OPTOM570: The Effects of dual focus MiSight contact lenses on Choroidal Thickness

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Bachelor of Optometry, Part IV

Year 2014

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Short title:	MiSight and Choroidal Thickness
Text word count:	4459
Tables:	0
Figures	4
Keywords	Dual focus, contact lens, choroidal thickness

Abstract

Purpose: To investigate the effects of dual focus MiSight soft contact lenses on the human choroidal thickness.
Participants: Nine young adults, 18-24 years old, with spherical equivalent refraction ranging from -0.75 dioptres to -4.25 dioptres (D).
Methods: Dual focus soft contact lenses which have a central correction zone surrounded by concentric treatment zones that induce a 2D myopic retinal defocus were used for distant viewing in the test eye. The control eye had a spherical single vision soft contact lens which provided best spherical correction for distant viewing. Participants wore the dual focus soft contact lenses in the right eye and the single vision soft contact lenses in the left eye while viewing a video at 6m for 60 minutes. Choroidal thickness in both eyes was measured at 20 minutes intervals.
Results: Comparison between the test and the control eyes revealed a statistically significant increase in choroidal thickness after 60 minutes (P=0.016). The absolute choroidal thickness change in the test eye induced by the dual focus soft contact lens has also been found to be statistically significant (P=0.027) with an average increase of 13.50μm after 60 minutes. Absolute choroidal thickness change in the left eye was found not to be statistically significant (P=0.26).
Conclusions: Dual focus contact lenses provide normal visual acuity while simultaneously creating retinal defocus. This data suggests that dual focus contact lenses can induce an increase in choroidal thickness in response to the imposed myopic retinal defocus without compromising visual function.

Introduction

The choroid is an organised and complex structure that has been intensively studied in the last few decades. One of the most well-known characteristics of the choroid is that it is highly vascularised and it has the highest rate of blood flow when compared to all the other tissues in the human body[1]. This is possible due to the intricate vasculature design within the choroid also known as the choriocapillaris - a dense capillary bed responsible for nourishing the posterior segment of the eye with oxygen and nutrients[2]. While the majority of the choroid consists of its vasculature; melanocytes, fibroblasts, intrinsic choroidal neurons and supporting connective tissues are also present and each of these components contribute towards the overall functioning of the choroid[1,3]. Other functions of the choroid include light absorption with melanocytes, heat dissipation, thermoregulation and modulation of intraocular pressure by facilitating the drainage of aqueous humour[1].

The dynamics of choroidal thickness has been broadly investigated via the process of emmetropisation, where different components of the eyes develop concurrently such that the axial length is approximate to the focal length of the eye[4]. It has been shown in both avian and primate models that positive lenses (creating a myopic defocus) and negative lenses (which create a hyperopic defocus) will create a predictable change in eye growth. A consensus exists between studies that a myopic defocus (the focal plane in front of the retina) causes a significant amount of choroidal thickening while a hyperopic defocus will result in the thinning of the choroid. This change in choroidal thickness precedes the scleral mediated changes in eye size in response to defocus[5,6]. These results have been proven to be applicable to the human choroid as the responses to retinal defocus induced by lenses are similar[6,7]. Read et al concluded that a central foveal myopic or hyperopic defocus induced by spherical lenses have a significant effect on the choroidal thickness[6]. In another study by Chakraborty et al, it was proposed that the change in axial length of the eye is closely associated with the change in choroidal thickness and that the two entities work together to control the process of emmetropisation[7].

All of the functional elements found in the choroid work together to maintain the homeostasis within the retina, however, when the choroid is affected by various diseases; the function of the retina will also be compromised. Ünsal et al concluded that there is a significant decrease in the thickness of choroids which are affected by proliferative diabetic retinopathy and diabetic macular oedema as supported by a similar study done by Adhi et al[8,9]. It is also noted that patients with diabetic retinopathy will develop areas of non-perfusion secondary to diabetic choroidopathy along with other retinal signs such as micro aneurysms and vessel tortuosity[9,10]. This indicates that the change in choroidal function thus a change in choroidal thickness could be used as a future marker to monitor the progression of the disease[8,10]. Another common retinal disorder that adversely impacts the choroid is glaucoma which is defined as a multifactorial disease marked by the progressive loss of the nerve fibre layer. Evidence also suggests that there is a change in the choroidal blood flow

over the duration of the disease. Siesky et al mentioned that Indocyanine green angiography has been used in patients with glaucoma to demonstrate a reduction in the rate of choroidal filling and the sluggish movement of blood into and out of the choroid[11]. However, it is unclear whether the disruption in blood flow would cause a change in the choroidal thickness in glaucoma patients as a recent review done by Banitt have gathered that there are inconsistent findings regarding this – he has found that in six publications, the authors stated there was no significant difference in choroidal thicknesses between glaucoma patients and normal subjects but three other publications have determined that the choroid in the peripapillary region was thinner in glaucoma patients[12]. Age Related Macular Degeneration (ARMD) is the leading cause of blindness in people over 50 years old in industrialized areas. There are two main theories behind the pathogenesis of ARMD; the first one attributes the cause of dysfunction in photoreceptors to be a result of atrophy in the retinal pigmented epithelium (RPE) while the other theory attributes this insult to choroidal vascular insufficiency[13]. McLeod et al concluded that dry ARMD is mainly due to atrophy in the RPE which could be secondary to the degeneration of choriocapillaris. On the other hand, in wet ARMD there was a definite drop out of choriocapillaris with or without atrophy in the RPE[13]. Interestingly, another study by Woods et al which looked at the relationship between ARMD and choroidal thickness have found that there was a reduction in retinal thickness but choroidal thickness remains unaffected and this finding was also supported by a study done by Manjunath et al[13,14].

Although there is a consensual agreement in the change in choroidal thickness observed in human participants, the exact mechanism of how this occurs remains unknown. One of the proposed mechanisms involves changes in tonus of non-vascular smooth muscle based on how quickly choroidal thickness changes in chick models. This led to reasons to believe that it is actually the contraction of these smooth muscles that is responsible for the thickening and thinning of the choroid and not by osmotic means which is another popular proposition[3,6]. Changes in the synthesis of osmotically active molecules will change the tonicity of the choroid which could also be the mechanism behind choroidal expansion as water is most commonly moved when osmotically active molecules are moved. This is supported by the fact that choroids undergoing recovery from myopic defocus synthesize a much larger amount of proteoglycans than normal choroids. The proteoglycans produced are highly sulphated and anionic thus they are extremely hydrophilic which is why they function as sponges in the extracellular matrix – attracting water into the choroid and ultimately increasing choroidal thickness[3]. Another intriguing theory suggests that the change in choroidal profile is due to the shift in vascular permeability. An influx of fluid from choroidal vasculature resulting from an increase in vascular permeability causes proteins to migrate into the extracellular matrix which is quickly followed by passive fluid flow into the choroid. This is reinforced by various studies where the components within the suprachoroidal fluid is measured and it was found that in thickened choroids, there was a thirty percent increase in protein content when compared to baseline and in

experimentally thinned choroids, less protein constituents were found[3]. Moreover, in an investigation involving the injection of large fluorescein molecules into the choroid; a bigger amount was found in thickened choroids than in form deprived (thus thinner) or normal choroids – again emphasizing the idea of increased vascular permeability behind the thickening of the choroid[3]. Jung et al suggest that the underlying mechanism could be a combination of autoregulation of blood flow (via a neuronal component within the choroid) and the shifting of fluid and molecules between the plasma and the choroidal extracellular matrix. Their study aimed to investigate the changes in subfoveal choroidal thickness before and after haemodialysis, a procedure commonly used to control the volume and composition of body fluid via the removal of water and uraemic substances. The consequences of haemodialysis include decreased blood pressure, reduced serum osmolarity and decreased plasma volume. The choroidal thickness is changed firstly due to a drop in the blood pressure which causes the autoregulatory system of the choroid to initiate parasympathetic vasodilation. This consequently results in the increase in choroidal thickness due to the larger diameters of the choroidal blood vessels and also because of an increased influx of osmotic molecules thus ultimately attracting water[15]. Interestingly, a study that was conducted recently examined the effects of sildenafil citrate (which is more commonly known as Viagra) on choroidal thickness. Sildenafil citrate acts as a potent vasodilator by inhibiting PDE-5 which is present in all vascular tissues and it also enhances the action of Nitric Oxide which ultimately increases the relaxant effects on smooth muscle cells. Kim et al have identified in their study that both choroidal thickness and perfusion increase in response to systemic sildenafil which demonstrates the hypothesis revolving around the change in choroidal blood flow[16,17]. However, there are also contradicting findings regarding this theory; recent research involving the change in systemic systolic blood pressure after cardiac exercises have failed to demonstrate that a change in blood pressure results in the change in choroidal thickness[18]. Although the current trend of thought concerning the alteration in choroidal thickness is gravitating towards the blood flow hypothesis, much more research will need to be conducted to fill in this gap in knowledge.

Traditionally with various imaging modalities such as ultrasonography and Indocyanine green angiography, it has not been possible to obtain the full appreciation of choroidal structures. However, with the relatively recent emergence of optical coherence tomography (OCT), better visualisation of the choroidal anatomy became achievable[19]. The two most commonly used prototypes commercially available are the time domain optical coherence tomographers (TDOCT) and the more advanced spectral domain optical coherence tomographers (SDOCT). TDOCTs are generally slower in image acquisition in comparison to SDOCTs and the reason being the need to constantly change its reference arm length within the interferometer to match the tissue length that's being scanned. In this scenario, it is often a trade-off between resolution and the time needed for the scan. On the other hand, SDOCTs do not require the mechanical scanning of the reference arm. Instead, a detection

arm within the interferometer is used and directly converts the length of the tissue into depth information via Fourier transformation[20]. This also means that SDOCTs are able to provide both high speed and high resolution ophthalmic imaging. Another type of OCT exists in the name of spectral domain optical Doppler tomographer (SDODT). Using methods similar to the Doppler ultrasound, SDODT allows real-time imaging of blood flow within vessels as small as 10μm even within the choroid[20]. This has the potential in aiding with the investigation of certain mechanisms of the choroid such as choroidal blood flow and the change in choroidal thickness.

Although Read[6] and Chakraborty[7] have demonstrated changes in human choroidal thickness with the use of various plastic lenses, very few studies exist which have explored the effects of dual focus contact lens induced defocus on the choroid. This study aims to investigate the effects of MiSight contact lenses (a dual focus contact lens designed to reduce the rate of myopia progression) on the thickness of the human choroid.

Methods and Materials

Participants

Nine young adults aged between 18 – 23 years old were recruited into the study in total. They were all self-identified Eastern Asians and of those, 4 were male and 5 were female. Prior to the study, they were required to have undergone a comprehensive eye examination in the past year to ensure no significant pathologies or binocular vision problems that could alter choroidal thickness. They all achieved a best corrected Snellen visual acuity of no less than 6/6 and their spherical equivalent refractions were between -0.75D to -4.25D. All of the participants were habitual contact lens wearers to avoid discomfort or the need to adapt to contact lenses which could affect the final results. Anyone with astigmatism higher than -0.75DC in either eye were excluded as we have chosen to use spherical contact lenses only and any significant amount of astigmatism could cause unwanted accommodative efforts thus altering the final outcome.

As all of the participants were myopes who were similar in age and from the same ethnic region, no stratification was needed to isolate certain factors having an effect on the change in choroidal thickness. All of the participants were regarded as one group.

Approval from the University of Auckland Human Participants Ethics Committee was obtained, and all subjects gave written informed consent. All subjects were treated in accordance with the Declaration of Helsinki.

Testing Conditions and Materials

A room with adjustable lighting conditions was chosen and the lumination of the room was kept at approximately 10lux as bright light conditions might have a thickening effect on the choroid[21]. The room lumination was measured using a lux metre (TES Digital Light Meter TES-1335). Participants were seated 6 meters away from a white screen at the end of the room and were required to watch a video (Tangled, The Walt Disney Company, California, USA) which was projected onto the white screen by a projector. The distance between the screen and the participants was measured using a laser distance meter and they were positioned immediately next to the SDOCT (RS-3000 Advance, Nidek, Japan) to ensure timely measurements.

Contact Lenses

The MiSight daily contact lenses (Coopervision, The Cooper Company, California, USA) are dual-focus soft contact lenses. They were designed with a central correction zone surrounded by a series of treatment and correction zones. These zones fall within the confines of the pupil in order to simultaneously achieve good acuity with the correction zones and a 2.00D myopic retinal defocus with the treatment zones[22].

The other type of contact lenses used in this study was the 1-Day Acuvue TruEye soft contact lenses (Johnson & Johnson, New Jersey, USA). These are single vision contact lenses and they do not purposely stimulate retinal defocus.

Procedures

Based on the participants' habitual contact lens prescriptions, a MiSight daily contact lens was fitted onto their right eyes and a 1-Day Acuve TruEye contact lens was fitted onto their left eyes. The procedures of monocular over refraction followed by binocular balancing were then carried out to ensure a best corrected Snellen visual acuity of at least 6/6 and that their accommodative states were balanced with each respective contact lens in place.

Participants were then instructed to remove the fitted contact lenses and put on their habitual corrections. An over refraction and binocular balancing test was performed on each participant with their habitual corrections to ensure appropriate refractive and accommodative statuses.

The participants were seated 6 metres from the screen on which the video was projected. Given that tasks such as accommodation and exercise could cause a transient increase in choroidal thickness, they were instructed to concentrate on the video for 20 minutes with their habitual corrections which served as the stabilisation period for it is known that the human choroid takes approximately 20 minutes to achieve a significant amount of change in thickness while adapting to any changes in accommodative demands[7,23]. The purpose of this

stabilisation period was to relax the participants' accommodative systems in order to normalise any possible accommodative effects to the choroid prior to the experiment.

After the stabilisation period, participants were instructed to promptly insert the previously fitted contact lenses into their respective eyes. An OCT scan set to the Macula Line HD, Choroidal Mode was performed on each eye and this serves as the baseline choroidal thickness measurement at time zero for each participant. Subsequent OCT images of the choroid for both eyes were captured at 20 minutes, 40 minutes and 60 minutes after the baseline images in the presence of a retinal defocus for the right eye and no defocus for the left eye.

All of the data collection occurred at the same time of day during the different days to eliminate the known effects of diurnal variation of the human choroid[7].

Participants were monitored throughout the whole experiment to ensure diligent concentration and to prevent any accommodative activities which could affect the choroidal thickness.

Data Analysis

A total of 8 choroidal OCT images were obtained from each participant, summing up to 72 OCT images which were exported from the OCT. These images were then imported onto ImageJ (National Institutes of Health, Maryland, USA) which is an image processing programme. As shown in figure 1, the multipoint tool was selected on ImageJ and the subfoveal posterior edge of the retinal pigmented epithelium was marked as point 1 whereas the inner boundary of the choroid-sclera interface was marked as point 2. These points were unanimously agreed by 3 observers, 1 of which was a blinded observer as they were not aware of the sequencing of the images. A previous study utilising the same model and manufacture of OCT have defined the scale between one pixel and choroidal thickness in micrometre to be 1 to 4.39256 μm. This conversion factor was used in ImageJ, allowing the exported data to be in the micrometre scale[23].

These sets of data were then exported from ImageJ onto Excel (Microsoft Corp., Washington, USA). The absolute change in choroidal thickness compared to baseline was found for each participant at each time mark for both the right and left eye. These results were analysed with a paired 2 tailed t-test using the Excel programme to investigate whether there was any significant difference in the alteration in choroidal thicknesses between the two eyes with their respective baseline measurements. The absolute change in choroidal thicknesses were also averaged between the 9 participants for each eye and graphed to obtain a visual trend of the outcomes. A paired 2 tailed t-test was completed for this series of results for the evaluation of statistical significance.

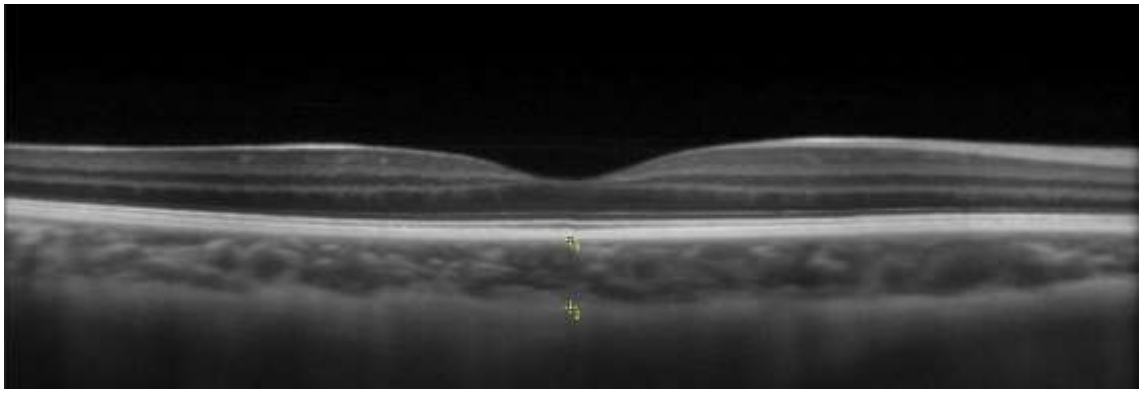

Fig 1. Exported OCT image showing an image of a participant's choroid. Point 1 is defined as the subfoveal posterior border of the retinal pigmented epithelium while point 2 is defined as the inner boundary of the choroid-sclera interface. The displacement between the two points represents the choroidal thickness.

Results

Comparison between the Right and Left eyes

An average of the absolute changes in choroidal thickness was calculated for each eye at each time point across the 9 participants. At 20mintues, there was an average increase in choroidal thickness of 7.69µm ± 7.79µm in the right eye and an average decrease in choroidal thickness of 0.34µm ± 7.30µm in the left eye. An increase of 9.42µm ± 4.51µm and an increase of 1.94µm ± 7.96µm were found at 40 minutes for the right and left eyes respectively. At 60 minutes, the choroids continued to thicken for both eyes where the right eyes averaged a 13.50µm ± 6.89µm increase and the left eyes averaged a 2.35µm ± 4.65µm increase in thickness.

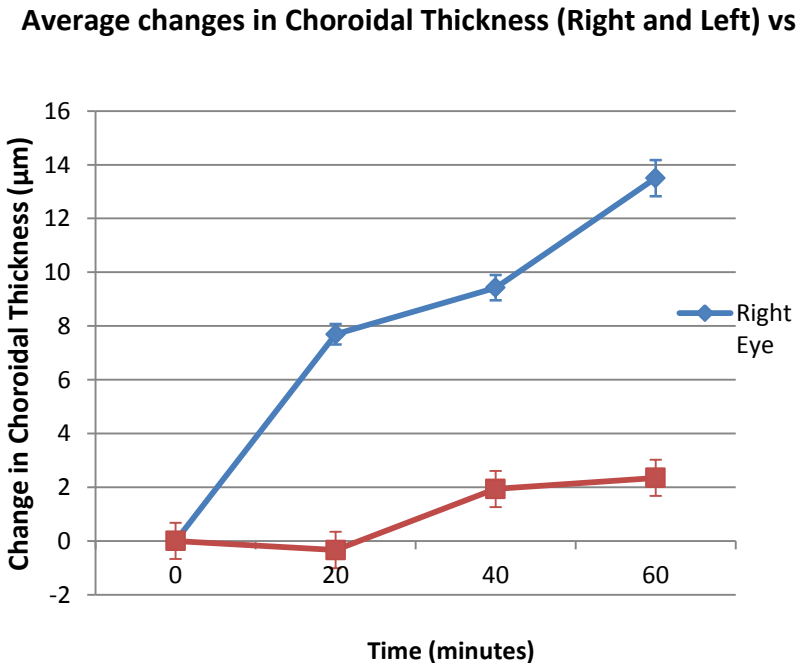

Fig. 2 Graph showing the mean changes in choroidal thicknesses (microns) over 60 mintues. *Filled diamonds* represent all the averaged values from the right eyes wearing the MiSight contact lenses. *Filled squares* represent all the averaged values from the left eyes which were fitted with TruEye contact lenses.

For the right eye, the slope of linear regression (4.22, R^2=0.93, Fig 2) suggests that there is an average increase of 4.22μm in choroidal thickness every 20 minutes whereas the slope of linear regression (0.93, R^2=0.79, Fig 1) in the left eye proposes a noticeably less average increase in choroidal thickness of 0.93μm every 20 minutes.

A 2-tailed t-test for means was performed and the difference in the change in choroidal thickness between the right and left eye was statistically significant (p=0.016). In other words, there is a statistically significant difference in the alteration in choroidal thicknesses between the MiSight contact lens and the TruEye contact lens.

Choroidal Thickness change for the Right Eye

The absolute change in choroidal thickness in each participant was obtained by calculating the difference between the choroidal thickness at each time point and the choroidal thickness at baseline which was defined immediately after the stabilisation period. At 20 minutes, there was a change in choroidal thickness ranging from a 9.64μm decrease in thickness to a rapid 17.88μm increase in thickness. At 40 minutes, the range was a 5.06μm to 16.70μm increase in thickness whereas at 60 minutes, the range was a 7.67μm to 21.38μm increase in choroidal thickness.

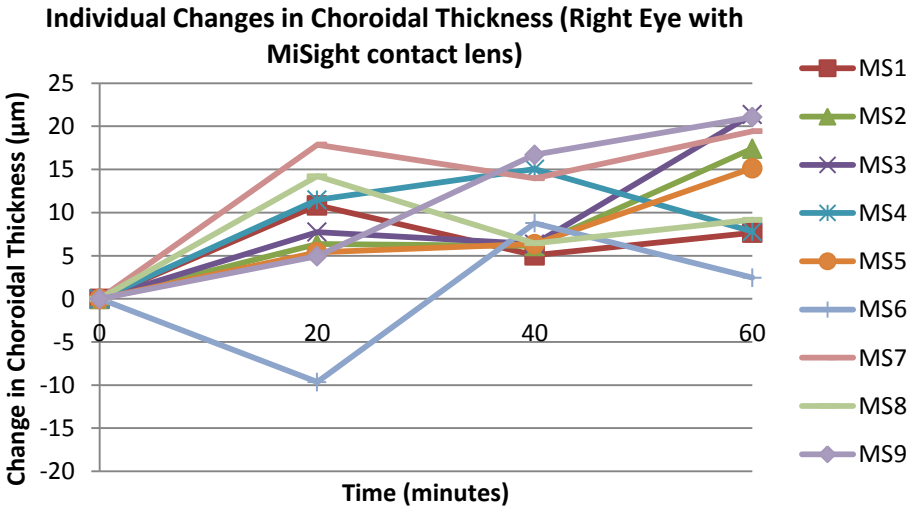

Fig. 3 A graph displaying the individual changes in choroidal thicknesses in the right eye wearing the MiSight contact lens. "MS" denotes MiSight and the numerical that follows after "MS" denotes the participant number.

Figure 3 illustrates the overall positive trend of the effect of MiSight contact lens on choroidal thickness. A paired, 2-tailed t-test was performed comparing the absolute difference in choroidal thickness at baseline (which was 0) and the mean absolute change in choroidal thickness obtained at 20, 40 and 60 minutes. From this analysis, it was found that

the increase in choroidal thickness with the MiSight contact lenses is statistically significant (p=0.027).

Choroidal Thickness change for the Left Eye

At 20 minutes, the participants responded variably with one participant achieving an increase in choroidal thickness of 11.15μm to another participant's choroidal thickness dropping by 8.24μm. This variability is again observed at 40 minutes where the change in choroidal thickness ranged from an increase of 11.85μm to a decrease in 15.25μm. However, at 60 minutes, the set of data seems to have stabilized yielding a range of 8.87μm increase to a 3.59μm decrease in choroidal thickness.

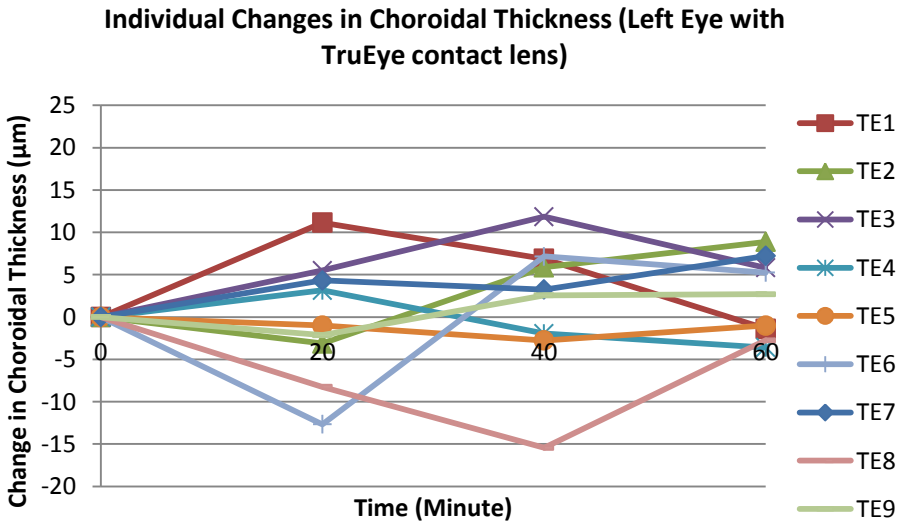

Fig 4. A graph displaying the individual changes in choroidal thicknesses in the left eye wearing the TruEye contact lens. "TE" denotes TruEye and the numerical that follows after "TE" denotes the participant number.

Figure 4 illustrates the lack of an obvious positive or negative trend when measuring the absolute change in choroidal thickness over time. A 2-tailed t-test was also performed for this data and the results suggest that the change in choroidal thickness is statistically insignificant with Acuvue TruEye contact lenses (p=0.26).

Discussion

The results from this study have shown that dual focus MiSight contact lenses can alter the thickness of the human choroid significantly when compared to the control eyes which did not experience any retinal defocus as they were best corrected with spherical contact lenses. The changes that were observed following 60 minutes of defocus followed a positive trend, where significant increase in choroidal thickness was seen. Although the changes in choroidal thickness were small in magnitude, the results were indeed statistically significant

and consistent with the current understanding of defocus induced choroidal thickness changes in humans.

MiSight contact lenses were designed with the incorporation of two treatment zones to achieve a two dioptres myopic retinal defocus while still providing good central correction. A myopic retinal defocus will result in the perception of a blurred image as the image plane no longer coincides with the retinal plane. There had been a number of studies carried out using chicks and primates models and the results have been largely consistent where ocular changes occur in a predictable manner as the retinal plane moves anteriorly to compensate for any myopic defocus and it moves posteriorly to compensate for hyperopic defocus. It has been found that the choroid and the sclera both play an important part in the movement of the retinal plane but recent studies suggest that the action of the choroid precedes that of the sclera[1]. Our study which involved short term exposure of retinal image defocus produced findings that are agreeable to the current trend of thoughts where the choroid quickly responded to a myopic defocus by increasing its thickness.

The results from this study indicated an average increase of 13.50μm in choroidal thickness across all of the participants which is considered to be small when compared against other studies previously performed on animal models. Kee et al and Zhu et al both underwent investigations concerning the effects of lens induced defocus on chick choroids. Kee et al have found that there was a rapid and significant decrease in choroidal thickness by approximately 60μm within 60 minutes of 15D hyperopic defocus[24]. Similarly, Zhu et al achieved similar results with an average 89μm increase in choroidal thickness for chicks which experienced a 10D myopic defocus for 60 minutes[25]. One of the reasons for this variability in the magnitude of choroidal thickness change could simply be because of the difference in the abilities for the choroid to alter its thickness between species[7]. The intensity and the duration of the defocus could have also potentially played a role in this variability. Moreover, the fact that most of these studies have chosen to use animals which were still infants may contribute towards the difference as it is at this stage unknown whether age is a factor in facilitating the change in choroidal thickness in humans[7].

Chakraborty et al recently undertook an investigation on the effects of prolonged retinal defocus on the human choroid. The study involved thirteen young adults who were induced with a 12 hours monocular myopic defocus caused by a +1.5D lens, causing their choroidal thicknesses to increase by an average of 14μm after 3 hours[7]. This amount of change in choroidal thickness is highly consistent to our finding of an average increase of 13.5μm with a 2D myopic defocus after 60 minutes.

A recent study carried out by Chiang et al looked at the changes in human choroidal thickness caused by retinal defocus which had been induced by spherical soft contact lenses[23]. After 60 minutes of 2D myopic monocular defocus, the myopic group showed an

average increase of approximately 15μm in choroidal thickness – again, very similar to the results obtained in this study.

Limitations in this Study

Accommodation was not actively controlled in this study as a distance of 6m can be regarded as infinity and the effects of accommodation should be negligible. Monocular over refraction and binocular balancing performed after the fitting of the contact lenses should have also eliminated the chances of an accommodative element potentially affecting the results of this study. One weakness of this study could therefore be the small chance of an accommodative component altering the final outcomes of the results.

Another limitation in this study would be the fact that the exact mechanism of the alteration of choroidal thickness is still unknown thus preventing us from gaining further insight of how the MiSight contact lens affects choroidal thickness. The relatively small sample size in our study could also mean that our results may not be completely representative of the general population.

Conclusion

The results obtained from this study will aid in the understanding of emmetropisation and the mechanism behind the dynamics of the choroidal profile. Furthermore, the results suggest that choroidal thickness increases with the use of MiSight contact lenses thus the usage of this lens could potentially have a much greater implication than myopic control. Since the thickening of the choroid could be attributed to an increase in choroidal blood flow, it could be possible that dual focus soft contact lenses will have a future role in slowing down the progression of certain retinal diseases of ischemic nature such as diabetic retinopathy[8,9], glaucoma[11,12] and age related macular degeneration[13,14]. Further studies will need to be done to pinpoint the exact mechanism of choroidal thickening due to retinal defocus in hope that a novel therapy will emerge which will slow down the progression of aforementioned retinal diseases while simultaneously providing good distant vision for everyday use.

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