effective for myopic children with fast myopia progression, and the treatment effect was unlikely to be affected by near phoria.

### 1.2.3 Progressive addition spectacles

A 2-year randomized controlled trial, involving 64 Chinese myopic children in Hong Kong, found no difference in axial elongation between the progressive addition spectacles (PAS) (+1.50 D Add) and the SVS groups (Edwards et al. 2002). Another three-arm randomized controlled trial conducted in Taiwan, using PAS and SVS as controls to a pharmaceutical treatment, showed no statistical difference between the two control groups in myopia progression in terms of SER over 18 months, although the power of the Add of the PAS was not reported (Shih et al. 2001).

PAS with stronger Add (+2.00 D) were investigated in the Correction of Myopia Evaluation Trial (COMET), which showed a difference of 0.11 mm in axial length and 0.20 D in SER and between the PAS and SVS groups over three years (Gwiazda et al. 2003). Although demonstrating statistical significance, this small treatment effect over three years was not clinically significant. However, further analysis revealed that PAS was beneficial for a particular subgroup: for children with larger accommodation lag in conjunction with near esophoria, PAS demonstrated a more significant treatment effect of 0.64 D (Gwiazda et al. 2003).

Based on the hypothesis that children with near-work esophoria could benefit more from PAS, the subsequent COMET2 study demonstrated a statistically significant, but again, clinically insignificant treatment effect of 0.28 D over three years for children with these binocular vision characteristics (Gwiazda et al. 2011). A small treatment effect of PAS has been reported elsewhere, including 0.17 D over 18 months in Japanese children (Hasebe et al. 2008) and 0.26 D over two years in

Chinese children (Yang et al. 2009).

Given the small treatment effect observed, the use of PAS cannot be justified as a recommendation for myopic children. In addition to a clinically insignificant treatment effect observed in wearing PAS, the comparatively low prevalence of esophoria (14.8%) in myopic children further limited the use of PAS in myopia control (Walline et al. 1998).

### 1.2.4 Peripheral defocus modifying spectacles

Peripheral defocus modifying spectacles are designed to only alter the curvature of the image shell by adding positive power in the periphery while maintaining central vision correction (Sankaridurg et al. 2010). Three types of these lenses, varying in the size of the central optic zone and the amount of relative positive power in the periphery, have been evaluated in a 12-month clinical trial, but all failed to demonstrate any myopia retarding effect when the SVS group were used as a comparison (Sankaridurg et al. 2010).

### 1.2.5 Defocus incorporated multiple segments spectacles

A 2-year double-masked controlled trial in Hong Kong, equally randomized 183 Chinese children aged 8 to 13 years and with myopia 1.00 – 5.00 D into wearing SVS or defocus incorporated multiple segments (DIMS) spectacles that incorporated myopic defocus of +3.50 D in the mid-periphery (Lam et al. 2020). Over two years, the mean ± standard error (SD) axial elongation was 0.21 ± 0.02 mm in the DIMS

group, which was significantly lower compared to 0.55 ± 0.02 mm in the SVS group, indicating that the specially designed lenses were effective in retarding axial elongation in children. However, further independent studies are required to confirm the myopia control effect using this lens design.

## 1.3 Contact lenses for myopia control

### 1.3.1 Conventional soft contact lenses

Two 3-year randomized controlled trials were conducted to compare myopia progression of children wearing conventional soft contact lenses (SCL) with those using SVS, to investigate whether the use of SCL increases myopia progression (caused myopic creep) (Horner et al. 1999, Walline et al. 2008). There were no significant differences in changes of SER (Horner et al. 1999), or both SER and axial length (Walline et al. 2008) between SCL and control groups over three years, indicating that conventional SCL do not increase or decrease myopia progression, compared with SVS.

### 1.3.2 Rigid gas permeable contact lenses

A 2-year study, which randomized a total of 428 myopic children of Chinese ethnicity into rigid gas permeable (RGP) contact lenses and SVS groups, yielded no difference in either change in axial length or SER between the two treatment groups (Katz et al. 2003). A three-year randomized trial, the Contact Lens and Myopia Progression study (CLAMP), was conducted in a Caucasian population and used SCL

as a control treatment to improve subject retention (Walline et al. 2001). Although a statistical difference of 0.63 D in SER was observed between the RGP lenses and control groups over three years (mean ± SD, 1.56 ± 0.95 D vs 2.19 ± 0.89 D), the changes in axial length were not significantly different, indicating that RGP lenses were ineffective in retarding axial elongation in myopic children (Walline et al. 2004). The contradictory results of SER and axial elongation were attributed to corneal flattening induced by rigid lenses during the run-in period (1-month or 2-month period for subjects to adapt to RGP lens wear), which was reversible during the 3-year study (Walline et al. 2004).

### 1.3.3 Peripheral defocus modifying soft contact lenses

To date, the effectiveness of two types of peripheral defocus modifying SCL for myopia control have been explored. They are termed as concentric-ring center-distance bifocal SCL and gradient-design multifocal SCL, respectively, due to applications of distinct optical designs.

#### 1.3.3.1 Concentric-ring center-distance bifocal soft contact lenses

Table 1.2 summarizes the efficacy of four types of concentric-ring center-distance bifocal SCL tested in clinical trials for myopia control. It was shown that the use of these lenses significantly slowed axial elongation compared with the control treatment using conventional SCL or SVS (Table 1.2), indicating these lenses are effective in retarding axial elongation in children, despite differences in lens Add and duration of the study period.

Notably, commercially available MiSight SCL, which are designed based on Dual-Focus SCL (Anstice & Phillips 2011), demonstrated a higher reduction rate in axial elongation over three years than over two years (52% vs 36%) (Ruiz-Pomeda et al. 2018, Chamberlain et al. 2019), compared to controls using SCL or SVS. Use of the Defocus Incorporated Soft Contact (DISC) lenses with +2.50 D Add (the highest add amongst concentric-ring SCL incorporated with fixed positive power) were investigated but were found to be less effective than other concentric-ring SCL designs in reducing axial elongation, showing only a 31% reduction in axial elongation (Lam et al. 2014). Commercially available Vistakon Acuvue Bifocal SCL, with a range of +0.25 D to +3.75 D Add, which were chosen to eliminate eso-fixation disparities at near viewing completely, have been investigated for myopic children with near esophoria and demonstrated a 50% reduction in axial elongation. However, these results cannot be generalized to children without fixation disparity at near distance (Aller et al. 2016).

Table 1.2 Concentric-ring center-distance bifocal soft contact lenses for controlling childhood myopia

| Study | Age (Yrs) | Ethnicity | SER A (D) | Duration (months) | Intervention Control treatment | Number of subjects | Method of assignment | Mean ± SD axial elongation (mm) | Mean ± SD increase in SER (D) | Myopia control, based on axial elongation (mm) [%] | Number of dropouts |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Chamberlain et al. (2019) | 8 – 12 | Caucasian | 0.75 – 4.00<br>A < 1.00 | 36 | MiSight SCL (+2.00 D Add)<br>SCL | 109<br>144 | Randomized | 0.30 ± 0.27<br>0.62 ± 0.30 | 0.51 ± 0.64<br>1.24 ± 0.61 | 0.32 [52%] | 53<br>56 |
| Ruiz-Pomeda et al. (2018) | 8 – 12 | Caucasian | 0.75 – 4.00<br>A < 1.00 | 24 | MiSight SCL (+2.00 D Add)<br>SVS | 46<br>33 | Randomized | 0.28<br>0.44 | 0.45<br>0.74 | 0.16 [36%] | 5<br>0 |
| Aller et al. (2016) | 8 – 18 | Diverse | 0.50 – 6.00<br>A ≤ 1.00 | 12 | Vistakon Acuvue SCL<br>SCL | 38<br>40 | Randomized | 0.05 ± 0.14<br>0.24 ± 0.17 | 0.22 ± 0.34<br>0.79 ± 0.43 | 0.19 [80%] | —— |
| Lam et al. (2014) | 8 – 13 | Chinese | 1.00 – 5.00<br>A ≤ 1.00 | 24 | DISC lens (+2.50 D Add)<br>SCL | 111<br>110 | Randomized | 0.25 ± 0.23<br>0.37 ± 0.24 | 0.59 ± 0.49<br>0.79 ± 0.56 | 0.12 [31%] | 46<br>47 |
| Anstice & Phillips (2011) | 11 – 14 | Caucasian | 1.25 – 4.50<br>A < 1.25 | 20 | Dual-Focus SCL (+2.00 D Add)<br>SCL | 40 | Cross-over | Period 1<br>0.11 ± 0.09<br>0.22 ± 0.10<br>Period 2<br>0.02 ± 0.10<br>0.14 ± 0.09 | 0.44 ± 0.33<br>0.69 ± 0.38<br>0.17 ± 0.35<br>0.38 ± 0.38 | 0.11 [50%]<br>—— | —— |

SER – Spherical Equivalent Refraction (negative power, unless otherwise specified)

A – Astigmatism

SCL – Soft Contact Lens(es)

SVS – Single Vision Spectacles

DISC – Defocus Incorporated Soft Contact

1.3.3.2 Gradient-design multifocal soft contact lenses

Table 1.3 summarizes the efficacy of five types of gradient-design multifocal SCL for myopia control, two of which were shown to be ineffective in retarding axial elongation in children: experimental Soft Radial Refractive Gradient (SRRG) SCL and Biofinity Multifocal D. Although the mean axial elongation over two years in children wearing SRRG SCL was 0.14 mm slower than those wearing SVS, the difference was not significant (P = 0.08) (Paune et al. 2015). For Biofinity Multifocal D, mean axial elongation [95% CI] over three years in the high Add group (0.42 mm [0.38 – 0.47 mm]) was significantly lower than in the medium Add group (0.58 mm [0.54 – 0.63 mm]), and in the control group (0.66 mm [0.61 – 0.71 mm]), and no significant difference was observed in the latter two groups (Walline et al. 2020). In contrast, the use of Proclear Multifocal D (Walline et al. 2013), Anti-Myopia contact lenses (Sankaridurg et al. 2011), and low-addition multifocal SCL (Fujikado et al. 2014) were shown to be effective in slowing axial elongation in children, demonstrating a reduction rate ranging between 29% to 47% (Table 1.3). A randomized study by Garcia-Del Valle AM et al. (2021), compared the effect of Esencia lens with SCL in retarding axial elongaton in myopic children. A significantly slower axial elongation of 0.09 mm over 12 months was observed in the Esencia lens group compared with SCL group (Garcia-Del Valle et al. 2021). In addition to an Add of +2.00 D, the Esencia lens was incorpared with a reverse geometry design, to optimize the lens centration and provide a stabilized peripheral defocus (Garcia-Del Valle et al. 2021). However, further studies with longer duration are warranted.

Table 1.3 Gradient-design multifocal soft contact lenses for controlling childhood myopia

| Study | Age (Yrs) | Ethnicity | SER A (D) | Duration (months) | Intervention Control treatment | Number of subjects | Method of assignment | Mean ± SD axial elongation (mm) | Mean ± SD increase in SER (D) | Myopia control, based on axial elongation (mm) [%] | Number of dropouts |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Garcia-Del Valle AM et Al. (2021) | 7 – 15 | Spanish | 0.75 – 8.75 | 12 | Esencia lens (+2.00 D Add) | 36 | Randomized | 0.13 ± 0.12 | 0.28 ± 0.35 | 0.09 [41%] | 4 |
| | | | | | SCL | 34 | | 0.22 ± 0.14 | 0.57 ± 0.52 | | 8 |
| Walline et al. (2020) | 7 – 11 | Caucasian | 0.75 – 5.00 | 36 | Biofinity Multifocal D (+2.50 D Add) | 98 | Randomized | 0.42 | 0.60 | 0.24 [36%] | 1 |
| | | | | | Biofinity Multifocal D (+1.50 D Add) | 98 | | 0.58 | 0.89 | 0.08 [12%] | 0 |
| | | | | | SCL | 98 | | 0.66 | 1.05 | —— | 1 |
| PaunéJ et al. (2015) | 9 – 16 | Caucasian | 0.75 – 7.00 A ≤ 1.50 | 24 | SRRG SCL | 30 | Non-randomized | 0.38 ± 0.21 | 0.56 ± 0.51 | 0.14 [27%] | 11 |
| | | | | | Orthokeratology | 29 | | 0.32 ± 0.20 | 0.32 ± 0.53 | 0.20 [38%] | 11 |
| | | | | | SVS | 41 | | 0.52 ± 0.22 | 0.98 ± 0.58 | —— | 20 |
| Fujikado et al. (2014) | 6 – 16 | Japanese | 0.75 – 3.50 A < 1.00 | 12 | Low-addition SCL | —— | Cross-over | 0.09 ± 0.08 | 0.37 ± 0.33 | 0.08 [47%] | —— |
| | | | | | SCL | | | 0.17 ± 0.08 | 0.50 ± 0.18 | | |
| Walline et al. (2013) | 8 – 11 | Caucasian | 1.00 – 6.00 A ≤ 1.00 | 24 | Proclear Multifocal D (+2.00 D Add) | 40 | Cohort study | 0.29 ± 0.03 | 0.51 ± 0.06 | 0.12 [29%] | 13 |
| | | | | | SCL | 27 | | 0.41 ± 0.03 | 1.03 ± 0.06 | | —— |
| Sankaridurg et al. (2011) | 7 – 14 | Chinese | 0.75 – 3.50 A ≤ 1.00 | 12 | Novel SCL | 45 | Cohort study | 0.27 | 0.57 | 0.13 [33%] | 2 |
| | | | | | SVS | 40 | | 0.40 | 0.86 | | 1 |

A – Astigmatism

SER – Spherical Equivalent Refraction (negative power, unless otherwise specified)

SVS – Single Vision Spectacles

SCL – Soft Contact Lens(es)

SRRG – Soft Radial Refractive Gradient

1.3.3.3 Safety of peripheral defocus modifying soft contact lenses for myopia control

Although shown to be effective in retarding axial elongation, limited information is available about the adverse events of peripheral defocus modifying SCL described in Sections 1.3.3.1 and 1.3.3.2. However, a retrospective review on the adverse events reported in six randomized studies revealed a total incidence of ocular adverse events of 8.9 per 100 patient years in all SCL wearers, based on data of 518 children (aged seven to 15 years) who had worn daily disposable conventional SCL or multifocal SCL (Cheng et al. 2020). Of these adverse events, lens-related adverse events and corneal infiltrative occurrences accounted for an incidence of 4.5 and 0.3 per 100 patient years, respectively. No cases of microbial keratitis were observed, suggesting that the use of SCL in experimental settings is safe, irrespective of conventional or multifocal design.

1.3.3.4 Mechanisms for myopia control in peripheral defocus modifying soft contact lenses

Customized SCL, such as Dual-Focus, DISC lenses, SRRG, and Anti-Myopia SCL are specifically designed to induce myopic peripheral defocus, as this defocus has been suggested to be protective against myopia progression (Liu & Wildsoet 2011, Liu & Wildsoet 2012). Although Proclear Multifocal D and Vistakon Acuvue Bifocal lenses are currently commercially available for presbyopia correction, they have similar design principles to customized lenses for myopia control that intentionally modify peripheral refraction.

Of these lenses, Dual-focus, Anti-Myopia, SRRG, and Proclear Multifocal D SCL, were shown to be capable of inducing myopic defocus in the periphery of the retina (Sankaridurg et al. 2011, Lopes-Ferreira et al. 2013, Ticak & Walline 2013,

Lopes-Ferreira et al. 2015, Paune et al. 2016), but limited information about defocus profile is available for other lens designs. Furthermore, there is a lack of investigation on the causal relationship between axial elongation and peripheral defocus changes after wearing these lenses, raising the question of whether it is the modified peripheral defocus which underlies the mechanism of myopia control of these lenses.

## 1.3.4 Orthokeratology

### 1.3.4.1 Efficacy of orthokeratology reported in cohort studies

Several cohort studies have demonstrated that orthokeratology (ortho-k) is effective in retarding myopia in children, with control effects ranging from 30% to 63% in terms of retarding axial elongation (Table 1.4). In Hong Kong, a 2-year pilot study revealed a significantly slower mean increase in axial length in the ortho-k group, which was 0.25 mm less than that of a historical control group wearing SVS (Cho et al. 2005). However, this pilot study only involved children with astigmatism less than 2.00 D and wearing mainly spherical ortho-k lenses.

As toric ortho-k was recommended for myopic eyes with corneal astigmatism over 1.50 D to provide better centration and unaided vision in the daytime, a non-randomized study, Toric Orthokeratology – Slowing Eyeball Elongation (TO-SEE) study, was conducted to investigate the effectiveness of toric ortho-k in retarding myopia progression in children with corneal-derived astigmatism of 1.25 D to 3.50 D (Chen et al. 2012). The study revealed a significant treatment effect of 0.34 mm mean reduction in axial elongation in children wearing toric ortho-k compared with those in controls wearing SVS over two years (Chen et al. 2013). Further analysis demonstrated that moderate-to-high astigmatism did not stimulate myopia progression, as axial elongation was not associated with baseline astigmatism and

initial corneal toricity (Chen et al. 2013).

A 2-year cohort study was conducted in Japan, with an allocation of subjects to the ortho-k and SVS group by self-selection. Kakita et al. reported significant axial retardation of 0.23 mm in the ortho-k group compared to the SVS group after two years of lens wear (Kakita et al. 2011). However, there was a 3-month delay in the measurement of baseline axial length in the ortho-k group, which may have led to an underestimation of retardation of axial growth induced by ortho-k, possibly accounting for the lower myopia control rate of 36% reported in this study, compared with 46% (Cho et al. 2005) and 56% (Chen et al. 2013) reported in the Hong Kong cohort studies. After completion of the 2-year study reported by Kakita et al (2011), Hiraoka et al. (2012) reported results from 29 and 30 children in the ortho-k and SVS groups, respectively, who were willing to continue their previous treatment for another three years. It was shown that the significant treatment effect was limited to the first three years, as differences in axial elongation between the two groups were found not significant for the remaining two years (Hiraoka et al. 2012).

Unlike the previously mentioned studies, which only involved children with low to moderate myopia, a retrospective study performed in Mainland China recruited children with high myopia up to 10.00 D (Zhu et al. 2014). In these highly myopic eyes, ortho-k could only achieve myopia reduction up to 6.00 D. with the residual myopia being corrected with spectacles after stabilization of the ortho-k treatment. The study revealed that ortho-k effectively reduced axial elongation by 0.36 mm compared with SVS over two years, demonstrating an overall control rate of 51% in retarding axial elongation (Zhu et al. 2014). Further analysis showed that axial elongation was slowed by 0.35 mm, 0.47 mm, and 0.28 mm for the low (≤ 3.00 D), moderate (> 3.00 D and < 6.00 D), and high myopia subgroups (≥ 6.00 D),

respectively, indicating that the myopia control effect of ortho-k was comparable among children with low to high myopia.

The studies discussed so far were conducted in Asian children. With respect to the efficacy of ortho-k in Caucasian children, cohort studies conducted in US and Spain also showed a significant treatment effect of 0.32 mm (Walline et al. 2009) and 0.22 mm (Santodomingo-Rubido et al. 2012) over two years, respectively, although different control treatments were used (Table 1.4).

Table 1.4 Orthokeratology for controlling childhood myopia

| Study | Age (Yrs) | Ethnicity | Myopia/[SER] A (D) | Duration (months) | Method of assignment | Intervention & control treatment | Number of subjects | Mean ± SD axial elongation (mm) | Increase in SER (D) | Myopia control. based on axial elongation (mm) [%] | Number of dropouts |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Cho et al. (2005) | 7 – 12 | Chinese | 0.25 – 4.50<br>A < 2.00 | 24 | Historic data | Ortho-k<br>SVS | 43<br>35 | 0.29 ± 0.27<br>0.54 ± 0.27 | —— | 0.25 [46%] | 8<br>—— |
| Walline et al. (2009) | 8 – 11 | Caucasian | 0.75 – 4.00<br>A < 1.00 | 24 | Historic data | Ortho-k<br>SCL | 40<br>28 | 0.25 ± 0.27<br>0.57 ± 0.27 | —— | 0.32 [56%] | 12<br>—— |
| Kakita et al. (2011) | 8 – 16 | Japanese | 0.50 – 10.00 | 24 | Self-selection | Ortho-k<br>SVS | 45<br>60 | 0.39 ± 0.27<br>0.61 ± 0.24 | —— | 0.22 [36%] | 3<br>10 |
| Hiraoka et al. (2012) | 8 – 12 | Japanese | 0.50 – 5.00 | 60 | Self-selection | Ortho-k<br>SVS | 29<br>39 | 0.99 ± 0.47<br>1.41 ± 0.68 | —— | 0.42 [30%] | 7<br>9 |
| Santodomingo et al. (2012) | 6 – 12 | European | 0.75 – 4.00<br>A < 1.00 | 24 | Self-selection | Ortho-k | 31<br>30 | 0.47<br>0.69 | 0.34 | 0.22 [32%] | 2<br>6 |
| Cho & Cheung (2012) | 6 – 10 | Chinese | [0.50 – 4.00]<br>A ≤ 1.25 | 24 | Randomized | Ortho-k | 51<br>51 | 0.36 ± 0.24<br>0.63 ± 0.26 | —— | 0.27 [43%] | 14<br>10 |
| Charm & Cho (2013) | 8 – 11 | Chinese | ≥ 5.75<br>≥ 5.00 | 24 | Randomized | Ortho-k<br>SVS | 26<br>26 | 0.19 ± 0.21<br>0.51 ± 0.32 | 0.00<br>1.00 | 0.32 [63%] | 14<br>10 |
| Chen et al. (2013) | 6 – 12 | Chinese | [0.50 – 5.00]<br>A: 1.25 – 3.50 | 24 | Self-selection | Ortho-k<br>SVS | 43<br>37 | 0.31 ± 0.27<br>0.64 ± 0.31 | 0.00<br>1.13 | 0.33 [52%] | 8<br>14 |
| Swarbrick et al. (2015) | 8 –16 | Asian | [1.00 – 4.00]<br>A < 1.50 | 12 | Randomized crossover | Ortho-k<br>RGP | 32 | -0.04 ± 0.08<br>0.09 ± 0.09 | -0.07<br>0.37 | 100% | 8 |
| Zhu et al. (2014) | 7 – 14 | Chinese | Low: [0.50 – 2.75]<br>Moderate: [3.00 – 5.75]<br>High: ≥ [6.00]<br>All: A ≤ 1.25 | 24 | Retrospective | Ortho-k<br>SVS | 65<br>63 | 0.34 ± 0.29<br>0.70 ± 0.35 | —— | Total:51%<br>Low: 49%<br>Moderate: 59%<br>High: 46% | —— |
| Guo et al. (2021) | 6 – <11 | Chinese | [0.75 – 4.00]<br>A < 2.50 | 12 | Randomized | 6 mm BOZD Ortho-k<br>5 mm BOZD Ortho-k | 34<br>36 | 0.17 ± 0.13<br>0.04 ± 0.15 | —— | —— | 2<br>10 |

A – Astigmatism; BOZD – Back Optic Zone Diameters

SER – Spherical Equivalent Refraction (negative power, unless otherwise specified)

Ortho-k – Orthokeratology

SCL – Soft Contact Lens(es)

SVS – Single Vision Spectacles

RGP – Rigid Gas Permeable

1.3.4.2 Efficacy of orthokeratology reported in randomized trials

The 2-year randomized Myopia in Orthokeratology (ROMIO) Study revealed a significant treatment effect with slower axial elongation of 0.27 mm over SVS for children with myopia between 0.50 D and 4.00 D treated with ortho-k for two years (Table 1.4) (Cho & Cheung 2012). Further analysis showed that axial elongation was associated with initial age and treatment, but not with initial myopia, suggesting that younger children, especially those with rapid progression, could benefit greatly from ortho-k (Cho & Cheung 2012).

Full reduction of high myopia with commercially available ortho-k lenses for low to moderate myopia can cause significant corneal staining, heavy lens binding, and severe lens decentration, thus increasing the risk of compromising corneal health (Chen et al. 2012). Based on these clinical observations, partial reduction ortho-k was recommended for highly myopic children, using SVS to correct residual refractive error to maintain a clear vision in the daytime. The 2-year High Myopia – Partial Reduction Orthokeratology (HM-PRO) study, equally randomizing highly myopic children with SER of at least 5.75 D into SVS group and treatment group, which involved partial reduction (target reduction of 4.00 D) by ortho-k combined with SVS to correct the residual refractive error in the daytime. A significant treatment effect of 0.32 mm over two years from partial ortho-k treatment, compared to SVS, indicated that this treatment modality is effective in slowing axial elongation in high myopic children (Charm & Cho 2013). The two-year Variation of Orthokeratology Lens Treatment Zone (VOLTZ) Study, randomized myopic children with myopia 0.75 – 4.00 D into 6 mm back optic zone diameters (BOZD) ortho-k group and 5 mm group (Guo et al. 2021). It was revealed that a smaller BOZD slowed axial elongation by 0.13 mm compared to conventional 6 mm BOZD ortho-k lenses over one year (Guo et al. 2021).

1.3.4.3 Axial elongation after discontinuation of orthokeratology

It is a major concern that rebound may occur after discontinuation of ortho-k. A 14-month study in Hong Kong, consisting of two periods, each lasting seven months, investigated the effects of discontinuation and resumption of ortho-k (Cho & Cheung 2017). Subjects were children from the previous ROMIO (Cho & Cheung 2012) and TO-SEE studies (Chen et al. 2012). In the first seven months, a significantly faster axial elongation was observed in children who discontinued ortho-k compared to those who continued ortho-k lens wear (0.153 mm vs 0.087 mm) and SVS (0.153 mm vs 0.082 mm) (Cho & Cheung 2012). However, this increased rate in axial elongation was not worse than the rate in children wearing SVS during the preceding 2-year trial (TO-SEE and ROMIO studies), indicating that it may not be a rebound effect, but more likely a resumption of natural eye growth in children who discontinued ortho-k. In addition, after the resumption of ortho-k in the subsequent seven months, axial elongation was comparable to those who did not stop ortho-k lens wear (0.059 mm vs 0.068 mm) (Cho & Cheung 2012).

1.3.4.4 Safety of orthokeratology

Non-significant adverse events after wearing ortho-k, such as mild corneal staining (Cho & Cheung 2012, Santodomingo-Rubido et al. 2012, Charm & Cho 2013, Chen et al. 2013, Zhu et al. 2014), conjunctivitis (Cho & Cheung 2012), mild corneal erosions (Kakita et al. 2011, Hiraoka et al. 2012, Santodomingo-Rubido et al. 2012), sterile corneal infiltrates (Guo et al. 2021), and microcysts (Guo et al. 2021) were reported in some clinical trials, but no confirmed cases of microbial keratitis. These non-significant adverse events were resolved satisfactorily after lens discontinuation and no permanent damage occurred. It has been estimated that children wearing ortho-k lenses have 7.87 times higher chance of getting non-significant adverse events compared to those wearing SVS (Li et al. 2016).

Regarding significant adverse events, in a retrospective study, based on practitioner-reported cases, the incidence of microbial keratitis was estimated to be 13.9 per 10,000 patient years for children wearing ortho-k for an average duration of two years (Bullimore et al. 2013). However, as only two cases of microbial keratitis were confirmed among 677 practitioner-reported cases, the small sample size may lead to low precision of estimated incidence of microbial keratitis.

Higher numbers of microbial keratitis were reported between 1997 to 2001 in East Asia, particularly in Mainland China. A review on 123 cases of microbial keratitis reported between 2001 to 2007 worldwide, aimed to determine the trend of microbial keratitis incidence in ortho-k wearers (Watt & Swarbrick 2007). Of these cases, 40%, 29%, and 6% were from Mainland China, Taiwan, and Hong Kong, respectively. Pseudomonas aeruginosa and Acanthamoeba were found to account for 37% and 33% of these corneal infections, respectively. Use of tap water, poor hand hygiene, as well as poor compliance with lens wear routines, were regarded as the major risk factors for microbial keratitis (Watt & Swarbrick 2007). The reports of microbial keratitis peaked in 2001 and significantly reduced thereafter, which was likely to be a result of tightened regulations on ortho-k practice put in place by the Chinese government. As non-compliance in the care of ortho-k lenses and accessories could increase the risk of microbial contamination (Cho et al. 2009, Cheung et al. 2016, Wang et al. 2020), it is important to reinforce the compliance of children and guardians in following instructions to lower the risk of microbial infections. Severe adverse events can be minimized with stringent guidelines and compliance (Cho et al. 2008, Liu & Xie 2016).

#### 1.3.4.5 Mechanisms for myopia control in orthokeratology

Currently, the mechanism for myopia control in ortho-k remains unclear. Although several studies confirmed that ortho-k lenses reform relative peripheral defocus from being hyperopic (pre-treatment) to being myopic (post-treatment) (Queiros et al. 2010, Kang &

Swarbrick 2011, Ticak & Walline 2013), no causal relationship has been established between peripheral defocus and the retardation effect in ortho-k. Furthermore, the highest myopic peripheral defocus induced by ortho-k was found to be almost equal to the amount of myopia that had been centrally corrected, suggesting these defocus changes are highly likely to be a byproduct of central correction by ortho-k (Queiros et al. 2010).

In contrast, the significantly increased total ocular HOA, as well as their components, after ortho-k have been suggested to account for the myopia control effect observed (Hiraoka et al. 2015, Lau et al. 2018, Kim et al. 2019). An analysis based on data from 103 myopic children who underwent ortho-k for two years, with adjustment for initial age, sex, and refractive error, showed that elevated total ocular HOA, spherical aberrations, and individual positively shifted primary spherical aberration for a 6-mm pupil, were associated with slower axial elongation, thus supporting HOA as a potential contributor to the control effect of ortho-k (Lau et al. 2020).

Two other two longitudinal studies on the relationship between ocular HOA and axial elongation in children have been reported, but caution may be needed when interpreting their results. In the first study, Hiraoka et al. (2015) revealed that elevated total ocular HOA, spherical, and comatic aberrations for a 4-mm pupil were associated with slower axial elongation over one year in 55 ortho-k-treated children with a mean age of 10.3 years. However, this study was limited by a lack of adjustment for baseline age and sex, as these confounding factors may affect ocular HOA and axial elongation. In the second study, Kim et al. (2019) used a multivariate analysis to investigate the relationship between ocular HOA for a 6-mm pupil and axial elongation over one year. Although ocular HOA and comatic aberration were found to be negatively associated with axial elongation, the interpretation of this result is limited by a small sample size (n = 17), particularly since a multivariate analysis was used in this study.

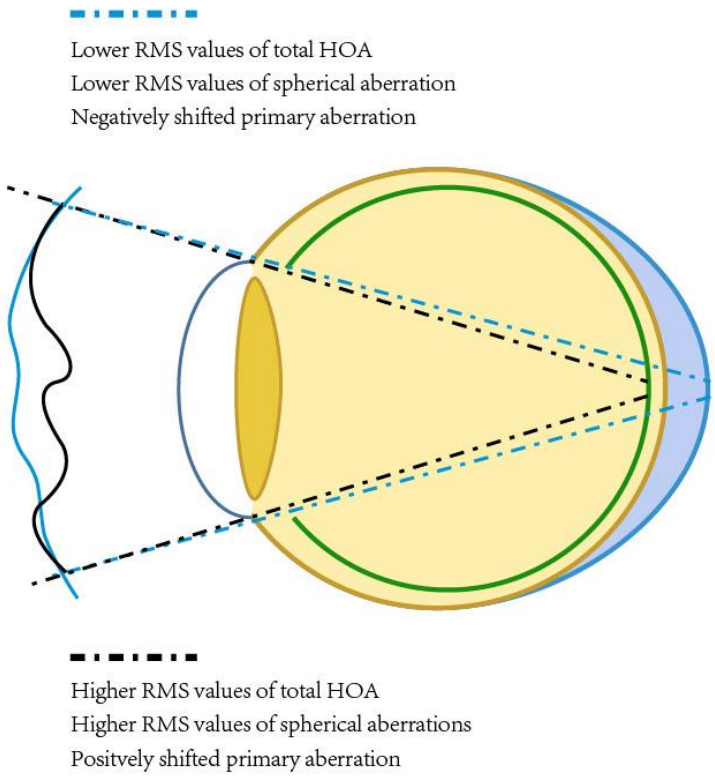



Figure1.1 Relationship between ocular aberrations and axial elongation in children undergoing orthokeratology
HOA – Higher-order aberration(s)
RMS – Root mean square

## 1.4 Pharmaceutical interventions for myopia control

### 1.4.1 Pirenzepine

A 1-year multi-center randomized clinical trial demonstrated that twice-daily use of 2% pirenzepine gel resulted in a treatment effect of 0.37 D, which was more effective than 0.14 D for once-daily use, when compared to placebo (Tan et al. 2005). A subsequent 2-year randomized study showed that the mean increase of 0.58 D in the twice-daily pirenzepine-treated group was significantly lower than 0.99 D in the placebo group, but there was no significant difference in axial elongation between the pirenzepine-treated group and placebo group (0.28 mm vs 0.40 mm) (Siatkowski et al. 2008). In addition, there were unwanted side-

effects, including papillae/follicles, medication residue, and accommodative dysfunction, making twice-daily use of the 2% pirenzepine unlikely to be a recommended option for myopia control in children. Pirenzepine is also not commercially available.

### 1.4.2 Cyclopentolate

To date, only one randomized clinical trial has investigated the effectiveness of 1% cyclopentolate in the retardation of myopia progression in children. A 1-year study involving a total of 96 school-aged children (6 – 14 years), who were randomized into three treatment groups of 1% cyclopentolate every night, 1% atropine every other night, and placebo. It was demonstrated that the annual increase of 0.58 D in the cyclopentolate-treated group was significantly lower than 0.91 D in the placebo-treated group, but significantly higher than the 0.22 D in the atropine-treated group (Yen et al. 1989). However, the difference of 0.36 D in an annual increase of refractive error between the cyclopentolate-treated group and the control group was clinically insignificant, indicating that 1% cyclopentolate was not effective in slowing myopia progression. The only side-effect related to 1% cyclopentolate was a transient blurred vision the next morning following night-time use.

### 1.4.3 Atropine

Since 1% atropine was first reported to be successful in slowing the progression of childhood myopia in 1979 (Bedrossian 1979), numerous studies have been conducted to explore its effectiveness at various concentrations (Shih et al. 1999, Kennedy et al. 2000, Romano & Donovan 2000, Chiang et al. 2001, Shih et al. 2001, Syniuta & Isenberg 2001). However, these studies had major design flaws, such as a lack of axial length measurement and failure to control for potential confounding factors, leading to insufficient evidence to support atropine as an effective intervention for myopia control (Saw et al, 2002). Another

major problem compromising the credibility of these studies is the improper self-dilution of atropine at various (low) concentrations, which involved diluting 1% atropine with distilled water in the laboratory, as this process unavoidably results in fluctuations of concentration, particularly as concentrations as low as 0.01% were used. In addition, there were concerns about contamination and storage problems of the atropine after dilution.

Among the studies reported, two, albeit with limitations, did provide some insights into the use of atropine for myopia control. The first, a 2-year randomized study compared the annual myopia progression rate between treatment groups of 0.5%, 0.25%, and 0.1% atropine, using 0.5% tropicamide as a control treatment (Shih et al. 1999). Despite a lack of measurement of axial elongation, the introduction of several confounding factors (use of BS and under-correction with SVS), and problematic use of 0.5% tropicamide as the control treatment, this study was the first to indicate that the efficacy of atropine for myopia control depends on its concentration. It revealed an annual progression rate of 0.04 D in the 0.5% group, 0.45 D in the 0.25% group, 0.47 D in the 0.1% group, which were all significantly lower than 1.06 D in the control group (Shih et al. 1999).

The second study, a randomized controlled trial, was the first to initiate combined treatment in atropine research, by combining 0.5% atropine with PAS (Shih et al. 2001). It was shown that, after 18 months, the mean progression rate in the combined group was 0.41 D, which was significantly lower than 1.19 D and 1.40 D observed in the PAS and SVS alone groups, respectively, indicating that combined treatment of 0.5% atropine and PAS was more effective in retarding myopia progression than control treatments (Shih et al. 2001).

Currently, the main evidence to support the use of atropine as an effective intervention for myopia control has come from Atropine for the Treatment Of childhood Myopia studies (ATOM1 & ATOM2) (Chua et al. 2006, Tong et al. 2009, Chia et al. 2012, Chia et al. 2014, Chia et al. 2016), and the Low-Concentration Atropine for Myopia Progression study

(LAMP) (Yam et al. 2019, Yam et al. 2020).

#### 1.4.3.1 Atropine 1%

The ATOM1 study revealed that nightly and monocular use of 1% atropine eye drops over two years significantly slowed axial elongation by 0.40 mm when compared to the placebo group (Chua et al. 2006). In the subsequent 1-year washout period after the children discontinued monocular use of 1% atropine, a rebound effect was observed, with the mean myopia progression in the atropine-treated eyes significantly higher than that observed in the placebo-treated eyes (1.14 D vs 0.38 D) (Tong et al. 2009). However, the difference in axial elongation between atropine-treated and placebo-treated eyes in the third year was not reported. Nevertheless, such a steep increase in myopia progression after cessation of atropine differed considerably from the natural course of myopia progression in children, which involves gradual slowing down of progression with age, as was observed in the placebo-treated eyes. After three years, although the final axial elongation at the end of the third year was both statistically and clinically significantly lower in the 1% atropine-treated eyes than the placebo-treated eyes (Mean ± SD, 0.29 ± 0.37 mm vs 0.52 ± 0.45 mm), adverse side-effects, such as photophobia and blurred near vision, in combination with the apparent rebound effect observed in the 1-year washout period, precluded the use of 1% atropine as a mainstream treatment for retardation of myopia progression in children.

#### 1.4.3.2 Atropine 0.5% and 0.1%

ATOM2 examined the efficacy of binocular use of 0.5% and 0.1% atropine for retardation of myopia progression as well as rebound effect following discontinuation. Application of 0.01% atropine was used as the control treatment (Chia et al. 2012, Chia et al. 2014, Chia et al. 2016). The study consisted of three phases.

In phase one, a concentration-related treatment effect of atropine was observed, with a

mean ± SD axial elongation over two years of 0.27 ± 0.25 mm for the 0.5% group, 0.28 ± 0.28 mm for the 0.1% group, and 0.41 ± 0.32 mm for the 0.01% group (Chia et al. 2012). However, intolerable photophobia (pupil dilation of approximately 3 mm) and decreased accommodation (reduction of more than 10.00 D) were commonly seen in both the 0.5% and 0.1% atropine groups (Chia et al. 2012).

In phase two, a 1-year washout period, concentration-dependent rebound effects were observed, with mean myopia progression of 0.87 D, 0.68 D, and 0.28 D for 0.5%, 0.1% and 0.01% groups, respectively (Chia et al. 2014). Mean ± SD axial elongation was also significantly greater in the 0.5% (0.35 ± 0.20 mm) and 0.1% (0.33 ± 0.18 mm) groups, compared to the 0.01% group (0.19 ± 0.13 mm) (Chia et al. 2014).

In phase three, children who demonstrated fast myopia progression of at least 0.50 D during the washout period were re-treated with 0.01% atropine for another two years. The overall 5-year mean myopia progression was 1.38 D, 1.83 D, and 1.98 D in the 0.01%, 0.1%, and 0.5% groups, respectively, indicating minimal myopia progression (rebound), in terms of SER, in the 0.01% atropine group (Chia et al. 2016). However, no significant differences in overall 5-year axial elongation were found among the three groups. Considering negligible side-effects, insignificant rebound effect, and minimal myopia progression (SER) over five years in the 0.01% group, the authors of ATOM2 recommended 0.01% atropine as the optimal concentration for myopia control, rather than 0.5% or 0.1% atropine (Chia et al. 2016).

#### 1.4.3.3 Atropine 0.01% – 0.05%

Notably, ATOM2 was limited by its lack of a real control group (placebo or SVS group), making the effectiveness of 0.01% atropine uncertain. However, no significant difference in axial elongation was found between the 0.01% atropine group in ATOM 2 and the placebo group in ATOM1, suggesting that 0.01% atropine is ineffective in retarding axial elongation

in children.

The more recent LAMP study consisted of four study phases. The study equally randomized 438 myopic children, aged four to 12 years, into 0.05%, 0.025%, 0.01% atropine, and placebo treatment groups in phase one, which lasted for one year. Compared with the placebo, mean axial elongation was significantly slowed by 0.21 mm and 0.13 mm in the 0.05% and 0.025% groups, respectively (Yam et al. 2019). But axial elongation was only slowed by 0.05 mm for the 0.01% atropine group compared with the placebo group, with no significant difference in axial elongation between the two groups, indicating that 0.01% atropine was ineffective in slowing axial elongation (Yam et al. 2019).

In phase two, which also lasted for one year, subjects in the 0.5%, 0.025%, and the 0.01% atropine groups continued their previous treatment, while those in the placebo group were switched over to use 0.05% atropine, thereby removing a true control group from the study (Yam et al. 2020), albeit an ethically correct decision. Over two years (phase one and phase two), the axial elongation in the 0.05% group was significantly lower than that in the 0.025% and 0.01% groups (mean ± SD, 0.39 ± 0.35 mm vs 0.50 ± 0.33 mm, 0.39 ± 0.35 mm vs 0.59 ± 0.38 mm, respectively), with no significant difference observed between the latter two lower concentration groups (Yam et al. 2020).

Regarding side-effects, all three concentrations of atropine were well-tolerated over two years, with mean increases in photopic pupil sizes of 1.25 mm, 0.67 mm, and 0.60 mm in the 0.05%, the 0.025%, and 0.01% atropine groups, respectively, and mean losses in accommodation amplitudes of 2.05 D, 1.66 D, and 0.63 D, respectively (Yam et al. 2020). Based on these findings, Yam et al. concluded that, among the three options, 0.05% atropine is the optimal concentration for myopia control.

However, myopia control with atropine involves consideration of retardation of axial length, rebound effect after discontinuation, as well as side-effects. As such, long-term

effectiveness, safety, and patients' acceptance must be taken into consideration. Phase three of LAMP is ongoing, to determine the rebound effect of discontinuation of 0.5%, 0.025%, and 0.01% atropine. The optimal concentration that can achieve the best balance over a long term has yet to be determined.

#### 1.4.3.4 Atropine 0.01% and 0.02%

A 1-year trial, which allocated 400 myopic children to treatment with atropine eye drops or SVS by self-selection was conducted by Fu et al. (2020). Children who chose atropine treatment were subsequently randomized to either the 0.01% or the 0.02% atropine groups. After one year, the mean axial elongation was significantly slowed by 0.16 mm and 0.09 mm for the 0.02% and 0.01% groups, respectively, when compared to those wearing SVS (Fu et al. 2020). The significant control effect observed in the 0.01% atropine group conflicted with the results of the LAMP study, where 0.01% atropine was proven ineffective in retarding axial elongation over one year. However, it should be noted that the probability value observed (0.039) is not significant if Bonferroni adjustments were taken into account for multiple comparisons. In addition, Fu et al. dispensed 0.01% and 0.02% atropine by diluting 1% atropine with saline on the bench and dispensed the eyedrops with a monthly replacement schedule. This diluting procedure could introduce confounding factors, as the concentration of the atropine may fluctuate with each dilution and storage over one month.

In contrast, well-packed single-dose preservative-free, 0.01% atropine eye drops were used in the LAMP study, which guaranteed a stable concentration of atropine. In addition, Fu et al.'s study was not a randomized trial, making these results less reliable as scientific evidence than the LAMP study, which was a randomized controlled trial. In addition, Fu et al. only assessed the efficacy of 0.01% and 0.02% atropine for one year, making the long-term efficacy of 0.02% atropine uncertain. The results obtained from phase two of LAMP provided further insight, as the efficacy of 0.025% atropine was found to be not significantly better

than 0.01% over two years in LAMP Phase 2 (Yam et al. 2020). Considering that the efficacy of atropine is concentration-dependent, there is no reason to believe 0.02% atropine would perform better than 0.025% atropine.

In Fu et al.'s study, the mean pupil dilation of 0.78 mm and decrease in accommodation of 1.50 D in the 0.02% group were comparable to 0.69 mm and 1.61 D for the 0.01% group. This was in agreement with an earlier study, which reported that 0.02% atropine was the maximum concentration that could be used without clinical signs or symptoms, and further reduction of the concentration to 0.01% did not seem to result in a decrease in atropine-associated signs or symptoms (Cooper et al. 2013).

Table 1.5 Atropine for controlling childhood myopia

| Study | Age (Yrs) | Ethnicity | Myopia/[SER] A (D) | Duration (months) | Method of assignment | Intervention & control treatment | Number of subjects | Mean ± SD axial elongation (mm) | Increase in SER (D) | Myopia control. based on axial elongation (mm) [%] | Number of dropouts |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Chua et al. (2006) | 6 – 12 | 93% Chinese | [1.00 – 6.00] A < 1.50 | 24 | Randomized | Monocular 1% | 100 | -0.02 ± 0.35 | 0.28 ± 0.92 | 0.40 [100%] | 34 |
| | | | | | | Placebo | 100 | 0.38 ± 0.38 | 1.20 ± 0.69 | | 10 |
| Chia et al. (2012) | 6 – 12 | 91% Chinese | ≥ [2.00] A < 1.50 | Phase 1: 24 | Randomized | 0.5% | 161 | 0.27 ± 0.25 | 0.30 ± 0.60 | —— | 21 |
| | | | | | | 0.1% | 155 | 0.28 ± 0.28 | 0.38 ± 0.60 | | 14 |
| | | | | | | 0.01% | 84 | 0.41 ± 0.32 | 0.49 ± 0.63 | | 9 |
| Chia et al. (2014) | | | | Phase 2: 12 | —— | Discontinuation of 0.5% | 136 | 0.35 ± 0.20 | 0.87 ± 0.52 | —— | 25 |
| | | | | | | 0.1% | 139 | 0.33 ± 0.18 | 0.68 ± 0.45 | | 16 |
| | | | | | | 0.01% | 70 | 0.19 ± 0.13 | 0.28 ± 0.33 | | 14 |
| Chia et al. (2016) | | | | Phase 3: 24 | —— | Retreat with 0.01% if progression ≥ 0.50 | Retreat/ untreat | Over five years | | | |
| | | | | | | Initial 0.5% | 93/43 | 0.87 ± 0.49 | 1.98 ± 1.10 | | 9 |
| | | | | | | Initial 0.1% | 82/57 | 0.85 ± 0.53 | 1.83 ± 1.16 | —— | 5 |
| | | | | | | Initial 0.01% | 17/43 | 0.75 ± 0.48 | 1.38 ± 0.38 | | 3 |
| Yam et al. (2019) | 4 – 12 | Chinese | ≥ 1.00 A ≤ 2.50 | Phase 1: 12 | Randomized | 0.05% | 109 | 0.20 ± 0.25 | 0.27 ± 0.61 | 0.21 [51%] | 7 |
| | | | | | | 0.025% | 108 | 0.29 ± 0.20 | 0.46 ± 0.45 | 0.12 [29%] | 17 |
| | | | | | | 0.01% | 110 | 0.36 ± 0.29 | 0.59 ± 0.61 | 0.05 [12%] | 13 |
| | | | | | | Placebo | 111 | 0.41 ± 0.22 | 0.81 ± 0.20 | —— | 18 |
| Yam et al. (2020) | 4 – 12 | Chinese | ≥ 1.00 A ≤ 2.50 | 24 (Phase 1 & 2) | Randomized | 0.05% | 93 | 0.39 ± 0.35 | 0.55 ± 0.86 | | 16 |
| | | | | | | 0.025% | 86 | 0.50 ± 0.33 | 0.85 ± 0.73 | | 22 |
| | | | | | | 0.01% | 91 | 0.59 ± 0.38 | 1.12 ± 0.85 | —— | 19 |
| | | | | | | Placebo (Phase 1) + 0.01% (Phase 2) | 80 | 0.58 ± 0.33 | 1.00 ± 0.77 | | 31 |
| Fu et al. (2020) | 6 – 14 | Chinese | [1.25 – 6.00] A < 2.00 | 12 | Randomized | 0.02% | 138 | 0.30 ± 0.21 | 0.38 ± 0.35 | 0.16 [35%] | 21 |
| | | | | | | 0.01% | 142 | 0.37 ± 0.22 | 0.47 ± 0.45 | 0.09 [20%] | 23 |
| | | | | | Self-selection | No eye drops | 120 | 0.46 ± 0.35 | 0.70 ± 0.60 | —— | 20 |

A – Astigmatism

SER – Spherical Equivalent Refraction (negative power, unless otherwise specified)

1.4.3.5 Safety of atropine for myopia control

To date, the safety of 0.5%, 0.1%, and 0.01% atropine eye drops for myopia control has been assessed for a maximum period of five years in ATOM 2, with a wash-out period in the third year. The study demonstrated that the use of 0.01% atropine was associated with the least side-effects. Taking into consideration that atropine is toxic, an investigation into the long-term safety of the application of atropine eye drops, especially at higher concentrations, is warranted.

It has been shown that unavoidable side-effects, including photophobia, blurred near vision, allergic conjunctivitis, and dermatitis on the eyelids, as well as a significant rebound effect, were confined to children using concentrations higher than 0.01% (that is, 1%, 0.5%, 0.1%) for myopia control (Sections 1.4.4.1 and 1.4.4.2). Concerning 0.05% and 0.025% atropine, although most side-effects were well-tolerated and were regarded as non-significant (Section 1.4.4.3), but the rebound effect is unknown as the third year of investigation on discontinuation in the LAMP study is still in progress.

1.4.3.6 Mechanisms for myopia control in atropine

a. Relaxation of accommodation

Topical use of atropine for myopia control was initially based on the hypothesis that excessive accommodation induced by near work results in eye growth in children (Bedrossian 1979). In line with this hypothesis, the cycloplegic action of atropine, which relaxes the accommodation response of the eye, would contribute to the slower eye growth observed in the use of atropine. However, this hypothesis seems highly inadequate to explain the effect of atropine on myopia progression, as the use of both BS and PAS, which could relax the accommodation at near viewing, was shown to be ineffective in inhibiting myopia progression (Sections 1.2.2 and 1.2.3).

In addition, experiments in chick eyes with dominant intraocular nicotinic receptors, in which atropine should not produce cycloplegia and pupil dilation, showed that experimentally induced myopia could be retarded effectively by intravitreal injections of atropine (Stone et al. 1991, McBrien et al. 1993). These animal studies indicate that atropine exerts its action on myopia control via a non-accommodative mechanism.

By extrapolating from animal studies to humans, it is believed that atropine slows myopia progression in children through a muscarinic receptor-dependent mechanism, other than relaxing accommodation (McBrien et al. 1993).

b. Via muscarinic receptors in the eye

Atropine is a nonselective muscarinic antagonist, with an affinity for all five subtypes of muscarinic acetylcholine receptors (M1-M5), which are present in the retina (Hutchins & Hollyfield 1985), choroid, and sclera of the human eye (Qu et al. 2006). In animal studies, the M2 receptor was excluded as a candidate receptor to affect eye growth, as the M2 antagonists were ineffective in inhibiting eye growth in chicks (Stone et al. 1991). As both M4 and M1 muscarinic receptors were confirmed to be involved in the inhibition of form-deprivation myopia by muscarinic antagonists in a mammal model, it was suggested that atropine exerts its action to retard axial elongation via M1 and M4 receptors (Arumugam & McBrien 2012).

However, the possibility that atropine exerts its action on muscarinic receptors in retinal amacrine cells was ruled out, as ablation of cholinergic amacrine cells did not prevent atropine from inhibiting axial elongation in chicks (Fischer et al. 1998). An animal model showed that injection of atropine inhibited eye growth and caused choroidal thickening in chicks, whereas muscarinic agonists stimulated eye growth and resulted in choroidal thinning (Nickla et al. 2013). It was also revealed that there was a significant increase in choroidal thickness after either short-term use of 1% (Zhang et al. 2016) or 0.01% atropine (Sander et al. 2019). Based on these findings, muscarinic receptors in the choroid may be associated

with retarding effect of atropine in controlling myopia progression.

As axial elongation is the result of the overall expansion of the globe, it is reasonable to believe that atropine exerts its action on muscarinic receptors in multiple tissues of the eye. However, further studies are warranted to clarify its pathway of action.

c. Via increased stiffness of sclera

As over 95% of human myopia is an outcome of increased axial length (McBrien & Gentle 2003), the sclera, the outer fibrous shell of the eyeball, must expand accordingly to accommodate the deformed globe. Significant thinning of the posterior sclera was observed in post-mortems of highly myopic human eyes (Curtin et al. 1979). Although it remains unclear how this thinning of the sclera occurs, it is suggested that biomechanical weakness in the scleral tissue contributes to scleral remodeling, along with axial elongation in myopic eyes (Phillips et al. 2000).

In addition, it was found that, along with stagnation of axial length elongation, the scleral fibrous layer thickened in form-deprived chicks after injection of atropine, suggesting that atropine acts throughout the scleral fibrous layer to inhibit eye growth (Gallego et al. 2012). Topical use of atropine may increase scleral stiffness and, accordingly, interfere with a deformation of the globe. However, there is a lack of evidence from human eyes to support this hypothesis.

## 1.5 Combined treatment

Previous strategies for myopia control, regardless of whether optical or pharmaceutical in nature, have mainly focused on the investigation of the effectiveness of monotherapy versus control treatment (Sections 1.2 to 1.4). To discover more effective strategies, research has shifted towards investigations of combinations of two treatments for myopia control, particularly low-concentration atropine together with optical strategies.

### 1.5.1 Combining 0.5% atropine with progressive addition spectacles

Shih et al. investigated the effectiveness of combining 0.5% atropine with PAS over 18 months, using PAS and SVS as control treatments in a randomized study on myopia control. They reported that the combined treatment was effective in slowing myopia progression (Shih et al. 2001) (Section 1.4.4). However, due to a lack of axial length measurement in any of the treatment groups, the effectiveness of combining 0.5% atropine with PAS, in terms of retarding axial elongation, is unknown.

### 1.5.2 Combining 0.01% atropine with orthokeratology

Kinoshita et al. equally assigned 40 myopic children, aged 8 –12 years, with SER between 1.00 D to 6.00 D, into the combined treatment of 0.01% atropine and ortho-k or ortho-k alone (Kinoshita et al. 2018). Their 1-year result showed that axial elongation in the combined treatment group was significantly slower than the ortho-k alone group (mean ± SD, 0.09 ± 0.12 mm vs 0.19 ± 0.15 mm). Subsequently, after recalculation of the sample size required, a total of 80 subjects were enrolled for the 2-year study, of whom 73 completed the 2-year monitoring (Kinoshita et al. 2020). Axial elongation in the combined treatment group was found to be not significantly slower than that of the ortho-k alone group over two years (mean ± SD, 0.29 ± 0.20 mm vs 0.40 ± 0.23 mm), indicating no additive effect of 0.01% atropine, when used in conjunction with ortho-k. Further analyses revealed that, for the subgroup of children with low initial SER (1.00 to 3.00 D), children who underwent the combined treatment had slower axial elongation compared to those who wore ortho-k lenses alone (0.30 ± 0.22 mm vs 0.48 ± 0.22 mm), but for children with moderate to high initial SER (3.01 to 6.00 D), no significant difference in axial elongation was observed between the two treatment groups (0.27 ± 0.15 mm vs 0.25 ± 0.17 mm). In addition, for children undergoing combined treatment, the axial elongation was comparable between the two subgroups (low

initial SER vs moderate to high initial SER). While for children receiving ortho-k alone, more rapid axial elongation was observed in children with low initial SER than those with moderate to high baseline SER. Based on these observations, it was suggested that children with low initial SER can benefit more from the combined treatment (Kinoshita et al. 2020).

However, the 0.01% atropine eye drops used by Kinoshita et al., were diluted by adding physiological saline to 1% atropine at a ratio of 1: 99, and the stability of the concentration of 0.01% atropine was not monitored. It should be noted that 0.01% atropine was only introduced after three months of ortho-k treatment, not at the commencement of ortho-k treatment. It is uncertain whether the delay affected the effectiveness of the treatment.

In addition, Kinoshita et al. did not refit children until a decrease in unaided visual acuity (UVA) of at least 0.30 logarithm of the minimum angle of resolution (logMAR) was found. This may introduce a confounding situation, as subjects with fast progression were significantly under-corrected for undefined periods in the 2-year study (limited information was provided on the duration of under-correction). Further studies with better study design are warranted on the investigation of an additive effect of the use of 0.01% atropine in conjunction with ortho-k.

A recent four-arm clinical trial randomized 154 children of Chinese ethnicity, aged eight to 12 years and with SER 1.00 to 6.00 D, into treatment groups of receiving 0.01% atropine combined with ortho-k, 0.01% atropine and SVS, ortho-k and placebo, SVS and placebo (Zhao et al. 2020). The preliminary one-month results showed that the axial length remained unchanged in children receiving 0.01% atropine and ortho-k, or those receiving ortho-k and placebo, while there was a significant increase in axial length in those receiving 0.01% atropine and placebo (mean ± SD, 0.04 ± 0.00 mm) or those receiving SVS and placebo (mean ± SD, 0.06 ± 0.06 mm). To further the understanding of the role of the choroid in myopia control, choroidal thickness was measured and compared among treatment groups. It

was found that the choroidal thickness was significantly increased by a mean of 14.1 μm, 9.4 μm, 5.5 μm in children receiving 0.01% atropine combined with ortho-k, ortho-k and placebo, and 0.01% atropine combined with SVS, while no significant change in choroidal thickness was observed in those receiving control treatment (i.e. SVS and placebo) (Zhao et al. 2020). Despite a significant thickening in the choroidal thickness in all three treatment groups, it is impossible to explore the relationship between changes in choroidal thickness and axial elongation over such a short monitoring period (one month). As the 2-year trial is still ongoing, the long-term effectiveness of the combination of 0.01% atropine and ortho-k is unknown.

# Chapter 2 Knowledge gaps and objectives

It is believed that different mechanisms are involved in pharmaceutical and optical interventions for myopia control (Sections 1.3.3.4, 1.3.4.5, 1.4.4.6), therefore, it is possible that a better control effect may be achieved by combining these two strategies. A combination of low-concentration atropine and ortho-k may be a good starting point to investigate the additive myopia control effect (Cho & Tan 2018).

As 0.01% atropine causes negligible ocular side-effects, it is reasonable to use this concentration to determine whether the use of atropine in conjunction with ortho-k is beneficial. To date, the first study investigating the presence of additive effect between 0.01% atropine and ortho-k yielded an insignificant effect in combined treatment compared with ortho-k alone in all subjects (Kinoshita et al. 2020). Another study by Zhao et al. (2020), which commenced later than the current study, is still ongoing (Section 1.5.2). However, there were some issues with the design of the study by Kinoshita et al., leading to less than convincing scientific evidence. Thus, further studies of better design are warranted to provide further insight into this new strategy for myopia control.

Kinoshita et al. (2018 & 2020) provided limited information about changes in ocular parameters, including unaided visual acuity, residual myopia, pupil sizes, the amplitude of accommodation, choroidal thickness, and ocular HOA in their study of combined treatment of 0.01% atropine and ortho-k. It is essential that these changes are carefully recorded and compared, as they may have an influence on axial elongation in children. Both photopic and mesopic pupil sizes, which are important indicators of side-effects, were documented in the ATOM and LAMP studies (Chua et al. 2006, Chia et al. 2012, Chia et al. 2016, Yam et al. 2019, Yam et al. 2020). However, these measurements of pupil diameters were taken without any repeatability assessment, which may lead to errors, particularly in children. To fill this

research gap, it is necessary to assess the repeatability of pupil size measurements for the equipment used in children, to avoid misinterpreting variations in measurements as differences between treatment groups.

Neither the mechanisms of atropine nor ortho-k for myopia control are fully understood. The initial study by Kinoshita et al. (2018) indicated an additive effect with the use of 0.01% atropine with ortho-k over one year, but more studies are needed for confirmation. In addition, by comparing the differences in ocular characteristics, along with their changes, between children using combined 0.01% atropine with ortho-k and ortho-k alone, further insights may be obtained on the mechanism for either combined treatment or ortho-k alone.

The current Atropine 0.01% with Orthokeratology (AOK) study (reported in this thesis) aimed to address some of the main research gaps identified, given that no reports of combination therapy were available at the commencement of this AOK study. Four experiments were conducted to address the following objectives of the current AOK study:

- To assess the repeatability of photopic and mesopic pupil size measurements in children (Chapter 3)
- To investigate if there was an additive effect when 0.01% atropine was used in conjunction with ortho-k over a 2-year study period (Chapter 4)
- To investigate the changes in choroidal thickness in eyes treated with combined 0.01% atropine and ortho-k treatment or ortho-k alone, as well as the associations between these changes (if any) and axial elongation (Chapter 5)
- To outline and compare pre- and post-treatment retinal image quality in eyes treated with combined 0.01% atropine and ortho-k or ortho-k alone, as well as the associations between metrics of ocular aberrations and axial elongation (Chapter 6)

Chapter 3 describe a cross-sectional study to determine and compare the repeatability of

pupil size measurements using OPD-Scan III in myopic children wearing SVS or ortho-k lenses, or receiving combined treatment of 0.01% atropine and ortho-k.

Chapter 4 describes the 2-year randomized controlled trial to investigate whether there is an additive effect when 0.01% atropine was used together with ortho-k, by comparing axial elongations in subjects receiving the combined treatment with those of subjects undergoing ortho-k alone. The associations between ocular parameters (e.g. pupil size, accommodation) and axial elongation are also explored and discussed.

Chapter 5 describes and compares changes in choroidal thickness in the combined treatment group with that of the ortho-k alone group and the associations between these changes and axial elongation.

Chapter 6 describes and compares the pre- and post-treatment retinal image quality between the two groups of subjects and associations between metrics of ocular aberrations and axial elongation.

Chapter 7 is a summary of research findings, limitations, and future research directions.

# Chapter 3 Repeatability of pupil size measurements with OPD-Scan III in myopic children

## 3.1 Introduction

Pupil size in humans is affected by surrounding illumination (Mathur et al. 2014, Guillon et al. 2016), age (Netto et al. 2004, Cakmak et al. 2010, Linke et al. 2012, Guillon et al. 2016), refractive error (Cakmak et al. 2010, Linke et al. 2012, Guillon et al. 2016), cognitive effects (Kloosterman et al. 2015), and anti-muscarinic agents, such as atropine (Chua et al. 2006, Chia et al. 2016, Yam et al. 2020). As an indication of pupil dilation, changes in pupil diameter were measured in clinical trials on atropine, to monitor the mydriatic effects of atropine (Chia et al. 2012, Chia et al. 2016, Yam et al. 2019, Yam et al. 2020). However, these studies showed disparate post-treatment changes in pupil size. For instance, using different pupilometers, the mean change of photopic pupil size of 0.60 mm to 0.74 mm and mesopic pupil size of 0.26 mm to 1.15 mm have been reported in different studies using 0.01% atropine as one of the interventions (Chia et al. 2012, Yam et al. 2020).

It is therefore important to know the repeatability of pupil diameter measurements from a particular pupillometer, as it facilitates the interpretation of clinical results related to the use of atropine. In this study, the OPD-Scan III (Nidek Inc., Tokyo, Japan) was used to assess changes in pupil size. This pupillometer combines the use of a built-in infrared camera to capture mesopic images, and a topographer using an intense light source to stimulate and assess the photopic pupil reaction. It has the advantages of speed of measurement and ease of operation.

As no study has previously assessed the repeatability of OPD-Scan III for pupil size measurement, either on adults or on children, this experiment was performed to determine

and compare the repeatability of pupil size measurements with OPD-Scan III in three groups of myopic children: SVS (subjects wearing spectacles), OK (subjects wearing ortho-k lenses), and AOK (those receiving combined treatment of 0.01% atropine and ortho-k).

## 3.2 Methods

### 3.2.1 Ethics approval

Ethics approval was obtained from the Human Subject Ethics Subcommittee of the School of Optometry of The Hong Kong Polytechnic University. Children and parents provided assent and informed consent, respectively. All procedures followed the tenets of the Declaration of Helsinki.

### 3.2.2 Subjects

Children of Chinese ethnicity and aged six to 13 years with normal ocular health (except myopia) were included. For SVS subjects, low myopia (1.00 D to 4.00 D, inclusive) and no more than 2.50 D astigmatism were required. For OK and AOK subjects, they must have worn ortho-k lenses and/or using 0.01% atropine for at least six months. Exclusion criteria were abnormalities of the pupil, any eye surgery, any history of trauma, and any systemic diseases with ocular complications.

### 3.2.3 Examination procedures

All examinations were performed by the same examiner. After an initial assessment of ocular health and refractive errors, the subjects were exposed to normal room lighting (56 lux) for 1 min, followed by 2 min of dark adaptation with the room lights off (2 lux) in a closed room. The inclusion of 2-min dark adaptation is to ensure that the eyes of subjects were fully adapted to the environment before measurements. In addition, to avoid fatigue, the

time for each set of measurement was limited to no more than 5 min.

Pupil size measurements were taken twice 15 min apart for the right eye only, using OPD-Scan III, under mesopic illuminance (3.5 lux), followed by photopic illuminance (125.6 lux). A lab technician verified the room lighting and the internal illuminance of the pupillometer monthly using a photometer, to ensure consistent illuminance for the measurements. The pupillometer was realigned before each measurement. During measurement, the room lights were kept off, while subjects' left eyes were occluded. They were fogged to relax accommodation by fixating on the internal instrument target (a balloon). For two sets of measurements under either mesopic or photopic conditions, the first three consecutive data capture, which differed less than 0.50 mm, were recorded and averaged for analyses.

### 3.2.4 Statistic analyses

SPSS Statistics Version 25 (IBM Corp, Armonk, NY, USA) was used to analyze the data. A probability (p) value of less than 0.05 was chosen to indicate statistical significance, except where multiple comparisons were made, in which case, Bonferroni-adjusted p of less than 0.017 (0.05/3) was used to indicate significance. To compare the gender proportions among three groups of subjects, Chi-squared tests of proportions were used. The distribution of data (demographics and pupil sizes) were explored using Kolmogorov-Smirnov test.

For normalized data, one-way analysis of variance (ANOVA) was used to explore the difference among groups. If a significant difference was observed among the three groups of subjects, post hoc tests were performed to determine the significance between any two groups. For non-normally distributed data, Kruskal-Wallis test was employed, followed by individual Mann-Whitney tests, to determine the significance between any two groups.

Intraclass correlation coefficient (ICC) was determined between the two sets of pupil size measured under mesopic and photopic conditions, respectively. The correlation between the mean and the between-set difference (i.e. bias) was explored using Pearson's correlation test. If no significant correlation was observed, Bland-Altman plot displaying the mean of bias and 95% limits of agreement of the difference for a specific data set was plotted. Coefficients of repeatability (CR) were calculated as 1.96 times SD of the bias.

## 3.3 Results

Table 3.1 Comparison of pupil size among the three groups of subjects (pooled data – if no significant difference between all or any two groups, as indicated)

| | SVS (n = 16) | OK (n = 34) | AOK (n = 30) | p' | Pooled | ICC (95% CI) | LoA |
|---|---|---|---|---|---|---|---|
| M1, mm | 6.97 ± 0.73 | 7.07 ± 0.64 | 7.17 ± 0.51 | 0.56 | 7.09 ± 0.61 (all 3 groups) | 0.98* (0.97 to 0.99) | Lower: -0.32* (95% CI: -0.37 to -0.26) |
| M2, mm | 7.04 ± 0.76 | 7.11 ± 0.63 | 7.18 ± 0.61 | 0.77 | 7.12 ± 0.61 (all 3 groups) | | Upper: 0.24* (95% CI: 0.18 to 0.29) |
| p | -- | -- | -- | | 0.07 | | |
| P1, mm | 3.29 ± 0.34 | 3.44 ± 0.40 | 3.74 ± 0.46 | 0.001 | 3.39 ± 0.39 (SVS + OK) | 0.98 (0.96 to 0.99) for both AOK and SVS+OK groups | For the SVS + OK group: Lower: -0.21 (95% CI: -0.27 to -0.15) Upper: 0.25 (95% CI: 0.19 to 0.31) |
| P2, mm | 3.27 ± 0.35 | 3.42 ± 0.40 | 3.73 ± 0.43 | 0.001 | 3.37 ± 0.38 (SVS + OK) | | For the AOK group: Lower: -0.24 (95% CI: -0.32 to -0.15) Upper: 0.27 (95% CI: 0.18 to 0.35) |
| p | -- | -- | 0.56 | | 0.25 | | |

SVS – Single Vision Spectacles: OK – Orthokeratology: AOK – Atropine combined with orthokeratology

M1 – 1st mesopic pupil size measurement; M2 – 2nd mesopic pupil size measurement

P1 – 1st photopic pupil size measurement; P2 – 2nd photopic pupil size measurement

p – Probability value of paired t-test for differences between the two measurements

p' – Probability value of one-way ANOVA for difference among three groups

ICC – Intraclass correlation coefficient; CI – Confidence Intervals: LoA – Limits of Agreement

Bold – Indicates significance

*– With exclusion of an outlier (> 3SD)

In all, 80 subjects (16 SVS, 34 OK, and 30 AOK) were measured. There was no significant difference in the gender ratio among the three groups of subjects ($\chi^2$, $p = 0.073$). Compared with the OK and AOK group, SVS subjects were younger (Kruskal-Wallis test, $p = 0.01$; followed by Mann-Whitney test, $p = 0.01$ and $p < 0.001$, respectively), and had higher SER (Kruskal-Wallis test, $p < 0.001$; followed by Mann-Whitney test; both $p < 0.001$). However, there was no significant difference in either age or SER between the OK and AOK groups (Mann-Whitney test, both $p > 0.017$).

Mesopic pupil sizes were not significantly different among the three groups for each set of measurements ($p = 0.56$, 0.77) (Table 3.1), hence the data were pooled for further analyses. Mean difference of two sets of measurement (i.e. bias) was -0.03 (95% CI: -0.07 to 0.00) mm, with 95% limits of agreement of -0.34 (95% CI: -0.40 to -0.28) to 0.27 (95% CI: 0.21 to 0.33) and a CR of 0.31 (95% CI: 0.27 to 0.38). Excluding one outlier (SVS subject) with bias more than three SD from the mean, the bias was -0.04 (95% CI: -0.07 to -0.01) mm, with a CR of 0.28 and smaller 95% limits of agreement (Table 3.1). As biases were not significantly correlated with means of two sets of mesopic measurements (Pearson's $r = -0.02$, $p = 0.83$), Bland-Altman graph was plotted (excluding the outlier) (Figure 3a).

A significant difference in photopic pupil size between groups was found (One-way ANOVA, $p = 0.001$). Post hoc test revealed that both 1st (P1) and 2nd set (P2) of photopic pupil size measurement in the AOK group were significantly larger than in SVS (P1: $p = 0.002$, P2: $p = 0.001$) and OK group (both $p = 0.01$). Since no significant differences in photopic pupil size (either P1 or P2) were observed between the SVS and OK groups for each set of measurements (P1: $p = 0.748$, P2: $p = 0.683$), the data of these two groups were combined (SVS+OK) for repeatability analysis. Biases were not significantly correlated with the means of two sets of photopic measurements in the AOK group (Pearson's $r = -0.25$, $p = 0.19$), or in pooled data of SVS+OK group (Pearson's $r = -0.04$, $p = 0.80$). Bland-Altman

plots of the photopic pupil size measurement for SVS + OK and AOK groups are shown in Figures 3b and 3c, respectively, with bias of 0.02 (95% CI: -0.01 to 0.05) mm for SVS + OK group, and 0.01 (95% CI: -0.03 to 0.06) mm for the AOK group. The 95% limits of agreement in the SVS + OK and the AOK groups are shown in Table 3.1. The CR was 0.25 for AOK and 0.23 for the SVS + OK group.

Figure 3.1a

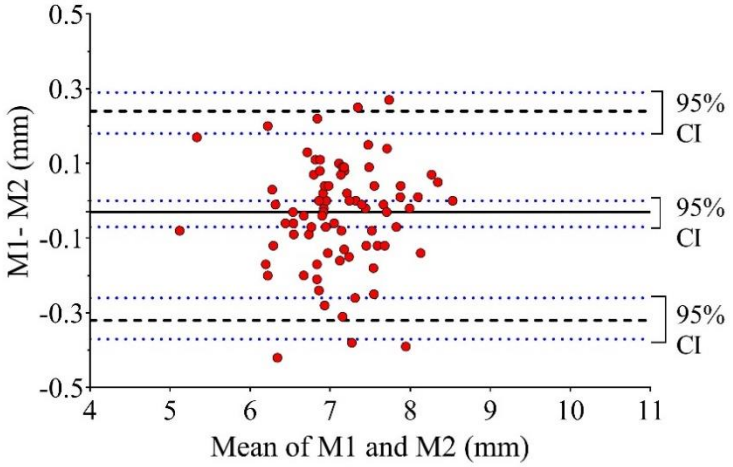



Figure 3.1b

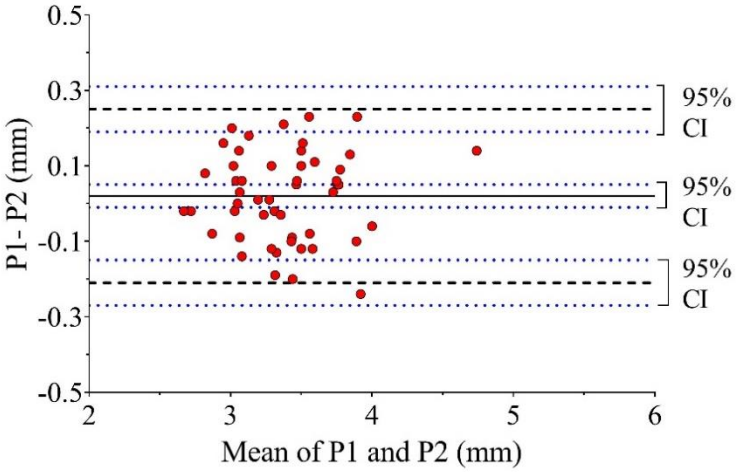



Figure 3.1c

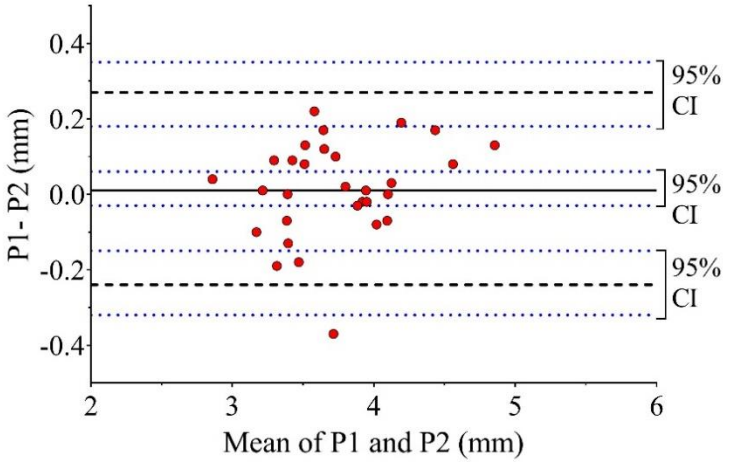



**Figure 3.1 Bland and Altman plots of between-set differences in pupil size measurements against means of difference**

(a) Pooled mesopic pupil size data of three groups (n = 79), with exclusion of an outlier (> 3SD);

(b) Pooled photopic pupil size data of single vision spectacles and orthokeratology subjects (n = 50);

(c) Photopic pupil size data of the combined treatment group (n = 30).

M1 – 1$^{st}$mesopic pupil size measurement; M2 – 2$^{nd}$ mesopic pupil size measurement

P1 – 1$^{st}$ photopic pupil size measurement; P2 – 2$^{nd}$ photopic pupil size measurement

CI – Confidence Interval

The solid line – The mean between-set difference in pupil sizes

The dashed lines –The upper and lower 95% limits of agreements

The upper and lower blue dotted lines – The 95% CI

## 3.4 Discussion

This study is the first to assess the repeatability of pupil size measurement in children, as previous studies have only assessed the repeatability of pupil size measurements in adults (Wachler & Krueger 1999, Schnitzler et al. 2000, Kohnen et al. 2003, Spadea et al. 2005). Wachler and Krueger examined a small sample of seven healthy subjects with a wide age range (i.e. 28 to 42 years) and found the CR to range from 0.6 to 1.4 mm under dim to very bright illuminance (Wachler & Krueger 1999). Some studies only assessed the repeatability of pupil diameter measurement under scotopic light conditions (illuminance levels below 0.05 lux) in adults, as scotopic pupil size was used as an indication for selection of refractive surgery modality (Schnitzler et al. 2000, Kohnen et al. 2003, Mantry et al. 2005, Spadea et al. 2005). In the studies assessing scotopic pupil size, the CR ranged between 0.70 mm to 1.10 mm, regardless of whether a digital or handheld infrared pupillometer was used (Schnitzler et al. 2000, Kohnen et al. 2003, Spadea et al. 2005). In the current study, the key findings were that using OPD-Scan III at a single visit, the CR of mesopic and photopic pupil size measurements were 0.28 mm (for three groups combined) and not more than 0.25 mm (0.25 mm for the AOK group and 0.23 mm for the SVS + OK group), respectively, in children aged seven to 13 years. These small CR values indicated that OPD-Scan III assessment of the mesopic and photopic pupil size is highly repeatable in children.

There may be great fluctuation in pupil size measurements in children because of a lack of cooperation and the presence of constant oscillations of pupil diameter, which are regarded to be independent of eye movements or changes in illumination (McLaren et al. 1992). In the current study, several attempts were made to control

possible factors that could affect the size of the pupil. Firstly, to ensure that eyes were fully adapted to the environment, all subjects had to undergo dark adaptation before measurement. Secondly, their eyes were relaxed during measurement to as far as possible reduce the influence of accommodation variations. Thirdly, the illuminance of the internal light source was fixed to avoid variations in illuminance during measurement. Fourthly, readings of three consecutive captures were averaged as the real-time value of each measurement to avoid fluctuations that may occur from a single capture. For data analyses, given that the undergoing treatment could also influence the repeatability of taking pupil parameters, differences in means of pupil size among three groups were examined before plotting and calculation of CR and limits of agreement.

The results of the current study showed that pupil sizes under mesopic conditions did not differ among the three groups of subjects, indicating that the treatments used in this study did not affect the mesopic pupil size. The ICC value obtained for the pooled data (mesopic pupil size) indicated excellent repeatability and the CR obtained was only 0.28 mm. Photopic pupil size only differed for the AOK group, which may be due to the use of 0.01% atropine leading to mild mydriasis and, hence, a larger photopic pupil size. For photopic pupil size, the ICC and CR values for AOK and SVS + OK subjects were comparable, indicating excellent repeatability and that the use of 0.01% atropine had minimal effect on the repeatability.

Clinically, 0.50 mm is the smallest reading that can be taken with a pupillary distance (PD) rule, and a difference of 0.4 mm in pupillary diameter or greater between the two eyes has been suggested to be anisocoria (Lam et al. 1996). Therefore, the discrepancy of repeated measurements for a reliable pupillometer is anticipated to be not more than 0.50 mm. In the current study, the average discrepancy

of repeated measures obtained for OPD-Scan III is close to zero for both photopic and mesopic pupil size measurements (ranging between -0.04 to 0.01), indicating minimal bias between measurements. There was no trend observable that bias between measurements tended to get larger as the mean of pupil size increased in any of the three Bland-Altman plots. In addition, limits of agreement, for both mesopic and photopic pupil size measurements, did not exceed ± 0.50 mm. The limits of agreement for mesopic measurements was 0.10 wider than for the photopic measurements (Table 3.1 and Figure 3.1) but would be considered insignificant in clinical settings when natural fluctuation in pupil size is taken into consideration (McLaren et al. 1992).

It was reported that, after being treated with ortho-k for two years, axial elongation in children with larger pre-treatment scotopic pupils was significantly slower than those with smaller ones, suggesting that pupil size may play a role in myopia control using ortho-k (Chen et al. 2012). While it is still unknown if pupil size influences the myopia control effect of atropine, the dilated pupil size is however considered a side-effect of atropine, which may affect vision. Thus, it is important to take accurate measurements of pupil size in clinical studies including the use of atropine and/or ortho-k, to further understand the role of pupil size in myopia control. To indicate a meaningful change, the minimal measured detectable change should not be less than the CR determined from a repeatability assessment (Bland & Altman 2003). Based on the CR values obtained in the current study, a difference of at least 0.29 mm and 0.25 mm in mesopic and photopic pupil sizes, respectively, would be required to determine whether clinically significant changes are present when OPD-Scan III is used to assess pupil size in children.

## 3.5 Conclusion

The results show that measurements of mesopic and photopic pupil size of children taken with the OPD-Scan III were very repeatable. The CR for both mesopic and photopic pupil sizes were small, and changes in mesopic and photopic pupil sizes that are lower than 0.28 mm and 0.25 mm, respectively, are unlikely to reflect a real or significant change in children.

---

Paper published from work reported in this chapter:

Tan Q, Ng ALK, Cheng GPM, Woo VCP, Cho P (2021). Repeatability of pupil size measurements with NIDEK OPD-Scan III in myopic children. Ophthalmic Physiol Optics 41: 431-436

# Chapter 4 Combined 0.01% Atropine with Orthokeratology (AOK) study: a 2-year randomized controlled trial on retarding axial elongation

## 4.1 Introduction

The AOK study was conducted to explore whether there is an additive effect on myopia control with the use of 0.01% atropine in conjunction with ortho-k. Axial elongation was compared over two years in subjects receiving combined 0.01% atropine with ortho-k versus ortho-k alone.

There are two reasons for the decision not to include a treatment group using 0.01% atropine. Firstly, it is important to note that monotherapy of 0.01% atropine has been shown to produce a treatment effect of only 0.05 mm over one year, which was too small to reach either a statistical or a clinical significance (Yam et al. 2019). In ATOM2, axial elongation of subjects using 0.01% atropine was almost equivalent to that of historical controls treated with placebo over two years (Chia et al. 2012). Such a failure of 0.01% atropine to retard axial elongation renders it unethical to offer single use of 0.01% atropine to myopic children, especially those experiencing rapid myopia progression. Secondly, a lack of a parallel arm of monotherapy of 0.01% atropine will not affect the investigation of a possible additive effect between 0.01% atropine and ortho-k, as ortho-k alone was set as a comparator.

Kinoshita and co-workers reported significant initial slower axial elongation in subjects undergoing combined ortho-k and 0.01% atropine compared to those using

ortho-k alone (mean ± SD, 0.09 ± 0.12 mm vs 0.19 ± 0.15 mm) after one year of monitoring (Kinoshita et al. 2018). However, they failed to observe an additive effect of the combined treatment at the end of two years of monitoring (Kinoshita et al. 2020) (Section 1.5.2). The study design of the AOK study differed from that conducted by Kinoshita et al. (2020) in many aspects. Firstly, the subjects in the AOK study, subjects were younger (6 – < 11 years) and had lower baseline myopia (1.00 – 4.00 D). Secondly, 0.01% atropine was used together with ortho-k lens wear commencing on the first overnight rather than after three months of ortho-k treatment. Thirdly, subjects with UVA poorer than 0.18 logMAR were refitted to improve vision, while Kinoshita et al. used a 0.30 logMAR decrease in UVA as an indication for lens refitting. Finally, measurement of pupil size and accommodation were performed to best monitor the effect of atropine, whereas no data in this respect were provided by Kinoshita et al. (2020).

## 4.2 Methods

### 4.2.1 Ethics approval

Ethical approval was obtained from the Human Subject Ethics Subcommittee of the School of Optometry of The Hong Kong Polytechnic University and the Institutional Review Board of The University of Hong Kong/Hospital Authority Hong Kong West Cluster. A certificate for the clinical trial/medicinal test was obtained from the Pharmacy and Poison Board, Department of Health of Hong Kong. All children provided assent and parents provided informed consent before participation, with all procedures following the tenets of the Declaration of Helsinki.

## 4.2.2 Study design

The AOK study was an interventional, single-masked, randomized, 2-year study (ClinicalTrials.gov number, NCT02955927). Eligible subjects were randomized into either the AOK group using combined 0.01% atropine with ortho-k, or the OK group using ortho-k alone at a ratio of 1:1. The randomization was performed using a commercial spreadsheet random number generator (Excel; Microsoft, Redmond, Washington, USA). Treatment in the AOK group consisted of instillation of one drop of 0.01% atropine in each eye, 10 min before nightly wear of ortho-k lenses, while subjects in the OK group only wore ortho-k lenses nightly. As it was impossible to mask subjects and investigators who performed the follow-up about the assigned treatment, only the measurement of axial length (the primary outcome) was masked.

## 4.2.3 Subjects and materials

Table 4.1 Entry criteria of the AOK study

| Inclusion criteria | Exclusion criteria |
|---|---|
| · Children of Chinese ethnicity<br>· Aged 6 – < 11 years<br>· Myopia between 1.00 – 4.00 D (inclusive)<br>· Astigmatism (negative cylinder) not more than 2.50 D, with axes 180 ± 30 (other axes not more than 0.50 D)<br>· Difference in SER < 1.00 D between the two eyes<br>· BCVA of at least 0.10 logMAR or better in either eye<br>· Corneal toricity (measured by topography) less than 2.00 D in either eye<br>· Normal ocular health other than myopia<br>· Agree to be randomized and to attend the scheduled aftercare visits | · Any contraindication to the use of atropine (e.g. known allergies or cardiovascular disease, epilepsy)<br>· Any contraindication to orthokeratology (e.g. history of ocular inflammation or infection, strabismus or amblyopia)<br>· History of myopia control treatment (e.g. atropine, contact lenses, bifocal, or multifocal spectacles)<br>· Systemic condition which might affect refractive development (e.g. Marfan's syndrome, Down syndrome)<br>· Ocular conditions which might affect refractive error (e.g. ptosis or cataract) |

AOK – Atropine combined with orthokeratology

SER – Spherical Equivalent Refraction (negative power, unless otherwise specified)

BCVA – Best-Corrected Visual Acuity

Subjects were recruited through local newspaper advertising and word-of-mouth. Those who fulfilled the entry criteria (Table 4.1) at a screening visit were invited to participate in lens insertion and removal training (IR training) sessions. Subjects and/or their parents needed to pass the IR training, by mastering lens handling skills, before becoming eligible for randomization, otherwise, they were excluded.

Table 4.2 Orthokeratology lenses, solutions for lens care, and atropine eye drops used in the AOK study

| Orthokeratology lenses | | |
|---|---|---|
| KATT BE Free Lens (Precision Technology Services, Vancouver, B.C., Canada) | Material | HDS 100 |
| | Oxygen permeability | 100 Barrer |
| | Back vertex power | +0.50 D |
| | Replacement period | 12 months |
| | Total diameter | 10.2, 10.6, 11.0, 11.2 mm |
| | Optical zone | 6 mm |
| | Central thickness | 0.20 mm |
| Lens care solutions | Purpose | |
| Ophtecs (Ophtecs Corporation Tokyo, Japan) | Rubbing | $O_2$ Daily Care Solution Pure |
| | Rinsing | Cleadew saline |
| | Disinfecting | Cleadew GP |
| | Aid lens insertion and removal | Tiare W Artificial tears |
| AIM Atropine eye drops 0.01% (Single-dose, preservative-free atropine eye drops from Aseptic Innovative Medicine Co., Ltd., Taiwan) | | |

AOK – Atropine combined with orthokeratology

All subjects were fitted with a pair of four-zone ortho-k lenses, with parameters calculated using Eye Care Practitioner Software (Precision Technology Services, Vancouver, B.C., Canada), based on corneal topography, non-cycloplegic manifest refraction, and the horizontal visible iris diameter (Table 4.2). At the 8-mm chord of the cornea, if the difference in corneal sag between the horizontal and vertical

meridians was more than 30 μm, a toric lens design was used; otherwise, a spherical design was used, according to the manufacturer's recommendation.

A full correction was targeted for all subjects. Lens refitting/reordering was performed if:

1) UVA in either eye was worse than 0.18 logMAR after stabilization of treatment, or
2) non-cycloplegic residual SER was equal to or higher than 0.50 D at any visit after stabilization of treatment, or
3) moderate to severe decentration of a lens (lens decentration of more than 1 mm) was observed.

Complimentary contact lens care solutions for rinsing, disinfecting, insertion, and removal of lenses, were provided to facilitate subjects' compliance with regular replacement (Table 4.2).

Single-dose preservative-free 0.01% atropine eye drops (Aseptic Innovative Medicine Co., Ltd., Taiwan) were dispensed to AOK subjects to prevent cross-contamination from the use of multi-dose eye drops. With the aim of tracking and monitoring subjects' compliance with daily application, used vials of atropine eye drops were collected at follow-up visits and three new boxes (30 vials per box) were dispensed every three months. Subjects were instructed to adhere to eight hours of lens wear every night, but to discontinue lens wear and/or instilling of atropine eye drops during ill health or in the presence of any abnormal ocular symptoms. During the study, subjects demonstrating any contraindication to continuation of ortho-k treatment or atropine eye drops, such as significant adverse events, failing to achieve the desired myopic reduction after modification of lens parameters, non-compliant with lens wear or use of atropine eye drops, or loss to follow-up were excluded from the study At each follow-up visit, both subjects and parents were asked if they

encountered any problems (symptoms). By definition, any abnormal events, regardless of whether they appeared relevant to ortho-k or atropine use, should be documented as adverse events (e.g. hospitalization due to injury). However, only ocular adverse events and systemic adverse events that require at least 1-week discontinuation of ortho-k lens wear and/or use of 0.01% atropine were reported in this thesis.

### 4.2.4 Examination procedures

Table 4.3 Examination procedures

| Non-cycloplegic examinations | Equipment | Data collection | After-care |
|---|---|---|---|
| UVA | High contrast (100%) ETDRS charts (Precision Vision, La Salle, IL) | √ | √ |
| Slit-lamp microscopy | TOPCON SL7 and TOPCON IMAGEnet system (Version 2000, Topcon Corp., Tokyo, Japan) | √ | √ |
| Subjective refraction | Trial frame and trial lenses | √ | √ |
| BCVA | ETDRS charts (Precision Vision, La Salle, IL) | √ | √ |
| Amplitude of accommodation | Royal Air Force rule (Harlow, Essex, UK) | √ | |
| Corneal topography | Medmont E300 corneal topographer (Version 6.1.2; Medmont Pty. Ltd., Camberwell, Australia) | √ | √ |
| Pupil size | OPD-Scan III (Nidek Inc., Tokyo, Japan) | √ | |
| Ocular aberration | COAS (Wave-front Sciences Ltd., New Mexico, USA) | √ | |
| Choroidal thickness | SD-OCT (Heidelberg Engineering, Inc., Heidelberg, Germany) | √ | |
| Intraocular pressure | NIDEK NT-2000 (Nidek Co., Ltd., Aichi, Japan) | √ | |
| Cycloplegic examinations | | | |
| Subjective refraction | Trial lens set | √ | |
| BCVA | ETDRS charts (Precision Vision, La Salle, IL) | √ | |
| Axial length | Zeiss IOLMaster (Carl Zeiss Meditec AG, Jena, Germany) | √ | |
| Fundus | Binocular indirect ophthalmoscopy and fundus camera (Topcon TRC NW8 retinal camera; Topcon Corp., Tokyo, Japan) | √ | |

UVA – Unaided Vision Acuity
BCVA – Best Corrected Vision Acuity
ETDRS – Early Treatment Diabetic Retinopathy Study

COAS – Complete Ophthalmic Analysis System
SD-OCT – Spectral Domain Optical Coherence Tomography

Clinical care was provided throughout the study period. Parents were able to contact research staff via telephone 24 hours a day, allowing subjects and parents to report any abnormal ocular or systematical events (e.g., acute red eye, itching and ocular pain, unusual secretions, hospitalization) as soon as possible so that immediate referral to an ophthalmologist could be arranged if indicated.

All subjects were required to attend a cycloplegic data-collection visit after the first month of lens wear, and at 6-monthly intervals after the commencement of lens wear. In addition, all subjects were required to attend routine aftercare visits (after first overnight wear and 1-week, 2-week, 3-week, and every 3 months after commencement of lens wear) at the Optometry Clinic of The Hong Kong Polytechnic University. Unscheduled visits, where necessary, were arranged to ensure good lens fitting and ocular integrity. Additionally, AOK subjects were required to attend 3-monthly visits at Grantham Hospital of The University of Hong Kong for the prescription of 0.01% atropine eye drops, as well as ocular health assessment by an ophthalmologist.

Table 4.3 summarizes examinations that were performed at data-collection and aftercare visits.

#### 4.2.4.1 Aided and unaided visual acuity, ocular health, and amplitude of accommodation

Following the procedure reported previously (Cheung et al. 2007), high contrast (100%) UVA and best-corrected visual acuity (BCVA) were measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) charts (Precision Vision, La Salle, Illinois, USA) under normal room lighting at a distance of four meters. The

examination procedures for visual acuity assessment were as follows:

1) Read the middle letter of the first line (guessing was allowed throughout the procedure). If correct, read the next line down, until a wrong reading was found.
2) Return to the last line in which the middle letter was correctly read. Read all the letters in this line. If at least four letters were correctly read, try to read all the letters the next line down, until less than four letters were correctly read in the line.
3) Terminate at the line with less than four letters correctly read. The result of visual acuity was the sum of scores at the terminated line (numbers of letters correctly read × -0.02) and the logMAR reading of the last line, in which at least four letters were correctly read.

Ocular health was assessed using a slit-lamp (TOPCON slit-lamp SL7; Topcon Corp., Tokyo, Japan) and any abnormality noted graded according to the Efron grading scales (Efron 1998). Photographs of the anterior segment, where necessary, were taken using the TOPCON IMAGEnet system (Version 2000, Topcon Corp., Tokyo, Japan). With best corrected for distance, three measurements of the amplitude of accommodation were performed with the push-up method, using Royal Air Force Rule (Harlow, Essex, UK) for each eye. The averaged value of three measurements was recorded for analysis.

4.2.4.2 Corneal topography

At each visit, corneal topography was measured using the Medmont E300 corneal topographer (Version 6.1.2; Medmont Pty. Ltd., Camberwell, Australia). Four maps with a score of at least 98 were captured for each eye and used for analysis. In line with guidelines provided by the manufacturer, a subtractive tangential map was used to evaluate the lens centration after overnight lens wear.

4.2.4.3 Photopic and mesopic pupil sizes

With illuminance internally controlled and fixed, pupil sizes were measured with an OPD-Scan III (Nidek, Gamagori, Japan) under photopic (125.6 lux) and mesopic illuminance (3.5 lux) in a closed room with lights off (2 lux). To prepare the eye for measurement, 1-min adaptation to the environment (56 lux) with room lights on, followed by 2-min dark adaptation to the room with lights off, was conducted before each measurement. The results of the first three measurements with differences less than 0.50 mm, were averaged for analysis.

4.2.4.4 Ocular tonometry

Ocular tonometry was performed to monitor the internal ocular pressure (IOP) using NIDEK NT-2000 (Nidek Co., Ltd., Aichi, Japan). The first three measurements with between-measurement differences less than 3 mm Hg were recorded. Any subject showing an IOP higher than 21 mmHg in either eye at any visit was excluded.

4.2.4.5 Axial length

After completing pre-cycloplegic examinations, pupil dilation was performed using two drops of 1% cyclopentolate administered 5 min apart. Measurement of axial length was performed by a masked examiner at least 30 min after cycloplegia, using Zeiss IOLMaster (Carl Zeiss Meditec AG, Jena, Germany). Composite readings that were automatically calculated from five readings with a maximum difference of 0.02 mm and a signal-to-noise ratio above five, were used for the analysis of axial length.

4.2.4.6 Fundus examination

After cycloplegia, the fundus was examined at baseline visit and 6-monthly intervals after the commencement of lens wear, using binocular indirect ophthalmoscopy to ensure no abnormality was present before or after the study

treatment. Nine 45-degree fundus photographs were taken using a fundus camera (Topcon TRC NW8 retinal camera; Topcon Corp., Tokyo, Japan).

### 4.2.5 Sample size calculation

At least 24 subjects in each group were required to complete the 2-year study to achieve 80% power to detect a minimum difference of 0.18 mm (approximately 0.50 D) in axial elongation in two years with a 5% level of significance (two-tailed), using the within-group SD of 0.25 mm from the ROMIO study (Cho & Cheung 2012). Assuming there will be a 20% dropout rate over two years, at least 60 eligible subjects would be recruited and commenced the treatment.

### 4.2.6 Statistic analysis

Only data from the right eye of subjects who completed the 2-year study were used for data analyses. Statistical analyses were performed using IBM SPSS Statistics for Windows (Version 25.0. IBM Corp., Armonk, New York, USA).

The Normality of the data was first explored using the Kolmogorov-Smirnov test. Crosstab analysis was used to compare the gender ratio, and unpaired t-tests were used to compare the baseline characteristics. After confirming a normal distribution, 2-way repeated measures analyses of variance (RM ANOVA) were used to compare changes in parameters (e.g. axial length, pupil sizes, accommodation, cycloplegic SER, UVA, and BCVA) in the two groups of subjects, with post hoc analyses to examine between-group or between-visit differences, where appropriate.

A linear mixed model was used to assess the influence of predictive variables (baseline age, sex, cycloplegic SER, photopic and mesopic pupil sizes, and accommodation) on axial elongation in each group and all subjects, with first-order

autoregressive covariance structure and restricted maximum likelihood estimation. Individual slope and intercept were included as random effects and an unstructured covariance matrix was used to control for inter-subject variation. Effects of changes in pupil size (under mesopic and photopic conditions) and amplitude of accommodation on axial elongation were examined in a second linear mixed model with the same modeling as the first. A p-value < 0.05 (unadjusted) was considered statistically significant.

Subjects were also classified into different sub-groups based on axial elongation. The mean axial elongation was 0.36 mm in ortho-k treated eyes in the ROMIO study (Cho & Cheung 2012). Selecting the 50th percentile of 0.36 mm (0.18 mm) as the cut-off value for dividing subjects into different subgroups, axial elongation in the current study was classified into slow (< 0.18 mm), moderate (0.18–< 0.36 mm), and rapid (≥ 0.36 mm).

Ocular adverse events were classified as severe, significant, or insignificant according to principles described for continuous contact lens wear (Morgan et al. 2005, Sankaridurg et al. 2010). For an accurate recording of adverse events, both eyes of each subject were considered at every visit, and bilateral events were counted as two events. Corneal staining at grade two or above, using Efron's grading scale (Efron 1998), in terms of depth and/or extent at any visit was regarded as an adverse event.

## 4.3 Results

### 4.3.1 Subjects and dropouts

A total of 214 subjects were assessed for eligibility between November 2016 to March 2018, of whom 100 subjects passed the screening assessment and received IR training. Seventy-two subjects and/or their parents fulfilled the lens handling

requirements after completing the training (Figure 4.1). After random assignment to either the AOK or OK group, three AOK subjects and one OK subject refused their allocated intervention and were thus excluded, leaving 68 subjects (i.e. 33 AOK and 35 OK subjects) who commenced the treatment. No significant differences in age, sex, SER, axial length, pupil sizes, BCVA, or accommodation were found between the two groups of subjects at the baseline visit (all $p > 0.05$) (Table 4.1).

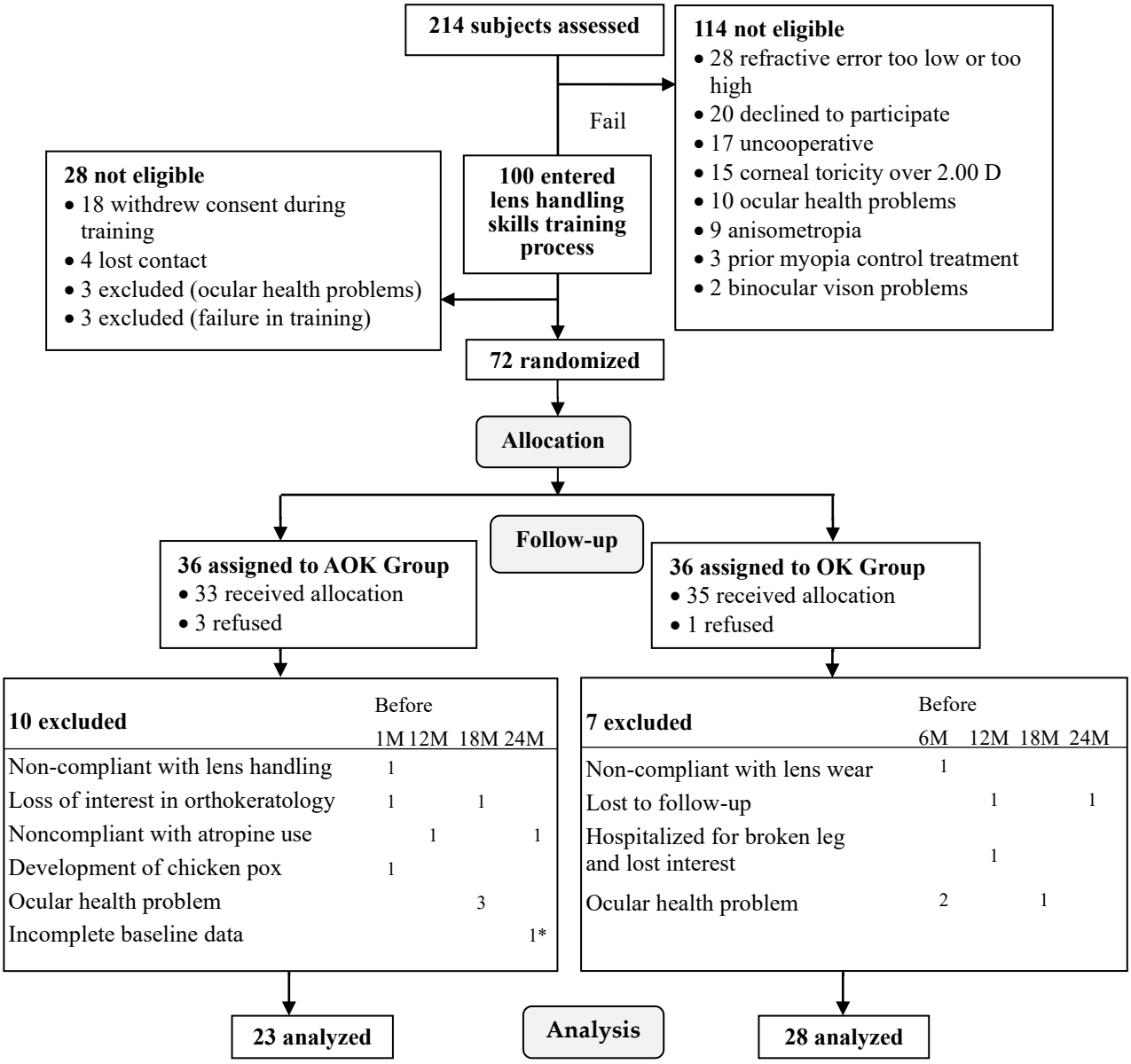



**Figure 4.1 Flow chart showing subject recruitment and dropouts**

AOK – Combined atropine with orthokeratology
OK – Orthokeratology alone
* – Excluded at 24-month visit

Table 4.4 Demographics and baseline data (Mean ± SD) of subjects who completed the 2-year study and dropouts

| | All | | | Completed | | | Excluded | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | AOK (n = 33) | OK (n = 35) | p | AOK (n = 23) | OK (n = 28) | p | AOK (n = 10) | p' | OK (n = 7) | p' |
| Age (years) | 9.14 ± 1.17 | 9.14 ± 1.14 | 0.990 | 9.17 ± 1.02 | 9.13 ± 1.17 | 0.885 | 9.04 ± 1.51 | 0.754 | 9.16 ± 1.07 | 0.476 |
| Male/Female | 11/22 | 15/20 | 0.383 | 9/14 | 12/16 | 0.507 | 2/8 | 0.187 | 3/4 | 1.000 |
| Axial Length (mm) | 24.44 ± 0.62 | 24.46 ± 0.78 | 0.921 | 24.49 ± 0.60 | 24.40 ± 0.81 | 0.667 | 24.32 ± 0.69 | 0.477 | 24.67 ± 0.64 | 0.678 |
| SER (D) | 2.69 ± 0.92 | 2.85 ± 0.92 | 0.486 | 2.71 ± 0.97 | 2.81 ± 0.97 | 0.717 | 2.64 ± 0.85 | 0.828 | 2.98 ± 0.76 | 0.943 |
| Mesopic pupil size (mm) | 6.31 ± 0.77 | 6.49 ± 0.85 | 0.347 | 6.33 ± 0.78 | 6.55 ± 0.90 | 0.354 | 6.25 ± 0.81 | 0.793 | 6.26 ± 0.61 | 0.476 |
| Photopic pupil size (mm) | 3.21 ± 0.31 | 3.14 ± 0.28 | 0.332 | 3.23 ± 0.31 | 3.16 ± 0.30 | 0.446 | 3.17 ± 0.33 | 0.595 | 3.04 ± 0.17 | 0.649 |
| BCVA (logMAR) | -0.04 ± 0.06 | -0.03 ± 0.05 | 0.476 | -0.03 ± 0.05 | -0.03 ± 0.05 | 0.715 | -0.06 ± 0.06 | 0.102 | -0.05 ± 0.04 | 0.191 |
| Accommodation (D) | 13.2 ± 2.1 | 12.8 ± 2.2 | 0.348 | 13.8 ± 2.1 | 13.0 ± 2.4 | 0.170 | 11.9 ± 1.3 | 0.020 | 11.9 ± 1.3 | 0.707 |

AOK – Combined atropine with orthokeratology

OK – Orthokeratology alone

SER – Spherical Equivalent Refraction (negative power, unless otherwise specified)

BCVA – Best Corrected Visual Acuity

p – Probability value of unpaired t-test for differences between groups (Crosstab analysis was used to compare the gender ratio).

p' – Probability value of unpaired t-test for differences between those who completed the 2-year study and dropouts in each group (Crosstab analysis was used to compare the gender ratio)

Ten AOK subjects and seven OK subjects were excluded at different stages of the study for various reasons (Figure 4.1). Of note, six subjects (three in each group) were excluded due to ocular health issues (Section 4.3.4.3). A total of 23 AOK subjects (15 females, 9 males) and 28 OK subjects (16 females, 12 males) completed the 2-year study. Despite dropouts, there was an absence of significant differences in the baseline data between the two groups of subjects who completed the 2-year study (all $p > 0.05$) (Table 4.1). Except for excluded subjects in the AOK group who had a lower amplitude of accommodation ($p = 0.020$), there were no significant differences in other baseline characteristics between those who completed the 2-year study and dropouts (all $p > 0.05$). However, the difference in the amplitude of accommodation (< 2.0 D) between subjects who completed the 2-year study and dropouts in the AOK group was clinically insignificant, considering the young age and robust amplitude of accommodation of the subjects at the baseline visit. In the OK group, there were no significant differences in baseline characteristics between those who completed the study and dropout cases (all $p > 0.05$).

### 4.3.2 Axial elongation

Figure 4.2 shows the axial elongation in both groups of subjects over two years. Over two years, the overall mean axial elongation in the AOK group was 0.14 mm slower than that in the OK group (mean ± SD, 0.17 ± 0.20 mm vs 0.31 ± 0.19 mm, $p = 0.01$, Table 4.2). A significant group by visit interaction was observed for axial elongation ($p = 0.045$, Table 4.2), indicating a significant difference in axial elongation between the two groups. Further post hoc analyses showed that axial elongation in the AOK group was significantly lower than that in the OK group at all post-treatment visits (all $p < 0.05$, Table 4.2).

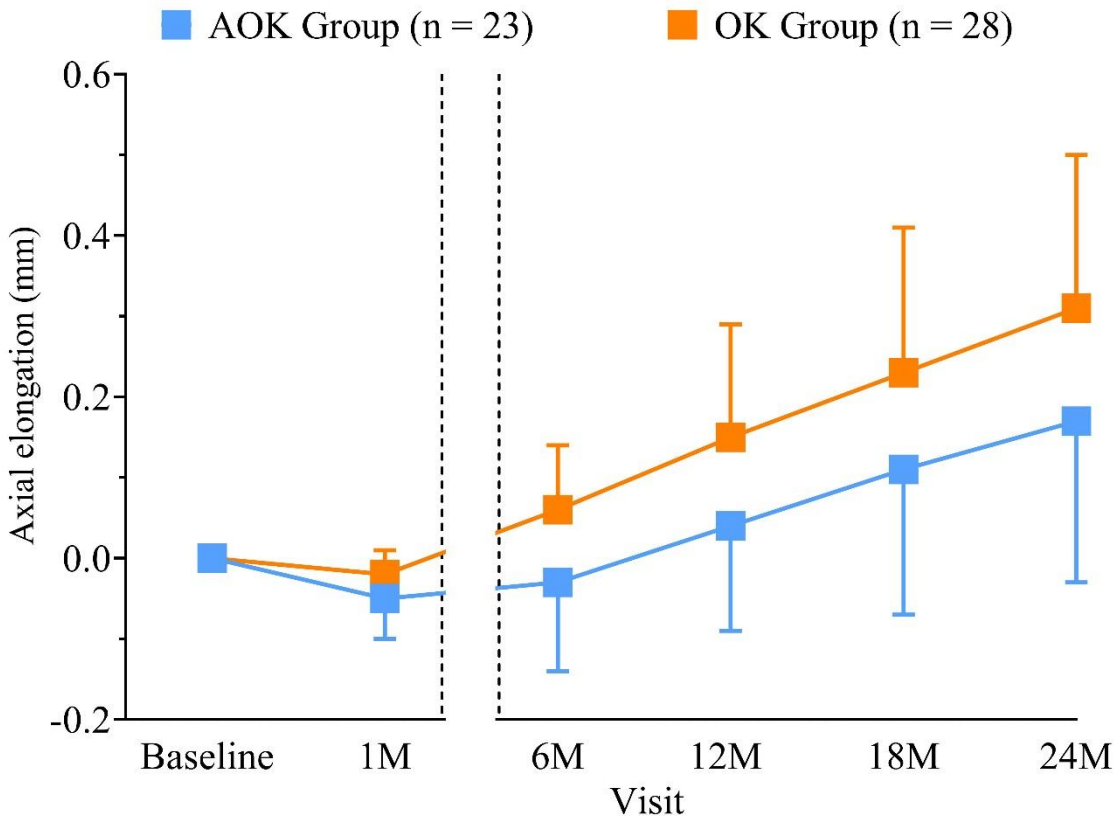



Figure 4.2 Cumulative axial elongation in the two groups of subjects over two years
AOK – Combined atropine with orthokeratology
OK – Orthokeratology alone
Vertical dashed lines – Indicating the 1-month visit, which was different from the remaining visits that performed 6-monthly after the commencement of lens wear

Table 4.5 Changes in parameters (Mean ± SD) in the two groups of subjects

| Parameters | Group | Mean ± SD | | | | | Group x visit interaction (F, p) | p' (12M vs 24M) | |
|---|---|---|---|---|---|---|---|---|---|
| | | 1M | 6M | 12M | 18M | 24M | | AOK (n = 23) | OK (n = 28) |
| Axial elongation | AOK | -0.05 ± 0.05 | -0.03 ± 0.11 | 0.04 ± 0.13 | 0.11 ± 0.18 | 0.17 ± 0.20 | 3.56, 0.045 | < 0.001 | < 0.001 |
| | OK | -0.02 ± 0.03 | 0.06 ± 0.08 | 0.15 ± 0.14 | 0.23 ± 0.17 | 0.31 ± 0.19 | | | |
| | P† | 0.002 | 0.001 | 0.006 | 0.013 | 0.010 | | | |
| Changes in photopic pupil (mm) | AOK | 0.72 ± 0.43 | 0.50 ± 0.37 | 0.40 ± 0.34 | 0.55 ± 0.37 | 0.76 ± 0.46 | 2.99, 0.036 | 0.003 | 0.096 |
| | OK | -0.01 ± 0.18 | -0.05 ± 0.28 | 0.02 ± 0.29 | 0.07 ± 0.30 | 0.24 ± 0.39 | | | |
| | P† | < 0.001 | < 0.001 | < 0.001 | < 0.001 | < 0.001 | | | |
| Changes in mesopic pupil (mm) | AOK | 0.71 ± 0.35 | 0.66 ± 0.40 | 0.62 ± 0.50 | 0.76 ± 0.45 | 0.81 ± 0.49 | 1.07, 0.369 | 0.878 | 0.140 |
| | OK | 0.09 ± 0.34 | 0.09 ± 0.40 | 0.14 ± 0.51 | 0.13 ± 0.54 | 0.37 ± 0.57 | | | |
| | P† | < 0.001 | < 0.001 | 0.001 | < 0.001 | 0.005 | | | |
| Changes in accommodation (D) | AOK | -0.9 ± 2.0 | -1.6 ± 2.1 | -1.3 ± 2.0 | -2.2 ± 2.3 | -2.2 ± 2.1 | 0.75, 0.491 | 0.033 | 0.721 |
| | OK | -0.6 ± 2.8 | -0.7 ± 2.4 | -0.7 ± 2.4 | -1.1 ± 2.5 | -1.2 ± 2.3 | | | |
| | P† | | | 0.183 | | | | | |
| Changes in cycloplegic SER (D) | AOK | 2.91 ± 0.77 | 3.08 ± 0.97 | 3.07 ± 0.94 | 3.04 ± 1.03 | 2.81 ± 0.98 | 2.95, 0.029 | 0.118 | 0.865 |
| | OK | 3.00 ± 1.00 | 3.03 ± 0.99 | 2.87 ± 1.00 | 2.67 ± 1.10 | 2.72 ± 1.03 | | | |
| | P† | | | 0.528 | | | | | |

AOK – Combined atropine with orthokeratology

OK – Orthokeratology alone

SER – Spherical Refractive Error (negative power, unless otherwise specified)

p– Probability value of RM ANOVA, with post hoc analyses (P†) for differences between groups over time

p' – Post hoc analyses for differences in parameters between 12-month and 24-month visits in each group

Bold – Indicates significance

Further analyses of the 6-monthly axial length changes revealed a significant between-group difference in axial elongation for the first 6-month period (paired t-test, p = 0.001, Table 4.3), but not for the subsequent three 6-monthly periods (all p > 0.05, Table 4.3). In the AOK group, axial elongation in the first 6-month period was significantly less than that for the second, third, and fourth 6-monthly periods (p < 0.001, p < 0.001, p = 0.001, respectively), whilst no difference in axial elongation was found among the second, third, and fourth 6-monthly periods (adjusted p > 0.013). In the OK group, no significant difference in axial elongation was observed between any 6-monthly period (all p > 0.013).

Table 4.6 Comparison of 6-monthly axial elongation between the two groups

| 6-monthly | AOK (n = 23) | 95% CI | OK (n = 28) | 95% CI | p |
|---|---|---|---|---|---|
| 1st | -0.03 ± 0.11 | -0.07 to 0.01 | 0.06 ± 0.08 | 0.03 to 0.10 | 0.001 |
| 2nd | 0.08 ± 0.06^ | 0.05 to 0.11 | 0.09 ± 0.07 | 0.07 to 0.12 | 0.422 |
| 3rd | 0.06 ± 0.06^ | 0.04 to 0.09 | 0.08 ± 0.07 | 0.05 to 0.10 | 0.224 |
| 4th | 0.06 ± 0.07^ | 0.03 to 0.09 | 0.08 ± 0.07 | 0.06 to 0.11 | 0.423 |

AOK – Combined atropine with orthokeratology

OK – Orthokeratology alone

CI – Confidence Interval

p – Probability value of unpaired t-test for between-group difference

^Significantly different from the 1st 6-monthly increase in the AOK group (paired t-tests: all p < 0.002)

Bold – Indicating significance observed

Analyses with a linear mixed model (Model 1) showed that among all the predicting factors, axial elongation was not significantly associated with any of the baseline parameters (beta: -0.35 to 0.09, all p > 0.05; Model 1, Table 4.4) in either group or pooled subjects. Axial elongation in all subjects was significantly associated with the changes in photopic pupil size (beta: -0.03, p = 0.038; Model 2, Table 4.4), but not with either the changes in mesopic pupil sizes or changes in the accommodation (beta: -0.02 to 0.00, all p > 0.05; Model 2, Table 4.4).

Table 4.7 Fixed effects of baseline and change in ocular parameters on axial elongation, with estimates (β) and significance of the influence

| | All subjects | | AOK Group (N = 23) | | OK Group (N = 28) | |
|---|---|---|---|---|---|---|
| Model 1– Baseline parameters | β | p | β | p | β | p |
| Intercept | -0.23 | 0.357 | -0.26 | 0.534 | -0.35 | 0.247 |
| Sex | 0.00 | 0.929 | 0.04 | 0.524 | -0.02 | 0.707 |
| Baseline age | -0.01 | 0.652 | -0.01 | 0.784 | -0.01 | 0.560 |
| Baseline SER | 0.01 | 0.661 | 0.01 | 0.644 | 0.01 | 0.732 |
| Baseline mesopic pupil size | 0.02 | 0.579 | -0.03 | 0.653 | -0.01 | 0.866 |
| Baseline photopic pupil size | 0.00 | 0.963 | 0.08 | 0.609 | 0.09 | 0.410 |
| Baseline accommodation | 0.01 | 0.176 | 0.02 | 0.289 | 0.02 | 0.131 |
| Time | 0.01 | < 0.001 | 0.01 | < 0.001 | 0.01 | < 0.001 |
| Model 2– Changes of parameters | | | | | | |
| Intercept | -0.02 | 0.419 | -0.02 | 0.505 | -0.01 | 0.672 |
| Changes of mesopic pupil size | -0.02 | 0.170 | -0.02 | 0.243 | -0.02 | 0.924 |
| Changes of photopic pupil size | -0.03 | 0.038 | -0.03 | 0.084 | 0.00 | 0.924 |
| Changes of accommodation | 0.00 | 0.531 | 0.00 | 0.611 | 0.00 | 0.329 |
| Time | 0.01 | < 0.001 | 0.01 | < 0.001 | 0.01 | < 0.001 |

AOK – Combined atropine with orthokeratology

OK – Orthokeratology alone

SER – Spherical Equivalent Refraction (negative power, unless otherwise specified)

Bold – Indicates significance

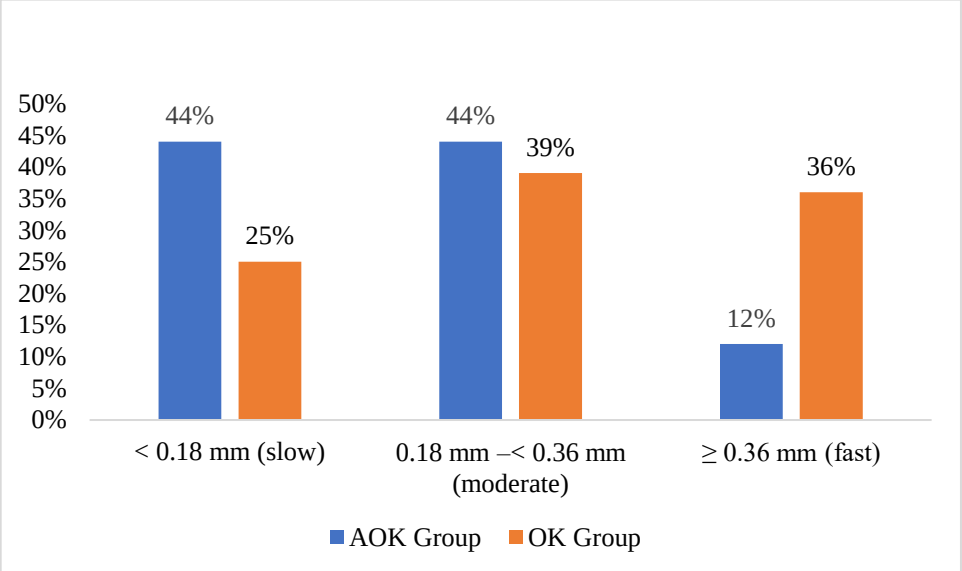



Figure 4.3 Percentages of subjects demonstrating different grades of overall axial elongation over two years in the two groups
AOK – Combined atropine with orthokeratology
OK – Orthokeratology alone

As shown in Figure 4.3, there was a higher percentage of subjects with rapid axial elongation in the OK group than in the AOK group (36% vs 12%). However, the proportions of subjects with slow, moderate, and fast axial elongation were not significantly different between the two groups ($\chi^2$, p = 0.143).

## 4.3.3 Changes in spherical equivalent refraction, pupil sizes, and accommodation

### 4.3.3.1 Cycloplegic residual spherical equivalent refraction

After 1-month treatment, cycloplegic SER was significantly reduced in each group, compared with the refractive error at the baseline visit (paired t-test, both p < 0.001). Thereafter, the refractive status remained stable, as there were no further changes in either group of subjects (RM ANOVA with post hoc comparisons, p > 0.05). At the 24-month visit, the mean ± SD cycloplegic residual SER was 0.10 ± 0.47 D in the OK group and +0.10 ± 0.46 D in the AOK group. Over two years, the effect of the group by visit interaction on cycloplegic residual SER was insignificant (RM ANOVA, p = 0.230), but the main effect of the group on cycloplegic residual SER reached significance (RM ANOVA, p = 0.015). Post hoc analyses showed that residual SER was more positive in the AOK group than in the OK group at 6-month, 12-month, and 18-month visits (all p < 0.05), with the between-group difference that did not reach a clinical significance (< 0.50 D, ranged between 0.30 D and 0.46 D). The residual SER did not differ between the two groups at the 1-month and 24-month visits (post hoc analyses, both p > 0.05).

### 4.3.3.2 Unaided vision acuity

Compared with baseline BCVA, UVA was not significantly reduced at any of the subsequent post-treatment visits in either group of subjects (RM ANOVA with post hoc comparisons, all p > 0.05). No significant between-group differences in either

UVA or BCVA were found at any post-treatment visit (RM ANOVA, all $p > 0.05$). Good UVA was maintained until the end of the 2-year treatment in both groups, with 0.03 ± 0.10 logMAR and -0.01 ± 0.07 logMAR in the OK and AOK groups, respectively.

#### 4.3.3.3 Changes in pupil size and accommodation

Changes in mesopic and photopic pupil sizes in the AOK group were significantly greater than those in the OK group at all post-treatment visits (RM ANOVA with post hoc analyses, all $p < 0.001$, Table 4.5). Changes in mesopic and photopic pupil sizes were stable during the 2-year study period in each group, as the effect of time was not significant (RM ANOVA, both $p > 0.05$). Although AOK subjects showed more reduction in accommodation, the changes were not significantly different from those in the OK group at all post-treatment visits (RM ANOVA, $p = 0.183$, Table 4.5).

### 4.3.4 Symptoms and adverse events

#### 4.3.4.1 Symptoms

Table 4.8 presents a summary of symptoms reported by AOK and OK subjects. A higher percentage of subjects suffered from photophobia in the AOK group than in the OK group ($\chi^2$, $p = 0.034$), but there was no difference in the percentage of subjects experiencing any other symptom between the two groups (all $p > 0.05$, Table 4.8). Photophobia, accompanied by halos, was reported by three AOK subjects, one at the 2-week visit and two after the 1-month visit. Another AOK subject had photophobia, but without a halo, after six weeks of treatment. In the AOK group, the halos and/or photophobia generally lasted less than two hours after awakening in the morning, and subjects regarded these symptoms as tolerable and reported no inconvenience caused.

Thus, no photochromatic spectacles were dispensed. In the OK group, the halos were reported to be evident in dim lighting (e.g. at nightfall), which disappeared under good lighting. Symptoms of itching and dry eye were reported in both groups (Table 4.8), but these symptoms were mostly limited to during lens wear or transient after use of 0.01% atropine. Blurred vision was reported (Table 4.8) after six months of treatment in both groups, which was mainly attributed to myopia progression, and the symptoms disappeared after lens refitting. No ocular irritation, dizziness, nausea, or loss of balance was reported by any subject over the 2-year study period.

Table 4.8 Summary of symptoms reported by two groups of subjects

| Symptoms | AOK (n = 33) | OK (n = 35) | p |
|---|---|---|---|
| Photophobia | 1 | 0 | 0.299 |
| Halo | 1 | 2 | 0.590 |
| Photophobia and halo | 3 | 0 | 0.068 |
| Blurred vision | 4 | 6 | 0.559 |
| Itching | 3 | 4 | 0.751 |
| Dry eye | 1 | 1 | 0.966 |

AOK – Combined atropine with orthokeratology

OK – Orthokeratology alone

p – Probability value of comparison of the percentage of subjects between the two groups, using Crosstab analyses

4.3.4.2 Ocular adverse events

A total of 45 events (25 in 14 AOK subjects, 20 in 13 OK subjects) were observed over the 2-year study period (Table 4.9), with most adverse events occurring during the second year of the study (15 events in the 1$^{st}$ year vs 20 events in the 2$^{nd}$ year). However, the percentage of subjects having adverse events did not differ significantly between the two groups (all $p > 0.05$, Table 4.9). No severe adverse event (e.g. microbial keratitis) was observed, and none of the observed adverse events resulted in a reduction of BCVA or permanent damage to ocular health.

Table 4.9 Number of ocular adverse events (number of subjects) occurring in the two groups of subjects

| Adverse events | AOK (n = 33) | | OK (n = 35) | | Total | p (AOK vs OK) | |
|---|---|---|---|---|---|---|---|
| | 1st year | 2nd year | 1st year | 2nd year | | 1st year | 2nd year |
| Infiltrative keratitis | 0 | 2(1) | 2(1) | 0 | 4(2) | 0.173 | 0.142 |
| Corneal erosion | 1(1) | 0 | 2(1) | 0 | 3(2) | 0.594 | N/A |
| Contact lens-associated papillary conjunctivitis | 2(1) | 2(1) | 0 | 0 | 4(2) | 0.142 | 0.142 |
| Hordeolum | 0 | 3(2) | 0 | 3(3) | 6(5) | N/A | 0.941 |
| Allergic conjunctivitis | 2(1) | 0 | 0 | 2(1) | 4(2) | 0.142 | 0.167 |
| Bacterial conjunctivitis# | 4(2) | 4(2) | 2(2) | 4(2) | 14(8) | 0.363 | 0.932 |
| Viral conjunctivitis* | 0 | 2(1) | 0 | 0 | 2(1) | N/A | 0.142 |
| Conjunctival cyst | 0 | 1(1) | 0 | 0 | 1(1) | N/A | 0.301 |
| Asymptomatic infiltrate | 0 | 2(1) | 0 | 3(2) | 5(3) | N/A | 0.673 |
| ≥ Grade 2 staining (Efron's scale) | 0 | 0 | 0 | 2(1) | 2(1) | N/A | 0.167 |

AOK – Combined atropine with orthokeratology
OK – Orthokeratology alone
N/A – Not Applicable (for crosstab analysis, as no occurrence of specific adverse events were observed in both groups in the 1st or 2nd year)
# The first two events of bacterial conjunctivitis were diagnosed with a culture of the tissues swabbed from lower conjunctival; the remaining 12 events were based on slit-lamp examination and history taken.
*Diagnosed based on slit-lamp examination and history taken

Six dropouts (three from each group) experienced ocular health issues leading to termination of treatment. In the AOK group, after one year of treatment, one subject had bilateral infiltrative keratitis; one developed a small conjunctival cyst (width less than 1 mm, found by the investigator during slit-lamp examination) on the corneal limbus in the left eye, although no symptom/discomfort was reported by the subject; and one had bilateral viral conjunctivitis (diagnosed based on slit-lamp examination and history taken) after lens wear during a bout of fever. Parents of these three subjects decided to withdraw from the study. In the OK group, one subject developed bilateral infiltrative keratitis after 1-month lens wear and their parents decided to

withdraw from the study; a second had repeated bacterial conjunctivitis (based on slit-lamp examination and history taken) during the first month of treatment, in spite of re-education of personal hygiene; and a third experienced recurrence of unilateral peripheral corneal erosion even after modifications of lens fitting. For these six subjects, lens wear and atropine (in AOK subjects) were discontinued immediately at the onset of the ocular symptoms. The three with infiltrative keratitis or bacterial conjunctivitis underwent at least 1-week treatment with topical antibiotics (0.5% levofloxacin, TID), depending on the recovery rate. One AOK subject who suffered binocular viral conjunctivitis (diagnosed based on slit-lamp examination and history taken), received a 2-week treatment of artificial tears and antibiotics (0.5% chloramphenicol, BID), the latter medication was used to avoid further bacterial infection. All six subjects were excluded from the study when: 1) good ocular health was restored after treatment; 2) no sequelae were observed at the follow-up visit one month after treatment with antibiotics.

The most frequent adverse event observed in the two groups of subjects was bacterial conjunctivitis (14 events in 8 subjects, Table 4.9), which accounted for 31% of the total adverse events. Of the four AOK and two OK subjects who developed bacterial conjunctivitis (two diagnosed based on slit-lamp examination and history taken, and two based on culture results), ocular health was restored after lens discontinuation and 1-week treatment with antibiotics. These subjects and their parents were re-educated before the resumption of lens wear and use of atropine, where appropriate, to ensure good personal hygiene and proper lens use and care. Except for one OK subject who had recurrent bacterial conjunctivitis (diagnosed based on slit-lamp examination and history), and was thus excluded, no sequelae were observed in the remaining five subjects at subsequent follow-up visits during the

remaining study period.

Six reports of hordeolum, occurring in five subjects (two AOK subjects and three OK subjects, Table 4.6), resolved rapidly (within one week) after daily warm compress. These subjects were advised to perform a warm compress at least twice weekly thereafter, to avoid recurrence. However, one AOK subject had a recurrent hordeolum in the left upper eyelid eight months after the first event, which also recovered rapidly after warm compress treatment. Four events of allergic conjunctivitis occurred in two subjects (one in each group) after exposure to pollen outdoors. The condition resolved after 2-week discontinuation of treatment, and no medication was required. Although these adverse events (hordeolum, allergic conjunctivitis) accounted for 22% of total ocular adverse events, it should be noted that they could not be solely attributed to ortho-k lens wear or use of atropine eye drops.

4.3.4.3 Non-orthokeratology-related adverse events

Two hospitalizations were documented during the study, both of which were not due to the allocated treatment (ortho-k and/or use of atropine): one OK subject was hospitalized for two weeks due to a leg fracture before the 12-month visit, and one AOK subject was quarantined for two weeks after contracting chickenpox in the second week of study treatment. These two subjects were later excluded, as their parents decided to quit the study after full recovery. Two AOK subjects had transient facial allergic contact dermatitis after hiking. Although there were no ocular complications, ortho-k lens wear and use of atropine eye drops were still discontinued for one week and treatment resumed after the allergic reaction had subsided (one week later).

## 4.4 Discussion

It is well documented that ortho-k significantly slows axial elongation by approximately 50% in comparison with wearing SVS (Section 1.3.4). In the current study, KATT BE Free lenses, which had not been previously evaluated for efficacy in myopia control, were used for overnight ortho-k in all subjects. Using unpaired t-test to examine the difference in axial elongation among studies, it was shown that the mean ± SD axial elongation, after 2-year of treatment, in the OK group (0.31 ± 0.19 mm) was not significantly different from that of ortho-k subjects in the ROMIO study (0.36 ± 0.24 mm, $p = 0.368$), TO-SEE study (0.31 ± 0.27 mm, $p = 1.000$), or the study by Zhu et al. (0.34 ± 0.29 mm, $p = 0.617$) (Cho & Cheung 2012, Chen et al. 2013, Zhu et al. 2014). Axial elongation in children treated with ortho-k has previously been reported to be negatively associated with initial age, but not with initial myopia (Cho & Cheung 2012, Cho & Cheung 2017). The age of the OK subjects in the current study (mean ± SD, 9.1 ± 1.1) did not differ significantly from those in ROMIO (9.2 ± 1.1, $p = 0.718$) or TO-SEE studies (9.4 ± 1.4, $p = 0.358$), but younger than those in the study performed by Zhu et al. (9.8 ± 1.6, $p = 0.038$). Based on these findings, it can be concluded that KATT BE Free lens was as effective as other ortho-k lenses in retarding axial elongation in children.

Undoubtedly, there was an additive effect between 0.01% atropine and ortho-k, as axial elongation was additionally slowed by 0.14 mm in the combined treatment over two years, compared to ortho-k alone (mean ± SD, 0.17 ± 0.20 mm vs 0.31 ± 0.19 mm). The initial age and myopia of either AOK or OK subjects were not significantly different from that of the control group in the ROMIO study (mean ± SD, age: 9.39 ± 1.00 years; myopia: 2.23 ± 0.84 D, one-way ANOVA, both $p > 0.05$). Using the control group in the ROMIO study as a historical control (mean ± SD axial

elongation over two years, 0.63 ± 0.26 mm), axial elongation in the current study was slowed by approximately 50% and 73% in the OK and AOK groups, respectively. Thus, the additive effect of 0.01% atropine and ortho-k was approximately 23%, in terms of reduction rate.

In the current study, there was no single arm of 0.01% atropine treatment, thus it is difficult to determine whether there is a synergistic effect between 0.01% atropine and ortho-k. The LAMP study (Yam et al. 2019) demonstrated that use of 0.01% atropine alone only slowed axial elongation by 0.05 mm compared with the placebo over one year (mean ± SD, 0.36 ± 0.29 mm vs 0.41 ± 0.22 mm), indicating monotherapy of 0.01% atropine produced a one-year reduction rate of 12% for myopia control. There was no control group in phase two of the LAMP study (placebo group switched to 0.05% atropine), making it is impossible to know the control effect/reduction rate of 0.01% atropine over two years. However, there was a natural slowing down of axial elongation during atropine treatment, given that axial elongation in the 0.05%, 0.025%, and 0.01% atropine groups during phase two, was 10%, 24%, and 29% slower, respectively, than during phase one (Yam et al. 2020), suggesting that the control effect/reduction rate of atropine may attenuate over time. In line with this reasoning, it is reasonable to anticipate an overall reduction rate of not more than 12% over two years in monotherapy with 0.01% atropine. It appears that the additive effect between 0.01% atropine and ortho-k in terms of reduction rate (23%) was higher than the anticipated reduction rate of single-use of 0.01% atropine alone (12%). However, as younger subjects with higher baseline SER were enrolled in the 0.01% atropine group (LAMP study) than that in the AOK group (mean ± SD; age, 8.4 ± 1.8 vs 9.2 ± 1.0 years; baseline SER, 3.99 ± 1.94 D vs 2.67 ± 0.97 D, both $p < 0.05$), direct comparison either in terms of reduction rate and axial elongation may

not be appropriate. It is therefore still unclear whether there is a synergistic effect between 0.01% atropine and ortho-k.

As a single mainstream treatment, higher concentration atropine (1%, 0.5%, and 0.1%) was excluded, due to side-effects (Section 1.4.4) outweighing their efficacy. Of the lower concentrations (0.05%, 0.025%, and 0.01% atropine) tested, Yam et al. (2020) reported that 0.05% atropine treatment was the most effective in controlling axial elongation over two years and that it was not associated with apparent side-effects. However, a proportion of 9.1% and 28.5% of children undergoing 0.05% atropine treatment, progressed more than 2.00 D and 1.00 D in SER over two years, respectively (Yam et al. 2020). This indicates that the use of 0.05% alone was not potent enough to inhibit myopia progression in some rapid progressors to a more reasonable level (i.e. less than 1.00 D). This condition also applies to monotherapy of ortho-k, as shown in the ROMIO study, 54% of the children treated with ortho-k had axial elongation more than 0.36 mm (approximately 1.00 D in SER), and 15% demonstrated more than 0.72 mm increase in axial length (approximately 2.00 D in SER) over two years (Cho & Cheung 2012).

In the current study, 10 children (36%) treated with ortho-k alone had rapid axial elongation (overall ≥ 0.36 mm), showing a mean ± SD axial elongation of 0.51 ± 0.23 mm over two years compared to that of 0.31 ± 0.19 mm in all OK subjects. The percentage of rapid axial elongation of 36% in the OK group was not significantly different from that of 54% in those treated with ortho-k in the ROMIO study ($\chi^2$, $p = 0.142$), indicating a consistent proportion of children undergoing ortho-k still demonstrating rapid eye growth. In comparison, the percentage of rapid eye growth was only 12% (three children, range: 0.40 – 0.62 mm) in the AOK group, which was marginally significantly lower than in the OK group ($\chi^2$, $p = 0.065$), and significantly

lower than those treated with ortho-k alone in the ROMIO study ($\chi^2$, p = 0.001). The median age of fast progressors in the two treatment groups are comparable (median [range], AOK: 8.4 [8.1 – 9.0], OK: 8.9 [6.1 – 10.7] years, p = 0.550), indicating that the lower proportion of fast progressors in the AOK group was a result of treatment, rather than a difference in the baseline age. Based on this evidence, it can be concluded that adding 0.01% atropine to ortho-k could markedly reduce the occurrence of rapid axial elongation in young children. In line with this observation, leveling off of rapid progression in combined 0.01% atropine with ortho-k was also observed in a retrospective study, which showed that rapid axial elongation in ortho-k treatment reduced from 0.46 ± 0.16 mm per year to 0.14 ± 0.14 mm per year with the addition of 0.01% atropine in a cohort of young children (mean ± SD age, 8.3 ± 1.5 years) (Chen et al. 2019). It appears that younger myopic children (< 9 years) could benefit more from combined 0.01% atropine and ortho-k treatment, as this specific group was found most vulnerable to faster axial elongation during ortho-k treatment (Cho & Cheung 2017, Wang et al. 2017).

Another benefit of combined treatment of 0.01% atropine and ortho-k is an achievement of a better balance between efficacy and side-effects, compared to single- use of either atropine or ortho-k. Figure 4.4 shows the mean axial elongations over two years in several randomized studies that included ortho-k and/or atropine. Although direct comparison of the axial elongation across studies is inappropriate, there is a general tendency indicating that combined treatment of 0.01% atropine and ortho-k may result in minimal eye growth across these treatments, by achieving an anticipated reduction rate of 73% in axial elongation. This reduction rate was higher than 33%, 52%, and 54% achieved with treatment of 0.05%, 0.1%, 0.5% atropine, respectively, if using 0.01% concentration in LAMP as a control.

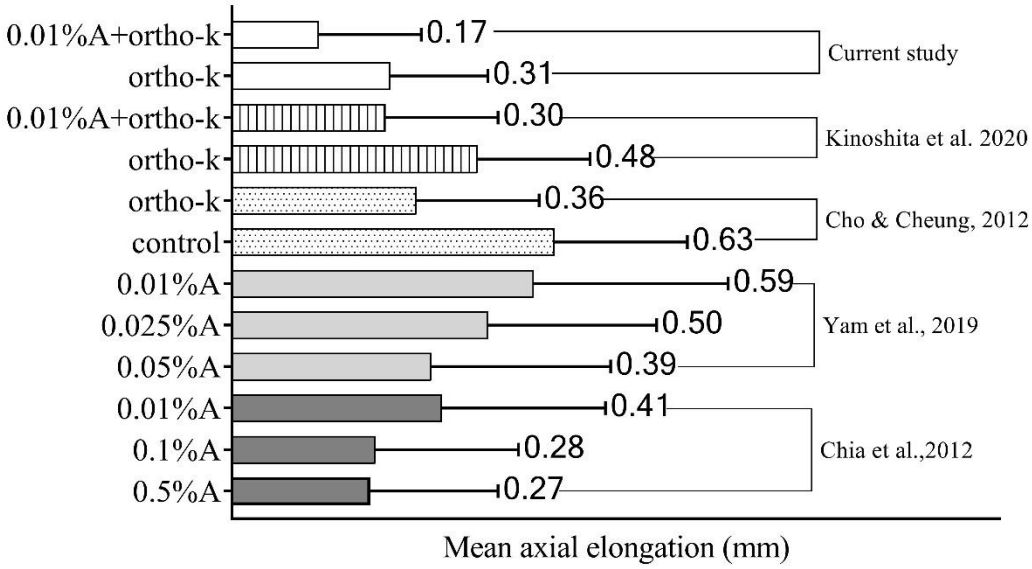



Figure 4.4 Mean axial elongation over two years across studies
For the study conducted by Kinoshita et al., only the axial elongations in a subgroup of children with initial SER lower than 3.00 D were illustrated, as an additive effect between 0.01% atropine and ortho-k was observed in this subgroup (A – Atropine; ortho-k – orthokeratology; SER – Spherical Equivalent Refraction, with negative power, unless otherwise specified).

In the current study, the combined treatment led to negligible side-effects. Nightly use of 0.01% atropine did not compromise the performance of ortho-k in reducing refractive errors, as post-treatment habitual visual acuity and residual refraction were not significantly different between the two groups of subjects. Besides, increases in photopic and mesopic pupil sizes were less than 1.0 mm after combining 0.01% atropine and ortho-k, explaining why few subjects had transient photophobia or halo in the combined treatment group. Also, in comparison with a mean reduction of 1.1 D in OK subjects, nightly use of 0.01% atropine resulted in a decrease of 2.1 D in the amplitude of accommodation in the AOK group, which may not be clinically significant, considering the young initial age (mean ± SD, 9.1 ± 1.1 years) and the robust baseline accommodation (mean ± SD, 13.2 ± 2.1 D) of subjects receiving the combined treatment.

Changes in pupil size and accommodation in atropine-treated eyes were well-

documented in both the LAMP and ATOM studies (Table 4.10). Although direct comparison of these results may not be appropriate, as different methods for measurements were adopted, the tendency for 0.01% atropine to have a minimal influence on pupil size and accommodation is obvious, irrespective of whether combined treatment was employed. In line with the minimal changes in pupil size and accommodation, in the current study, no subject requested photochromic or progressive glasses. By contrast, in ATOM2, 70%, 61%, and 6% of the subjects receiving atropine 0.5%, 0.1%, and 0.01%, respectively, requested combined photochromatic progressive glasses (Chia et al. 2012). In LAMP, 33%, 44%, and 34% of the subjects in the 0.05%, 0.025%, and 0.01% atropine group, respectively, requested photochromic glasses (Yam et al. 2020). The comparable rate of using photochromic glasses among different treatment groups in the LAMP study was possibly related to parents' intention to protect subjects against possible photophobia, when they were informed that photochromic glasses would be offered in case of side-effects.

Table 4.10 Comparison of changes in pupil size and accommodation in subjects using atropine in previous studies and the current study (at 24-month visit)

| | AOK | LAMP | | | ATOM2 | | |
|---|---|---|---|---|---|---|---|
| Study and group | 0.01% + ortho-k (n = 23) | 0.5% (n = 93) | 0.025% (n = 86) | 0.01% (n = 91) | 0.5% (n = 139) | 0.1% (n = 141) | 0.01% (n = 75) |
| Changes in photopic pupil size (mm) | 0.73 ± 0.46 | 1.25 ± 1.13 | 0.67 ± 0.87 | 0.60 ± 0.84 | 3.11 ± 1.10 | 2.25 ± 1.01 | 0.74 ± 0.75 |
| Changes in mesopic pupil size (mm) | 0.81 ± 0.48 | 0.69 ± 0.64 | 0.34 ± 0.62 | 0.26 ± 0.58 | 3.54 ± 1.14 | 2.71 ± 1.12 | 1.15 ± 0.71 |
| Changes in accommodation (D) | -2.1 ± 2.1 | -2.0 ± 3.1 | -1.7 ± 2.8 | -0.6 ± 3.1 | -11.8 ± 4.4 | -10.1 ± 4.3 | -4.6 ± 4.2 |

AOK – Atropine combined with orthokeratology

LAMP – Low-concentration Atropine for Myopia Progression

ATOM2 –Atropine for the Treatment Of childhood Myopia 2

The mechanism of neither atropine nor ortho-k for myopia control is fully understood, making it more challenging to clarify the mechanism underlying the additive effect between 0.01% atropine and ortho-k. However, two hypotheses were raised, based on current knowledge on the possible pharmaceutical action for atropine and the optical mechanism for ortho-k. Firstly, it is apparent that the direct effect of atropine on axial elongation, at least partially, contributes to the additive effect between 0.01% atropine and ortho-k. As atropine may exert its action in myopia control via muscarinic receptors in the retina and sclera (Section 1.4.4.6), the quantity and activity of those muscarinic receptors may be altered in ortho-k treated eyes, thus possibly making the action of atropine stronger in ortho-k treated eyes than without ortho-k treatment.

Secondly, in the current study, slower axial elongation was associated with a larger increase in the photopic pupil size, but not with any baseline parameters (age, sex, mesopic and photopic pupil size, and the amplitude of accommodation), changes in mesopic pupil size, and amplitude of accommodation, suggesting that photopic pupil size may play a role in the control effect of ortho-k. The enlarged photopic pupil may lead to an increase in the magnitude of ocular HOA (Applegate et al. 2007), which is suggested to be one of the etiologies of myopia progression (Section 1.1.2.3) and which underly the mechanism of control effect in ortho-k (Section 1.3.4.5). The use of 0.01% atropine leads to pupil dilation and a reduction in accommodation, which could potentially lead to a significant elevation in HOA during near and distance viewing in ortho-k treated eyes. However, there is limited information in the literature regarding the effect of photopic pupil size and ocular HOA on myopia control in either ortho-k alone or combined 0.01% atropine with ortho-k.

As the between-group difference in axial elongation was only observed for the

first 6-month period, but not for the remainder of the study, this suggests that no further additive effect from combined treatment occurred after the first six months of treatment. Considering a minimal rebound effect (0.28 D) after discontinuation of 0.01% atropine was observed (Chia et al. 2014), the use of 0.01% atropine in combined treatment may only be required for six or 12 months, followed by monotherapy of ortho-k. This modality may produce a comparable additive effect and cut down the expense of atropine eye drops. The additive effect between 0.01% atropine and ortho-k can be strengthened by switching the use of atropine from nightly use to daily application, as the two treatments overlap greatly in the daytime in this modality. Other feasible strategies to reinforce the additive effect would be to increase the instilling frequency of 0.01% atropine (e.g. twice daily), or combining 0.05% atropine with ortho-k, without causing a significant increase in ocular side-effects. Such studies into the effectiveness of combination treatment are warranted.

## 4.5 Conclusion

An additive effect was observed between 0.01% atropine and ortho-k, as axial elongation was slowed by 0.14 mm more with combined treatment of 0.01% atropine and ortho-k than with ortho-k alone over two years. The combined 0.01% atropine with ortho-k treatment was well-tolerated, with only a few reversible ocular adverse events and negligible side-effects. However, the mechanism underlying such an additive effect remains unknown, investigations into the relationship between axial elongation and possible optical factors (e.g. ocular HOA) are warranted to further the understanding of the mechanism underlying the additive effect of 0.01% atropine and ortho-k.

---

Papers published from work reported in this chapter:

Tan Q, Ng ALK, Choy BNK, Cheng GPM, Woo VCP, Cho P (2020). One-year results of 0.01% atropine with orthokeratology (AOK) study: a randomised clinical trial. Ophthalmic Physiol Optics 40:557-56

Tan Q, Ng ALK, Cheng GPM, Woo VCP, Cho P (2019). Combined atropine with orthokeratology for myopia control: study design and preliminary results. Curr Eye Res 44:671-678

# Chapter 5 Changes in choroidal thickness following combined 0.01% atropine with orthokeratology versus orthokeratology alone

## 5.1 Introduction

Choroidal thickness in children is affected by several factors, including age (Park & Oh 2013, Zhang et al. 2015, Jin et al. 2016, Ohsugi et al. 2018), refractive error (Jin et al. 2016, Fontaine et al. 2017), axial length (Zhang et al. 2015, Jin et al. 2016), and axial elongation (Fontaine et al. 2017, Ohsugi et al. 2018). Choroidal thickness in children may change in response to interventions, such as the use of atropine (Zhang et al. 2016, Chiang et al. 2020, Zhao et al. 2020), ortho-k (Chen et al. 2016), and imposed defocus (Wang et al. 2016, Chiang et al. 2020).

Previous studies have revealed that short-term use of atropine could lead to a significant increase in choroidal thickness in both children (Zhang et al. 2016, Chiang et al. 2020, Zhao et al. 2020) and myopic adults (Sander et al. 2019). Zhang and coworkers (2016) reported that, after 1-week administration of 1% atropine, the choroid was thickened by a mean of 15.5 μm in Chinese children aged 5 to 10 years, with SER between 3.50 D to +4.63 D. The authors attributed the choroidal thickening to a direct effect of 1% atropine on the muscarinic receptors in the choroid and a relaxing of accommodation resulting from cycloplegia (Zhang et al. 2016), based on previous observations that choroidal thickness decreased during accommodation (Woodman et al. 2012, Woodman-Pieterse et al. 2015). Chiang et al. (2020) revealed that there was a significant choroid thickening of 21.0 μm after 1-week nightly use of 0.3% atropine in Chinese children aged 6 to 15 years (SER between 0.75 D to 4.50 D) and that the thickening was sustained over the 6-month treatment period. The effect of atropine on

choroidal thickness may be reduced at lower concentrations (i.e. a dose-dependent effect). Preliminary 1-month results of a four-arm randomized controlled trial revealed that nightly use of one drop of 0.01% atropine led to a small (5.5 μm), but a significant thickening of the choroid in a cohort of children aged 8 to 12 years, with SER between 1.00 D to 6.00 D (Zhao et al. 2020). Similarly, in myopic adults with SER between 0.75 D to 6.00 D, instillation of one drop of 0.01% atropine caused a significant increase in choroidal thickness by a mean of 6.0 μm in 60 mins (Sander et al. 2019). However, to date, no study has revealed a presence of an association between choroidal thickening and the retardation effect of atropine in myopia control.

There are inconsistent reports about the effect of ortho-k on choroidal thickening in children (Gardner et al. 2015, Chen et al. 2016, Li et al. 2019). Gardner and coworkers (2015) revealed no significant changes in myopic children (aged 11 to 15 years), over nine months of ortho-k treatment. In contrast, Chen et al. reported that the choroid was significantly thickened by a mean of 11.0 μm and 24.0 μm after 1-week and 3-week ortho-k treatment, respectively, in children aged seven to 17 years (Chen et al. 2016). A better explanation was suggested by Li et al. who reported that, despite a significant and maintained choroid thickening of approximately 16.0 μm over 12-month ortho-k treatment, more thickening in choroid was associated with less axial elongation over a 13-month observation period (12-month ortho-k followed by 1-month discontinuation) in Chinese children. Their results indicated that the amount of choroidal thickening may play a role in the effectiveness of ortho-k for myopia control (Li et al. 2019).

An additive effect, when compared to ortho-k alone, was observed when 0.01% atropine was used in conjunction with ortho-k to retard axial elongation (Chapter 4), but the mechanism underlying such an effect is not clear. As both 0.01% atropine and ortho-k could affect the choroidal thickness, it is of great interest to know how the choroid responded to the

combined treatment of 0.01% atropine and ortho-k. Although it was revealed recently that comparable choroidal thickening was induced in combined 0.01% atropine and ortho-k to that by ortho-k alone over one month (14.1 μm vs 9.4 μm) (Zhao et al. 2020), it is still unknown whether there are significant long-term changes in choroidal thickness as a result of the combined treatment, or if there is an association between these changes and axial elongation. To gain a better understanding of the mechanism underlying the additive effect in combination of 0.01% atropine and ortho-k for myopia control, changes in choroidal thickness were compared over two years between the AOK and OK groups, and association of these changes with axial elongation in each group and for all subjects were determined.

## 5.2 Methods

### 5.2.1 Ethics approval

See Section 4.2.1.

### 5.2.2 Subjects

See Section 4.2.3.

### 5.2.3 Examination procedures

Before cycloplegia, choroidal thickness was measured using the Spectralis SD-OCT (Heidelberg Engineering, Inc., Heidelberg, Germany). High-speed scanning and enhanced depth imaging mode were selected for measurements. Three measurements were firstly taken at the baseline visit, each comprising six foveal centered 30-degree long radial line scans (i.e. each line consisting of 30 frames and separated by 30-degree). Of the three baseline measurements, the one that demonstrated the highest quality, in terms of a quality index (at least 25 dB), served as the reference image for all follow-up scans at subsequent data

collection visits. To ensure that the same retinal locations as the baseline visit were scanned at subsequent data collection visits, automatic real-time tracking was adopted. All measurements at follow-up visits were carried out within ± 2 h of the measurement time of the baseline visit, to reduce the influence of diurnal variations in choroidal thickness (Brown et al. 2009, Chakraborty et al. 2011, Tan et al. 2012). The first three measurements with full choroidal image and with a quality index over 25 dB, were saved and later exported for further semi-automated segmentations, using customized software (Alonso-Caneiro et al. 2013). The choroidal thickness was defined as the thickness between the outer retinal pigment epithelium/Bruch's membrane complex and the inner choroidoscleral interface, with horizontal scans of the eye. Manual correction of the segmentations was performed where appropriate.

### 5.2.4 Statistic analyses

Only data from the right eye of subjects who completed the 2-year study were used for data analyses. Normality of the data was explored using the Kolmogorov-Smirnov test. After confirming a normal distribution, unpaired t-test was used to compare baseline age, SER, and choroidal thickness; RM ANOVA was used to compare choroidal thickness or its changes in the two groups of subjects over two years, with post hoc analyses to examine between-group or between-visit differences. Crosstab analysis was used to compare the gender ratio between the two groups of subjects.

A linear mixed model was used to assess the influence of baseline choroidal thickness on axial elongation in each group and all subjects, with first-order autoregressive covariance structure and restricted maximum likelihood estimation (Model 1). Individual slope and intercept were included as random effects and an unstructured covariance matrix was used to control inter-subject variation. As described in Section 4.3.2, axial elongation was not

significantly associated with any of the baseline parameters, including sex, age, SER, pupil size, and amplitude of accommodation, therefore none of these baseline parameters was considered in the linear mixed model analyses on the association between the baseline choroidal thickness and axial elongation. In Model 2, the effects of the post-treatment changes in choroidal thickness on axial elongation were examined, with the same modeling as the first. A p-value $< 0.05$ was considered statistically significant.

## 5.3 Results

### 5.3.1 Subject demographics

See Section 4.3.1.

### 5.3.2 Changes in spherical equivalent errors, pupil sizes, and accommodation

See Section 4.3.3.

### 5.3.3 Choroidal thickness and changes over time

Fifty-one subjects (23 AOK and 28 OK) completed the 2-year study and there was no significant difference in the baseline choroidal thickness between the AOK and OK groups (mean ± SD, AOK: 239.8 ± 40.3 μm; OK: 237.6 ± 45.5 μm P = 0.857). There were missing choroidal thickness data for one OK subject at the 1-month visit and two OK subjects at both 18-month and 24-month visits. Therefore, a total of 48 subjects (23 AOK and 25 OK) were included in the RM ANOVA analyses. No significant differences in baseline choroidal thickness ( p = 0.726, Table 5.1), age (AOK: 9.2 ± 1.0 years; OK: 9.2 ± 1.2 years; p = 0.976), SER (AOK: 2.71 ± 0.97 D; OK: 2.82 ± 1.02 D; p = 0.725), and gender ratio (Female/Male, AOK: 12/11; OK:14/11; p = 0.790) between the two groups of subjects were found.

Table 5.1 Summary of choroidal thickness results over time

| Visit | Mean ± SD | | | | P (AOK vs OK) | |
|---|---|---|---|---|---|---|
| | AOK (n = 23) | | OK (n = 25) | | | |
| | Choroidal thickness (μm) | Changes (μm) | Choroidal thickness (μm) | Changes (μm) | Choroidal thickness | Changes |
| Baseline | 239.8 ± 40.3 | N/A | 239.8 ± 46.0 | N/A | 0.726 | N/A |
| 1M | 252.8 ± 45.5* | 17.5 ± 12.5 | 247.2 ± 47.4* | 7.4 ± 10.6 | 0.675 | 0.003 |
| 6M | 255.4 ± 46.9* | 20.1 ± 19.3 | 242.4 ± 49.1 | 2.5 ± 14.1 | 0.346 | 0.001 |
| 12M | 260.2 ± 51.2* | 25.1 ± 24.1 | 241.5 ± 47.0 | 1.6 ± 15.5 | 0.187 | < 0.001 |
| 18M | 258.2 ± 52.8* | 22.7 ± 24.1 | 237.2 ± 43.1 | -2.6 ± 15.5 | 0.133 | < 0.001 |
| 24M | 256.8 ± 52.7* | 20.9 ± 21.5 | 235.0 ± 46.6 | -4.9 ± 15.6^ | 0.132 | < 0.001 |

AOK – Combined atropine with orthokeratology

OK – Orthokeratology alone

N/A – Not Applicable

P – Probability value of post hoc analyses for differences between groups at each visit

Bold – Indicating significance observed

*Significantly different from the baseline choroidal thickness in each group (post hoc analyses: all P < 0.001 in the AOK group, P = 0.033 in the OK group)

^Significantly different from the changes in choroidal thickness at the 1-month visit in the OK group (post hoc analyses: P = 0.042)

Choroidal thickness was not different between the two groups at all visits (all $p > 0.05$, Table 5.1). In the AOK group, the choroid thickness at the 1-month visit was thicker than that at the baseline visit ($p < 0.001$, Table 5.1); no further changes were observed in subsequent visits (post hoc analyses, all $p > 0.05$). In the OK group, no changes were observed at any visit (post hoc analyses, all $p > 0.05$), except at 1-month when a thicker choroid, compared to baseline, was found ($p = 0.033$, Table 5.1).

Figure 5.1 illustrates the trend of choroid thickness changes in the two groups of subjects over two years. There was a significant group by visit interaction for the changes in choroid thickness (RM ANOVA, $p = 0.012$), and post hoc analyses showed that the changes were significantly different between the two groups of subjects at all post-treatment visits (all $p < 0.05$, Table 5.1).

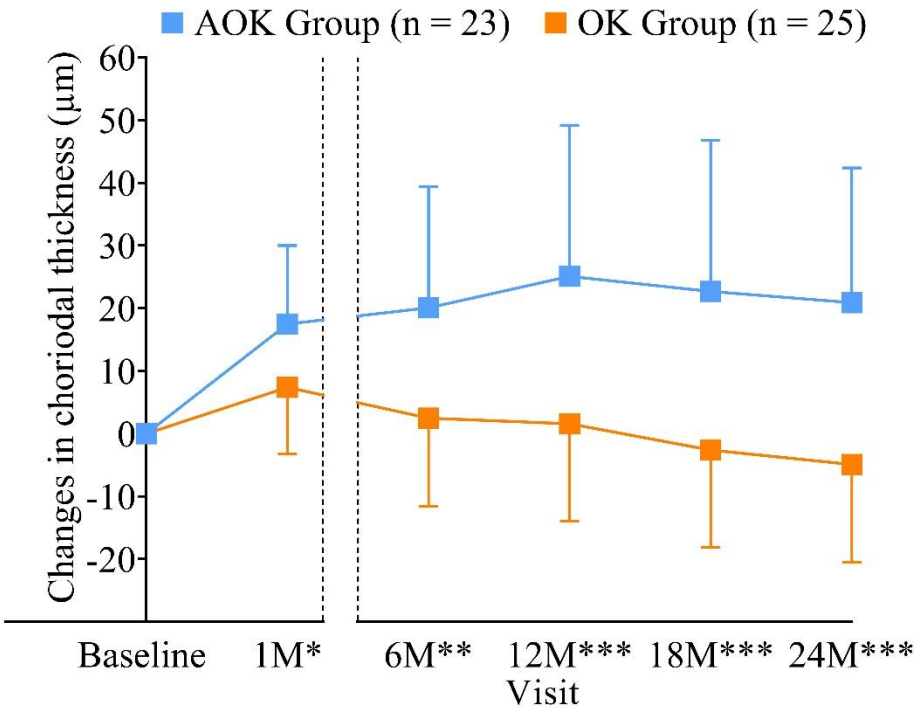



Figure 5.5 Comparison of changes in choroidal thickness (Mean ± SD, µm) between the two groups of subjects over time
AOK – Combined atropine with orthokeratology
OK – Orthokeratology alone
Vertical dashed lines – Indicating the 1-month visit, which was different from the remaining visits that were performed 6-monthly after the commencement of lens wear
Probability value *< 0.05, **< 0.01, ***< 0.001 of post hoc analyses for difference between the two groups at post-treatment visits

In the AOK group, the greatest thickening in the choroid occurred at the 12-month visit, but post hoc analyses showed no significant differences between any of the two post-treatment visits (i.e. 1-, 6-, 12-, 18-, 24-month visits) (all $p > 0.05$). In the OK group, the greatest and only change in choroidal thickness occurred at the 1-month visit (mean ± SD, 7.4 ± 10.6 µm).

### 5.3.4 Association between changes in choroidal thickness and axial elongation

Axial elongation observed in the AOK group was significantly slower than that in the

OK group (Section 4.3.2). From the linear mixed model analyses (Model 1, Table 5.2), axial elongation was not associated with baseline choroidal thickness ($p > 0.05$). Model 2 demonstrated that slower axial elongation was associated with a greater increase in choroidal thickness in each group and for the pooled data (including all subjects) (β: -0.01 to 0.00, all $p < 0.001$, Table 5.1).

Table 5.2 Fixed effects and parameter estimates (β) of the influences of the choroidal thickness (baseline and changes over time) on axial elongation in the two groups of subjects

| | Pooled data (n = 51) | | AOK Group (n = 23) | | OK Group (n = 28) | |
|---|---|---|---|---|---|---|
| Model 1– Baseline choroidal thickness | β | p | β | p | β | p |
| Intercept | 0.01 | 0.896 | 0.07 | 0.565 | -0.05 | 0.675 |
| Baseline choroidal thickness | 0.00 | 0.741 | 0.00 | 0.419 | 0.00 | 0.731 |
| Time | 0.01 | < 0.001 | 0.01 | < 0.001 | 0.01 | < 0.001 |
| Model 2– Changes of choroidal thickness | | | | | | |
| Intercept | -0.01 | 0.649 | -0.01 | 0.607 | 0.00 | 0.852 |
| Change of choroidal thickness | 0.00 | < 0.001 | 0.00 | < 0.001 | 0.00 | < 0.001 |
| Time | 0.01 | < 0.001 | 0.01 | < 0.001 | 0.01 | < 0.001 |

AOK – Combined atropine with orthokeratology

OK – Orthokeratology alone

p – Probability value of association

Bold – Indicates significance

## 5.4 Discussion

This study was the first to compare changes in choroidal thickness in subjects receiving combined 0.01% atropine and ortho-k treatment with those wearing ortho-k lenses alone, over an extended period of two years. There was a greater post-treatment thickening of the choroid in the AOK group than in the OK group at all post-treatment visits, with a between-group difference in choroidal thickening of 10.1 μm at the 1-month visit, and 25.8 μm at the 24-month visit (Table 5.1). The reasons underlying a gradual increase in the between-group difference in the choroidal thickening were due to a thinning of the choroid in the OK group, albeit small, at the 18-month (mean ± SD, -2.6 ± 15.5 μm) and 24-month visits (-4.9 ± 15.6 μm), while the choroidal thickening in the AOK group was sustained since the 1-month visit

(Table 5.1). However, it should be noted that the intra-observer CR for choroidal thickness measurements with Spectralis SD-OCT at a single visit, when a customized software and manual correction (where appropriate) was used for segmentation of the choroid (Lau et al. 2019), was reported to be 10.0 μm. In the current study, the procedures described by Lau et al. (2019) were employed. Taking the CR reported into consideration, a change in choroidal thickness less than 10.0 μm is likely to be a measurement error and may not be clinically significant. Hence, in the OK group, the mean changes in choroidal thickness at all post-treatment visits were not clinically significant, while those observed in the AOK group at all post-treatment visits (Table 5.1) were both statistically and clinically significant.

There was an axial shortening in both AOK and OK groups at the 1-month visit (mean ± SD, AOK vs OK, -0.05 ± 0.05 mm vs -0.02 ± 0.03 mm), and 35% and 37% of this shortening can be attributable to the thickening of the choroid in the AOK and OK groups, respectively. Besides, a recent study revealed that overall axial length (both eyes considered) was shortened by a mean of 0.03 mm over one week in children wearing ortho-k lenses with different compression factors in each eye (1.75 D or 0.75 D) (Lau et al. 2019). The effect of ortho-k on ocular biometrics stabilized by the end of 1-week ortho-k treatment, with choroidal thickening accounting for 35% of the axial shortening (Lau et al. 2019). Based on these findings, it appears that the amount of thickening in the choroid only explains approximately 35% of axial shortening over a short treatment duration in ortho-k treated eyes (i.e. one week or one month), without taking into consideration the amount due to measurement error. Over two years, there was no further thickening of the choroid after the 1-month visit in the AOK group, whilst the changes in choroidal thickness in the OK group were clinically insignificant at all post-treatment visits. These results indicate that there was a stabilizing effect of treatment on the choroidal thickness after 1-month of ortho-k lens wear. In addition, compared to mean axial elongation of 0.17 mm and 0.31 mm in the AOK and OK

group over two years (Section 4.3.2), these changes in choroidal thickness were negligible. The results suggest that the axial elongation was not a direct result of the changes in choroidal thickness.

As a vascular structure, the choroid of the eye has the function of secreting growth factors and adjusting the position of the retina by changing its thickness (Nickla & Wallman 2010). It was hypothesized that the choroid may play a role in the modulation of axial elongation by delivering the signal cascade starting at the retina to the sclera to modulate scleral growth involved in axial elongation (Wallman & Winawer 2004, Nickla & Wallman 2010). The control effect of atropine in retarding myopia progression was hypothesized to be related to the muscarinic receptors in the choroid (Section 1.4.4.6). However, to date, there is no evidence in humans showing that atropine causes choroidal thickening through the muscarinic receptors. The exact mechanism of choroidal thickening resulting from atropine remains unknown.

Chiang et al. (2020) revealed that, in children aged six to 14 years undergoing 0.3% atropine, there was significant additional choroidal thickening of 11.9 μm, 13.1μm, 10.2 μm, and 11.8 μm after 60 mins of exposure to myopia defocus of +2.0 D at 1-week, 3-month, and 6-month visits, respectively. This result suggested that a different mechanism of action was involved in atropine and myopic defocus in choroidal thickening (Chiang et al. 2020). In addition, it was confirmed that the peripheral retinas of ortho-k treated eyes were imposed with relative myopic defocus induced by ortho-k lenses (Queiros et al. 2010, Kang & Swarbrick 2011, Ticak & Walline 2013). It was reported that even after a short duration of exposure, myopic defocus could cause significant choroidal thickening in children wearing SVS or treated with atropine (Wang et al. 2016, Chiang et al. 2020). It is possible that the significant choroidal thickening in the AOK group, may have resulted from the effect of both 0.01% atropine and relative myopic defocus induced by ortho-k.

A recent four-arm clinical trial compared the changes in choroidal thickness in children undergoing combined 0.01% atropine and ortho-k, ortho-k and placebo, 0.01% atropine and SVS, and SVS and placebo (control), over a short period of one month (Section 1.5.2). The methodology in Zhao et al.'s study differed from the current study in many aspects. Firstly, they measured the choroidal thickness after complete mydriasis using 0.5 % tropicamide, while choroid thickness was assessed under non-cycloplegic conditions in the current study. It has been reported that the use of tropicamide causes a decrease in choroidal thickness in 45 mins (Kara et al. 2014, Yuvacı et al. 2015). The use of tropicamide may be a confounding factor in the measurement of choroidal thickness. Secondly, Zhao et al. (2020) used manually assessed choroidal thickness for analysis, and the inter-observer CR value for this assessment was 6.0 μm. Based on this CR, changes in choroidal thickness over one month was clinically significant in subjects receiving 0.01% atropine and ortho-k (mean ± SD, 14.1 ± 12.9 μm) and those undergoing ortho-k and placebo (9.4 ± 9.1 μm), but not in those undergoing treatment with 0.01% atropine and SVS (5.5 ± 9.4 μm) and those in the control group (-4.8 ± 9.9 μm). In comparison, in the current study, choroidal thickening reached clinical significance (> 10.0 μm) only in the AOK group, but not in the OK group. Thirdly, older subjects were involved in Zhao et al.'s study (e.g. mean ± SD, 10.2 ± 1.1 years vs 9.2 ± 1.0 years in the AOK group, $p = 0.001$), although the baseline SER was not significantly different between the two studies for either combined treatment (0.01% atropine and ortho-k) or the ortho-k alone group (i.e. ortho-k and placebo group in Zhao et al.'s study) (unpaired t-test, $p = 0.126$, 0.785). Despite these differences, neither the 1-month changes in choroidal thickness in the combined 0.01% atropine and atropine nor in the ortho-k alone group (i.e. ortho-k and placebo in Zhao et al.'s study), were significantly different between Zhao et al.'s and the current study (unpaired t-test, $p = 0.290$, 0.433, respectively), suggesting that there were consistent changes in choroidal thickness after treatment of combined 0.01% atropine and

ortho-k or ortho-k alone.

Concerning long-term changes in choroidal thickness, only one study has assessed the changes in cycloplegic choroidal thickness in ortho-k treated eyes, over 12 months (Li et al. 2019). It was reported that the mean ± SD changes in choroidal thickness were 16.0 ± 11.0 μm, 21.0 ± 13.0 μm, and 19.0 ± 14.0 μm, after 1-month, 6-month, and 12-month treatment of ortho-k, respectively, in children aged nine to 14 years. All the changes in choroidal thickness reported by Li et al. (2019) were significantly greater than those found in the OK group in the current study (unpaired t-test, all $p < 0.01$). These discrepancies may arise from the differences in the methodology, especially since Li et al. (2019) performed a manual assessment of choroidal thickness, which was dependent on observers' experience. Based on the CR value (approximately 5 μm according to Li et al. 2019) for choroidal thickness assessments, the post-treatment changes in choroidal thickness were clinically significant in their study. However, in the current study, the changes in choroidal thickness in the OK group were only statistically significant at the 1-month visit (Table 5.1), without reaching clinical significance. Nevertheless, in the current study, as well as the study by Li et al. (2019) and Zhao et al. (2020), only the sub-foveal choroidal thickness was measured and compared. The choroid in the periphery may be significantly thickened in response to ortho-k treatment, given that imposition of the relative myopic defocus was mainly induced in the peripheral retina in ortho-k treated eyes. To date, it remains unknown how choroidal thickness changes in the periphery after ortho-k, especially since full correction of central refraction is targeted in ortho-k (i.e. minimal residual defocus was expected to be imposed on the fovea). The pupil size is another factor to be considered, as the effect of relative myopic defocus on choroidal thickening in ortho-k treated eyes, may be reduced by a constricted pupil under photopic conditions. Further studies that assess the changes in choroidal thickness in the periphery, particularly under photopic conditions, are warranted, to provide a better understanding of the

changes in choroidal thickness after ortho-k.

## 5.5 Conclusion

The current study was the first to compare long-term changes in choroidal thickness in subjects receiving combined 0.01% atropine and ortho-k with those wearing ortho-k alone, over an extended period (two years). The choroid was significantly thickened by a mean of 17.5 μm after 1-month treatment in the combined treatment group, and the amount of thickening was maintained until the end of the 2-year study period. In comparison, minimal changes in choroidal thickness, which was regarded as clinically insignificant (less than 10 μm), were observed in subjects undergoing ortho-k alone. Approximately 35% of the axial shortening at the 1-month visit can be explained by the changes in choroidal thickness in both groups of subjects. There were significant between-group differences in the choroidal thickness changes at all post-treatment visits, and the thickened choroid observed in the AOK group is highly likely to be a result of the atropine.

# Chapter 6 Relationship between ocular aberrations and axial elongation in combined 0.01% atropine with orthokeratology versus orthokeratology alone

## 6.1 Introduction

In humans, ocular aberrations, including LOA (i.e. defocus and regular astigmatism) and ocular HOA, can result from the cornea and internal optics, with the latter being insusceptible to correction with conventional optical methods (Charman 2005). It has been suggested that ocular HOA promote myopia progression by degrading retinal image quality (Charman 2005, Hughes et al. 2020). This hypothesis has been supported by several cross-sectional studies, which consistently showed that myopic children suffer from elevated levels of HOA compared with their hyperopic or emmetropic counterparts (He et al. 2002, Kirwan et al. 2006, Little et al. 2014). However, there are equivocal findings in longitudinal studies, which showed either a positive (Zhang et al. 2013), negative (Hiraoka et al. 2017, Lau et al. 2018), or no association between ocular HOA and myopia progression (Philip et al. 2014) (Section 1.1.3.3).

Together with its well-established effect in retarding axial elongation (Sections 1.3.4.1 and 1.3.4.2), overnight ortho-k leads to thinning of the central corneal epithelium and thickening of the mid-peripheral cornea (Swarbrick et al. 1998, Alharbi & Swarbrick 2003), consequently reshaping the cornea and a significantly altered level of ocular HOA (Gifford et al. 2013, Lian et al. 2014), which is sustained over time (Hiraoka et al. 2015, Lau et al. 2020). A negative association between ocular HOA and axial elongation has been observed after ortho-k treatment in several longitudinal studies (Hiraoka et al. 2015, Lau et al. 2018, Kim et

al. 2019), suggesting that the effect of myopia control observed with ortho-k may be attributable to increased ocular HOA. However, their conclusions were based on ocular HOA results for fixed pupil diameters (4 mm or 6 mm), rather than for natural ones (Hiraoka et al. 2015, Lau et al. 2018, Kim et al. 2019). These results may result in an overestimation of HOA experienced by subjects undergoing ortho-k, as a constricted pupil diameter of less than 4 mm is normally observed in human eyes under photopic conditions throughout the day (Kobashi et al. 2012). In addition, pupil size varies among individuals and may also affect the control effect of ortho-k, especially as a greater treatment effect for ortho-k was observed in subjects with larger scotopic pupil sizes (Chen et al. 2012). As such, aberration assessments for the natural pupil are more relevant than for fixed pupil diameters (4 mm or 6 mm), as metrics for investigation of the relationship between ocular HOA and axial elongation in ortho-k treated eyes.

In the AOK study, an additive effect was observed between 0.01% atropine and ortho-k, with subjects in the AOK group having a larger photopic pupil size than those in the OK group (Chapter 4). As ocular HOA was obtained as a function of the entry pupil (Charman 2005), the natural ocular HOA experienced in the AOK group should theoretically increase with enlarged pupil size. Although the mean residual SER was minimal in the two groups (< 0.25 D) (Section 4.3.3.1), uncorrected LOA, which should be theoretically as small as the residual SER, may combine with or interact with HOA in determining retinal image quality. Thus, it is necessary to include both LOA and HOA in investigating how aberration affects retinal image quality and axial eye growth. To date, no study has assessed and compared the retinal image quality in combined 0.01% atropine with ortho-k and ortho-k alone, nor the relationships between these aberration metrics (i.e. LOA and HOA) and axial elongation after treatment. To address these research gaps, pre- and post-treatment retinal image quality was compared between the AOK and OK group, and the associations between aberration metrics

and axial elongation were explored in this study, to further the understanding of the mechanism underlying the additive effect of 0.01% atropine and ortho-k.

## 6.2 Methods

### 6.2.1 Ethics approval

See Section 4.2.1.

### 6.2.2 Subjects

See Section 4.2.3.

### 6.2.3 Examination procedures

Monochromatic ocular aberrations at wavelength 555 μm were captured using a Complete Ophthalmic Analysis System (COAS) (Wave-front Sciences Ltd., New Mexico, USA) before cycloplegia. As accommodation may influence the measurement, a Maltese cross target, through a beam splitter and Badal lens, was fixed externally with a fixed incandescent lamp (5.3 lux). The position of the target was altered to correct for the distance non-cycloplegic SER error, to as far as possible ensure a 0 D accommodative demand during the measurement. The room illumination was turned off to avoid the influence of stray light on the measurements. During measurement, subjects were instructed to view the external target and the instrument was adjusted such that the pupil was centered on the instrument measurement axis. The first five wave-front measurements without a blink (each consisting of 25 measurements captured within two seconds) were taken for each eye and data were fitted with a Zernike polynomial expansion up to the $6^{th}$ radial order.

The outliers of data, which presented a difference in pupil diameter > ± 0.50 mm or a difference in defocus > ± 0.50 D from the sample median, were screened out using customized software, followed by data exportation for each subject at each study visit. The measured coefficients were imported into a Matlab customized program, which scaled the

coefficients for the measured pupil diameter under mesopic conditions (5.3 lux) in COAS down to the natural photopic diameters measured with the OPD-Scan III under photopic conditions (125.6 lux) or a fixed 3-mm pupil, following the method described by Schwiegerling (Schwiegerling 2011). After re-scaling, individual Zernike coefficients of 2nd- to 6th-orders aberrations, root mean square (RMS) of 2nd-order aberrations ($\boldsymbol{Z_2^0}$ , $\boldsymbol{Z_2^{-2}}$, and $\boldsymbol{Z_2^2}$ combined), total higher-order aberrations (3rd- to 6th-orders inclusive, total HOA), spherical-like aberrations ($\boldsymbol{Z_4^0}$ and $\boldsymbol{Z_6^0}$ combined, SA), and coma-like aberrations ($\boldsymbol{Z_3^{-1}}, \boldsymbol{Z_3^1}, \boldsymbol{Z_5^{-1}}$ and $\boldsymbol{Z_5^1}$ combined, Coma) at each visit were used for statistical analysis. The first three Zernike terms (0- to 1st-order aberration) were omitted in this study, considering that these terms only displace images and have minimal influence on the quality of the retinal image (Charman 2005). Thus, LOA in this study only consists of three of the terms of 2nd-order aberrations (i.e. $\boldsymbol{Z_2^0}$ , $\boldsymbol{Z_2^{-2}}$, and $\boldsymbol{Z_2^2}$).

The three-dimension visual Strehl ratio (VST), based on a scaled optical transfer function, was determined according to a method described previously (Collins et al. 2006), by including all Zernike terms (2nd- to 6th-orders, inclusive) or HOA terms only (3rd- to 6th-orders inclusive) for a photopic pupil, with the former named overall VST and the latter HOA-VST. VST measures the light intensity of an optical system at the image plane compared to that which is aberration-free with a value ranging between 0 and 1 (the higher value, the better the image quality) (Mahajan 2005).

### 6.2.3 Statistical analyses

Only data from the right eye was used for analyses in all subjects (Section 4.2.6). After confirming the normality of the data using the Kolmogorov-Smirnov test, RM ANOVA with post hoc analyses was used to examine between-group or between-visit differences and to compare overall VST, HOA-VST, individual coefficients, and RMS of ocular aberrations for

a 3-mm pupil (e.g. LOA, total HOA, Coma, and SA) in the two groups of subjects.

A series of linear mixed models were constructed with first-order autoregressive covariance structure and restricted maximum likelihood estimation, with individual slope and intercept included as random effects and unstructured covariance matrix to control inter-subject variations. Baseline characteristics, including sex, age, SER, pupil size (mesopic and photopic), and amplitude of accommodation, were not associated with axial elongation (Section 4.3.2), therefore these were not considered for adjustment in any of the linear mixed models.

The first linear mixed model (Model 1) was used to assess the influence of baseline ocular HOA (RMS) and individual LOA terms ($\boldsymbol{Z_2^0}$, $\boldsymbol{Z_2^{-2}}$, and $\boldsymbol{Z_2^2}$) on axial elongation in each group and all subjects (pooled data). If baseline total HOA or any of LOA terms were significantly associated with axial elongation in Model 1, they would be adjusted; otherwise, they were excluded in the following linear mixed models.

To identify specific RMS or aberration terms in association with axial elongation, several linear mixed models (Models 2 – 4) were used to examine the effect of changes in RMS values of HOA (total HOA, Coma, and SA) and individual Zernike coefficients on axial elongation. A p-value $< 0.05$ was considered statistically significant.

## 6.3 Results

### 6.3.1 Subject demographics

See Section 4.3.1.

### 6.3.2 Pupil size, the amplitude of accommodation, cycloplegic spherical equivalent refraction

Table 6.1 summarizes the data of pupil size, accommodation, cycloplegic SER over two

years of the 51 subjects (23 AOK and 28 OK) who completed the 2-year study. RM ANOVA on photopic pupil size revealed a significant group by visit interaction ($p < 0.001$), with post hoc analyses indicating that the photopic pupil size was significantly greater in the AOK group compared to the OK group at all post-treatment visits ($p < 0.001$). There was no significant difference in either mesopic pupil size or amplitude of accommodation between the two groups of subjects at all visits (all $p > 0.05$, Table 6.1). Although SER in the AOK group was more plus than in the OK group at the 6-, 12-, and 18-month visits ($p < 0.05$), these differences were not clinically significant (Section 4.3.3.1)

### 6.3.3 Retinal image quality for a photopic pupil

No significant differences in overall VST were observed between the two treatment groups at any visit (all $p > 0.05$, Figure 6.1a). In both groups, overall VST after treatment was significantly increased since the baseline visit (all $p < 0.001$). In the AOK group, except that the overall VST at the 24-month visit was significantly lower than that at the 6-month visit ($p = 0.008$), no significant difference in overall VST was observed between any of the post-treatment visits. In the OK group, except that the overall VST at the 1-month visit was significantly higher than those at 18-month and 24-month visits ($p = 0.005$, 0.001, respectively), no significant difference in overall VST was observed between any of the post-treatment visits (all $p > 0.05$).

For HOA-VST, significant between-group differences were observed at 1-, 6-, 12-, 24-month visits (all $p < 0.05$), but not at the 18-month visit ($p = 0.104$, Figure 6.1b). In each group, post-treatment HOA-VST was significantly decreased since the baseline visit (all $p < 0.001$), and sustained over time, as no significant difference was observed between any post-treatment HOA-VST (all $p > 0.05$).

Table 6.1 Photopic and mesopic pupil diameters (mean ± standard deviation, mm), the amplitude of accommodation (D), cycloplegic subjective refraction of the two groups of subjects over two years

| Metric | Group | Mean ± SD | | | | | | Group x visit interaction (F, p) | p' (12M vs 24M) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Baseline | 1-month | 6-month | 12-month | 18-month | 24-month | | AOK | OK |
| Photopic pupil (mm) | AOK | 3.23 ± 0.31 | 3.96 ± 0.54 | 3.72 ± 0.44 | 3.63 ± 0.46 | 3.78 ± 0.52 | 3.99 ± 0.61 | | | |
| | OK | 3.16 ± 0.30 | 3.15 ± 0.24 | 3.12 ± 0.33 | 3.18 ± 0.34 | 3.24 ± 0.40 | 3.40 ± 0.45 | 11.54, < 0.001 | 0.004 | 0.149 |
| | p† | 0.446 | < 0.001 | < 0.001 | < 0.001 | < 0.001 | < 0.001 | | | |
| Mesopic pupil (mm) | AOK | 6.33 ± 0.78 | 7.03 ± 0.58 | 6.99 ± 0.59 | 6.97 ± 0.58 | 7.09 ± 0.58 | 7.14 ± 0.50 | | | |
| | OK | 6.55 ± 0.90 | 6.65 ± 0.80 | 6.64 ± 0.84 | 6.69 ± 0.92 | 6.69 ± 0.86 | 6.92 ± 0.87 | 8.40, < 0.001 | 1.000 | 0.181 |
| | p† | 0.243 | | | | | | | | |
| Amplitude of accommodation (D) | AOK | 13.8 ± 2.1 | 12.9 ± 2.0 | 12.3 ± 1.6 | 12.5 ± 1.4 | 11.6 ± 1.1 | 11.7 ± 1.2 | | | |
| | OK | 13.0 ± 2.4 | 12.3 ± 2.7 | 12.3 ± 1.5 | 12.2 ± 1.1 | 11.8 ± 1.1 | 11.7 ± 1.0 | 0.53, 0.469 | 0.049 | 1.000 |
| | p† | 0.404 | | | | | | | | |
| Cycloplegic SER (D) | AOK | 2.71 ± 0.97 | +0.20 ± 0.38 | +0.37 ± 0.46 | +0.36 ± 0.38 | +0.33 ± 0.38 | +0.10 ± 0.46 | | | |
| | OK | 2.81 ± 0.97 | +0.19 ± 0.47 | +0.01 ± 0.45 | +0.06 ± 0.46 | 0.14 ± 0.50 | 0.10 ± 0.47 | 1.47, 0.230 | 0.177 | 1.000 |
| | p† | 0.717 | 0.944 | 0.007 | 0.016 | 0.001 | 0.145 | | | |

AOK – Combined 0.01% atropine with orthokeratology (n = 23)

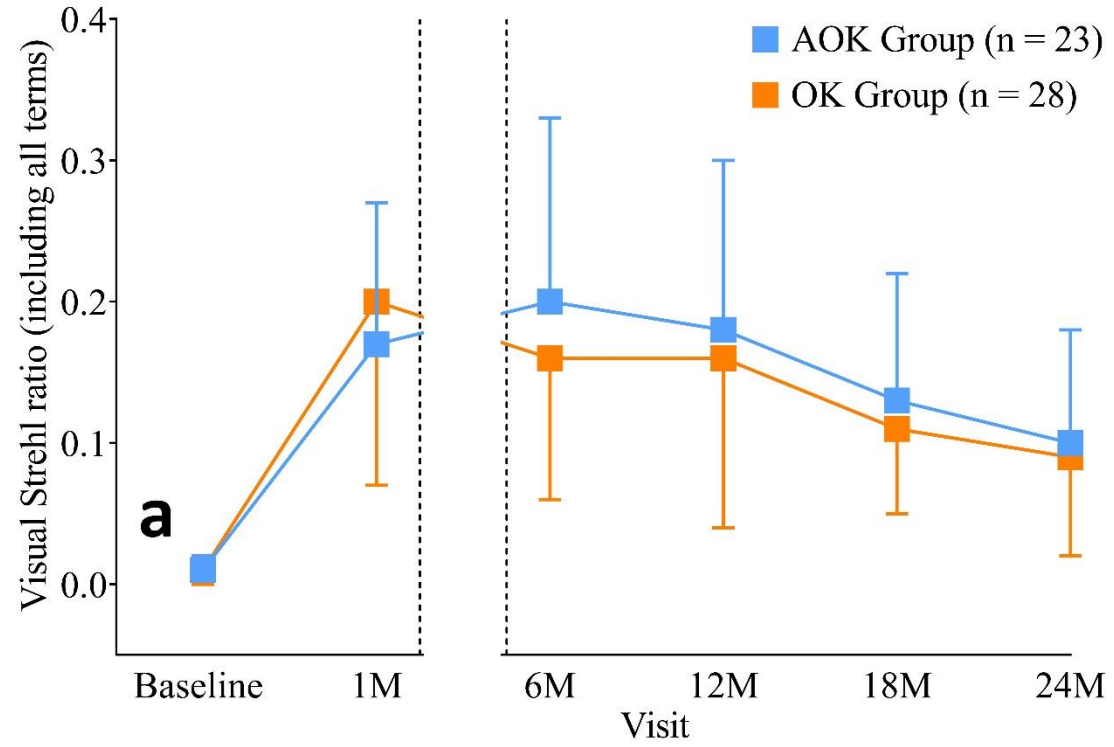
OK – Orthokeratology alone (n = 28)

SER – Spherical Equivalent Refraction (negative power, unless otherwise specified)

p – Probability value of two-way RM-ANOVA, with P† indicating that the probability value of post hoc test for differences between groups at each visit

p' –Probability value of post hoc analyses for differences in parameters between 12-month and 24-month visit in each group

Bold – indicates significance


Visual Strehl ratio (including all terms)
0.4
0.3
0.2
0.1
0.0
a
AOK Group (n = 23)
OK Group (n = 28)
Baseline
1M
6M
12M
18M
24M
Visit

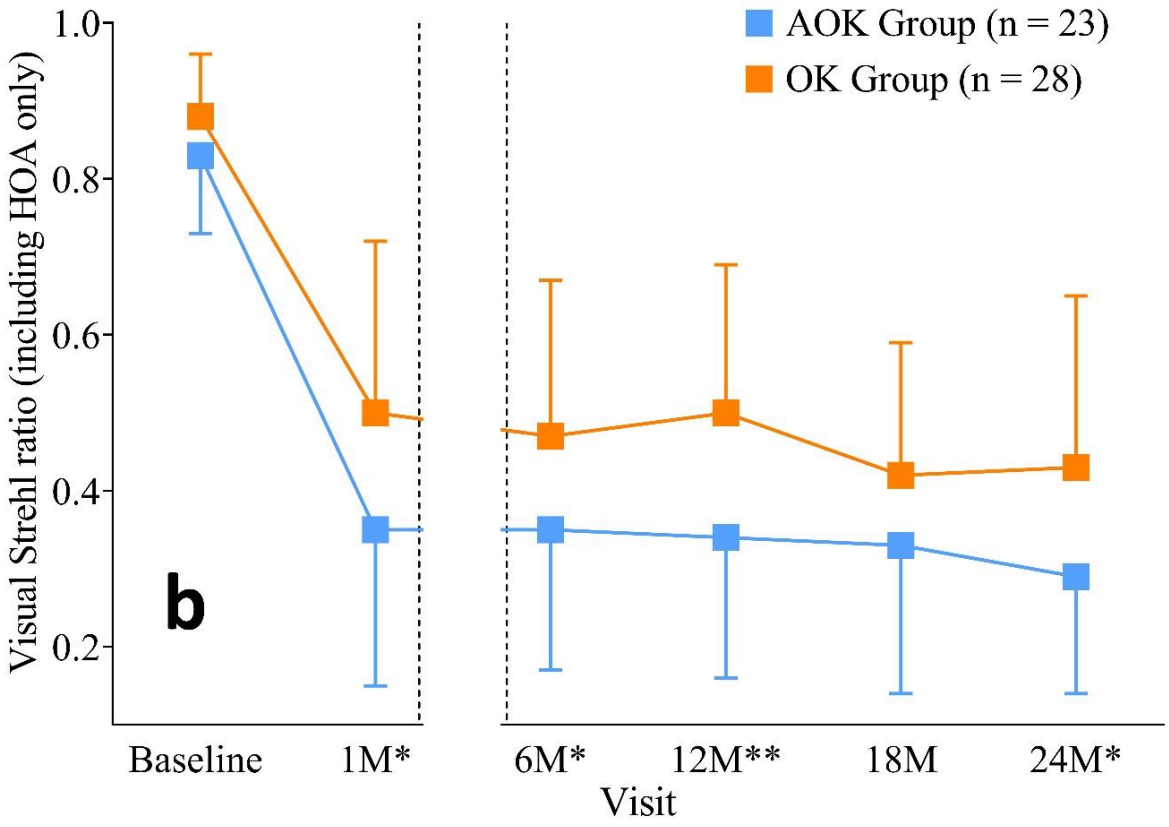

Visual Strehl ratio (including HOA only)
1.0
0.8
0.6
0.4
0.2
b
AOK Group (n = 23)
OK Group (n = 28)
Baseline
1M*
6M*
12M**
18M
24M*
Visit

Figure 6.1 The trend of visual Strehl ratio change over time in the two groups of subjects
(a) Visual Strehl ratio determined from all Zernike terms (2nd - to 6th-orders inclusive)
(b) Visual Strehl ratio determined from higher-order aberrations terms only (3rd- to 6th-orders inclusive)
Probability value *< 0.05, **< 0.01 of post hoc comparisons for the difference in visual Strehl ratio between the two groups at any visit
Vertical dashed lines – Indicating the 1-month visit, which was different from the remaining visits performed 6-monthly after the commencement of lens wear
AOK – Combined atropine with orthokeratology
OK – Orthokeratology alone
HOA – Higher-Order Aberration(s)

### 6.3.4 Relationship between ocular higher-order aberrations and axial elongation

Table 6.2 summarizes significant associations observed between axial elongation and some aberration metrics from each group of subjects and pooled data. Baseline RMS value of total HOA and coefficients of LOA terms ($\boldsymbol{Z_2^0}$, $\boldsymbol{Z_2^{-2}}$, and $\boldsymbol{Z_2^2}$) were not associated with axial elongation in each group or all subjects considered together (all $p > 0.05$, Model 1).

For pooled data, slower axial elongation was associated with greater increases in the RMS values of total HOA, SA, and Coma (total RMS: $\beta = -0.17$, $p < 0.001$, Model 2; SA: $\beta = -0.12$, $p = 0.012$; Coma: $\beta = -0.15$, $p = 0.030$, Model 3), a greater decrease in the RMS values of LOA ($\beta = 0.02$, $p = 0.014$, Model 2), a higher level of positive SA ($\boldsymbol{Z_4^0}$) ($\beta = -0.17$, $p = 0.014$, Model 4), and a higher level of negative vertical coma ($\boldsymbol{Z_3^{-1}}$) and tertiary horizontal astigmatism ($\boldsymbol{Z_6^2}$) ($\boldsymbol{Z_3^{-1}}$: $\beta = 0.16$, $p = 0.047$; $\boldsymbol{Z_6^2}$: $\beta = 3.57$, $p = 0.035$; Model 4).

In the AOK group, slower axial elongation was associated with greater increases in the RMS values of total HOA and Coma (total RMS: $\beta = -0.18$, $p < 0.001$, Model 2; Coma: $\beta = -0.17$, $p = 0.024$, Model 3), a greater decrease in the RMS values of LOA ($\beta = 0.02$, $p = 0.008$, Model 2), a higher level of $\boldsymbol{Z_3^{-1}}$, $\boldsymbol{Z_6^2}$, and horizontal hexafoil ($\boldsymbol{Z_6^6}$) ($\boldsymbol{Z_3^{-1}}$: $\beta = 0.25$, $p = 0.015$; $\boldsymbol{Z_6^2}$: $\beta = 4.45$, $p = 0.016$; $\boldsymbol{Z_6^6}$: $\beta = 7.15$, $p = 0.046$; Model 4).

In contrast, in the OK group, no association was found between RMS values of LOA, any HOA terms, or individual Zernike terms (Models 2 – 4, all $p > 0.05$, Table 6.2).

Table 6.2 Statistically significant associations between ocular aberration metrics and axial elongation in the two groups of subjects

| | Pooled data (n = 51) | | AOK Group (n = 23) | | OK Group (n = 28) | |
|---|---|---|---|---|---|---|
| Model 1 – Baseline total HOA (RMS) and LOA terms ($\boldsymbol{Z_2^0}$ , $\boldsymbol{Z_2^{-2}}$, and $\boldsymbol{Z_2^2}$) | β | p | β | p | β | p |
| Intercept | -0.03 | 0.622 | -0.03 | 0.772 | -0.08 | 0.247 |
| Time | 0.01 | < 0.001 | 0.01 | < 0.001 | 0.01 | < 0.001 |
| Model 2 – Changes of LOA and total HOA (RMS) | | | | | | |
| Intercept | -0.01 | 0.724 | -0.02 | 0.469 | 0.00 | 0.907 |
| Changes of LOA | 0.02 | 0.014 | 0.02 | 0.008 | 0.01 | 0.214 |
| Changes of total HOA | -0.17 | < 0.001 | -0.18 | 0.001 | -0.04 | 0.646 |
| Time | 0.01 | < 0.001 | 0.01 | < 0.001 | 0.01 | < 0.001 |
| Model 3 – Changes of Coma and SA (RMS) | | | | | | |
| Intercept | -0.01 | 0.493 | -0.02 | 0.458 | -0.01 | 0.758 |
| Changes of Coma | -0.12 | 0.030 | -0.17 | 0.024 | -0.04 | 0.620 |
| Changes of SA | -0.15 | 0.012 | -0.13 | 0.059 | -0.20 | 0.236 |
| Time | 0.01 | < 0.001 | 0.01 | < 0.001 | 0.01 | < 0.001 |
| Model 4 – Individual Zernike terms | | | | | | |
| Intercept | -0.03 | 0.209 | -0.02 | 0.420 | -0.01 | 0.797 |
| $\boldsymbol{Z_3^{-1}}$ | 0.16 | 0.047 | 0.25 | 0.015 | 0.01 | 0.959 |
| $\boldsymbol{Z_4^0}$ | -0.17 | 0.014 | -0.12 | 0.100 | -0.12 | 0.510 |
| $\boldsymbol{Z_6^2}$ | 3.57 | 0.035 | 4.45 | 0.016 | -4.08 | 0.566 |
| $\boldsymbol{Z_6^6}$ | 4.03 | 0.155 | 7.15 | 0.046 | -5.55 | 0.561 |
| Time | 0.01 | < 0.001 | 0.01 | < 0.001 | 0.01 | < 0.001 |

AOK – Combined atropine with orthokeratology

OK – Orthokeratology alone

HOA – Higher-Order Aberration(s)

LOA – Lower-Order Aberration(s)

RMS – Root Mean Square

Coma – $\boldsymbol{Z_3^{-1}}, \boldsymbol{Z_3^1}, \boldsymbol{Z_5^{-1}}$ and $\boldsymbol{Z_5^1}$ combined

SA – $\boldsymbol{Z_4^0}$ and $\boldsymbol{Z_6^0}$ combined

p – Probability value of association

Bold – Indicates significance

### 6.3.5 Ocular aberrations for a 3-mm pupil

No significant differences were observed between the two groups for RMS values of any aberration metric (i.e. LOA, total HOA, Coma, and SA) or individual Zernike terms (all p > 0.05). Table 6.3 shows mean ± SD of individual Zernike coefficients (2$^{nd}$- to 4$^{th}$-orders

inclusive) for a 3-mm pupil in two groups of subjects at baseline and 24-month visits. Coefficients of 5th- to 6th-orders were not listed, given that their means were small (< 0.001 μm).

Table 6.3 Mean ± standard deviation individual Zernike coefficients (2nd- to 4th-orders inclusive) for a 3-mm pupil in two groups of subjects at baseline and 24-month visits

| | Baseline (μm) | | 24-month (μm) | |
|---|---|---|---|---|
| | AOK Group (n = 23) | OK group (n = 28) | AOK Group (n = 23) | OK group (n = 28) |
| $Z_2^{-2}$ | 0.00 ± 0.04 | -0.02 ± 0.06 | -0.06 ± 0.07 | -0.08 ± 0.07 |
| $Z_2^0$ | 1.09 ± 0.34 | 1.12 ± 0.33 | 0.33 ± 0.26 | 0.45 ± 0.22 |
| $Z_2^2$ | -0.10 ± 0.10 | -0.13 ± 0.11 | -0.14 ± 0.13 | -0.12 ± 0.10 |
| $Z_3^{-3}$ | 0.01 ± 0.02 | 0.00 ± 0.02 | 0.01 ± 0.03 | 0.00 ± 0.02 |
| $Z_3^{-1}$ | 0.00 ± 0.03 | 0.00 ± 0.02 | -0.02 ± 0.07 | -0.01 ± 0.04 |
| $Z_3^1$ | 0.00 ± 0.02 | 0.00 ± 0.01 | 0.02 ± 0.06 | 0.02 ± 0.06 |
| $Z_3^3$ | 0.00 ± 0.01 | 0.00 ± 0.01 | -0.01 ± 0.02 | -0.01 ± 0.02 |
| $Z_4^{-4}$ | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.01 | 0.00 ± 0.01 |
| $Z_4^{-2}$ | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.01 | 0.00 ± 0.01 |
| $Z_4^0$ | 0.01 ± 0.01 | 0.01 ± 0.01 | 0.03 ± 0.03 | 0.01 ± 0.04 |
| $Z_4^2$ | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.02 | 0.00 ± 0.02 |
| $Z_4^4$ | 0.02 ± 0.01 | 0.00 ± 0.01 | 0.00 ± 0.01 | 0.00 ± 0.01 |

AOK – Combined atropine with orthokeratology

OK – Orthokeratology alone

## 6.4 Discussion

This study was the first to examine the relationship between ocular aberrations (i.e. LOA and HOA) for a natural photopic pupil and axial elongation, either in subjects undergoing ortho-k alone or those receiving 0.01% atropine combined with ortho-k over an extended period (two years). Combining 0.01% atropine and ortho-k induced a larger photopic pupil size without worsening retinal image quality compared with ortho-k alone. The major findings were that slower axial eye growth was associated with a greater increase in the RMS values of total HOA and Coma, a greater decrease in the RMS value of LOA, a higher level of some HOA terms ($Z_3^{-1}$, $Z_6^2$, and $Z_6^6$) in the AOK group, while no such associations were

observed in the OK group (Table 6.2). This suggests that the better control effect in retarding axial elongation resulting from the combined treatment may be related to the post-treatment profile of both LOA and HOA associated with an enlarged photopic pupil.

It was suggested that degraded retinal image quality as a result of elevated ocular aberrations, particularly HOA, may act as a stimulus to myopic progression in children (Charman 2005, Hughes et al. 2020). In the current study, the retinal image quality described in terms of overall VST, which was determined from LOA together with HOA terms when subjects' accommodation was relaxed (i.e. distance viewing), did not differ between the AOK and OK groups. Thus, the retinal image quality at distance viewing is unlikely to play a role in the additive effect from the combined treatment (Section 4.3.2).

However, the eye accommodates more during excessive near work, which was raised as one of the environmental risk factors that influences myopia progression in children (Section 1.3.2.2). In eyes corrected with SVS, the main change to the HOA profile during accommodation is a negative shift in primary SA ($Z_4^0$) (Plainis et al. 2005, Thibos et al. 2013, Thibos et al. 2013). It has also been suggested that primary SA ($Z_4^0$) in combination with defocus ($Z_2^0$), may provide a directional cue to the retina to optimize image quality and, consequently, alter axial eye growth (Buehren et al. 2007). However, the exact profile of HOA and defocus in children undergoing ortho-k or combined treatment of 0.01% atropine and ortho-k was not assessed in the current study, making it unclear whether the retinal image quality is different between the two groups, and whether ocular aberration metrics at near viewing are associated with axial elongation. Future analyses/studies regarding ocular HOA and LOA as well as their interaction (e.g. $Z_4^0$ and $Z_2^0$) during different accommodative responses are warranted.

In each group, overall VST was significantly lower than HOA-VST at all visits, indicating that LOA together with HOA degraded retinal image quality more than HOA alone

in ortho-k treated eyes. However, it is interesting to observe that retinal image quality was improved, rather than degraded, after treatment in both groups (Figure 6.1a). The improved retinal image quality was mainly attributable to a correction of LOA after treatment, particularly defocus ($Z_2^0$) (Table 6.3), regardless of increased HOA. For example, over the two years and for a fixed 3-mm pupil, mean ± SD RMS of total HOA increased from 0.04 ± 0.01 μm to 0.11 ± 0.05 μm, and from 0.03 ± 0.01 μm to 0.09 ± 0.04 μm in the AOK and OK groups, respectively.

Of note, the recommendation of reporting ocular aberrations using a standardized pupil size (Thibos et al. 2002) was followed, thus the magnitude of ocular aberrations was not compared between the two groups across different photopic pupil sizes in the current study. Aberration for a photopic pupil of an individual eye at each visit was only included in the linear mixed modeling, which examined the associations between aberration metrics and axial elongation. There may be a higher level of ocular HOA in the AOK group due to a dilated photopic pupil and/or a relaxed tonic accommodation after the use of 0.01% atropine. It has been reported that HOA (e.g. the primary SA ($Z_4^0$)) could be significantly increased after relaxing physiologic tonic accommodation when a higher concentration (1%) of atropine was imposed (Hiraoka et al. 2013). Also, the magnitude of HOA and individual Zernike terms could be elevated exponentially with larger pupil size and vice versa (Applegate et al. 2007).

As there was no between-group difference in any of the terms of LOA for a fixed 3-mm pupil at all visits, the use of 0.01% atropine did not introduce a relaxation in tonic accommodation at distance viewing in the AOK group. The remaining factor affecting ocular aberrations to be considered is pupil size, particularly as a larger photopic pupil size was observed in the AOK group (Table 6.1). An exponential increase in HOA for larger pupil size, particularly the primary SA ($Z_4^0$), was observed in previous studies conducted on adults

(Joslin et al. 2003, Berntsen et al. 2005). Berntsen et al. (2005) found that there was a negligible contribution of the primary SA ($Z_4^0$) to the increase in total HOA RMS for a 3-mm pupil after ortho-k, whilst the increase in primary SA was almost equal to that in the total HOA RMS when the pupil size increased to 5 mm. Joslin et al. (2003) found primary SA ($Z_4^0$) was the most affected individual Zernike terms after ortho-k, and the quadrupled and doubled SA ($Z_4^0$ and $Z_6^0$ combined) for a 6-mm and 3-mm pupil, respectively, were mainly driven by the increase in the primary SA. Previous longitudinal studies used a fixed pupil size to analyze HOA and examine their relationship with axial elongation in children (Hiraoka et al. 2015, Kim et al. 2019, Lau et al. 2020), thus the effect of different pupil sizes on the increase of HOA in these studies is unknown. Nevertheless, in the current study for a 3-mm pupil, 2-fold, 3-fold, and 4-fold increases in RMS values of the total HOAs, primary SA ($Z_4^0$), and SA ($Z_4^0$ and $Z_6^0$ combined) were observed over two years in the two groups, in comparison to a 2-fold, 4-fold, and 14-fold increase for a 6-mm pupil, respectively, reported by Lau et al. (Lau et al. 2020). These comparatively small increases in HOA metrics explain why no association between any HOA metrics and axial elongation was observed in the OK group (Table 6.2), in comparison to significant associations revealed in previous studies using larger pupil size for analyses (Hiraoka et al. 2015, Kim et al. 2019, Lau et al. 2020).

It was suggested that a higher level of Coma after ortho-k was related to lens decentration (Hiraoka et al. 2009). In the current study, mild lens decentration (less than 1 mm) was allowed for all subjects, without causing a significant decrease in UVA (i.e. worse than 0.18 logMAR) (Tan et al. 2019). There was no between-group difference in the individual Zernike coefficients of Coma (i.e. $Z_3^{-1}$, $Z_3^1$, $Z_5^{-1}$, and $Z_5^1$), indicating that lens decentration was comparable between the two groups. Therefore, the significant association between axial elongation and Coma and in the AOK group was more likely to be a consequence of an enlarged photopic pupil size rather than an introduction of more lens

decentration in this group. Slower axial elongation was associated with negatively shifted vertical coma ($Z_3^{-1}$), but not with the other three component terms of Coma (i.e. $Z_3^1$, $Z_5^{-1}$, and $Z_5^1$), suggesting that an association between axial elongation and Coma was mainly attributable to vertical coma. The borderline significant (p = 0.059) association between SA and axial elongation in the AOK group, may be attributable to a narrow spread of axial elongation (Table 6.1) and/or small sample size (23 subjects) in this group, given that, for the pooled data, axial elongation was associated with both SA ($Z_4^0$ and $Z_6^0$ combined) and the primary SA ($Z_4^0$) (Table 6.2). Although horizontal astigmatism ($Z_6^2$) and horizontal hexafoil ($Z_6^6$) was found to be associated with axial elongation in the AOK group, the mean coefficients (< 0.001 μm) of these Zernike terms before and after treatment were too small to make a significant contribution to total HOA and retinal image quality. The associations between axial elongation and ocular aberration metrics in the AOK group only suggest that an optical mechanism may be involved in combining 0.01% atropine and ortho-k in retarding axial elongation. Future interventional studies using mydriasis drugs (e.g. phenylephrine) in combination with ortho-k are warranted, to confirm whether ocular aberrations for an enlarged pupil size affect the axial growth in ortho-k treated eyes.

## 6.5 Conclusions

Combined 0.01% atropine with ortho-k over two years resulted in a larger photopic pupil and less axial elongation, without worsening retinal image quality compared with ortho-k alone. Slower axial eye growth was associated with a greater increase in the magnitudes of total HOA and Coma, a greater decrease in LOA, and negatively shifted vertical coma in the AOK group only. These results suggested that a better control effect in retarding axial elongation, which resulted from combined treatment relative to ortho-k alone, may be related to the post-treatment profile of ocular aberrations associated with an enlarged photopic pupil.

# Chapter 7 Conclusions

## 7.1 Summary

The main objective of this study was to investigate whether there was an additive effect between 0.01% atropine and ortho-k in controlling the progression of childhood myopia over two years, by comparing the axial elongation in children who underwent combined 0.01% atropine and ortho-k treatment with those receiving ortho-k alone (Chapter 4). After two years of treatment, axial elongation was slowed by a mean of 0.14 mm more in the combined treatment group than by ortho-k alone (0.17 ± 0.20 mm vs 0.31 ± 0.19 mm), indicating an additive effect in retarding axial elongation with the addition of 0.01% atropine to ortho-k therapy. Based on the assumption that 0.18 mm change in axial length is equal to 0.50 D (Rabbetts & Mallen 2007), changes in SER was approximately 0.47 D and 0.86 D in the AOK and OK group over two years, respectively, indicating a between-group difference of 0.39 D (less than 0.50 D). However, this difference interpreted as SER changes may not reflect actual change in SER. Nevertheless, axial elongation, which is the major parameter of concern in myopia control, was slowed by 45% in the AOK group relative to the OK group, indicating an improved control effect if combining 0.01% atropine with ortho-k compared with ortho-k alone. Furthermore, the use of 0.01% atropine with ortho-k was well-tolerated, comparable to ortho-k alone. No significant adverse events occurred in either treatment over the 2-year study period, although a significant increase in photopic pupil size was found in the combined treatment (0.73 ± 0.46 mm vs 0.24 ± 0.39 mm at 24-month visit) and more photophobia and halo were reported in the combined treatment group.

OPD-Scan III was used in this study to record pupil size changes along with the treatment. As no study has assessed the repeatability of OPD-Scan III for pupil size measurement, either on adults or on children, an individual analysis was performed to

determine and compare the repeatability of pupil size measurements with OPD-Scan III in myopic children wearing SVS, and those receiving ortho-k or combined treatment of 0.01% atropine and ortho-k (Chapter 3). The CR values for both mesopic and photopic pupil size measurements were 0.28 mm and 0.25 mm, respectively. Since changes in mesopic and photopic pupil sizes in the AOK group were higher than the CR values, there was indeed pupil dilation, albeit less than 1 mm, in children receiving combined treatment of 0.01% atropine and ortho-k, and the changes were not due to errors of measurement.

To gain a better understanding of the possible mechanism that underlies the additive effect when using the combined treatment, post-treatment changes in choroidal thickness were compared between the two treatment groups, and the association between these changes and axial elongation was also determined (Chapter 5). Significantly greater choroidal thickening over two years was found in subjects receiving the combined treatment than in those using ortho-k alone. Contrary to previous reports, the sustained choroidal thickening (20.9 ± 21.5 μm at the 24-month visit) was only present in the combined treatment group, while a thinning (-4.9 ± 15.6 μm at the 24 month-visit) of the choroid over two years was observed in the ortho-k alone group. However, the repeatability of choroidal thickness measurements using the SD-OCT revealed a CR value of 10.0 μm. Based on this, there was indeed choroidal thickening over two years in the combined treatment group compared to a highly stabilized choroid thickness in the ortho-k alone group. Greater choroidal thickening was associated with slower axial elongation in the combined treatment group or if all subjects were considered together, suggesting that a thickened choroid may play a role in the better control effect observed in the combined treatment when compared with ortho-k alone. Future studies are warranted to see whether the thickening in the choroid observed in the AOK group subsides after discontinuation of the treatment, and the duration it may take to return to baseline profile.

A significant increase in HOA after ortho-k is well-documented in the literature, and retrospective studies suggested that increased HOA may underly the control effect observed in ortho-k treatment. Both LOA and HOA contribute to the retinal image quality, albeit the former can be fully corrected. No study has assessed the ocular aberrations for a natural photopic pupil in eyes undergoing combined treatment of 0.01% atropine and ortho-k or ortho-k alone, as well as the relationships between aberrations and axial elongation after treatment. This research gap was addressed by performing further analyses on the results obtained from the AOK study in Chapter 6. The key findings were that in eyes treated with combined 0.01% atropine and ortho-k treatment, slower axial eye growth was associated with a greater increase in the RMS values of total HOA and Coma, a greater decrease in the RMS value of LOA, and a higher level of some HOA terms (e.g. $Z_3^{-1}$) for a photopic pupil. However, no associations were observed between axial eye growth and any of the aberration metrics in eyes treated with ortho-k alone. These results suggest that a greater increase in HOA and decrease in LOA for a non-cycloplegic photopic pupil may contribute to the additive effect observed with the use of the combined treatment of 0.01% atropine and ortho-k when compared with ortho-k alone.

## 7.2 Limitations and future research directions

One limitation of this study is the comparison of the treatment effect of combining 0.01% atropine and ortho-k versus ortho-k alone for only two years. It is uncertain whether there is a better control effect in combined treatment beyond two years of treatment. Secondly, there was no single arm of using 0.01% atropine or SVS as a comparison in the current study. However, it would be unethical to offer monotherapy of 0.01% atropine or SVS to children expecting myopia control. Parents with children demonstrating fast progression are also more likely to refuse these options, leading to selection bias. Thirdly, although

parents were required to return used empty vials of 0.01% atropine, the exact profile of usage is unknown. One AOK subject was excluded due to non-compliance in atropine use, and the non-compliance was confirmed when the parent admitted that they squeezed out the eye drops without using it.

As treatment was discontinued at the end of the 2-year study, axial elongation in children undergoing combining 0.01% atropine and ortho-k was not monitored, making it uncertain whether there is a rebound effect after discontinuation, given a rebound effect, albeit small, was observed in 0.01% atropine treatment (Section 1.4.4.3). Future studies of long-term therapy beyond two years (e.g. three or five years), which include monitoring of rebound effect after discontinuation of treatment are warranted. The optimum concentration for combined therapy is yet to be determined, particularly as the effect of atropine for myopia control and pupil dilation is concentration-dependent (Section 1.4). As an optical mechanism is suggested to underly the additive effect of the combined treatment, application of 0.01% atropine can be switched from nightly use to daily use, or increased to twice daily (e.g. AM and PM), to enhance the optical interactions between the two treatments through a dilated pupil during daily activities. Future studies are warranted to explore these possibilities.

# References

Adler D & Millodot M (2006): The possible effect of undercorrection on myopic progression in children. Clin Exp Optom 89: 315-321.

Alharbi A & Swarbrick HA (2003): The effects of overnight orthokeratology lens wear on corneal thickness. Invest Ophthalmol Vis Sci 44: 2518-2523.

Aller TA, Liu M & Wildsoet CF (2016): Myopia control with bifocal contact Lenses: a randomized clinical trial. Optom Vis Sci 93: 344-352.

Alonso-Caneiro D, Read SA & Collins MJ (2013): Automatic segmentation of choroidal thickness in optical coherence tomography. Biomed Opt Express 4: 2795-2812.

Anstice NS & Phillips JR (2011): Effect of dual-focus soft contact lens wear on axial myopia progression in children. Ophthalmology 118: 1152-1161.

Applegate RA, Donnelly WJ, 3rd, Marsack JD, Koenig DE & Pesudovs K (2007): Three-dimensional relationship between high-order root-mean-square wavefront error, pupil diameter, and aging. J Opt Soc Am A Opt Image Sci Vis 24: 578-587.

Arumugam B & McBrien NA (2012): Muscarinic antagonist control of myopia: evidence for M4 and M1 receptor-based pathways in the inhibition of experimentally-induced axial myopia in the tree shrew selective muscarinic antagonist control of myopia. Invest Ophthalmol Vis Sci 53: 5827-5837.

Asakuma T, Yasuda M, Ninomiya T, Noda Y, Arakawa S, Hashimoto S, Ohno-Matsui K, Kiyohara Y & Ishibashi T (2012): Prevalence and risk factors for myopic retinopathy in a Japanese population: the Hisayama Study. Ophthalmology 119: 1760-1765.

Bedrossian RH (1979): The effect of atropine on myopia. Ophthalmology 86: 713-717.

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

Berntsen DA, Sinnott LT, Mutti DO & Zadnik K (2011): Accommodative lag and juvenile-onset myopia progression in children wearing refractive correction. Vision Res 51: 1039-1046.

Bland JM & Altman DG (2003): Applying the right statistics: analyses of measurement studies. Ultrasound Obstet Gynecol 22: 85-93.

Brown JS, Flitcroft DI, Ying GS, Francis EL, Schmid GF, Quinn GE & Stone RA (2009): In vivo human choroidal thickness measurements: evidence for diurnal fluctuations. Invest Ophthalmol Vis Sci 50: 5-12.

Buehren T, Iskander DR, Collins MJ & Davis B (2007): Potential higher-order aberration cues for sphero-cylindrical refractive error development. Optom Vis Sci 84: 163-174.

Bullimore MA, Sinnott LT & Jones-Jordan LA (2013): The risk of microbial keratitis with overnight corneal reshaping lenses. Optom Vis Sci 90: 937-944.

Cakmak HB, Cagil N, Simavli H, Duzen B & Simsek S (2010): Refractive error may influence mesopic pupil size. Curr Eye Res 35: 130-136.

Chakraborty R, Read SA & Collins MJ (2011): Diurnal variations in axial length, choroidal thickness, intraocular pressure, and ocular biometrics. Invest Ophthalmol Vis Sci 52: 5121-5129.

Chamberlain P, Peixoto-de-Matos SC, Logan NS, Ngo C, Jones D & Young G (2019): A 3-year randomized clinical trial of MiSight lenses for myopia control. Optom Vis Sci 96: 556-567.

Chang MA, Congdon NG, Bykhovskaya I, Munoz B & West SK (2005): The association between myopia and various subtypes of lens opacity: SEE (Salisbury Eye Evaluation) project. Ophthalmology 112: 1395-1401.

Charm J & Cho P (2013): High myopia-partial reduction ortho-k: a 2-year randomized study. Optom Vis Sci 90: 530-539.

Charman WN (1999): Near vision, lags of accommodation and myopia. Ophthalmic Physiol Opt 19: 126-133.

Charman WN (2005): Aberrations and myopia. Ophthalmic Physiol Opt 25: 285-301.

Charman WN (2005): Wavefront technology: past, present and future. Cont Lens Anterior Eye 28: 75-92.

Chen C, Cheung SW & Cho P (2013): Myopia control using toric orthokeratology (TO-SEE study). Invest Ophthalmol Vis Sci 54: 6510-6517.

Chen CC, Cheung SW & Cho P (2012): Toric orthokeratology for highly astigmatic children. Optom Vis Sci 89: 849-855.

Chen X, Sankaridurg P, Donovan L, Lin Z, Li L, Martinez A, Holden B & Ge J (2010): Characteristics of peripheral refractive errors of myopic and non-myopic Chinese eyes. Vision Res 50: 31-35.

Chen Z, Niu L, Xue F, Qu X, Zhou Z, Zhou X & Chu R (2012): Impact of pupil diameter on axial growth in orthokeratology. Optom Vis Sci 89: 1636-1640.

Chen Z, Xue F, Zhou J, Qu X & Zhou X (2016): Effects of orthokeratology on choroidal thickness and axial Length. Optom Vis Sci 93: 1064-1071.

Chen Z, Huang S, Zhou J, Xiaomei Q, Zhou X & Xue F (2019): Adjunctive effect of orthokeratology and low dose atropine on axial elongation in fast-progressing myopic children - a preliminary retrospective study. Cont Lens Anterior Eye 42: 439-442.

Cheng D, Schmid KL & Woo GC (2008): The effect of positive-lens addition and base-in

prism on accommodation accuracy and near horizontal phoria in Chinese myopic children. Ophthalmic Physiol Opt 28: 225-237.

Cheng D, Woo GC, Drobe B & Schmid KL (2014): Effect of bifocal and prismatic bifocal spectacles on myopia progression in children: three-year results of a randomized clinical trial. JAMA Ophthalmol 132: 258-264.

Cheng X, Brennan NA, Toubouti Y & Greenaway NL (2020): Safety of soft contact lenses in children: retrospective review of six randomized controlled trials of myopia control. Acta Ophthalmol 98: e346-e351.

Cheung SW, Cho P, Chui WS & Woo GC (2007): Refractive error and visual acuity changes in orthokeratology patients. Optom Vis Sci 84: 410-416.

Cheung SW, Boost M, Shi GS & Cho P (2016): Microbial contamination of periorbital tissues and accessories of children. Optom Vis Sci 93: 612-618.

Chia A, Chua WH, Cheung YB, Wong WL, Lingham A, Fong A & Tan D (2012): Atropine for the treatment of childhood myopia: safety and efficacy of 0.5%, 0.1%, and 0.01% doses (Atropine for the Treatment of Myopia 2). Ophthalmology 119: 347-354.

Chia A, Chua WH, Wen L, Fong A, Goon YY & Tan D (2014): Atropine for the treatment of childhood myopia: changes after stopping atropine 0.01%, 0.1% and 0.5%. Am J Ophthalmol 157: 451-457 e451.

Chia A, Lu QS & Tan D (2016): Five-year clinical trial on atropine for the treatment of myopia 2: myopia control with atropine 0.01% eyedrops. Ophthalmology 123: 391-399.

Chiang MF, Kouzis A, Pointer RW & Repka MX (2001): Treatment of childhood myopia with atropine eyedrops and bifocal spectacles. Binocul Vis Strabismus Q 16: 209-215.

Chiang ST, Turnbull PRK & Phillips JR (2020): Additive effect of atropine eye drops and short-term retinal defocus on choroidal thickness in children with myopia. Sci Rep 10: 18310.

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

Cho P, Cheung SW, Mountford J & White P (2008): Good clinical practice in orthokeratology. Cont Lens Anterior Eye 31: 17-28.

Cho P, Boost M & Cheng R (2009): Non-compliance and microbial contamination in orthokeratology. Optom Vis Sci 86: 1227-1234.

Cho P & Cheung SW (2012): Retardation of myopia in orthokeratology (ROMIO) study: a 2-year randomized clinical trial. Invest Ophthalmol Vis Sci 53: 7077-7085.

Cho P & Cheung SW (2017): Discontinuation of orthokeratology on eyeball elongation (DOEE). Cont Lens Anterior Eye 40: 82-87.

Cho P & Cheung SW (2017): Protective role of orthokeratology in reducing risk of rapid axial elongation: a reanalysis of data from the ROMIO and TO-SEE studies. Invest Ophthalmol Vis Sci 58: 1411-1416.

Cho P & Tan Q (2018): Myopia and orthokeratology for myopia control. Clin Exp Optom.

Chua WH, Balakrishnan V, Chan YH, Tong L, Ling Y, Quah BL & Tan D (2006): Atropine for the treatment of childhood myopia. Ophthalmology 113: 2285-2291.

Chung K, Mohidin N & O'Leary DJ (2002): Undercorrection of myopia enhances rather than inhibits myopia progression. Vision Res 42: 2555-2559.

Cline D, Hofstetter HW & Griffin JR. Dictionary of visual science, Butterworth-Heinemann. 1997.

Collins MJ, Buehren T & Iskander DR (2006): Retinal image quality, reading and myopia. Vision Res 46: 196-215.

Cooper J, Eisenberg N, Schulman E & Wang FM (2013): Maximum atropine dose without clinical signs or symptoms. Optom Vis Sci 90: 1467-1472.

Curtin BJ, Iwamoto T & Renaldo DP (1979): Normal and staphylomatous sclera of high myopia. An electron microscopic study. Arch Ophthalmol 97: 912-915.

Dirani M, Chan YH, Gazzard G, Hornbeak DM, Leo SW, Selvaraj P, Zhou B, Young TL, Mitchell P, Varma R, Wong TY & Saw SM (2010): Prevalence of refractive error in Singaporean Chinese children: the strabismus, amblyopia, and refractive error in young Singaporean children (STARS) study. Invest Ophthalmol Vis Sci 51: 1348-1355.

Edwards MH, Li RW, Lam CS, Lew JK & Yu BS (2002): The Hong Kong progressive lens myopia control study: study design and main findings. Invest Ophthalmol Vis Sci 43: 2852-2858.

Efron N (1998): Grading scales for contact lens complications. Ophthalmic Physiol Opt 18: 182-186.

Emsley HH. Optics of Vision, Vol. 1: Optics of vision, Hatton Press, London. 1955; 102-103.

Fan DS, Lam DS, Lam RF, Lau JT, Chong KS, Cheung EY, Lai RY & Chew SJ (2004): Prevalence, incidence, and progression of myopia of school children in Hong Kong. Invest Ophthalmol Vis Sci 45: 1071-1075.

Fischer AJ, Miethke P, Morgan IG & Stell WK (1998): Cholinergic amacrine cells are not required for the progression and atropine-mediated suppression of form-deprivation myopia. Brain Res 794: 48-60.

Flitcroft DI, He M, Jonas JB, Jong M, Naidoo K, Ohno-Matsui K, Rahi J, Resnikoff S, Vitale S & Yannuzzi L (2019): IMI - Defining and Classifying Myopia: A Proposed Set of Standards for Clinical and Epidemiologic Studies. Invest Ophthalmol Vis Sci 60: M20-m30.

Fontaine M, Gaucher D, Sauer A & Speeg-Schatz C (2017): Choroidal thickness and ametropia in children: a longitudinal study. Eur J Ophthalmol 27: 730-734.

French AN, Morgan IG, Burlutsky G, Mitchell P & Rose KA (2013): Prevalence and 5- to 6-year incidence and progression of myopia and hyperopia in Australian schoolchildren. Ophthalmology 120: 1482-1491.

Fu A, Stapleton F, Wei L, Wang W, Zhao B, Watt K, Ji N & Lyu Y (2020): Effect of low-dose atropine on myopia progression, pupil diameter and accommodative amplitude: low-dose atropine and myopia progression. Br J Ophthalmol.

Fujikado T, Ninomiya S, Kobayashi T, Suzaki A, Nakada M & Nishida K (2014): Effect of low-addition soft contact lenses with decentered optical design on myopia progression in children: a pilot study. Clin Ophthalmol 8: 1947-1956.

Fulk GW, Cyert LA & Parker DE (2000): A randomized trial of the effect of single-vision vs bifocal lenses on myopia progression in children with esophoria. Optom Vis Sci 77: 395-401.

Gallego P, Martinez-Garcia C, Perez-Merino P, Ibares-Frias L, Mayo-Iscar A & Merayo-Lloves J (2012): Scleral changes induced by atropine in chicks as an experimental model of myopia. Ophthalmic Physiol Opt 32: 478-484.

Gao LQ, Liu W, Liang YB, Zhang F, Wang JJ, Peng Y, Wong TY, Wang NL, Mitchell P & Friedman DS (2011): Prevalence and characteristics of myopic retinopathy in a rural Chinese adult population: the Handan Eye Study. Arch Ophthalmol 129: 1199-1204.

Garcia-Del Valle AM, Blázquez V, Gros-Otero J, Infante M, Culebras A, Verdejo A, Sebastián J, García M, Bueno S & Piñero DP (2021): Efficacy and safety of a soft contact lens to control myopia progression. Clin Exp Optom 104: 14-21.

Gardner DJ, Walline JJ & Mutti DO (2015): Choroidal thickness and peripheral myopic defocus during orthokeratology. Optom Vis Sci 92: 579-588.

Gifford P, Li M, Lu H, Miu J, Panjaya M & Swarbrick HA (2013): Corneal versus ocular aberrations after overnight orthokeratology. Optom Vis Sci 90: 439-447.

Goss DA, Grosvenor TP, Keller JT, Marsh-Tootle W, Norton TT & Zadnik K (1997): Optometric clinical practice guideline care of the patient with myopia. American Optometric Association 243: 63141-67881.

Grosvenor T (1987): A review and a suggested classification system for myopia on the basis of age-related prevalence and age of onset. Optom Vis Sci 64: 545-554.

Guillon M, Dumbleton K, Theodoratos P, Gobbe M, Wooley CB & Moody K (2016): The effects of age, refractive status, and luminance on pupil Size. Optom Vis Sci 93: 1093-1100.

Guo B, Cheung SW, Kojima R & Cho P (2021): One-year results of the Variation of Orthokeratology Lens Treatment Zone (VOLTZ) Study: a prospective randomised clinical trial. Ophthalmic Physiol Opt 41: 702-714.

Gwiazda J, Thorn F, Bauer J & Held R (1993): Myopic children show insufficient accommodative response to blur. Invest Ophthalmol Vis Sci 34: 690-694.

Gwiazda J, Grice K & Thorn F (1999): Response AC/A ratios are elevated in myopic children. Ophthalmic Physiol Opt 19: 173-179.

Gwiazda J, Hyman L, Hussein M, Everett D, Norton TT, Kurtz D, Leske MC, Manny R, Marsh-Tootle W & Scheiman M (2003): A randomized clinical trial of progressive addition lenses versus single vision lenses on the progression of myopia in children. Invest Ophthalmol Vis Sci 44: 1492-1500.

Gwiazda J, Thorn F & Held R (2005): Accommodation, accommodative convergence, and response AC/A ratios before and at the onset of myopia in children. Optom Vis Sci 82: 273-278.

Gwiazda J, Chandler D & al. CSe (2011): Progressive-addition lenses versus single-vision lenses for slowing progression of myopia in children with high accommodative lag and near esophoria. Invest Ophthalmol Vis Sci 52: 2749-2757.

Hasebe S, Ohtsuki H, Nonaka T, Nakatsuka C, Miyata M, Hamasaki I & Kimura S (2008): Effect of progressive addition lenses on myopia progression in Japanese children: a prospective, randomized, double-masked, crossover trial. Invest Ophthalmol Vis Sci 49: 2781-2789.

Hayashi K, Ohno-Matsui K, Shimada N, Moriyama M, Kojima A, Hayashi W, Yasuzumi K, Nagaoka N, Saka N, Yoshida T, Tokoro T & Mochizuki M (2010): Long-term pattern of progression of myopic maculopathy: a natural history study. Ophthalmology 117: 1595-1611, 1611.e1591-1594.

He JC, Sun P, Held R, Thorn F, Sun X & Gwiazda JE (2002): Wavefront aberrations in eyes of emmetropic and moderately myopic school children and young adults. Vision Res 42: 1063-1070.

He M, Xiang F, Zeng Y, Mai J, Chen Q, Zhang J, Smith W, Rose K & Morgan IG (2015): Effect of time spent outdoors at school on the development of myopia among children in China: a randomized clinical trial. JAMA 314: 1142-1148.

Hiraoka T, Mihashi T, Okamoto C, Okamoto F, Hirohara Y & Oshika T (2009): Influence of induced decentered orthokeratology lens on ocular higher-order wavefront aberrations and contrast sensitivity function. J Cataract Refract Surg 35: 1918-1926.

Hiraoka T, Kakita T, Okamoto F, Takahashi H & Oshika T (2012): Long-term effect of overnight orthokeratology on axial length elongation in childhood myopia: a 5-year follow-up study. Invest Ophthalmol Vis Sci 53: 3913-3919.

Hiraoka T, Miyata K, Nakamura Y, Miyai T, Ogata M, Okamoto F & Oshika T (2013): Influences of cycloplegia with topical atropine on ocular higher-order aberrations. Ophthalmology 120: 8-13.

Hiraoka T, Kakita T, Okamoto F & Oshika T (2015): Influence of ocular wavefront

aberrations on axial length elongation in myopic children treated with overnight orthokeratology. Ophthalmology 122: 93-100.

Hiraoka T, Kotsuka J, Kakita T, Okamoto F & Oshika T (2017): Relationship between higher-order wavefront aberrations and natural progression of myopia in schoolchildren. Sci Rep 7: 7876.

Holden BA, Fricke TR, Wilson DA, Jong M, Naidoo KS, Sankaridurg P, Wong TY, Naduvilath TJ & Resnikoff S (2016): Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. Ophthalmology 123: 1036-1042.

Hoogerheide J, Rempt F & Hoogenboom WP (1971): Acquired myopia in young pilots. Ophthalmologica 163: 209-215.

Horner DG, Soni PS, Salmon TO & Swartz TS (1999): Myopia progression in adolescent wearers of soft contact lenses and spectacles. Optom Vis Sci 76: 474-479.

Huang YC, Chu YC, Wang NK, Lai CC, Chen KJ, Hwang YS & Wu WC (2019): Impact of etiology on the outcome of pediatric rhegamtogenous retinal detachement. Retina 39 118-126.

Hughes RP, Vincent SJ, Read SA & Collins MJ (2020): Higher order aberrations, refractive error development and myopia control: a review. Clin Exp Optom 103: 68-85.

Hutchins J & Hollyfield J (1985): Acetylcholine receptors in the human retina. Invest Ophthalmol Vis Sci 26: 1550-1557.

Ip JM, Huynh SC, Robaei D, Rose KA, Morgan IG, Smith W, Kifley A & Mitchell P (2007): Ethnic differences in the impact of parental myopia: findings from a population-based study of 12-year-old Australian children. Invest Ophthalmol Vis Sci 48: 2520-2528.

Ip JM, Saw SM, Rose KA, Morgan IG, Kifley A, Wang JJ & Mitchell P (2008): Role of near work in myopia: findings in a sample of Australian school children. Invest Ophthalmol Vis Sci 49: 2903-2910.

Jin JX, Hua WJ, Jiang X, Wu XY, Yang JW, Gao GP, Fang Y, Pei CL, Wang S & Zhang JZ (2015): Effect of outdoor activity on myopia onset and progression in school-aged children in northeast china: the sujiatun eye care study. BMC Ophthalmol 15: 1.

Jin P, Zou H, Zhu J, Xu X, Jin J, Chang TC, Lu L, Yuan H, Sun S, Yan B, He J, Wang M & He X (2016): Choroidal and retinal thickness in children with different refractive status measured by swept-source optical coherence tomography. Am J Ophthalmol 168: 164-176.

Jones LA, Sinnott LT, Mutti DO, Mitchell GL, Moeschberger ML & Zadnik K (2007): Parental history of myopia, sports and outdoor activities, and future myopia. Invest Ophthalmol Vis Sci 48: 3524-3532.

Joslin CE, Wu SM, McMahon TT & Shahidi M (2003): Higher-order wavefront aberrations in corneal refractive therapy. Optom Vis Sci 80: 805-811.

Kakita T, Hiraoka T & Oshika T (2011): Influence of overnight orthokeratology on axial elongation in childhood myopia. Invest Ophthalmol Vis Sci 52: 2170-2174.

Kang P & Swarbrick H (2011): Peripheral refraction in myopic children wearing orthokeratology and gas-permeable lenses. Optom Vis Sci 88: 476-482.

Kara N, Demircan A, Karatas G, Ozgurhan EB, Tatar G, Karakucuk Y, Basci A & Demirok A (2014): Effects of two commonly used mydriatics on choroidal thickness: direct and crossover effects. J Ocul Pharmacol Ther 30: 366-370.

Katz J, Schein OD, Levy B, Cruiscullo T, Saw SM, Rajan U, Chan TK, Yew Khoo C & Chew SJ (2003): A randomized trial of rigid gas permeable contact lenses to reduce progression of children's myopia. Am J Ophthalmol 136: 82-90.

Kennedy RH, Dyer JA, Kennedy MA, Parulkar S, Kurland LT, Herman DC, McIntire D, Jacobs D & Luepker RV (2000): Reducing the progression of myopia with atropine: a long term cohort study of Olmsted County students. Binocul Vis Strabismus Q 15: 281-304.

Kim J, Lim DH, Han SH & Chung TY (2019): Predictive factors associated with axial length growth and myopia progression in orthokeratology. PLoS One 14: e0218140.

Kinoshita N, Konno Y, Hamada N, Kanda Y, Shimmura-Tomita M & Kakehashi A (2018): Additive effects of orthokeratology and atropine 0.01% ophthalmic solution in slowing axial elongation in children with myopia: first year results. Jpn J Ophthalmol 62: 544-553.

Kinoshita N, Konno Y, Hamada N, Kanda Y, Shimmura-Tomita M, Kaburaki T & Kakehashi A (2020): Efficacy of combined orthokeratology and 0.01% atropine solution for slowing axial elongation in children with myopia: a 2-year randomised trial. Sci Rep 10: 12750.

Kirwan C, O'Keefe M & Soeldner H (2006): Higher-order aberrations in children. Am J Ophthalmol 141: 67-70.

Kloosterman NA, Meindertsma T, van Loon AM, Lamme VA, Bonneh YS & Donner TH (2015): Pupil size tracks perceptual content and surprise. Eur J Neurosci 41: 1068-1078.

Kobashi H, Kamiya K, Ishikawa H, Goseki T & Shimizu K (2012): Daytime variations in pupil size under photopic conditions. Optom Vis Sci 89: 197-202.

Kohnen T, Terzi E, Buhren J & Kohnen EM (2003): Comparison of a digital and a handheld infrared pupillometer for determining scotopic pupil diameter. J Cataract Refract Surg 29: 112-117.

Koomson NY, Amedo AO, Opoku-Baah C, Ampeh PB, Ankamah E & Bonsu K (2016): Relationship between reduced accommodative lag and myopia Progression. Optom Vis Sci.

Lam BL, Thompson HS & Walls RC (1996): Effect of light on the prevalence of simple anisocoria. Ophthalmology 103: 790-793.

Lam CS, Tang WC, Tse DY, Tang YY & To CH (2014): Defocus Incorporated Soft Contact (DISC) lens slows myopia progression in Hong Kong Chinese schoolchildren: a 2-year

randomised clinical trial. Br J Ophthalmol 98: 40-45.

Lam CSY, Tang WC, Tse DY, Lee RPK, Chun RKM, Hasegawa K, Qi H, Hatanaka T & To CH (2020): Defocus Incorporated Multiple Segments (DIMS) spectacle lenses slow myopia progression: a 2-year randomised clinical trial. Br J Ophthalmol 104: 363-368.

Lam DS, Fan DS, Lam RF, Rao SK, Chong KS, Lau JT, Lai RY & Cheung EY (2008): The effect of parental history of myopia on children's eye size and growth: results of a longitudinal study. Invest Ophthalmol Vis Sci 49: 873-876.

Lau JK, Vincent SJ, Collins MJ, Cheung SW & Cho P (2018): Ocular higher-order aberrations and axial eye growth in young Hong Kong children. Sci Rep 8: 6726.

Lau JK, Cheung SW, Collins MJ & Cho P (2019): Repeatability of choroidal thickness measurements with Spectralis OCT images. BMJ Open Ophthalmol 4: e000237.

Lau JK, Wan K, Cheung SW, Vincent SJ & Cho P (2019): Weekly changes in axial length and choroidal thickness in children during and following orthokeratology treatment with sifferent compression factors. Transl Vis Sci Technol 8: 9.

Lau JK, Vincent SJ, Cheung SW & Cho P (2020): Higher-order aberrations and axial elongation in myopic children treated with orthokeratology. Invest Ophthalmol Vis Sci 61: 22.

Lee TT & Cho P (2013): Relative peripheral refraction in children: twelve-month changes in eyes with different ametropias. Ophthalmic Physiol Opt 33: 283-293.

Li SM, Kang MT, Wu SS, Liu LR, Li H, Chen Z & Wang N (2016): Efficacy, safety and acceptability of orthokeratology on slowing axial elongation in myopic children by meta-analysis. Curr Eye Res 41: 600-608.

Li Z, Hu Y, Cui D, Long W, He M & Yang X (2019): Change in subfoveal choroidal thickness secondary to orthokeratology and its cessation: a predictor for the change in axial length. Acta Ophthalmol 97: e454-e459.

Lian Y, Shen M, Huang S, Yuan Y, Wang Y, Zhu D, Jiang J, Mao X, Wang J & Lu F (2014): Corneal reshaping and wavefront aberrations during overnight orthokeratology. Eye Contact Lens 40: 161-168.

Lim R, Mitchell P & Cumming RG (1999): Refractive associations with cataract: the Blue Mountains Eye Study. Invest Ophthalmol Vis Sci 40: 3021-3026.

Lin LL, Shih YF, Hsiao CK & Chen CJ (2004): Prevalence of myopia in Taiwanese schoolchildren: 1983 to 2000. Ann Acad Med Singapore 33: 27-33.

Linke SJ, Baviera J, Munzer G, Fricke OH, Richard G & Katz T (2012): Mesopic pupil size in a refractive surgery population (13,959 eyes). Optom Vis Sci 89: 1156-1164.

Little JA, McCullough SJ, Breslin KM & Saunders KJ (2014): Higher order ocular aberrations and their relation to refractive error and ocular biometry in children. Invest

Ophthalmol Vis Sci 55: 4791-4800.

Liu HH, Xu L, Wang YX, Wang S, You QS & Jonas JB (2010): Prevalence and progression of myopic retinopathy in Chinese adults: the Beijing Eye Study. Ophthalmology 117: 1763-1768.

Liu Y & Wildsoet C (2011): The effect of two-zone concentric bifocal spectacle lenses on refractive error development and eye growth in young chicks. Invest Ophthalmol Vis Sci 52: 1078-1086.

Liu Y & Wildsoet C (2012): The effective add inherent in 2-zone negative lenses inhibits eye growth in myopic young chicks. Invest Ophthalmol Vis Sci 53: 5085-5093.

Liu YM & Xie P (2016): The safety of orthokeratology-a systematic review. Eye Contact Lens 42: 35-42.

Lopes-Ferreira D, Ribeiro C, Neves H, Faria-Ribeiro M, Queirós A, Villa-Collar C, Jorge J & González-Méijome JM (2013): Peripheral refraction with dominant design multifocal contact lenses in young myopes. J Optom 6: 85-94.

Lopes-Ferreira DP, Neves HI, Faria-Ribeiro M, Queiros A, Fernandes PR & Gonzalez-Meijome JM (2015): Peripheral refraction with eye and head rotation with contact lenses. Cont Lens Anterior Eye 38: 104-109.

Lu B, Congdon N, Liu X, Choi K, Lam DS, Zhang M, Zheng M, Zhou Z, Li L, Liu X, Sharma A & Song Y (2009): Associations between near work, outdoor activity, and myopia among adolescent students in rural China: the Xichang Pediatric Refractive Error Study report No. 2. Arch Ophthalmol 127: 769-775.

Mahajan VN (2005): Strehl ratio of a Gaussian beam. J Opt Soc Am A Opt Image Sci Vis 22: 1824-1833.

Mantry S, Banerjee S, Naroo S & Shah S (2005): Scotopic measurement of normal pupil size with the Colvard pupillometer and the Nidek auto-refractor. Cont Lens Anterior Eye 28: 53-56.

Marcus MW, de Vries MM, Junoy Montolio FG & Jansonius NM (2011): Myopia as a risk factor for open-angle glaucoma: a systematic review and meta-analysis. Ophthalmology 118: 1989-1994.e1982.

Mathur A, Gehrmann J & Atchison DA (2014): Influences of luminance and accommodation stimuli on pupil size and pupil center location. Invest Ophthalmol Vis Sci 55: 2166-2172.

McBrien NA, Moghaddam HO & Reeder AP (1993): Atropine reduces experimental myopia and eye enlargement via a nonaccommodative mechanism. Invest Ophthalmol Vis Sci 34: 205-215.

McBrien NA & Gentle A (2003): Role of the sclera in the development and pathological complications of myopia. Prog Retin Eye Res 22: 307-338.

McLaren JW, Erie JC & Brubaker RF (1992): Computerized analysis of pupillograms in studies of alertness. Invest Ophthalmol Vis Sci 33: 671-676.

Medina A (1987): A model for emmetropization. The effect of corrective lenses. Acta Ophthalmol (Copenh) 65: 565-571.

Meng W, Butterworth J, Malecaze F & Calvas P (2011): Axial length of myopia: a review of current research. Ophthalmologica 225: 127-134.

Mitchell P, Hourihan F, Sandbach J & Wang JJ (1999): The relationship between glaucoma and myopia: the Blue Mountains Eye Study. Ophthalmology 106: 2010-2015.

Morgan PB, Efron N, Maldonado-Codina C & Efron S (2005): Adverse events and discontinuations with rigid and soft hyper Dk contact lenses used for continuous wear. Optom Vis Sci 82: 528-535.

Mutti DO, Sholtz RI, Friedman NE & Zadnik K (2000): Peripheral refraction and ocular shape in children. Invest Ophthalmol Vis Sci 41: 1022-1030.

Mutti DO, Mitchell GL, Moeschberger ML, Jones LA & Zadnik K (2002): Parental myopia, near work, school achievement, and children's refractive error. Invest Ophthalmol Vis Sci 43: 3633-3640.

Mutti DO, Mitchell GL, Hayes JR, Jones LA, Moeschberger ML, Cotter SA, Kleinstein RN, Manny RE, Twelker JD & Zadnik K (2006): Accommodative Lag before and after the Onset of Myopia. Invest Ophthalmol Vis Sci 47: 837-846.

Mutti DO, Hayes JR, Mitchell GL, Jones LA, Moeschberger ML, Cotter SA, Kleinstein RN, Manny RE, Twelker JD & Zadnik K (2007): Refractive error, axial length, and relative peripheral refractive error before and after the onset of myopia. Invest Ophthalmol Vis Sci 48: 2510-2519.

Mutti DO, Sinnott LT, Mitchell GL, Jones-Jordan LA, Moeschberger ML, Cotter SA, Kleinstein RN, Manny RE, Twelker JD & Zadnik K (2011): Relative peripheral refractive error and the risk of onset and progression of myopia in children. Invest Ophthalmol Vis Sci 52: 199-205.

Negrel AD, Maul E, Pokharel GP, Zhao J & Ellwein LB (2000): Refractive error study in children: sampling and measurement methods for a multi-country survey. Am J Ophthalmol 129: 421-426.

Netto MV, Ambrosio R, Jr. & Wilson SE (2004): Pupil size in refractive surgery candidates. J Refract Surg 20: 337-342.

Nickla DL & Wallman J (2010): The multifunctional choroid. Prog Retin Eye Res 29: 144-168.

Nickla DL, Zhu X & Wallman J (2013): Effects of muscarinic agents on chick choroids in intact eyes and eyecups: evidence for a muscarinic mechanism in choroidal thinning. Ophthalmic Physiol Opt 33: 245-256.

Ohsugi E, Mitamura Y, Shinomiya K, Niki M, Sano H, Nagasawa T, Shimizu Y, Nagasato D & Tabuchi H (2018): Changes in choroidal thickness in healthy pediatric individuals: a longitudinal study. Int J Ophthalmol 11: 1179-1184.

Park KA & Oh SY (2013): Choroidal thickness in healthy children. Retina 33: 1971-1976.

Paune J, Morales H, Armengol J, Quevedo L, Faria-Ribeiro M & Gonzalez-Meijome JM (2015): Myopia control with a novel peripheral gradient soft lens and orthokeratology: A 2-Year Clinical Trial. Biomed Res Int 2015: 507572.

Paune J, Thivent S, Armengol J, Quevedo L, Faria-Ribeiro M & Gonzalez-Meijome JM (2016): Changes in peripheral refraction, higher-order aberrations, and accommodative lag with a radial refractive gradient contact lens in young myopes. Eye Contact Lens.

Philip K, Sankaridurg P, Holden B, Ho A & Mitchell P (2014): Influence of higher order aberrations and retinal image quality in myopisation of emmetropic eyes. Vision Res 105: 233-243.

Phillips JR, Khalaj M & McBrien NA (2000): Induced myopia associated with increased scleral creep in chick and tree shrew eyes. Invest Ophthalmol Vis Sci 41: 2028-2034.

Plainis S, Ginis HS & Pallikaris A (2005): The effect of ocular aberrations on steady-state errors of accommodative response. J Vis 5: 466-477.

Qu J, Zhou X, Xie R, Zhang L, Hu D, Li H & Lu F (2006): The presence of m1 to m5 receptors in human sclera: evidence of the sclera as a potential site of action for muscarinic receptor antagonists. Curr Eye Res 31: 587-597.

Queiros A, Gonzalez-Meijome JM, Jorge J, Villa-Collar C & Gutierrez AR (2010): Peripheral refraction in myopic patients after orthokeratology. Optom Vis Sci 87: 323-329.

Rabbetts R & Mallen E (2007): Chapter 21. Distribution and ocular dioptrics of ametropia. Bennett and Rabbetts' Clinical Visual Optics. 4th ed. Butterworth-Heinemann: 425.

Romano PE & Donovan JP (2000): Management of progressive school myopia with topical atropine eyedrops and photochromic bifocal spectacles. Binocul Vis Strabismus Q 15: 257-260.

Rose KA, Morgan IG, Ip J, Kifley A, Huynh S, Smith W & Mitchell P (2008): Outdoor activity reduces the prevalence of myopia in children. Ophthalmology 115: 1279-1285.

Rose KA, Morgan IG, Smith W, Burlutsky G, Mitchell P & Saw SM (2008): Myopia, lifestyle, and schooling in students of Chinese ethnicity in Singapore and Sydney. Arch Ophthalmol 126: 527-530.

Ruiz-Pomeda A, Perez-Sanchez B, Valls I, Prieto-Garrido FL, Gutierrez-Ortega R & Villa-Collar C (2018): MiSight Assessment Study Spain (MASS). A 2-year randomized clinical trial. Graefes Arch Clin Exp Ophthalmol 256: 1011-1021.

Sander BP, Collins MJ & Read SA (2019): Short-term effect of low-dose atropine and hyperopic defocus on choroidal thickness and axial length in young myopic adults. J Ophthalmol 2019: 4782536.

Sankaridurg P, Donovan L, Varnas S, Ho A, Chen X, Martinez A, Fisher S, Lin Z, Smith EL, 3rd, Ge J & Holden B (2010): Spectacle lenses designed to reduce progression of myopia: 12-month results. Optom Vis Sci 87: 631-641.

Sankaridurg P, Holden B, Smith E, 3rd, Naduvilath T, Chen X, de la Jara PL, Martinez A, Kwan J, Ho A, Frick K & Ge J (2011): Decrease in rate of myopia progression with a contact lens designed to reduce relative peripheral hyperopia: one-year results. Invest Ophthalmol Vis Sci 52: 9362-9367.

Santodomingo-Rubido J, Villa-Collar C, Gilmartin B & Gutierrez-Ortega R (2012): Orthokeratology vs. spectacles: adverse events and discontinuations. Optom Vis Sci 89: 1133-1139.

Santodomingo-Rubido J, Villa-Collar C, Gilmartin B & Gutierrez-Ortega R (2012): Myopia control with orthokeratology contact lenses in Spain: refractive and biometric changes. Invest Ophthalmol Vis Sci 53: 5060-5065.

Schnitzler EM, Baumeister M & Kohnen T (2000): Scotopic measurement of normal pupils: Colvard versus Video Vision Analyzer infrared pupillometer. J Cataract Refract Surg 26: 859-866.

Schwiegerling J (2011): Scaling pseudo-Zernike expansion coefficients to different pupil sizes. Opt Lett 36: 3076-3078.

Shen L, Melles RB, Metlapally R, Barcellos L, Schaefer C, Risch N, Herrinton LJ, Wildsoet C & Jorgenson E (2016): The association of refractive error with glaucoma in a multiethnic population. Ophthalmology 123: 92-101.

Shih YF, Chen CH, Chou AC, Ho TC, Lin LL & Hung PT (1999): Effects of different concentrations of atropine on controlling myopia in myopic children. J Ocul Pharmacol Ther 15: 85-90.

Shih YF, Hsiao CK, Chen CJ, Chang CW, Hung PT & Lin LL (2001): An intervention trial on efficacy of atropine and multi-focal glasses in controlling myopic progression. Acta Ophthalmol Scand 79: 233-236.

Shih YF, Ho TC, Hsiao CK & Lin LL (2006): Visual outcomes for high myopic patients with or without myopic maculopathy: a 10 year follow up study. Br J Ophthalmol 90: 546-550.

Siatkowski RM, Cotter SA, Crockett RS, Miller JM, Novack GD & Zadnik K (2008): Two-year multicenter, randomized, double-masked, placebo-controlled, parallel safety and efficacy study of 2% pirenzepine ophthalmic gel in children with myopia. J AAPOS 12: 332-339.

Sng CC, Lin XY, Gazzard G, Chang B, Dirani M, Lim L, Selvaraj P, Ian K, Drobe B, Wong TY & Saw SM (2011): Change in peripheral refraction over time in Singapore Chinese children. Invest Ophthalmol Vis Sci 52: 7880-7887.

Spadea L, Giammaria D, Ferrante R & Balestrazzi E (2005): Pre-excimer laser and post-excimer laser refractive surgery measurements of scotopic pupil diameter using 2 pupillometers. Ophthalmology 112: 1003-1008.

Stone RA, Lin T & Laties AM (1991): Muscarinic antagonist effects on experimental chick myopia. Exp Eye Res 52: 755-758.

Swarbrick HA, Wong G & O'leary DJ (1998): Corneal response to orthokeratology. Optom Vis Sci 75: 791-799.

Syniuta LA & Isenberg SJ (2001): Atropine and bifocals can slow the progression of myopia in children. Binocul Vis Strabismus Q 16: 203-208.

Tan CS, Ouyang Y, Ruiz H & Sadda SR (2012): Diurnal variation of choroidal thickness in normal, healthy subjects measured by spectral domain optical coherence tomography. Invest Ophthalmol Vis Sci 53: 261-266.

Tan DT, Lam DS, Chua WH, Shu-Ping DF & Crockett RS (2005): One-year multicenter, double-masked, placebo-controlled, parallel safety and efficacy study of 2% pirenzepine ophthalmic gel in children with myopia. Ophthalmology 112: 84-91.

Tan Q, Ng AL, Cheng GP, Woo VC & Cho P (2019): Combined Atropine with Orthokeratology for Myopia Control: Study Design and Preliminary Results. Curr Eye Res 44: 671-678.

Thibos LN, Applegate RA, Schwiegerling JT & Webb R (2002): Standards for reporting the optical aberrations of eyes. J Refract Surg 18: S652-660.

Thibos LN, Bradley A & López-Gil N (2013): Modelling the impact of spherical aberration on accommodation. Ophthalmic Physiol Opt 33: 482-496.

Thibos LN, Bradley A, Liu T & López-Gil N (2013): Spherical aberration and the sign of defocus. Optom Vis Sci 90: 1284-1291.

Ticak A & Walline JJ (2013): Peripheral optics with bifocal soft and corneal reshaping contact lenses. Optom Vis Sci 90: 3-8.

Tong L, Huang XL, Koh AL, Zhang X, Tan DT & Chua WH (2009): Atropine for the treatment of childhood myopia: effect on myopia progression after cessation of atropine. Ophthalmology 116: 572-579.

Tsai ASH, Wong CW, Lim L, Yeo I, Wong D, Wong E, Ang CL, Ong SG, Lee SY & Tan G (2019): Pediatric retinal detachment in an Asian population with high prevalence of myopia: clinical characteristics, surgical outcomes, and prognostic factors. Retina 39: 1751-1760.

Vongphanit J, Mitchell P & Wang JJ (2002): Prevalence and progression of myopic retinopathy in an older population. Ophthalmology 109: 704-711.

Wachler BS & Krueger RR (1999): Agreement and repeatability of infrared pupillometry and

the comparison method. Ophthalmology 106: 319-323.

Walline JJ, Mutti DO, Zadnik K & Jones LA (1998): Development of phoria in children. Optom Vis Sci 75: 605-610.

Walline JJ, Mutti DO, Jones LA, Rah MJ, Nichols KK, Watson R & Zadnik K (2001): The contact lens and myopia progression (CLAMP) study: design and baseline data. Optom Vis Sci 78: 223-233.

Walline JJ, Jones LA, Mutti DO & Zadnik K (2004): A randomized trial of the effects of rigid contact lenses on myopia progression. Arch Ophthalmol 122: 1760-1766.

Walline JJ, Jones LA, Sinnott L, Manny RE, Gaume A, Rah MJ, Chitkara M & Lyons S (2008): A randomized trial of the effect of soft contact lenses on myopia progression in children. Invest Ophthalmol Vis Sci 49: 4702-4706.

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

Walline JJ, Greiner KL, McVey ME & Jones-Jordan LA (2013): Multifocal contact lens myopia control. Optom Vis Sci 90: 1207-1214.

Walline JJ, Walker MK, Mutti DO, Jones-Jordan LA, Sinnott LT, Giannoni AG, Bickle KM, Schulle KL, Nixon A, Pierce GE & Berntsen DA (2020): Effect of high add power, medium add power, or single-vision contact lenses on myopia progression in children: The BLINK randomized clinical trial. JAMA 324: 571-580.

Wallman J & Winawer J (2004): Homeostasis of eye growth and the question of myopia. Neuron 43: 447-468.

Wang B, Naidu RK & Qu X (2017): Factors related to axial length elongation and myopia progression in orthokeratology practice. PLoS One 12: e0175913.

Wang D, Chun RK, Liu M, Lee RP, Sun Y, Zhang T, Lam C, Liu Q & To CH (2016): Optical defocus rapidly changes choroidal thickness in schoolchildren. PLoS One 11: e0161535.

Wang J, Liu L, Boost M, Yap M & Cho P (2020): Risk factors associated with contamination of orthokeratology lens cases. Cont Lens Anterior Eye 43: 178-184.

Watt KG & Swarbrick HA (2007): Trends in microbial keratitis associated with orthokeratology. Eye Contact Lens 33: 373-377; discussion 382.

Weizhong L, Zhikuan Y, Wen L, Xiang C & Jian G (2008): A longitudinal study on the relationship between myopia development and near accommodation lag in myopic children. Ophthalmic Physiol Opt 28: 57-61.

Woodman-Pieterse EC, Read SA, Collins MJ & Alonso-Caneiro D (2015): Regional changes in choroidal thickness associated with accommodation. Invest Ophthalmol Vis Sci 56: 6414-6422.

Woodman EC, Read SA & Collins MJ (2012): Axial length and choroidal thickness changes accompanying prolonged accommodation in myopes and emmetropes. Vision Res 72: 34-41.

Wu PC, Tsai CL, Hu CH & Yang YH (2010): Effects of outdoor activities on myopia among rural school children in Taiwan. Ophthalmic Epidemiol 17: 338-342.

Wu PC, Tsai CL, Wu HL, Yang YH & Kuo HK (2013): Outdoor activity during class recess reduces myopia onset and progression in school children. Ophthalmology 120: 1080-1085.

Xiang F, He M & Morgan IG (2012): The impact of parental myopia on myopia in Chinese children: population-based evidence. Optom Vis Sci 89: 1487-1496.

Xu L, Wang Y, Wang S, Wang Y & Jonas JB (2007): High myopia and glaucoma susceptibility the Beijing Eye Study. Ophthalmology 114: 216-220.

Yam JC, Jiang Y, Tang SM, Law AKP, Chan JJ, Wong E, Ko ST, Young AL, Tham CC, Chen LJ & Pang CP (2019): Low-Concentration Atropine for Myopia Progression (LAMP) Study: a randomized, double-blinded, placebo-controlled trial of 0.05%, 0.025%, and 0.01% atropine eye drops in myopia control. Ophthalmology 126: 113-124.

Yam JC, Li FF, Zhang X, Tang SM, Yip BHK, Kam KW, Ko ST, Young AL, Tham CC, Chen LJ & Pang CP (2020): Two-year clinical trial of the Low-Concentration Atropine for Myopia Progression (LAMP) study: phase 2 report. Ophthalmology 127: 910-919.

Yang Z, Lan W, Ge J, Liu W, Chen X, Chen L & Yu M (2009): The effectiveness of progressive addition lenses on the progression of myopia in Chinese children. Ophthalmic Physiol Opt 29: 41-48.

Yuvacı İ, Pangal E, Yuvacı S, Bayram N, Ataş M, Başkan B, Demircan S & Akal A (2015): An evaluation of effects of different mydriatics on choroidal thickness by examining anterior chamber parameters: The Scheimpflug Imaging and Enhanced Depth Imaging-OCT Study. J Ophthalmol 2015: 981274.

Zhang JM, Wu JF, Chen JH, Wang L, Lu TL, Sun W, Hu YY, Jiang WJ, Guo DD, Wang XR, Bi HS & Jonas JB (2015): Macular choroidal thickness in children: The Shandong Children Eye Study. Invest Ophthalmol Vis Sci 56: 7646-7652.

Zhang N, Yang XB, Zhang WQ, Liu LQ, Dong GJ, Chen TW, Liao M & Liao X (2013): Relationship between higher-order aberrations and myopia progression in schoolchildren: a retrospective study. Int J Ophthalmol 6: 295-299.

Zhang Z, Zhou Y, Xie Z, Chen T, Gu Y, Lu S & Wu Z (2016): The effect of topical atropine on the choroidal thickness of healthy children. Sci Rep 6: 34936.

Zhao W, Li Z, Hu Y, Jiang J, Long W, Cui D, Chen W & Yang X (2020): Short-term effects of atropine combined with orthokeratology (ACO) on choroidal thickness. Cont Lens Anterior Eye.

Zhu MJ, Feng HY, He XG, Zou HD & Zhu JF (2014): The control effect of orthokeratology on axial length elongation in Chinese children with myopia. BMC Ophthalmol 14: 141.

# Appendix 1 - Publications from this thesis

Peer-reviewed publications:

- Tan Q, Ng ALK, Cheng GPM, Woo VCP, Cho P (2021): Repeatability of pupil size measurements with NIDEK OPD-Scan III in myopic children. Ophthalmic Physiol Optics 41: 431-436

| Contribution | Author(s) |
|---|---|
| Conceptualization | CP, TQ |
| Funding acquisition | CP, CGPM, WVCP |
| Investigation | TQ, CP |
| Methodology | TQ, CP |
| Data collection | TQ |
| Data analysis | TQ, CP |
| Project administration/ Supervision | CP |
| Visualization | TQ, CP |
| Writing - first draft | TQ |
| Writing - review & editing | TQ, CP, NALK, CGPM, WVCP |

- Vincent SJ, Tan Q, Ng ALK, Cheng GPM, Woo VCP, Cho P (2020). Higher-order aberrations and axial elongation in combined 0.01% atropine with orthokeratology for myopia control. Ophthalmic Physiol Optics 40: 728-737.

| Contribution | Author(s) |
|---|---|
| Conceptualization | CP, VSJ |
| Funding acquisition | CP, CGPM, WVCP |
| Investigation | VSJ, TQ |
| Methodology | TQ, VSJ, CP |
| Data collection | TQ |
| Data analysis | VSJ, TQ |
| Project administration/Supervision | CP |
| Visualization | VSJ, TQ, CP |
| Writing - first draft | VSJ |
| Writing - review & editing | VSJ, TQ, CP, NALK, CGPM, WVCP |

- Tan Q, Ng ALK, Choy BNK, Cheng GPM, Woo VCP, Cho P (2020). One-year results of 0.01% atropine with orthokeratology (AOK) study: a randomized clinical trial. Ophthalmic Physiol Optics 40: 557-566

| Contribution | Author(s) |
|---|---|

| | |
|---|---|
| Conceptualization | CP, CGPM, WVCP |
| Funding acquisition | CP, CGPM, WVCP |
| Investigation | TQ, NALK, CBNK |
| Methodology | TQ, CP |
| Data collection | TQ |
| Data analysis | TQ, CP |
| Project administration/Supervision | CP |
| Visualization | TQ, CP |
| Writing - first draft | TQ |
| Writing - review & editing | TQ, CP, NALK, CBNK, CGPM, WVCP |

- Tan Q, Ng ALK, Cheng GPM, Woo VCP, Cho P (2019). Combined atropine with orthokeratology for myopia control: study design and preliminary results. Curr Eye Res 44: 671-678

| Contribution | Author(s) |
|---|---|
| Conceptualization | CP, CGPM, WVC |
| Funding acquisition | CP, CGPM, WVCP |
| Investigation | TQ, NALK |
| Methodology | TQ, CP |
| Data collection | TQ |
| Data analysis | TQ, CP |
| Project administration/ Supervision | CP |
| Visualization | TQ, CP |
| Writing - first draft | TQ |
| Writing - review & editing | TQ, CP, NALK, CGPM, WVCP |

- Cho P, Tan Q (2019). Myopia and orthokeratology for myopia control. Clin Exp Optom 2019; 102:364-77

| Contribution | Author(s) |
|---|---|
| Conceptualization | CP |
| Writing - first draft | CP, TQ |
| Writing - review & editing | CP, TQ |

## Referred abstracts:

- Tan Q, Ng ALK, Choy BNK, Cheng GPM, Woo VCP, Cho P. One-year results of 0.01% atropine with orthokeratology (AOK) study: a randomized clinical trial. The Global Specialty Lens Symposium (GSLS) 2020, 23-25 January, Las Vegas, USA
- Tan Q, Ng ALK, Cheng GPM, Woo VCP, Cho P. Study design and preliminary results of 0.01% atropine with orthokeratology (AOK) study. The BCLA Asia Conference 2019, 18-20 October, Singapore

# Appendix 2 – Information sheet

Research Study Information Sheet

Title of Project:

Combined atropine with orthokeratology in childhood myopia control (AOK) -A randomized controlled trial


Project Leader:

Prof. Pauline Cho — SO (Tel: 2766 6100)

Dr. Choy, Nga Kwan Bonnie — Department of Ophthalmology, The University of Hong Kong, Grantham Hospital (Tel: 2518 1430)

Investigators:

Dr. Ng, Lap Ki Alex — Department of Ophthalmology, The University of Hong Kong, Grantham Hospital (Tel: 2518 1430)

Ms. Sin-Wan Cheung — SO (Tel: 9250 )

Ms. Qi Tan — SO (Tel: 5392 )

Miss Bi-Yue Guo

SO (Tel: 5425 )

Why is the study being performed?

Both orthokeratology (ortho-k) and atropine have been demonstrated to be effective in slowing myopic progression in children. It has been shown that the rate of axial length elongation can be retarded from 43% to 52% by ortho-k. Atropine (1% concentration) is a drug used in clinical practice for pupil dilatation as well as relaxing accommodation. It also has been used to slow myopia progression but with limited popularity due to children's low tolerance of its side effects such as photophobia attributable to pupil dilation and blurred near vision resulting from accommodation relaxation. However, 1/100 of the usual concentration (from 1% down to 0.01%), has recently been shown to be effective in slowing myopia progression by up to 50%. Unlike 1% atropine, a 0.01% concentration has almost negligible side effects and most patients can tolerate the treatment well. The mechanisms of both atropine and ortho-k on slowing myopia are not clearly understood. However, it is believed that these two methods exert their effects via different pathways. Therefore, by combining these two methods, additional effects may be achieved. To date, no studies have explored this issue. This two-year, randomised study is jointly organized by School of Optometry of The Hong Kong Polytechnic University (PolyU) and Department of Ophthalmology of The University of Hong Kong. The aim of this study is to recruit at least 60 subjects and investigate if there is an additional effect on retardation of myopia progression by using combined 0.01% atropine with ortho-k versus ortho-k alone.

What do volunteers for the study have to do?

If you and your child volunteer for the study, you will be asked to:

1 sign an informed consent form, that states you understand the information presented.

2 provide personal information (your child) such as name, age, gender, histories of general and ocular health, and details of visual correction treatment(s) that your child used/are using. All information, results and data will be kept confidential.

3 agree to be randomized into ONE of the following groups:
   (1) Group 1, using combined 0.01% atropine with ortho-k
   (2) Group 2, using ortho-k alone
   If your child is in Group 1, your child will be provided with 0.01% atropine eye drops and a pair of ortho-k lenses. If your child is in Group 2, your child will be only provided with a pair of ortho-k lenses. All contact lens solutions to care for your lenses are provided free of charge and should be used according to instructions given. Your child MUST also have a pair of updated backup glasses (own expenses ordered from our clinic) to use in case your child has to stop ortho-k lens wear anytime during the study.

4 bring your child to attend eye examinations on a regular basis (or as indicated if needed) during the 2-year study period. Each will last for 30 minutes to 2 hours, depending on the tests required (see detailed schedule listed at the end of this information sheet). In general, all subjects will be required to attend at least 14 schedule visits at the Optometry Clinic of PolyU clinic during the 2-year study period (see Table 1). Additional visits may be arranged if indicated.

5 bring your child to the Graham Hospital (GH) to collect the atropine eye drops (see Table 2) if your child is assigned to Group 1. There are up to 8 visits at GH. Three months' supply of atropine will be prescribed to your child at every visit for the first year. In the second year,

atropine will be dispensed at 4-month interval. Your child is not allowed to use the atropine eye drops until the first morning of ortho-k lens wear.

If your child passes the tests in the first meeting, s/he will be asked to:

6 learn how to use the ortho-k lenses. Your child will not be allowed to continue in the study if s/he cannot manage to learn to use the lenses.

7 attend the regular visits to check vision, refractive error and anterior conditions of the eyes at PolyU and GH. Ortho-k lens fitting will be followed up at PolyU.

8 have cycloplegic eye examination before lens wear (at baseline visit) and every six months after lens wear (see Table 1). Two drops of 1% cyclopentolate will be instilled in your eyes to relax the focusing muscles temporarily. Cyclopentolate eye drops are commonly used in clinical practice for children assessment. Refractive status and ocular condition will be measured after muscles are relaxed. Your child may not be able to read books or watch television with his/her own glasses and may be sensitive to light during the first 24 hours after instillation of the eye drops. A more detailed description of the main and side effects of these eye drops can be found at the end of this information sheet (see Table 3).

9 return the lenses and lens solution upon the completion or withdrawal of the study. For those assigned to combined therapy, atropine eye drops should also be returned. To monitor the decreasing effect of ortho-k after ceasing lens wear, you and your child are required to come back every 1-2 weeks until refraction and corneal topographical changes are stabilized.

Potential Risks

- Ortho-k lens wear
  Under normal circumstances, with proper lens care and regular aftercare visits, it is safe to use the lenses. However, non-compliance may lead to inflammation, infection, and potential loss of vision. Most of the common complications that may occur with ortho-k lens wear are listed at the end of this information sheet.
- 0.01% Atropine eye drops
  Risks of using 0.01% atropine include pupil dilatation and blurring of near vision, which may require near glass use. As mentioned, these effects are expected to be minimal, although we will still monitor these during the course of treatment. Other uncommon side effects of atropine use include allergic reactions. All children in this study will have immediate access to ophthalmologists in case any problems arise. Common and uncommon side effects of 0.01% atropine eye drops are listed at the end of this information sheet. After cessation of atropine therapy, there may be a rebound effect. Currently, there are no clear guidelines regarding the duration of use of the atropine therapy.
- Cycloplegic eye drops
  Your child may experience mild discomfort, photophobia and near vision disturbance due to the effect of the eye drops. The effects are transient and will not cause any harm to the eyes, although occasionally people may have allergic reaction to the eye drops (see Table 2 for more details).

<u>Should any clinically significant problems be observed at any visit during the study, appropriate clinical actions, including cessation of lens wear, cessation of atropine or referral to</u>

ophthalmologist, will be taken, especially in case of any corneal compromised conditions. Please note that you will be required to bear the medical expenses.

Benefits

Your child will receive regular eye examinations during the study. She/he will receive either combined 0.01% atropine with ortho-k (if she/he is in Group 1) or ortho-k treatment alone (if she/he is in Group 2) during the study according to randomization. Both interventions used in this study had been shown to be effective in retarding myopia growthUpon the completion of the study, you will know the condition of her/his eyes such as refraction and ocular health condition.

Note: All ortho-k lenses and atropine eye drops MUST be returned to the investigator at the end of the study.

Remuneration

There will be no remuneration.

Can a volunteer withdraw from the study?

Yes, you can stop participating in the study at any time with no penalty.

Can I get more information on the study?

Yes, please contact Ms Tan on 5392 and she will try to answer any questions you may have.

This study has been approved by the Departmental Research Committee (DRC) of the School of Optometry of The Hong Kong Polytechnic University. If you have any complaints about the conduct of this research study, please do not hesitate to contact Miss Cherrie Mok, Secretary of the Human Subjects Ethics Sub-Committee (HSESC) of The Hong Kong Polytechnic University in writing (c/o Research Office of the University) stating clearly the responsible person and department of this study as well as the HSESC Reference Number HSEARS20160406005.

## Complications associated with ortho-k lens wear

* Mild lens binding to the cornea on awakening which should dislodge easily on blinking (Never forcefully remove a lens on the eye. You and your child will be taught how to dislodge a bound lens safely and easily by our researcher).
* Solution allergy (redness/itchiness)
* Fluctuation of vision on certain days after myopia reduction (this could happen if the lenses did not center properly when your child wore them the night before)
* Mild corneal staining (mild abrasion which can be caused by improper lens insertion, dust or foreign particles under the lens, improperly cleaned lens etc.)
* Non-compliance or poor compliance can result in corneal abrasion, red eye and discomfort. Corneal ulceration may result if the condition is not detected earlier or if left untreated. It is therefore important to attend regular aftercare consultation.

## Side effects of 0.01% atropine

* Common side effects include blurred vision, eye itching, burning, or stinging.
* Uncommon side effects include:
  Severe allergic reactions (rash; hives; itching; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue); difficulty urinating; dry mouth; eye pain; fever; flushing or dryness of the skin; irregular or rapid heartbeat; unsteadiness on your feet. Once uncommon

side effects happened, your child MUST stop using it immediately and go to hospital as soon as possible for help.

If your child has any suspected lens-related problems during the study, please contact Ms Tan (5392- ) immediately.

If your child has any suspected atropine-related problems:
During office hour, please contact Dr Bonnie Choy (2518-1430) at Department of Ophthalmology, Grantham Hospital, 125 Wong Chuk Hang Road, Aberdeen, Hong Kong
Outside office hour, please go to the Accident and Emergency Room of Queen Mary Hospital, 102 Pokfulam Road, Hong Kong

Please contact Ms Tan (5392 ) anytime if you need any assistance.

Table 1 Schedule of study follow-up visits

| Schedule | Eye drops | Estimated time | Test (s) |
|---|---|---|---|
| Screening | × | 1 hours | refraction, binocular tests, ocular health assessment |
| IR Teaching | × | 90 minutes | handling of lenses |
| Baseline* | ✓ | 2 hours | Data collection: vision and refraction, ocular parameters, binocular tests, eyeball length, ocular health assessment & lens ordering |
| Delivery | × | 30 minutes | delivery of lenses, evaluation of lens fitting |
| First overnight | × | 30 minutes | evaluation of lens fitting, ocular health assessment |
| 1-week | × | 1 hour | Ortho-k after care: vision and refraction, ocular health assessment |
| 2-week | × | | |
| 3-week | × | | |
| 1-month* | × | 2 hours | Data collection: vision and refraction, ocular parameters, binocular tests, eyeball length, ocular health assessment |
| 3-month | × | 1 hour for the first year, 30 minutes for the second year | Ortho-k after care: vision and refraction, ocular health assessment |
| 6-month* | ✓ | 2 hours | Data collection: vision and refraction, ocular parameters, binocular tests, eyeball length, ocular health assessment |
| 9-month | × | 30 minutes | Ortho-k after care: vision and refraction, ocular health assessment |

| | | | |
|---|---|---|---|
| 12-month* | ✓ | 2 hours | Data collection: vision and refraction, ocular parameters, binocular tests, eyeball length, ocular health assessment |
| 15-month | × | 30 minutes | Ortho-k after care: vision and refraction, ocular health assessment |
| 18-month* | ✓ | 2 hours | Data collection: vision and refraction, ocular parameters, binocular tests, eyeball length, ocular health assessment |
| 21-month | × | 30 minutes | Ortho-k after care: vision and refraction, ocular health assessment |
| 24-month* | ✓ | 2 hours | Data collection: vision and refraction, ocular parameters, binocular tests, eyeball length, ocular health assessment |
| 1 – 4 weeks after ceasing lens wear | × | 30 minutes | Stablization of ortho-k: vision and refraction, ocular parameters, eyeball length, ocular health assessment |

Extra visits may be arranged if lens fitting is not optimal or if your child cannot demonstrate satisfactory insertion/removal technique.

* Cycloplegic eye drops will be instilled in this visit, whose effects are listed in Table 3.

Table 2 Schedule of atropine follow-up visits for AOK subjects

| Schedule | Eye drops | Estimated time | Test (s) |
|---|---|---|---|
| Prescription before Delivery visit | × | 30 minutes | Prescription and delivery of atropine eye drops |
| 3-month | × | 30 minutes | Prescription and delivery of atropine eye drops, ocular health assessment |
| 6-month | × | 30 minutes | Prescription and delivery of atropine eye drops, ocular health assessment |
| 9-month | × | 30 minutes | Prescription and delivery of atropine eye drops, ocular health assessment |
| 12-month* | ✓ | 1 hour | Prescription and delivery of atropine eye drops, ocular health assessment |
| 16-month | × | 30 minutes | Prescription and delivery of atropine eye drops, ocular health assessment |
| 20-month | × | 30 minutes | Prescription and delivery of atropine eye drops, ocular health assessment |
| 24-month* | ✓ | 1 hour | Prescription and delivery of atropine eye drops, ocular health assessment |

* Cycloplegic eye drops will be instilled in this visit, whose effects are listed in Table 3.

Table 3 Detailed list of cycloplegic eye drops information, possible reactions and reaction time

| | |
|---|---|
| Drug name | 1% Cyclopentolate |
| Drug effects | ∗ Cycloplegia – temporary paralysis of focusing muscles |

| | |
|---|---|
| | ∗ Pupil dilation |
| Indication | ∗ Help to yield more accurate assessment of the length of the eyeball, especially in far-sightedness, pseudo-nearsightedness and squint |
| Recovery time | ∗ 24 hours |
| Possible side effects | ∗ Foggy vision, eye pain<br>∗ Incoherent speech<br>∗ Hallucination<br>∗ Imbalance |
| Overdose | ∗ Excessive dosage may result in exaggerated symptoms as noted as above |
| Cautions | ∗ Blurred near vision within the first few hours of eye drops instillation<br>∗ Light sensitivity, sunglasses and a wide brimmed hat/cap may help to provide better comfort<br>∗ AVOID outdoor activities in open daylight and vigorous activities which require the use of near vision within 12 hours of eye drops instillation |

# Appendix 3 – Consent form

Title of Study

Combined atropine with orthokeratology in childhood myopia control (AOK) -A randomized control trial

Subject Consent Form

Have you read the information sheet provided? Yes / No

Have you had an opportunity to ask questions and discuss this study?

Yes / No

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

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

Have you been informed about the various myopic control options (bifocal/multifocal spectacles/contact lenses, and atropine) available

in the market? Yes / No

Who provided the information / answered your questions?

Mr / Ms _____

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

Do you understand that you are free to withdraw from the study

- at any time Yes / No
- without having to give a reason Yes / No
- without affecting your future care (as applicable) Yes / No

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

Name of child: _____ Signature _____

| | Parent (or guardian) | Researcher |
|---|---|---|
| Signature | _____ | _____ |
| Name | _____ | _____ |
| Date | _____ | _____ |

Combined atropine with orthokeratology in childhood myopia control (AOK) -A randomized controlled trial

Researcher:
Dr. Ng, Lap Ki Alex, Dept of Ophthalmology, The University of Hong Kong
Prof. Cho, Pauline, School of Optometry, The Hong Kong Polytechnic University

1. I confirm that I have read and understood the information sheet for the above study and have had the opportunity to ask questions.
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
3. I understand I have the rights of access to personal data and publicly available study results, if and when needed. Under the laws of Hong Kong (in particular the Personal Data (Privacy) Ordinance, Cap 486), I enjoy or may enjoy rights for the protection of the confidentiality of my personal data, such as those regarding the collection, custody, retention, management, control, use (including analysis or comparison), transfer in or out of Hong Kong, non-disclosure, erasure and/or in any way dealing with or disposing of any of my personal data in or for this study. For any query, I should consult the Privacy Commissioner for Privacy Data or his office (Tel No. 2827 2827) as to the proper monitoring or supervision of my personal data protection so that my full awareness and understanding of the significance of compliance with the law governing privacy data is assured. By consenting to participate in this study, I expressly authorize:
    - the principal investigators and their research team and the Institutional Review Board of the University of Hong Kong / Hospital Authority Hong Kong West Cluster and the Departmental Research Committee (DRC) of the School of Optometry of The Hong Kong Polytechnic University responsible for overseeing this study to get access to, to use, and to retain my personal data for the purposes and in the manner described in this informed consent process; and
    - the relevant government agencies (e.g. the Hong Kong Department of Health) to get access to my personal data for the purposes of checking and verifying the integrity of study data and assessing compliance with the study protocol and relevant requirements.

I agree to take part in the above study.

Name of child: _____ Signature _____

| | Parent (or guardian) | Researcher |
|---|---|---|
| Signature | _____ | _____ |
| Name | _____ | _____ |
| Date | _____ | _____ |

# Appendix 4 – Ethic approval

No.
編號 **100757**

[regulation 36B(3)]
[第36B(3) 條]

**PHARMACY AND POISONS ORDINANCE**
**藥 劑 業 及 毒 藥 條 例**
**(Chapter 138)**
**(第 138 章)**

PR/CT 0118/2016 (AL)

**CERTIFICATE FOR CLINICAL TRIAL / MEDICINAL TEST***
**臨 牀 試 驗 / 藥 物 測 試 * 證 明 書**

It is hereby certified that Dr. NG L.K. Alex
現 證 明 (*Name and address* 姓 名 或 名 稱 及 地 址)
Department of Ophthalmology, The University of Hong Kong, Room 301, 3/F, Block B, Cyberport 4, Cyberport, Hong Kong
is authorized, subject to the conditions endorsed hereon, to establish a clinical trial on human beings/medicinal test on animals* in respect of
已 獲 准 以
Atropine Eye Drops 0.01%***
(*Name of product or substance* 製 品 或 物 質 的 名 稱)

to be conducted by 1. Dr. NG L.K. Alex
對 人 類 進 行 臨 牀 試 驗 / 對 動 物 進 行 藥 物 測 試 *，並 且 由 (*Name(s) of person(s) concerned* 有 關 的 人 的 姓 名 或 名 稱)
at 1. Queen Mary Hospital, HK; Grantham Hospital, HK; and Optometry Clinic, The Hong Kong Polytechnic University, KLN
於 (*Name and address of institution where applicable* 機 構 的 名 稱 及 地 址(如 適 用 的 話))
進行。但須受本證明書上所批註的條件規限。

2. This certificate will be valid until 5 October,2021
本 證 明 書 的 有 效 期 至 止。

Hong Kong.
香 港

6 October,2016 (Date)
(日 期)

PHARMACY & POISONS BOARD * HONG KONG *

(Y. F. YEUNG) (代 行)
for *Pharmacy and Poisons Board*
藥 劑 業 及 毒 藥 管 理 局

**CONDITIONS**
條件

1. The holder of the Certificate is required to submit local drug related safety reports, yearly progress reports, final study report of the clinical trial in accordance with the "Notice of requirement on reporting of local drug related safety report, progress report and final study report in clinical trial" issued by the Drug Office.

證明書持有人須按照藥物辦公室發出的《關於本地藥物安全事故報告、進度報告及臨牀試驗最後研究報告呈報規定的通知》，提交與本地藥物有關的安全事故報告、年度進度報告及臨牀試驗最後研究報告。

CTMT09 (Feb 2015)

香港大學
University of Hong Kong

醫院管理局
HOSPITAL AUTHORITY

香港大學及醫管局港島西醫院聯網研究倫理委員會

**Institutional Review Board of the University of Hong Kong/**
**Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB)**

Address: Rm 901, Administration Block, QMH Tel 2255 3923 2255 4086 Fax 2255 4735

Dr. Alex Ng
Ophthalmology
(Room 301, Level 3 Block B, Cyberport 4), HKU
07-Sep-16

Dear Dr. Ng,

IRB Reference Number: **UW 16-404**

The HKU/HA HKW IRB is authorized by a joint agreement of the University of Hong Kong and Hospital Authority Hong Kong West Cluster to review and monitor clinical research. It serves to ensure that research complies with the Declaration of Helsinki and acts in accordance to ICH GCP guidelines, local regulations and Hospital Authority and the University policies.

In accordance with our standard operating procedures, we have duly performed ethics and scientific review of your application/submission. We hereby write to inform you that your application/submission has been approved by a full review with details shown below.

| | |
|---|---|
| **Protocol title** | : Combined atropine with orthokeratology in childhood myopia control (AOK) -A randomized controlled trial |
| **Study site(s)** | : Grantham Hospital and Queen Mary Hospital |
| **Date of full review** | : 24-08-2016 (Date/Month/Year)(Membership of the review panel is listed at the end of this letter in note 1) |
| **Documents approved** | : 01. Clinical Research Ethics Review Application Form |
| | : 02. Study Protocol; Version 2 dated 5th July 2016 |
| | : 03. Revised Information Sheet and Consent Form; Version 4 dated 31082016 (English and Chinese) |
| **Documents reviewed** | : 04. Email from Departmental Research Committee of The Hong Kong Polytechnic University; dated 19-May-2016 |
| | : 05. Short CV of Principal Investigator |
| ***Regular Progress Report(s) Required*** | : Every 12 months from the date of initial approval and during the period of the study |

You, being the principal investigator of the study at your study site, are reminded to comply with our requirements and to maintain communication with us during the period of the study by undertaking the principal investigator's responsibilities including (but not limited to):

- if the study is an industry-sponsored clinical study, submitting to us a copy of the fully executed indemnity agreement satisfying the Hospital Authority's requirement prior to commencement of the study (if it has not been submitted yet);
- observing and complying with all applicable requirements under our standard operating procedure ("HKU/HA HKW IRB SOP"), the Declaration of Helsinki and the ICH GCP (if applicable);
- submitting regular progress report(s) at the required intervals (as specified above) in accordance with the requirements in the IRB SOP;
- not implementing any amendment/change to any approved study document/material without our written approval, except where necessary to eliminate any immediate hazard to the subjects or if an amendment/change is only of an administrative or logistical nature;
- notifying us of any new information that may adversely affect the rights, safety or well-being of the subjects or the proper conduct of the study;
- reporting any deviation from the study protocol or compliance incident that has occurred during the study and may adversely affect the rights, safety or well-being of any subject in accordance with the requirements in the IRB SOP;
- submitting safety reports on all SAEs observed at your study site or SUSARs reported from outside your study site in accordance with the requirements in the IRB SOP; and
- submitting a final report in accordance with the requirements in the IRB SOP upon completion or termination of the study at your study site.