Investigation of Myopic Periphery Affecting Choroidal Thickness

THESIS

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Abstract

The purpose of this study was to investigate whether thickening occurs in the human choroid in response to peripheral myopic refractive blur from orthokeratology. The hypothesis is that thickening may partially account for any effect of axial length and/or slowed progression of myopia with corneal reshaping lenses. A study done by Read et al. took axial length and choroidal measurements after patients monocularly wore lenses inducing three diopters of myopic or hyperopic defocus for two, thirty minute sessions. The study found that small but significant changes in axial length occurred. A similar opposite effect for choroidal thickness was also noted. This implies that changes in axial length found in other methods incorporating peripheral myopic defocus may be due to changes in choroidal thickness (Read, Collins and Sander, 2010).

Measurements were taken before and after 1, 3, and 6 months of successful orthokeratology. Subjects are 9 children with an age range of 11-15. The primary outcome for the IMPACT study was choroidal thickness measured using images from the Zeiss Cirrus HD-OCT. Choroidal images were then uploaded into Photoshop for analysis of thickness and total cross sectional area with adjusted pixel to micron scales. Three thickness measurements each were made in central foveal, superior, temporal, and nasal gazes. The Cirrus HD-OCT has been found to be capable of obtaining detailed, repeatable images of the choroid beneath the retina. The images were all analyzed by a
masked investigator who is unaware of when the image was taken. In addition, peripheral axial length was measured in the four fields of gaze (central, nasal, temporal, and superior) with the Zeiss IOLMaster, and subfoveal choroidal thickness changes were measured with a Lenstar biometer.

All subjects responded to the orthokeratology treatment well, with acceptable acuity and physiologic response to overnight wear. It is interesting to note that no correlation was found between the results of the Lenstar and OCT subfoveal measures. A closer look at the data suggests that the Lenstar may struggle to obtain strong choroidal signals with thicker choroids. Spearman analysis resulted in a general negative relationship between the number of readable Lenstar measurements and choroidal thickness by OCT which was statistically significant at the baseline and 1 month visits (-0.769, p = 0.015; and -0.804, p = 0.009 respectively). None of three methods for measurement of choroidal thickness resulted in a significant thickening or thinning. Therefore the hypothesis of the study was not confirmed.

The Lenstar was not found to be a very accurate method to measure choroidal thickness. More importantly the current study was able to successfully monitor choroidal thickness by OCT analysis. This is a quick, non-invasive, and relatively simple technique. Therefore, it is important for all future investigations of ocular growth to include a choroidal measurement to monitor for any confounding responses of the choroid. This study demonstrated the ease and accuracy of obtaining these measures.
Dedication

This document is dedicated to my family. I would not have been able to complete this work without their support, guidance, and love.
Acknowledgments

This project is not simply the effort of one person, and there have been many individuals helping me along the way. I truly appreciate all of the professional help I have received while completing this project. I would specifically like to thank Dr. Jeffrey J. Walline for his guidance concerning orthokeratology lenses. Finally, I cannot put into words the utmost appreciation I have for the efforts of my advisor, Dr. Donald O. Mutti. It has been quite a journey we have had together!
Vita

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Chapter 1: Literature Review

Myopia is a condition in which distant light is focused before it reaches the retina, and therefore causes blurred distance vision. This is correctable with the use of minus spectacle lenses, contact lenses, or refractive surgery. All these treatment options have the goal of focusing light onto the retina creating a clear distant image. A study done by Vitale et al. found the prevalence of myopia in the United States in individuals over 20 years old to be 33.1% of the population (Vitale, Cotch, Ferris, Sperduto and Ellwein, 2008). Another study done by Vitale compared the prevalence of myopia in individuals over the age of 12 in the National Health and Nutrition Examination Survey to a similar study done in the 1970s. They utilized the same method as in the 1970s to identify myopic individuals. They found the prevalence of myopia in the United States to be 41.6% of individuals age 12-54, which is a significant increase compared to the 25% reported in the survey thirty years prior (Vitale, Sperduto and Ferris, 2009). The estimated cost for the correction of this refractive error was found to be at least $3.8 billion annually (Vitale, Cotch, Sperduto and Ellwein, 2006). From a public health perspective, the annual cost alone is enough to spark interest in slowing the progression of this condition. However, myopia is more than a cost concern as studies have shown that an increased risk for retinal detachment(1993), and glaucoma(Mitchell, Hourihan, Sandbach and Wang, 1999) exist among myopic individuals.
The first step toward achieving this goal of reduced progression rates is to look at animal models. One commonly used experimental condition is lens compensation. If a particular lens is worn during the emmetropization process when the animal is young, the eye will adjust axial length to compensate for the induced refractive blur. Hyperopic blur places the focal point behind the retina and will stimulate axial elongation, and myopic blur will place the focal point in front of the retina and inhibit growth. There are many animal studies that have demonstrated this effect. A study done by Wildsoet with chicks was designed to investigate four questions involving lens compensation. First, what are the relative contributions of the choroid and sclera in compensating for the refractive errors imposed by the lenses? Second, what effect does prohibiting communication between the retina and the brain by means of optic nerve section or tetrodotoxin (TTX) treatment have on the compensation for hyperopic or myopic defocus? Third, is there a parallel decline with age in the amount of myopia induced by form deprivation and negative lenses? Finally, what effect does forcing vision through the lenses have on the emmetropization response? The investigators glued PMMA lenses of varying powers on White Leghorn chicks. They fit a lens over one eye and left the other eye uncovered. For experiment one, 6-7 chicks were fit with each powered lens (-15, -6, +6, +15 diopters) over one eye from day 3 to day 8 of age. Measurements were made before and after the lens wear period and every few days during the “recovery period”. This experiment found that compensation for the refractive error occurred. The effect was nearly complete in the chicks with induced myopia from positive lenses; they had 82% compensation. In the case of the chicks with hyperopia induced with minus lenses, the compensation was
substantial but incomplete as only 54% compensation was found. They reported that changes in ocular length were a significant component of the compensation (ANOVA $F_{4,19} = 10.9$, $P<0.05$). They also found that vitreous chamber length is highly correlated with the refractive error imposed by the lenses ($r = 0.98$, $P<0.01$). The eyes with imposed myopia developed thicker choroids which pushed the retina forward and compensated for the induced myopic blur ($P<0.05$). The opposite effect was found with the eyes that had induced hyperopia resulting in thinner choroids ($p = 0.05$). The induced refractive error disappeared quickly in the “recovery period”. This “re-emmetropization” process once again involved the choroid. The second experiment compared chicks fit with -15, -6, or +6 diopter lenses on one eye and a diffuser on the other eye with the ones fit in the original study. No significant differences were found between the two groups. This indicates that compensation of one eye to refractive blur was not significantly affected by the diffuser condition in the contralateral eye. In the third and fourth experiments, optic nerve section and intravitreal TTX were performed, respectively. The eyes with induced myopia were not affected by either treatment as compared to the original experiment. For the eyes with induced hyperopia there was a difference between the two treatments. The optic nerve section group responded to the minus lenses but did not have as much of an effect as those in the original experiment while the TTX group still demonstrated the effect. Overall these experiments show that the chicks were able to demonstrate lens compensation and that the effect did not require a connection between retina and brain (Wildsoet and Wallman, 1995).
The ability to compensate for induced defocus seems to be conserved throughout various species. A study done by Shen et al. investigated whether lens compensation occurred in lower vertebrate eyes. This study looked at the effect of lens compensation and form deprivation on the tilapia eye. Twenty-five fish were weighed and killed, then had their eyes measured to establish norms. Nine other groups were tested with varying lens powers and goggle types with about seven fish in each group. The results revealed that axial length was proportional to weight. They also found that the fish were capable of lens compensation, though not complete compensation. The +15D group became on average +7.7 ± 1.6D, while the -12D group had on average -8.4D ± 0.8D. The groups that were allowed to recover were able to do so within 2 weeks. Form deprivation myopia was also found in all three weight groups. The amount of induced myopia had a negative correlation with weight (Shen and Sivak, 2007).

Another study investigated the lens compensation effect on guinea pigs (Howlett and McFadden, 2009). They wanted to find a mammalian model that became myopic quickly and was less expensive than monkeys. Fifty-six guinea pigs were fit with varying powers of lenses over one eye, and either no lens or a plano lens over the other eye for five or ten days. They measured refractive error and ocular length at the end of these periods. A significant compensation was found after five days with nearly complete compensation after ten days. Relative to the plano group, plus and minus lenses induced myopia or hyperopia, affected ocular length, and choroidal thickness similar to the effect found in chicks. However the change in vitreous chamber depth was ±100 microns and the change in choroidal thickness was ±40 microns. Therefore the choroidal effect does
not appear to be as responsible for refractive error compensation in the guinea pig as in the chick; the vitreous chamber depth change seems more important in the guinea pig. In general the guinea pig was found to be a mammalian model that demonstrates lens compensation (Howlett et al., 2009).

A 1995 study by Hung et al. investigated whether lens compensation could occur in a higher mammalian model such as rhesus monkeys (Hung, Crawford and Smith, 1995). Eleven infant rhesus monkeys were fit with lightweight helmets housing 25mm diameter spectacle lenses in front of the monkeys’ eyes at a vertex distance of 7mm. These lenses had various powers of +6.0, +3.0, plano, -3.0, and -6.0 diopters. The helmets were worn for a period of 72-113 days. Two of the three monkeys reared with a +3D lens showed a relative reduction in the rate of vitreous chamber elongation in the treated eye and an increase in hyperopia. Two of three monkeys reared with -3.0D lenses showed a relative increase in the axial growth rates of the non-fixating eyes, and relative myopic changes in refractive error. The two monkeys reared with +6.0D lenses showed an increase in hyperopia but not complete compensation. The two monkeys fit in -6.0D lenses had different results. One monkey showed the most consistent refractive-error changes among the four -6D subjects, while the other had alternations in the direction of anisometropia throughout the study. This study showed that while monkeys were not able to completely compensate for higher amount of induced refractive blur, a relatively consistent amount of compensation was possible, especially at lower levels of induced refractive blur (Hung et al., 1995).
A similar study was performed in 2000 by Whatham et al. with ten marmoset monkeys (Whatham and Judge, 2001). This study took ten infant marmoset monkeys between the ages of 8-13 weeks and fit one eye in various powered soft contact lenses for 5-9 weeks. They found the eyes with plus powers were more hyperopic relative to the untreated eye, and the eyes with minus lenses were more myopic as compared to the untreated eye (+2.39 ± 0.24D and -2.48 ± 0.91D respectively) (Whatham et al., 2001).

The responsiveness of animal eyes to defocus has stimulated similar questions about whether human children’s refractive error development could be influenced by defocus. Gwiazda et al. set out to explore reasons why near work might be associated with myopia (Gwiazda, Thorn, Bauer and Held, 1993). This study tested the accommodative ability of emmetropes and myopes. There were 64 children included in the study: 48 were emmetropic while 16 were myopic. They found that myopic children accommodated significantly less than emmetropic children. Gwiazda suspected that children who accommodate less may actually be inducing axial growth due to the slightly hyperopic blur that occurs during accommodative lag (Gwiazda et al., 1993).

Concurrently studies were being done on slowing the progression of myopia in humans using possible methods that might reduce hyperopic defocus, such as under-correcting myopia (Chung, Mohidin and O'Leary, 2002), and accommodative control with bifocal or progressive addition lenses (Fulk, Cyert and Parker, 2000; Gwiazda, Hyman, Hussein, Everett, Norton, Kurtz, Leske, Manny, Marsh-Tootle and Scheiman, 2003). The study done by Chung et al. was designed to investigate the effect of myopic defocus on myopia progression in humans (Chung et al., 2002). This was a two-year
prospective study on 94 myopes between the ages of 9 and 14. The subjects were randomly assigned to an under-corrected group or a fully corrected control group. The under-corrected group was blurred by +0.75D at distance for the two year period. The results were contrary to those in the animal models. The under-corrected group actually progressed faster and showed more axial elongation than the fully corrected group (ANOVA, $F_{1,374} = 14.32, p<0.01$). The investigators suspected defocus in any direction in humans stimulates myopia progression (Chung et al., 2002). A possible limitation of the study is the fact that they only under corrected by 0.75D with all myopes. This may not have produced enough myopic defocus to signal slowed myopic growth. While this would explain an absence of slowed progression, it does not explain why the progression actually accelerated.

Another study done by Fulk et al. investigated whether bifocal spectacles reduce the progression of childhood myopia in children with near point esophoria (Fulk et al., 2000). The theory was children with near point esophoria had high accommodative lags, which would simulate hyperopic blur on the retina and may therefore induce faster myopia progression. If the child were fit with a bifocal lens that prevented the hyperopic blur, then myopia progression may slow. This was a randomized clinical trial where 40 children were fit in single vision lenses and 42 children were fit into +1.50D bifocal spectacles. The children, aged 6-12.9 years, were followed for a 30-month period. The primary outcome was the difference between the 30-month and baseline spherical equivalent refractive error. For the children completing the full 30 months of follow up, the bifocal group progressed an average of 0.99D and the single vision group progressed
1.24D (adjusted for age, p = 0.046). The investigators concluded that the use of bifocal lenses for children with near point esophoria can slow myopia progression to a slight degree (Fulk et al., 2000). This is a minimal effect of only a 0.25 D step or less, which is clinically insignificant.

A similar study done by Gwiazda et al. used progressive addition lenses (Gwiazda et al., 2003). 469 children (ages 6-11 years) with myopia between -1.25 and -4.50D spherical equivalent were randomly assigned to receive +2.00D add progressive addition lenses (PAL) or single vision lenses (SVL). These children were followed for a period of 3 years and had periodic cycloplegic autorefraction and A-scan ultrasonography performed to monitor for myopia progression. After three years, spherical myopia progression was \(-1.28 \pm 0.06\)D in the PAL group and \(-1.48 \pm 0.06\)D in the SVL group. This resulted in a difference of \(0.20 \pm 0.08\)D myopia progression which was statistically significant (p = 0.004). Again the clinical significance of 0.20D of progression over a three year period is minimal. The reduced myopia progression also mostly occurred within the first year, with little to no difference between groups in the remaining 2 years of the study (Gwiazda et al., 2003).

None of these human investigations produced results similar to the animal models. All three studies were designed to affect foveal refractive error by reducing foveal defocus. Smith hypothesized that too much emphasis was being put on central defocus, and discovered that peripheral refractive error was more crucial. A series of studies on monkeys performed by Smith, which induced peripheral defocus and/or eliminated foveal signaling, found that peripheral refractive error was more critical in the
emmetropization process of monkeys (Smith, Hung and Huang, 2009; Smith, Kee, Ramamirtham, Qiao-Grider and Hung, 2005; Smith, Ramamirtham, Qiao-Grider, Hung, Huang, Kee, Coats and Paysse, 2007).

First Smith et al. set out to investigate whether form deprivation to the peripheral retina alone could induce myopic progression, and then once lens wear was discontinued, whether the monkey eyes could recover even in the absence of foveal signaling (Smith et al., 2005). Thirty-six infant rhesus monkeys (aged 1-3 weeks) were randomly assigned into control (n=24) and peripheral form-deprivation (n=12) groups. The peripheral form-deprivation group was further split into groups using either 4 or 8 mm apertures (n=6 in each group). These lenses were attached to plastic helmets that were worn for 13 to 15 weeks. The experimental monkeys were found as a group to be significantly less hyperopic/more myopic than those of the control monkeys (mean = +0.03 ± 2.39D vs. +2.39 ± 0.92 D; two-sample t-test, p = 0.006; median = +0.38 D vs. +2.35 D, Mann-Whitney test, p = 0.003). The refractive errors for all the treated monkeys were inversely correlated with vitreous chamber depth ($r^2 = 0.61$, $p = 0.003$). This showed that the peripheral retina alone could induce foveal myopic progression even in the presence of clear central vision. A second study then looked at the ability of the monkey eye to re-emmetropize. In one eye each of seven randomly chosen monkeys, an argon laser was used to photocoagulate the central 5 to 6 degrees of the retina. This would eliminate the fovea and parafovea. When the recovery process was complete, no significant difference was found in the refractive errors of the foveal ablated eyes versus the fellow non-treated eyes ($+0.80 ± 0.71$D vs. $+0.79$D $± 0.76$D; paired t-test, $p = 0.91$). Also the average
degree of anisometropia between the eyes of the argon-treated monkeys (0.29 ± 0.24D) was similar to that of the non-treated monkeys (0.14 ± 0.17D; two-sample t-test, p = 0.24). This study showed that the fovea was not necessary for the emmetropization process in infant rhesus monkeys (Smith et al., 2005).

Another study done by Smith et al. in 2007 investigated whether an intact fovea was necessary for normal emmetropization or vision-induced myopia produced by form deprivation (Smith et al., 2007). Thirteen rhesus monkeys at three weeks of age had foveal ablation by laser photocoagulation performed on one eye. Five of these monkeys were allowed unrestricted vision while the remaining eight were fit with a diffuser lens over the treated eye from the day of treatment to five months of age. After the observation period, the monkeys that were allowed unrestricted vision were on average -0.15 ± 0.35D less hyperopic in the treated eyes than their fellow control eyes. However this difference was not statistically significant (paired t-test, p = 0.23). No inter-ocular differences were found in vitreous chamber depth for these foveally ablated monkeys allowed unrestricted vision (paired t-test, p = 0.71). This indicates that foveal ablation did not cause the emmetropization process to fail. For the monkeys fit with diffusers over the treated eye, the anisometropia was significantly larger than that for the age-matched controls (2.52 ± 2.02D vs. 0.19 ± 0.12D; two-sample t-test, p = 0.01). The median anisometropia for the treated animals was significantly more myopic (-1.16D vs. -0.03D; Mann-Whitney U test, p = 0.04). The average inter-ocular differences in vitreous chamber depth for form-deprive monkeys with foveal ablation (0.55 ± 0.55mm) were significantly greater than for the age-matched controls (0.10 ± 0.05mm, two sample t-test,
p = 0.05), or the monkeys reared with monocular foveal ablations (0.04 ± 0.04mm, two sample t-test, p = 0.03). These results indicate that form deprivation myopia still occurred even without intact central vision. Overall monkeys with foveal ablation demonstrated an ability to emmetropize and to respond similarly to form deprivation as animals with intact foveae would (Smith et al., 2007).

A third study by Smith et al. investigated whether similar results could be found with hyperopic defocus with or without foveal involvement in rhesus monkeys (Smith et al., 2009). Eight monkeys were fit with -3.0D lenses that had 6mm circular apertures that were centered on each eye’s entrance pupil. The idea was that the monkeys would preferentially look through the central aperture thereby inducing hyperopic defocus only in the peripheral retina. Comparison data were collected from eight monkeys that were fit with full field -3.0D lenses as opposed to the lenses with a central aperture. A second method was used with 6 other monkeys. In this group signals from the fovea were eliminated by laser photoablation in one eye, and then the monkeys were fit with -3.0D lenses. Comparison data were collected from five monkeys treated with foveal ablation but allowed unrestricted vision. The lenses in both groups were worn from age 3 weeks until age 5 months. An overall control group of 28 monkeys was reared with normal unrestricted vision and four monkeys were reared with helmets holding plano lenses. At the end of the treatment period the median refractive error for the right and left eyes of the -3D aperture group was significantly more myopic than for the control animals (Mann-Whitney U test; right eyes, +0.38D vs. +2.50D, p = 0.01, left eyes, +1.28D vs. +2.56D, p = 0.0008). This shows that induced foveal myopia occurred in response to
peripheral hyperopia even with central clear apertures in place. They also compared the refractive outcomes between the monkeys reared with peripheral-only induced hyperopic blur and those with full field minus lenses. The -3D aperture group showed the same average refractive error compared to the full field -3D group (+0.36 ± 2.69D vs. +0.46 ± 2.49D; two sample t-test, p = 0.94) and median refractive error (-0.25D vs. +0.38D; Mann-Whitney U test, p = 0.87); compensation with apertures was the same as compensation to full field lenses. In the laser treated group, there was no statistical difference between the refractive error of the laser treated eye with -3.0D lenses as compared to the fellow untreated eye with -3.0D lenses (paired t-test, p = 0.09). Median refractive errors for the fellow and laser-treated eyes of the monkeys in the -3.0D laser group were comparable to those of the left and right eyes of the monkeys with intact retinas fit with -3.0D lenses (Mann-Whitney U test, p = 0.85 and 1.00). However the median refractive errors for the laser-treated eyes of the monkeys in the -3.0D laser group were significantly more myopic/less hyperopic than the right eyes of the control monkeys (+0.13 D vs. +2.50 D, Mann-Whitney U test, p = 0.001) and the laser-treated eyes of the laser control monkeys reared with unrestricted vision (+0.13 D vs. +2.50 D, Mann-Whitney U test, p = 0.02). In general these findings are all in agreement with Smith’s previous studies involving the peripheral retina and form deprivation. Hyperopic defocus is just as capable of inducing myopic refractive error in monkeys as form deprivation, with or without foveal involvement (Smith et al., 2009).

These monkey studies seem to suggest that the fovea is not required to induce refractive error changes. Defocus of the peripheral retina alone is capable of inducing
refractive changes and may even play a more significant role than the fovea. The ability of the eye to respond to peripheral defocus in the presence of clear central foveal vision suggests that the periphery can override the central signal. The theory is that the peripheral retina comprises a much larger retinal area than the fovea alone. The previous human studies only investigated the effect of under-correcting central refractive error; perhaps a model with peripheral defocus may have better results.

The monkey studies showed that peripheral hyperopic defocus resulted in a more myopic foveal refractive error. Could peripheral myopic defocus slow myopia progression in humans? A study done by Sankaridurg et al. set out to investigate this theory (Sankaridurg, Donovan, Varnas, Ho, Chen, Martinez, Fisher, Lin, Smith, Ge and Holden, 2010). Sankaridurg et al. wanted to investigate the effect of a few novel spectacle lens designs that would induce peripheral myopic defocus over a 12 month period (Sankaridurg et al., 2010). The study enrolled 210 Chinese children aged 6 to 16 years with myopia (-0.75 to -3.50D sphere, cylinder ≤-1.50D). These children were randomized into four groups wearing one of three novel lens designs or single vision-only spectacles for one year. Lens type I had a rotationally symmetrical design with a central aperture of 20mm. The surrounding area was a progressive design up to a relative +1.0D. Lens type II had a rotationally symmetrical design with a central aperture of 14mm. Its surround progressive addition area had a relative spherical equivalent of +2.0D. Lens type III was an asymmetric design with a 10mm radius aperture nasal, temporal, and inferior, but not superiorly. Its surrounding area provides a progressive relative spherical equivalent of +1.9D. After lens dispensing, central, nasal, temporal
cycloplegic auto-refraction, along with ocular axial length measurements were taken after six and twelve months of wear. Myopic progression in eyes wearing the control spectacle lenses at 6 and 12 months was -0.55 ± 0.35D and -0.78 ± 0.50D, respectively. No statistically significant differences were found with any of the novel spectacle designs. However when they adjusted the age range to younger children (6-12 years) and parental history of myopia (n=100), there was significantly less progression (-0.68 ± 0.47D vs. -0.97 D ± 0.48D) with lens type III. This was a mean difference as compared to controls of 0.29D (std error, 0.11, p = 0.038); (Sankaridurg et al., 2010).

The study authors admit they had issues actually measuring any substantial reduction of peripheral hyperopic defocus when wearing the spectacles, and therefore it is in question whether the relative peripheral myopic defocus occurred at all. The treatment effect also may not have occurred because the study used older children; only when they adjusted the age were significant results found. It also seems the aperture sizes were rather large, and it is curious to think whether different, better results would occur with smaller aperture sizes.

A number of studies have also been performed utilizing two contact lens methods: dual-focus soft contact lenses similar to multifocal contact lenses, and orthokeratology (Anstice and Phillips, 2011; Cho and Cheung, 2012; Cho, Cheung and Edwards, 2005; Hiraoka, Kakita, Okamoto, Takahashi and Oshika, 2012). The method of using contact lenses to induce peripheral myopic defocus is appealing compared to spectacles because the treatment is directly on the cornea. This assures the peripheral defocus is stable on the eye and is delivering the desired treatment to the periphery in all fields of gaze.
A study done by Anstice et al. tested the efficacy of an experimental Dual-Focus soft contact lens in reducing myopia progression (Anstice et al., 2011). Forty children aged 11-14 years with a spherical equivalent refractive error between -1.25D and -4.50D in the least myopic eye were fit into the soft Dual-Focus contact lens in one eye and a single vision lens in the other eye. The subjects were randomly assigned to one of two groups. The first group wore the Dual-Focus lens over the dominant eye with the single vision lens over the non-dominant eye. The second group wore the Dual-Focus lens over the non-dominant eye and the single vision lens over the dominant eye. The lenses were worn for a period of ten months and then switched to the opposite eyes for a second ten month period. The primary outcome was the change in spherical equivalent refractive error as measured by cycloplegic autorefraction. A secondary outcome of axial eye length was measured by partial coherence interferometry. For period 1 the mean change in spherical equivalent refractive error with the Dual-Focus lenses (-0.44 ± 0.33D) was less than the single vision lenses (-0.69 ± 0.38D; p<0.001). The mean increase in ocular axial length was also reduced in the Dual-Focus lenses (0.11 ± 0.09mm) as compared to the single vision lenses (0.22 ± 0.10mm; p<0.001). They reported that in seventy percent of the children, myopia progression was slowed by thirty percent or more in the eye with the Dual-Focus lens. Similar results were found in the second period after switching which eye was wearing the Dual-Focus lens. In general the Dual-Focus lens was found to slow the progression of myopia as compared to a fellow eye in single vision distance only (Anstice et al., 2011).
A two-year pilot study done by Cho et al. investigated if orthokeratology can effectively reduce and control myopia in children (Cho et al., 2005). They monitored 35 children aged 7-12 years undergoing orthokeratology and compared the rates of change with a group of 35 children from a previous study to act as the control. The entry criteria were spherical equivalent refractive error between -0.25 and -4.50D with less than -2.00D of astigmatism, and visual acuity of least 0.06 logMAR. For the orthokeratology subjects, they monitored changes in corneal curvature, refractive errors, axial length, and vitreous chamber depth. After the 24 months the axial length changes for the orthokeratology and control subjects were 0.29 ± 0.27mm and 0.54 ± 0.27mm respectively (unpaired t-test; p = 0.012). Increases in vitreous chamber depths were 0.23 ± 0.25mm and 0.48 ± 0.26mm for the orthokeratology and control subjects respectively (p = 0.005). This study suggests that orthokeratology can be used to both correct myopia and slow the progression of it (Cho et al., 2005).

A similar study done by Walline et al. also investigated the possibility of orthokeratology lenses slowing eye growth (Walline, Jones and Sinnott, 2009). This study fit forty children ages 8 to 11 years with refractive error between -0.75 and -4.00D myopia and less than 1.00D of astigmatism in corneal reshaping lenses. They matched subjects to soft contact lens wearers from another myopia control study. They used A-scan ultrasonography to monitor axial length and vitreous chamber depth. Both axial length (mean difference in annual change = 0.16mm, p = 0.0004) and vitreous chamber depth (mean difference in annual change = 0.10mm, p = 0.006) were found to be reduced in the corneal reshaping group as compared to soft contact lenses. This results further
confirm that orthokeratology appears to slow ocular growth in myopic children (Walline et al., 2009). However neither of these studies was a prospective, randomized clinical trial.

Cho et al. set up a two year randomized clinical trial using orthokeratology for myopia control (Cho et al., 2012). Subjects were 102 children age 6 to 10 years with myopia between 0.50 and 4.00D with less than or equal to 1.25D of astigmatism randomly assigned to wear orthokeratology lenses or single vision glasses for a two year period. Seventy-eight subjects (37 in the orthokeratology group, and 41 in the control group) completed the study. Axial length was measured at baseline and repeated every 6 months for the length of the study. The average axial elongation at the conclusion of the study was 0.36 ± 0.24mm and 0.63 ± 0.26mm in the orthokeratology and control groups, respectively (p<0.01). On average subjects in the orthokeratology group had slower increase in axial elongation by 43% compared to the single vision lenses group (Cho et al., 2012).

A study done by Hiraoka et al. looked at the long term effect of orthokeratology wear on axial length in myopic children (Hiraoka et al., 2012). In this study they compared orthokeratology treated children to those wearing spectacles over a five year period. The inclusion criteria were children aged 8-12 years, with noncycloplegic autorefracton (spherical equivalent) from -0.50 to -5.00D in both eyes and less than or equal to 1.50D of astigmatism. There were 59 subjects in total, 29 of which were put in the orthokeratology group, and 30 were put in the spectacle group. The primary outcome was axial length, which was measured periodically throughout the study. Forty-three
subjects, 22 in the orthokeratology group, and 21 in the spectacle group, finished the study. The change in axial length for the orthokeratology and spectacle groups over the five year period were 0.99 ± 0.47mm and 1.41 ± 0.68mm, respectively. This was a statistically significant difference (p = 0.0236, unpaired t-test). When broken down by year, the difference of axial length elongation was statistically different for the first (p = 0.0002), second (p = 0.0476), and third years (p = 0.03485), but not the fourth (p = 0.0938), and fifth years (p = 0.8633). The authors hypothesized that the effect may reduce over time due to the fact that the spectacle treated or control group may no longer be progressing themselves, making significant differences harder to find. However, it should be noted that eyes were still growing at 0.17mm per year by the end of the study. Overall the study supports the idea that orthokeratology lenses are associated with slowed axial length growth, but the optimal treatment period has not been well established yet (Hiraoka et al., 2012)

In the earlier animal model experiments, particularly in the chick, choroidal thickness was analyzed and found to play a large role in axial length changes. Choroidal thickness measurements in the human and monkey studies were often not included. This was mostly due to a lack of non-invasive procedures that could accurately obtain them. A study done by Read et al. took axial length and choroidal measurements after patients monocularly wore lenses inducing three diopters of myopic or hyperopic defocus (Read et al., 2010). This study was comprised of 28 young adult subjects between the ages of 21 and 30. There were 14 myopes and 14 emmetropes. Biometric measurements of axial length and choroidal thickness were taken before and after each of two, thirty minutes
sessions of distance viewing while monocularly wearing the lenses. The different lenses included -3.0D, +3.0D, Bangerter foil, and a control of no lens. These were worn in separate sessions on separate days, and in random order. The other eye was fully corrected with no defocus induced. The study found that after two sessions, sixty minutes total, significant changes in axial length occurred. A significant increase in axial length (+8 ± 14 microns; p = 0.03) was found after hyperopic defocus was induced, while a significant decrease in axial length (-13 ± 14 microns; p = 0.0001) was found after myopic defocus was induced. A small increase in axial length was also noted after diffuse defocus with the Bangerter foil (+6 ± 13 microns; p = 0.053). They also discovered an interesting result from choroidal thickness. When performing manual analysis of the A-scan reading from the Lenstar, they noticed an additional peak (P4) that represented the choroidal/sclera interface.

![Figure 1: Example of A-Scan from Read et al.](image)

Figure 1: Example of A-Scan from Read et al.
If they manually adjusted the calipers, they could also measure the choroidal thickness. This had not been previously done in human lens compensation/defocus studies. They reported a statistically significant amount of choroidal thickening in the myopic defocus condition (+12 ± 16 microns; \( p = 0.004 \)). This finding is approximately equal and opposite to the axial length change found in the myopic defocus condition. However no significant choroidal thinning occurred with the -3.0D lens. Overall the study found very small but significant axial length changes occur in response to myopic, hyperopic, or generalized defocus, and at least in the case of myopic defocus the choroid played a significant role (Read et al., 2010).

Read utilized a new piece of equipment, the Lenstar LS 900 optical biometer, which was able to give measurements of axial length and choroidal thickness. However, Read admitted that the accuracy of the choroidal thickness measurements are poorer than those of axial length. He reports a mean coefficient of variation of 5.8\% for choroidal measurements as compared to 0.04\% for axial length (Read et al., 2010). Other studies have utilized optical coherence tomography as a technique to both image and measure the choroid (Branchini, Regatieri, Flores-Moreno, Baumann, Fujimoto and Duker, 2012; Hirata, Tsujikawa, Matsumoto, Hangai, Ooto, Yamashiro, Akiba and Yoshimura, 2011b; Margolis and Spaide, 2009b; Ouyang, Heussen, Mokwa, Walsh, Durbin, Keane, Sanchez, Ruiz-Garcia and Sadda, 2011; Rahman, Chen, Yeoh, Patel, Tufail and Da Cruz, 2011). Two of these studies have used Enhanced Depth Imaging Optical Coherence tomography (EDI OCT) imaging with the Heidelberg Spectralis spectral-domain OCT and were able
to accurately obtain in vitro subfoveal choroidal thickness measurements. (Margolis and Spaide, 2009a; Rahman et al., 2011).

A pilot study done by Margolis et al. set out to measure the macular choroidal thickness in normal eye at different points using the EDI OCT technique on the Heidelberg Spectralis (Margolis et al., 2009b). This was a retrospective study done on 54 eyes of 30 patients that previously had EDI OCT images taken. The mean age of subjects was 50.4 years with a range of 19 to 85 years. Fourteen of the patients were female and the mean refractive error was -1.3 D ± 2.1D. They found that the choroid was thickest underneath the fovea (mean = 287 ± 76 microns). This decreased at a faster rate nasally with an average of 145 ± 57 microns 3mm nasal to the foveal while the average 3mm temporal to the fovea was 261 ± 77 microns. They also found a negative correlation between age and subfoveal choroidal thickness (r = -0.424; p = 0.001). Regression analysis revealed that 1.56 microns of thinning occurred for every year of life (Margolis et al., 2009b). Thus it is possible to image and measure the choroid using the EDI OCT imaging technique, but is this process repeatable, and how much inter-observer variability is there?

A study done by Rahman looked at intra-observer and inter-observer repeatability (Rahman et al., 2011). This study took 50 consecutive, healthy, young, adult volunteers and ran two good-quality horizontal and vertical line scans through the fovea of each eye. The OCT scans were performed by two retinal specialists that were experienced at performing scans using the spectral domain OCT Heidelberg Spectralis. The mean age of the subjects was 38 ± 5 years with a range of 30-49 years. The mean subfoveal choroidal
thickness was 332 ± 90 microns for the right eyes and 332 ± 91 microns for the left eyes. Intraobserver coefficient of repeatability (CR) was ±23 microns (95% confidence interval (CI) = 19-26 microns) while inter-observer and intra-session CRs were larger at ±32 microns (95% CI, 30-34) and ±34 microns (95% CI, 32-36), respectively. They concluded that changes greater than 32 microns were therefore relevant and significant when using multiple observers. With a single observer, changes greater than 23 microns will be relevant (Rahman et al., 2011).

A Heidelberg Spectralis was not a piece of equipment available in our lab. The OSU College of Optometry did possess a Zeiss Cirrus HD OCT. Is it possible for the Cirrus HD-OCT to image and measure choroidal thickness? A study done by Ouyang used both a Cirrus HD-OCT and a prototype longer wavelength (1050nm) spectral domain OCT for enhanced imaging of the choroid (Ouyang et al., 2011). Fifty-nine eyes from 30 subjects were examined with both devices. The mean choroidal thickness (ChT) was calculated for each Early Treatment Diabetic Retinopathy Study subfield. Subfoveal ChT was found to be 297.8 ± 82.2 microns. ChT was greatest in the superior outer subfield and thinnest in the nasal outer subfield. Predictive models for macular ChT included axial length and/or age. They also found inter-observer 95% limits of agreement ranged from -13.3 to 10.7 microns (mean bias = 1.3 microns) in all subfields, and an inter-device difference of only 11.7 ± 9.1 microns (Ouyang et al., 2011) This suggests that the HD-OCT was nearly as accurate as a prototype long wave OCT specifically designed to image the choroid. Since this was a comparison to a prototype piece of
equipment, it is necessary to compare the measurements by HD-OCT to previously studied methods such as EDI OCT with the Heidelberg Spectralis.

A study done by Branchini compared the reproducibility of subfoveal choroidal thickness measurements with three different spectral domain OCT systems (Branchini et al., 2012). Scanning patterns included HD 1-line raster on the Zeiss Cirrus, EDI line scan with the Spectralis, and retina cross line on the Optovue RTVue. In an attempt to take measurements in the same exact anatomical spot, all measurements were taken as close to the central fovea as possible and 750 microns in the nasal and temporal directions. Images were taken and analyzed with each instrument on 28 eyes of 28 subjects (7 male, 21 female) with an average age of 35.2 years and a range of 23-64 years. Eighteen subjects were white, 5 subjects were Asian, 3 were Hispanic, and 2 were African American. They reported that a 2-way ANOVA with Bonferroni’s post-test adjustment for multiple comparisons showed no significant difference in the average subfoveal choroidal thickness \( (p > 0.05) \) for any location: subfoveal, 750 microns temporal, and 750 microns nasal to the fovea. The measurements of ChT from any pair of the three instruments were strongly correlated. The Pearson correlation among all two system pairs was greater than 0.9 \( (p<0.0001) \). In their population of young and healthy adults with normal vision, there was good reproducibility among images for Cirrus, Spectralis, and RTVue.

All of the studies on choroidal thickness seem to agree that choroidal thinning occurs more rapidly nasally from the fovea than in any other direction, and that there is a negative correlation between age and choroidal thickness (Margolis et al., 2009a; Hirata,
Tsujikawa, Matsumoto, Hangai, Ooto, Yamashiro, Akiba and Yoshimura, 2011a; Ouyang et al., 2011; Branchini, Regatieri, Flores-Moreno, Baumann, Fujimoto and Duker, 2011). These studies suggest that OCT is a repeatable and feasible non-invasive method for documenting choroidal thickness.

Our hypothesis is that peripheral myopic defocus results in an increase in choroidal thickness. The minimum thickness difference that might be meaningful clinically in terms of diopters of refractive error is a change of 90 microns, which approximately equals a 0.25 diopter shift in refractive error (where 1mm = 2.75D). The results of this study will help to further understand the underlying mechanism of the slowed progression of myopia previously reported in other studies (Anstic et al., 2011; Cho et al., 2012; Cho et al., 2005; Hiraoka et al., 2012; Walline et al., 2009). A negative finding of no choroidal thickening will further support the hypothesis that slowed axial growth is truly accounting for the slowed progression of myopia with corneal reshaping contact lenses. A positive finding of choroidal thickening will give a new interpretation to clinical results with corneal reshaping lenses, perhaps that they affect refractive error by transient changes in the choroid, not purely by changing the growth of the eye. These results may also point to the location of the biochemical changes resulting from peripheral myopic defocus. Further, longer-term studies would then be justified to investigate the limits of this effect, whether it is permanent, and if it eventually affects ocular growth.
Chapter 2: Methods

Design

This study was a patient based experiment utilizing a pre/post design where each subject’s baseline data served as the control. Measurements of the variables investigated were taken before and after 1, 3, and 6 months of successful fitting with corneal reshaping contact lenses, then compared back to baseline data. No control group was necessary since results are comparisons to the subjects’ own initial baseline data.

Sample Size

This study was comprised of 9 individuals between the ages of 11-15 years. The most conservative study investigating repeatability of OCT measurements similar to this study showed overall 95% limits of agreement to be about ±45 microns (Branchini et al., 2012). This accounts for intra-observer, inter-observer, and inter-session variability. Given that confidence intervals of 95% are 1.96X the standard deviation (SD) we can safely assume a SD of about ±23 microns between measurement occasions. Previous studies done over a similar time period have reported effects of at least a 0.25 diopter in refractive error (Anstice et al., 2011; Cho et al., 2012; Cho et al., 2005; Hiraoka et al., 2012; Walline et al., 2009). A physical measurement of axial length that equals the minimal effect of a 0.25 diopter is 90 microns (2.75D per mm of axial length). Using
these values in a paired data sample size formula that assumes a confidence interval of ±90 microns and a standard deviation of ±23 microns gives a requirement of less than 1 person. Traditionally, statistical analysis requires a minimum of 6 subjects. Therefore 9 subjects should be sufficient to provide meaningful results with each subject at baseline serving as his own control for change in choroidal thickness after treatment.

Recruitment

The research followed the tenets of the Declaration of Helsinki. All subjects signed consent forms after being notified of the purpose, risk, and benefits of the study. Subjects under the age of 18 were given an assent form and a parent or guardian was given a consent form to sign.

IRB approval was sought for children between the ages of 8-15 years. This age range was intended to match closely to other corneal reshaping studies to allow for comparison (Anstice et al., 2011; Cho et al., 2012; Cho et al., 2005; Hiraoka et al., 2012; Walline et al., 2009). A partial waiver of HIPAA research authorization was also requested for recruitment purposes. This allowed for an internal chart review of all patients 8-15 years of age with a diagnosis of myopia in the last 3 years at The OSU College of Optometry. During the chart review, patients were identified that met eligibility criteria at the time of their last appointment and added to a list of potential subjects. All those identified were mailed a recruitment postcard. Signs with brochures were also posted in the optometry clinics at OSU. This recruitment provided nine subjects
that completed the enrollment process which surpassed the minimum requirement of 6 subjects.

An audit was run of all patients in The Ohio State University College of Optometry patient base for subjects of qualifying age with the ICD code for myopia (367.1). This audit resulted in a total of 1132 potential candidates. The primary investigator pulled each chart for a review to identify if the patient appeared to qualify for the study based on entry criteria. In total, 204 of the 1132 were identified as eligible potential subjects and a postcard was sent to the parents' address. These mailings combined with other recruitment techniques such as brochures in the contact lens and pediatric clinics resulted in 16 initial visits. Of the 16 initial visits, 11 concluded in confirmation of eligibility and official enrollment of the subject in the study. Two of the eleven decided to drop out of the study due to not wanting to proceed with GP lens wear, and both instances occurred before the 1 month follow-up visit.
<table>
<thead>
<tr>
<th>Eligibility Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Refractive Error</strong></td>
<td>Cycloplegic autorefraction was used to determine these criteria. Sphere component of the prescription must be between -1.00 and -4.00 D. The refractive astigmatism must be less than -1.00 DC.</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>All subjects must be 8-15 years of age at the time of the baseline examination.</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>Either gender, however females who are pregnant or planning to become pregnant were excluded due to variable refractive error.</td>
</tr>
<tr>
<td><strong>Visual Acuity</strong></td>
<td>All subjects must have 20/20 or better best-corrected visual acuity in each eye.</td>
</tr>
<tr>
<td><strong>Ocular Health</strong></td>
<td>All subjects must be free of eye disease and binocular vision problems (i.e., strabismus, amblyopia, oculomotor nerve palsies, corneal disease, etc.) that may affect vision or contact lens wear.</td>
</tr>
<tr>
<td><strong>Systemic Health</strong></td>
<td>All subjects must be free of systemic disease that may affect vision or vision development (i.e., diabetes, Down Syndrome, etc.)</td>
</tr>
<tr>
<td><strong>Contact Lens Wear</strong></td>
<td>Subjects must have no current or previous corneal reshaping contact lens wear, gas permeable contact lens wear, or soft bifocal contact lens wear.</td>
</tr>
<tr>
<td><strong>Other studies</strong></td>
<td>Subjects cannot concurrently participate in other clinical studies that may affect their vision (i.e., contact lenses, pirenzepine, or bifocal myopia control studies), ocular comfort, or their ability to attend scheduled visits.</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td>Patients may not be taking medications that may affect corneal wound healing such as topical corticosteroids.</td>
</tr>
<tr>
<td><strong>Ocular Surgery</strong></td>
<td>Patients who have had intraocular or corneal surgery were excluded.</td>
</tr>
</tbody>
</table>

Table 1: Eligibility criteria for the study.
Rationale for Eligibility Criteria

*Refractive Error:* The minimum refractive error was set to -1.00D to assure patient motivation to wear the corrective contact lenses, and to allow enough of a treatment to induce a significant amount of peripheral myopic defocus. The maximum refractive error was set to -4.00D because this is close to the limit of myopia correction generally considered possible with overnight corneal reshaping. The limit of 1.00DC of astigmatism was established due to issues with de-centering of lenses. Refractive error limitations were also set to attempt to maintain limits similar to other corneal reshaping studies (Anstice et al., 2011; Cho et al., 2012; Cho et al., 2005; Hiraoka et al., 2012; Walline et al., 2009).

*Age:* Children were at least 8 years old at the time of the baseline examination because children less than 8 years of age may lack the maturity to handle the responsibility of contact lens care. The maximum age was set to 15 years of age at the time of baseline examination because cessation of myopia progression has been found to typically occur at age 16.7 years for boys and 15.2 years for girls (Goss and Winkler, 1983). This placed subjects within an age range of possible progression of myopia.

*Visual Acuity:* These criteria exist to assure that the subjects were healthy and to minimize potential confounding variables that may affect the validity of the data.

*Ocular health:* These criteria exist to assure that the subjects were healthy and to minimize potential confounding variables that may affect the validity of the data.
**Systemic health:** These criteria exist to assure that the subjects were healthy and to minimize potential confounding variables that may affect the validity of the data.

**Contact lens wear:** No previous corneal reshaping contact lens wear, GP, or bifocal contact lens wear to eliminate the possibility that the effect we are investigating has already occurred.

**Other studies:** We do not want to include subjects that may have ocular growth, progression of myopia, or choroidal changes through means of a drug or device from participation in other studies. This will help minimize confounding by unknown variables.

**Medications:** Patients taking medications that may affect corneal wound healing were not enrolled in order to maximize the safety of contact lens wear.

**Ocular surgery:** Patients who have had intraocular or corneal surgery were excluded in order to enhance safe contact lens wear and refractive error results that will not be affected by refractive surgery.

**Primary Outcome Measure**

The primary outcome for the study was choroidal thickness. This was measured using images from the Zeiss Cirrus HD-OCT. The images were uploaded into and analyzed by Adobe Photoshop with adjusted pixel to micron scales. Three thickness measurements were made on one image taken at each location centrally (Figure 2) and at 30° in three peripheral gazes: superior (Figure 3), temporal (Figure 4), and nasal (Figure 5). Inferior gaze was excluded due to interference from the upper eyelid. The Cirrus HD-OCT has been found to be capable of obtaining detailed, repeatable images of the choroid.
beneath the retina (Rahman et al., 2011). Thirty degrees peripheral gaze was chosen for both feasibility and to allow for measurement near the border of the orthokeratology treatment zone. The peripheral gaze measurements were taken approximately 1.7 mm from the center of the pupil. This was calculated using the tangent of 30º and a distance of 3.00 mm (apparent anterior chamber depth). With a fitting goal of a 4.0 mm treatment zone, the 30º peripheral gaze measures would be close to this border 2.0 mm from the center of the pupil.
Figure 2: Raw OCT view of the central retina and choroid.
Baseline (left) and 6 months (right)

Figure 3: Raw OCT view of the superior retina and choroid.
Baseline (left) and 6 months (right)
Figure 4: Raw OCT view of the temporal retina and choroid.
Baseline (left) and 6 months (right)

Figure 5: Raw OCT view of the nasal retina and choroid.
Baseline (left) and 6 months (right)
These images were adjusted to increase contrast to allow for optimal choroidal viewing and exported in JPEG format. The images were then uploaded into Photoshop to allow for calculations of thickness and total cross sectional area. While using the internal OCT measurement tool it was discovered that the OCT artificially elongates the image vertically. If a cross is made with the measurement tool the vertical line is significantly longer than the horizontal line when both represent a 1000 micron length. In Photoshop it was calculated that vertical is twice as long as horizontal. Therefore, once uploaded into Photoshop the image height is adjusted to half to account for this vertical stretching. The magnetic lasso tool within the program allowed for outlining of borders. This was used to outline the RPE, each lateral side of the image, and posterior surface of the choroid, which were then analyzed for total cross sectional area. The total area was divided by chord length to allow a calculation of average thickness across the image. Subfoveal choroidal thickness was also measured using the ruler tool in Photoshop.

Figure 6: Photoshop use of the Magnetic Lasso tool to outline the choroid. The white line represents the chord length.
Secondary Outcome Measure

Axial length was a secondary outcome. This measurement allows for comparison of the relationship between choroidal thickness, axial length, and refractive error. Axial length was taken using a Lenstar LS 900 biometer. This instrument is similar to the IOLMaster and A-scan ultrasound in that it can take axial biometric measurements of the eye. The LS 900 can measure axial length, vitreous chamber depth, lens thickness, and anterior chamber depth using partial coherence interferometry. The LS 900 has the added advantage that it can measure retinal thickness. The instrument takes 5 measurements and the averages of these were reported. The instrument has also been used by Read to make foveal choroidal thickness measurements with limited accuracy (Read et al., 2010). The study will compare the results of central choroidal thickness by the method used by Read with the Lenstar and our OCT image analysis. In addition, ocular length was measured centrally and at 30° in the three peripheral fields of gaze (nasal, temporal, and superior).
with the Zeiss IOLMaster. Five measurements were taken in each field of gaze and averaged.

**Other Covariates**

Other measures were taken for various reasons such as management of the contact lenses and assessment of the size of treatment effect. These include cycloplegic autorefraction, peripheral autorefraction at 30° in the 3 peripheral gaze directions, Complete Ophthalmic Analysis System (COAS) aberrometry, visual acuity, corneal topography, slit lamp examination, and dilated fundus examination.

Cycloplegic auto-refraction was utilized to determine entry eligibility and monitor refractive error. Measurements were taken 25 minutes after instillation of the second of a series of two drops of 1% tropicamide separated by 5 minutes. The peripheral autorefraction was taken to analyze if peripheral myopic defocus was actually occurring. Cycloplegic autorefraction is preferred over subjective refraction due to better repeatability, and decreased potential for bias (Zadnik, Mutti and Adams, 1992). Manifest refraction was used clinically to monitor the treatment effectiveness and to make clinical adjustments to contact lens power and fit.

The COAS is an aberrometer that was utilized to evaluate spherical aberration. These measurements were taken at each visit that images of the retina and choroid were taken. The results were used to assess the amount of spherical aberration induced by the treatment.

High contrast visual acuity was measured with and without correction from each eye. This is a repeatable, quick, and easy measurement to take in children. High contrast
visual acuity allows results to be compared to other studies, and is a good indicator of visual function as well as treatment safety and effectiveness.

Corneal topography was performed using the Humphrey ATLAS Corneal Topography System model 990. One measurement with a “High Confidence” level was recorded for each eye. This measurement is essential for the fitting process of the corneal reshaping lenses. It is also utilized to monitor the treatment effect and to manage the contact lenses clinically.

Slit lamp examination was performed to monitor the anterior health of the eye. BioGlo was used in the slit lamp examination to document any corneal staining associated with contact lens use/complications. A dilated fundus exam was performed at the initial visit to assess posterior ocular health as an eligibility criterion.

Fitting Procedure

Fitting of the Paragon CRT contact lenses was performed at the initial visit as described by the manufacturer’s fitting guide. Keratometry values and Manifest Refraction are necessary to determine initial lens selection from the fitting set. The fitting guide provides an initial lens selector slide rule. The flat keratometry value is set and lens parameters are specified based on the sphere component of the manifest refraction. Lens parameters include base curve (BC), return zone depth (RZD), and landing zone angle (LZA). The BC parameter, also called the treatment zone, is largely responsible for the refractive correction and accomplishes this by changing the shape of the anterior cornea. The RZD is a mid-peripheral curve that returns the lens to the cornea and is responsible for controlling centration and positioning the treatment zone. The LZA allows the lens to
settle safely on the mid-periphery of the cornea and assists centration and adjusts edge lift.

The initial lenses were inserted and immediately evaluated for fit with fluorescein. The lens should present with more than 4 millimeters treatment zone (central touch), centered appearance, appropriate edge lift, tangent touch in the mid-periphery, and a fluorescein pattern revealing a “Black, Green, Black, Green” pooling pattern. Adjustments were made to BC, RZD, and LZA as described by the fitting guide to achieve optimum fitting relationship. If the lens was sitting too high or laterally decentered on the cornea, a 25 micron increase in RZD was made to help drop and center the lens. A decrease in RZD of 25 microns was prompted if minimal treatment zone was noted. If the lens was dropping inferiorly on the cornea, a decrease of LZA by 1 degree was made. A decrease of LZA was also done if minimal edge lift was noted.

“Sphere/Cylinder Refraction Over Lens” was performed to verify proper BC selection and refractive error correction was achieved. Any under-treatment was corrected by flattening the BC, while over-treatment was managed by steepening the BC. Overall the initial fit and any trouble shooting at follow up visits were done according to the fitting guide (Institute, 2002). The lens care solution was Alcon Opti-Free GP. Patients were instructed on proper insertion and removal procedures, and how to properly disinfect the contact lenses.
Table 2: Schedule of study visits and tests performed at each visit.

### Baseline Visit

At the baseline visit the subjects and subjects’ legal guardians were given information about the study and what to expect. Any questions were answered and time was given to allow both the guardian and child to consider enrollment. If they elected to enroll in the study the guardian was asked to sign a parental permission form and the child was asked to sign an assent form. A brief history was taken to assure the subject
met all entry criteria. Visual acuity, subjective refraction, anterior segment evaluation, DFE, topography, COAS, central Lenstar measurement, cycloplegic auto refraction in primary, superior, nasal and temporal gazes, and IOLMaster and OCT images were taken in the same four gazes as well. If the subject met all entry criteria a contact lens fitting was scheduled. Using the lens calculator slide rule the lenses were selected from the fitting set or ordered if not available.

Fitting Visit

At the fitting visit the subject was asked if any changes in health history have occurred, visual acuity was taken, pupils, EOMs, and anterior segment examination were performed. A drop of 1% proparacaine was instilled in each eye. The lenses were then inserted by the Principal Investigator (DG). Acuity with the lenses in place was taken and the fitting evaluation was performed with the help of BioGlo instilled in each eye. Fitting adjustments were made based on the fitting guide. Once an optimum fitting relationship was achieved over-refraction was performed to verify proper BC selection. After the final lenses were decided upon the subject was trained on insertion and removal procedures. The patient needed to demonstrate ability to insert and remove the lenses on their own. If this could not be achieved, the guardian was instructed on proper insertion and removal and asked to demonstrate the ability to safely perform these on the child. Finally the patient was given a case and Opti-Free GP to care for the lenses. The subjects were instructed to rinse and rub the lenses immediately upon removal and to store completely submerged in the Opti-Free GP solution throughout the day. Before insertion they were again instructed to rub the lenses and insert, then rinse the case and allow to air dry over
night. A one day follow up visit was set up before the subject left and they were instructed to wear the lenses in to the first follow up visit.

One Day Follow Up

The patient wore the lenses to this study visit. Before removing the lenses, visual acuity and over-refraction were performed again. The lens fit was assessed again with the use of BioGlo. The lenses were then removed and visual acuity was taken without the lenses. A subjective refraction was performed to assess best corrected visual acuity. Topography was also performed to analyze the treatment effect after one night. Anterior segment health was also examined. If adjustments were warranted, such as decentering of lenses, the fitting guide was followed. If the fit was acceptable and the topography showed central treatment a one week follow up was set up. The patient was again reminded of proper wear and care of the lenses.

One week follow up

The lenses were not worn by the subjects at this visit. Patients were asked to bring the lenses so lens evaluation could occur if necessary. Visual acuity without the lenses were taken and subjective refraction was performed to assess best corrected visual acuity. Topography was again repeated to assess treatment effect. If changes in lens parameters were warranted the fitting guide was followed. A one month follow up visit was then scheduled and patients were reminded of proper wear and care of lenses.

1, 3, and 6-Month Follow Ups

All the same procedures were followed as at the one week visit. Additionally cycloplegic autorefraction, OCT imaging, IOLMaster, COAS, and Lenstar measurements
were all repeated. If contact lens wear and the patient response were both satisfactory, the patient was given more Opti-Free GP solution, a new case, and again reminded of proper wear and care of the lenses. If at any of these visits Snellen visual acuity was not 20/20 OU, the lenses were evaluated and changes were made to try to improve vision. A one to two week follow up was set up at which the same procedures as the initial one week follow up were performed. It should be noted that most visits were scheduled in the afternoon. Having all the visits in the same general time of day avoids variation due to circadian affects on the choroid (Chakraborty, Read and Collins, 2012).

Data Analysis

The study used paired Wilcoxon Signed Rank analysis of the 1-, 3-, and 6-month post treatment choroidal thickness compared to baseline measurements. This non-parametric test was selected due to the small sample size. No corrections for multiple comparisons were made and the significance level was set to p<0.05. Subjects acted as their own controls. To minimize bias, all image files were masked with codes by a third party and then analyzed in random order after the 1-, 3-, and 6-month visits. Therefore the investigator was masked to both whom the images belonged to and when the images were taken. Masking of the location of the choroidal location (central, superior, nasal, and temporal) was not possible. All image analysis was performed by the Principal Investigator (DG) in order to limit inter-observer variation as well.
Chapter 3: Results

Subject Characteristics

The study had a total of 9 subjects enroll and complete all follow up visits. The age range was from 11 to 15 years with an average age of 13.61 ± 1.25 years. There were 6 females and 3 males. Ethnicity was 7 Caucasian subjects and 2 were African-American. All eyes were healthy, and subjects reported no history of any eye disease including strabismus, amblyopia, trauma, surgery, or any systemic disease that would contraindicate contact lens wear. Before initiating the orthokeratology treatment some baseline values were established to help monitor the success and safety of the fitting. Auto-refraction findings from the baseline visit revealed an average central spherical equivalent refractive error of -2.25 ± 0.95D. Average steep Sim K value was found to be 43.59 ± 0.75D, while the average flat Sim K value was 42.89 ± 1.00D. The average shape factor at baseline was 0.28 ± 0.05. This indicates the cornea had normal prolate asphericity. The average spherical aberration value was found to be -0.31 ± 0.17 microns. These values can be found in Table 3.

Safety

Throughout the study the subjects’ ocular health in response to orthokeratology was monitored by evaluating the anterior segment. This evaluation included lids/lashes,
bulbar conjunctiva injection, palpebral conjunctiva papillae, corneal epithelium staining, corneal stroma edema, corneal endothelium, anterior chamber, iris, and von Herrick angles. Data analysis was performed on bulbar conjunctiva injection, palpebral
<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>1 month</th>
<th>3 month</th>
<th>6 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central SEQ (D)</td>
<td>-2.25 ± 0.95</td>
<td>-0.24 ± 1.03</td>
<td>-0.45 ± 1.01</td>
<td>-0.28 ± 1.28</td>
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<tr>
<td>Central Ref Error J0 (D)</td>
<td>-0.035 ± 0.22</td>
<td>-0.048 ± 0.14</td>
<td>-0.19 ± 0.51</td>
<td>0.19 ± 0.29</td>
</tr>
<tr>
<td>Central Ref Error J45 (D)</td>
<td>0.052 ± 0.1</td>
<td>0.044 ± 0.13</td>
<td>0.026 ± 0.23</td>
<td>0.052 ± 0.21</td>
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<tr>
<td>Sim K Flat (D)</td>
<td>42.89 ± 1.00</td>
<td><strong>41.26 ± 1.25</strong></td>
<td><strong>41.43 ± 1.55</strong></td>
<td><strong>41.57 ± 1.46</strong></td>
</tr>
<tr>
<td>Sim K Steep (D)</td>
<td>43.59 ± 0.75</td>
<td><strong>41.90 ± 1.21</strong></td>
<td><strong>42.33 ± 1.37</strong></td>
<td><strong>42.15 ± 1.36</strong></td>
</tr>
<tr>
<td>Shape Factor</td>
<td>0.28 ± 0.05</td>
<td><strong>-0.34 ± 0.41</strong></td>
<td><strong>-0.24 ± 0.34</strong></td>
<td><strong>-0.24 ± 0.82</strong></td>
</tr>
<tr>
<td>Spherical aberration (μ)</td>
<td>-0.31 ± 0.17</td>
<td><strong>-1.03 ± 0.33</strong></td>
<td><strong>-1.03 ± 0.38</strong></td>
<td><strong>-1.1 ± 0.14</strong></td>
</tr>
<tr>
<td>Cirrus Central ChT (μ)</td>
<td>243.7 ± 70.2</td>
<td>248.3 ± 69.7</td>
<td>246.0 ± 62.6</td>
<td>233.1 ± 58.8</td>
</tr>
<tr>
<td>Cirrus T ChT (μ)</td>
<td>149.0 ± 54.9</td>
<td>167.9 ± 65.6</td>
<td>153.6 ± 44.2</td>
<td>175.4 ± 51.5</td>
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<tr>
<td>Cirrus S ChT (μ)</td>
<td>149.3 ± 63.5</td>
<td>147.4 ± 64.8</td>
<td><strong>112.1 ± 29.1</strong></td>
<td>125.4 ± 48.3</td>
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<td>Cirrus N (μ)</td>
<td>145.2 ± 39.6</td>
<td>146.0 ± 37.7</td>
<td><strong>171.2 ± 43.0</strong></td>
<td>162.8 ± 43.5</td>
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<td>IOLMaster Central eye length (mm)</td>
<td>24.85 ± 0.73</td>
<td>24.81 ± 0.70</td>
<td>24.84 ± 0.70</td>
<td>24.87 ± 0.70</td>
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<tr>
<td>IOLMaster T eye length (mm)</td>
<td>23.94 ± 0.65</td>
<td>23.92 ± 0.63</td>
<td>23.92 ± 0.67</td>
<td>23.99 ± 0.69</td>
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<tr>
<td>IOLMaster S eye length (mm)</td>
<td>24.48 ± 0.88</td>
<td>24.53 ± 0.83</td>
<td>24.51 ± 0.87</td>
<td>24.51 ± 0.86</td>
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<tr>
<td>IOLMaster N eye length (mm)</td>
<td>24.48 ± 0.76</td>
<td><strong>24.39 ± 0.79</strong></td>
<td>24.39 ± 0.75</td>
<td>24.46 ± 0.73</td>
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<td>Lenstar Central ChT (μ)</td>
<td>230.1 ± 32.4</td>
<td>223.1 ± 28.9</td>
<td>211.3 ± 51.8</td>
<td>186.6 ± 42.8</td>
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<td>OCT Subfoveal ChT (μ)</td>
<td>272.5 ± 80.6</td>
<td>275.7 ± 62.6</td>
<td>280.9 ± 71.5</td>
<td>265.19 ± 56.6</td>
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<td>Periph SEQ S (D)</td>
<td>-2.41 ± 1.64</td>
<td>-3.39 ± 2.11</td>
<td>-3.64 ± 2.23</td>
<td><strong>-3.58 ± 1.36</strong></td>
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<tr>
<td>Periph SEQ N (D)</td>
<td>-1.77 ± 1.2</td>
<td><strong>-3.06 ± 1.48</strong></td>
<td>-2.55 ± 1.60</td>
<td><strong>-3.02 ± 2.32</strong></td>
</tr>
<tr>
<td>Periph SEQ T (D)</td>
<td>-1.54 ± 1.39</td>
<td>-2.00 ± 1.99</td>
<td>-2.37 ± 1.63</td>
<td>-1.92 ± 1.73</td>
</tr>
</tbody>
</table>

Table 3: The average values and standard deviations of the variables at each study visit.

Significant differences from baseline are marked in bold.
conjunctiva papillae, and corneal epithelium staining. These three items are most likely to be affected negatively by gas-permeable contact lens wear. A decimalized Efron grading scale (The Vision Care Institute, LLC) was used to monitor ocular health. Normal was given a value of zero, trace a value of 1, mild a value of 2, moderate a value of 3, and severe a value of 4. If assessment was between two levels, a value of 0.5 between the values was assigned. Due to the small sample size all analyses of repeated measures were done by non-parametric Wilcoxon Signed Ranks testing. Significant differences over time were found for both OD and OS bulbar conjunctiva at the 6 month visit as compared to baseline (p = 0.034 for both). However the level of bulbar injection in each eye was a grade of 0.5 ± 0.66 at 6 months (8/9 at grade 1 or less (89%)) as compared to 0.11 ± 0.22 at baseline (9/9 at grade 1 or less (100%)). Since both values are less than trace this difference is relatively clinically insignificant. A significant difference as compared to baseline was also found for palpebral conjunctiva papillae for OS only (p = 0.046). The 6 month visit had an average value of grade 0.83 ± 0.79 (7/9 at grade 1 or less (78%)) as compared to 0.28 ± 0.36 (9/9 at grade 1 or less (100%)). Again both these values are less than trace so this is also relatively clinically insignificant and would not warrant any change of the contact lens fitting or wear. There was no significant change in corneal epithelial staining through the study. Only one adverse event occurred throughout the fitting process. Subject 7 had a sensitivity reaction to the solution a trial lens from the fitting set was stored in. She developed grade 4 epithelial staining with grade 2 bulbar injection. The fitting process was discontinued and the patient received 1 drop of Moxeza in office and was given Optive Sensitive artificial tears to use every 0.5 hours for the
remainder of the day and then as needed. A follow up visit occurred the following morning. Ocular health was significantly improved, with no injection or corneal staining/edema present, and distance visual acuity was correctable to 20/20. Contact lens wear was re-initiated that night. This event was reported to the IRB, who required no further action. No other complications arose throughout the remainder of the study.

The orthokeratology fitting process was performed as described in the methods section. As a group, significant treatment was achieved by the 1 month follow up visit, and was maintained throughout the remainder of the study. Successful treatment was determined by the primary investigator considering entering uncorrected visual acuity, topographical analysis, subjective refractive error, cycloplegic autorefraction, and uncorrected Snellen visual acuity. At the 1 month visit acuity was already found to be 20/20 to 20/25+ in 8/9 subjects (88.9%), with the remaining subject being a 20/25 to 20/30+. This subject was 20/20 to 20/25+ for both the 3 and 6 month visits. Overall at the 3 and 6 month visits 8/9 (88.9%) subjects were 20/20 to 20/25+.

Subject 7 experienced reduced acuity worse than 20/40 at both the 3 and 6 month visit. This was interesting since the patient had been 20/20 to 20/25+ at the 1 month visit. At the 3 month visit the subject reported no symptoms of blurred vision throughout the day, but vision was found to be reduced with a significant refractive error. Further questioning revealed the subject was not wearing the lenses for a full 8 hours overnight. Longer overnight wear time was suggested and an end of day 1 week follow up appointment was scheduled. At the follow up visit visual acuity was back to 20/20 to 20/25+. For the 6 month visit the patient reported some mild discomfort the previous
night, and she did not wear the lenses. Therefore, vision was reduced that day as
compared to other days. The subject reported no chronic issues with blurred vision but
tested as worse than 20/40. Ocular health appeared normal and the lenses fit properly so
she was instructed to continue wear with a one week follow up suggested. The subject
was able to return a few weeks later, and acuity was improved to 20/25 to 20/30+.
Assessment of vision with the lenses on was 20/20 and over-refraction was +0.25 OD and
plano OS, indicating proper BC selection with good centration and treatment zone on
topography.

Ocular Biometric Changes from Baseline

The central refractive error spherical equivalent was significantly different from
baseline at all three follow up visits (p=0.008, p=0.008, and p=0.008; Figure 8). The
refractive error shifted towards plano which is an expected result of orthokeratology
treatment. The flat simulated keratometry value at all three follow up visits was
significantly flatter as compared to baseline due to the orthokeratology treatment
(p=0.008, p=0.008, and p=0.011; Figure 9). The steep simulated keratometry values were
also all significantly flatter than baseline (p=0.008, p=0.008, and p=0.008; Figure 10).
The Shape Factor was significantly less positive/more negative than baseline at all follow
up visits due to the more oblate shape induced by orthokeratology (p=0.008, p=0.008,
and p=0.008; Figure 11). The spherical aberration zero frequency term $Z_4^0$ from the
COAS was significantly more minus at all three follow up visits (p=0.008, p=0.011, and
p=0.028; Figure 12). This change in spherical aberration also indicates a more oblate
corneal shape. These changes were all expected to occur as a result of successful and maintained orthokeratology treatment. These values can be found in Table 3.

Figure 8: Average central spherical equivalent refractive error (D) as determined by autorefraction. An asterisk indicates a statistically significant change from baseline. Error bars indicate ±SEM.
Figure 9: Average flat Sim K value (D). An asterisk indicates a statistically significant change from baseline. Error bars indicate ±SEM.
Figure 10: The average steep Sim K value (D). An asterisk indicates a statistically significant change from baseline. Error bars indicate ±SEM.
Figure 11: Average shape factor (Q). An asterisk indicates a statistically significant change from baseline. Error bars indicate ±SEM.
To monitor the amount of peripheral myopic defocus induced as a result of the orthokeratology treatment, central and peripheral spherical refractive error performed by autorefration was analyzed. At baseline, central spherical refractive error was $-2.25 \pm 0.95$D. Compared to the spherical refractive error in $30^\circ$ superior, nasal, temporal gazes we can see that nasal ($-1.77 \pm 1.2$D) and temporal ($-1.54 \pm 1.39$D) values are less myopic, while superior ($-2.41 \pm 1.64$D) is slightly more myopic than central. These values are all reported in Table 3. As previously mentioned central spherical equivalent myopia was

Figure 12: Average spherical aberrations (microns). An asterisk indicates a statistically significant change from baseline. Error bars indicate ±SEM.
significantly reduced as compared to baseline in the 1-, 3-, and 6-month visits as an expected result of successful orthokeratology treatment. Looking at the peripheral refractive errors in Table 3 all values at the 1-, 3-, and 6-month follow up visits were as myopic or more myopic than baseline. These were found to be significant for superior retina at the 6 month visit, and nasally at the 1 and 6 month visit (p = 0.021, p = 0.021, and p = 0.021 respectively).

All significant changes from baseline were correlated with the change in central spherical equivalent refractive error (Table 4). Spherical aberration was not, most likely due to sample size of 6 due to some missing data.
<table>
<thead>
<tr>
<th></th>
<th>Central SEQ (D)</th>
<th>Sim K Flat</th>
<th>Sim K Steep</th>
<th>Sph. Aberr.</th>
<th>Shape Factor</th>
<th>RPR Nasal</th>
<th>RPR Temp.</th>
<th>RPR Sup.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central SEQ (D)</td>
<td>1.000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sim K Flat</td>
<td>-0.71* 0.032</td>
<td>1.000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sim K Steep</td>
<td>-0.71* 0.032</td>
<td>0.92* &lt;0.001</td>
<td>1.000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spherical aberration</td>
<td>-0.60 0.21</td>
<td>0.77 0.072</td>
<td>0.81* 0.050</td>
<td>1.000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shape Factor</td>
<td>-0.77* 0.016</td>
<td>0.98* &lt;0.001</td>
<td>0.93* &lt;0.001</td>
<td>0.71 0.11</td>
<td>1.000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RPR Nasal</td>
<td>-0.80* 0.010</td>
<td>0.94* &lt;0.001</td>
<td>0.86* 0.003</td>
<td>0.77 0.072</td>
<td>0.97* 0.000</td>
<td>1.000</td>
<td></td>
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</tr>
<tr>
<td>RPR Temporal</td>
<td>-0.78* 0.013</td>
<td>0.85* 0.003</td>
<td>0.92* &lt;0.001</td>
<td>0.77 0.072</td>
<td>0.90* 0.001</td>
<td>0.88* 0.002</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>RPR Superior</td>
<td>-0.90* 0.001</td>
<td>0.79* 0.012</td>
<td>0.74* 0.024</td>
<td>0.37 0.47</td>
<td>0.87* 0.002</td>
<td>0.90* 0.001</td>
<td>0.82* 0.007</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Table 4: Correlation Matrix. Central Spherical Equivalent (SEQ), Simulated Flat K Value (SimKFlat), Simulated Steep K Value (SimKStp), Spherical Aberration, Shape Factor, Relative Peripheral Refraction (RPR) Nasal, Temporal, and Superior. An asterisk represents statistically significant correlation with p-value below.
Ocular length measurements were taken with an IOLMaster in central and 30º temporal, superior and nasal gazes at each visit to monitor for any ocular growth or changes. The average values are reported in Table 3. There is no general trend in changes of ocular length measurements. The only significant difference was found in nasal gaze at the 1 month visit. At this visit the average nasal ocular length was found to be significantly shorter than baseline (24.39 ± 0.79mm vs. 24.48 ± 0.76mm, p = 0.011). On average no ocular growth was found throughout the study.

Photoshop analysis using a pixel to micron conversion was performed on the Cirrus OCT 5 line raster images in central and 30º temporal, superior, and nasal gazes. An average thickness was found for each image by taking the area of the choroid and dividing it by the chord length of the visible choroid. Table 3 contains all the results of these analyses. There does not appear to be a general trend of change in the average choroidal thickness over time. There are only two statistically different values as compared to baseline. The first is the superior gaze at the 3 month visit, which showed a thinning of 37.13 microns (p = 0.038). The other was also at the 3 month visit in nasal gaze, which showed a thickening of 26.06 microns (p = 0.038). At the 6 month visit this significant change was not repeated. The Lenstar LS 900 biometer was also used to measure subfoveal/central choroidal thickness. The average values are reported in Table 3. No significant change was found using this technique either. A third method using Photoshop to measure a single subfoveal choroidal thickness was also performed to
compare to the Lenstar measurements. The average values are reported in Table 3. This method also did not find any significant changes over time.

A comparison of the results of subfoveal choroidal thickness as determined by Lenstar and Cirrus OCT was performed. Spearman correlation analysis did not result in a significant correlation between the Lenstar and Cirrus OCT data ($r_s = -0.322, p = 0.116$). Spearman correlation analysis was also done comparing Cirrus OCT subfoveal thickness and the number of readable A-scans on the Lenstar. This resulted in an overall trend of negative correlation between OCT subfoveal thickness and the number of readable Lenstar A-scans (Figure 13). Specifically, at the baseline and 1 month visits a significant negative correlation was found (-0.769, $p = 0.015$; and -0.804, $p = 0.009$ respectively). The thicker the choroid by OCT, the lower the number of readable traces from Lenstar. Figure 14 shows a readable P4, similar to Figure 1, while Figure 15 does not have a readable P4.
Figure 13: Number (n) of valid Lenstar readings vs. OCT subfoveal thickness. This trend was statistically significant at the baseline and 1 month visits (-0.769, p = 0.015; and -0.804, p = 0.009 respectively).
Figure 14: Example of "Good" Lenstar reading from IMPACT.

Figure 15: Example of “Bad” Lenstar reading from IMPACT.
Experiments in several animal species have shown that myopic defocus can slow the axial growth of the eye (Howlett et al., 2009; Smith et al., 2009; Wildsoet et al., 1995). Wildsoet et al. showed that the ability of chicks to respond to myopic defocus occurred largely by a choroidal response (Wildsoet et al., 1995). Another study done on guinea pigs demonstrated a similar choroidal thickening response to myopic defocus (Howlett et al., 2009). Smith has shown in monkeys that only peripheral exposure to myopic defocus is required to inhibit axial elongation (Smith et al., 2009). Overnight orthokeratology or center near soft bifocal contact lenses are clinical methods for supplying peripheral myopic defocus in children. A number of studies have used orthokeratology or dual-focus soft contact lenses to induce peripheral myopic defocus in myopic children in an attempt to slow myopia progression and found some success (Anstice et al., 2011; Cho et al., 2012; Cho et al., 2005; Hiraoka et al., 2012; Walline et al., 2009). The exposure to peripheral myopia may not have to be chronic to induce choroidal responses. A study done by Read et al. was able to demonstrate measureable axial length changes in response to two 30-minute sessions of either induced hyperopic or myopic defocus (Read et al., 2010). A significant increase in axial length (+8 ± 14 microns; p = 0.03) was found after hyperopic defocus was induced, while a significant
decrease in axial length (-13 ± 14 microns; p = 0.0001) was found after myopic defocus was induced. Interestingly they reported a statistically significant amount of choroidal thickening in the myopic defocus condition (+12 ± 16 microns; p = 0.004). This is approximately equal and opposite to the axial length change (Read et al., 2010). Though slight, this choroidal response, if applied to continuous defocus over a longer time period, such as 6 months to years, may compound and result in the differences in axial length of 100 microns or more previously reported by human peripheral myopic defocus studies.

The purpose of the current study was to determine whether this choroidal expansion occurred in children after chronic exposure to peripheral myopic defocus from overnight orthokeratology.

**Orthokeratology**

All subjects responded to the orthokeratology treatment well, with acceptable acuity and physiologic response to overnight wear. By the 1 month visit 8/9 subjects were at better than 20/25+ Snellen visual acuity during the day; the remaining subject was 20/30+ or better. This level of acuity along with the OD spherical equivalent central autorefraction results averaging near plano showed an effective visual correction by the 1 month study visit. These visual outcomes were well maintained throughout the study. In Table 3, the average OD central autorefraction results held relatively steady near plano for all remaining visits. Also of note, the ocular health remained stable as well. Specifically looking at bulbar injection, corneal epithelial staining, and palpebral papillary reaction, all levels stayed below the Efron grading of trace and did not become
clinically significant, except for one adverse event from a solution reaction to a misused cleaning solution during the fitting process.

To determine if peripheral myopic defocus occurred, peripheral autorefraction in 30° temporal, superior, and nasal gazes were taken at each study visit. The average findings at each visit are reported in Table 3. As previously stated, baseline central spherical refractive error was -2.25 ± 0.95 D, while nasal (-1.77 ± 1.2D) and temporal (-1.54 ± 1.39D) values were less myopic, and superior (-2.41 ± 1.64D) was slightly more myopic than central. Therefore peripheral refractive error was largely less myopic than central refractive error, except for in the superior region, which are all typical in the myopic eye (Atchison, Pritchard and Schmid, 2006). With traditional refractive correction, a mostly peripheral hyperopic defocus would be induced (Tabernero, Vazquez, Seidemann, Uttenweiler and Schaeffel, 2009). After orthokeratology treatment was well established, central refractive error approached plano, while the peripheral refractive error at the very least stayed myopic. The results show all peripheral measurements became even more myopic than at baseline. In some instances these were found to be statistically significant, such as superior gaze at the 6 month visit, and nasally at the 1 and 6 month visit (p = 0.021, p = 0.021, and p = 0.021 respectively). In a related finding, the spherical aberration term from COAS measurement showed an increasing level of positive spherical aberration. These results demonstrate that the orthokeratology treatment effectively induced peripheral myopic defocus.
Ocular Length

IOLMaster was used to monitor axial length in all these same gazes. Table 3 shows the average values at each study visit. No ocular growth was found throughout the length of the study. This is interesting to note because in a sample of myopic children some ocular growth would have been expected. The typical rate of myopic progression in children is about 0.50D per year, or about 90 microns of axial elongation in 6 months. This amount is about double the 95% limits of agreement between occasions for the IOLMaster and Lenstar (Chan, Cho and Cheung, 2006; Schulle and Berntsen, 2013; Sheng, Bottjer and Bullimore, 2004). Similar to the statistical power to detect that level of change in choroidal thickness, the sample size of 9 should have power of 0.80 at $\alpha = 0.05$ to detect a change in ocular length of $\pm 25$ microns. According to Munnerlyn’s Formula with a treatment zone of 4 mm, the effect on axial length would be 5.33 microns per diopter. Therefore the effect would be a minimum of 5.33 microns to 21.32 microns with our spherical refractive error criteria of -1.00 D to -4.00 D. This effect would not be enough to cause an axial length growth of 90 microns to be missed. The lack of control group does not allow for a direct comparison or conclusions about whether CRT slowed myopic progression. However, speculation that ocular growth was slowed by the CRT treatment would be consistent with results as found in similar peripheral myopic defocus investigations.

Choroidal Thickness

This leads to the study’s main question of whether the human choroid is able to respond to this myopic defocus by thickening and bringing the retina closer to the image.
Therefore any true ocular growth would be partially masked by this change in choroidal thickness. Again this was monitored in three ways. The first technique was using Photoshop to analyze OCT images and obtain an average choroidal thickness in each gaze. The second was a central measurement by manual analysis of Lenstar LS 900 biometer A-scan results similar to Read et al (Read et al., 2010). The third was to use Photoshop with OCT central images to take subfoveal measurement to allow for comparison with the Lenstar results.

Looking at the results of all choroidal thickness measurements reported in Table 3 no general trend is apparent. None of three methods for measurement resulted in a significant thickening or thinning. Therefore the hypothesis of the study, that peripheral myopic defocus would thicken the choroid, either locally in the periphery or at the fovea, was not confirmed.

Cirrus OCT vs. Lenstar LS 900

No correlation was found between the results of the Lenstar and OCT subfoveal measures. Not every A-scan produced by the Lenstar was able to be analyzed for choroidal thickness. The study done by Read also had some difficulty and reported more variability with choroidal measurements than with axial length measurements (Read et al., 2010). The primary investigator of IMPACT noted that with some subjects, the Lenstar produced more readable A-scans than others. See Figure 13 for an example of “Good” Lenstar results, and Figure 14 for an example of “Bad” Lenstar results. Compare these to Figure 1 which shows the example in the Read paper. A closer look at the data suggests that the Lenstar may struggle to obtain strong choroidal signals with thicker
choroids. Spearman analysis resulted in a general negative trend as shown in Figure 12 between readable A-scans and subfoveal choroidal thickness as determined by OCT analysis. This trend was statistically significant at the baseline and 1 month visits (-0.769, \( p = 0.015 \); and -0.804, \( p = 0.009 \) respectively). This brings into question the ability of the Lenstar LS 900 biometer to accurately obtain choroidal thickness measures.

Limitations

A few limitations were identified by the investigators. Obviously the study has a relatively small sample size with only 9 subjects. This limited the range of \( p \) values and therefore correction for multiple comparisons was not performed. However, all significant changes from baseline were expected and consistent with effective central corneal flattening during orthokeratology. The sample size calculation as described in the methods section determined that only 1 subject was necessary to find the expected result. Another limitation could be the age range. The age range of the sample was only 11-15 years. This range is on the upper end of the time period of when refractive progression and ocular growth occur for myopes. A younger age group may have had different results. The study was largely designed around the findings of the Read experiment, which used all young adults, so the choroidal response should have still been present in the 11-15 year old age range. It was determined that the baseline values of the subjects’ right eye would suffice as the control for comparison of the choroidal thickness. This is sufficient for the main purpose of investigating choroidal response to myopic defocus. However the lack of a control group did not allow for analysis of any slowed ocular length growth as in previous myopic defocus studies.
Further Directions

Based upon the results of the study, a few further investigations are warranted. First, the Lenstar was not found to be a very accurate method to measure choroidal thickness; this brings in question the results of the Read study investigating ocular length as a response to defocus. It would be interesting to perform a similar study except using OCT analysis to measure the choroid instead of the Lenstar. Actually, a recent study from the Read laboratory using OCT analysis of the choroid has shown changes to the circadian patterns for choroidal thickness after wearing monocular +1.50D lenses (Chakraborty et al., 2012). More importantly the current study was able to successfully monitor choroidal thickness by OCT analysis. This is a quick, non-invasive, and relatively simple technique. Therefore, it is important for all future investigations of ocular growth to include a choroidal measurement to monitor for any confounding responses of the choroid. This study demonstrated the ease and accuracy of obtaining these measures.


