

Short-Term Effect of Diffusion Optics Technology™ (DOT)
Contrast Management Spectacle Lenses on Ocular Biometrics
and Lag of Accommodation in Emmetropic Children

by

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Author's Declaration

This thesis consists of material all of which I authored or co-authored: see Statement of Contributions included in the thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Statement of Contributions

Asiya Jabeen was the sole author for Chapters 1 to 6, which were written under the supervision of Dr. Lyndon Jones and were not written for publication.

This thesis consists of one manuscript written for publication. Exceptions to sole authorship of material are as follows:

Research presented in Chapter 7:

This research was conducted at the University of Waterloo by Asiya Jabeen under the supervision of Dr. Lyndon Jones. Dr. Lyndon Jones, Dr. Doerte Luensmann, Asiya Jabeen, Jill Woods, and Jennifer Hill contributed to the study design. Asiya Jabeen was responsible for participant recruitment. Dr. Doerte Luensmann, Asiya Jabeen, and Jennifer Hill participated in the statistical analysis. Asiya Jabeen wrote the draft manuscript, to which all co-authors provided intellectual input.

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As lead author of Chapter 7, I contributed to conceptualizing the study design, conducting data collection and analysis, and drafting and submitting manuscripts. My coauthors provided guidance during each step of the research and feedback on draft manuscripts.

Abstract

Purpose:

Myopia, a prevalent refractive error of the eye, is experiencing a rapid increase in prevalence. According to Holden et al., approximately 50% of the global population is projected to be myopic by the year 2050. In response to this growing concern, various myopia control treatments have been developed, including spectacles, contact lenses, and pharmaceutical options. One innovative treatment is the use of Diffusion Optics Technology™ (DOT) spectacle lenses. These lenses are designed to modulate retinal contrast, thereby reducing signals for axial elongation. The lenses incorporate thousands of microscopic dots to manage contrast, which helps reduce signal disparities between adjacent cones while maintaining good visual acuity and functional peripheral vision. However, there is a lack of published literature on the generalized effects of these contrast management spectacles (CMS) on ocular structures over a short period of wear. This thesis aimed to address this gap and determine the short-term effect of CMS on ocular structures and lag of accommodation. Additionally, the thesis also examined the repeatability of various methods of measurement of choroidal thickness.

Methods and Materials:

Chapters 3, 4, 5, 6: This study was a two-visit, prospective, randomized, controlled, participant-masked trial involving 30 emmetropic participants aged 8 to 14. The participants' eligibility was confirmed during a screening visit, which utilized non-

cycloplegic auto-refraction to ensure that the spherical equivalent was between +1.00D and -0.75D, with astigmatism not exceeding -0.75DC.

During the first study visit, ocular biometrics were assessed using the IOL Master and a Topcon DRI OCT for baseline measurements. The parameters measured included central corneal thickness (CCT), anterior chamber depth (ACD), crystalline lens thickness (LT), retinal thickness, choroidal thickness, choroidal vascularity index (CVI), and axial length (AL). After these measurements, participants were randomly assigned to wear either CMS spectacles with a 0.2 DOT pattern that covered the entire lens surface or clear +3.00D control spectacles (which acted as a positive control to induce myopic defocus). While wearing the spectacles, participants watched an age-appropriate video for 60 minutes. After 30 minutes and again after 60 minutes of viewing, the IOL Master and OCT examinations were repeated. On the second visit, participants wore spectacles that they had not used during the first visit, and the same measurements were repeated. Subsequently, the baseline OCT scans from both visits were exported, and sub-foveal choroidal thickness was measured using four different methods to evaluate the repeatability between methods. The most reliable measurement method was then used for further analysis.

Chapter 7: This was a single-visit, prospective, randomized, subject-masked study. Participants were eligible if they had $\pm 1.00D$ mean sphere prescription or less and they had no history of previous myopia control treatment. The logMAR visual acuity was measured, and ocular dominance was tested using the sighting method. Participants then

wore a pair of plano CMS spectacles with a 0.2 DOT pattern that covered the entire lens surface and standard plano spectacles (control) in a randomized order and, after 5 minutes of adaptation to the lenses, ten open-field autorefraction measurements (Grand Seiko 5500) were taken for each eye, with the target at 6m and 40cm. Analysis was conducted on the mean auto-refraction to determine differences in the lag of accommodation (LOA) between lens types for the right eye and also for the dominant eye.

Results:

Chapters 3,4,5,6: A total of 30 participants were enrolled in the study and completed all assessments (17 females and 13 males). The mean age of the participants was 10.9 ± 1.7 years (median 11 years, ranging from 8 to 13 years). The mean refractive error was $+0.35 \pm 0.29$ spherical equivalent refraction (SER).

- **Chapter 3:** After one hour of wearing CMS spectacles, a two-way RMANOVA revealed a statistically significant reduction in AL ($6\mu\text{m}$) with $p = 0.001$. Similarly, a significant difference in CCT was observed, with $p < 0.001$ between baseline and both the 30-minute and 60-minute time points. Additionally, pairwise comparisons indicated a significance of $p = 0.02$ at the 30-minute time point between CMS and control spectacles. A similar reduction in AL ($6\mu\text{m}$) was noted with +3.00 control spectacles after one hour of wear. A significant difference ($p < 0.001$) was also observed for both ACD and LT with the +3.00D control spectacles at baseline versus 30 minutes and baseline versus 60 minutes. Furthermore, pairwise comparisons demonstrated significant differences between CMS

and +3.00 control spectacles at the 30-minute (2.16 μm) time point for CCT and at both 30 (0.04 mm, 0.04 mm) and 60-minute (0.04 mm, 0.04 mm) time points for ACD and LT.

- **Chapter 4:** When comparing the different methods of measurement for choroidal thickness, the manual method overestimated the choroidal thickness by 40 μm when compared to the semi-automated and automated AI-based method. Although repeatability between the measurements was satisfactory, the manual method did not show an acceptable Bland-Altman agreement when compared to the other three methods. However, a good agreement was observed between the semi-automated and the automated methods.

- **Chapters 5 & 6:** The retinal thickness, choroidal thickness, and CVI were measured at all nine Early Treatment Diabetic Retinopathy Study (ETDRS) regions. In terms of choroidal thickness, only the outer inferior region of the retina showed a significant difference ($p = 0.02$) between the 30-minute and 60-minute marks when using CMS spectacles. Additionally, a significant difference was found between the CMS spectacles and the +3.0 control spectacles at the 30-minute point in 4 out of 9 macular regions. In contrast, no significant differences were found in any of the regions when using the +3.00D control spectacles. The retinal thickness and CVI did not exhibit any significant differences in any of the nine ETDRS regions for both CMS and +3.00D control spectacles.

Chapter 7: A total of 30 participants (20 females and 10 males) with a mean age of 10.4 ± 2.8 (7 to 17) years completed the study. There was no significant difference in right eye mean LOA with CMS ($+0.57 \pm 0.39\text{D}$) versus control spectacles ($+0.62 \pm 0.34\text{D}$); Mann-

Whitney U test, $p = 0.64$. For dominant eyes, LOA values were $+0.60 \pm 0.40D$ and $+0.68 \pm 0.33D$ with CMS and control spectacles, respectively ($p = 0.25$, not significant). Additionally, no significant difference was observed in mean LOA between males and females or between age groups (7-11 years vs 12-17 years) for either right or dominant eyes with CMS or control spectacles (all $p = > 0.05$).

Conclusions:

Chapter 3: Short-term wear of full-field myopia control CMS did not result in significant changes in anterior segment biometrics, retinal thickness, choroidal thickness, CVI and AL. There was only a minimal decrease of $3 \mu m$ in CCT after 60 minutes of wear however, this minimal change was considered clinically insignificant.

Chapter 4: This study concluded that manual, semi-automated, OCT inbuilt software and AI-based customized software methods are reproducible and repeatable. The manual method tends to overestimate the ChT and is time-consuming, as compared with both automated methods, which showed encouraging results for the OCT based TABS automated software.

Chapters 5 & 6: Short-term exposure to full-field CMS did not lead to any notable changes in retinal or choroidal thickness. However, a significant difference in choroidal thickness was noted between the spectacles at the 30-minute time point, suggesting a rapid yet transient response. Further research with larger sample sizes and extended monitoring durations may be necessary to determine the clinical significance of these transient

changes. Similarly, short-term exposure to CMS and +3.00D control spectacles did not lead to any notable change in CVI.

Chapter 7: Full-field CMS had no significant effect on LOA compared to standard single-vision spectacle lenses, indicating no differential impact on accommodative response over the short period of lens wear tested.

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Dedication

With heartfelt love and enduring devotion, I dedicate this thesis to my family.

To my grandfather, Iqbal Pasha Sultan,

Your unwavering support and motivation have been a cornerstone of my journey. From the early days of my schooling to the completion of this PhD, your belief in me never wavered. Your wisdom, encouragement and love have been my guiding light.

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Thank you for inspiring me to reach for the stars.

Table of Contents

Examining Committee Membership	ii
Author's Declaration	iii
Statement of Contributions	iv
Abstract	v
Acknowledgments	xi
Dedication	xiii
List of Figures	xx
List of Tables	xxvii
List of Abbreviations	xxxix
Chapter 1 – Introduction	1
1.1 Anatomy of the Human Eye	1
1.2 Process of Emmetropization	5
1.3 Abnormal Eye Growth	7
1.3.1 Myopia	8
1.3.2 Prevalence	9
1.3.3 Theories on myopia onset and progression	10
1.3.4 Structural Changes in Myopia	15
1.3.5 Pathological Ocular Changes in Myopia	17
1.4 Myopia Control Treatment	18
1.4.1 MiYOSMART Spectacles	18
1.4.2 HALT Spectacles	20

1.4.3 CARE Spectacles.....	22
1.4.4 MiSight spectacles	23
1.5 Summary of literature review and need for clinical study.....	25
Chapter 2 – Thesis rationale	27
Chapter 3 - Effect of short-term wear of contrast management spectacles on anterior segment biometrics and axial length.....	33
3.1 Introduction	33
3.2 Methods	34
3.3 Statistical Analysis	36
3.4 Results	36
3.4.1 Axial Length (AL)	37
3.4.2 Central Corneal Thickness (CCT).....	38
3.4.3 Anterior Chamber Depth (ACD).....	39
3.4.4 Crystalline Lens Thickness (LT).....	40
3.4 Discussion and Conclusion	42
Chapter 4 – Testing repeatability in methods of choroidal thickness measurement using optical coherence tomography.....	45
4.1 Introduction.....	45
4.2 Methods	47
4.2.1 Image Analysis	48
4.3 Statistical Analysis	52
4.4 Results	52
4.4.1 Repeatability Analysis.....	53

4.4.2 Method Agreement	54
4.4.3 Comparison between Automated (TABS) and Automated (AI-based)	62
Chapter 5 -Effect of short-term wear of contrast management spectacles on retinal and choroidal thickness	77
5.1 Introduction.....	77
5.2 Methods	79
5.3 Statistical Analysis	81
5.4 Results	81
5.4.1 Retinal Thickness.....	82
5.4.1.1 Inner Superior Retinal Thickness	83
5.4.1.2 Outer Superior Retinal Thickness	84
5.4.1.3 Inner Inferior Retinal Thickness	85
5.4.1.4 Outer Inferior Retinal Thickness	86
5.4.1.5 Central Retinal Thickness.....	87
5.4.1.6 Inner Nasal Retinal Thickness	88
5.4.1.7 Outer Nasal Retinal Thickness	89
5.4.1.8 Inner Temporal Retinal Thickness	90
5.4.1.9 Outer Temporal Retinal Thickness	91
5.4.2 Choroidal Thickness.....	92
5.4.2.1 Inner Superior Choroidal Thickness	92
5.4.2.2 Outer Superior Choroidal Thickness.....	93
5.4.2.3 Inner Inferior Choroidal Thickness	94

5.4.2.4 Outer Inferior Choroidal Thickness.....	95
5.4.2.5 Central Choroidal Thickness	96
5.4.2.6 Inner Nasal Choroidal Thickness.....	97
5.4.1.7 Outer Nasal Choroidal Thickness.....	98
5.4.1.8 Inner Temporal Choroidal Thickness	99
5.4.1.9 Outer Temporal Choroidal Thickness	100
5.5 Discussion and Conclusion	101
Chapter 6 -Effect of short-term wear of contrast management spectacles on choroidal vascularity index	105
6.1 Introduction.....	105
6.2 Methods	107
6.3 Statistical Analysis	108
6.4 Results	108
6.4.1 Choroidal Vascularity Index (CVI).....	109
6.4.1.1 Inner Superior CVI.....	110
6.4.1.2 Outer Superior CVI.....	111
6.4.1.3 Inner Inferior CVI	112
6.4.1.4 Outer Inferior CVI	113
6.4.1.5 Central CVI.....	114
6.4.1.6 Inner Nasal CVI.....	115
6.4.1.7 Outer Nasal CVI.....	116
6.4.1.8 Inner Temporal CVI.....	117

6.4.1.9 Outer Temporal CVI.....	118
6.5 Discussion and Conclusion	119
Chapter 7 - Evaluation of lag of accommodation with full-field Diffusion Optics Technology™ (DOT) contrast management spectacle lenses	121
7.1 Introduction	121
7.2 Material and methods	124
7.2.1 Study Design.....	124
7.2.2 Measurement of lag of accommodation	125
7.3 Statistical analysis.....	126
7.4 Results	127
7.4.1 Lag of accommodation with contrast management and control spectacles.....	128
7.4.1.1 Right eyes – all eligible participants	128
7.4.1.2 Dominant eyes – all eligible participants.....	130
7.4.2 LOA in younger vs older participants	132
7.4.3 LOA in male vs female participants.....	133
7.5 Discussion.....	134
7.6 Conclusion	136
Chapter 8 - General Discussion	137
8.1 Dissertation summary.....	137
8.2 Limitations.....	141
8.3 Future Work	142
Letter(s) of Copyright Permission	Error! Bookmark not defined.

References.....	171
Appendix A.....	194
Appendix B	195
Appendix C	196

List of Figures

Figure 1-1: Anatomy of the Human Eye.....	1
Figure 1-2: Fundus Image showing the Optic Disc on the right and the Macula on the left in the image	4
Figure 1-3: Anatomy of the Retina showing all ten layers and the cells within.	5
Figure 1-4: Sample refractive error caused by abnormal eye growth..	7
Figure 1-5: Myopic refractive error and its correction.	9
Figure 1-6: Near work results in a lag of accommodation response	12
Figure 1-7: Relative peripheral hyperopic defocus	14
Figure 1-8: The design of Defocus Incorporated Multiple Segments (DIMS) spectacle lens.	20
Figure 1-9: The Design of High Aspheric Lenslet Target (HALT) spectacle lens	21
Figure 1-10: The patented lens picture of the Cylindrical Annular Refractive Element (CARE) spectacle lenses	23
Figure 1-11: Representing the Diffusion Optical Technology (DOT) lens design.	24
Figure 1-12: Showing the Diffusion Optical Technology (DOT) lens design.	25
Figure 2-1: Above - commercially available DOT Spectacles with approx. 5 mm clear central zone, below – full-field DOT spectacles used in this thesis.	31
Figure 3-1: Example of an anterior segment scan using the IOL Master 700.....	35
Figure 3-2: Mean axial length for contrast management spectacles and +3.00 control spectacles at Baseline and after 30 and 60 minutes of wear (right eye).	38
Figure 3-3: Mean central corneal thickness for contrast management spectacles and +3.00 control spectacles at Baseline and after 30 and 60 minutes of wear (right eye).	39
Figure 3-4: Mean anterior chamber depth for contrast management spectacles and +3.00 control spectacles at Baseline and after 30 and 60 minutes of wear (right eye).	40
Figure 3-5: Mean lens thickness for contrast management spectacles and +3.00 control spectacles at Baseline and after 30 and 60 minutes of wear (right eye).	42
Figure 4-1: Example of a SFCT measurement using the arrow tool function in Image J	49

Figure 4-2: Example of a SFCT measurement using the Image J tool on the pre-segmented Scan	50
Figure 4-3: Example of an SFCT measurement using the inbuilt automated software of the DRI Triton OCT	51
Figure 4-4: Example of a segmented and binarized image obtained using the AI-based automated software	52
Figure 4-5: The Bland-Altman Plot showing the agreement between the manual and semi-automated methods of choroidal thickness measurements at visit 1.	56
Figure 4-6: The Bland-Altman Plot showing the agreement between the manual and semi-automated methods of choroidal thickness measurements at visit 2.	56
Figure 4-7: The Bland-Altman Plot showing the agreement between the manual and automated (TABS) methods of choroidal thickness measurements at visit 1.	57
Figure 4-8: The Bland-Altman Plot showing the agreement between the manual and automated (TABS) methods of choroidal thickness measurements at visit 2.	57
Figure 4-9: The Bland-Altman Plot showing the agreement between the manual and automated (AI-based) methods of choroidal thickness measurements at visit 1.	58
Figure 4-10: The Bland-Altman Plot showing the agreement between the manual and automated (AI-based) methods of choroidal thickness measurements at visit 2.	58
Figure 4-11: The Bland-Altman Plot showing the agreement between the semi-automated and automated (TABS) methods of choroidal thickness measurements at visit 1.	59
Figure 4-12: The Bland-Altman Plot showing the agreement between the semi-automated and automated (TABS) methods of choroidal thickness measurements at visit 2.	59
Figure 4-13: The Bland-Altman Plot showing the agreement between the semi-automated and automated (AI-based) methods of choroidal thickness measurements at visit 1.	60
Figure 4-14: The Bland-Altman Plot showing the agreement between the semi-automated and automated (AI-based) methods of choroidal thickness measurements at visit 2.	60
Figure 4-15: The Bland-Altman Plot showing the agreement between the two automated methods of choroidal thickness measurements at visit 1.	61

Figure 4-16: The Bland-Altman Plot showing the agreement between the two automated methods of choroidal thickness measurements at visit 2.	61
Figure 4-17: Early Treatment Diabetic Retinopathy Study (ETDRS) regions of the choroid....	63
Figure 4-18: The Bland-Altman Plot showing the agreement between two automated methods for measuring the choroidal thickness in the inner superior region at visit 1.	64
Figure 4-19: The Bland-Altman Plot showing the agreement between two automated methods for measuring the choroidal thickness in the inner superior region at visit 2.	64
Figure 4-20: The Bland-Altman Plot showing the agreement between two automated methods for measuring choroidal thickness in the outer superior region at visit 1.	65
Figure 4-21: The Bland-Altman Plot showing the agreement between two automated methods for measuring choroidal thickness in the outer superior region at visit 2.	65
Figure 4-22: The Bland-Altman Plot showing the agreement between two automated methods for measuring the choroidal thickness in the inner inferior region at visit 1.	66
Figure 4-23: The Bland-Altman Plot showing the agreement between two automated methods for measuring the choroidal thickness in the inner inferior region at visit 2.	66
Figure 4-24: The Bland-Altman Plot showing the agreement between two automated methods for measuring the choroidal thickness in the outer inferior region at visit 1.	67
Figure 4-25: The Bland-Altman Plot showing the agreement between two automated methods for measuring the choroidal thickness in the outer inferior region at visit 2.	67
Figure 4-26: The Bland-Altman Plot showing the agreement between two automated methods for measuring the choroidal thickness in the central region at visit 1.	68
Figure 4-27: The Bland-Altman Plot showing the agreement between two automated methods for measuring the choroidal thickness in the central region at visit 2.	68
Figure 4-28: The Bland-Altman Plot showing the agreement between two automated methods for measuring the choroidal thickness in the inner nasal region at visit 1.	69
Figure 4-29: The Bland-Altman Plot showing the agreement between two automated methods for measuring the choroidal thickness in the inner nasal region at visit 2.	69

Figure 4-30: The Bland-Altman Plot showing the agreement between two automated methods for measuring the choroidal thickness in the outer nasal region at visit 1.	70
Figure 4-31: The Bland-Altman Plot showing the agreement between two automated methods for measuring the choroidal thickness in the outer nasal region at visit 2.	70
Figure 4-32: The Bland-Altman Plot showing the agreement between two automated methods for measuring the choroidal thickness in the inner temporal region at visit 1.	71
Figure 4-33: The Bland-Altman Plot showing the agreement between two automated methods for measuring the choroidal thickness in the inner temporal region at visit 2.	71
Figure 4-34: The Bland-Altman Plot showing the agreement between two automated methods for measuring the choroidal thickness in the outer temporal region at visit 1.	72
Figure 4-35: The Bland-Altman Plot showing the agreement between two automated methods for measuring the choroidal thickness in the outer temporal region at visit 2.	72
Figure 5-1: Posterior segment scan using the Triton DRI OCT.....	80
Figure 5-2: Retinal and Choroidal ETDRS regions.	82
Figure 5-3: Mean inner superior retinal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye.	83
Figure 5-4: Mean outer superior retinal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye.	84
Figure 5-5: Mean inner inferior retinal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye.	85
Figure 5-6: Mean outer inferior retinal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye.	86
Figure 5-7: Mean central retinal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye.	87

Figure 5-8: Mean inner nasal retinal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye. The error bars represent the standard deviation.	88
Figure 5-9: Mean outer nasal retinal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye.	89
Figure 5-10: Mean inner temporal retinal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye.	90
Figure 5-11: Mean outer temporal retinal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye.	91
Figure 5-12: Mean inner superior choroidal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye.	92
Figure 5-13: Mean outer superior choroidal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye.	93
Figure 5-14: Mean inner inferior choroidal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye.	94
Figure 5-15: Mean outer inferior choroidal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye.	95
Figure 5-16: Mean central choroidal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye.	96

Figure 5-17: Mean inner nasal choroidal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye.	97
Figure 5-18: Mean outer nasal choroidal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye.	98
Figure 5-19: Mean inner temporal choroidal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye.	99
Figure 5-20: Mean outer temporal choroidal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye.	100
Figure 6-1: Example of a choroidal segmentation scan and image binarization for CVI measurement using AI-based automated software.	108
Figure 6-2: Choroidal vascularity index ETDRS regions.	109
Figure 6-3: Mean inner superior choroidal vascularity index with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye.	110
Figure 6-4: Mean outer superior choroidal vascularity index with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye.	111
Figure 6-5: Mean inner inferior choroidal vascularity index with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye.	112
Figure 6-6: Mean outer inferior choroidal vascularity index with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye.	113

Figure 6-7: Mean central choroidal vascularity index with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye.	114
Figure 6-8: Mean inner nasal choroidal vascularity index with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye.	115
Figure 6-9: Mean outer nasal choroidal vascularity index with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye.	116
Figure 6-10: Mean inner temporal choroidal vascularity index with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye.....	117
Figure 6-11: Mean outer temporal retinal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye.	118
Figure 7-1:The scatter plot shows the correlation of LOA between the contrast management and control spectacles in the right eyes of each participant (n=30).	129
Figure 7-2: The Box and Whisker plot shows the distribution of LOA with contrast management and control spectacles in the right eye.	130
Figure 7-3: The scatter plot shows the correlation of LOA with contrast management and control spectacles in the dominant eye of each participant.	131
Figure 7-4: The Box and whisker plot shows the distribution of LOA between contrast management and control spectacles in the dominant eye.	132

List of Tables

Table 3-1: Mean axial length, central corneal thickness, anterior chamber depth, and lens thickness at baseline and after 30 and 60 minutes of wear for the right eye (n=30)	36
Table 4-1: Mean repeatability of Manual, Semi-Automated, Automated (TABS) and Automated (AI-based software).	53
Table 4-2: Mean difference between Manual, Semi-automated, Automated (TABS), and Automated (AI-based) methods of choroidal thickness measurement at visit 1 and visit 2 ..	55
Table 4-3: Mean differences between the two automated methods at all ETDRS regions for visit 1 and visit 2.....	63
Table 5-1: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline, 30 minutes and 60 minutes at the inner superior retinal region of the right eye.	83
Table 5-2: Mean $\pm$ SD retinal thickness and two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline 30 minutes and 60 minutes at the outer superior retinal region of the right eye.	84
Table 5-3: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline 30 minutes and 60 minutes at the inner inferior retinal region of the right eye.....	85
Table 5-4: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline 30 minutes and 60 minutes at the outer inferior retinal region of the right eye.....	86
Table 5-5: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline 30 minutes and 60 minutes at the central retinal region of the right eye.	87
Table 5-6: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline, 30 minutes and 60 minutes at the inner nasal retinal region of the right eye.....	88

Table 5-7: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline 30 minutes and 60 minutes at the outer nasal retinal region of the right eye.	89
Table 5-8: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline 30 minutes and 60 minutes at the inner temporal retinal region of the right eye.	90
Table 5-9: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline 30 minutes and 60 minutes at the outer temporal retinal region of the right eye.	91
Table 5-10: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline 30 minutes and 60 minutes at the inner superior choroidal region of the right eye.	92
Table 5-11: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline 30 minutes, and 60 minutes T the outer superior choroidal region of the right eye.	93
Table 5-12: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline 30 minutes and 60 minutes at the inner inferior choroidal region of the right eye.	94
Table 5-13: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline 30 minutes and 60 minutes at the outer inferior choroidal region of the right eye.	95
Table 5-14: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline 30 minutes and 60 minutes at the central choroidal region of the right eye.	96
Table 5-15: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline, 30 minutes and 60 minutes at the inner nasal choroidal region of the right eye.	97

Table 5-16: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline 30 minutes and 60 minutes at the outer nasal choroidal region of the right eye.	98
Table 5-17: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline 30 minutes and 60 minutes at the inner temporal choroidal region of the right eye.	99
Table 5-18: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline 30 minutes and 60 minutes at the outer temporal choroidal region of the right eye.	100
Table 6-1: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline 30 minutes and 60 minutes at the inner superior region of the right eye.	110
Table 6-2: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline 30 minutes and 60 minutes at the outer superior region of the right eye.	111
Table 6-3: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline 30 minutes and 60 minutes at the inner inferior region of the right eye.	112
Table 6-4: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline 30 minutes and 60 minutes at the outer inferior region of the right eye.	113
Table 6-5: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline 30 minutes and 60 minutes at the central region of the right eye.	114
Table 6-6: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline 30 minutes and 60 minutes at the inner nasal region of the right eye.	115

Table 6-7: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline 30 minutes and 60 minutes at the outer nasal region of the right eye.	116
Table 6-8: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline 30 minutes and 60 minutes at the inner temporal region of the right eye.	117
Table 6-9: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline 30 minutes and 60 minutes at the outer temporal region of the right eye.	118
Table 7-0-1: Participant characteristics (n = 30).....	128
Table 7-0-2:Lag of accommodation with contrast management and control spectacles in the right eye and dominant eye for the age groups 7-11 years (n=19) and 12-17 years (n=11); Mean $\pm$ SD, (median).....	133
Table 7-0-3:Lag of accommodation with contrast management and control spectacles in the right eye and dominant eye for male (n=10) and female (n=20) participants (Mean $\pm$ SD, (median)).....	133

List of Abbreviations

ACD	Anterior Chamber Depth
AI	Artificial Intelligence
AL	Axial Length
CARE	Cylindrical Annular Refractive Element
CCT	Central Corneal Thickness
ChT	Choroidal Thickness
CMS	Contrast Management Spectacles
CVI	Choroidal Vascularity Index
D	Diopters
DIMS	Defocus Incorporated Multiple Segment
DOT.....	Diffusion Optics Technology
ETDRS	Early Treatment Diabetic Retinopathy Study
HALT	High Aspheric Lenslet Target
IMI	International Myopia Institute
LOA	Lag of Accommodation
LT	Lens Thickness
MMD	Myopic Macular Degeneration
MEM	Monocular Estimate Method
OCT	Ocular Coherence Tomography
PALs	Progressive Additional Lenses
RD	Retinal Detachment
SD OCT	Spectral Domain Optical Coherence Tomography
SER	Spherical Equivalent Refraction
SFCT	Sub-foveal Choroidal Thickness
SS OCT	Swept Source Optical Coherence Tomography
TABS	Topcon Advanced Boundary Segmentation

VoMD Volume of Myopic Defocus

Chapter 1 – Introduction

1.1 Anatomy of the Human Eye

The human eyeball is a fluid-filled sphere enclosed in layers and protected by the bony socket known as the orbit. Six extraocular muscles are attached to the eye, allowing it to move up, down, left, right, and rotate.¹ The axial length of the eye, which is the distance between its anterior and posterior poles, measures about 24 mm in children and adults.² At birth, the eyeball is approximately 16 mm long, growing rapidly to 22-23 mm by the age of three.³ The human eye can be divided into outer, middle, and inner layers (see Figure 1-1).

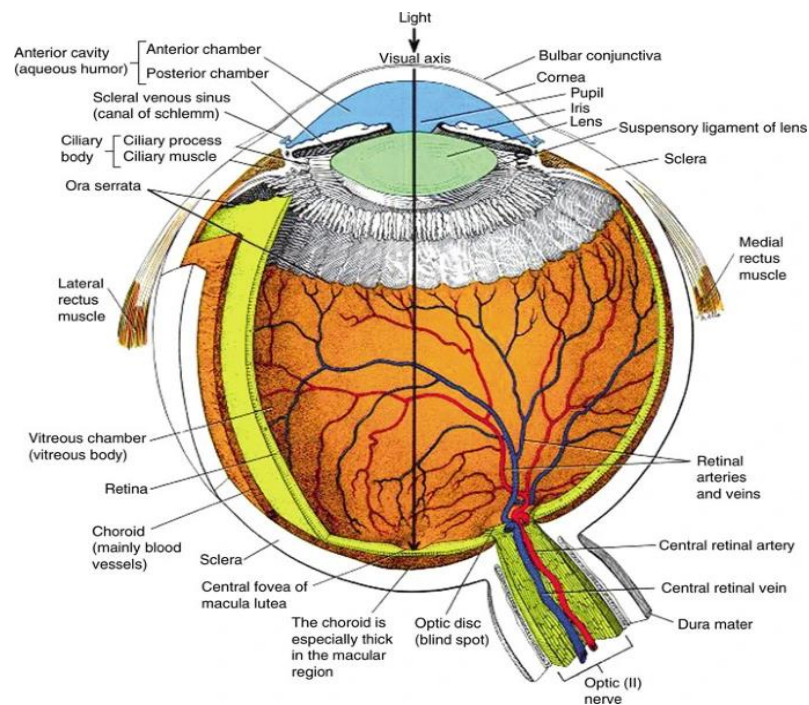


Figure 1-1: Anatomy of the Human Eye. Image reproduced with permission from Kristina Irsch & David L.

Guyton. *Encyclopedia of Biometrics*. Springer Nature, 2015, P. 427 – 433.

The outermost layer of the eye consists of the cornea and sclera. The cornea, which is transparent and avascular, is convex and aspheric in shape. Its thickness ranges from 0.5 to 0.6 mm, with an anterior curvature of 7.8 mm and a posterior curvature of 6.5 mm.⁴ As a major refractive element of the eye, the cornea contributes approximately 43 Diopters (D) to the eye's total refractive power. The cornea consists of five distinct layers, each serving a specific function.⁴ Immediately posterior to the cornea is the anterior chamber, which contains aqueous humor – a clear, colorless fluid that provides nutrients to the posterior cornea, crystalline lens, and Iris. The sclera is a continuation of the cornea and features collagen fibers that extend from the cornea.¹ It is an opaque layer, penetrated by numerous blood vessels and nerves. The sclera maintains the eyeball's shape and protects it from external and internal forces.¹

The middle layer of the eye is known as the uvea, which includes the choroid at the back, the ciliary body, and the iris at the front.⁵ The iris, the visible part of the uvea, appears as a perforated disc. The central opening, called the pupil, regulates the amount of light entering the eye and adjusts in size depending on the lighting conditions and other factors. The iris contains two sets of muscles: the sphincter muscles, which constrict the pupil, and the dilator muscles, which dilate it.⁵ The color of the iris can range from blue to brown and is determined by the amount and distribution of melanin pigmentation. Situated in front of the choroid, the ciliary body consists of involuntary muscle that changes the shape of the crystalline lens during the process of accommodation.^{1,5} During accommodation, the ciliary muscles contract, and the zonular fibers attached to the lens relax. This process reduces the radius of curvature of the lens, enabling the eye to focus on close objects.¹

The choroid, the most posterior and largest component of the uvea, is situated between the sclera and Bruch's membrane.¹ This vascular layer of the eye is characterized by its loosely arranged blood vessels, which are organized into three distinct layers: the choriocapillaris, which contains small-diameter blood vessels; Steller's layer with medium-sized blood vessels; and Haller's layer, comprising large blood vessels.⁶ The choroid transitions into the sclera via the suprachoroidal layer. Notably, the choroid exhibits one of the highest blood flow rates in the body, underscoring its critical role in supplying nutrients to the outer retina.¹ The choroid's thickness varies, being thinner anteriorly and thicker posteriorly, with an average sub foveal thickness of 250 to 350 μm in young adults.⁷ Its primary function is to provide nutrients to the retinal photoreceptor layer.⁶ Additionally, the choroid plays a role in retinal thermoregulation by maintaining choroidal blood flow, although the underlying mechanism remains unclear.^{6,7} Recent research has also highlighted choroids' involvement in modulating eye growth and its influence on the process of emmetropization.⁷

The retina, the innermost layer of the eye, lines the entire posterior portion of the eye, except for the optic nerve. It extends forward to the ora serrata, where it meets the ciliary body. The macula, located at the center of the retina, measures about 5.5 mm and covers roughly 15-20 degrees of the visual field, providing clear and sharp central vision.^{1,8} Within the macula is the foveal centralis, a small vascular pit situated 5 degrees temporal and 2 degrees inferior to the optic axis. The optic disc is located 13 degrees nasal to the macula and has a diameter of 1.7 mm. It lacks photoreceptors and is known as the "blind

spot” of the eye (see **Figure 1-2**). The optic nerve carries visual information from the eye to the brain’s visual cortex.⁹



Figure 1-2: Fundus Image showing the Optic Disc on the right and the Macula on the left in the image

The retina consists of ten layers, as seen in **Figure 1-3**. These layers are arranged such that light passes through the non-light-sensitive layers before reaching the light-sensitive photoreceptor layer. Within these ten layers of retina, various types of cells perform specific tasks to help transmit the incoming visual information to the brain.^{8,9} These cells include rods and cones. Rods, which are usually much thinner than cones, cover the peripheral area of the retina and are sensitive to low light levels. Cones, abundant in the center of the fovea, are sensitive to the higher light levels.⁹ The increased density of cones in the center of the macula provides the highest resolution and sharp, colorful vision. Signals generated by the rods and cones are transmitted to the neurons of the

bipolar cells, which in turn transmit the signals to the ganglion cells. The visual signals then leave the eye through the optic nerve via the axons of the ganglion cells.⁹

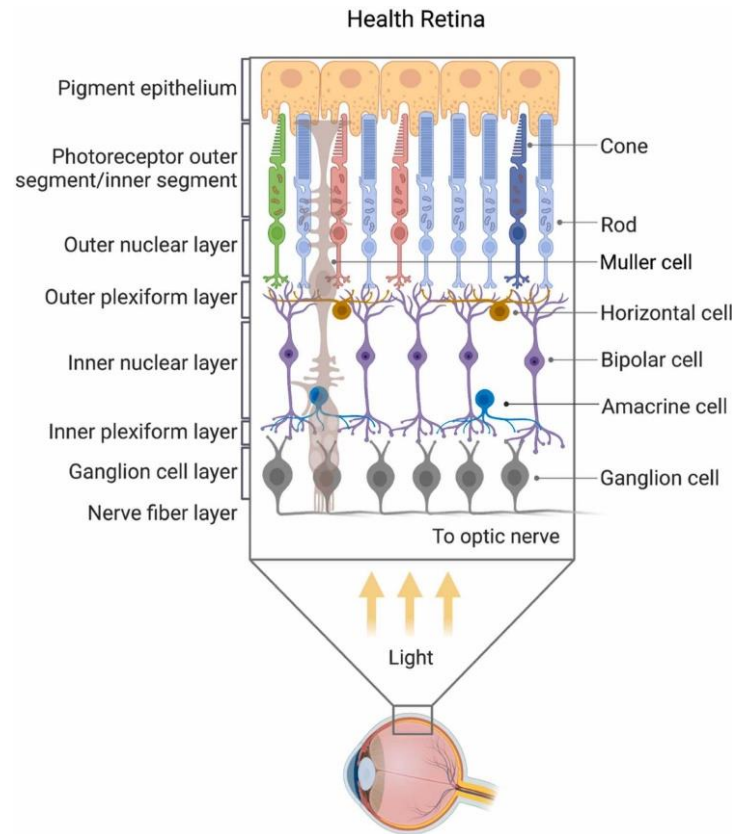


Figure 1-3: Anatomy of the Retina showing all ten layers and the cells within. *Image is obtained from Jie Zhang, Lei Shi, The Retina: A window in which to view the pathogenesis of Alzheimer's disease. ¹⁰Aging Research Reviews 77, 101590 (2022).*

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1.2 Process of Emmetropization

Emmetropization is the developmental process by which the components of the eye grow and adjust to match its axial length, achieving an optimal refractive state, where an unaccommodated eye is focused in the distance.¹¹ This process involves a complex interaction of genetics and environmental factors that guide the eye's growth and refractive development.¹² Emmetropization is believed to be a result of both passive and

active processes.¹³ Passive emmetropization involves physical and genetic factors modulating eye growth, and active emmetropization involves environmental factors that significantly influence the retinal image, feedback mechanism, and axial length adjustments.¹³

The process of emmetropization commences during postnatal development. Newborn eyes experience a series of refractive changes as they begin to perceive retinal images.¹⁴ At birth, infants typically exhibit hyperopia of approximately $+2.37 \pm 0.12$ D within the first 3 months.^{15,16} This initial hyperopia is followed by a rapid reduction in refractive error, decreasing to approximately $+1.10 \pm 0.07$ D by 15 months of age.^{15,16} This reduction in hyperopia is achieved through slow, modulated growth, which leads to emmetropia by the age of 6.¹⁶ During this critical phase, the crystalline lens and cornea undergo refractive adjustment to harmonize with the axial growth of the eye.¹⁷ Additionally, scleral expansion and remodeling occur, potentially due to secretory growth factors from the choroid.¹⁶

To understand the process of emmetropization, numerous investigations have been conducted using animal models to explore the underlying mechanisms and the role of vision in postnatal eye growth. Experimental animal models include a wide variety of species, including macaque and marmoset monkeys,¹⁸ tree shrews,¹⁹ guinea pigs,²⁰ mice,²¹ chickens,²² fish models,²³ and many more.²⁴ For instance, chickens have been shown to reduce hyperopic refractive error from 18 to 3 D within the first 8 weeks of life, a similar pattern of hyperopia reduction is observed in humans, primarily during the first year of

life.¹⁶ In another experiment, newborn chick eyes were able to compensate from +15 to -10 D refractive lenses placed in front of the eye during emmetropization by adjusting axial growth.²⁵ Studies on marmoset monkey eyes and chick models have demonstrated that the choroid also plays a role in emmetropization, by altering its thickness and adjusting the position of the retina when defocus is imposed.²⁶⁻²⁸

1.3 Abnormal Eye Growth

During development, the eye continues to grow while adjusting its refractive state to achieve normal vision through emmetropization. However, the retinal feedback mechanism continues to operate even after the eye has achieved a state of emmetropia.¹⁵ The retina plays a crucial role in detecting defocus and providing feedback to regulate eye growth. In some cases, the feedback mechanism may become dysregulated, leading to excess or insufficient eye growth, potentially resulting in refractive errors such as myopia or hyperopia, as illustrated in **Figure 1-4**.²⁹

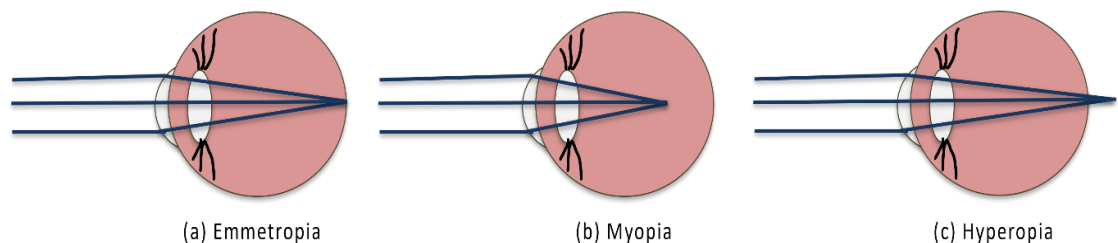


Figure 1-4: Sample refractive error caused by abnormal eye growth. (a). Emmetropia (normal vision) is the state of refraction where light is focused perfectly on the retina (b). Myopia (near-sightedness) occurs when the axial length is too long, and the light is focused in front of the retina (c). Hyperopia (far-sightedness) occurs when the axial length is too small, and the light is focused behind the retina.

1.3.1 Myopia

Myopia is the refractive condition of the eye where the image of a distant object is focused in front of the retina when accommodation is at rest, resulting in blurred vision. Error! Reference source not found. illustrates how light rays focus in front of the retina in myopic eyes.³⁰ There are two primary types of myopia, axial myopia and refractive myopia, with axial myopia being more prevalent.³⁰ Axial myopia occurs when the axial length of the eye exceeds the refractive power of the cornea and/or crystalline lens.³¹ In contrast, refractive myopia arises when the refractive power of the cornea and sometimes the crystalline lens is disproportionately high relative to the axial length.³⁰ The progression of myopia or the myopic shift, is initially rapid and gradually decelerates as the rate of axial elongation slows.³¹ In cases of early-onset myopia, characterized by a rapid rate of axial elongation in children, myopia progresses at a consistent rate and takes longer to decelerate compared to later-onset myopia.¹⁷ This indicates that the rate of change in refractive error during early onset tends to remain elevated for an extended duration before decreasing down. Myopia is typically corrected by using a concave lens in front of the eye, which adjusts the focus of light rays onto the retina, as illustrated in **Figure 1-5**.

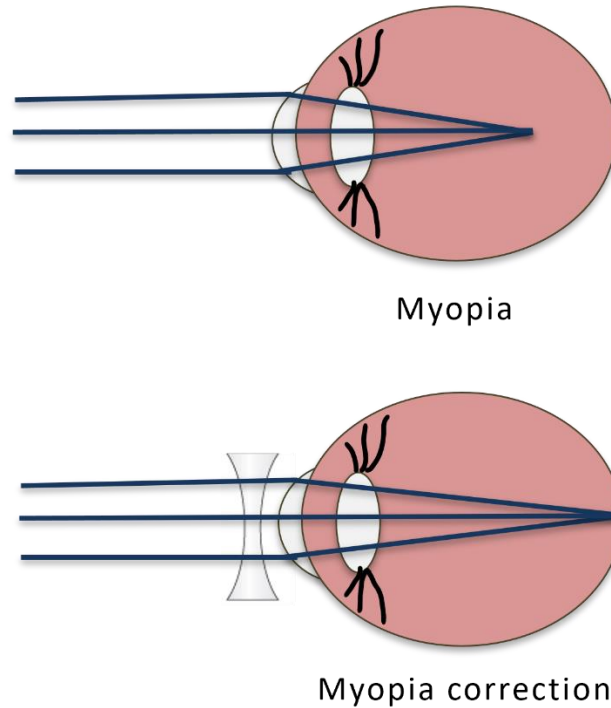


Figure 1-5: Myopic refractive error and its correction. Myopia can be modified using a concave lens, by adding a concave lens to the optical system the image formed in front of the retina can be moved back to the retina.

Myopia can be classified according to various categories, including degree of refractive error, clinical manifestations, and age of onset. The most widely used classification system is based on the degree of refractive error, measured in diopters.³⁰ Myopia is categorized into three types: mild, moderate, and high myopia. Mild myopia is defined by a spherical equivalent (SER) ranging from ≤ -0.50 D to -1.50 D. Moderate myopia is defined by SER between -1.50 D and -5.00 D. High myopia is identified by a SER of -5.00 D or greater.³⁰

1.3.2 Prevalence

The prevalence of myopia has been increasing worldwide and varies significantly by region.³² The prevalence is higher in East Asian countries compared to Western

countries.³³ In countries such as South Korea, Taiwan, and China, the prevalence of myopia is between 84% to 97% in teenagers and young adults in urban areas.³⁴ In a study conducted by Wang et al., the prevalence of myopia in Chinese schoolchildren was 63% between 6 to 18 years.³⁵ In the United States, the prevalence of myopia among children is 42% in urban areas, with a nationwide prevalence of approximately 36%.³⁶ Nearly 224 million people worldwide, or almost 3% of the population around the world, have high myopia, with a refractive error of more than -6.00 D.³⁷ It is also indicated that by the year 2050, nearly 50% (5 billion) of the world's population could be myopic, with the prevalence of high myopia expected to reach 10% (1 billion).³⁸

1.3.3 Theories on myopia onset and progression

Numerous animal studies have been conducted to understand the mechanism of myopia development and, currently, several theories on myopia development are widely accepted. These include the accommodative lag theory, mechanical tension theory, peripheral hyperopic refraction theory and the contrast theory.^{24,25,39-41}

1.3.3.1 Lag of Accommodation

A lag of accommodation occurs when the accommodative response is insufficient relative to the accommodative stimulus, with both parameters measured in diopters, might lead to blurred vision at near.⁴² This phenomenon is predicted based on the understanding that hyperopic blur, induced by a high lag of accommodation during prolonged near activities, results in abnormal axial growth of the eye, as illustrated in **Figure 1-6**.^{42,43} Several studies have reported that myopes exhibit a reduced

accommodative response compared to emmetropes, leading to insufficient response to blur.⁴²⁻⁴⁴ This hypothesis suggests that myopic children treated with plus lenses for near work may experience reduced accommodative lag and can result in slowed myopia progression. However, this concept is controversial, while some believe that the lag of accommodations is a cause of myopia, others argue that it is a consequence of myopia.⁴⁵ For instance, studies have found that myopic children and young adults have higher levels of esophoria and accommodative lag at near compared to emmetropes.^{46,47} Additionally, another study has reported that myopes have reduced variability in accommodative response, reduced accommodative facility, and elevated accommodative convergence (AC/A) ratios.⁴⁷ Another study evaluating accommodative lag before, during, and after the onset of myopia found that increased accommodative lag was common in children after they become myopic, suggesting that while it might not be a predictable factor for the onset of myopia, it is a significant characteristic in myopic children after onset.⁴⁵ Overall, the relationship between accommodative lag and the development of myopia is complex and still not fully understood.

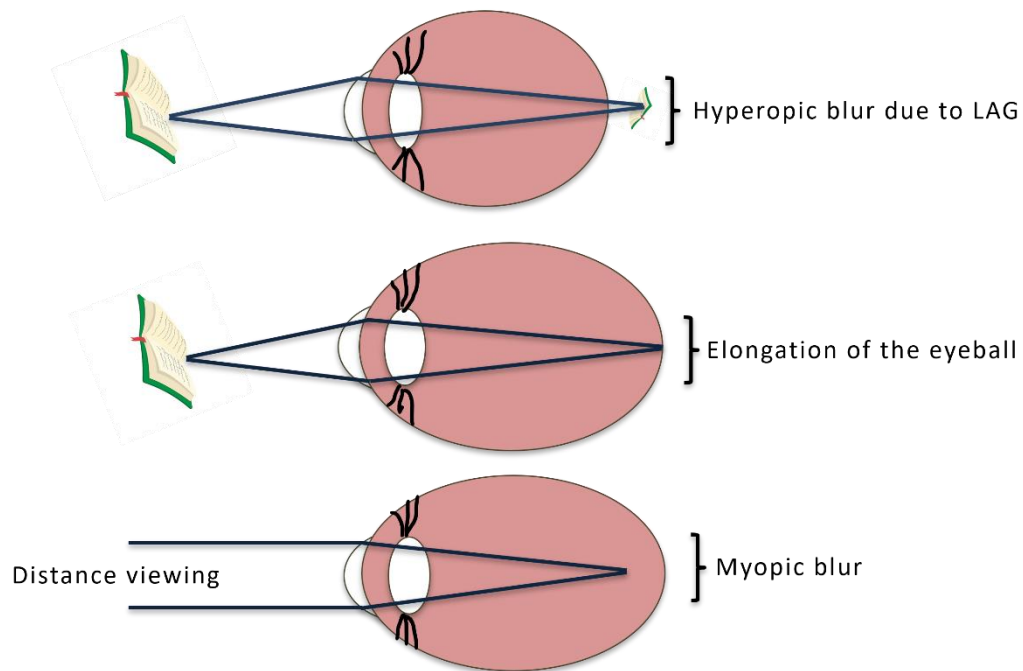


Figure 1-6: Near work results in a lag of accommodation response and associated hyperopic defocus, that results in axial elongation to focus the light rays onto the retina. Subsequent viewing at far results in a small transient myopia (near work-induced transient myopia).

1.3.3.2 Mechanical Tension Theory

The eye responds to transient changes in axial length following short periods of accommodation, leading to the proposed mechanical tension theory. This theory suggests that during near work, the ciliary muscle contracts to accommodate, resulting in the forward and inward pull of the choroid. This action restricts the equatorial growth of the eye.⁴³ This contraction of the ciliary muscle increases the tension of the ciliary-choroidal complex and decreases the circumference of the sclera, leading to the prolate shape of the eye. Over time, this sustained tension may cause the eye to elongate axially, resulting in myopia.^{43,48}

Another consequence of reaching this critical point is that the tension results in increased accommodative efforts and a higher lag of accommodation.^{43,49,50} A study by Mutti et al. indicated that accommodation caused the eye to become more prolate, which provides evidence that the ciliary-choroidal tension can influence the shape of the eye.⁴⁹ Another longitudinal study on children who developed myopia found an increase in peripheral hyperopia two years after the onset of myopia, suggesting a relatively more prolate shape of the eye.⁵¹

1.3.3.3 Peripheral Refraction/ Hyperopic Defocus Theory

The theory of peripheral refraction, also known as peripheral hyperopic defocus, plays a significant role in myopia development and progression. This theory suggests that the peripheral refractive state of the eye can influence axial elongation, leading to myopia development.⁵² In emmetropes, the peripheral retina typically experiences myopic defocus. However, in myopes, due to the prolate shape of the eye, the retina experiences hyperopic defocus, which may lead to myopia progression.⁵³ This hyperopic defocus signals the eye to elongate axially. The axial elongation is regulated by the feedback mechanism that attempts to bring the peripheral image into focus by increasing the axial length of the eye, which, consequently, leads to an increase in myopia centrally.⁵³ Some studies have shown that long-term exposure to lenses induces hyperopic defocus, accelerates axial elongation, and ultimately leads to myopia progression, as illustrated in **Figure 1-7.**⁵⁴

Several animal studies have been conducted to support the theory of hyperopic defocus.^{39,40,55} For instance, studies on chick and monkey models have shown that inducing peripheral hyperopia through specially designed lenses can lead to axial elongation and myopia development.^{25,56,57} Similarly, studies on children suggest that a greater amount of peripheral hyperopia leads to faster myopia progression.^{58,59} However, some studies on humans have failed to find a consistent association between peripheral hyperopia with myopia progression.^{60,61}

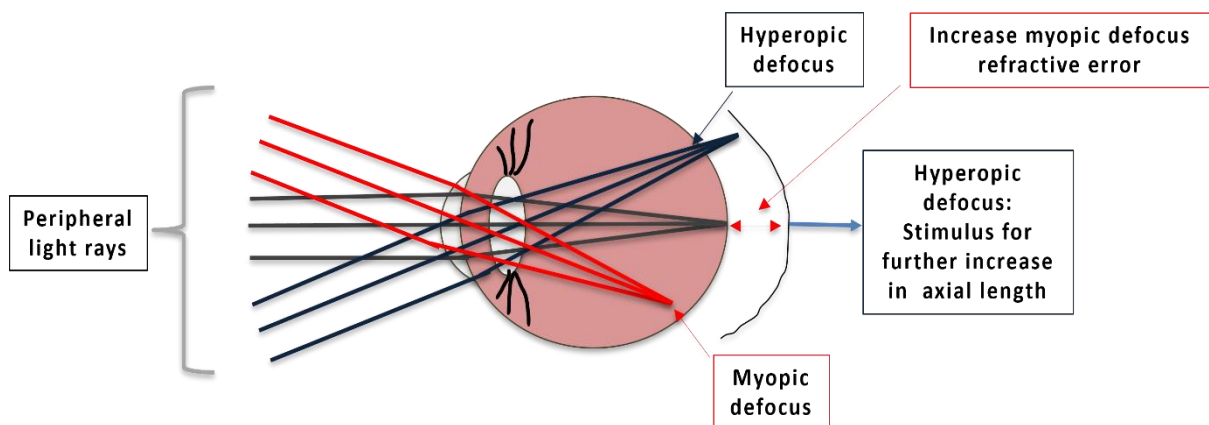


Figure 1-7: Relative peripheral hyperopic defocus (light rays (Blue) focused behind the retina) and relative peripheral myopic defocus (light rays (Red) focused in front of the retina) *Modified from David Berkow's thesis, [The relationship between peripheral refraction, optical correction and myopia progression](#).*

1.3.3.4 The Contrast Theory

The contrast theory on myopia progression provides a novel understanding of the influence of visual stimuli on ocular growth and refractive development. This theory suggests that the level of contrast in the environment plays a crucial role in axial elongation, which is a key factor in myopia development and progression.⁶² This theory states that high retinal contrast can overstimulate the retina, in particular to the bipolar cells, which are the first to detect contrast. This overstimulation signals the eye to continue

growing, resulting in axial elongation.⁶²⁻⁶⁴ This theory also suggests that near work disrupts the process of emmetropization and causes myopia by exposing the retina to large amounts of high-contrast information due to the artificial contrast from digital screens. Conversely, low retinal contrast signals the eye to halt or slow its growth.⁶⁴

Some genetic studies have provided an understanding of contrast theory. The mutation in the long and medium-wavelength cone opsin genes can lead to a reduction in the photopigments and cause insensitivity to light.⁶² The difference in the cone signaling between normal and mutated cones can produce abnormally high contrast signaling that stimulates eye growth. A study by Neitz et al. suggests that the retina of myopes has cone mosaics composed of normal and affected cones that are inefficient in absorbing light.⁶²

1.3.4 Structural Changes in Myopia

Given that axial myopia is more prevalent, alterations in the axial length of the eye are accompanied by modifications in the other ocular structures.

1.3.4.1 Anterior Segment

Cornea: The curvature of the cornea increases in myopia, contributing to the eye's overall refractive power. However, corneal thickness remains unchanged in both myopes and emmetropes.^{65,66}

Anterior Chamber Depth: The anterior chamber depth is greater in myopic eyes than in emmetropic eyes, which may also cause increased intraocular pressure.⁶⁷ However, no significant difference is observed in the anterior chamber angle between myopes and emmetropes.⁶⁷

Crystalline Lens: Research indicates that myopia causes a thinner crystalline lens as a compensatory mechanism to counterbalance the increased axial elongation, and the lens is positioned more posteriorly.^{65,68}

1.3.4.2 Posterior Segment

Compared to the anterior segment the posterior segment shows more prominent changes in myopic eyes.

Retina: As the eye elongates posteriorly, the retina stretches, resulting in thinning, especially in the peripheral regions.⁶⁹ This stretching also leads to a decrease in the density of the retinal pigment epithelium, which is crucial for supporting retinal health and function.⁷⁰ As a result, this can contribute to various retinal pathologies. A study by Jin et al. found that for every 1 mm increase in axial length, retinal thickness decreases by 7 μm in the periphery.⁷¹

Choroid: The choroidal thickness tends to decrease posteriorly as axial length increases. Moreover, with a higher degree of myopia, choroidal thickness is particularly reduced in the macular region.⁷² This thinning is more pronounced in individuals with high myopia compared to those with low myopia.⁷³ Alongside this thinning, some studies have indicated a decrease in choroidal blood flow and choroidal vascularity index in myopic eyes.^{74,75} According to a study by Zhu et al. for each diopter increase in myopia, choroidal thickness decreases by 13 μm , and for every 1 mm increase in axial length, choroidal thickness decreases by 23 μm .⁷³

Sclera: The scleral thickness decreases in myopia, similar to the choroid. This thinning occurs in both the anterior and posterior sclera, but it is more pronounced in the posterior segment.⁷⁶ In high myopes, this thinning can lead to various scleral pathologies. The thinning is associated with tissue rearrangement that occurs during the development of myopia.⁷⁷

1.3.5 Pathological Ocular Changes in Myopia

Individuals with myopia face an increased risk of ocular complications associated with high refractive error and axial length. Pathological myopia, a leading cause of blindness, is characterized by myopia of -6.00 diopters or greater, along with degenerative changes in the eye.⁷⁸ This condition is often accompanied by an axial length of 26.5 mm or more.⁷⁸ The progressive enlargement of the globe is associated with various pathological changes, including myopic macular degeneration (MMD), retinal detachment (RD), and glaucoma, and cataracts.^{78,79}

MMD is a significant concern, as individuals with high myopia of -6.00 diopters or more are 41 times more susceptible to developing MMD compared to those with a normal refractive error (emmetropes).⁸⁰ This degenerative condition affects the macula and can lead to progressive vision loss.⁸⁰ High myopes are also about 20 times more prone to retinal detachment, a serious condition where the retina separates from the underlying tissue, which can result in vision loss if not treated promptly.⁷⁹ Additionally, the risk of developing glaucoma is 14.4 times higher in high myopes, which can lead to irreversible vision loss if not managed properly.⁷⁹ The likelihood of developing cataracts increases with

high myopia, with individuals being 5.5 times more likely to develop them compared to those without myopia.⁸¹

The combination of high refractive error and axial elongation raises the risk of various ocular complications. Understanding these risks, the early detection and management are important to prevent severe visual impairment and blindness.

1.4 Myopia Control Treatment

Various treatments for myopia control have been researched to prevent or delay the onset of myopia and to slow its progression. These treatments include spectacles, contact lenses, and pharmacological options. For spectacles, the options are MiYOSMART spectacles,⁸² CARE spectacles,⁸³ HALT spectacles,⁸⁴ Myopilux Max prismatic bifocal spectacle,⁸⁵ and DOT spectacles.⁸⁶ In terms of contact lenses, treatment options consist of multifocal soft contact lenses, Biofinity Multifocal,⁸⁷ MiSight contact lenses,⁸⁸ and extended-depth focus lenses like Mark'ennovy Mylo, NaturalVue and orthokeratology lenses.⁸⁹ The pharmacological treatment involves using low-dose atropine and 7 – MX (Methylxanthine).⁹⁰⁻⁹³

While there are various options for myopia control treatment, this thesis will focus in detail on a few spectacle treatments.

1.4.1 MiYOSMART Spectacles

MiYOSMART™ spectacles (Hoya Vision Care, Bangkok, Thailand) utilize Defocus Incorporated Multiple Segments (DIMS) technology, which creates a simultaneous defocus effect based on the peripheral refraction theory. These spectacles consist of a central zone

and a treatment zone. The central zone, a 9.4 mm clear area, is responsible for the clear vision that focuses light on the retina. Surrounding the central zone is the treatment zone of 33 mm in diameter, comprising 396 segments arranged in a honeycomb pattern and the diameter of each segment is 1.03 mm, as illustrated in **Figure 1-8**.⁸² Each segment has a relative plus power of +3.50 D. The DIMS spectacle works by creating a myopic defocus that focuses light in front of the retina, with the dual focus design sending conflicting signals intended to slow myopia progression.

A two-year randomized clinical trial involving 160 Chinese children aged 8-13 years with myopia ranging from -1.00 to -5.00 D demonstrated that by wearing DIMS spectacles for two years resulted in a 52% decrease in myopia progression and 62% slower axial length growth compared to those wearing single vision spectacles.⁸² The mean SER progression in the DIMS spectacles was -0.34 D compared to -0.85 D in the single vision group over two years of wear.⁸² A follow-up study on six years of results of DIMS spectacle wear showed -0.92 D of decrease in myopia progression and 0.60 mm decrease in axial elongation.⁹⁴ Studies on a combination treatment of DIMS spectacle with atropine showed a greater effect than just DIMS or atropine alone over a period of 12 months.⁹⁵ A study by Chun et al. on the effects of DIMS spectacle and choroidal thickness showed an increase in choroidal thickness by $6.75 \pm 1.52 \mu\text{m}$ after 1 week of wear and $13.64 \pm 2.62 \mu\text{m}$ increase in choroidal thickness after 12 months of wear compared to single vision spectacles with $-3.17 \pm 1.48 \mu\text{m}$ choroidal thinning in 1 week and $-9.46 \pm 2.55 \mu\text{m}$ choroidal thinning after 12 months.⁹⁶

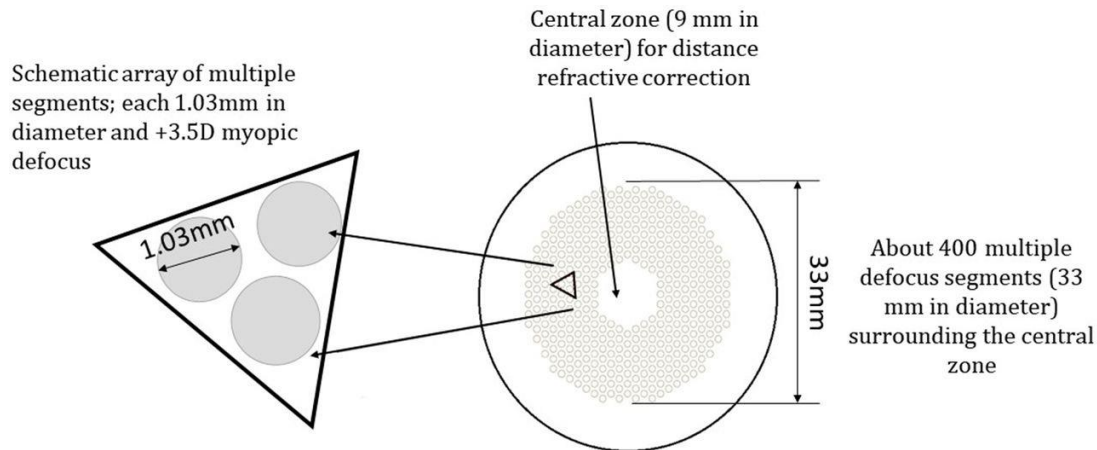


Figure 1-8: The design of Defocus Incorporated Multiple Segments (DIMS) spectacle lens. *Image reproduced with permission from Lam CSM, Tang WC, Defocus Incorporated Multiple Segments (DIMS) spectacle lens slow myopia progression: a 2-year randomized clinical trial, BJO2020;104:363-368⁸²*

1.4.2 HALT Spectacles

The Stellest[®] (Essilor, Charenton-le-Pont, Paris) HALT (High Aspheric Lenslet Target) spectacle lenses incorporate multiple aspheric lenslets arranged in concentric rings around a central clear zone. This design aims to induce a myopic defocus effect, which may be important for controlling myopia progression.⁹⁷ The HALT lens features 11 concentric rings of small aspherical lenslets with a 1.1 mm diameter extending to the edge of the lens. The area of the lens without the lenslet provides distance correction. HALT technology works on the concept of volume of myopic defocus (VoMD), which creates a volume of myopic defocus in front of the retina with varying power, as illustrated in **Figure 1-9**. By generating controlled peripheral defocus, these lenses are designed to alter the visual signals received by the retina, acting as a “stop signal”, inhibiting axial elongation.⁹⁷

A two-year study involving 170 children aged 8-13 years with SER of -0.75 to -4.75D who wore both HALT and single vision lenses showed a mean myopia progression of -0.53

D with 67% efficacy compared to -0.81 D with single vision spectacles.⁹⁸ Similarly, the HALT spectacles exhibit 0.23 mm slowed axial length growth with 64% efficacy, compared to 0.36 mm with single-vision spectacles. A three-year follow-up study on HALT spectacles reported a mean progression of -0.33 D and axial elongation of 0.14 mm compared to -0.56 D and 0.28 mm with single vision spectacles.⁸⁴

Illustration of the study device providing a volume of myopic defocus (VoMD) (white shell) in front of the retina through 11 concentric rings of contiguous lenslets (A=depth of VoMD and B=distance from the retina).

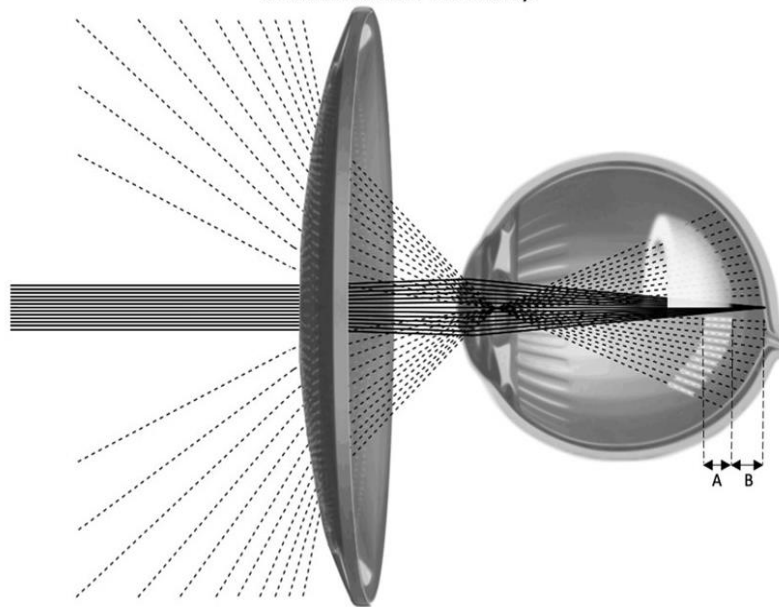


Figure 1-9: The Design of High Aspheric Lenslet Target (HALT) spectacle lens providing a volume of myopic defocus (VoMD) in front of the retina through the 11 concentric rings (A= Depth of VoMD and B = distance from the retina) Image reproduced with the permission from Bao J, Yang A, One-year myopia control efficacy of spectacle lenses with aspheric lenslets. *BJO* 2022; 106:1171-1176.⁸⁴

1.4.3 CARE Spectacles

The Cylindrical Annular Refractive Element (CARE™) spectacle (Zeiss, Oberkochen, Germany) lenses feature a central clear aperture with a diameter of 9.4 mm, surrounded by an annular micro-cylinder array, as illustrated in **Figure 1-10**. The micro-cylinder is arranged in a concentric pattern with a constant radial interval of 1.2 mm and the filling factor of the micro-cylinder is 60% in each period.⁸³ The unoccupied area between the adjacent micro-cylinder possesses the same power as the central clear aperture. The micro-cylinder contributes an additional + 8.00 D cylinder power to the base power of the occupied area. When light passes through the treatment zone, the wave emerging from the back surface of the lens exhibits a consistent disturbance caused by the micro-cylinder. These wave disturbances can be interpreted as high-order aberrations, which induce a blurred image on the peripheral retina.⁸³

A one-year result on the efficacy of CARE spectacles involving 118 children aged 8-12 years with myopia ranging from -1.00 to -4.00 showed a mean myopia progression of -0.56 D for CARE and -0.71 with single vision spectacles. Similarly, the axial length growth was 0.27 mm for CARE and 0.35 mm for single-vision spectacles.⁸³

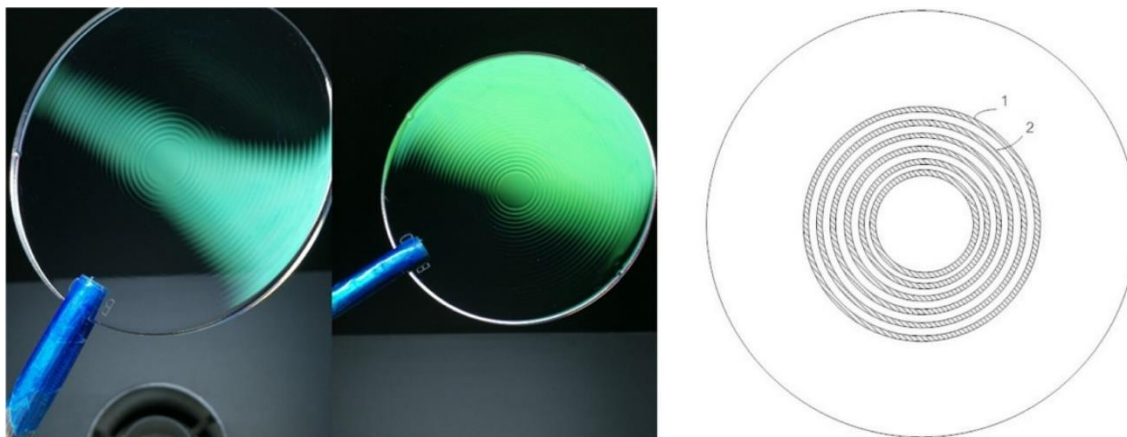


Figure 1-10: The patented lens picture of the Cylindrical Annular Refractive Element (CARE) spectacle lenses on the left and 1- the occupied annular micro cylinders and 2-the spacing of two adjacent micro-cylinders on the right. *The image is reproduced with permission from Xinting Liu, Pengqi Wang, One-year myopia control efficacy of cylindrical annular refractive element spectacle lenses, Acta Ophthalmologica, 2023, 101, 651–657.⁸³*

1.4.4 MiSight spectacles

MiSight spectacles (SightGlass Vision, Los Altos, CA, USA) utilize the Diffusion Optic Technology (DOT™) concept, which is based on the contrast reduction theory of myopia. The DOT lens integrates a single vision lens with a proprietary pattern of thousands of microscopic scattering DOTs, extending from edge to edge to form the treatment zone of the lens, as illustrated in **Figure 1-11** and **Figure 1-12**.⁸⁶ The commercially available DOT lens features a center aperture of approximately 5 mm in diameter, aligned with the optical center of the lens, which is surrounded by thousands of dots measuring 0.14 mm in diameter and 0.2 mm in height, with a spacing of 0.365 mm between the dots. The central aperture of the spectacle frame is customized for each wearer based on their pupillary distance and pupil center height. Unlike other myopia control spectacles that reduce peripheral hyperopic defocus, the DOT lenses aim to address the abnormal

contrast signaling in the myopic retina.⁸⁶ The one-year CYPRESS study by Rappon et al. demonstrated -0.40 D myopia progression, representing a 74% reduction in refractive error and a 0.15 mm slowed axial elongation compared to control spectacles.⁸⁶ A 4-year follow-up study with DOT spectacles showed a myopia control effect of 0.33 D myopia progression and 0.13 mm slowed axial elongation.⁹⁹

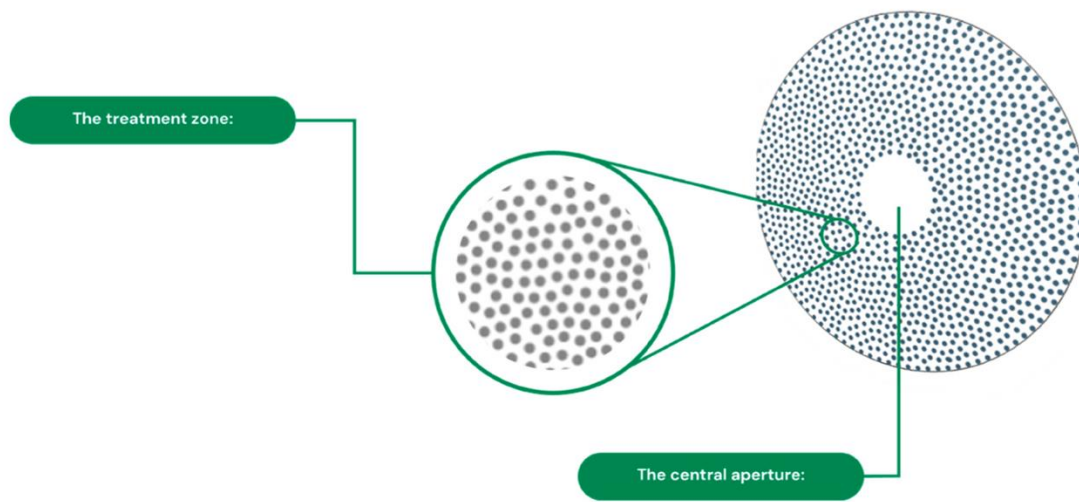


Figure 1-11: Representing the Diffusion Optical Technology (DOT) lens design. *Image obtained from [DOT White Paper 2023](#), with permission from [SightGlass Vision](#).*

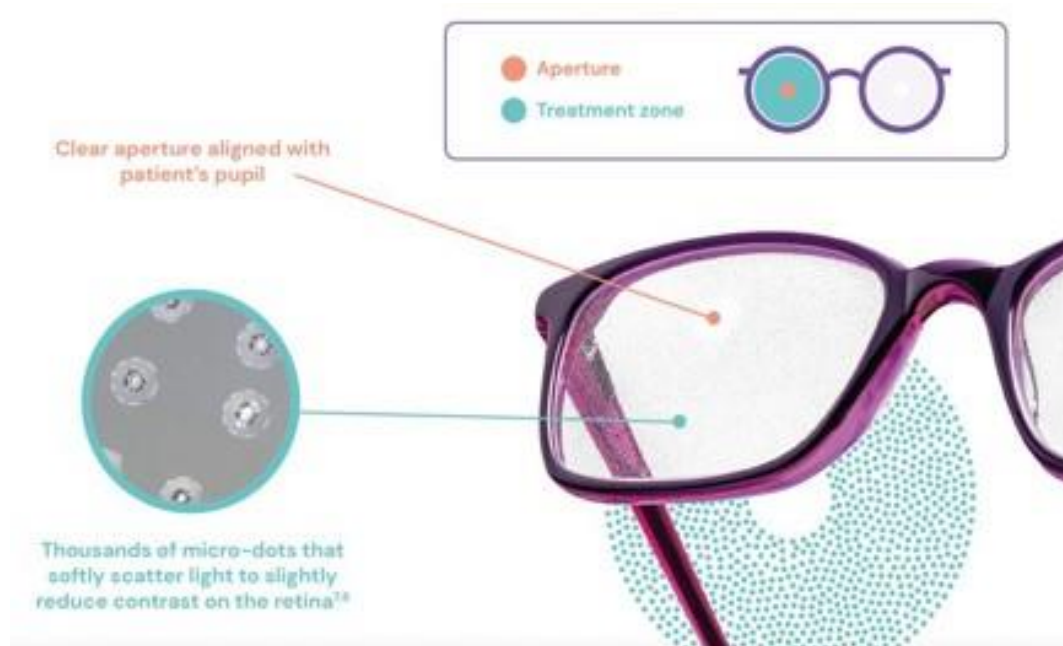


Figure 1-12: Showing the Diffusion Optical Technology (DOT) lens design. *Image obtained from [DOT White Paper 2023](#), with permission from [SightGlass Vision](#).*

1.5 Summary of literature review and need for clinical study

As discussed in the literature review above, myopia is a prevalent refractive condition of the eye that impacts nearly all ocular structures.¹⁰⁰ If not diagnosed or managed early, myopia may increase the risk of developing pathological changes in the eye, including retinal detachment, myopic maculopathy, and glaucoma, particularly in individuals with high myopia.⁷⁸ These complications highlight the importance of early detection and intervention. In recent years, various myopia control treatment options have emerged including spectacles, contact lenses, and pharmacological interventions. These treatments have demonstrated varying degrees of success in slowing myopia progression.^{82,83,86,88,91,92,95,99} Spectacles designed with specialized lenses such as multifocal or peripheral defocus lenses have shown promising results in reducing myopia

progression.^{57,83,84,94,99} Similarly, soft contact lenses and orthokeratology contact lenses have been effective in controlling myopia.^{88,89} Pharmacological treatments, particularly low-dose atropine eye drops have been widely studied for their efficacy in slowing myopia progression.⁹¹

While the precise mechanism of action of these various myopia control treatments are still under investigation, many studies have focused on their long-term effects on axial length and overall myopia progressions.^{46,82,83,90,94,97,99} However, to date, relatively little data is available on the impact of these treatments on the ocular structures such as those impacting the cornea, crystalline lens, retina, and choroid.^{96,101} This gap in knowledge highlights the need for a comprehensive assessment of the effects of myopia control treatment on the entire eye. Thus, this thesis aims to address this gap by investigating various parameters related to the use of a novel form of spectacle technology specifically designed to slow myopia progression.

Chapter 2 – Thesis rationale

Spectacles to slow the progression of myopia are garnering increasing interest. In comparison, pharmaceutical methods have an unclear mechanism of action, potential rebound effect, and unknown long-term complications from drug instillation.¹⁰² Contact lenses can be intricate to fit and may pose concerns for practitioners uncomfortable with fitting young children due to issues around compliance and potential infection and discomfort.¹⁰³ Spectacles are non-invasive and simple to prescribe to young children, making them a convenient option. They are generally well tolerated and are less intimidating, unlike other myopia control treatment options. However, some children might experience initial visual discomfort or adjustment issues when first wearing these spectacles.¹⁰⁴ Depending on the design prescribed, there might be slight visual distortions or peripheral blur, and it might take some time to get used to.¹⁰⁵ The rebound effect of the myopia control spectacles is unknown, but overall, the reported side effects to date are typically mild and temporary.¹⁰⁶

To date, relatively little data are available on the impact of spectacles on myopia progression and their mechanism of action. Few studies have determined the effect of spectacles such as progressive addition lenses (PALs) and defocus incorporated multiple segments lenses (DIMS) on structural and functional components of the eye, such as potential changes in the thickness of the choroid after wear and their effect on the lag of accommodation. Both PALS and DIMS have been shown to reduce myopia progression by addressing the hyperopic defocus and accommodative lag.^{107,108}

It is well known that humans have a lag of accommodation during prolonged near work, in that they do not focus precisely on the near object, but rather slightly behind the object of interest.¹⁰⁹ This lag of accommodation creates hyperopic retinal blur that signals eye growth, which might result in myopia onset or progression; some studies show that myopes tend to have a higher lag of accommodation than emmetropes.^{108,110-112} To our knowledge, no published literature extensively studied the effect of contrast management spectacles (CMS) that are designed to create a low level of blur on the retina, on the lag of accommodation and ocular structures. However, recent studies have shown that children wearing CMS experienced a notable reduction in myopia, with a difference of 0.52 D in spherical equivalent refraction (SER) and 0.20 mm in axial length over 4 years of wear.⁹⁹

Accurate measurement of ocular structures, especially choroidal thickness, is essential for understanding the effects of myopia control treatment on eye structures. Currently, various methods have been applied to determine the thickness of the choroid when examining the scans obtained using Optical Coherence Tomography (OCT), including manual, semi-automated, and automated approaches.^{113,114} Manual measurements, which involve the use of calipers to determine choroidal thickness directly on the OCT images, are notably time-consuming and susceptible to both inter- and intra-observer variability. In comparison, semi-automated measurements combine manual input with software assistance to improve efficiency and consistency. Automated methods, often employing advanced algorithms or machine learning techniques, aim to provide rapid and reproducible measurements with minimal intervention.^{113,115-118} Given the need for a

reliable measurement method in this context, this thesis evaluates the repeatability and reliability of each method.

To build on the current published work in the literature, this thesis investigated various issues relating to the use of a novel form of spectacle lens technology designed to slow the progression of myopia. Notably it:

- Measured the short-term effect of CMS on anterior segment biometrics;
- Tested the repeatability of different choroidal thickness measurement methods;
- Measured the short-term effect of CMS on retinal thickness, choroidal thickness, and choroidal vascularity index (CVI);
- Measured the short-term effect of CMS on the lag of accommodation.

All experiments in this study were conducted over a short duration and involved emmetropic children aged 6 to 17 years. A short-term approach was chosen to evaluate the eye's immediate physiological response to the optical intervention. This design helps identifying early changes in the key ocular parameters such as axial length and choroidal thickness, which are known to be predictive of long term ocular development.^{119,120} In the context of contrast management lenses, short-term wear can provide important insight into how the retina and other ocular structures respond to altered visual input. These early observations are essential for planning long-term studies and ensuring the intervention's safety and feasibility.

The decision to include emmetropic children within this specific age range was deliberate. This period represents a critical window in ocular development, during which the eye

continues to grow and remain responsive to environmental factors.^{121,122} Existing literature shows that even in the absence of refractive error, emmetropic eyes undergo axial elongation during childhood and adolescence, although more gradually than myopic eyes.^{123,124} Studying this group allows us to explore whether contrast-reducing patterns can influence structural changes in the eye before the onset of myopia.

As per the manufacturer's information, the SightGlass Vision DOT spectacle (CMS) lens design used in this thesis had a DOT size of 0.14 (± 0.03) mm, and the spacing between the DOTs was 0.365 mm, corresponding to approximately 17% of the lens coverage. This design resulted in a half-line decrease in the high contrast visual acuity when viewing through the DOT pattern. However, unlike commercially available DOT lenses, the spectacle lenses used in this study lacked a clear 5mm central zone. The entire lens was covered in DOTs, requiring participants to view through these DOTs. Using lenses with a fully covered DOT pattern enables the investigation of a uniform contrast reduction pattern across the entire visual field, providing insights into the maximal potential impact of contrast modulation on the ocular structures.



Figure 2-1: Above - commercially available DOT Spectacles with approx. 5 mm clear central zone, below – full-field DOT spectacles used in this thesis.

Additionally, +3.00 single vision lenses were employed as a positive control against the CMS. The use of +3.00D myopic defocus lenses is well established in the literature on ocular growth regulation and emmetropization.^{22,125,126} Both animal and human studies have consistently shown that imposed myopic defocus can inhibit axial elongation and slow myopia progression.¹²⁵⁻¹²⁹ Given that +3.00D defocus is known to produce a reliable

inhibitory effect on eye growth, it serves as an appropriate benchmark for validation and interpreting the effect of the CMS intervention.

Chapter 3 - Effect of short-term wear of contrast management spectacles on anterior segment biometrics and axial length

3.1 Introduction

Myopia is a common refractive error that primarily affects children and young adults. It typically develops at the age of 8.^{29,130} The underlying factor for the onset or development of myopia is still under investigation. However, the literature suggests that myopia most commonly results from an increase in the axial length of the eyeball or changes in the corneal or crystalline lens curvature.^{131,132} Many studies have shown a correlation between myopia and ocular biometrics that include central corneal thickness, anterior chamber depth, crystalline lens thickness, and axial length.^{133,134 135,136}

A recent study by Zhou et al. indicates that the thinner central corneal thickness might be a risk factor for myopia progression in children.¹³² Another study by Chang et al. suggests that myopic eyes have thinner corneal thickness and are positively correlated with increased axial length.¹³⁷ Similarly, a retrospective study by Srivannaboon showed a significant correlation between corneal thickness and the level of myopia.¹³⁸ Moreover, Richdale et al. reported a significant increase in axial length, vitreous chamber depth and ciliary ring diameter with increased myopia in adults. This increase in myopia was also associated with a steeper cornea and anterior lens surface and lens thickness.¹³⁶ Additionally, Miao et al. found a greater anterior chamber depth, greater axial length and increased white-to-white corneal diameter in patients with high axial myopia.¹³⁹

While some studies have measured the effect of myopia control treatment on ocular structures,¹⁴⁰⁻¹⁴² to our knowledge, no published study has investigated the short-term effect of contrast management spectacles on anterior segment biometrics and axial length. Therefore, this experiment aimed to measure the short-term effect of contrast management spectacles on the anterior segment biometrics (central corneal thickness (CCT), anterior chamber depth (ACD), crystalline lens thickness (LT)) and axial length (AL).

3.2 Methods

This was a 2-visit, prospective, randomized, participant-masked study. A total of 30 participants, aged between 8 to 14 years who were not receiving medication for any ocular or general health and who were not undergoing myopia control treatment, were recruited for this study. Participants with a spherical equivalent within +1.00D and -0.75D, as determined by the Grand Seiko WAM 5500 open-field autorefractor (Shigiya Machinery Works LTD, Hiroshima, Japan) under non-cycloplegic conditions, were included. The participants attended a screening visit where consent was obtained, and participant eligibility was determined. For this study, the order of the spectacles and the eye to be measured first was randomized. To control diurnal variation, the study measurements were taken approximately at the same time on both visits and at least 2 hours after waking.^{129,143}

Baseline anterior segment biometrics measurements: CCT, ACD, LT, and AL were obtained using the Zeiss IOL Master 700 (Carl Zeiss AG, Oberkochen, Germany).

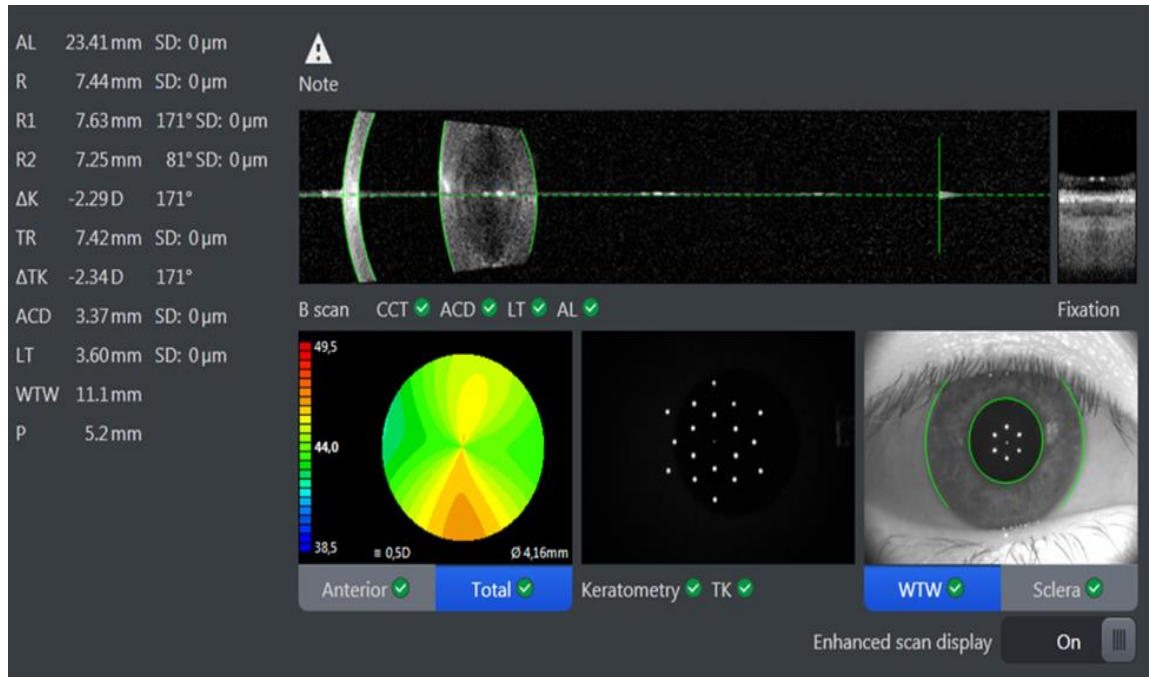


Figure 3-1: Example of an anterior segment scan using the IOL Master 700

Following the baseline measurements, participants were asked to wear the study spectacles in a randomized order for 60 minutes. The study spectacles were comprised of either contrast management spectacles (CSM) (SightGlass Vision, Los Altos, CA, USA) or +3.00 clear spectacle lenses (control). For this study, +3.00 spectacle lenses were used as a positive control to induce myopic defocus. A previous study demonstrated a significant reduction of 13 µm in axial length after an hour of short-term exposure to monocular myopic defocus using +3.00 lenses.¹²⁹ Participants wore the study spectacles and watched age-appropriate videos for 60 minutes at a 3m distance. Biometric scans were repeated after 30 minutes and 60 minutes of watching the videos. Participants returned for a second visit to wear the other type of spectacles (CMS or +3.00 control lenses) for 60 minutes, and the same procedures, including baseline scans, were repeated as described previously.

3.3 Statistical Analysis

Statistical analysis was conducted using IBM SPSS version 29 (IBM Corp Armonk, NY). Shapiro-Wilk test was used to test normality and Repeated Measures ANOVA was used to test the effect of the +3.00 control spectacles and CMS after 30 minutes and 60 minutes of wear. A paired t-test was used to compare the differences in baseline measurements between both visits. A p-value of <0.05 was considered statistically significant. All the data were analyzed for the right eye only.

3.4 Results

A total of 30 participants were enrolled in the study and completed all assessments (17 female, 13 male). The mean age of the participants was 10.9 ± 1.7 years (median 11 years, ranging from 8 to 13 years). The mean spherical equivalent refraction (SER) of the right eye was 0.35 ± 0.29 . All the data for AL, CCT, ACD, and LT were normally distributed when examined using the Shapiro-Wilk test ($p > 0.05$ for all). A Bonferroni correction was used to confirm the significance.

Table 3-1: Mean axial length, central corneal thickness, anterior chamber depth, and lens thickness at baseline and after 30 and 60 minutes of wear for the right eye (n=30)

OD	AL (mm)	CCT (μm)	ACD (mm)	LT (mm)
Baseline CMS	23.37 ± 0.76	558.66 ± 36.44	3.70 ± 0.30	3.42 ± 0.17
CMS 30 Minutes	23.37 ± 0.76	555.70 ± 36.02	3.70 ± 0.30	3.42 ± 0.17
CMS 60 Minutes	23.36 ± 0.76	555.83 ± 36.30	3.70 ± 0.31	3.42 ± 0.18
Baseline Control	23.38 ± 0.76	558.46 ± 36.86	3.69 ± 0.32	3.43 ± 0.20
Control 30 Minutes	23.37 ± 0.77	557.86 ± 36.85	3.74 ± 0.30	3.38 ± 0.17

Control 60 Minutes	23.37 ± 0.76	557.26 ± 37.45	3.74 ± 0.30	3.38 ± 0.16
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3.4.1 Axial Length (AL)

A two-way RMANOVA was performed to compare the effect of the +3.00 control spectacles and CMS on axial length at baseline (before spectacle wear), 30, and 60 minutes post-spectacle wear. RMANOVA showed a significant decrease in AL (0.006 mm or 6 μ m) before and after 1 hour of wearing both control ($p = 0.02$) and CMS ($p = 0.01$). The baseline measurements between visit 1 and visit 2 were also compared to test the repeatability, and no significant difference was observed in AL at baseline between both visits ($p > 0.05$). Similarly, pairwise comparison showed no significant difference between +3.00 control spectacles and CMS at both 30- and 60-minute intervals. No difference in spectacle use ($F_{1,29} = 0.696$, $P = 0.41$, Effect size = 0.02, Power = 0.12) but a significant difference between time points ($F_{1.818,52.726} = 5.182$, $P = 0.01$, Effect size = 0.07, Power = 0.80) was observed and no significant interaction between the spectacles and time ($F_{2, 58} = 2.380$, $P = 0.10$, Effect size = 0.76, Power = 0.46) were observed

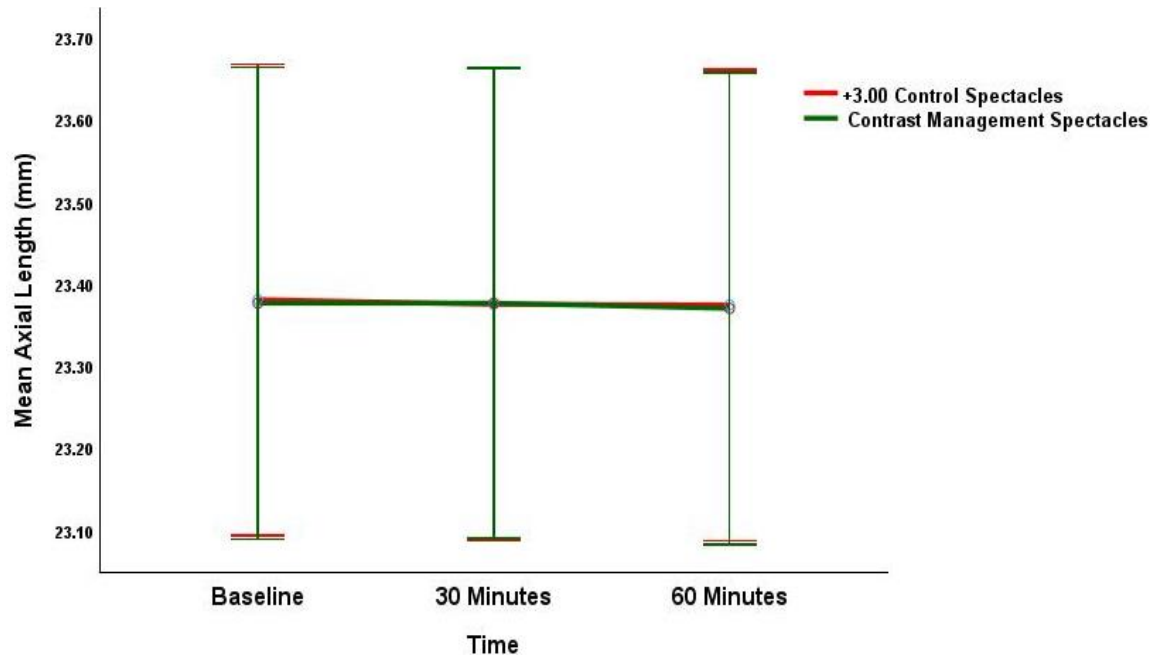


Figure 3-2: Mean axial length for contrast management spectacles and +3.00 control spectacles at Baseline and after 30 and 60 minutes of wear (right eye).

3.4.2 Central Corneal Thickness (CCT)

A two-way RMANOVA was performed to compare the effect of the +3.00 control spectacles and CMS on CCT at baseline (prior to spectacle wear), 30-, and 60-minutes post spectacle wear. RMANOVA showed no significant difference before and after the +3.00 control spectacle wear ($p = 1.00$). A significant reduction ($p < 0.001$) was seen in CCT between baseline and 30 minutes ($2.96 \mu\text{m}$), and baseline and 60 minutes for CMS ($2.83 \mu\text{m}$), however, no significant difference was observed between the 30- and 60-minute time points ($p = 1.00$). The pairwise comparison showed a significant difference of $p = 0.02$ at 30 minutes ($2.16 \mu\text{m}$), between +3.00 control spectacles and CMS. No difference in spectacle use ($F_{1,29} = 2.12$, $P = 1.56$, Effect size = 0.06, Power = 0.29) but a significant difference between time points ($F_{1.858,53.877} = 12.37$, $P < 0.001$, Effect size = 0.29, Power =

0.99) were observed. Similarly, significant interactions were observed between spectacles and time ($F_{2, 58} = 3.250$, $P = 0.04$, Effect size = 0.10, Power = 0.59) were observed.

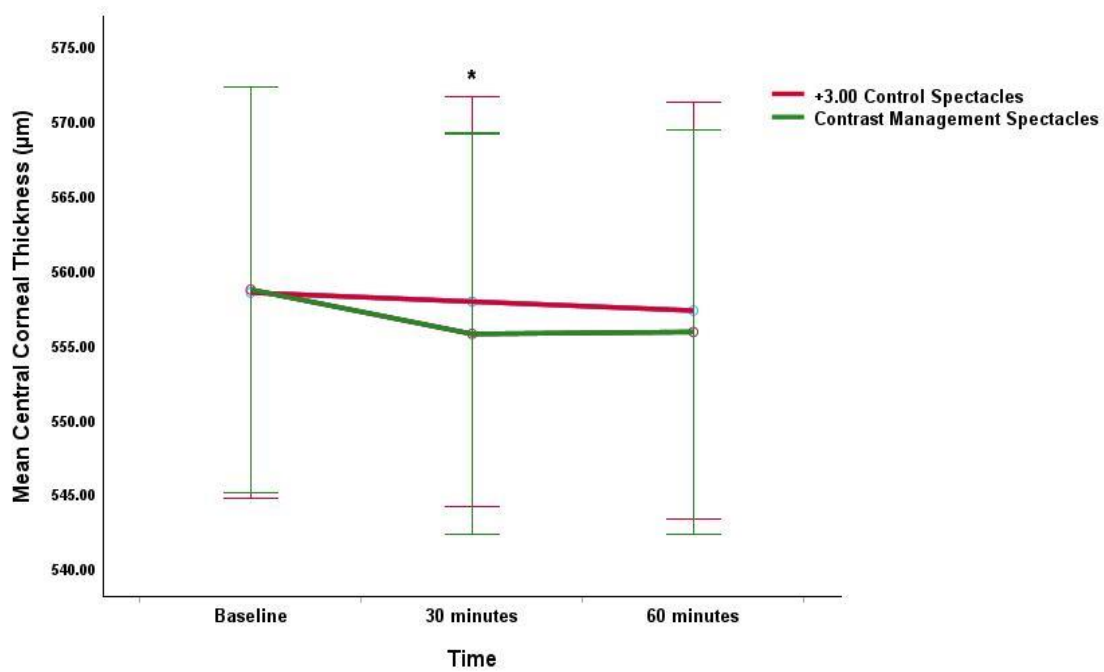


Figure 3-3: Mean central corneal thickness for contrast management spectacles and +3.00 control spectacles at Baseline and after 30 and 60 minutes of wear (right eye). * Represents a significant difference between spectacles.

3.4.3 Anterior Chamber Depth (ACD)

A two-way RMANOVA was performed to compare the effect of the +3.00 control spectacles and CMS on ACD at baseline (prior to spectacle wear), 30-, and 60-minute post-spectacle wear. An RMANOVA showed no significant difference before and after the CMS wear. A significant increase ($p < 0.001$) was seen in ACD between baseline and 30 minutes (0.049 mm), and between baseline and 60 minutes (0.050 mm), for +3.00 control spectacles; however, no significant difference was observed between the 30- and 60-minute time points. The pairwise comparison showed a significant difference ($p < 0.001$)

at 30 minutes and 60 minutes between the +3.00 control and CMS. A significant difference in spec use ($F_{1,29} = 12.75$, $P = 0.001$, Effect size = 0.30, Power = 0.93) and a significant difference between time points ($F_{1,222, 35.443} = 17.887$, $P < 0.001$, Effect size = 0.38, Power = 0.99) were observed. Similarly, significant interactions were observed between spectacles and time ($F_{2, 58} = 10.757$, $P < 0.001$, Effect size = 0.27, Power = 0.92) were observed.

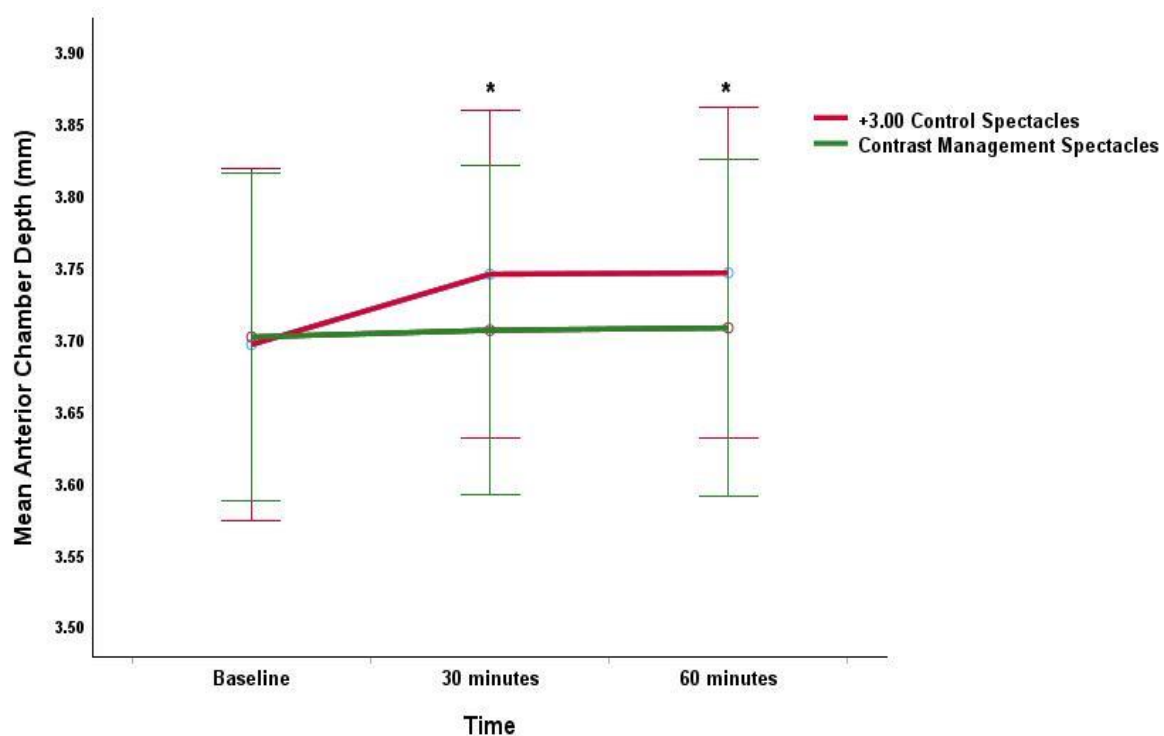


Figure 3-4: Mean anterior chamber depth for contrast management spectacles and +3.00 control spectacles at Baseline and after 30 and 60 minutes of wear (right eye). * Represents a significant difference between spectacles.

3.3.4 Crystalline Lens Thickness (LT)

A two-way RMANOVA was performed to compare the effect of the +3.00 control spectacles and CMS on LT at baseline (prior to spectacle wear), 30-, and 60-minute post-

spectacle wear. An RMANOVA showed no significant difference before and after the CMS wear. A significant difference ($p < 0.001$) was seen in LT between baseline and 30 minutes (0.05 mm), and between baseline and 60 minutes for +3.00 control spectacles (0.05 mm), indicating a decrease in LT, however, no significant difference was observed between 30- and 60-minute time points. The pairwise comparison showed a significant difference ($p < 0.001$) at 30 minutes and 60 minutes between +3.00 control spectacles and CMS. A significant difference in spec use ($F_{1,29} = 8.140$, $P = 0.008$, Effect size = 0.21, Power = 0.78) and a significant difference between time points ($F_{1,294, 37.540} = 8.111$, $P < 0.001$, Effect size = 0.21, Power = 0.85) were observed. Similarly, significant interactions were observed between spectacles and time ($F_{2, 58} = 8.315$, $P < 0.001$, Effect size = 0.22, Power = 0.85) were observed.

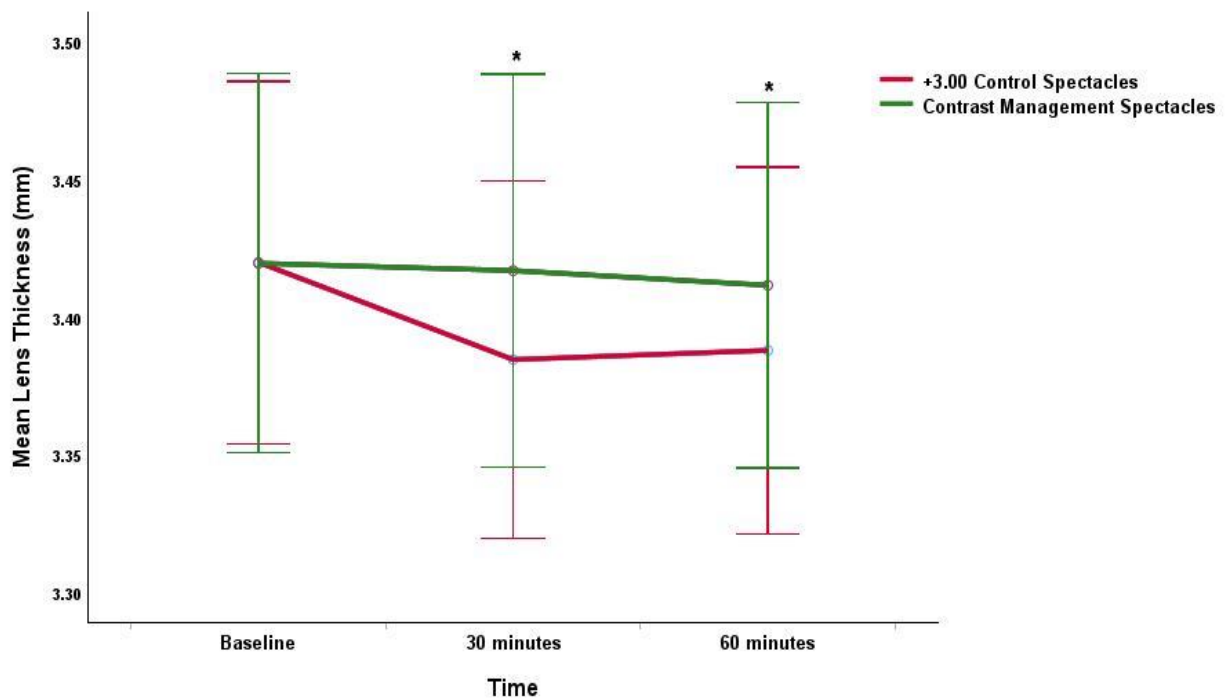


Figure 3-5: Mean lens thickness for contrast management spectacles and +3.00 control spectacles at Baseline and after 30 and 60 minutes of wear (right eye). *Represents a significant difference between spectacles.

3.4 Discussion and Conclusion

This study aimed to measure the short-term effect of CMS on the anterior segment biometrics and axial length in emmetropic children 8-14 years of age. The participants were instructed to focus on the TV screen at a 3m distance and avoid using phones or looking at close objects to prevent the effect of accommodation on axial length and anterior segment biometrics.^{135,144}

The study found no significant differences in the ACD, LT, and over 60 minutes of wearing the CMS. However, a statistically significant decrease in AL and CCT was observed after 60 minutes of wearing the CMS. The change in AL was relatively small, with an average reduction of 6 μm and a statistical significance of $p < 0.001$ between baseline and

60 minutes. The results from this study are similar to the findings of Yi et al. on short-term exposure to coaxial (one focal point +10.00D) and non-coaxial (multiple focal points +10.00D) plus power lenslets, which resulted in a significant reduction in AL.¹⁴⁵ This study involved six young subjects who viewed a movie through these lens designs, with AL measured using the Lenstar LS-900 biometer at baseline, 20 minutes, and 40 minutes post-exposure. The results demonstrated a significant decrease in AL of 5.7 μm for the coaxial design and 8.3 μm for the non-coaxial design after 40 minutes.¹⁴⁵ While both studies examined short-term exposure to positive test lenses, the study by Yi et al. utilized a +10.00D defocus, whereas the current study used plano CMS and +3.00 control spectacles.

Similarly, Guimaraes et al. investigated the short-term effect of defocus-incorporated multiple-segment (DIMS) lenses on myopic children from 4 to 17 years of age.¹⁴⁰ This study found a reduction in AL elongation of 2 μm with DIMS spectacles compared to 57 μm with Atropine 0.01% over six months. Although both studies included children, Guimaraes et al. conducted a retrospective analysis of data collected over six months, focusing on myopic children with a spherical equivalent of greater than -0.75D.¹⁴⁰ Moreover, the change in CCT was relatively small, with an average reduction of 3 μm and a statistical significance of $p < 0.001$ between baseline and 30 minutes and between baseline and 60 minutes. changes are not considered clinically significant.^{145,146}

Additionally, wearing the +3.00 myopic defocus control spectacles showed no notable changes in CCT. However, a statistically significant increase of 0.05 mm in ACD and a decrease of 0.05 mm in LT were observed; similarly, a significant reduction in AL of 6 μm

was noted with +3.00 myopic defocus control spectacles. These findings align with Read et al., who reported no significant difference in CCT, ACD, and LT after monocular exposure to +3.00 myopic defocus but did observe a significant reduction in AL by 13 μm .¹²⁹ The study by Read et al. involved near-emmetropic young adults with an age range of 20-27 years and refractive error of +0.25 to -1.12 D sphere, with cylinder power ranging from 0.00 to -1.00 DC. In our study, the participants' ages ranged from 8 to 13 years, with a refractive error of -0.25 to +1.12 D sphere and cylinder power ranging from -0.25 to -0.75 DC. Both studies used the IOL Master for AL measurement; however, a Pentacam was employed to measure the anterior eye biometrics in the Read et al. study.¹²⁹

In conclusion, short-term wear of myopia control contrast management spectacles results in a statistically significant reduction in AL and CCT after 1 hour of wear. However, these changes are minimal and might not be clinically significant.

After examining the impact of CMS on the anterior segment biometrics, the subsequent step was to assess the impact of CMS on the posterior segment. Given the significance of accuracy and repeatability in choroidal thickness measurements, the next chapter focused on evaluating various methodologies for measuring choroidal thickness in the same cohort of emmetropic children. The objective was to conduct a thorough assessment of different measurement methods to determine an accurate and repeatable method for choroidal thickness measurements.

Chapter 4 – Testing repeatability in methods of choroidal thickness measurement using optical coherence tomography

4.1 Introduction

The choroid, a vascular layer of the eye, has been shown to play a role in emmetropization.¹⁴⁷ Research indicates that choroidal thickness varies with age and the severity of myopia.⁶ Increasing evidence further highlights the choroid's significant role in myopia and associated pathologies such as myopic choroidal neovascularization, myopic macular degeneration, choroidal atrophy, and vitreomacular disorders.¹⁴⁸⁻¹⁵¹ Thinner choroidal thickness is notably linked to greater axial length and a higher degree of myopia,¹⁵² Making accurate and repeatable measurements of choroidal thickness is crucial. The average sub-foveal choroidal thickness (SFCT) in children is reported to range from 189 to 538 μm ,¹⁵³ while in young adults, it varies between 271 to 439 μm .¹⁴⁸ In children with myopia, the SFCT is observed to range from 108 to 359 μm ^{154,155} and in myopic adults, the SFCT falls between 96 to 245 μm .¹⁴⁸ According to Zhu et al. for each diopter increase in myopia, the SFCT decreases by 13 μm , and for every 1mm increase in axial length, it decreases by 23 μm .⁷³ In comparison, a study by Shao et al. indicates that in highly myopic eyes, the SFCT decreases by 5.1 μm per year of age, 9.2 μm with each 1D increase in myopia, and 22.6 μm for every 1mm increase in axial length.¹⁵⁵

Several methods have been adopted in the literature, with varying accuracy, to measure choroidal thickness (ChT). These include manual, semi-automated, and fully automated methods, and include recent advancements using artificial intelligence (AI)-

based automated software.¹⁵⁶⁻¹⁶⁵ The manual measurements require outlining the choroid boundary manually, which is time-consuming and tedious and inevitably brings inter-observer variability.^{164,165} Like the manual method, the semi-automated method is time-consuming and requires experienced practitioners to segment the choroidal layer properly.^{159,165}

Recently, imaging and measurement of choroidal thickness have improved with optical coherence tomography (OCT). These improvements include the use of a longer wavelength light beam in SS-OCT and the implementation of enhanced depth imaging mode in SD-OCT. These techniques facilitate the visualization of deeper layers of the eye, including the choroid and offer automated ChT measurements through OCT inbuilt software.^{166,167} However, manual intervention is still sometimes necessary for ChT segmentation accuracy, which might introduce bias. A recent study by Lee et al. on the measurement of ChT in healthy children showed a significant difference of 21 μm in SFCT between swept-source (Topcon Triton DRI, Plex Elite 9000, Inphenix SS-OCT) and spectral-domain (Cirrus HD SD 500, Spectralis SD, Optovue iVue80, 3D-OCT 1000) OCT, concluding that the measurements between the instruments are not interchangeable.¹⁶⁶

Current advancements in ChT measurements have led to the introduction of AI-based fully automated software, which offers better repeatability and requires less manpower.^{156,161,168-170} A study published by Lim et al. compared the manual measurement of SFCT between the Triton DRI-OCT and PLEX Elite 9000 with AI-automated techniques and suggests an excellent agreement in SFCT between the methods of

measurement.¹⁶¹ Other studies by Ibrahim et al. and Vupparaboina et al. show a good agreement between the AI-automated software and manual ChT measurements using the Heidelberg OCT.^{169,170}

The typical range of SFCT is between 250-350 μm , influenced by factors such as age, sex, diurnal variation, and refractive error.¹⁷¹ Consequently, it is crucial to employ a highly accurate and repeatable method of measuring ChT. This study, therefore, aimed to evaluate the repeatability of SFCT measurements using manual, semi-automated, automated (OCT Topcon Advanced Boundary Segmentation software) and AI-based automated software methods. Following this, the two highly repeatable methods were compared to measure the choroidal thickness at the Early Treatment Diabetic Retinopathy Study (ETDRS) regions of the choroid.

4.2 Methods

This was a 2-visit prospective study. A total of 30 emmetropic participants aged between 8 to 14 years were recruited for the study. These participants had a spherical equivalent within +1.00D and -0.75D and did not receive medication for any ocular or general health and were under no myopia control treatment. The participants attended a screening visit where consent was obtained, and the participant's eligibility was determined. The screening visit was followed by the study visits for eligible participants on the same day.

During the screening visit the following tests were conducted:

Autorefraction: The participants were asked to focus on a target while seated at a Grand Seiko WAM 5500 open-field autorefractor (Shigiya Machinery Works LTD, Hiroshima, Japan) that determined their non-cycloplegic prescription for both eyes.

Posterior segment scans of both eyes were taken for each participant using the 3D(H)+5LineCross Combi scan mode using the Triton Swept Source Optical Coherence Tomography (SS-OCT) (Topcon, Tokyo, Japan) for both visits. Three volume scans (each volume scan consists of 256 B-scans) were taken of each eye at each visit to test the repeatability of the measurements. The choroidal thickness was measured from the scans obtained from the OCT using the a) manual method of measurement by Image J software (Laboratory of Optical and Computational Instrumentation (LOCI), University of Wisconsin, USA) b) semi-automated measurements by the inbuilt software in the Triton OCT c) automated software for the choroidal thickness measurement (OCT Topcon Advanced Boundary Segmentation Software) d) AI-based automated software for the choroidal thickness measurement (Choroidal Analysis Research Lab (CAR), University of Pittsburgh, USA).

4.2.1 Image Analysis

4.2.1.1 Manual Method

Three repeated volume scans were conducted for the right eye. From each scan, one horizontal and one vertical scan featuring a pronounced foveal pit were selected. The

choroidal thickness was manually measured using the arrow tool function in the Image J software after calibrating the ruler scale for micron measurement. Measurements were taken at the center of the fovea using the foveal pit and the IS/OS (photoreceptor inner and outer segment) junction as reference points. The choroidal thickness from both horizontal and vertical scans was averaged, resulting in three measurements for each set of repeated scans (each comprising one horizontal and one vertical scan). These averaged measurements were subsequently utilized for analysis.

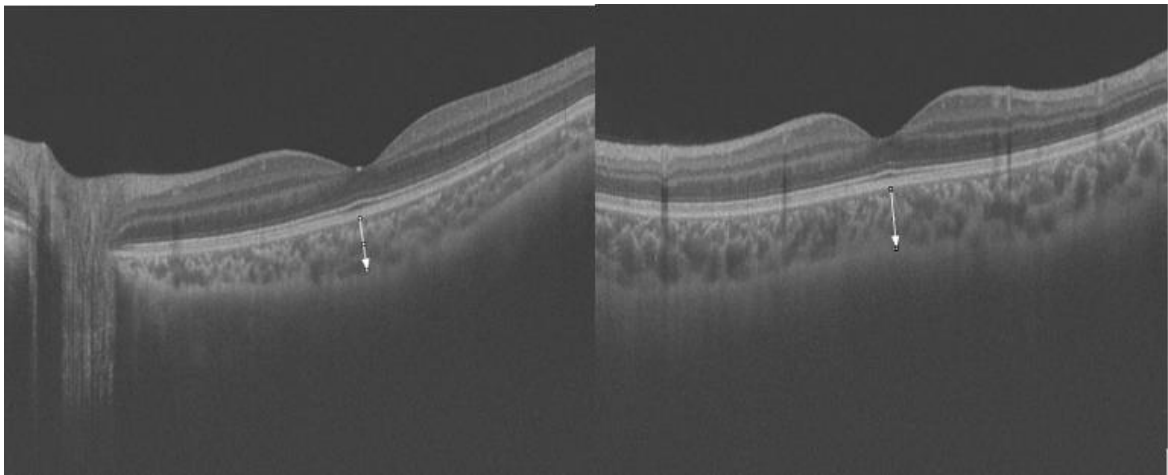


Figure 4-1: Example of a SFCT measurement using the arrow tool function in Image J in horizontal (left) and vertical scans (right) obtained from the DRI-Triton OCT (manual method).

4.2.1.2 Semi-Automated Method

In the semi-automated method, the same horizontal and vertical scans utilized in the manual measurement method were exported from the OCT, but these scans were pre-segmented for the anterior and posterior choroid by the TABS software in the OCT. If necessary, the segmentation was adjusted prior to export using the drawing tool available in the OCT TABS software. After exporting the images, the SFCT was measured in Image J using an arrow tool at the center of the fovea with the foveal pit and the IS/OS junction as

a reference point and the bottom green line (posterior choroid) as the endpoint as illustrated in **Figure 4-2** below. The choroidal thickness from both horizontal and vertical scans was averaged, resulting in three measurements for each set of repeated scans (each comprising one horizontal and one vertical scan). These averaged measurements were subsequently utilized for analysis.

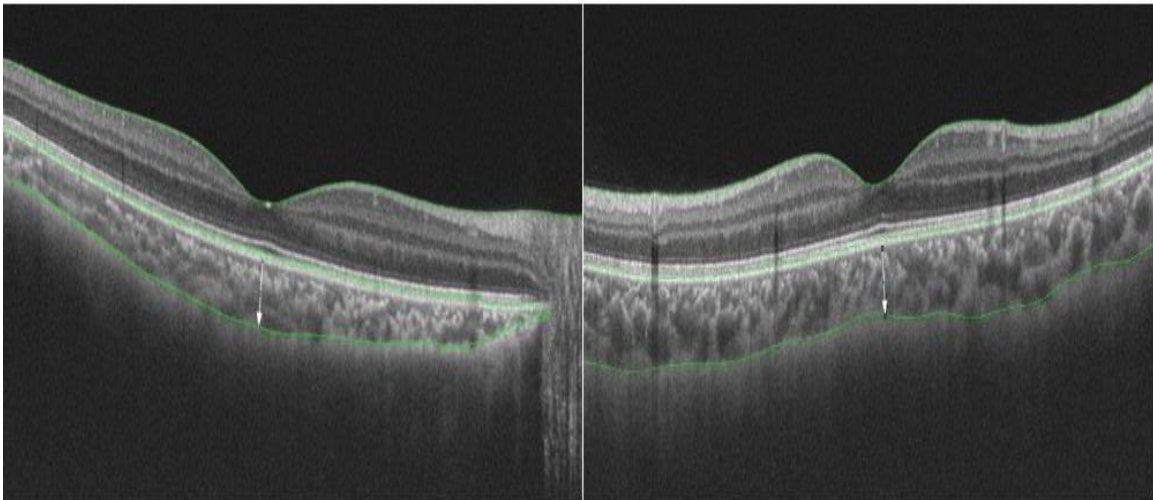


Figure 4-2: Example of a SFCT measurement using the Image J tool on the pre-segmented horizontal (left) and vertical scans (right) scan obtained from DRI-Triton OCT (semi-automated method).

4.2.1.3 Automated Method (OCT TABS™ software)

After each repeated volume scan an ETDRS map was generated by the Topcon Advanced Boundary Segmentation (TABS™) software in the Triton DRI OCT. The SFCT (central measurement circled in red in **Figure 4-3** below) from the ETDRS map was taken for each repeated scan and used for the analysis. ETDRS maps were generated by averaging the choroidal thickness from a volume scan that consisted of 256 B-scans.



Figure 4-3: Example of an SFCT measurement using the inbuilt automated software of the DRI Triton OCT (automated method OCT TABS™ software).

4.2.1.4 Automated Method (AI-based software)

These automated measurements were performed using a customized AI-based software designed to determine choroidal thickness.¹⁷⁰ The software processes the volume scans (each scan consists of 256 B scans) obtained from the 3D(H)+5 LineCross Combi scan mode in the DRI Triton OCT. The software crops the scans to focus on the area of interest and then generates binarized images. The binarization process converts grayscale or colored images into black-and-white areas, where white represents the luminal area and black represents the vascular area (blood vessels). After the binarization of all 256 scans, an ETDRS map was generated, showing the average choroid thickness from all 256 scans. Only the central measurement (SFCT) from the ETDRS map was used for the analysis.

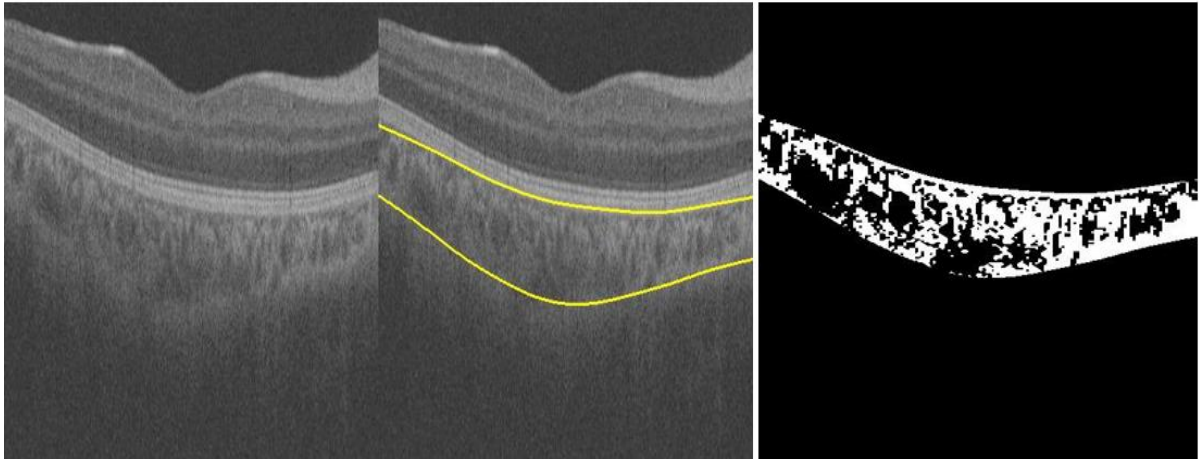


Figure 4-4: Example of a segmented and binarized image obtained using the AI-based automated software in one of the 256 scans exported from the DRI Triton OCT (Automated method (AI-based software)).

4.3 Statistical Analysis

Statistical analysis was performed using SPSS (IBM Corp Armonk, NY). The Shapiro-Wilk test assessed normality. Repeatability in SFCT between the three scans each individual visit and each method were analyzed a priori using RMANOVA. After confirming the repeatability, the SFCT data from each visit were pooled to assess the agreement between the four measurement methods using the Bland-Altman plot, and a paired t-test was used to test the difference between the methods. Following this analysis, Bland-Altman plots were generated to test the agreement of two automated methods at all ETDRS regions of the choroid.

4.4 Results

A total of 30 participants were enrolled in the study (17 female, 13 male). The mean age of the participants was 10.9 ± 1.7 years (median 11 years, ranging from 8 to 13 years). The mean refractive error was $+0.35 \pm 0.29$ spherical equivalent refraction (SER). All data

from the manual, semi-automated, and two automated methods were normally distributed when examined using the Shapiro-Wilk test ($p > 0.05$ for all).

4.4.1 Repeatability Analysis

For all four methods of ChT measurements applied, the repeatability between the scans from both the visits for all four methods was compared using the RMANOVA, and no statistically significant difference ($p > 0.05$ for all) was observed between the repeated measurements for all four methods for visit 1 (Manual: $F_{2, 58} = 0.058$, $P = 0.84$, Effect size = 0.002, Power = 0.05; Semi-automated: $F_{2, 58} = 0.742$, $P = 0.47$, Effect size = 0.025, Power = 0.16; TABS: $F_{2, 58} = 0.396$, $P = 0.61$, Effect size = 0.031, Power = 0.10; AI-based: $F_{2, 58} = 0.740$, $P = 0.45$, Effect size = 0.025, Power = 0.15) and visit 2 (Manual: $F_{2, 58} = 1.130$, $P = 0.32$, Effect size = 0.038, Power = 0.23; Semi-automated: $F_{2, 58} = 1.087$, $P = 0.32$, Effect size = 0.036, Power = 0.20; TABS: $F_{2, 58} = 1.169$, $P = 0.31$, Effect size = 0.039, Power = 0.22; AI-based: $F_{2, 58} = 1.578$, $P = 0.21$, Effect size = 0.052, Power = 0.28). The three scans from visit 1 were compared to the three scans from visit 2 using a paired t-test. No significant difference ($p > 0.05$ for all) was observed between the visits for any ChT measurement method.

Table 4-1: Mean repeatability of Manual, Semi-Automated, Automated (TABS) and Automated (AI-based software).

Methods/Repeatability	Manual	Semi-automated	Automated (TABS)	Automated (AI-based)
Visit 1				
Scan 1	344.70	304.10	300.70	295.90
Scan 2	343.05	310.90	298.20	293.20
Scan 3	343.03	304.70	298.00	293.60

Average	343.56 ± 93.56	306.56 ± 75.86	298.96 ± 73.55	294.23 ± 46.64
Visit 2				
Scan 1	344.00	300.00	300.20	292.60
Scan2	342.60	307.20	296.10	293.00
Scan 3	348.10	309.90	297.10	296.80
Average	344.90 ± 96.56	305.70 ± 76.91	297.80 ± 73.92	294.13 ± 46.18

4.4.2 Method Agreement

A Bland-Altman plot was used to assess the agreement between the four methods of choroidal thickness measurements. The agreement was evaluated by taking the average of all three volume scans collected at the respective visits. As shown in the bland-Altman plots below, the manual measurement method exhibited a weak agreement with the other three methods, displaying a larger bias across both visits. In contrast, a strong agreement was observed between the semi-automated method and the two automated measurement methods.

Similarly, a significant difference of $p < 0.001$ (for all) was observed when comparing the manual method and semi-automated, manual and automated (TABS), and manual and automated (AI-based software). However, no significant difference, $p > 0.05$ (for all), was observed between the semi-automated method and the two automated measurement methods. Though the mean bias was smaller between the two automated software's, based on the Bland-Altman plots, the AI-based automated method showed an upward slope, suggesting an increased difference between both methods with a thicker choroid.

The mean differences in the measurement methods are reported in Table 2. A positive value indicates that the method listed first resulted in a thicker SFCT.

Table 4-2: Mean difference between Manual, Semi-automated, Automated (TABS), and Automated (AI-based) methods of choroidal thickness measurement at visit 1 and visit 2

Method comparison	Visit 1	Visit 2
Manual vs Semi-automated	28.20 ± 31.40 µm	32.50 ± 25.50 µm
Manual vs Automated (TABS)	38.10 ± 23.70 µm	34.10 ± 29.30 µm
Manual vs Automated (AI-based)	39.30 ± 34.10 µm	38.64 ± 33.64 µm
Semi-automated vs Automated (TABS)	4.05 ± 32.40 µm	8.06 ± 19.90 µm
Semi-automated vs Automated (AI-based)	6.33 ± 31.80 µm	8.12 ± 39.10 µm
Automated (TABS) vs Automated (AI-based)	3.80 ± 31.10 µm	1.16 ± 26.80 µm

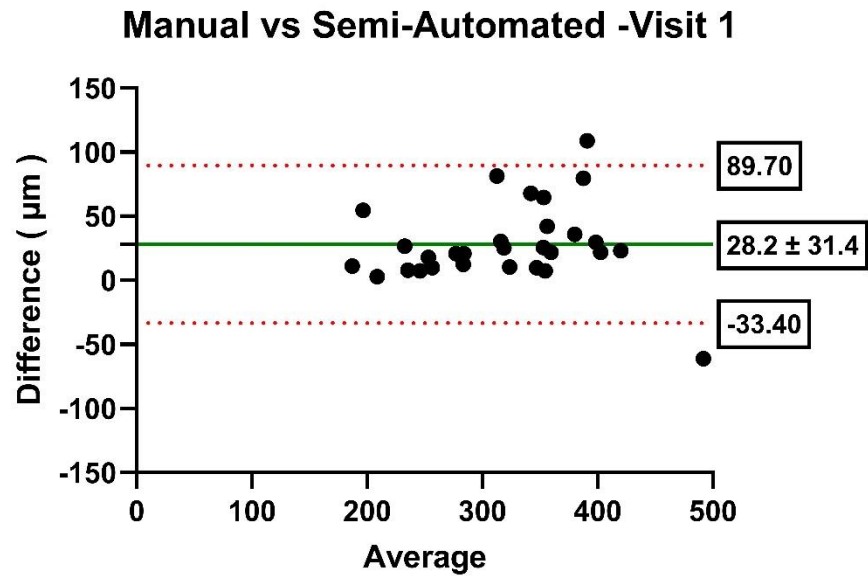


Figure 4-5: The Bland-Altman Plot showing the agreement between the manual and semi-automated methods of choroidal thickness measurements at visit 1. The green line is the mean difference $\pm$ SD, and the red dotted lines are the upper and lower 95% limits of agreement, with CI of 122. (The manual method determined a 28.2 μ m thicker choroid compared to the semi-automated method).

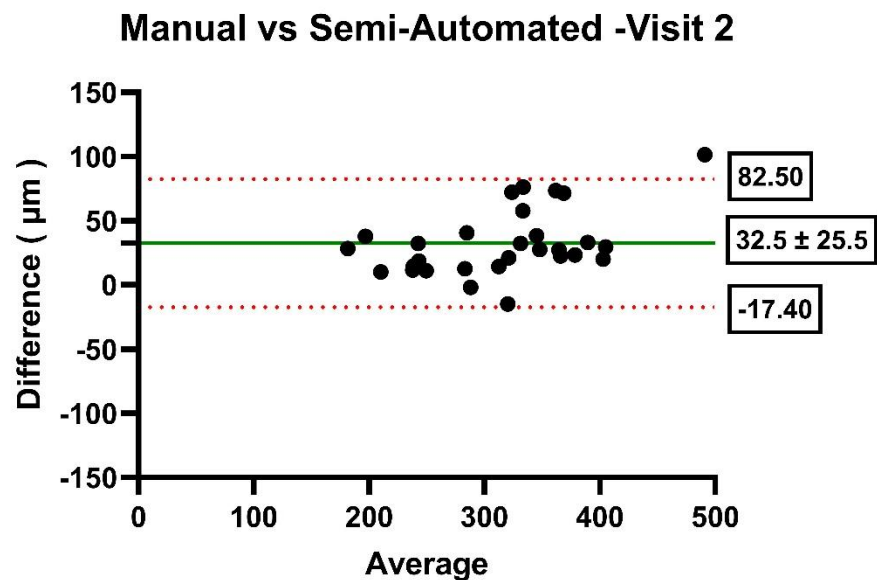


Figure 4-6: The Bland-Altman Plot showing the agreement between the manual and semi-automated methods of choroidal thickness measurements at visit 2. The green line is the mean difference $\pm$ SD and the red dotted lines are the upper and lower 95% limits of agreement, with CI of 99.9. (The manual method determined a 32.5 μ m thicker choroid compared to the semi-automated method).

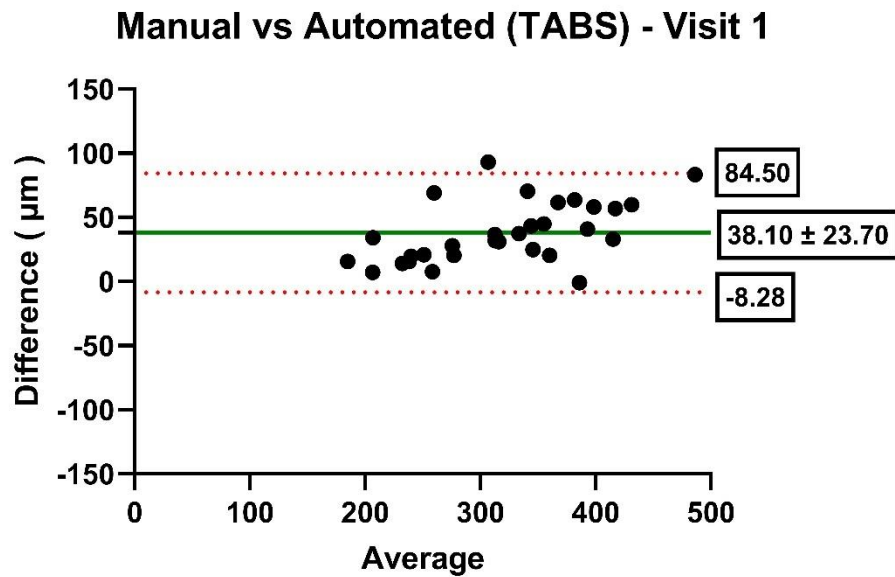


Figure 4-7: The Bland-Altman Plot showing the agreement between the manual and automated (TABS) methods of choroidal thickness measurements at visit 1. The **green line** is the mean difference $\pm$ SD and the **red dotted lines** are the upper and lower 95% limits of agreement, with CI of 92.5. (The manual method determined a 38.10 μm thicker choroid compared to the automated (TABS) method).

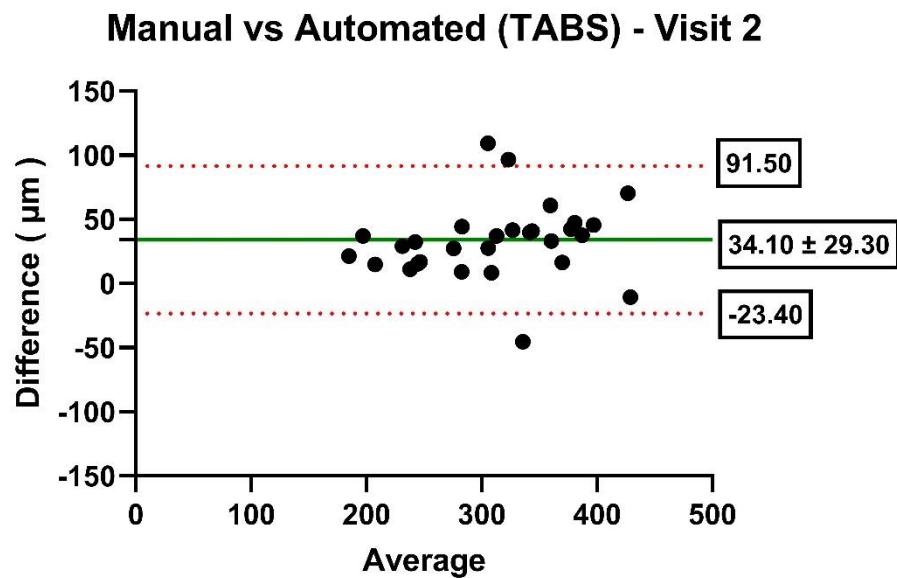


Figure 4-8: The Bland-Altman Plot showing the agreement between the manual and automated (TABS) methods of choroidal thickness measurements at visit 2. The **green line** is the mean difference $\pm$ SD and the **red dotted lines** are the upper and lower 95% limits of agreement, with CI of 114.9. (The manual method determined a 34.10 μm thicker choroid compared to the automated (TABS) method).

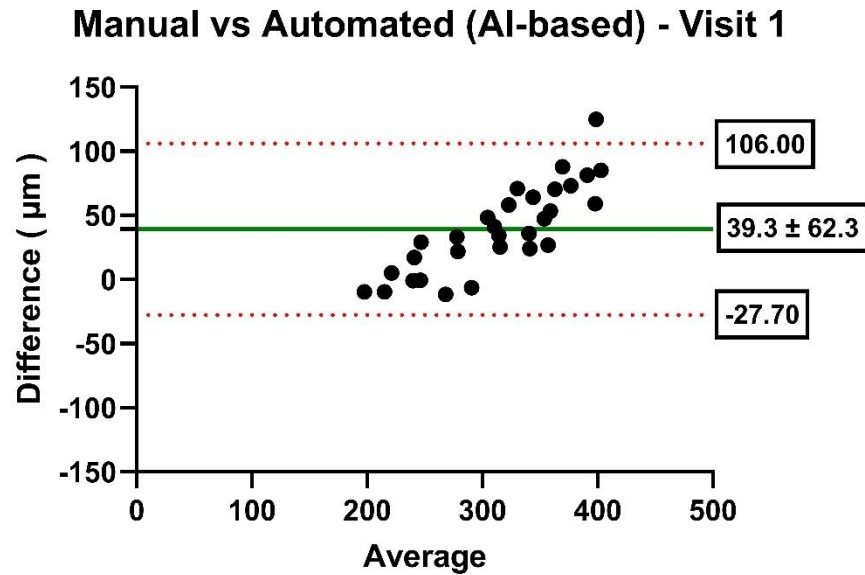


Figure 4-9: The Bland-Altman Plot showing the agreement between the manual and automated (AI-based) methods of choroidal thickness measurements at visit 1. The **green line** is the mean difference $\pm$ SD and the **red dotted lines** are the upper and lower 95% limits of agreement, with CI of 133.70. (The manual method determined a 39.30 μm thicker choroid compared to the automated (AI-based) method).

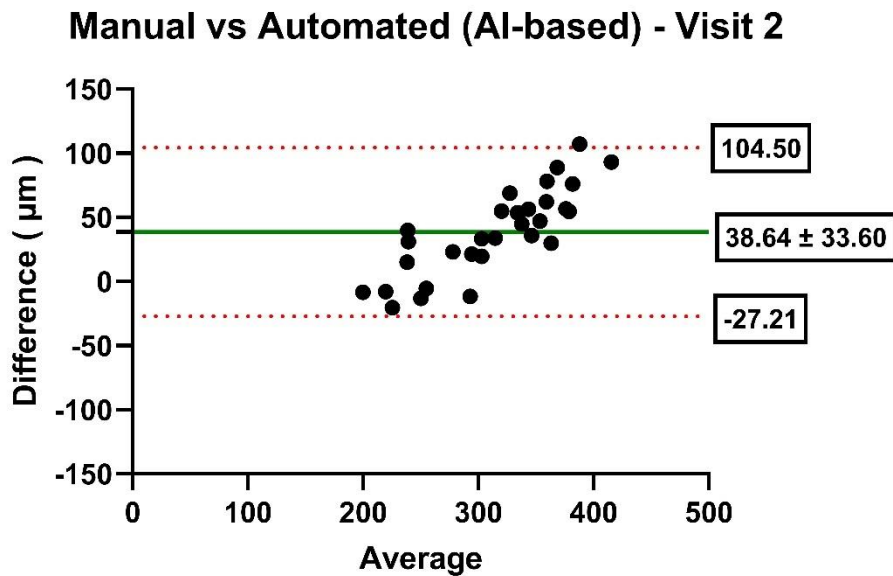


Figure 4-10: The Bland-Altman Plot showing the agreement between the manual and automated (AI-based) methods of choroidal thickness measurements at visit 2. The **green line** is the mean difference $\pm$ SD and the **red dotted lines** are the upper and lower 95% limits of agreement, with CI of 131.71. (The manual method determined a 38.64 μm thicker choroid compared to the automated (AI-based) method).

Semi-Automated vs Automated (TABS) - Visit 1

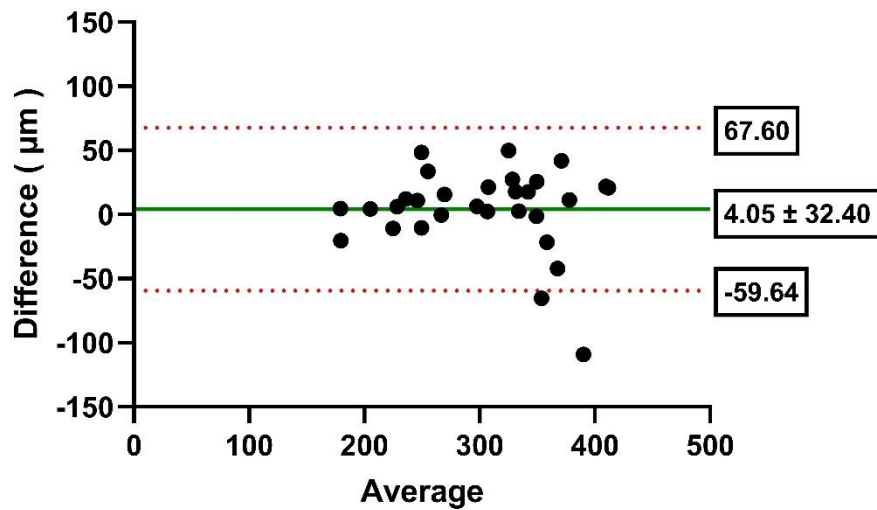


Figure 4-11: The Bland-Altman Plot showing the agreement between the semi-automated and automated (TABS) methods of choroidal thickness measurements at visit 1. The green line is the mean difference $\pm$ SD and the red dotted lines are the upper and lower 95% limits of agreement, with CI of 127.24. (The semi-automated method determined a 4.05 μ m thicker choroid compared to the automated (TABS) method).

Semi-Automated vs Automated (TABS) - Visit 2

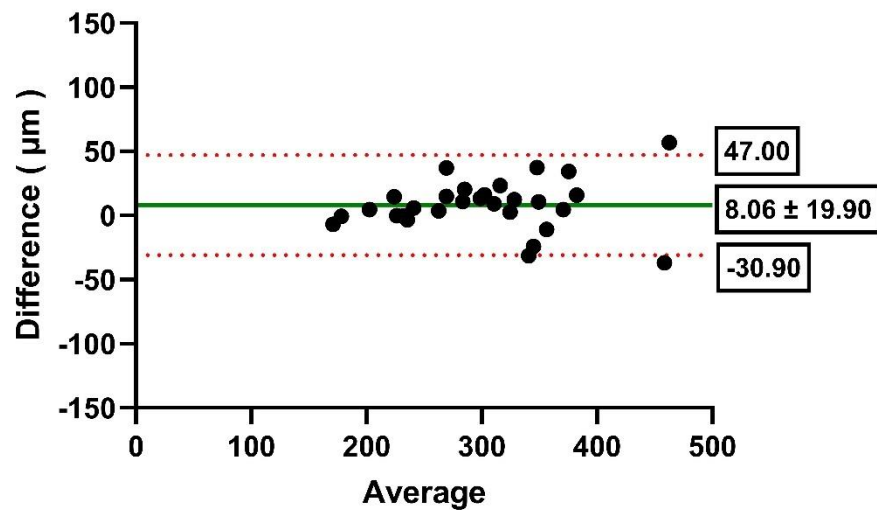


Figure 4-12: The Bland-Altman Plot showing the agreement between the semi-automated and automated (TABS) methods of choroidal thickness measurements at visit 2. The green line is the mean difference $\pm$ SD and the red dotted lines are the upper and lower 95% limits of agreement, with CI of 77.9. (The semi-automated method determined a 8.06 μ m thicker choroid compared to the automated (TABS) method).

Semi-Automated vs Automated (AI-based) - Visit 1

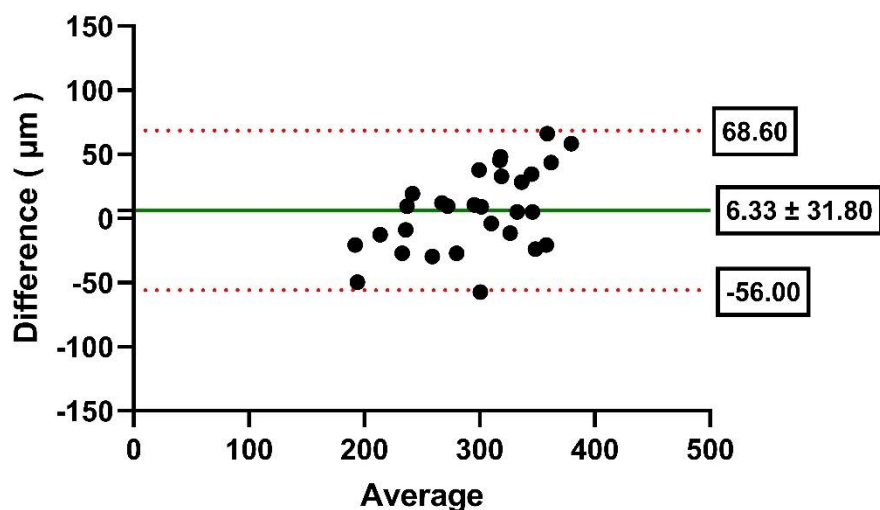


Figure 4-13: The Bland-Altman Plot showing the agreement between the semi-automated and automated (AI-based) methods of choroidal thickness measurements at visit 1. The green line is the mean difference $\pm$ SD and the red dotted lines are the upper and lower 95% limits of agreement, with CI of 124.6. (The semi-automated method determined a 6.33 μ m thicker choroid compared to the automated (AI-based) method).

Semi-Automated vs Automated (AI-based) - Visit 2

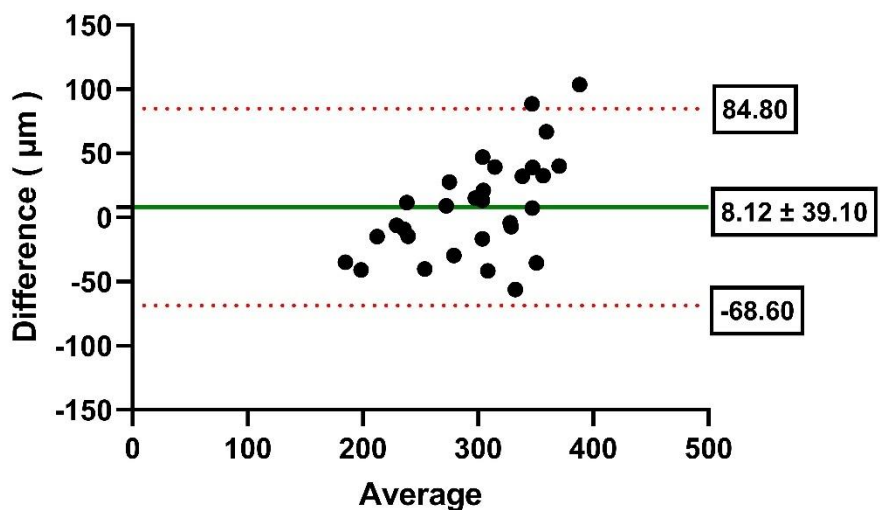


Figure 4-14: The Bland-Altman Plot showing the agreement between the semi-automated and automated (AI-based) methods of choroidal thickness measurements at visit 2. The green line is the mean difference $\pm$ SD and the red dotted lines are the upper and lower 95% limits of agreement, with CI of 133.40. (The semi-automated method determined a 8.12 μ m thicker choroid compared to the automated (AI-based) method).

Automated (TABS) vs Automated (AI-based) - Visit 1

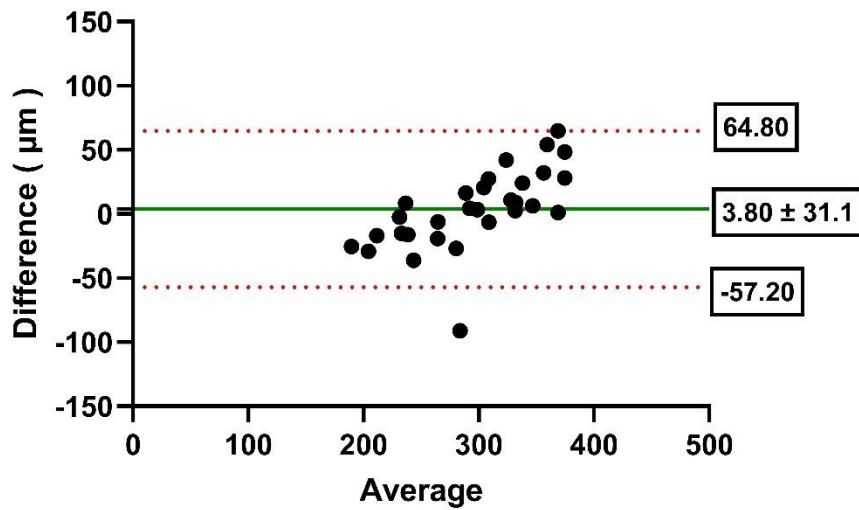


Figure 4-15: The Bland-Altman Plot showing the agreement between the two automated methods of choroidal thickness measurements at visit 1. The **green line** is the mean difference $\pm$ SD and the **red dotted lines** are the upper and lower 95% limits of agreement, with CI of 122.00. (The automated (TABS) method determined a 3.80 µm thicker choroid compared to the automated (AI-based) method).

Automated (TABS) vs Automated (AI-based) - Visit 2

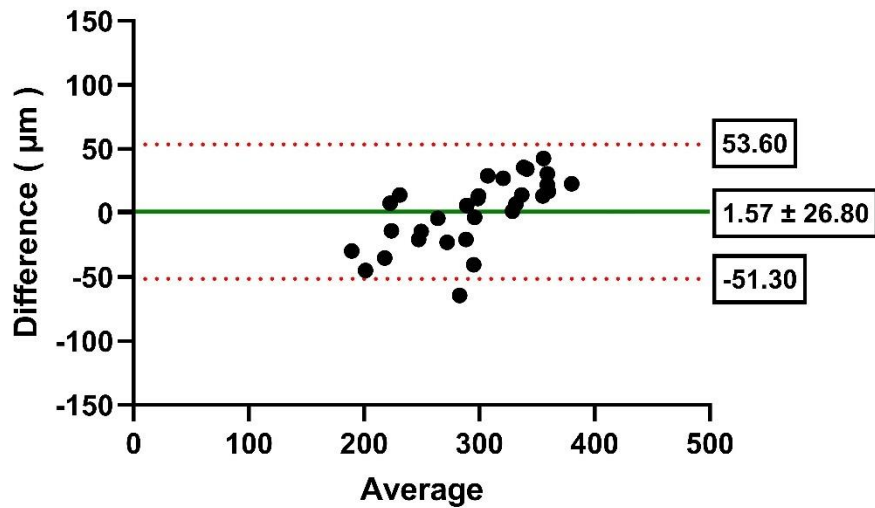


Figure 4-16: The Bland-Altman Plot showing the agreement between the two automated methods of choroidal thickness measurements at visit 2. The **green line** is the mean difference $\pm$ SD and the **red dotted lines** are the upper and lower 95% limits of agreement, with CI of 104.90. (The automated (TABS) method determined a 1.57 µm thicker choroid compared to the automated (AI-based) method).

4.4.3 Comparison between Automated (TABS) and Automated (AI-based)

As per the Blant Altman analysis, good agreement was observed between the automated (TABS) and automated (AI-based) methods for the SFCT, with minimal bias between both methods. However, the AI-based automated method exhibits a positive trend (upward slope), indicating a proportional bias. In this analysis, the agreement between automated (TABS) and automated (AI-based) methods was further compared at all 9 ETDRS regions of the choroid using the Blant Altman analysis for both visit 1 and visit 2. A paired t-test showed a significant difference ($p < 0.001$) between the automated (TABS) and automated (AI-based) methods at the superior quadrant for both visit 1 and visit 2. No significant difference ($p < 0.05$ for all) was observed in any other quadrants between the two methods. The mean differences between both automated methods at each region are shown in **Figure 4-17** below. A positive value indicates that the automated (TABS) method predicts a thicker ChT compared to the automated (AI-based) method. The linear regression plots in **Appendix B** clearly show the relationship between the two methods across all ETDRS regions.

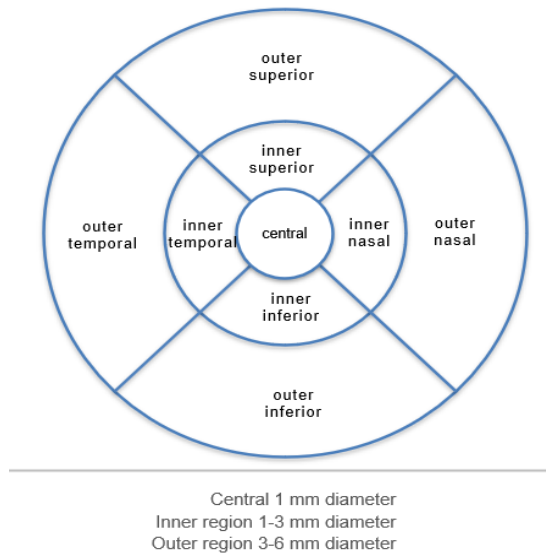


Figure 4-17: Early Treatment Diabetic Retinopathy Study (ETDRS) regions of the choroid

Table 4-3: Mean differences between the two automated methods at all ETDRS regions for visit 1 and visit 2.

TABS - AI-based software	Visit 1	Visit 2
Inner Superior	24.34 ± 34.29 μm	24.69 ± 35.07 μm
Outer Superior	31.84 ± 36.34 μm	32.38 ± 37.30 μm
Inner Inferior	3.06 ± 60.19 μm	- 3.30 ± 51.46 μm
Outer Inferior	- 9.12 ± 45.47 μm	- 5.35 ± 48.84 μm
Central	3.80 ± 31.11 μm	1.16 ± 26.76 μm
Inner Nasal	6.13 ± 34.56 μm	7.43 ± 27.96 μm
Outer Nasal	- 14.31 ± 28.92 μm	- 10.25 ± 22.48 μm
Inner Temporal	5.93 ± 36.56 μm	- 1.39 ± 22.40 μm
Outer Temporal	3.90 ± 35.05 μm	- 0.61 ± 17.39 μm

4.4.3.1 Inner Superior

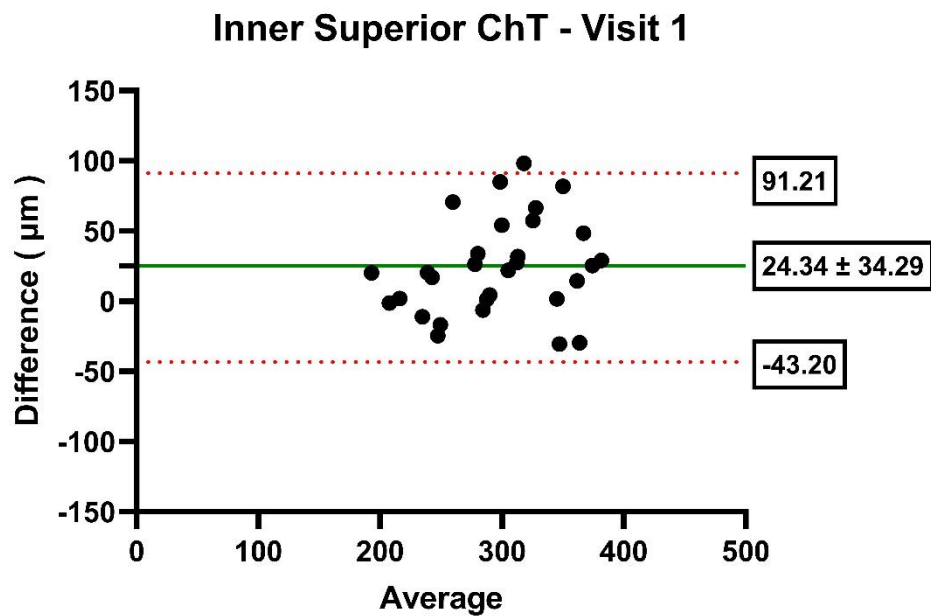


Figure 4-18: The Bland-Altman Plot showing the agreement between two automated methods for measuring the choroidal thickness in the inner superior region at visit 1. The green line is the mean difference $\pm$ SD and the red dotted lines are the upper and lower 95% limits of agreement. (The TABS software determined a 24.34 μm thicker choroid compared to the AI-based software).

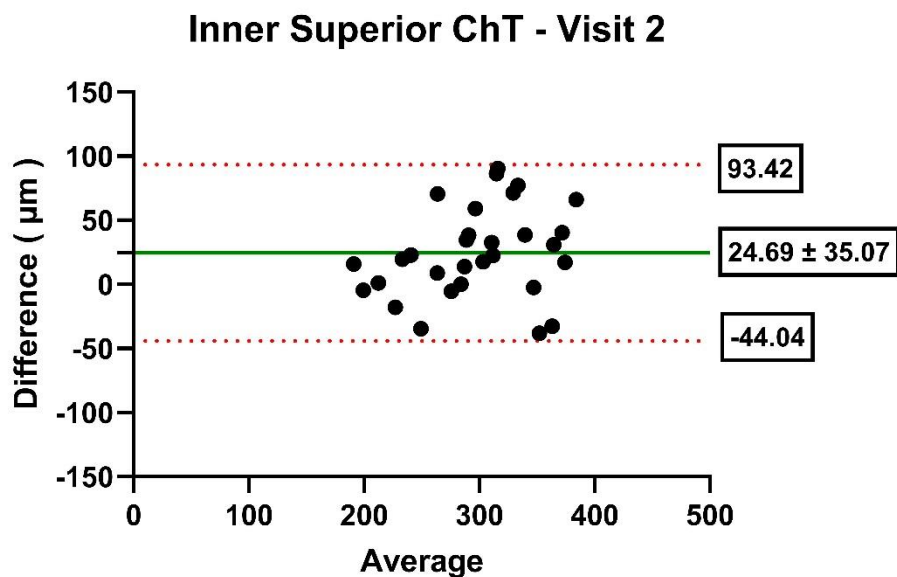


Figure 4-19: The Bland-Altman Plot showing the agreement between two automated methods for measuring the choroidal thickness in the inner superior region at visit 2. The green line is the mean difference $\pm$ SD and the red dotted lines are the upper and lower 95% limits of agreement. (The TABS software determined a 24.69 μm thicker choroid compared to the AI-based software).

4.4.3.2 Outer Superior

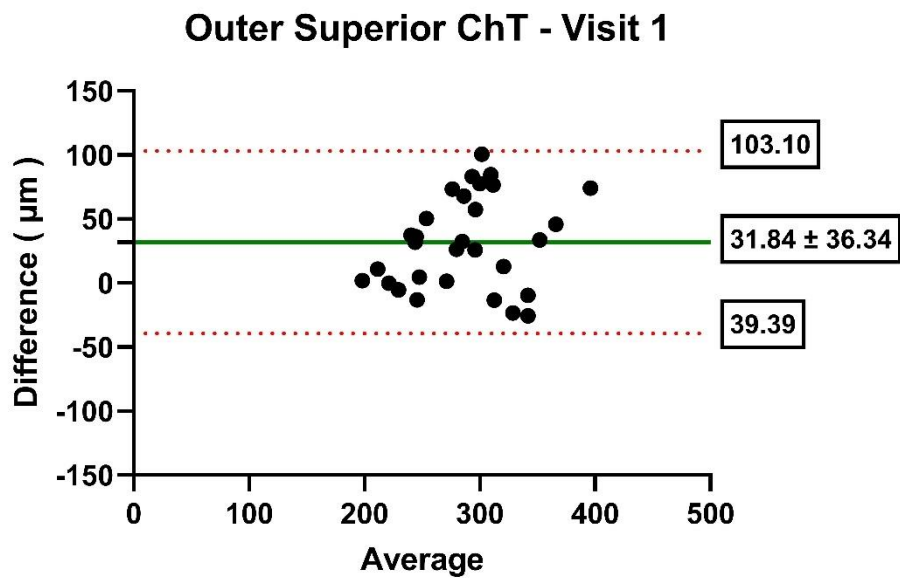


Figure 4-20: The Bland-Altman Plot showing the agreement between two automated methods for measuring choroidal thickness in the outer superior region at visit 1. The green line is the mean difference $\pm$ SD and the red dotted lines are the upper and lower 95% limits of agreement. (The TABS software determined a 31.84 μ m thicker choroid compared to the AI-based software).

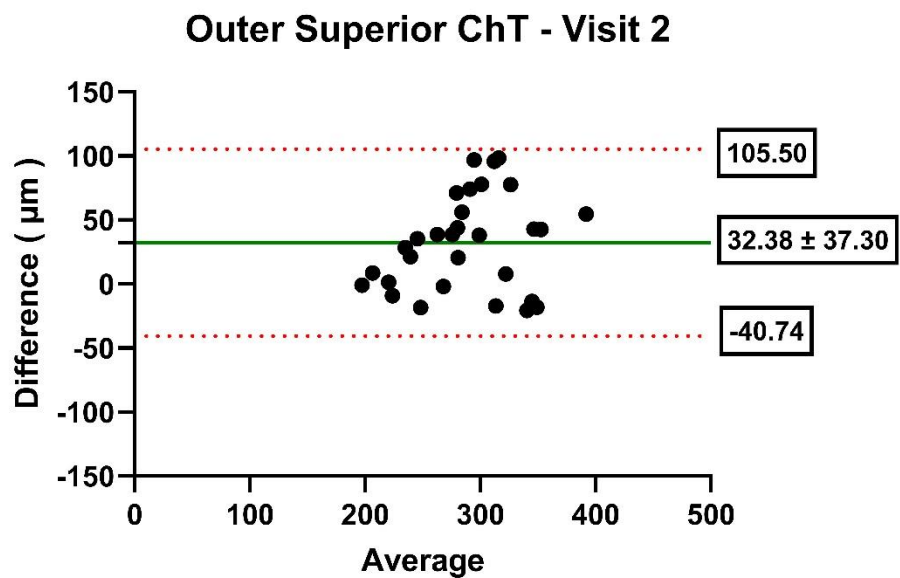


Figure 4-21: The Bland-Altman Plot showing the agreement between two automated methods for measuring choroidal thickness in the outer superior region at visit 2. The green line is the mean difference $\pm$ SD and the red dotted lines are the upper and lower 95% limits of agreement. (The TABS software determined a 32.38 μ m thicker choroid compared to the AI-based software).

4.4.3.3 Inner Inferior

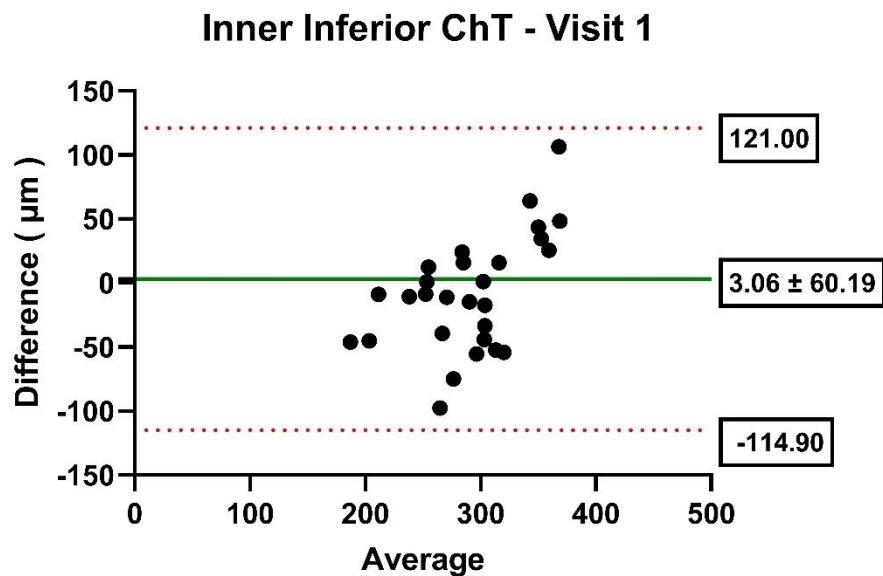


Figure 4-22: The Bland-Altman Plot showing the agreement between two automated methods for measuring the choroidal thickness in the inner inferior region at visit 1. The **green line** is the mean difference $\pm$ SD and the **red dotted lines** are the upper and lower 95% limits of agreement, with CI of. (The TABS software determined a 3.06 μm thicker choroid compared to the AI-based software).

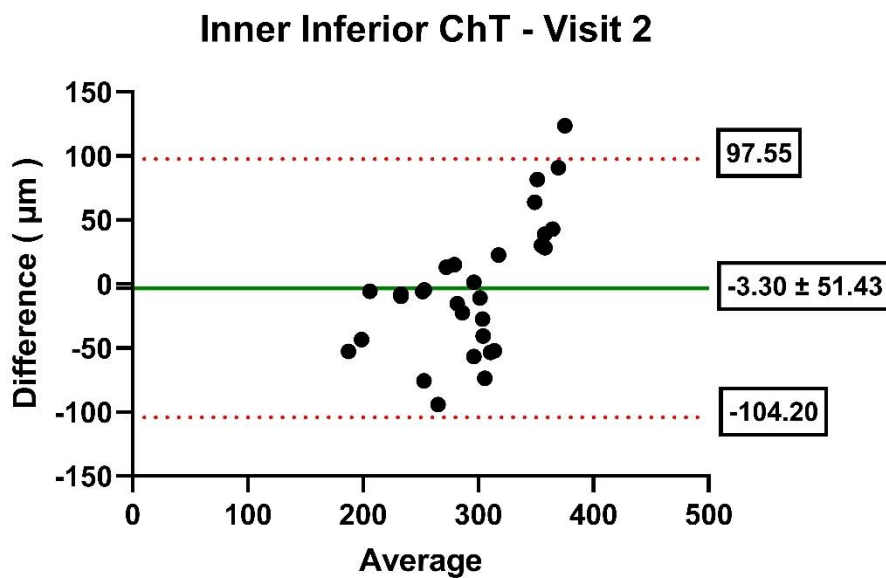


Figure 4-23: The Bland-Altman Plot showing the agreement between two automated methods for measuring the choroidal thickness in the inner inferior region at visit 2. The **green line** is the mean difference $\pm$ SD and the **red dotted lines** are the upper and lower 95% limits of agreement. (The TABS software determined a 3.30 μm thinner choroid compared to the AI-based software).

4.4.3.4 Outer Inferior

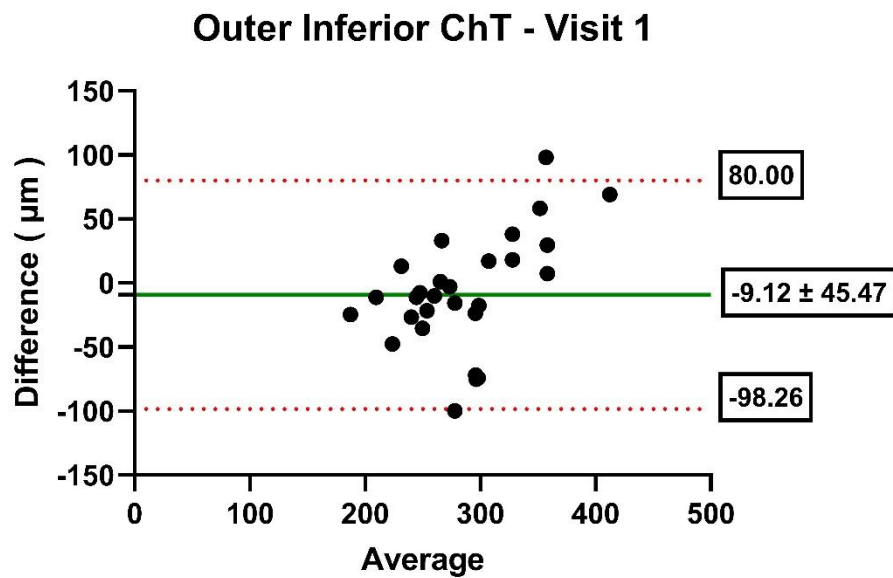


Figure 4-24: The Bland-Altman Plot showing the agreement between two automated methods for measuring the choroidal thickness in the outer inferior region at visit 1. The green line is the mean difference $\pm$ SD and the red dotted lines are the upper and lower 95% limits of agreement. (The TABS software determined a 9.12 µm thinner choroid compared to the AI-based software).

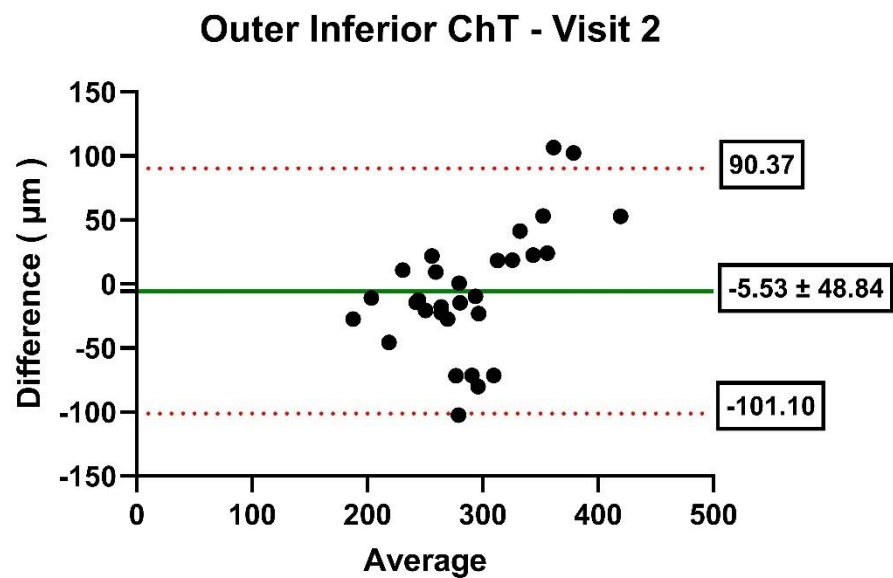


Figure 4-25: The Bland-Altman Plot showing the agreement between two automated methods for measuring the choroidal thickness in the outer inferior region at visit 2. The green line is the mean difference $\pm$ SD and the red dotted lines are the upper and lower 95% limits of agreement. (The TABS software determined a 5.53 µm thinner choroid compared to the AI-based software).

4.4.3.5 Central

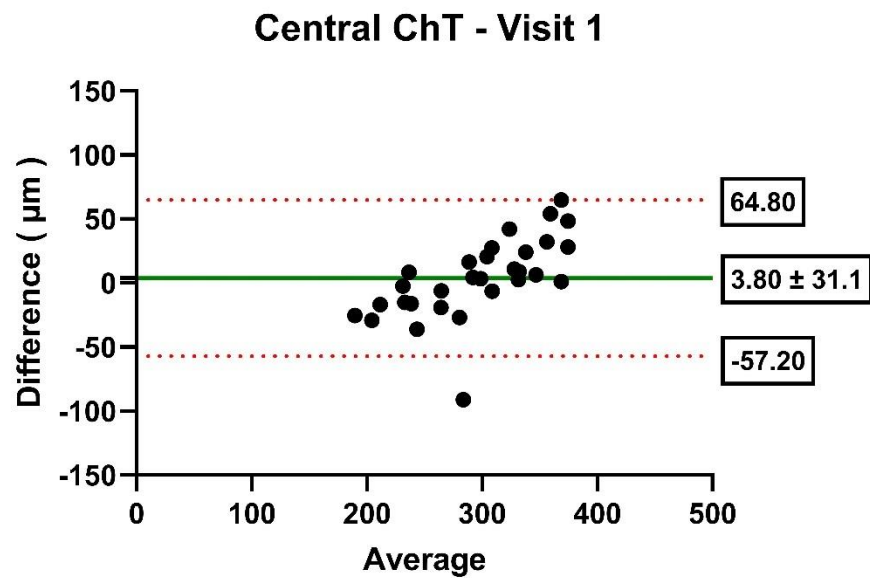


Figure 4-26: The Bland-Altman Plot showing the agreement between two automated methods for measuring the choroidal thickness in the central region at visit 1. The **green line** is the mean difference $\pm$ SD and the **red dotted lines** are the upper and lower 95% limits of agreement. (The TABS software determined a 3.80 μm thicker choroid compared to the AI-based software).

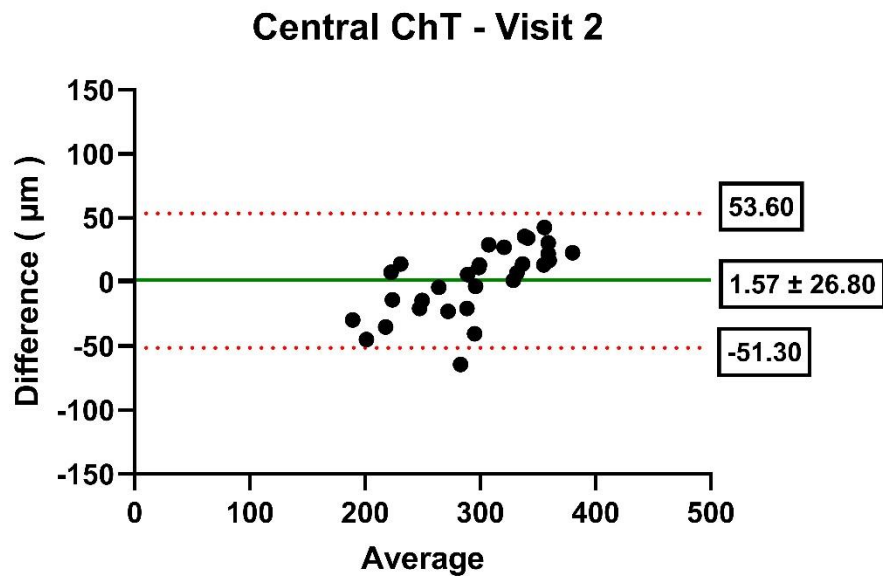


Figure 4-27: The Bland-Altman Plot showing the agreement between two automated methods for measuring the choroidal thickness in the central region at visit 2. The **green line** is the mean difference $\pm$ SD and the **red dotted lines** are the upper and lower 95% limits of agreement. (The TABS software determined a 1.57 μm thicker choroid compared to the AI-based software).

4.4.3.6 Inner Nasal

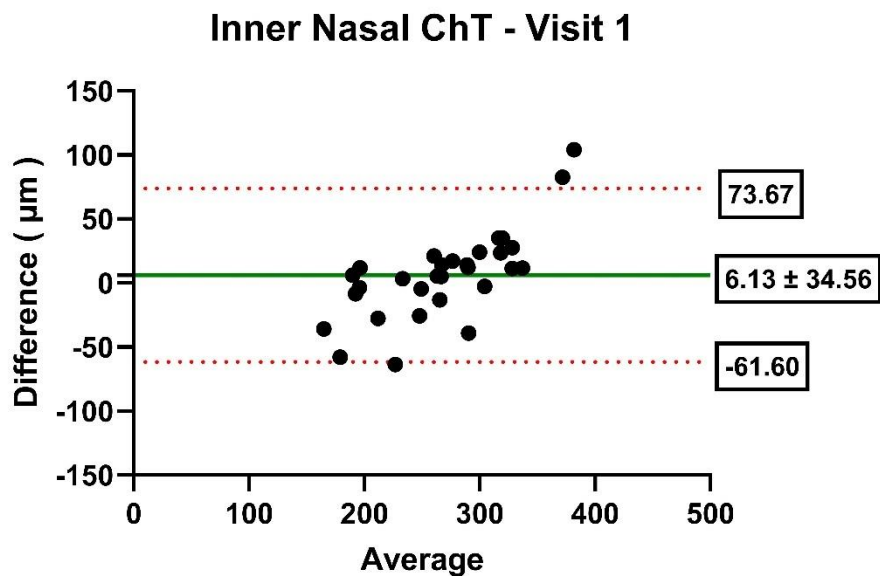


Figure 4-28: The Bland-Altman Plot showing the agreement between two automated methods for measuring the choroidal thickness in the inner nasal region at visit 1. The **green line** is the mean difference $\pm$ SD and the **red dotted lines** are the upper and lower 95% limits of agreement. (The TABS software determined a 6.13 μm thicker choroid compared to the AI-based software).

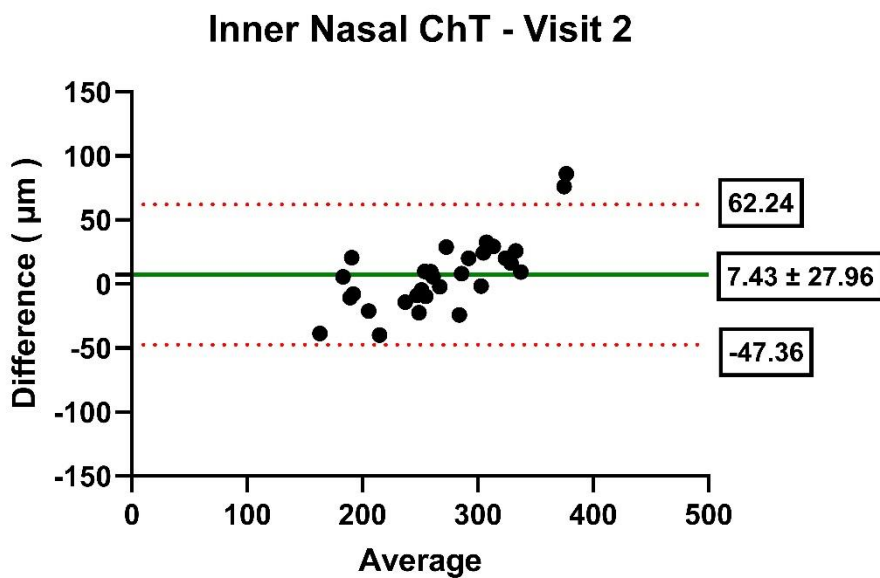


Figure 4-29: The Bland-Altman Plot showing the agreement between two automated methods for measuring the choroidal thickness in the inner nasal region at visit 2. The **green line** is the mean difference $\pm$ SD and the **red dotted lines** are the upper and lower 95% limits of agreement. (The TABS software determined a 7.43 μm thicker choroid compared to the AI-based software).

4.4.3.7 Outer Nasal

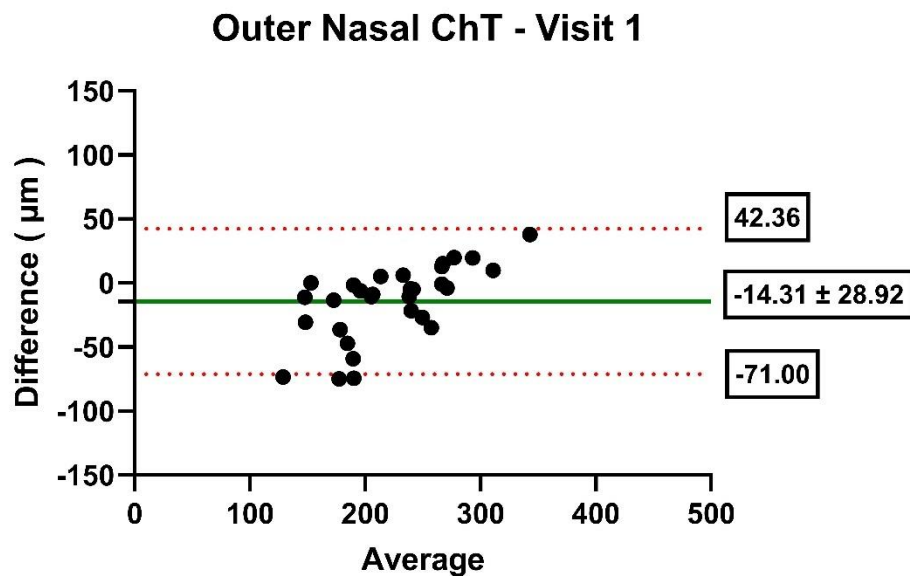


Figure 4-30: The Bland-Altman Plot showing the agreement between two automated methods for measuring the choroidal thickness in the outer nasal region at visit 1. The green line is the mean difference $\pm$ SD and the red dotted lines are the upper and lower 95% limits of agreement. (The TABS software determined a 14.31 μm thinner choroid compared to the AI-based software).

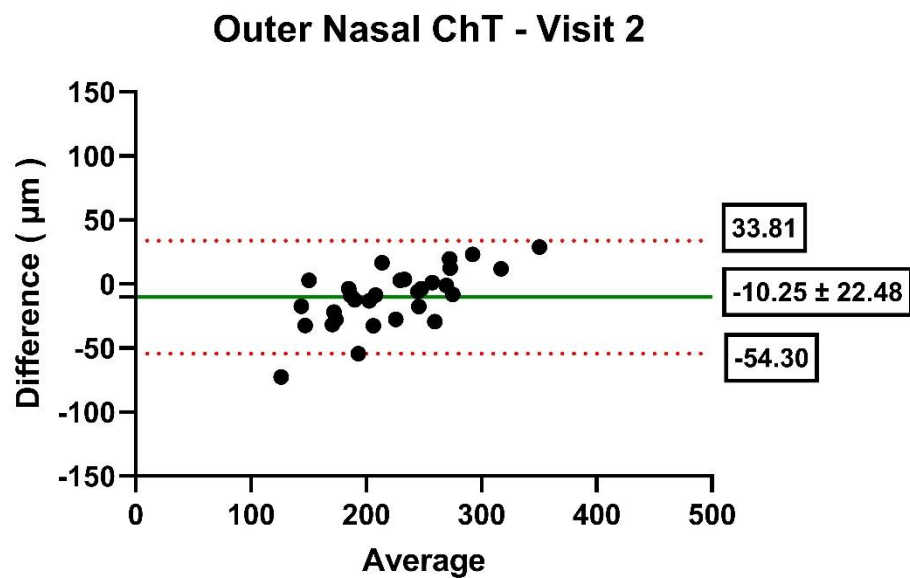


Figure 4-31: The Bland-Altman Plot showing the agreement between two automated methods for measuring the choroidal thickness in the outer nasal region at visit 2. The green line is the mean difference $\pm$ SD and the red dotted lines are the upper and lower 95% limits of agreement. (The TABS software determined a 10.25 μm thinner choroid compared to the AI-based software).

4.4.3.8 Inner Temporal

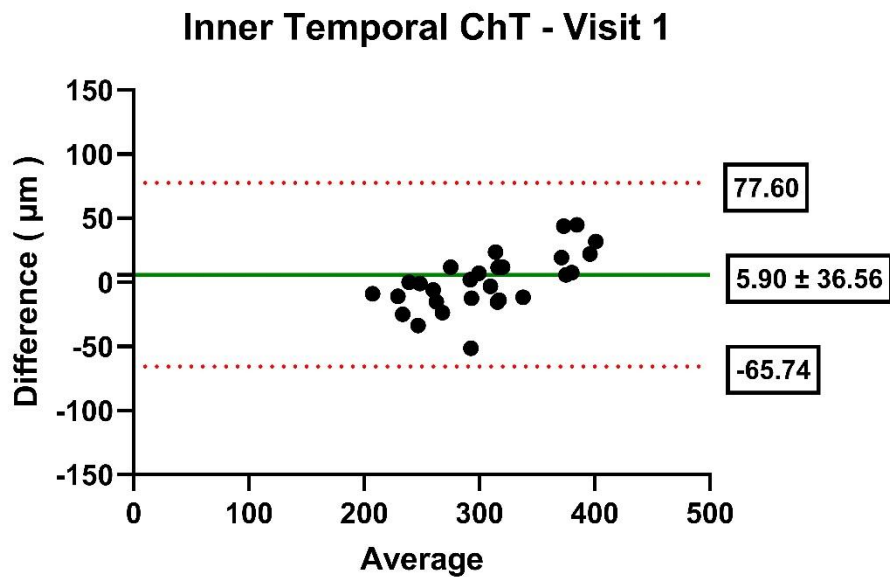


Figure 4-32: The Bland-Altman Plot showing the agreement between two automated methods for measuring the choroidal thickness in the inner temporal region at visit 1. The **green line** is the mean difference ± SD and the **red dotted lines** are the upper and lower 95% limits of agreement. (The TABS software determined a 5.90 µm thicker choroid compared to the AI-based software).

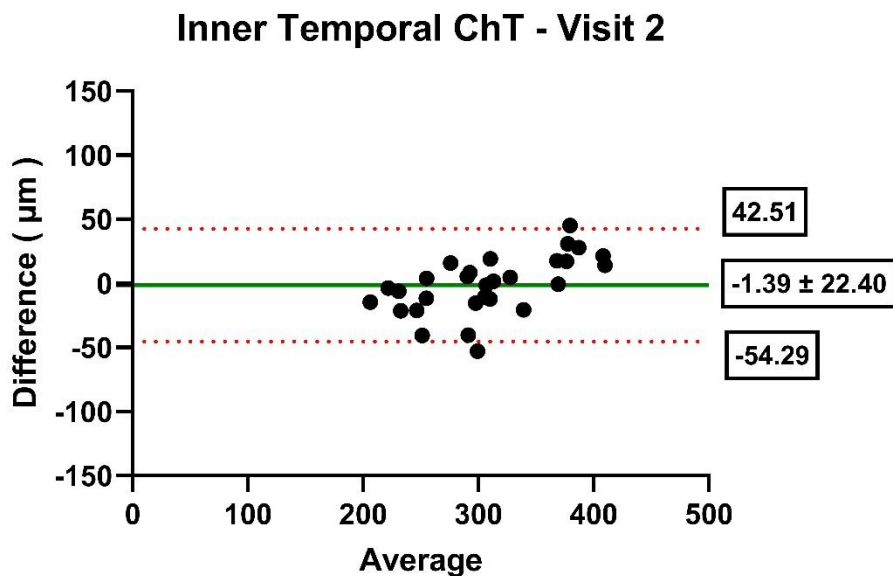


Figure 4-33: The Bland-Altman Plot showing the agreement between two automated methods for measuring the choroidal thickness in the inner temporal region at visit 2. The **green line** is the mean difference ± SD and the **red dotted lines** are the upper and lower 95% limits of agreement. (The TABS software determined a 1.39 µm thinner choroid compared to the AI-based software).

4.4.3.9 Outer Temporal

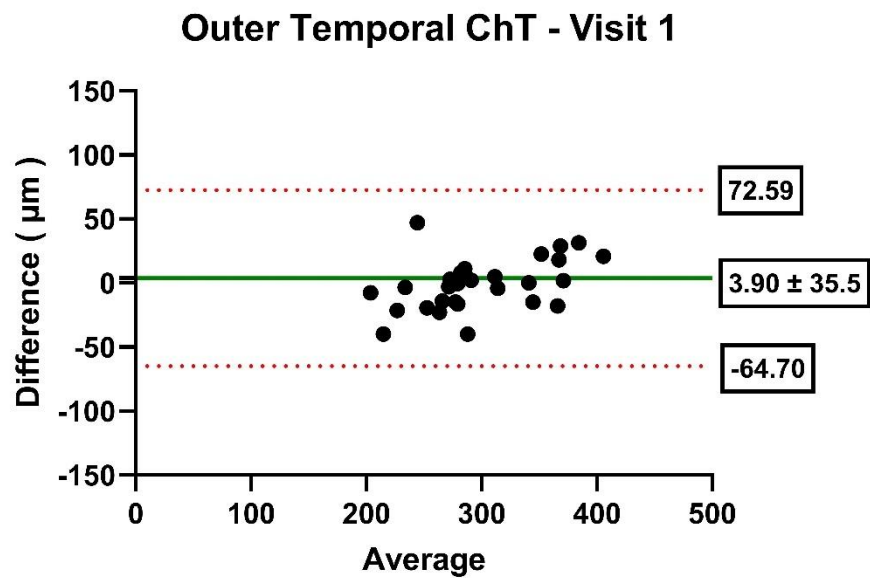


Figure 4-34: The Bland-Altman Plot showing the agreement between two automated methods for measuring the choroidal thickness in the outer temporal region at visit 1. The green line is the mean difference $\pm$ SD and the red dotted lines are the upper and lower 95% limits of agreement. (The TABS software determined a 3.90 μm thicker choroid compared to the AI-based software).

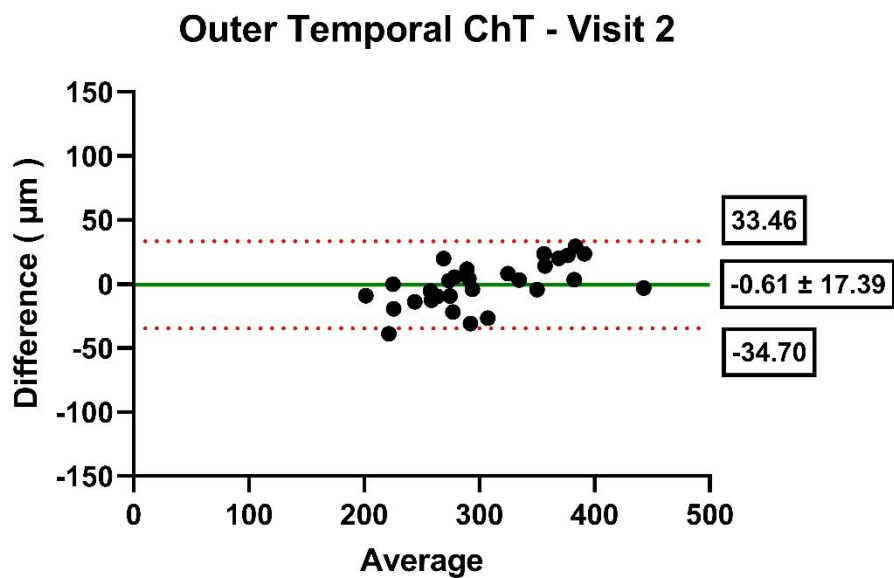


Figure 4-35: The Bland-Altman Plot showing the agreement between two automated methods for measuring the choroidal thickness in the outer temporal region at visit 2. The green line is the mean difference $\pm$ SD and the red dotted lines are the upper and lower 95% limits of agreement. (The TABS software determined a 0.61 μm thinner choroid compared to the AI-based software).

4.5 Discussion and Conclusion

This study showed generally satisfactory repeatability with the different methods of ChT measurements within and between visit 1 and visit 2. However, the Bland-Altman analysis suggests a weak agreement when comparing the manual method with the semi-automated and automated methods. Overall, the manual method of ChT measurements indicated a thicker choroid than other measurement methods. In contrast, a strong correlation was observed between the semi-automated, automated (OCT), and automated (customized) measurement methods. The range of SFCT found in this study was 215, which is similar to the SFCT range of 189 μm to 538 μm published by Read et al. in a study that measured SFCT using Copernicus SOCT-HR in children from ages 9 to 12 years. The study also suggested that the ChT increases significantly from early childhood to adolescence.¹⁵³

This study also provides an estimate of the repeatability of manual SFCT measurements using the swept source OCT device (DRI-Triton, Topcon). The mean difference between the measurements taken on visit 1 and visit 2 was less than 2 μm . These results are very similar to the study published by Rahman et al. where the repeatability in SFCT was measured in adult subjects using spectral domain OCT, with the mean difference between the scans being 2 μm for horizontal and 3.8 μm for vertical scans.¹⁶² In the current study, the SFCT measurements for both horizontal and vertical scans were averaged. Besides the manual method, the semi-automated and the two automated methods showed an excellent repeatability of < 5 μm .

According to the results of this study, the manual method determined a choroidal thickness that was approximately 40 μm larger compared to the other methods. However, a difference of less than 10 μm was observed between the semi-automated and automated measurement methods. The manual method results from this study contrast with the published literature by Vupparaboina et al., where no significant difference was observed between the customized AI-based automated software (used in our study) and the manual method, although their study sample size was only 5 subjects.¹⁷⁰ Similarly, a study by Zheng et al. compared a deep learning algorithm automated software with a manual method of ChT measurements and found no significant difference between the measurements, focusing on the overall segmentation of the choroidal boundary.¹⁶⁵ However, the manual method shows varying accuracy. A study by Waheeda Rahman et al. showed an intraobserver variability of 37 μm and interobserver variability of > 32 μm when SFCT was measured using the manual method. This discrepancy in the manual method may highlight the influence of subjective boundary identification that is inherent in manual segmentation, especially when locating the outer boundaries of the choroid, which are often less distinct and more variable. While the manual method is considered a reference in many studies, it can lead to an overestimation of choroidal thickness due to operator bias or inconsistencies in interpreting image boundaries.

This study was limited by the fact that only two volume scans were used for the manual and semi-automated measurements, whereas an average SFCT of 256 B-scans was generated by the TABS software and customized AI-based automated software from each measurement. Additionally, for the semi-automated measurements, the scans that were

already segmented by the OCT software were examined, and Image J was used to measure the SFCT. A true comparison was made between the TABS software and the automated AI-based software, which showed good agreement in terms of mean bias. The Bland-Altman analysis showed that the AI-based automated software demonstrates a positive trend, indicating a proportional bias. Thicker choroids were often overestimated compared to measurements taken with the TABS automated software. Additionally, the wider limits of agreement and the higher confidence intervals observed with the AI-based approach suggest greater variability and less predictability, particularly for thicker choroids or scans of lower image quality.

When comparing the ETDRS regions using both automated methods, the TABS automated software and the AI-based automated software displayed similar mean biases across all regions. However, the TABS automated software recorded a thicker choroidal measurement in the superior region during both visits. There are a few possible explanations for this. First, image quality and signal strength can decline less uniformly in the superior retina due to lid artifacts, which might affect the AI-based software more than the OCT automated software.^{172,173} While OCT software typically adjusts for drops in signal strength, AI methods may not generalize well in areas with frequent artifacts unless they've been specifically trained for those scenarios.^{172,173} Secondly, the superior choroid may have more anatomical variability or curvature, which the OCT software captures better, as it's often fine-tuned to accommodate the specific scan geometry and device optics.^{174,175} Similar results were published in the literature by Lee et al., who reported a

thicker choroid with DRI Triton SS-OCT when compared with the Heidelberg SS-OCT; the study found a mean difference of $21.40 \pm 33.13 \mu\text{m}$.¹⁷⁶

This study concluded that the manual method, semi-automated OCT inbuilt software, and AI-based customized software methods are all reproducible and repeatable. However, the manual method tends to overestimate choroidal thickness (ChT) and is time-consuming. Both automated methods demonstrated promising results regarding mean bias; however, the AI-based automated software exhibited proportional bias and discrepancies in choroidal thickness measurements in the superior region. As a result, the OCT-based TABS software was selected for further analysis.

Building upon the methodologies for the precise measurement of choroidal thickness outlined in this chapter, the subsequent chapter focused on investigating the short-term effect of CMS on the posterior segment of the eye. It specifically examined the impact on retinal and choroidal thickness in the same cohort of children.

Chapter 5-Effect of short-term wear of contrast management spectacles on retinal and choroidal thickness

5.1 Introduction

The retina and the choroid perform critical roles in the normal physiology of the eye, including emmetropization and maintaining eye growth regulation.^{6,148,177} Studies using optical coherence tomography (OCT) to measure retinal and choroidal thickness in children with refractive error have reported that both layers are thinner in myopia compared to emmetropia.^{71,178-180} The mean macular retinal thickness in children with myopia ranges from 101.3 to 241.3 μm , while the mean sub foveal choroidal thickness (SFCT) ranges from 108 to 359 μm in myopic children.^{154,155,181} Several studies have measured the effect of myopia on retinal and choroidal thickness.^{71,152,178-180,182-186} A study by Zhao et al. reported a significant decrease in parafoveal (1.5 mm from the fovea) and perifoveal (3.0 mm from the fovea) macular thickness between low myopes ($316.52 \pm 14.48 \mu\text{m}$, $294.63 \pm 11.60 \mu\text{m}$) and highly myopic eyes ($296.43 \pm 19.60 \mu\text{m}$, $266.43 \pm 19.60 \mu\text{m}$).¹⁸⁶

In contrast, a study by Wu et al. showed a significantly greater mean retinal thickness in the fovea (1 mm) ($187 \pm 17 \mu\text{m}$, $199 \pm 18 \mu\text{m}$) and foveola ($149 \pm 15 \mu\text{m}$, $165 \pm 19 \mu\text{m}$) between non-myopic and high myopic eyes.¹⁸⁵ However, a significant thinning was observed between non-myopes and high myopes in the inner and outer macular regions.¹⁸⁵ A study by Read et al. on children with myopia reported a statistically significant thinning of 6 μm in the parafoveal retinal thickness in myopic eyes compared to non-myopic eyes, with this difference being considered clinically insignificant.¹⁷⁹ In contrast, a study by Lim et al. suggests

that average macular retinal thickness is not dependent on the degree of myopia (spherical equivalent -0.25 to -14.25 D).¹⁷⁸

In addition to retinal thickness, highly myopic eyes exhibit significant choroidal thinning. A study by Muhiddin et al. reported that the thickness of the choroid decreases with higher myopia, which in turn affects the choroidal vasculature.¹⁵² The study also suggests that with each diopter of myopia, the choroidal thickness decreases by 13.62 μm .¹⁵² Another study by Teberik et al. showed a significant thinning of the choroid in patients with high myopia compared to emmetropes.¹⁸⁰ The study reported a mean SFCT of $218.80 \pm 102.2 \mu\text{m}$ in the myopic group and $331.8 \pm 99.0 \mu\text{m}$ in the emmetropic group.¹⁸⁰

Research studies have further focused on the short-term effect of optical stimuli on choroidal thickness.^{128,129,148,187-189} A study by Read et al. showed a significant increase in choroidal thickness of 12 μm in young emmetropic adults after 60 minutes of exposure to monocular myopic defocus of +3.00D.¹²⁹ Another study by Chiang et al. showed a 20 μm increase in SFCT in myopic eyes (-2.00 to -5.00D) exposed to +2.00 myopic defocus for 60 minutes; however, no difference in SFCT was seen in emmetropic eyes compared to myopic eyes.¹⁹⁰ Similarly, Wang et al. conducted a study on myopic children (-0.50 to -6.00D) who were randomly allocated to myopic defocus, control, and hyperopic defocus groups.¹²⁸ The study reported less thinning of the choroid of $-0.36 \pm 1.43 \mu\text{m}$ in children exposed to +3.00 myopic defocus for 2 hours compared to the $-5.03 \pm 1.48 \mu\text{m}$ in the control group without any intervention.¹²⁸

While many studies have measured the effect of various myopia control treatments on retinal and choroidal thickness,^{107,191-193} to our knowledge, no published literature to-date has determined the effect of contrast management spectacles (CMS) on retinal and choroidal thickness. Therefore, this study aimed to measure the short-term effect of CMS on the retinal and choroidal thickness.

5.2 Methods

This was a 2-visit, prospective, randomized, participant-masked study. A total of 30 participants, aged between 8 to 14 years, who were not receiving medication for any ocular or general health and were under no myopia control treatment, were recruited for this study. A spherical equivalent within +1.00D and -0.75D was required for inclusion, as determined by the Grand Seiko WAM 5500 open-field autorefractor (Shigiya Machinery Works LTD, Hiroshima, Japan) under non-cycloplegic conditions. The participants attended a screening visit where consent was obtained, and participant eligibility was determined.

For the study measurements, baseline posterior segment scans were obtained using the Triton DRI OCT (Topcon, Tokyo, Japan). Following the baseline measurements, participants were asked to wear study spectacles in a randomized order for 60 minutes. These comprised either CSM (SightGlass Vision, Los Altos, CA, USA) or +3.00 clear spectacle lenses (control). For this study, +3.00 spectacle lenses were used as a positive control to induce myopic defocus. A previous study has shown an increase in choroidal thickness after short-term exposure to +3.00 lenses.¹²⁸ Participants wore the study spectacles and watched age-appropriate videos for 60 minutes at a 3m distance. After 30 and 60 minutes of watching the videos, OCT scans were

collected. Participants returned for a second visit to wear the other type of spectacles (CMS or +3.00 spectacles lenses) for 60 minutes, and the same procedures, including baseline scans, were repeated as described previously. Both study visits occurred no earlier than 10 am to allow the choroidal thickness to settle after waking.^{194,195} To control for diurnal variation, the study measurements were taken approximately at the same time on both visits and minimum 2 hours after waking.^{194,195}

After completion of the study visits, the retinal thickness and choroidal thickness were obtained from the Early Treatment Diabetic Retinopathy (ETDRS) map generated by the OCT in-built TABS software.

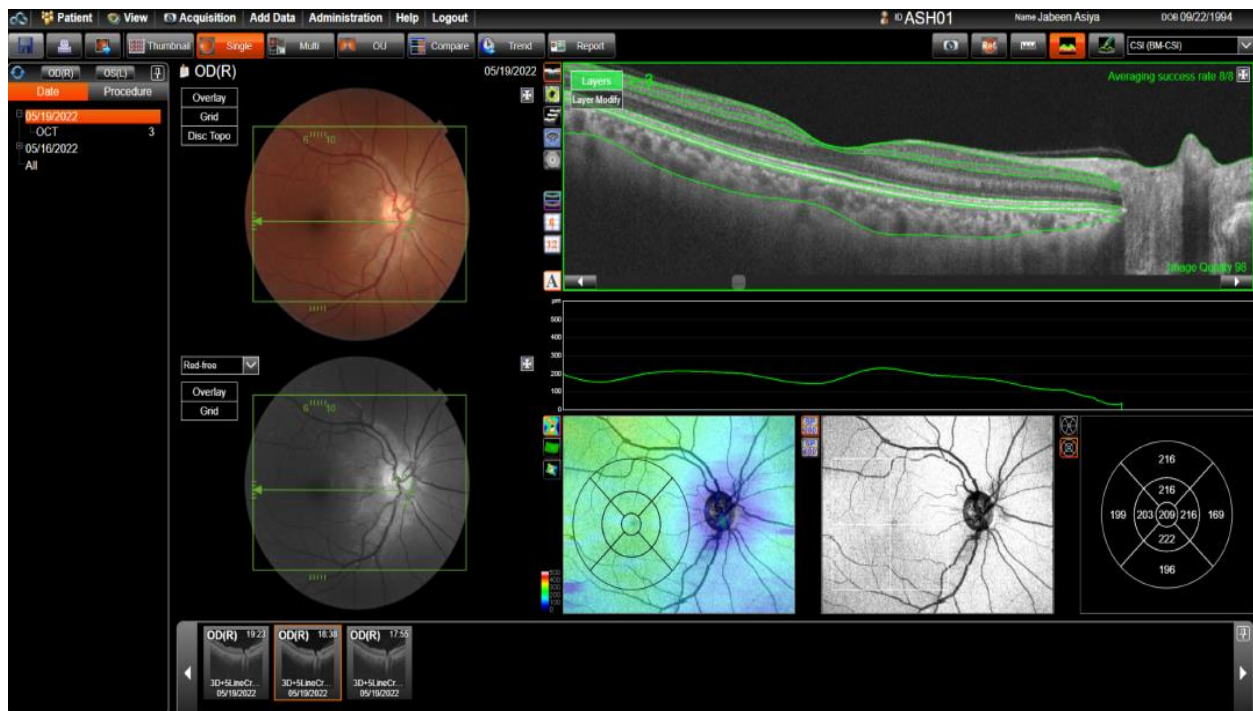


Figure 5-1: Posterior segment scan using the Triton DRI OCT.

5.3 Statistical Analysis

Statistical analysis was conducted using IBM SPSS version 29 (IBM Corp Armonk, NY). The Shapiro-Wilk test was used to test normality and Repeated Measures ANOVA was used to test the effect of +3.00 control spectacle and CMS after 30 minutes and 60 minutes of spectacle wear. A p-value of <0.05 was considered statistically significant. A Bonferroni correction was used to confirm the significance. All data were analyzed for the right eye only.

5.4 Results

A total of 30 participants were enrolled in the study and completed all assessments (17 female, 13 male). The mean age of the participants was 10.9 ± 1.7 years (median 11 years, ranging from 8 to 13 years). The right eye's mean spherical equivalent refraction (SER) was 0.35 ± 0.29 diopters. All retinal and choroidal thickness data were normally distributed when examined using the Shapiro-Wilk test ($p > 0.05$ for all). The data were analyzed at nine retina/choroidal regions, as described by the ETDRS and shown in **Figure 5-2**.

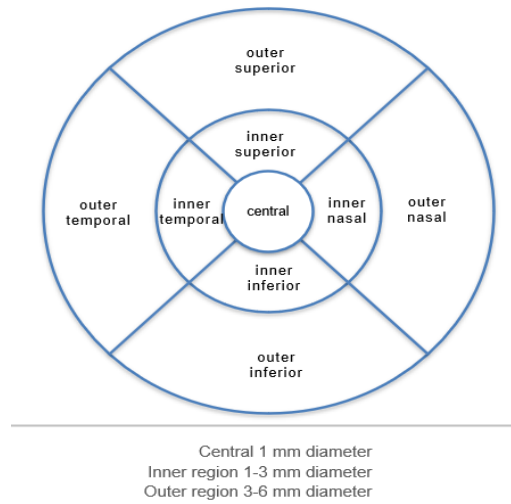


Figure 5-2: Retinal and Choroidal ETDRS regions.

5.4.1 Retinal Thickness

Figures 5-3 to 5-11 and **Appendix C** show retinal thickness for all ETDRS regions. Statistical results for the comparisons between the CMS and +3.00 control spectacles at baseline, 30, and 60 minutes of wear at all 9 ETDRS regions are shown in **Tables 5-1 to 5-9**.

5.4.1.1 Inner Superior Retinal Thickness

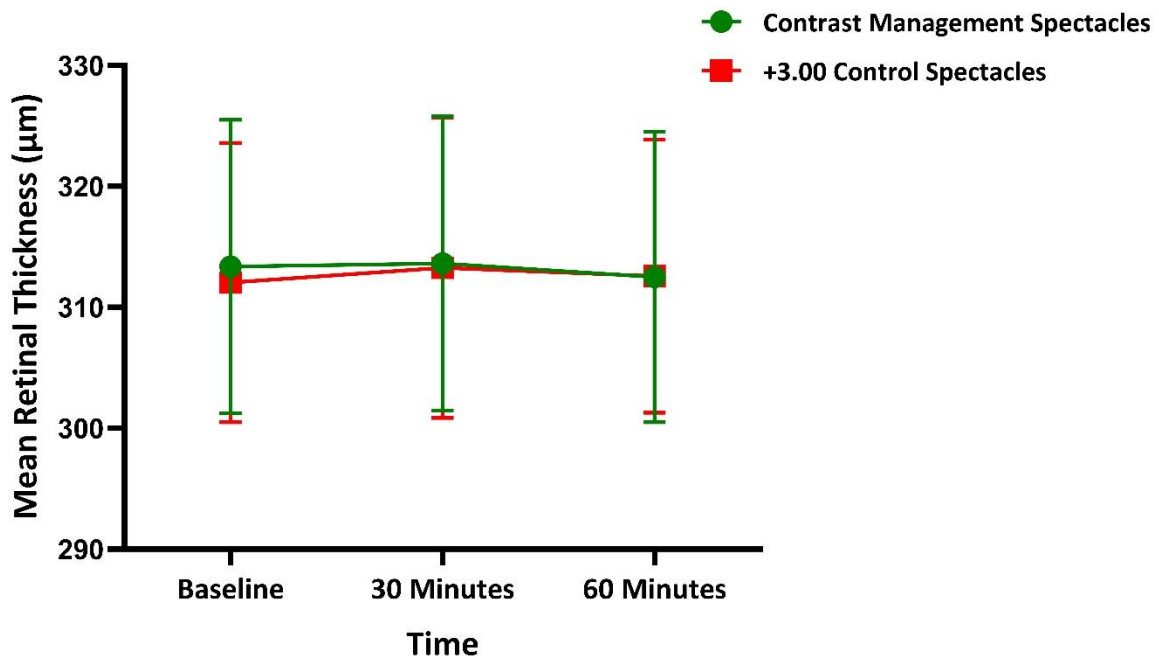


Figure 5-3: Mean inner superior retinal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye. The error bars represent the standard deviation.

Table 5-1: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline, 30 minutes and 60 minutes at the inner superior retinal region of the right eye.

Inner Superior	DF	F	P	Effect size	Power
Between types	1, 29	1.493	0.23	0.04	0.21
Across time	1.943, 56,342	1.841	0.168	0.06	0.36
Interaction	2, 58	0.876	0.40	0.02	0.18

5.4.1.2 Outer Superior Retinal Thickness

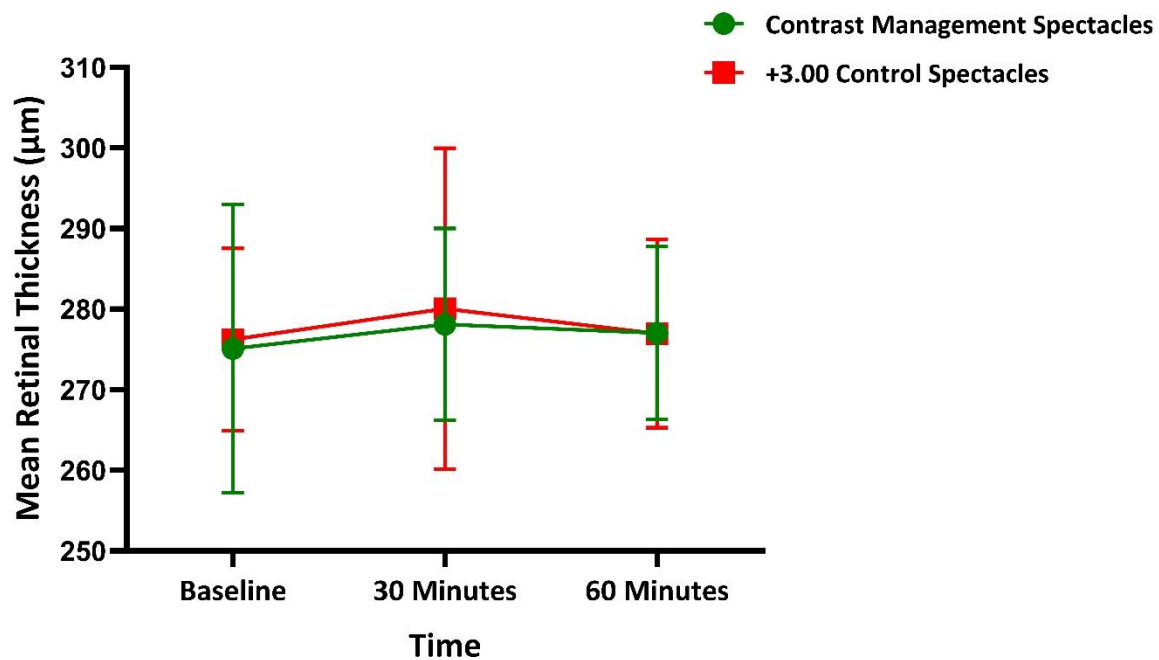


Figure 5-4: Mean outer superior retinal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye. The error bars represent the standard deviation.

Table 5-2: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline, 30 minutes and 60 minutes at the outer superior retinal region of the right eye.

Outer Superior	DF	F	P	Effect size	Power
Between types	1, 29	0.595	0.44	0.02	0.11
Across time	1.581, 45.846	2.274	0.11	0.07	0.39
Interaction	2, 58	0.181	0.78	0.006	0.07

5.4.1.3 Inner Inferior Retinal Thickness

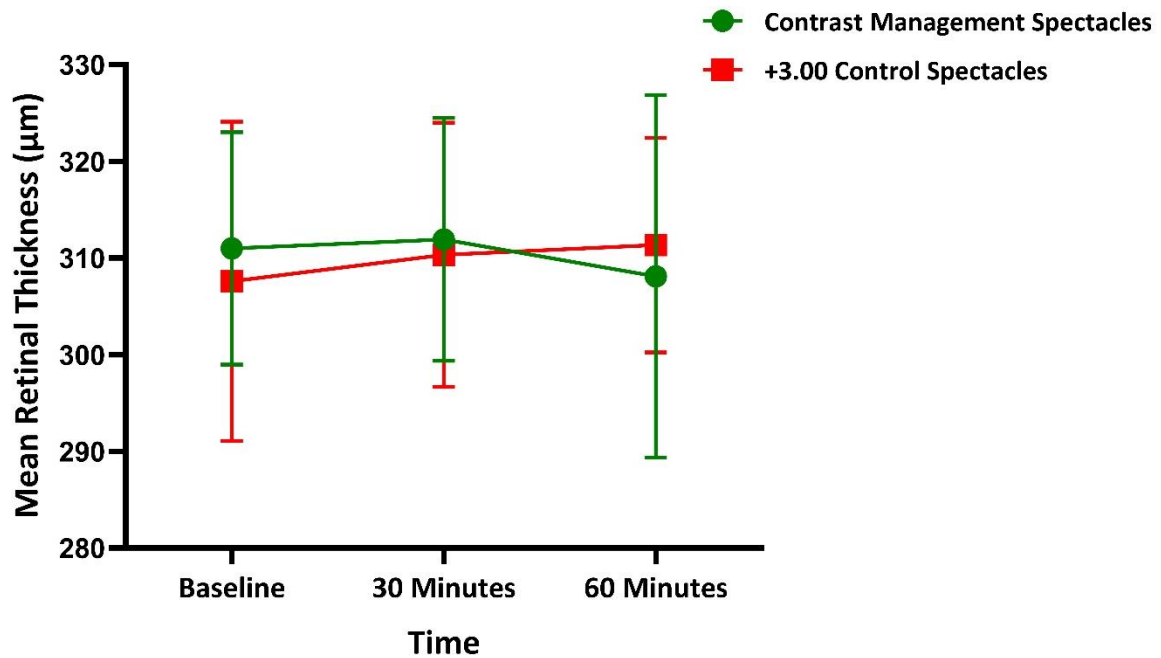


Figure 5-5: Mean inner inferior retinal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye. The error bars represent the standard deviation.

Table 5-3: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline, 30 minutes and 60 minutes at the inner inferior retinal region of the right eye.

Inner Inferior	DF	F	P	Effect size	Power
Between types	1, 29	0.140	0.71	0.005	0.06
Across time	1.606, 46.621	0.632	0.53	0.02	0.13
Interaction	2, 58	1.867	0.17	0.06	0.33

5.4.1.4 Outer Inferior Retinal Thickness

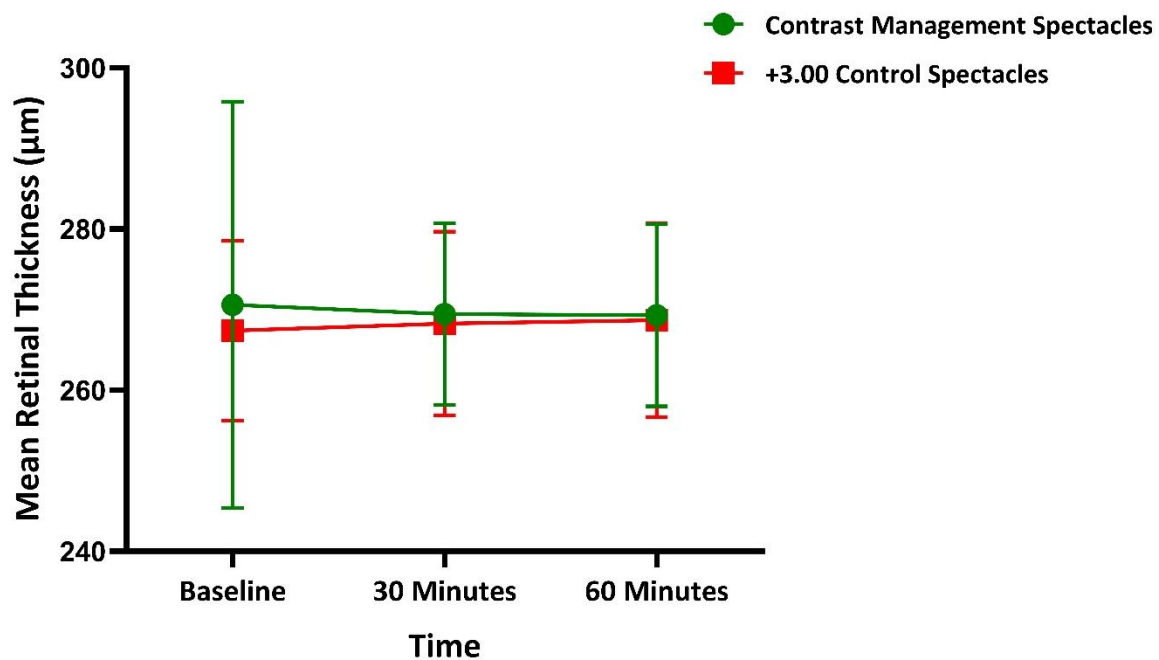


Figure 5-6: Mean outer inferior retinal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye. The error bars represent the standard deviation.

Table 5-4: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline, 30 minutes and 60 minutes at the outer inferior retinal region of the right eye.

Outer Inferior	DF	F	P	Effect size	Power
Between types	1, 29	1.611	0.21	0.05	0.23
Across time	1.093, 31.702	0.004	0.95	0.00	0.50
Interaction	2, 58	0.434	0.54	0.01	0.10

5.4.1.5 Central Retinal Thickness

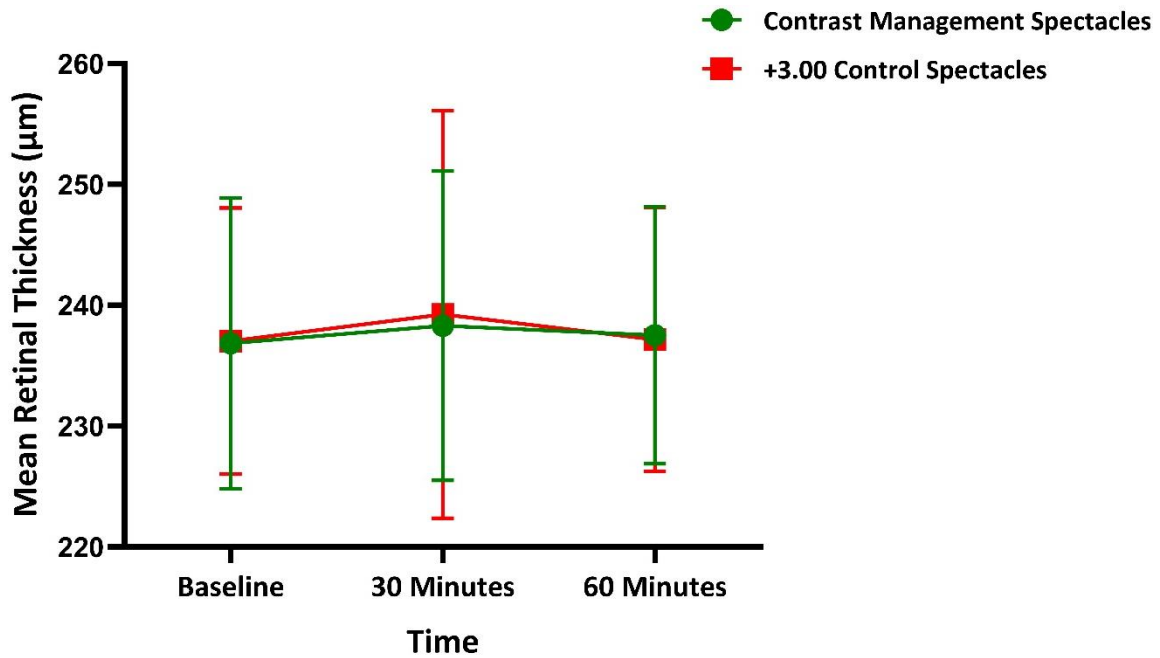


Figure 5-7: Mean central retinal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye. The error bars represent the standard deviation.

Table 5-5: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline, 30 minutes and 60 minutes at the central retinal region of the right eye.

Central	DF	F	P	Effect size	Power
Between types	1, 29	0.132	0.71	0.005	0.06
Across time	1.612, 46.745	1.898	0.15	0.06	0.33
Interaction	2, 58	0.159	0.76	0.005	0.07

5.4.1.6 Inner Nasal Retinal Thickness

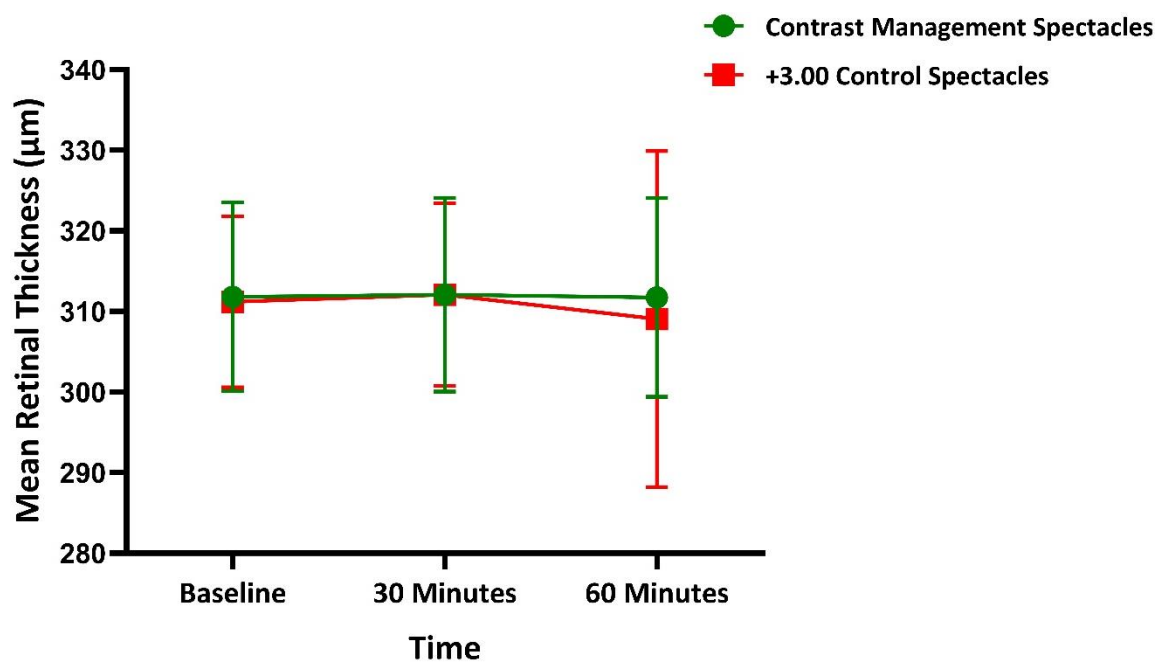


Figure 5-8: Mean inner nasal retinal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye. The error bars represent the standard deviation.

Table 5-6: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline, 30 minutes and 60 minutes at the inner nasal retinal region of the right eye.

Inner Nasal	DF	F	P	Effect size	Power
Between types	1, 29	1.094	0.30	0.03	0.17
Across time	1.169, 33.892	0.775	0.40	0.02	0.14
Interaction	2, 58	0.574	0.48	0.01	0.12

5.4.1.7 Outer Nasal Retinal Thickness

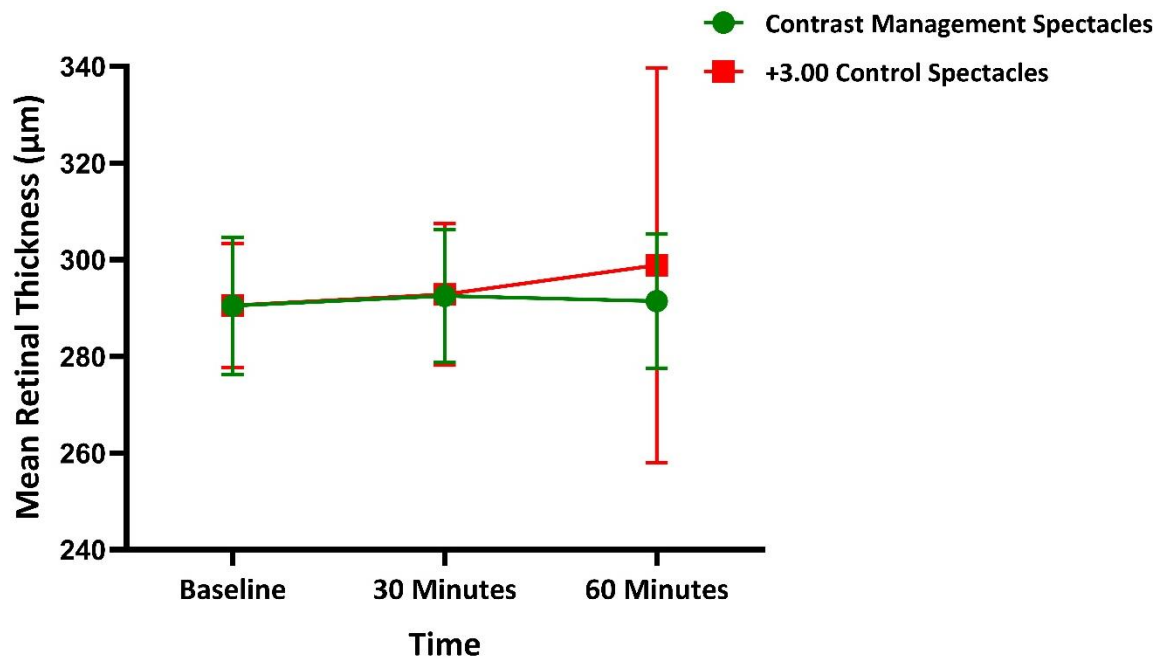


Figure 5-9: Mean outer nasal retinal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye. The error bars represent the standard deviation.

Table 5-7: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline, 30 minutes and 60 minutes at the outer nasal retinal region of the right eye.

Outer Nasal	DF	F	P	Effect size	Power
Between types	1, 29	1.239	0.27	0.04	0.19
Across time	1.091, 31.649	1.166	0.29	0.03	0.18
Interaction	2, 58	0.972	0.33	0.03	0.16

5.4.1.8 Inner Temporal Retinal Thickness

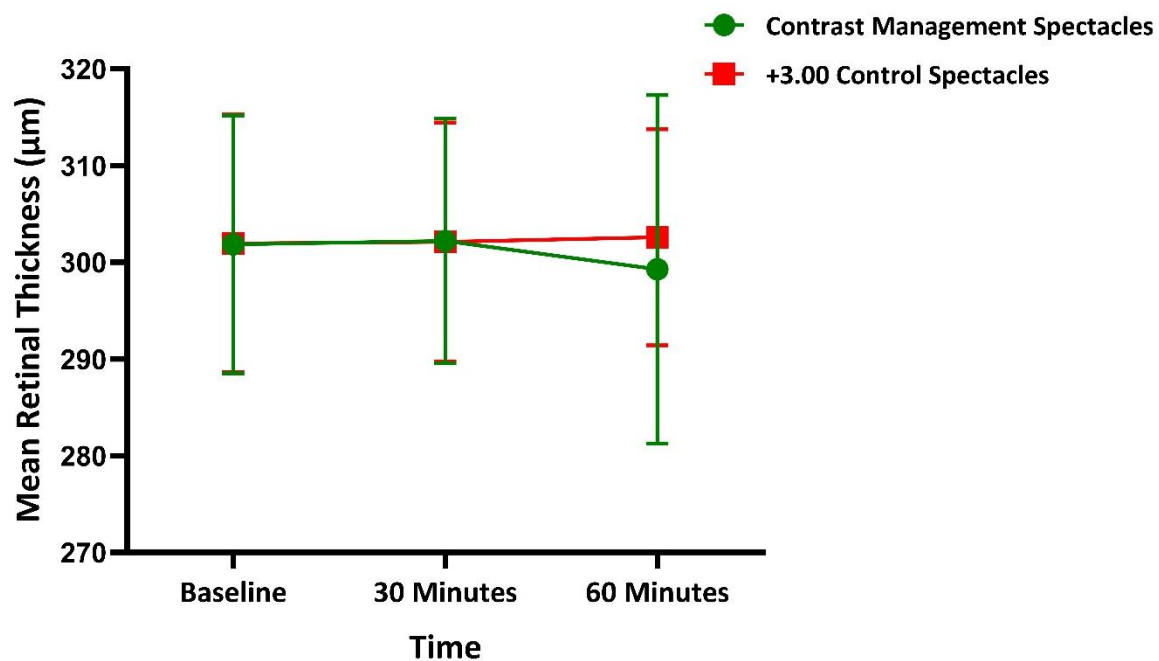


Figure 5-10: Mean inner temporal retinal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye. The error bars represent the standard deviation.

Table 5-8: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline, 30 minutes and 60 minutes at the inner temporal retinal region of the right eye.

Inner Temporal	DF	F	P	Effect size	Power
Between types	1, 29	1.124	0.29	0.03	0.17
Across time	1.402, 40.671	0.622	0.48	0.02	0.13
Interaction	2, 58	1.357	0.26	0.04	0.24

5.4.1.9 Outer Temporal Retinal Thickness

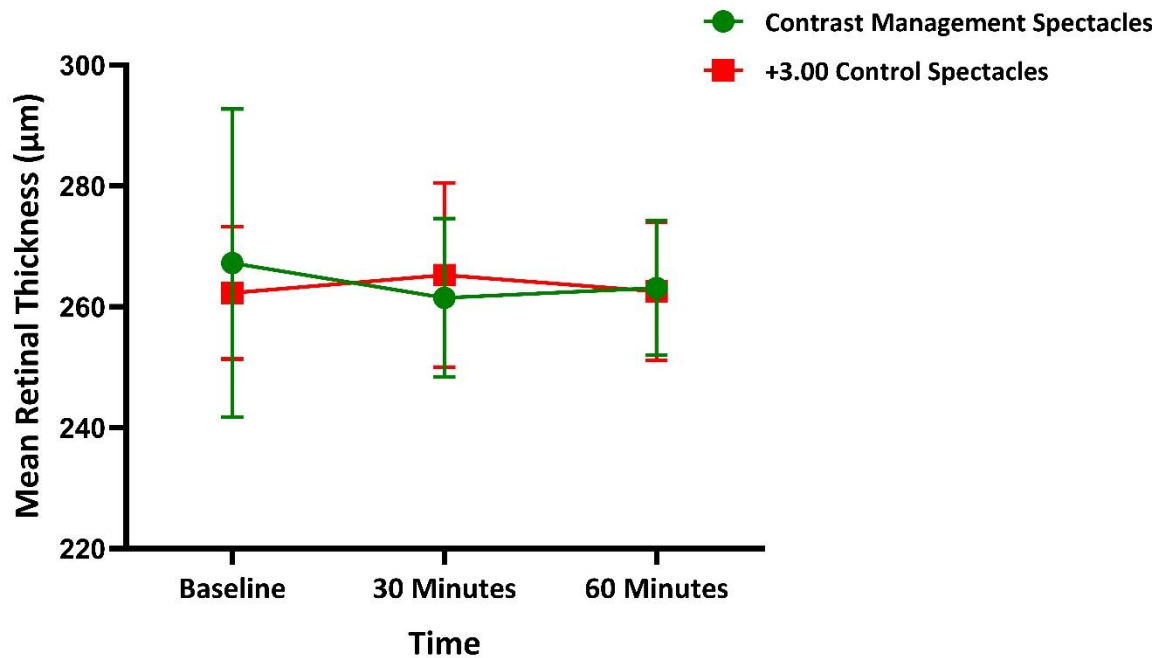


Figure 5-11: Mean outer temporal retinal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye. The error bars represent the standard deviation.

Table 5-9: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline, 30 minutes and 60 minutes at the outer temporal retinal region of the right eye.

Outer Temporal	DF	F	P	Effect size	Power
Between types	1, 29	0.118	0.73	0.004	0.06
Across time	1.300, 37.710	0.422	0.57	0.01	0.10
Interaction	2, 58	2.209	0.14	0.07	0.34

5.4.2 Choroidal Thickness

The choroidal thickness for all ETDRS regions are shown in **Figures 5-12 to 5-20** and **Appendix C**. Statistical results for the comparisons between the CMS and +3.00 control spectacles at baseline, 30, and 60 minutes of wear at all 9 ETDRS regions are shown in **Tables 5-10 to 5-18**

5.4.2.1 Inner Superior Choroidal Thickness

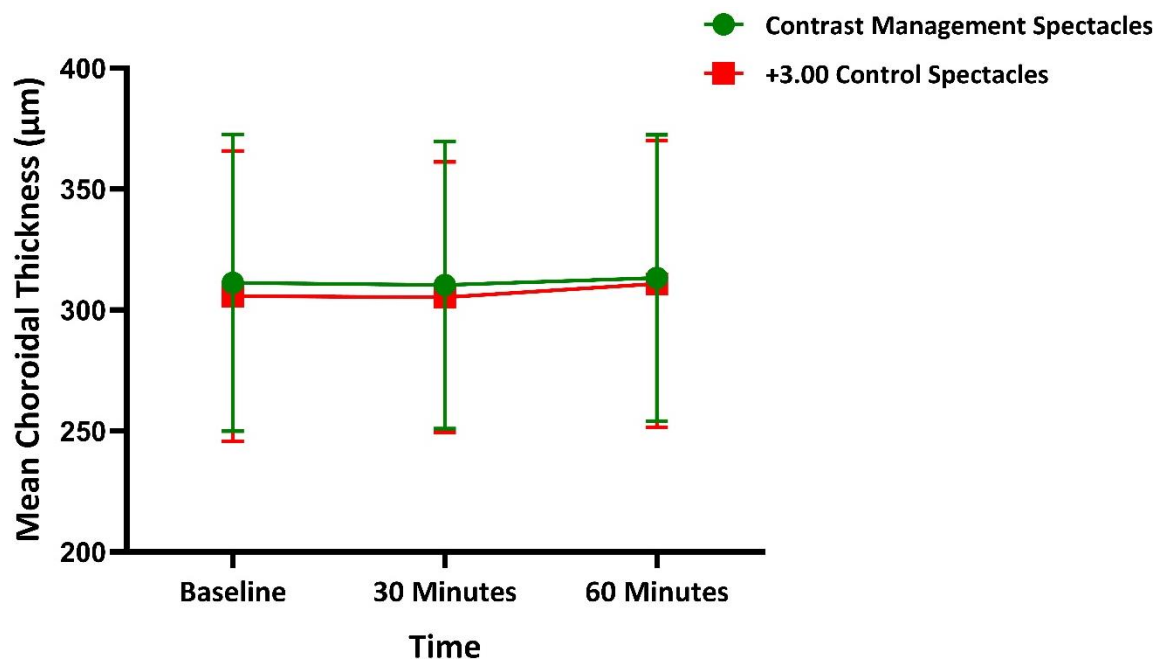


Figure 5-12: Mean inner superior choroidal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye. The error bars represent the standard deviation.

Table 5-10: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline, 30 minutes and 60 minutes at the inner superior choroidal region of the right eye.

Inner Superior	DF	F	P	Effect size	Power
Between types	1, 29	3.940	0.05	0.12	0.48
Across time	1.651, 47.893	3.190	0.05	0.09	0.53
Interaction	2, 58	0.520	0.58	0.01	0.12

5.4.2.2 Outer Superior Choroidal Thickness

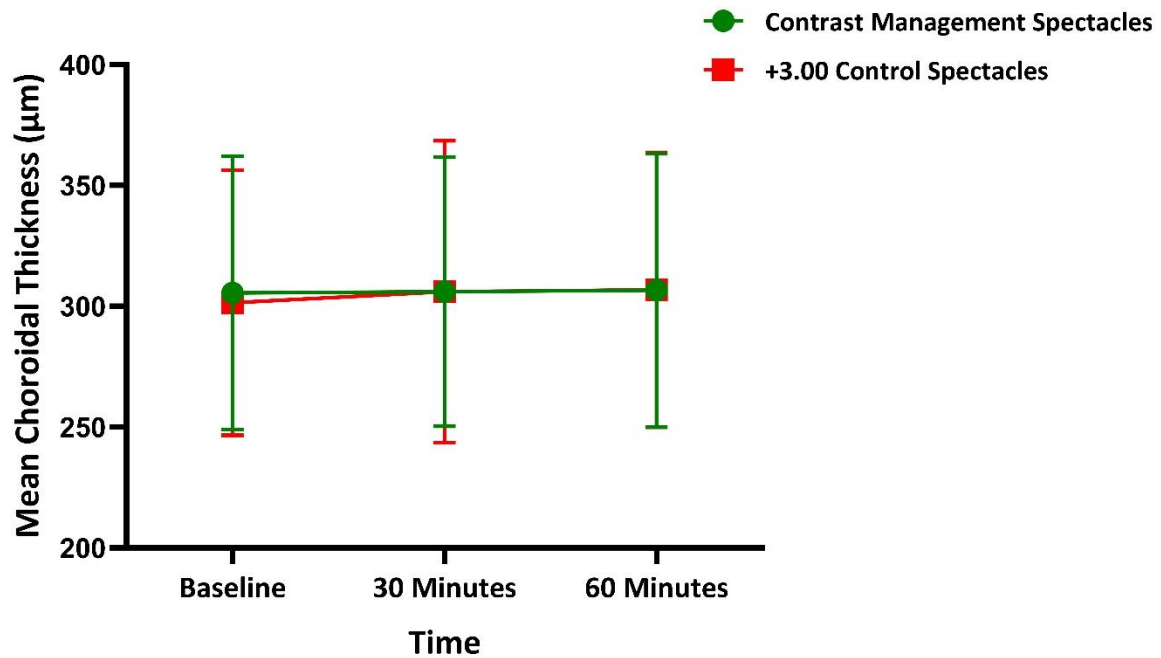


Figure 5-13: Mean outer superior choroidal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye. The error bars represent the standard deviation.

Table 5-11: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline, 30 minutes, and 60 minutes T the outer superior choroidal region of the right eye.

Outer Superior	DF	F	P	Effect size	Power
Between types	1, 29	0.443	0.51	0.01	0.09
Across time	1.501, 43.521	1.706	0.19	0.05	0.29
Interaction	2, 58	0.655	0.50	0.02	0.14

5.4.2.3 Inner Inferior Choroidal Thickness

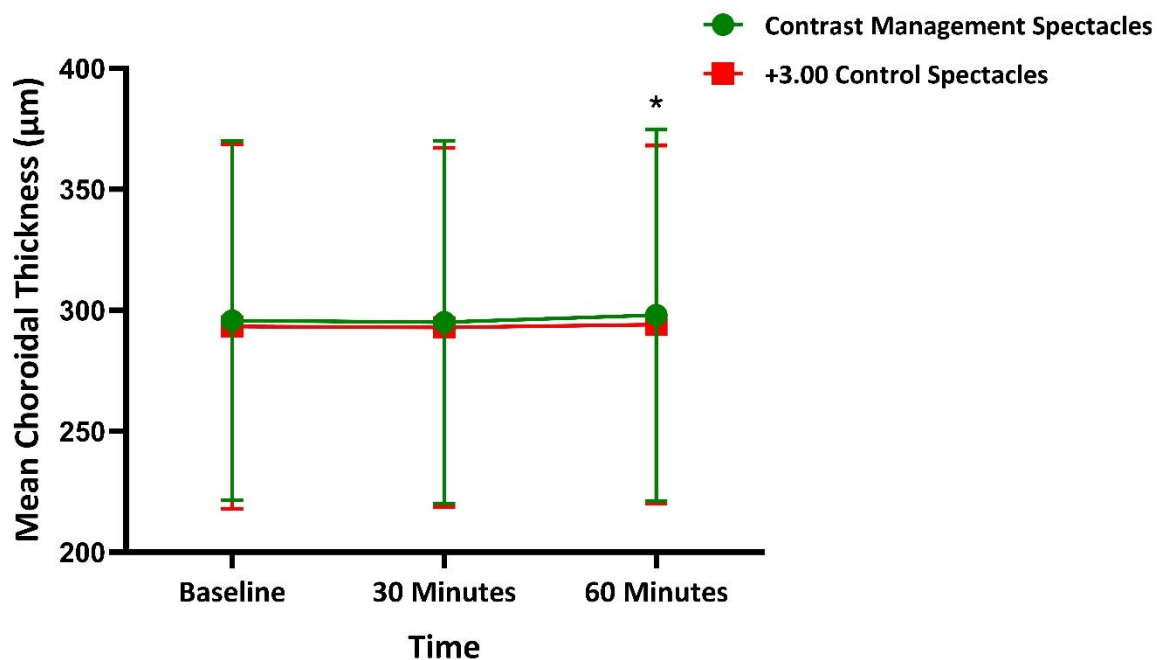


Figure 5-14: Mean inner inferior choroidal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye. The error bars represent the standard deviation.

Table 5-12: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline, 30 minutes and 60 minutes at the inner inferior choroidal region of the right eye.

Inner Inferior	DF	F	P	Effect size	Power
Between types	1, 29	1.304	0.04	0.04	0.19
Across time	1.686, 48.907	0.781	0.46	0.02	0.16
Interaction	5, 58	0.055	0.94	0.002	0.05
RMANOVA (CMS vs Control)	Baseline vs Baseline		30 Minutes vs 30 Minutes		60 Minutes vs 60 Minutes
P value	0.50		0.54		0.03

5.4.2.4 Outer Inferior Choroidal Thickness

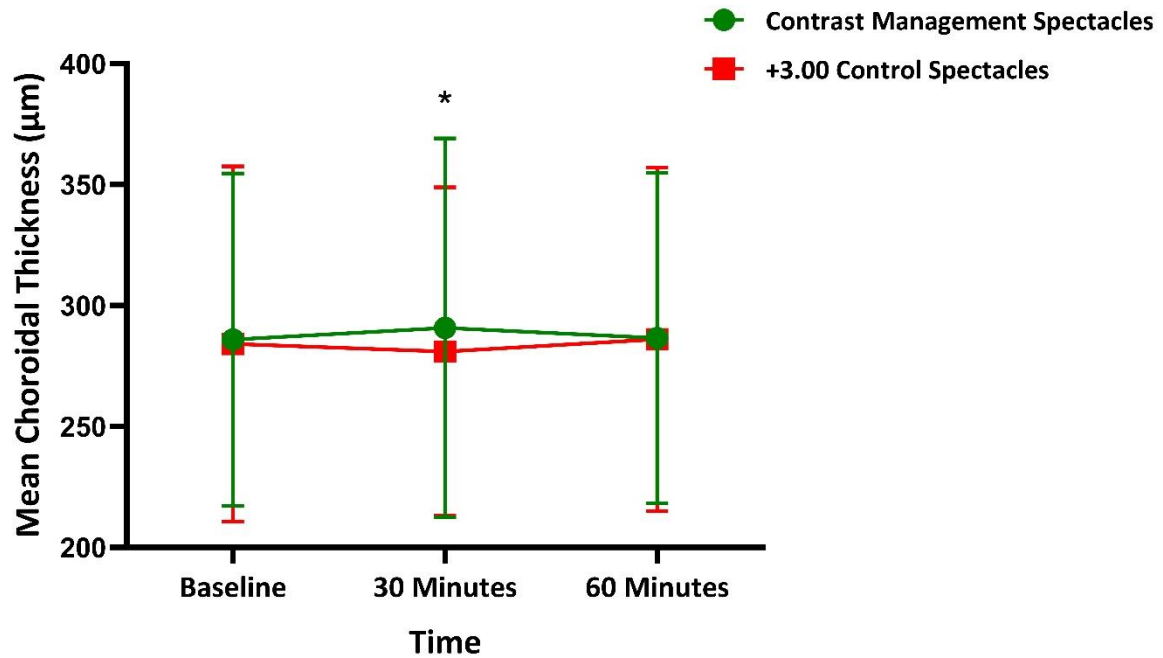


Figure 5-15: Mean outer inferior choroidal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye. The error bars represent the standard deviation.

Table 5-13: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline, 30 minutes and 60 minutes at the outer inferior choroidal region of the right eye.

Outer Inferior	DF	F	P	Effect size	Power
Between types	1, 29	9.704	0.04	0.25	0.85
Across time	1.301, 37.721	0.220	0.80	0.008	0.07
Interaction	2, 58	3.031	0.05	0.95	0.43
RMANOVA (CMS vs Control)	Baseline vs Baseline	30 Minutes vs 30 Minutes	60 Minutes vs 60 Minutes		
P value	0.38	0.01	0.80		

5.4.2.5 Central Choroidal Thickness

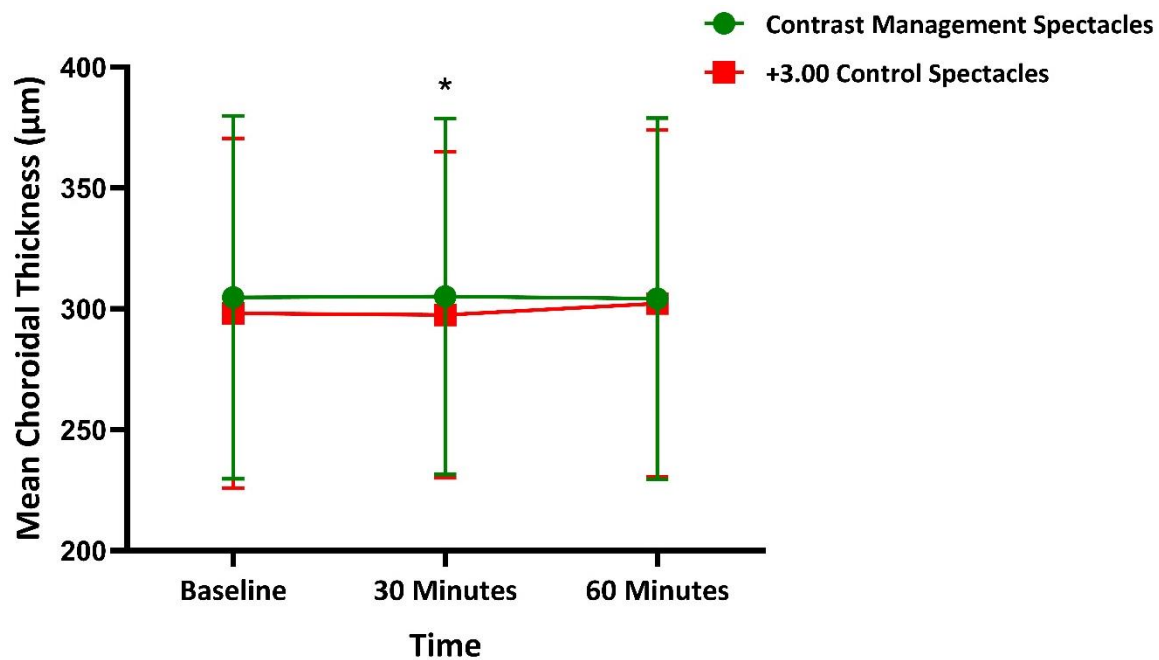


Figure 5-16: Mean central choroidal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye. The error bars represent the standard deviation.

Table 5-14: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline, 30 minutes and 60 minutes at the central choroidal region of the right eye.

Central	DF	F	P	Effect size	Power
Between types	1, 29	4.331	0.04	0.13	0.52
Across time	1.837, 53.272	0.650	0.51	0.02	0.14
Interaction	2, 58	1.901	0.16	0.06	0.37
RMANOVA (CMS vs Control)	Baseline vs Baseline	30 Minutes vs 30 Minutes	60 Minutes vs 60 Minutes		
P value	0.14	0.02	0.10		

5.4.2.6 Inner Nasal Choroidal Thickness

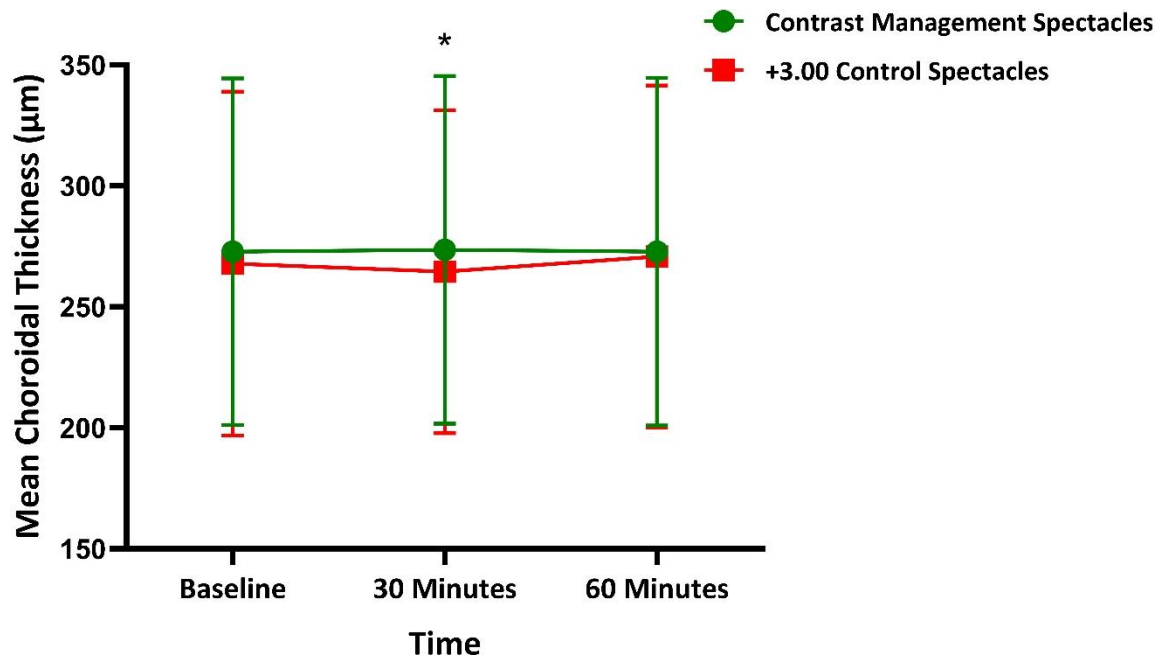


Figure 5-17: Mean inner nasal choroidal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye. The error bars represent the standard deviation.

Table 5-15: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline, 30 minutes and 60 minutes at the inner nasal choroidal region of the right eye.

Inner Nasal	DF	F	P	Effect size	Power
Between types	1, 29	7.793	0.009	0.21	0.77
Across time	1.991, 57.740	1.445	0.24	0.04	0.29
Interaction	2, 58	2.611	0.08	0.08	0.47
RMANOVA (CMS vs Control)	Baseline vs Baseline		30 Minutes vs 30 Minutes		60 Minutes vs 60 Minutes
P value	0.06		0.01		0.10

5.4.1.7 Outer Nasal Choroidal Thickness

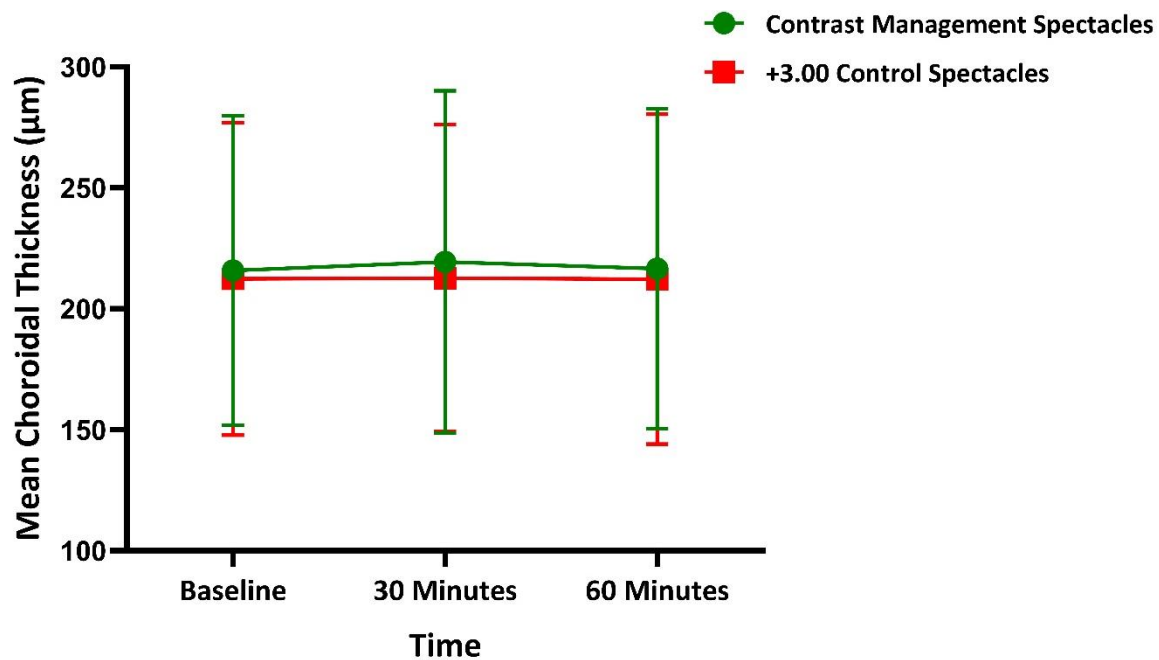


Figure 5-18: Mean outer nasal choroidal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye. The error bars represent the standard deviation.

Table 5-16: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline, 30 minutes and 60 minutes at the outer nasal choroidal region of the right eye.

Outer Nasal	DF	F	P	Effect size	Power
Between types	1, 29	8.695	0.06	0.23	0.81
Across time	1.626, 47.147	0.440	0.60	0.01	0.11
Interaction	2, 58	0.463	0.57	0.01	0.11

5.4.1.8 Inner Temporal Choroidal Thickness

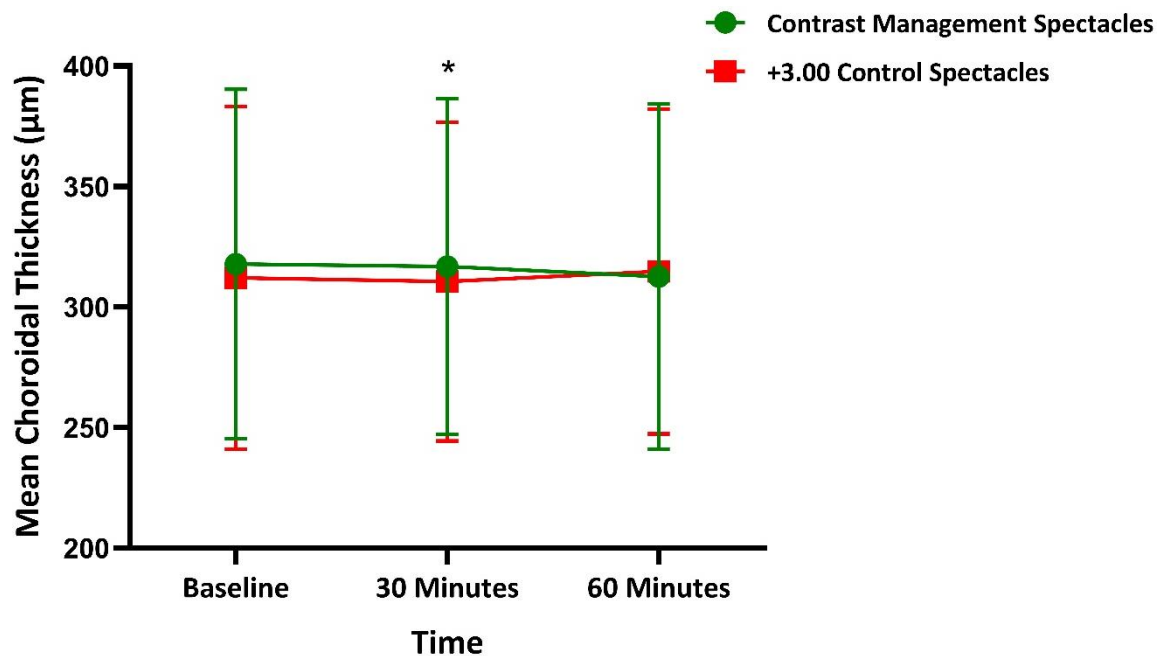


Figure 5-19: Mean inner temporal choroidal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye. The error bars represent the standard deviation.

Table 5-17: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline, 30 minutes and 60 minutes at the inner temporal choroidal region of the right eye.

Outer Temporal	DF	F	P	Effect size	Power
Between types	1, 29	4.708	0.03	0.14	0.56
Across time	1.525, 46.193	3.282	0.05	0.10	0.52
Interaction	2, 58	0.088	0.84	0.003	0.06
RMANOVA (CMS vs Control)	Baseline vs Baseline		30 Minutes vs 30 Minutes		60 Minutes vs 60 Minutes
P value	0.09		0.03		0.30

5.4.1.9 Outer Temporal Choroidal Thickness

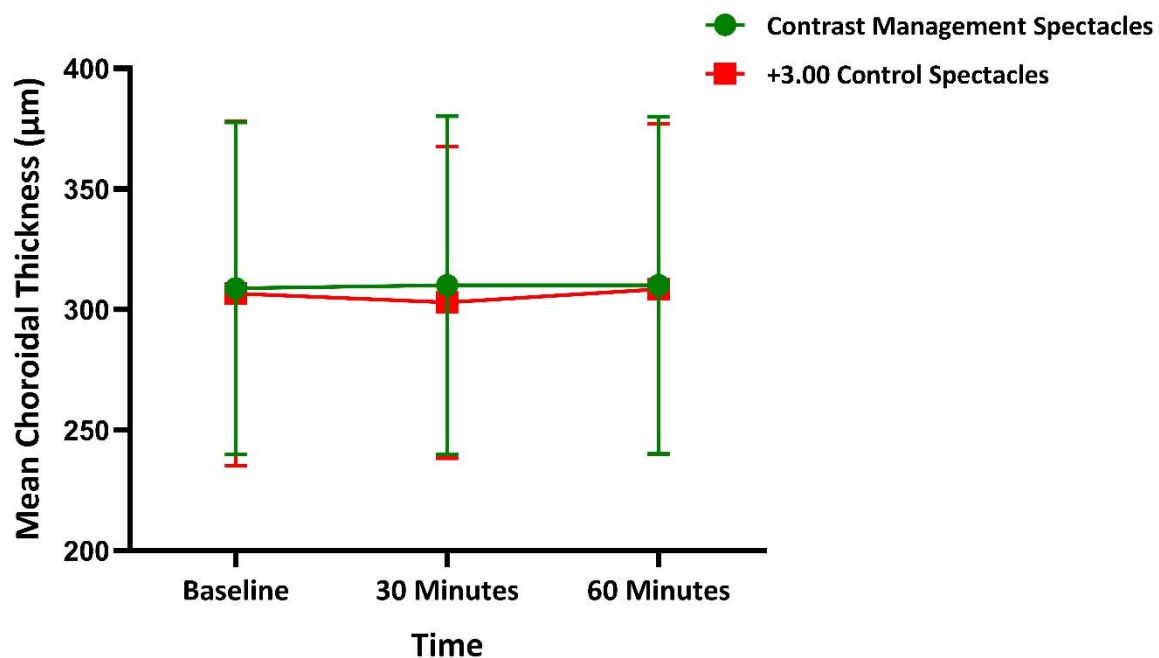


Figure 5-20: Mean outer temporal choroidal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye. The error bars represent the standard deviation.

Table 5-18: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline, 30 minutes and 60 minutes at the outer temporal choroidal region of the right eye.

Outer Temporal	DF	F	P	Effect size	Power
Between types	1, 29	3.239	0.08	0.10	0.41
Across time	1.921, 55.715	1.944	0.15	0.06	0.37
Interaction	2, 58	1.840	0.17	0.06	0.33

5.5 Discussion and Conclusion

This study aimed to measure the short-term effect of CMS on the thickness of the retina and choroid in emmetropic children aged between 8-14 years. The participants were instructed to focus on a TV screen at a 3m distance and avoid using phones or looking at close objects to avoid the effect of accommodation on the choroidal thickness.¹⁹⁶

Despite accounting for diurnal variation and accommodation effect on retinal and choroidal thickness, the study found no significant difference in the thickness of the retina or choroid over 60 minutes of CMS wear. However, a statistically significant difference was observed in the perifoveal outer inferior choroidal region, which showed a statistically significant difference between the 30- and 60-minute time points (5.01 μm) for CMS. The change was relatively small and is not considered clinically meaningful. Similarly, a study by Read et al. reported a statistically significant difference in the parafoveal zone of the retina between myopes and non-myopes, but the difference was only 6 μm and not considered clinically significant.¹⁷⁹ A recent study by Wang et al. on the short-term effect of 0.01% atropine in myopic children showed no significant difference in the retinal thickness but a modest increase of $11.12 \pm 13.96 \mu\text{m}$ in choroidal thickness after atropine treatment. However, this study was conducted over a period of 3 months, and the posterior segment scans were obtained using a SpectralisSD OCT, and the choroidal and retinal thicknesses were measured manually.¹⁹⁷

Another study by Chun et al. on the effect of defocus incorporated with multiple segments (DIMS) spectacles showed a significant increase in SFCT after a week of DIMS spectacle wear compared to single vision spectacles ($6.75 \pm 1.52 \mu\text{m}$ vs $-3.17 \pm 1.48 \mu\text{m}$).¹⁰⁷

In the current study, wearing +3.00 myopic defocus control spectacles for 60 minutes did not result in any significant changes in retinal or choroidal thickness across the nine ETDRS regions. A study by Wang et al. found a statistical difference in the mean choroidal thickness between the myopic defocus group and the control group after exposure to +3.00 monocular myopic defocus. The study found that myopic children exposed to +3.00 myopic defocus for 2 hours experienced less choroidal thinning compared to the control group without any intervention. Additionally, the increase in SFCT in the control group might have been affected by diurnal variation in choroidal thickness.¹²⁸ However, our study only included emmetropic participants and lacked a control group to observe true change over time. Furthermore, our exposure duration was only 1 hour, unlike the 2 hours in Wang et al.'s study. Another study by Read et al. reported a $12 \pm 16 \mu\text{m}$ increase in SFCT in young adults following a 60-minute exposure to +3.00 myopic defocus, measured using a Lenstar LS-900 optical biometer.¹²⁹ Although both studies followed a similar protocol of removing confounding variables, the study involved young adults aged between 20-31 years, unlike our study where the participant's age was between 8-13 years. Moreover, the study by Read et al. used a Lenstar biometer to scan the choroidal layer and the thickness was manually measured by calculating the distance between the peaks on A-scan, while in our study an OCT instrument was used to measure the choroidal thickness. Similar to the results in this study, a recent study by Ostrin et al. showed no significant difference in choroidal thickness after exposure to +3.00 myopic

defocus across different age groups (6-17, 18-30, and 31-45 years). The choroidal thickness measurements were obtained using an automated algorithm on the radial scans obtained from the Spectralis OCT.¹⁹⁸

In this study, while repeated measures ANOVA (RMANOVA) indicated no significant changes in choroidal thickness over the 60 minutes of wear for both the Contrast Management Spectacles (CMS) and the +3.00 control spectacles, post hoc pairwise comparisons revealed a statistically significant difference between the two lens types at the 30-minute mark. Specifically, significant differences were observed in the central ($7.69 \pm 4.19 \mu\text{m}$), outer inferior ($9.79 \pm 2.31 \mu\text{m}$), inner nasal ($9.10 \pm 2.77 \mu\text{m}$), and inner temporal ($6.20 \pm 5.46 \mu\text{m}$) regions. Additionally, at the 60-minute time point, a difference was noted in the inner inferior region ($3.96 \pm 8.33 \mu\text{m}$). These transient changes are consistent with findings from previous studies. For instance, the research by Chiang et al. reported rapid and reversible choroidal thickening of $20 \mu\text{m}$ in younger adults exposed to myopic defocus.¹⁹⁹ Similarly, Amorim de-Sousa et al. observed a significant increase in sub-foveal choroidal thickness of $17 \mu\text{m}$ after 30 minutes of wearing myopia control contact lenses,¹⁸⁷ while Chiang et al. found that myopic defocus induced choroidal thickening of $7 \mu\text{m}$ within 20 minutes in presbyopic adults.²⁰⁰ These studies indicate that the choroid can undergo rapid, albeit temporary, structural changes in response to myopic defocus stimuli.

In conclusion, short-term exposure to Contrast Management Spectacles did not result in any notable changes in retinal or choroidal thickness. However, a significant difference in

choroidal thickness was noted between the spectacles at the 30-minute time point, suggesting a rapid yet transient response. Further research with larger sample sizes and extended monitoring durations may be necessary to determine the clinical significance of these transient changes.

After investigating the short-term effect of CMS on retinal and choroidal thickness in this chapter, the next chapter shifts focus on a new parameter within myopia research, the choroidal vascularity index (CVI). Some studies have indicated that the choroidal vascularity index (CVI) can change even when the thickness of the choroid remains stable. The CVI is a measure of the vascular component within the choroid, and changes in either vascular density or the composition of the stroma may result in alterations to the CVI without influencing the overall thickness of the choroid.²⁰¹⁻²⁰³ Therefore, the objective was to determine whether changes in choroidal thickness due to myopia are attributable to alterations in the vascular or luminal areas.

Chapter 6-Effect of short-term wear of contrast management spectacles on choroidal vascularity index

6.1 Introduction

The choroidal vascularity index (CVI) has emerged as a relatively new and promising metric among the various parameters used to assess choroidal health. CVI represents the proportion of the choroid occupied by the vascular lumina and is defined as the ratio of the vascular area to the total choroidal area.²⁰⁴ CVI is calculated from the optical coherence tomography (OCT) posterior segment scans that provide insights into choroidal vascularity and its potential alterations in various ocular conditions.²⁰⁴ One such condition is high myopia.

Myopic eyes typically exhibit higher CVI than emmetropes, and the increase in CVI is negatively correlated with choroidal thinning.²⁰⁵⁻²⁰⁷ However, some studies have shown thinner CVI in myopes in macular and peripapillary regions.⁷⁵ For instance, a study by Qi et al. found a significantly lower CVI in the macular region of myopic eyes ($32.60 \pm 3.92\%$) compared to emmetropic eyes ($34.98 \pm 3.71\%$).⁷⁵ The study also reported a higher CVI in hyperopic eyes ($36.05 \pm 3.94\%$) compared to myopes and emmetropes.⁷⁵ Similarly, Alis et al. observed a significant decrease in CVI in young adults with myopia ($66 \pm 0.01\%$) and hyperopia ($64 \pm 0.02\%$) compared to emmetropic eyes ($68 \pm 0.03\%$).²⁰⁸ The lower CVI in myopia was attributed to a reduction in luminal area, whereas in hyperopia, it was due to excess stromal area.²⁰⁸

Conversely, a study by Alanazi on healthy adults shows that high myopes exhibit a higher CVI ($65.5 \pm 6.0\%$) compared to emmetropes ($59.6 \pm 7.0\%$).²⁰⁵ The study suggests that myopia is associated with stromal thinning rather than vascular thickening and also noted that CVI can be affected by diurnal variations.²⁰⁵ Another study by Yazdani et al. comparing the choroidal thickness and CVI in young adults, showed a thinner choroid in myopes compared to emmetropes and a slight decrease in CVI in emmetropes. The study suggested that the thinning of the total choroid is due to the thinning of the stromal area rather than the Luminal area.²⁰⁷

Given that CVI is a new parameter, there are very few studies on the effect of myopia control treatment on CVI in myopic eyes. Liu et al. reported no change in CVI throughout one year of orthokeratology lens wear, although a significant increase in stromal and luminal area was seen in the first three months, returning to baseline by the end of the study period.²⁰⁹ Another study on the choroidal changes during and after discontinuation of 0.01% atropine showed a decrease in CVI in children for both atropine-treated and placebo groups. The decrease in CVI in both groups was attributed to the thickening of the stromal choroidal area.²¹⁰

To our knowledge, no published literature to date has determined the effect of contrast management spectacles (CMS) on the CVI, similarly, no published literature measured the effect of +3.00 myopic defocus on CVI. Therefore, this study aimed to measure the short-term effect of CMS and +3.00 control spectacles on CVI.

6.2 Methods

This was a 2-visit, prospective, randomized, participant-masked study. A total of 30 participants, aged between 8 to 14 years, who were not receiving medication for any ocular or general health and were under no myopia control treatment, were recruited for this study. A spherical equivalent within +1.00D and -0.75D was required for inclusion, as determined by the Grand Seiko WAM 5500 open-field autorefractor (Shigiya Machinery Works LTD, Hiroshima, Japan) under non-cycloplegic conditions. The participants attended a screening visit where consent was obtained, and participant eligibility was determined.

For the study measurements, baseline posterior segment scans were obtained using the Triton DRI OCT (Topcon, Tokyo, Japan). Following the baseline measurements, participants were asked to wear study spectacles in a randomized order for 60 minutes, comprising either CSM (SightGlass Vision, Los Altos, CA, USA) or +3.00 clear spectacle lenses (control). For this study, +3.00 spectacle lenses were used as a positive control to induce myopic defocus. Participants wore the study spectacles and watched age-appropriate videos for 60 minutes at a 3m distance. OCT scans were collected after 30 and 60 minutes of watching the videos. Participants returned for a second visit to wear the other type of spectacles (CMS or +3.00 spectacle lenses) for 60 minutes, and the same procedures, including baseline scans, were repeated, as described previously. Both study visits occurred no earlier than 10 am to allow choroidal thickness and CVI to settle after waking. To control for diurnal variation the study measurements were taken approximately at the same time on both visits and at a minimum 2

hours after waking.²⁰⁵ After completion of the study visits, the CVI measurements were obtained using a fully automated Artificial Intelligence (AI) based fully automated software.

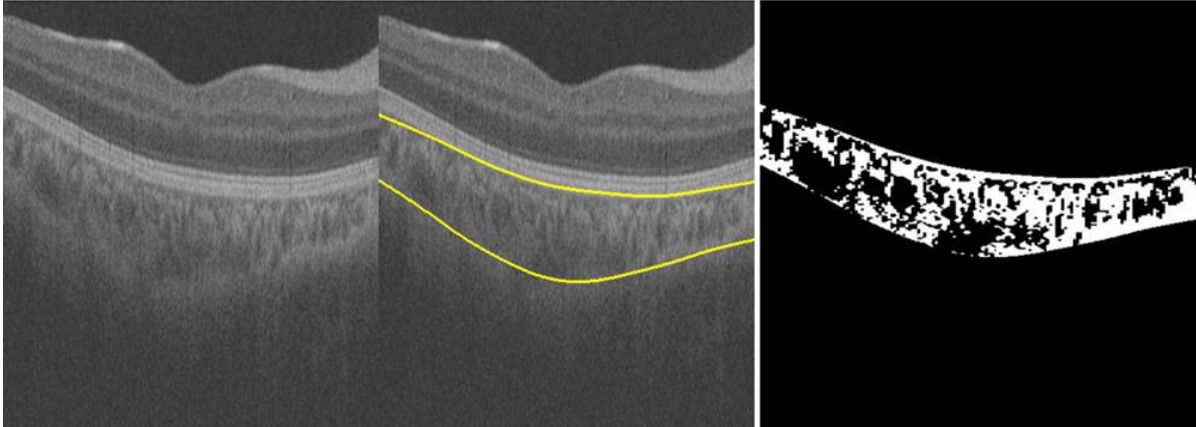


Figure 6-1: Example of a choroidal segmentation scan and image binarization for CVI measurement using AI-based automated software.

6.3 Statistical Analysis

Statistical analysis was conducted using IBM SPSS version 29 (IBM Corp Armonk, NY). Shapiro-Wilk test was used to test normality and Repeated Measures ANOVA was used to test the effect of +3.00 control spectacle and CMS after 30 minutes and 60 minutes of spectacle wear. A p-value of <0.05 was considered statistically significant. All data were analyzed for the right eye only.

6.4 Results

A total of 30 participants were enrolled in the study and completed all assessments (17 female, 13 male). The mean age of the participants was 10.9 ± 1.7 years (median 11 years, ranging from 8 to 13 years). The right eye's meanspherical equivalent refraction (SER) was 0.35 ± 0.29 diopters. All CVI data were normally distributed when examined using the

Shapiro-Wilk test ($p > 0.05$ for all). The data were analyzed in nine regions, as described by the ETDRS, as shown in **Figure 6-2**.

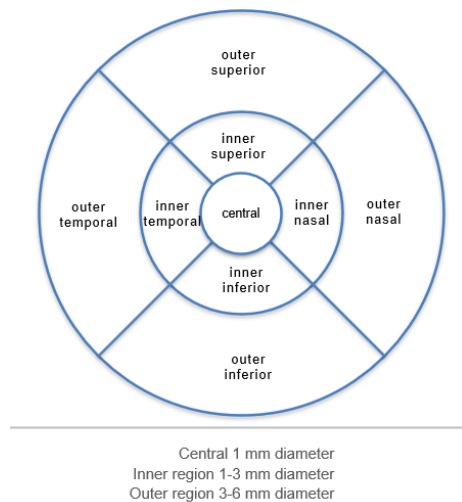


Figure 6-2: Choroidal vascularicity index ETDRS regions.

6.4.1 Choroidal Vascularicity Index (CVI)

The CVI for all ETDRS regions are shown in **Figures 6-3 to 6-11** and **Appendix C**. Statistical results for the comparisons between the CMS and +3.00 control spectacles at baseline, 30, and 60 minutes of wear at all 9 ETDRS regions are shown in **Tables 6-1 to 6-9**

6.4.1.1 Inner Superior CVI

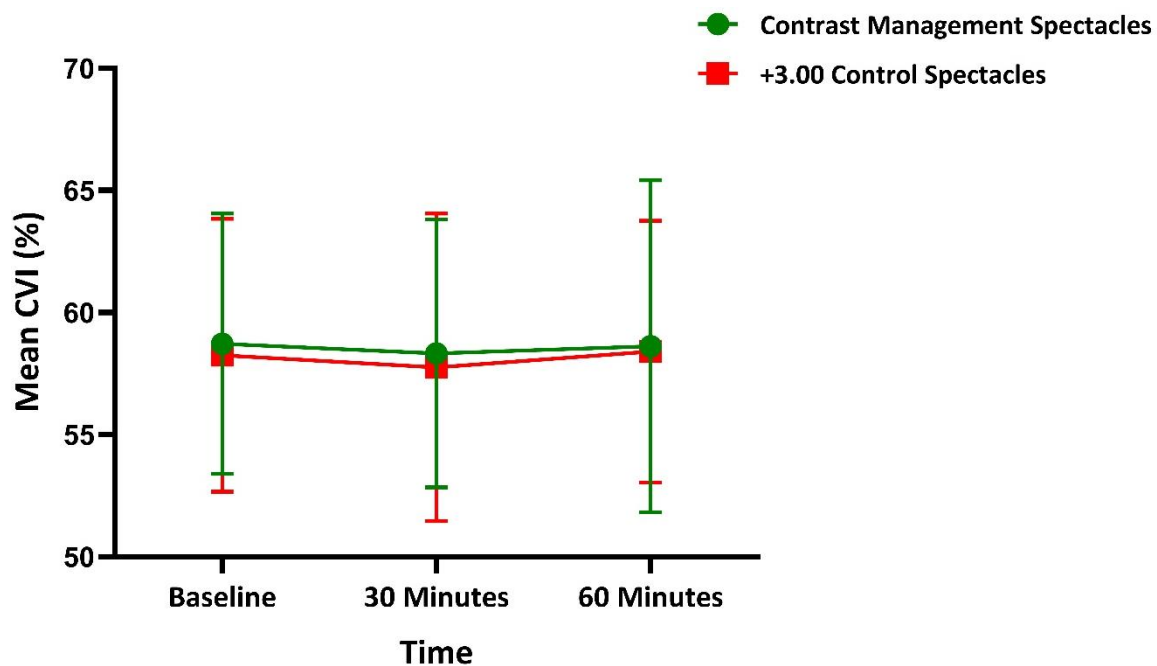


Figure 6-3: Mean inner superior choroidal vascularity index with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye. The error bars represent the standard deviation.

Table 6-1: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline, 30 minutes and 60 minutes at the inner superior region of the right eye.

Inner Superior	DF	F	P	Effect size	Power
Between types	1, 29	0.506	0.48	0.01	0.10
Across time	1.956, 56.726	0.410	0.66	0.01	0.11
Interaction	2, 58	0.069	0.93	0.002	0.06

6.4.1.2 Outer Superior CVI

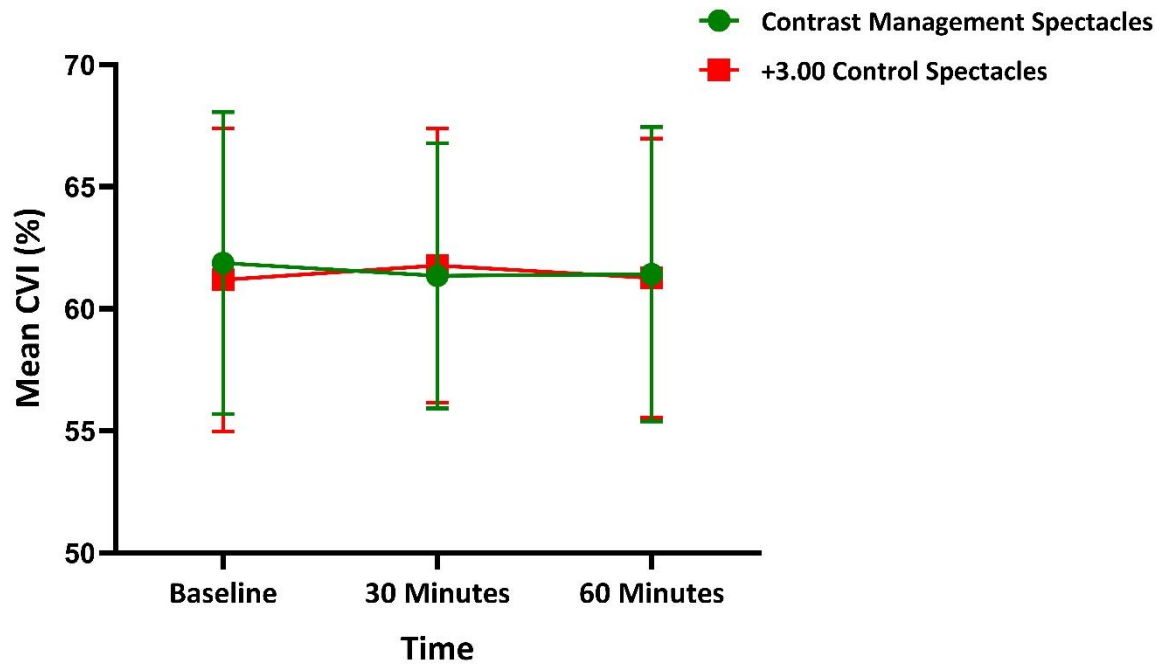


Figure 6-4: Mean outer superior choroidal vascularity index with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye. The error bars represent the standard deviation.

Table 6-2: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline, 30 minutes and 60 minutes at the outer superior region of the right eye.

Outer Superior	DF	F	P	Effect size	Power
Between types	1,29	0.081	0.77	0.003	0.05
Across time	1.474, 42.735	0.104	0.84	0.004	0.06
Interaction	2, 58	0.951	0.36	0.03	0.18

6.4.1.3 Inner Inferior CVI

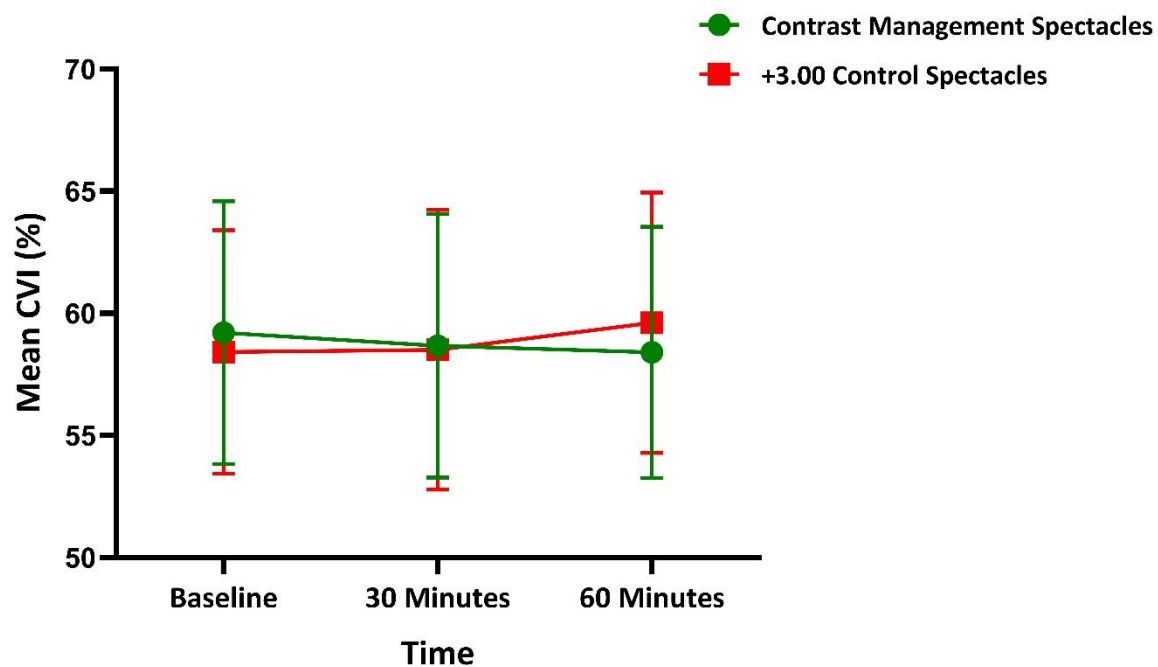


Figure 6-5: Mean inner inferior choroidal vascularity index with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye. The error bars represent the standard deviation.

Table 6-3: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline, 30 minutes and 60 minutes at the inner inferior region of the right eye.

Inner Inferior	DF	F	P	Effect size	Power
Between types	1, 29	0.027	0.87	0.001	0.05
Across time	1.983, 57.504	0.258	0.77	0.009	0.08
Interaction	2, 58	1.759	0.18	0.05	0.33

6.4.1.4 Outer Inferior CVI

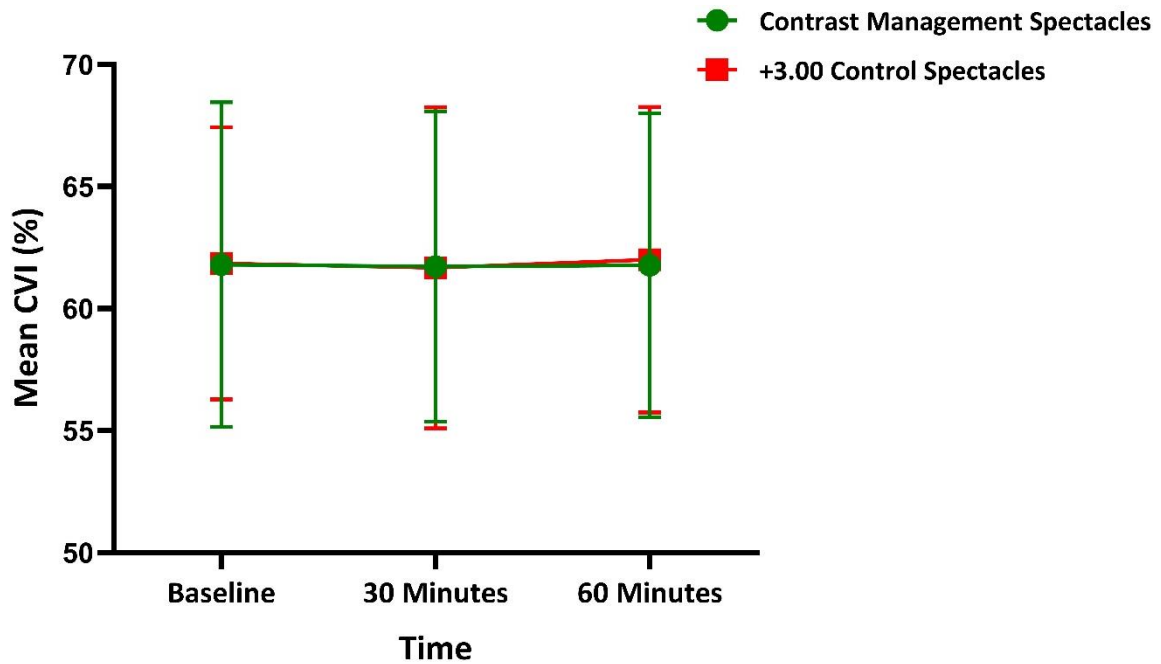


Figure 6-6: Mean outer inferior choroidal vascularity index with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye. The error bars represent the standard deviation.

Table 6-4: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline, 30 minutes and 60 minutes at the outer inferior region of the right eye.

outer Inferior	DF	F	P	Effect size	Power
Between types	1, 29	0.039	0.84	0.001	0.05
Across time	1.954, 56.663	0.084	0.91	0.003	0.06
Interaction	2, 58	0.040	0.95	0.001	0.05

6.4.1.5 Central CVI

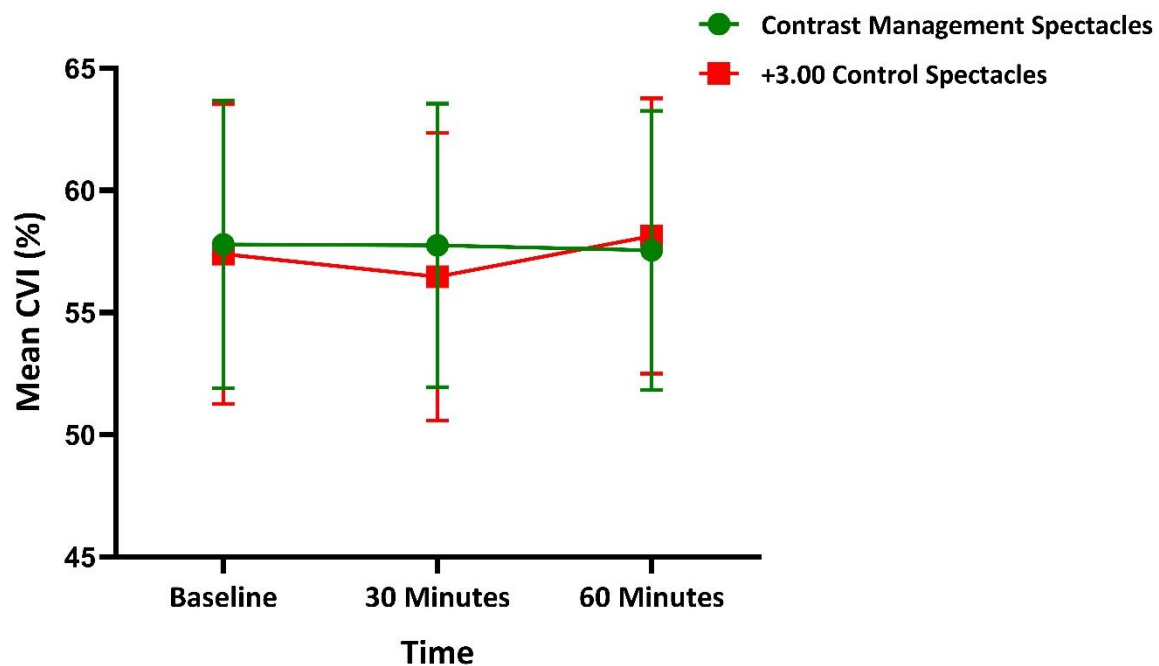


Figure 6-7: Mean central choroidal vascularity index with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye. The error bars represent the standard deviation.

Table 6-5: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline, 30 minutes and 60 minutes at the central region of the right eye.

Central	DF	F	P	Effect size	Power
Between types	1,29	0.393	0.53	0.01	0.09
Across time	1.905, 55.249	0.727	0.48	0.02	0.16
Interaction	2, 58	1.206	0.30	0.04	0.24

6.4.1.6 Inner Nasal CVI

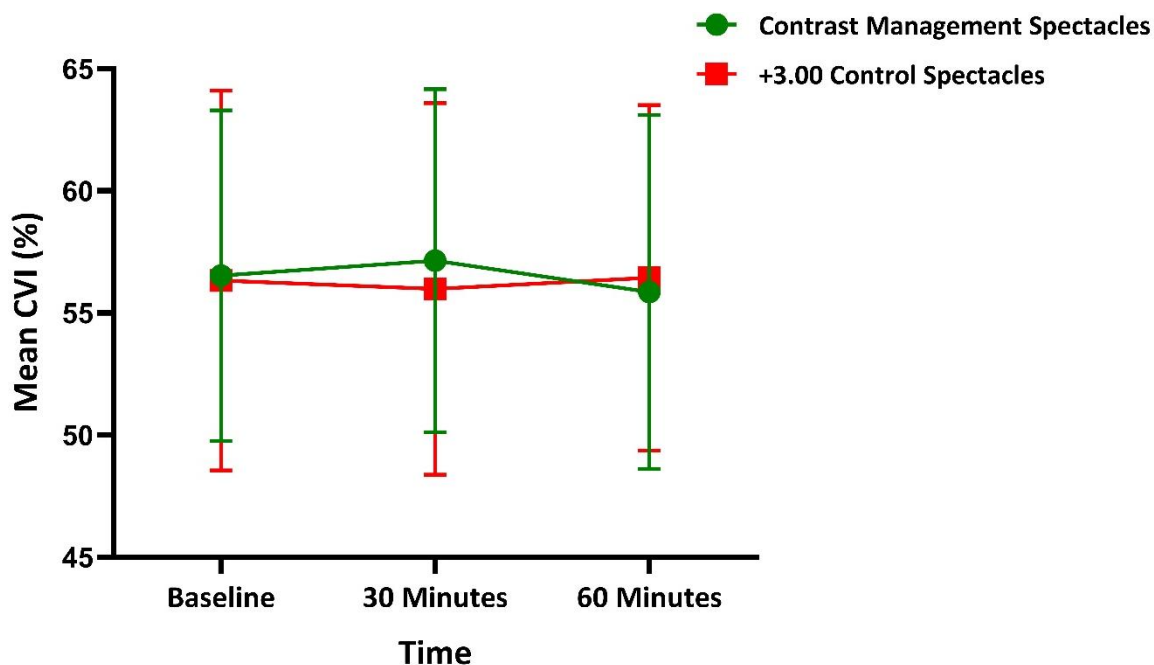


Figure 6-8: Mean inner nasal choroidal vascularity index with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye. The error bars represent the standard deviation.

Table 6-6: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline, 30 minutes and 60 minutes at the inner nasal region of the right eye.

Inner Nasal	DF	F	P	Effect size	Power
Between types	1, 29	0.137	0.71	0.005	0.06
Across time	1.930, 55.984	0.275	0.76	0.009	0.09
Interaction	2, 58	0.131	0.27	0.04	0.25

6.4.1.7 Outer Nasal CVI

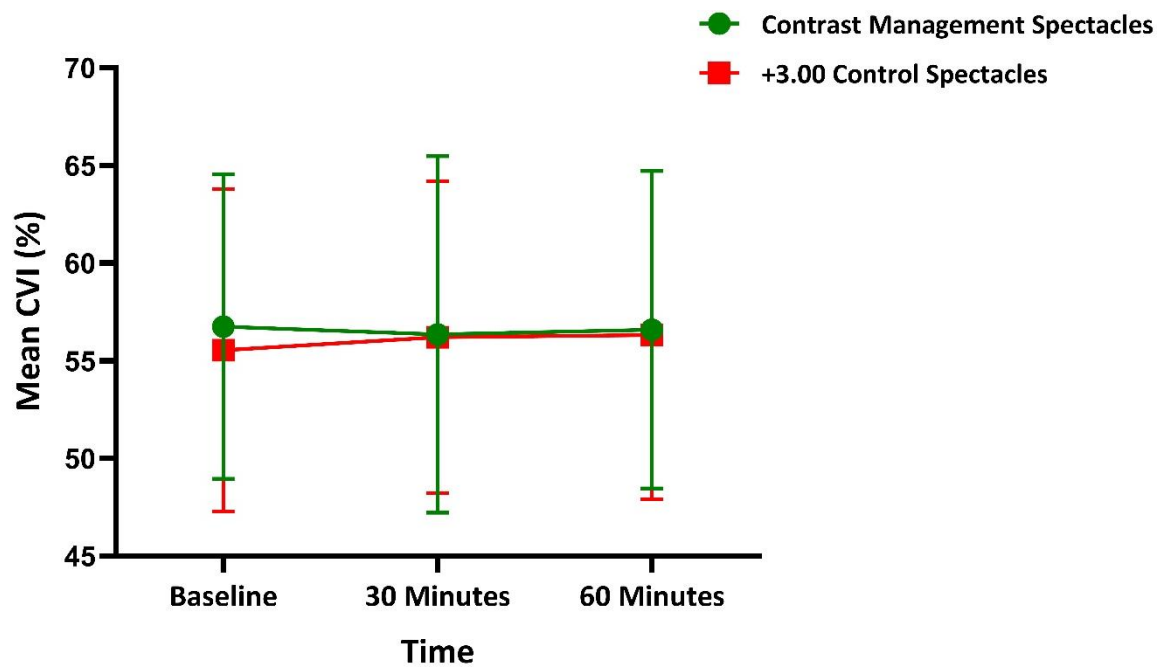


Figure 6-9: Mean outer nasal choroidal vascularity index with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye. The error bars represent the standard deviation.

Table 6-7: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline, 30 minutes and 60 minutes at the outer nasal region of the right eye.

Outer Nasal	DF	F	P	Effect size	Power
Between types	1, 29	1.202	0.28	0.04	0.18
Across time	1.891, 54.846	0.176	0.82	0.006	0.07
Interaction	2, 58	0.448	0.63	0.01	0.11

6.4.1.8 Inner Temporal CVI

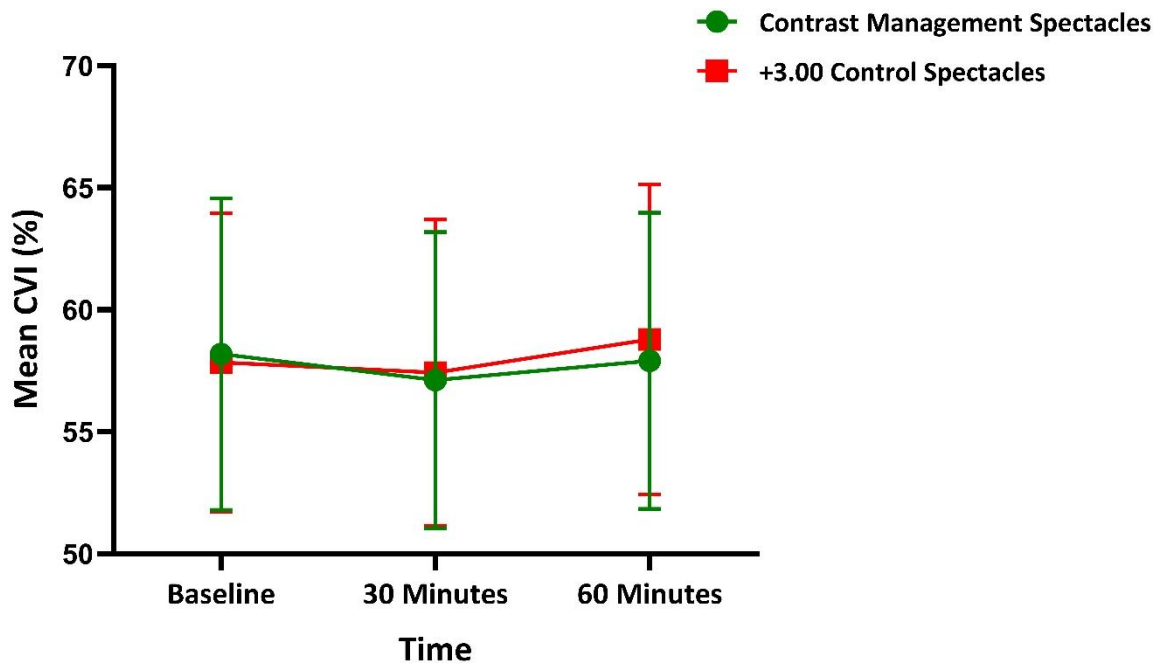


Figure 6-10: Mean inner temporal choroidal vascularity index with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye. The error bars represent the standard deviation.

Table 6-8: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline, 30 minutes and 60 minutes at the inner temporal region of the right eye.

Inner Temporal	DF	F	P	Effect size	Power
Between types	1, 29	0.252	0.62	0.009	0.07
Across time	1.986, 57.590	1.670	0.19	0.05	0.33
Interaction	2, 58	0.637	0.53	0.02	0.15

6.4.1.9 Outer Temporal CVI

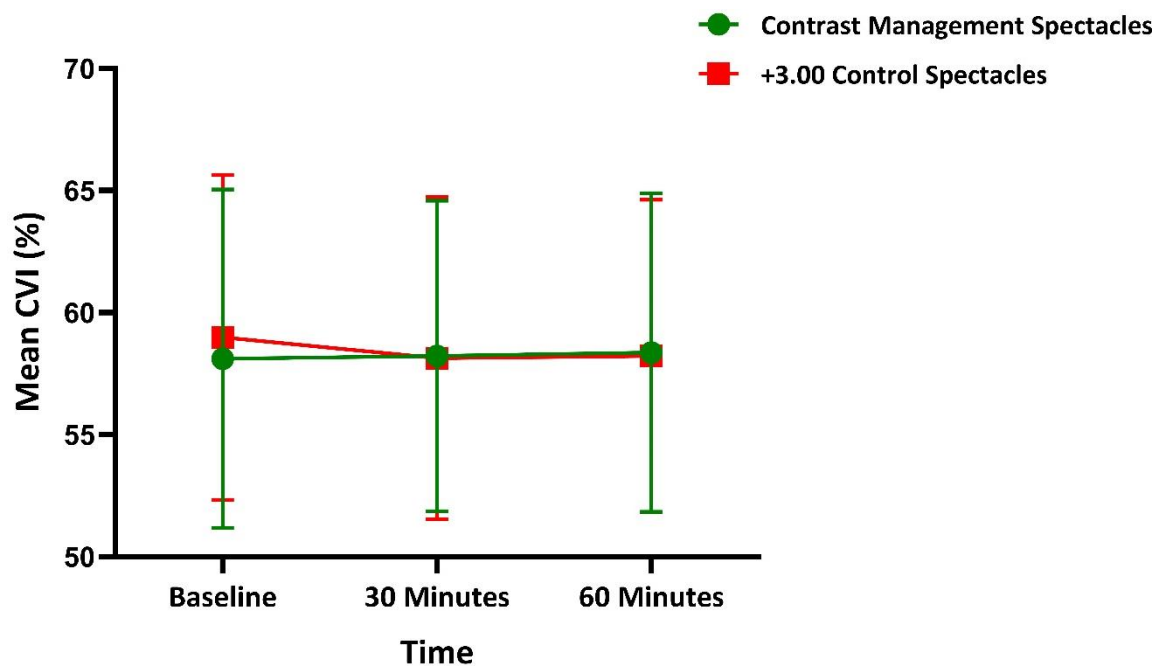


Figure 6-11: Mean outer temporal retinal thickness with contrast management spectacles and +3.00 control spectacles at baseline and after 30 and 60 minutes of wear for the right eye. The error bars represent the standard deviation.

Table 6-9: Two-way RMANOVA results for both contrast management spectacles and +3.00 control spectacles at baseline, 30 minutes and 60 minutes at the outer temporal region of the right eye.

Outer Temporal	DF	F	P	Effect size	Power
Between types	1, 29	0.266	0.61	0.009	0.07
Across time	1.785, 51.766	0.261	0.74	0.009	0.08
Interaction	2, 58	0.759	0.46	0.02	0.16

6.5 Discussion and Conclusion

This study measured the short-term effect of CMS and +3.00 control spectacles on the CVI in emmetropic children aged between 8-14 years. Both study visits were conducted at the same time of the day to avoid any potential diurnal variation impacts.

The study found no significant difference in the CVI over 60 minutes of CMS wear. Although there is very little published on the effect of myopia control on CVI, a study by Lee et al evaluated the changes in choroidal thickness and CVI during and after discontinuing long-term use of 0.01% atropine in myopic children.²¹⁰ The study included 153 children aged between 6 to 16 years, the children randomly received either 0.01% atropine or placebo treatment daily for 2 years followed by 1 year of washout. Swept-source OCT was used to measure CVI at baseline and at the end of the treatment and washout periods. During the treatment period, both groups showed a decrease in CVI, however, an increase in CVI was observed after the discontinuation of the placebo treatment.²¹⁰ While these results differ, so do the experiments undertaken. The mode of myopia reduction treatment is different (spectacle treatment vs a pharmacological agent). Although both studies have similar age ranges and used a similar OCT instrument to measure CVI, our study period was only 60 minutes, compared to a 2-year study by Lee et al.²¹⁰

This study marks the first investigation on the effect of +3.00 myopic defocus on the CVI, with no existing literature available for direct comparison. Previous research has demonstrated that +3.00 myopic defocus influences the choroidal thickness,^{129,188-190},

suggesting a possible impact on CVI. However, further studies are necessary to confirm its effect on CVI.

In conclusion, short-term exposure to CMS and +3.00 control spectacles did not lead to any notable change in CVI. Further research is required to investigate the impact of myopia-control spectacles on CVI in myopic individuals. Preliminary results indicate that a one-hour wear period of +3.00 myopia defocus lenses may not be sufficient to elicit a significant change in CVI. Therefore, it is imperative to conduct studies with extended wear of at least two hours duration to validate these findings and to better understand the potential long-term effect of myopia-control interventions on CVI.

Having comprehensively explored the short-term effects of CMS on both the anterior and posterior segment biometrics, the next step was to understand its impact on the functional component of the eye. Therefore, the next chapter aimed to evaluate the impact of CMS on the lag of accommodation (LOA).

Chapter 7 - Evaluation of lag of accommodation with full-field Diffusion Optics Technology™ (DOT) contrast management spectacle lenses

This chapter is extracted from a published article by Jabeen A, Luensmann D, Woods J, Hill JS, Jones L. Evaluation of Lag of Accommodation with Full-Field Diffusion Optics Technology™ (DOT) Contrast Management Spectacle Lenses in Emmetropic Children. *Clin Ophthalmol.* 2024 May 2; 18:1181-1190. [DOI https://doi.org/10.2147/OPHTH.S453790](https://doi.org/10.2147/OPHTH.S453790)

7.1 Introduction

Understanding the drivers of myopia onset and progression is essential to developing appropriate tools to prevent and/or control it – whether by optical, physical or pharmaceutical means. Accommodation, and specifically lag of accommodation (LOA) has been identified as a potential influence in both the onset and progression of myopia, though the literature is full of contradictions, as summarized in the paper on accommodation by the International Myopia Institute (IMI).¹¹² Several studies have shown higher LOA in myopic children compared to emmetropic children, as well as in those showing faster rates of myopia progression.^{109,211-215} The concern is that the hyperopic retinal defocus associated with higher LOA may drive axial elongation of the eye, resulting in myopia and/or myopia progression.^{24,213} Other studies suggested that degradation of the retinal image contrast may instead be the trigger.^{216,217} In either case, not all studies support the association of LOA and either onset or progression of myopia,^{110,218} though the interaction between contrast, accommodation and myopia is complicated. A drastic reduction in contrast results in form deprivation myopia, though ambient illumination has been shown to be an important

additional factor in modulating the degree of form deprivation myopia, with hyperopic shift seen with higher daylight levels of illumination.^{219,220} A less severe but still significant reduction in image contrast creates an effectively stimulus-free condition where accommodation drifts to what has been referred to as the “tonic” level, or around 1 diopter of accommodation,²²¹ which is at the high end of the range of normal LOA for children.²²²⁻²²⁶ Other studies have demonstrated that lower levels of contrast reduction have been shown to have little to no effect on accommodation.²²⁷⁻²²⁹

In terms of optical treatments for myopia, most efforts have been around designing contact lenses and spectacles that optically reduce or eliminate hyperopic defocus in the periphery, regardless of its cause. These include dual focus,²³⁰ extended depth-of-focus,²³¹ center distance²³² and orthokeratology contact lenses,²³³ as well as Highly Aspherical Lenslets (HAL),²³⁴ Defocus Incorporated Multiple Segments (DIMS),²³⁵ Peripheral Hyperopia Reduction Lens,²³⁶ executive bifocals,⁸⁵ and Progressive Addition Lens (PAL) spectacle designs.²¹⁸ A novel concept recently introduced utilizes contrast management to reduce retinal signals that have been associated with an extension of axial length in high myopia.^{237,238} This hypothesis arose from studying genetic sequencing in high myopes, where genetic mutations that changed the functionality of the long-(L) and middle-wavelength (M) cones were associated with high levels of myopia.²³⁹ Basically, the mutation caused adjacent cones with differing amounts of functional photopigments to signal the presence of contrast, even when there was no contrast in the image. The theory maintains that the natural outdoor environment provides a low natural contrast visual experience that elicits a low-level of activity in the bipolar cells of the retina. Subjecting humans to long exposures to high artificial contrast environments

such as that encountered in urban settings and when reading books and utilizing digital devices, along with insufficient time outdoors can cause an overstimulation of bipolar cells in the retina, leading to axial elongation.^{239,240}

Based on the contrast management hypothesis, SightGlass Vision (Los Altos, California, USA) developed Diffusion Optics Technology (DOT) spectacle lenses, designed to reduce and modulate the retinal contrast to decrease the signal for eye elongation. The lenses correct the refractive error and are combined with a proprietary pattern of thousands of microscopic dots to slightly lower contrast by softly scattering the light which passes through the lens, thereby modulating the contrast throughout the treatment zone of the lenses. The contrast management results in reduced signaling disparities between adjacent cones, while maintaining good visual acuity and functional peripheral vision. The commercially available lenses incorporate a 5-mm central aperture to assist in lens power verification and is positioned centered at the intermediate pupillary distance (PD) of each wearer so that near and far viewing will be primarily through the area of the lens with reduced contrast.^{237,238,240,241} Two-year results from an ongoing study showed promising results in reducing the rate of myopia progression.²⁴² Contrast management spectacle lenses are designed to reduce the retinal image contrast, which had been theorized to impact myopia onset and/or progression.^{216,217} However, there is currently no existing literature on how the contrast reducing pattern might impact LOA.

Therefore, this study aimed to evaluate the influence of full-field DOT spectacle lenses on LOA. The hypothesis was that there would be no impact of DOT spectacles on

accommodative response or accuracy when compared to control single vision spectacles. The full field DOT spectacle lenses were used in this study rather than commercially available DOT spectacles with 5mm clear central zone. Since the study aimed to test the effect of contrast reducing pattern on LOA, full-field DOT spectacle lenses were used. These lenses lacked the distinct clear central zone which is present in the commercially available DOT spectacles.

7.2 Material and methods

7.2.1 Study Design

This study was conducted in accordance with the Declaration of Helsinki and the University of Waterloo Guidelines for Research with Human Participants. Ethics clearance was obtained through the University of Waterloo Research Ethics Board (# 44567). An assent form was completed by all participants and the informed consent signed by parents/guardians prior to enrollment in the study. This study was registered with ClinicalTrials.gov (clinical trial identifier NCT05617794).

This was a prospective, randomized and subject-masked, pilot study involving 30 participants. The participants were enrolled in the study based on the following inclusion criteria (main criteria only): Age 6 to 18 years (inclusive); emmetropic by non-cycloplegic auto-refraction (both principle meridians ± 1.00 Diopters inclusive). Participants were not included if they had any history of myopia control treatment in the past year, any active ocular disease or infection, any binocular vision disorders or systemic condition that may affect the study outcome variables (including diabetes mellitus and hyperthyroidism), any use of systemic or topical medication that may affect the study outcome variables including atropine eye drops

or previous strabismus, refractive error or intraocular surgery. Participants were recruited from the clinical research site's volunteer database and from the community using marketing materials approved by the University of Waterloo Research Ethics Board. This study was conducted at the Centre for Ocular Research and Education (CORE), at the School of Optometry and Vision Science, University of Waterloo, Canada.

This was a single-visit study including the screening. At screening, participant eligibility was determined, and the following measurements taken: High contrast logMAR visual acuity at 6-meters, non-cycloplegic autorefraction and keratometry using a WAM 5500 open-field autorefractor (Grand Seiko, Fukuyama, Japan) at 6 meters, and ocular dominance assessed using the sighting method. Following the screening, eligible participants wore the study spectacles in randomized order. All spectacle lenses were made from Trivex material and had no optical power. The contrast management spectacle lens pair (DOT) consisted of light scattering dots 0.14 ± 0.03 mm in size applied uniformly over the entire lens surface. Unlike the commercially available product, the test lens used in this study did not have a clear central 5-mm aperture to ensure the subjects were looking through the contrast modulated design. The control spectacle lens pair used standard single-vision lenses with plano power.

7.2.2 Measurement of lag of accommodation

The participants were given 5 minutes of adaptation time, where the participants were asked to look at their surroundings while wearing each study spectacle design before conducting a distance target autorefraction at 6 meters and near target autorefraction at 40 cm. According to the literature, 40 cm is considered as a standard viewing distance and at this distance

accommodation is expected to have a minimal influence.^{243,244} To test the LOA the participant was asked to focus at the 0.4 LogMAR line on the near VA chart provided with the WAM 5500 held at 40 cm by a bar holder. Ten measurements were taken for each eye separately (right eye first, left eye second) and both eyes were uncovered while taking the measurements. These measurements were taken while the participants were wearing study spectacles. The average of these 10 measurements was used to calculate the LOA.

The participants were given 10 minutes of washout time between each type of spectacle wear. The instrument was calibrated before each participant. The accommodative lag was calculated as the difference between accommodative stimulus and the accommodative response as shown in the formula below:

$$\text{Accommodative response} = \text{Distance spherical equivalent refraction (DSER)} - \text{Near spherical equivalent refraction (NSER)}$$

$$\text{LOA} = \text{Accommodative stimulus} - \text{Accommodative Response}$$

7.3 Statistical analysis

Analysis was conducted using GraphPad Prism 8 (Dotmatics, San Diego, USA). Data for the right and dominant eyes only are reported. Descriptive statistics are provided on baseline variables (age, sex, VA distribution and refractive error distribution). The data for LOA were tested for normality based on the Shapiro-Wilk test (α level = 0.05). Data with normal distributions are displayed as mean $\pm$ standard deviation and were analyzed with a t-test.

Data with a non-normal distribution were analyzed with the Wilcoxon test and median values provided. The exploratory analysis on the difference in LOA between age group and sex were conducted using the Wilcoxon test. Study data are presented as mean, median described, individual participant data will not be shared.

7.4 Results

In total, 39 participants were enrolled in the study and 30 participants were included in the analyses cohort (**Table 7-1**). A total of nine participants were excluded from the study. Two participants failed the screening due to prescription range, and one participant discontinued from the study as they had difficulty understanding the instruction provided by the investigator. One participant's data were not included in the analysis due to a major protocol deviation noticed after the participant completed the study. Data from five participants were excluded from all analyses due to lead of accommodation or no accommodative response during the study. The mean age of all participants included in the analyses cohort was 10.4 ± 2.81 years (range 7 to 17 years).

Table 7-1: Participant characteristics (n = 30)

		OD	Dominant Eye
Refractive error (mean $\pm$ SD) (min, max)	Sphere	+0.43 $\pm$ 0.30 (-0.50, 0.87)	+0.42 $\pm$ 0.30 (-0.25, 0.87)
	Cylinder	-0.42 $\pm$ 0.25 (-1.00, 0.00)	-0.42 $\pm$ 0.24 (-1.00, -0.12)
Visual Acuity (logMAR) (min, max)		-0.05 $\pm$ 0.07 (-0.18, 0.12)	-0.07 $\pm$ 0.14 (-0.80, 0.12)

7.4.1 Lag of accommodation with contrast management and control spectacles

7.4.1.1 Right eyes – all eligible participants

Data for LOA from the right eyes were not normally distributed for either spectacle lens design (Shapiro-Wilk $p = 0.03$ for contrast management spectacles and $p = 0.05$ for control spectacles). The LOA data from the right eye were not statistically significantly different between contrast management and control spectacle lenses (Wilcoxon test , $p = 0.35$). **Figure 7-1** shows a moderate level of correlation between contrast management and control spectacle lenses ($R^2 = 0.61$).

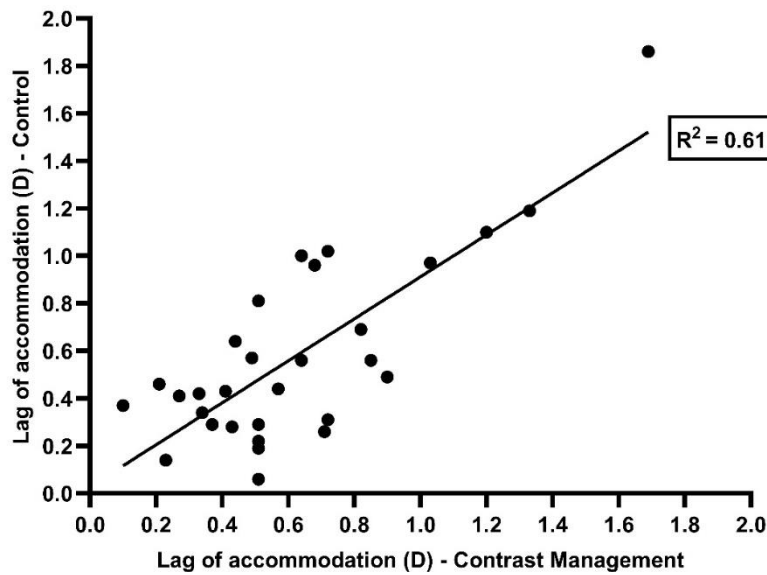


Figure 7-1: The scatter plot shows the correlation of LOA between the contrast management and control spectacles in the right eyes of each participant (n=30).

A box and whisker plot (**Figure 7-2**) shows the 5th and 95th percentiles with mean LOA of 0.57D $\pm$ 0.39D for the contrast management spectacles and 0.62D $\pm$ 0.34D for the control spectacles in the right eyes. The plot indicates a positively skewed data distribution for both contrast management and control spectacles. The 25th and 75th percentile were at 0.29D and 0.84D for the contrast management spectacles and 0.40D and 0.74D for the control spectacles. The graph also shows the interquartile range (IQR) of 0.55D for the contrast management spectacles and 0.34D for the control spectacles.

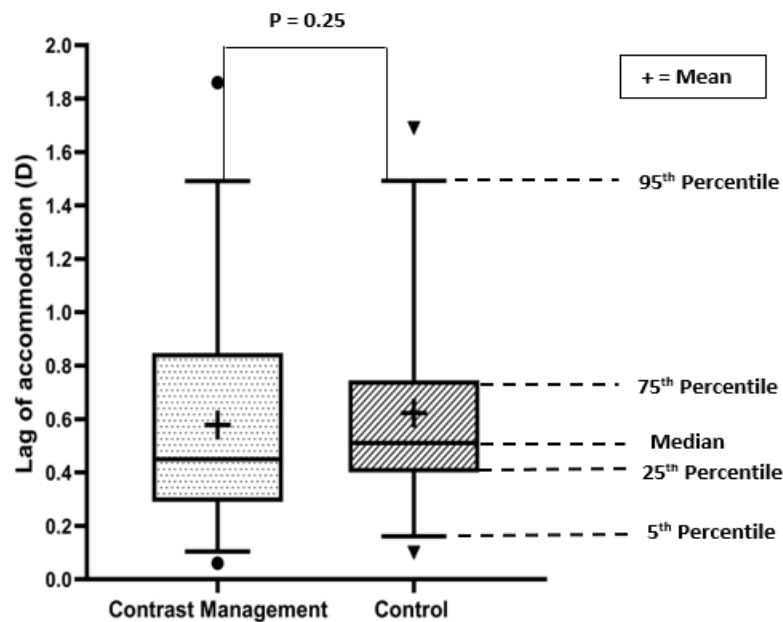


Figure 7-2: The Box and Whisker plot shows the distribution of LOA with contrast management and control spectacles in the right eye.

7.4.1.2 Dominant eyes – all eligible participants

As for the right eyes, data for the dominant eyes were not normally distributed (Shapiro-Wilk $p = 0.02$ for contrast management spectacles and $p = 0.02$ for control spectacles). Lag of accommodation data from contrast management spectacles and control spectacles for the dominant eye were not statistically significantly different (Wilcoxon test , $p = 0.25$) and showed a moderate level of correlation between both spectacle designs ($R^2 = 0.52$) (**Figure 7-3**).

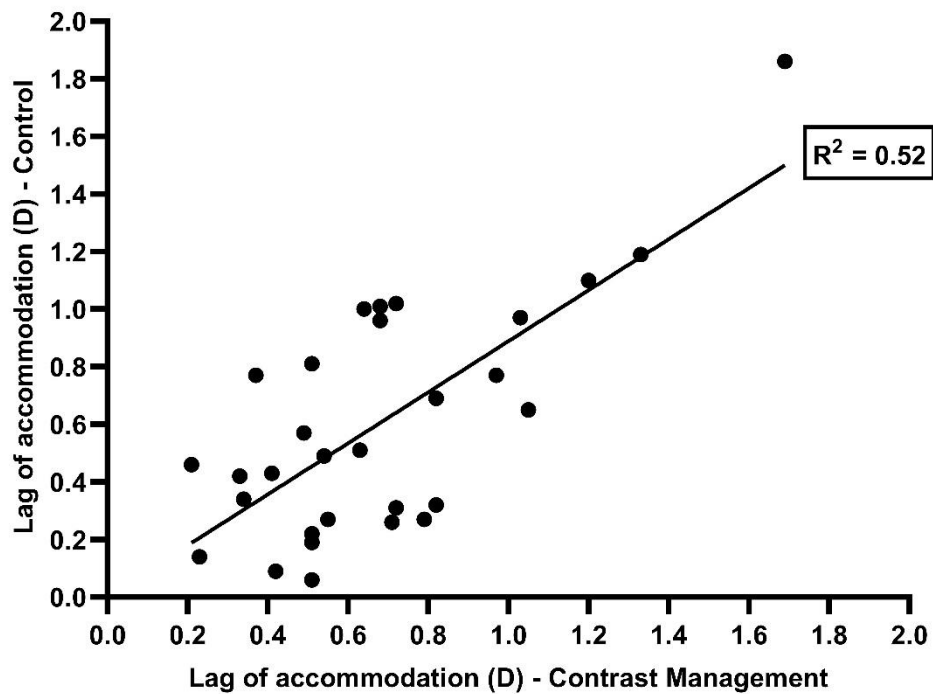


Figure 7-3: The scatter plot shows the correlation of LOA with contrast management and control spectacles in the dominant eye of each participant.

A box and whisker plot (**Figure 7-4**) was plotted at the 5th and 95th percentiles with the mean LOA of $0.60\text{D} \pm 0.40\text{D}$ for the contrast management and $0.68\text{D} \pm 0.33\text{D}$ for the control spectacles in the dominant eye. The plot indicates a positively skewed data distribution for both the contrast management spectacles and control spectacles. The 25th and 75th percentile were at 0.27D and 0.96D for the contrast management spectacles and 0.47D and 0.82D for the control spectacles. The graph also shows the interquartile range (IQR) of 0.69D for the contrast management spectacles and 0.35D for the control spectacles.

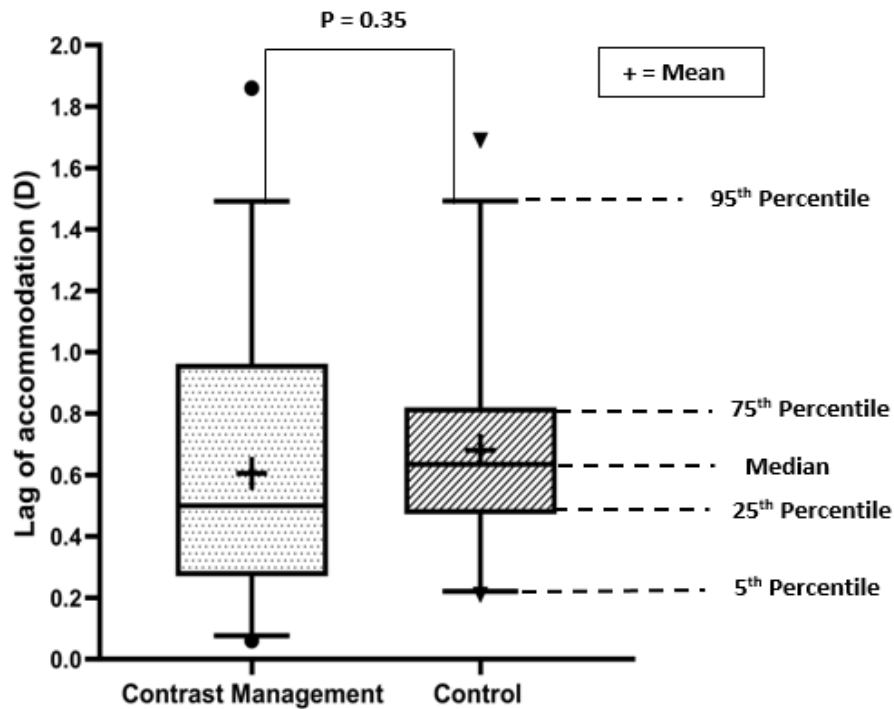


Figure 7-4: The Box and whisker plot shows the distribution of LOA between contrast management and control spectacles in the dominant eye.

Though this was a pilot study with a relatively small sample size, it was of interest to conduct additional exploratory analysis to determine if there was any effect of age or gender on the LOA between contrast management and control spectacles.

7.4.2 LOA in younger vs older participants

The right and dominant eye data were analyzed to test the difference in the mean LOA between the age groups 7-11 years ($n = 19$) and 12-17 years ($n = 11$) for the contrast management and control spectacles (**Table 7-2**). There were no significant different differences by age or spectacle lens design.

Table 7-2:Lag of accommodation with contrast management and control spectacles in the right eye and dominant eye for the age groups 7-11 years (n=19) and 12-17 years (n=11); Mean $\pm$ SD, (median)

	Right Eye			Dominant Eye		
Lag of accommodation	Age 7-11 years	Age 12-17 years	p-value	Age 7-11 years	Age 12-17 years	p-value
Contrast management	0.52D $\pm$ 0.29D (0.46D)	0.67D $\pm$ 0.51D (0.42D)	0.39	0.52D $\pm$ 0.32D (0.46D)	0.73D $\pm$ 0.50D (0.77D)	0.24
Control	0.58D $\pm$ 0.28D (0.51D)	0.66D $\pm$ 0.47D (0.44D)	0.64	0.61D $\pm$ 0.23D (0.55D)	0.79D $\pm$ 0.44D (0.72D)	0.32
p-value	0.50	0.95		0.17	0.78	

7.4.3 LOA in male vs female participants

The right and dominant eye data were further analyzed to test the difference in the mean LOA between male (n = 10) and female (n = 20) participants when wearing both spectacle designs. There were no significant differences by gender or spectacle lens design (**Table 7-3**).

Table 7-3:Lag of accommodation with contrast management and control spectacles in the right eye and dominant eye for male (n=10) and female (n=20) participants (Mean $\pm$ SD, (median))

	Right Eye			Dominant Eye		
Lag of accommodation	Male	Female	p-value	Male	Female	p-value
Contrast management	0.44D $\pm$ 0.25D (0.46)	0.64D $\pm$ 0.43D (0.44)	0.40	0.49D $\pm$ 0.33D (0.40)	0.65D $\pm$ 0.43D (0.58)	0.32
Control	0.62D $\pm$ 0.16D (0.60)	0.61D $\pm$ 0.42D (0.51)	0.94	0.58D $\pm$ 0.13D (0.55)	0.72D $\pm$ 0.39D (0.69)	0.26
p-value	0.09	0.99		0.47	0.59	

7.5 Discussion

These data confirmed the hypothesis that the mild decrease in contrast associated with the contrast management in the test design did not significantly impact LOA over a short period of wear of this novel design.²⁴⁵ Further, elimination of the central clear aperture in the research design used in this study confirms that the effect is indeed relevant to the contrast reduction feature in the product intended for commercial use.²⁴² The levels of LOA found for both groups in this study were within the expected ranges published in recent and historical studies using a variety of measurement techniques.^{222,225,226,246} A recent study found that LOA remains constant from 5 to 40 years of age and ranges between 0.00 to +1.00D.²²⁶ Similar findings were reported in school age children aged 4 to 15 years using Nott retinoscopy and real targets at varied distances,²²⁵ and in subjects from 3 to 40 years using an open-field autorefractor and minus lenses.²²² An earlier study reported a LOA of $0.28 \pm 0.44\text{D}$ in 4-year-old children and $0.45 \pm 0.30\text{D}$ in 12-year-old children with a weak dependency on age using the Monocular Estimate Method (MEM) of dynamic retinoscopy.¹¹² There was a consensus across studies that LOA increased with increasing demand. The results of a study of young adults confirmed a significantly higher LOA in myopic subjects compared to emmetropic subjects and cautioned that since the measurement of LOA is affected by method with differences as large as 0.50D, care should be taken when comparing values across studies with different methodologies.²²⁴ Other studies have compared LOA results with different techniques and have found agreement between autorefractors and MEM and Nott retinoscopy,^{247,248} but not with an infrared retinoscope.²⁴⁷ But for identifying myopic children

with very high accommodative lags ($\text{LOA} \geq 1.00\text{D}$), neither MEM nor Nott retinoscopy provided adequate sensitivity and specificity.²⁴⁹

This study used an open-field autorefractor widely used in clinical myopia studies that has shown to be reliable and efficient.²⁴⁹ The distance fixation target is positioned in the distance and therefore reduces the potential stimulus to accommodation, while the near target is placed in the required reading distance. It can also take multiple measurements in a short period of time.

While literature exists confirming small differences in accommodative amplitude and facility between dominant and non-dominant eyes,^{250,251} differences in LOA were not confirmed in those reports. Though sub-group sample sizes were small in this study, thereby limiting statistical power to detect differences, no statistically nor clinically significant differences were found in this study for LOA for any subgroup analysis (right eye versus dominant eye, age and sex).

Although the IMI report on the impact of accommodation on myopia suggested that it is more probable that the increased hyperopic defocus from LOA may be a consequence rather than a cause of myopia,¹¹² the lack of impact on accommodative measures in the low ametropes studied while wearing the contrast modulated spectacle design is still reassuring. Results for LOA with contact lens designs for myopia control that incorporate zones of relative plus power that could interfere with accommodation have been as varied as the designs available.^{230,252-256} Interestingly, orthokeratology has shown to be associated with a decreased LOA over time, as well as versus non-myopia control soft contact lens wearers and

spectacles,^{257,258} while increased LOA with MEM retinoscopy following 6 months of daily dosing of 0.125% atropine drops was reported.²⁴¹ When considering spectacle designs for myopia control, a significant decrease in LOA after 2 years of wearing DIMS spectacles compared to single vision glasses when measured using an open-field autorefractor was reported in one of the few studies reporting LOA.

This study was limited by the fact that all the participants involved in the study were emmetropic or had a very low prescription and therefore primarily represents children that are at a very early-stage of their onset of myopia or who may remain emmetropic. Additionally, the sample size was small, particularly for the exploratory sub-group analyses. The spectacles differed slightly from those used in clinical trials to determine efficacy, in that they had no clear center as is seen in the commercial product and were worn only for a short period of time. To better understand the implications of LOA and myopia with this novel design, future studies should focus on evaluating the long-term effect of LOA in an at-risk population.

7.6 Conclusion

The current study suggests that the contrast management lenses do not significantly impact LOA after for short-term wear.

Chapter 8- General Discussion

8.1 Dissertation summary

This thesis aimed to investigate the short-term impact of contrast management spectacles (CMS) on ocular biometrics and accommodative lag. It is structured around five objectives, which form the basis of chapters 3 to 7.

Chapter 3 investigated the impact of CMS on the anterior segment biometrics including central corneal thickness (CCT), anterior chamber depth (ACD), lens thickness (LT), and axial length (AL). To explore the effect, 30 emmetropic children aged 8 to 14 years were recruited and the Zeiss IOL master700 was utilized to measure these structures at various time points. To validate the results a myopic defocus of +3.00 DS was induced in both eyes using spectacles, which served as a positive control. After one hour of wearing the study spectacles, no significant difference was observed in the thickness of ACD, LT; however, a significant reduction of 6 μm was observed in AL. Interestingly, there was a minor 3 μm change in CCT. While this difference in CCT was statistically significant, its clinical relevance remains insignificant. Moreover, the +3.00D control spectacles did not yield any clinically significant results, but the change in AL from both spectacles was statistically significant. These findings suggest that short-term (60 minutes) of both CMS and +3.00D control spectacle wear does have impact on anterior segment biometrics or axial length in children. However, the duration and intensity of exposure are needed to observe meaningful changes in these parameters. This also highlights the need for further research on the long-term effects of CMS on ocular structures.

The subsequent step was to measure the effect of CMS on the posterior segment, which required an investigation of the most appropriate method of measuring choroidal thickness.

Chapter 4 focused on methodologies for the measurement of sub foveal choroidal thickness.

Posterior segment OCT scans were acquired from 30 emmetropic children aged between 8-14 during two separate visits, using the TOPCON Triton swept-source OCT. During each visit, three volume scans were conducted to evaluate both intra-visit and inter-visit repeatability. The sub foveal choroidal thickness was assessed using four methods: A manual method using Image J, semi-automated measurements using the OCT caliper, an automated measurement using OCT inbuilt software, and an AI-based automated software. RMANOVA for repeatability was not statistically significant across all methods. The manual method significantly overestimated choroidal thickness by over 35 μm , followed by the semi-automated methods, which exhibited an overestimation of approximately 8 μm . Both automated methods demonstrated strong agreement in terms of mean bias, differing by less than 3 μm from each other. However, the AI-based automated software showed a positive trend indicating proportional bias. Subsequently, comparisons of choroidal thickness measurements between the two automated methods were conducted across all Early Treatment Diabetic Retinopathy Study (ETDRS) regions. The results indicated that the inbuilt OCT software showed regional-specific reliability, and less variability compared to the AI-based automated software.

Chapter 5 looked at the short-term effect of CMS on the posterior segment of the eye, specifically focusing on the retinal thickness and choroidal thickness in 30 emmetropic

children over two visits. To mitigate the effects of diurnal variations and accommodation on the thickness of these layers, all measurements were taken at the same time of day for both visits, the TV screen was placed 3 m away, and participants watched an age-appropriate video. +3.00D control spectacles were used as positive control. Volume scans were obtained using the Triton swept-source OCT over 1 hour of wear to measure the thickness of these layers. TABS automated software, previously described in Chapter 4, was used to assess both retinal and choroidal thickness. Despite efforts to minimize confounding variables, the study found no significant differences in retinal and choroidal thickness between CMS and +3.00D control spectacles across any of the ETDRS regions. However, a statistically significant difference was observed in the perifoveal outer inferior choroidal region, 30- and 60-minute time points (5.01 μm) for CMS. Similarly, a significant difference was observed between both the spectacles at the 30-minute time point in 4 out of 9 macular regions. . This study underscores the necessity for further longitudinal research to understand the long-term effect of CMS on choroidal and retinal thickness.

Chapter 6 delved into the relatively new parameter of the choroidal vascularity Index (CVI) within myopia research. CVI serves as an indicator to determine whether changes in choroidal thickness in myopia are due to alterations in the vascular area or the luminal area. The methodology mirrors that of Chapter 5, using the Triton OCT to obtain volume scans and utilizing the same AI-based automated software from prior experiments to calculate CVI in 30 emmetropic children across two visits. Participants wore both CMS and +3.00D control spectacles, and OCT scans were performed over 1 hour of wear. All ETDRS regions were

assessed to compute the CVI. The results revealed no significant difference in CVI between the CMS and +3.00D control spectacles. Due to the lack of existing literature on the short-term effects of myopia control treatment, it is challenging to draw definitive conclusions regarding CVI's effectiveness in myopia progression and control. This finding indicates the need for further research to explore CVI and its relationship with myopia in greater depth.

Based on the findings presented in chapters 3-6, it has been demonstrated that short-term exposure to CMS does not affect ocular structures, including CCT, ACD, LT, retinal thickness, and choroidal thickness. Additionally, no alterations were observed in AL. Consequently, the subsequent step was to evaluate the impact of CMS on the functional component of the eye.

Chapter 7 evaluates the effect of CMS on the lag of accommodation (LOA) compared to single-vision spectacles. The participants were all emmetropic children with non-cycloplegic autorefraction within $\pm 1.00\text{D}$ in both principal meridians. They wore both CMS and single-vision spectacles with a 5-minute adaptation period for each eye. Autorefraction measurements were taken at 6 m and 40 cm to assess distance and near targets. LOA was calculated from the autorefraction results and the results showed no significant difference in LOA between CMS and single-vision spectacles. Both spectacles exhibited a LOA within $\pm 1.00\text{D}$. These findings suggest that CMS does not impact the LOA differently than the single-vision spectacles, at least over the short duration of wear. However, further research is needed to understand the long-term impact of CMS on the population at risk. This finding is important to understand the potential benefits and limitations of CMS.

The experiments conducted in this thesis provide a foundational understanding of the short-term effects of CMS on ocular biometrics and LOA. Through rigorous methodologies, reliable baseline data for choroidal thickness measurement in children aged 8-14 years have been established, providing a foundation for future research. These findings contribute to the growing knowledge of CMS and its potential role in managing myopia, offering valuable insights for clinical practice and further scientific investigation.

8.2 Limitations

While this dissertation provides valuable insights into the short-term effects of CMS, several limitations should be acknowledged:

- 1. Sample size and population:** The research focused on a specific age group of emmetropic children aged 6 to 18 years who had no or low prescriptions. This group represents children who are either at the very early stages of myopia onset or those who may remain emmetropic. Consequently, the findings may not be generalized to other age groups or individuals with varying degrees of myopia.
- 2. Short-term exposure:** The experiments focused on the short-term effects of 60 minutes of CMS and +3.00D control spectacles. This limited duration may not be enough to observe significant changes in ocular structures or functional components.
- 3. Observer limitations:** This experiment was limited by the fact that only one observer was available to measure the choroidal thickness across all four measurement methods in the experiment described in chapter 4. Having an additional observer would have helped to confirm the variability seen in the manual method.

4. **Other confounding variables:** While efforts were made to minimize the effects of diurnal variation, accommodation, and other factors on choroidal thickness, eliminating their influence remains challenging.
5. **DOT spectacle use:** The myopia control spectacles used in this study differ from the commercial product, which features a clear central zone. This discrepancy may affect the applicability of the findings to real-world scenarios. Future studies should consider using commercially available products to better reflect the practical applications.

8.3 Future Work

Though the study has shown CMS's impact on ocular structures, some unknown factors remain that can be studied further.

Chapter 3: Anterior Segment Biometrics

1. **Extended period:** Future studies may evaluate the long-term effects of CMS on the anterior segment over 60 minutes or longer, which may help determine if extended exposure could lead to subtle or gradual changes in ocular biometrics.
2. **Refractive error and age range:** Investigating the effects of CMS in myopic populations with varying degrees of myopia, while including a broader age range of participants to understand how different age groups may respond to the treatment.
3. **Ethnicity:** Further research can also compare the effect of CMS on various ethnic groups.

Chapter 4: Methodologies for measuring choroidal thickness

- 1. Method comparison:** Further refining and comparing the AI-based automated method with another custom design for more accuracy and consistency in the measurements, which may assist in standardizing choroidal thickness measurement techniques and improve their reliability.
- 2. Additional observer:** Adding an additional observer to test the reliability of the measurements and to assess the inter and interobserver variability. This will ensure that the measurements are consistent and reproducible across different observers.

Chapters 5&6: CMS and Posterior Segment

- 1. Extended wear period:** Future studies can evaluate the long-term effects of CMS on retinal thickness, choroidal thickness and CVI in both myopic and emmetropic children and compare the results between different myopia control interventions.
- 2. Scleral thickness:** With advancements in imaging techniques, further studies can focus on including scleral thickness in highly myopic populations, to better understand structural changes associated with high myopia.
- 3. CVI Investigation:** Since CVI is a fairly new parameter, further investigation into the relationship between CVI and myopia progression, both in the short-term and long-term, is essential. This research can provide valuable insight into choroidal blood flow and vessel thickness on overall choroidal thickness. Understanding these changes will help elucidate the mechanism underlying myopia progression and its control.

Chapter 7: CMS and Lag of Accommodation

1. **Extended wear period:** Evaluate the impact of prolonged CMS wear on accommodative lag over extended periods and in various viewing distances. This will help determine if the extended wear period affects the accommodative response differently than short-term wear.
2. **Comprehensive accommodative assessment:** Assessing accommodative metrics such as the amplitude of accommodation, accommodative facility, and accommodative response at different viewing distances. This will provide a more detailed understanding of CMS effects on the accommodative system and its potential benefits for myopia control.

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Appendix A

Chapter 4: In the manual method, the sub-foveal choroidal thickness of a subset of 15 participants was re-analyzed and segmented using a tangent. A repeated measures ANOVA (RMANOVA) was conducted to assess the repeatability of the measurements. The RMANOVA revealed no significant differences in the repeated measurements ($F_{1.11, 15.59} = 0.025$, $P = 0.89$, Effect Size = 0.02, Power = 0.05). These results are consistent with those obtained from segmentation without a tangent, as mentioned in the manual methods section of Chapter 4.

Appendix B

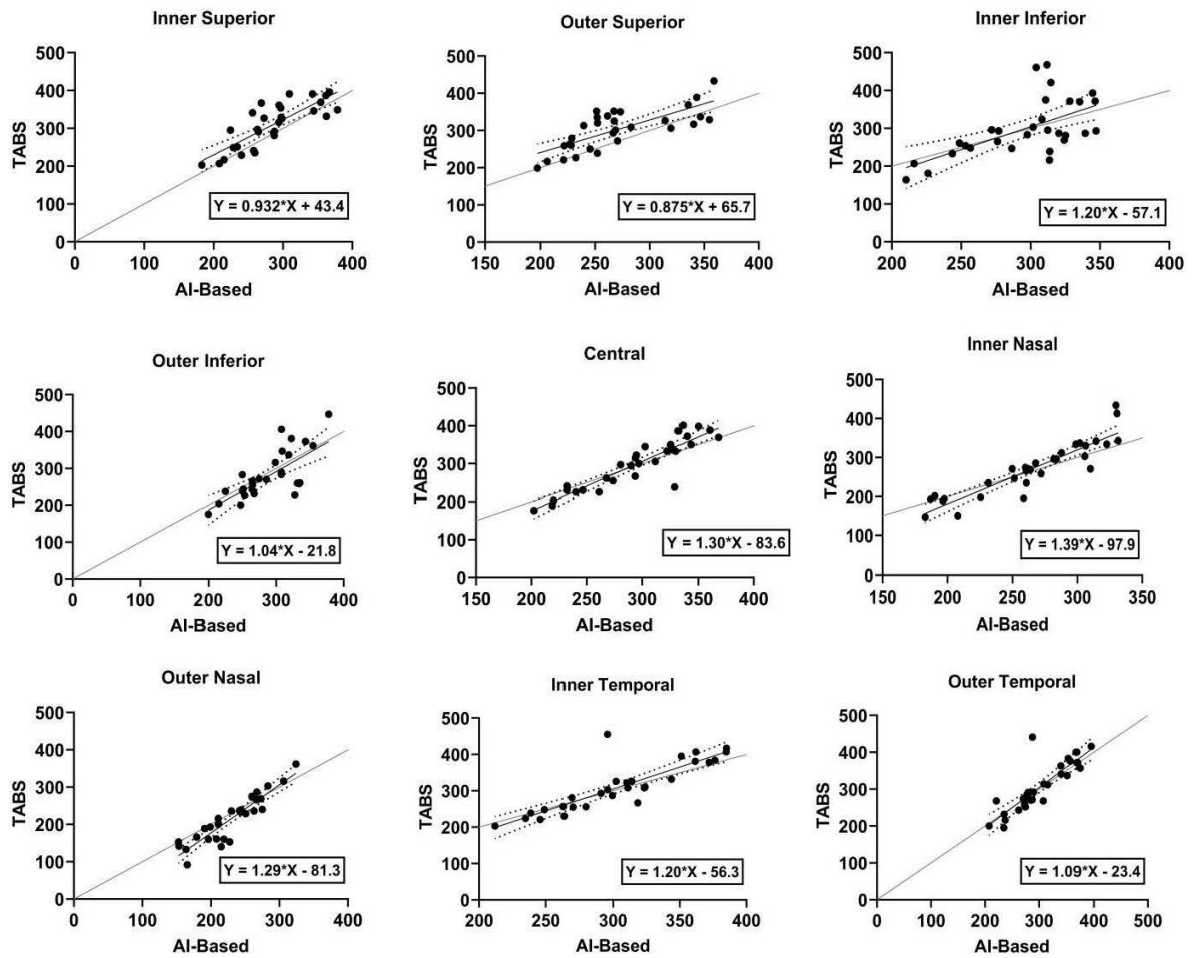


Figure 1: Relationship between Topcon Advanced Boundary Segmentation (TABS) and the AI-based automated software. The grey solid line represents the 1:1 (line of equality), and the dotted (...) line represents the 95% confidence interval.

Appendix C

Table 1: Mean $\pm$ SD (μm) retinal thickness for CMS and +3.00 D control spectacles at baseline, and after 30 and 60 minutes of spectacle wear for the right eye.

OD	Inner Superior	Outer Superior	Inner Inferior	Outer Inferior	Central	Inner Nasal	Outer Nasal	Inner Temporal	Outer Temporal
CMS Baseline	313.36 $\pm$ 12.16	275.11 $\pm$ 17.93	311.01 $\pm$ 12.03	270.59 $\pm$ 25.24	236.85 $\pm$ 12.05	311.83 $\pm$ 11.72	290.46 $\pm$ 14.22	301.94 $\pm$ 13.34	267.24 $\pm$ 25.52
CMS 30 Minutes	313.36 $\pm$ 12.16	278.11 $\pm$ 11.92	311.93 $\pm$ 12.58	269.43 $\pm$ 11.31	238.31 $\pm$ 12.80	312.09 $\pm$ 12.05	292.52 $\pm$ 13.76	302.20 $\pm$ 12.65	261.24 $\pm$ 13.14
CMS 60 Minutes	312.51 $\pm$ 12.02	277.04 $\pm$ 10.72	308.11 $\pm$ 18.73	269.30 $\pm$ 11.31	237.53 $\pm$ 10.65	311.75 $\pm$ 12.33	291.44 $\pm$ 13.82	299.27 $\pm$ 18.01	263.13 $\pm$ 11.12
Control Baseline	312.05 $\pm$ 11.55	276.24 $\pm$ 11.30	307.59 $\pm$ 16.51	267.37 $\pm$ 11.17	237.03 $\pm$ 11.03	311.22 $\pm$ 10.63	290.56 $\pm$ 12.87	301.94 $\pm$ 13.34	262.34 $\pm$ 10.98
Control 30 Minutes	313.28 $\pm$ 12.43	280.07 $\pm$ 19.92	310.34 $\pm$ 13.69	268.28 $\pm$ 11.41	239.25 $\pm$ 16.88	312.08 $\pm$ 11.32	292.83 $\pm$ 14.63	302.12 $\pm$ 12.34	265.05 $\pm$ 15.21
Control 60 Minutes	312.59 $\pm$ 11.31	276.98 $\pm$ 11.70	311.36 $\pm$ 11.10	268.69 $\pm$ 12.07	237.17 $\pm$ 10.92	309.05 $\pm$ 20.86	298.90 $\pm$ 40.88	302.57 $\pm$ 11.17	262.55 $\pm$ 11.45

Table 2: Mean $\pm$ SD (μm) choroidal thickness for CMS and +3.00 D control spectacles at baseline, and after 30 and 60 minutes of wear for the right eye

OD	Inner Superior	Outer Superior	Inner Inferior	Outer Inferior	Central	Inner Nasal	Outer Nasal	Inner Temporal	Outer Temporal
CMS Baseline	311.21 $\pm$ 61.35	305.57 $\pm$ 56.71	295.7 $\pm$ 74.33	286.00 $\pm$ 68.71	304.81 $\pm$ 75.11	272.86 $\pm$ 71.65	215.83 $\pm$ 64.02	317.90 $\pm$ 72.54	308.89 $\pm$ 68.89
CMS 30 Minutes	310.39 $\pm$ 59.45	306.10 $\pm$ 55.78	295.13 $\pm$ 75.08	290.80 $\pm$ 78.45	305.19 $\pm$ 73.73	273.60 $\pm$ 71.94	219.40 $\pm$ 70.80	316.86 $\pm$ 69.79	310.09 $\pm$ 70.09
CMS 60 Minutes	313.24 $\pm$ 59.27	306.64 $\pm$ 56.60	298.09 $\pm$ 76.87	286.64 $\pm$ 68.36	304.28 $\pm$ 74.68	272.79 $\pm$ 71.99	216.54 $\pm$ 66.91	321.62 $\pm$ 71.70	310.12 $\pm$ 69.95
Control Baseline	305.75 $\pm$ 60.15	301.40 $\pm$ 54.94	293.35 $\pm$ 75.31	284.21 $\pm$ 73.43	298.11 $\pm$ 72.47	267.91 $\pm$ 71.21	212.44 $\pm$ 64.70	312.20 $\pm$ 71.19	306.70 $\pm$ 71.41
Control 30 Minutes	305.33 $\pm$ 56.05	306.02 $\pm$ 62.45	292.89 $\pm$ 74.20	281.01 $\pm$ 68.00	297.50 $\pm$ 67.48	264.59 $\pm$ 66.86	212.72 $\pm$ 63.54	310.66 $\pm$ 66.16	303.04 $\pm$ 64.73
Control 60 Minutes	310.83 $\pm$ 59.37	306.82 $\pm$ 56.83	294.13 $\pm$ 74.06	286.02 $\pm$ 71.01	302.27 $\pm$ 71.81	270.86 $\pm$ 70.79	212.33 $\pm$ 68.25	314.83 $\pm$ 67.47	308.47 $\pm$ 68.61

Table 3: Mean $\pm$ SD (%) choroidal vascularity index for CMS and +3.00D control spectacles at baseline, and after 30 and 60 minutes of spectacle wear for the right eye.

OD	Inner Superior	Outer Superior	Inner Inferior	Outer Inferior	Central	Inner Nasal	Outer Nasal	Inner Temporal	Outer Temporal
CMS Baseline	58.72 $\pm$ 5.33	61.88 $\pm$ 6.19	59.20 $\pm$ 5.39	61.80 $\pm$ 6.66	57.79 $\pm$ 5.89	56.53 $\pm$ 6.77	56.74 $\pm$ 7.80	58.19 $\pm$ 6.39	58.11 $\pm$ 6.93
CMS_30 Minutes	58.33 $\pm$ 5.49	61.35 $\pm$ 5.44	58.67 $\pm$ 5.40	61.72 $\pm$ 6.37	57.75 $\pm$ 5.81	57.14 $\pm$ 7.03	56.35 $\pm$ 9.13	57.12 $\pm$ 6.07	58.23 $\pm$ 6.37
CMS_60 Minutes	58.62 $\pm$ 6.79	61.42 $\pm$ 6.03	58.40 $\pm$ 5.14	61.77 $\pm$ 6.22	57.55 $\pm$ 5.71	55.86 $\pm$ 7.25	56.59 $\pm$ 8.13	57.91 $\pm$ 6.07	58.36 $\pm$ 6.53
Control Baseline	58.25 $\pm$ 5.59	61.19 $\pm$ 6.21	58.41 $\pm$ 4.99	61.85 $\pm$ 5.57	57.40 $\pm$ 6.14	56.33 $\pm$ 7.78	55.54 $\pm$ 8.25	57.84 $\pm$ 6.11	58.99 $\pm$ 6.66
Control_30 Minutes	57.76 $\pm$ 6.30	61.77 $\pm$ 5.61	58.50 $\pm$ 5.73	61.67 $\pm$ 6.58	56.47 $\pm$ 5.89	55.99 $\pm$ 7.61	56.21 $\pm$ 7.99	57.42 $\pm$ 6.27	58.14 $\pm$ 6.61
Control_60 Minutes	58.40 $\pm$ 5.36	61.27 $\pm$ 5.72	59.61 $\pm$ 5.33	62.01 $\pm$ 6.27	58.14 $\pm$ 5.64	56.44 $\pm$ 7.08	56.32 $\pm$ 8.41	58.78 $\pm$ 6.35	58.23 $\pm$ 6.40