Effect of Multifocal Contact Lenses in Peripheral Refraction and in Accommodation of Young Subjects
Daniela Patrícia Lopes-Ferreira
UMinho | 2016

Universidade do Minho
Escola de Ciências

Daniela Patrícia Lopes-Ferreira

Effect of Multifocal Contact Lenses in Peripheral Refraction and in Accommodation of Young Subjects

October de 2016

Universidade do Minho
Escola de Ciências

Daniela Patrícia Lopes-Ferreira

Effect of Multifocal Contact Lenses in Peripheral Refraction and in Accommodation of Young Subjects

PhD Thesis in Optometry and Vision Sciences

PhD Thesis under Supervision of:
Prof. Doutor José Manuel González-Méijome
Professor Associado com agregação da Escola de Ciências
Universidade do Minho
and
Doutor Antonio Queirós Pereira
Professor Auxiliar da Escola de Ciências
Universidade do Minho

October de 2016

STATEMENT OF INTEGRITY

I hereby declare having conducted my thesis with integrity. I confirm that I have not used plagiarism or any form of falsification of results in the process of the thesis elaboration. I further declare that I have fully acknowledged the Code of Ethical Conduct of the University of Minho.

University of Minho, 28/10/2016

Full name: Daniela Patrícia Lopes-Ferreira

Signature: Daniela Patrícia Lopes-Ferreira

ACKNOWLEDGEMENTS

To God Who gave me the courage to never give up my dreams and academic goals, surrounding myself, always, with enthusiastic and friendly people.

Daniela Lopes-Ferreira

October, 2016

Recomeça...
Se puderes
Sem angústia
E sem pressa.
E os passos que deres,
Nesse caminho duro
Do futuro
Dá-os em liberdade.
Enquanto não alcances
Não descanses.
De nenhum fruto queiras só metade.

Miguel Torga

Abstract

Myopia is becoming a public health concern, with well documented evidence of rapid increasing prevalence in Asia, Europe and the United States of America. Further concerns arise from the fact that myopia onset takes place at an earlier age and progresses over a superior number of years, resulting in higher degrees of myopia in adulthood thus presenting an increased risk of visual loss related with severe eye disease.

Over the past 10 years, contact lenses have become an essential device in the strategies to control myopia progression and there is now evidence that different contact lens designs are effective in slowing-down myopia progression. Considering that such lenses have the potential to change the pattern of peripheral refraction and the depth of focus, the present thesis was developed with the aims of investigating the effect of different contact lens devices in the patter of axial and peripheral refractive error in young adults and their effect in the accommodative function.

The methods used included axial and peripheral refractive evaluation with an open field autorefractor; a system linked to autorefractometer to dynamic refractive data collection allowing to measure accommodative response and pupil size; a Hartmann-Shack (H-S) aberrometer was also used to determine axial optical aberrations and also a manufactured system linked to H-S to provide peripheral aberrations measurement.

We performed 7 trials involving 308 healthy non-myopic and myopic subjects. Results show myopic shift at peripheral refractive pattern of myopic eyes by wearing dominant design MFCL. Peripheral ocular aberrations in eyes fitted with MFCL also were modified; the trend was to increase, depending of design but mainly spherical aberration and coma. Accommodative function of unaided young eyes revealed LAG, mainly at higher accommodative demand. The accommodative facility and accuracy were not significantly modified by wear of MFCL independently of design. Comparison between methods of measuring peripheral refraction revealed that there were no differences between measurements using eye rotation or head rotation with and without MFCL; also were comparable measurements by using an open-field autorefractometer or an adapted H-S aberrometer.

The main conclusions were that peripheral refraction and peripheral aberrations could be modified differently by different design of MFCL. Accuracy and amount of accommodation not changed by wear of neither design of MFCL tested.

Resumo

A miopia é considerada um problema de saúde pública, mostrando evidências bem documentadas de prevalência na Asia, Europa e Estados Unidos da América. A razão de se levantar maior preocupação no aparecimento da miopia em idades precoces resulta do facto de havendo progressão durante um maior período de tempo a miopia ira ser mais alta na idade adulta, o que resulta em risco de perda severa da visão.

Nos últimos 10 anos, as lentes de contacto têm mostrado ser um dispositivo essencial na perspetiva de controlo da progressão da miopia, havendo atualmente várias evidências de eficácia, dependendo do tipo de lente. Considerando que as lentes de contacto representam potencial para alterar o padrão de refração periférica (RP) e profundidade de foco, esta tese foi desenvolvida com os objetivos de investigar o efeito de diferentes tipos de lentes de contacto no padrão refrativo axial e periférico assim como avaliar o seu efeito na função acomodativa.

Os métodos usados incluem a avaliação axial e periférica através de um autorefractómetro de campo aberto; um sistema acoplado ao autorefractómetro construído para permitir a medida dinâmica da refração permitindo a automática medida da função acomodativa e do diâmetro pupilar; um aberrómetro Hartmann-Shack (H-S) para determinar as aberrações axiais; assim como um dispositivo experimental acoplado ao H-S que permitiu a determinação das aberrações periféricas. Foram realizados 7 estudos envolvendo 308 indivíduos saudáveis míopes e não-míopes.

Os resultados mostram miopização periférica nos olhos adaptados com lente de contacto multifocal (LCMF) de desenho dominante. As aberrações oculares periféricas avaliadas em olhos adaptados com LCMF também revelaram alterações; a tendência foi no sentido do aumento, dependendo do desenho óptico, principalmente aberração esférica e coma. A função acomodativa em olhos jovens sem LC manifestou LAG, principalmente para as vergências mais reduzidas. A resposta acomodativa e a sua precisão não se alteraram com o uso LCMF, independentemente do desenho óptico. Realizaram-se também comparações entre métodos de avaliação da RP, verificando-se que as medidas realizadas através da rotação da cabeça ou dos olhos são comparáveis, com e sem LCMF; assim como as medidas realizadas através do autorefractómetro de campo aberto ou aberrómetro H-S adaptado.

As principais conclusões são que a RP e as aberrações periféricas podem ser alteradas com LCMF, dependendo do desenho. A função acomodativa não se mostrou variar com o uso de diferentes desenhos de LCMF.

Glossary of terms & Abbreviations

Add	Addition
AL	Axial length
CL	Contact Lenses
CSF	Contrast Sensitivity Function
D	Diopter
DoF	Depth of Focus
ER	Eye Rotation
FS	Sagittal Focal
FT	Tangential Focal
G-S	Gran-Seiko Autorefractor
HR	Head Rotation
H-S	Hartmann-Shack (wavefront sensor)
J_0	Astigmatic vector component with axis at 180°/90°
J_{45}	Astigmatic vector component with axis at 45°/135°
LAG	Accommodative LAG
Lead	Accommodative Lead
logMAR	The logarithm of minimum resolvable angle in arc minutes (visual acuity)
M	Spherical Equivalent
MFCL	Multifocal Contact Lenses
N	Nasal Hemifield of the Retina or the Visual Field
PALs	Progressive Addition Lenses
PR	Peripheral Refraction
PRP	Peripheral Refractive Pattern
RE	Refractive Error
RMS	Root Mean Square Error
Rx	Refraction
SA	Spherical Aberration
SD	Standard Deviation
T	Temporal Hemifield of the Retina or the Visual Field
T-test	T Student Test
VA	Visual Acuity

Table of Contents

Chapter 1

Chapter 2

Chapter 3

Chapter 4

Chapter 5

Chapter 6

Chapter 7

Chapter 8

Chapter 9

Chapter 10

List of Tables

Chapter 1

Chapter 2

Chapter 3

Chapter 6

Chapter 7

Chapter 8

List of Figures

Chapter 2

Chapter 3

Chapter 4

Chapter 5

Chapter 6

Chapter 7

Chapter 8

Chapter 9

Publications related with this Thesis

Papers

Included in this Thesis:

Lopes-Ferreira D, Queirós A, González-Méijome JM. **Relative Peripheral Refraction across 4 meridians after Orthokeratology and LASIK surgery.** Eye & Contact Lens 2016 (in peer-review);

Lopes-Ferreira D, Osório PR, Queirós A, González-Méijome JM**. Changes in Accommodative Response in Young Subjects Using Multifocal Contact Lenses.** Ophthalmic Physiol Opt 2016 (in peer-review);

Lopes-Ferreira D, Neves H, Isla L, Fernandes P, González-Méijome JM**. Combined Effect of Ocular and Multifocal Contact Lens Induced Aberrations on Visual Performance: Dominant vs Non-Dominant Design.** J Biomed Opt 2016 (in peer-review);

Lopes-Ferreira D, Jorge J, Peixoto-de-Matos SC, Faria-Ribeiro M, Queirós A, Lopez-Gil N, González-Méijome JM. **Peripheral Optical Quality with Two Different Multifocal Contact Lenses in Myopic Eyes.** Cont Lens Anterior Eye 2016 (in peer review);

Lopes-Ferreira D, Neves HI, Faria-Ribeiro M, Queirós A, Fernandes PR, González-Méijome JM**. Peripheral Refraction with Eye and Head Rotation with Contact Lenses**. Cont Lens Anterior Eye. 2014. doi: 10.1016/j.clae.2014.11.201;

Lopes-Ferreira D, Ribeiro C, Neves H, Faria-Ribeiro M, Villa-Collar C, Queirós A, Jorge J, González-Méijome JM. **Peripheral Myopization With Multifocal Contact Lenses Dominant Design In Myopic Patients.** J Optom 2013; 6(2): 85-94;

Queirós A, Lopes-Ferreira D, González-Méijome JM. **Astigmatic Peripheral Defocus with Different Contact Lenses: Review and Meta-Analysis.** Curr Eye Res. 2016 Feb 2:1-11;

González-Méijome JM, Jorge J, Faria-Ribeiro M, Lopes-Ferreira D, Peixoto-de-Matos SC, Legerton JA. **Strategies to Regulate Myopia Progression with Contact Lenses: A Review**. Eye Contact Lens. 2015.

Not included but related to this Thesis:

González-Méijome, J. M., Carracedo, G., Lopes-Ferreira, D., Faria-Ribeiro, M. A., Peixoto-de-Matos, S. C., Queirós, A. **Stabilization in early adult-onset myopia with corneal refractive therapy**. Contact Lens and Anterior Eye 2016, 39(1), 72-77.

Pauné J, Queirós A, Lopes-Ferreira D, Faria-Ribeiro M, Quevedo L, Gonzalez-Meijome JM**. Efficacy of a gas permeable contact lens to induce peripheral myopic defocus.** Optom Vis Sci. 2015 May;92(5):596-603.

González-Méijome JM, Faria-Ribeiro MA, Lopes-Ferreira DP, Fernandes P, Carracedo G, Queirós A. **Changes in Peripheral Refractive Profile after Orthokeratology for Different Degrees of Myopia**. Curr Eye Res. 2015 Mar 24:1-9;

Pauné J, Queirós A, Quevedo L, Neves H, Lopes-Ferreira D, González-Méijome JM. **Peripheral myopization and visual performance with experimental rigid gas permeable and soft contact lens design**. Cont Lens Anterior Eye 2014;37: 455–460;

Faria-Ribeiro M, Queirós A, Lopes-Ferreira D, Jorge J, González-Méijome JM. **Peripheral Refraction and Retinal Contour in Stable and Progressive Myopia.** Optom Vis Sci 2013; 90: 9-15;

Oral presentations

Lopes-Ferreira D, Fernandes P, Ferreira-Neves H, González-Méijome JM**. Efecto de las aberraciones oculares inducidas por lentes de contacto multifocales en el rendimiento visual.** OPTOM 2016 Madrid;

Lopes-Ferreira D, Queirós A, González-Méijome JM. **Changes in Accommodative Effort in Young Subjects Using Multifocal Contact Lenses.** APLO XI Open Conferences of Optometry, Lisbon (Portugal), November 2015;

Lopes-Ferreira D, Queirós A, González-Méijome JM. **Case Report: Stabilization in early adult-onset myopia with corneal refractive therapy.** APLO XI Open Conferences of Optometry, Lisbon (Portugal), November 2015;

Lopes-Ferreira D, Jorge J, Peixoto-de-Matos SC, Faria-Ribeiro M, Queirós A, Lopez-Gil N, González-Méijome JM. **Peripheral Refraction with Two Different Instruments with Multifocal Contact Lens.** 12th International Conference of Optometry and Visual Sciences – University of Minho, Braga, 2015;

Lopes-Ferreira D, Osorio R, González–Méijome JM. **Accommodative Fixation Response to Different Targets.** VISER Meeting 2014. Santiago Compostela. Octobre 2014;

Lopes-Ferreira D, Jorge J, Peixoto-de-Matos SC, Faria-Ribeiro M, Queirós A, Lopez-Gil N, González-Méijome JM. **Peripheral Optical Quality with Two Different Multifocal Contact Lenses in Myopic Eyes.** OPTOM Madrid, 2014.

Posters

Lopes-Ferreira D, Neves H, Faria-Ribeiro M, Queirós A, Fernandes P, González-Meijóme JM. **Peripheral Refraction with Eye and Head Rotation with Multifocal Contact Lenses.** 10th International Conference of Optometry and Visual Sciences – University of Minho, Braga, 2013;

Lopes-Ferreira D, Neves H, Faria-Ribeiro M, Queirós A, Fernandes P, González-Méijome JM. **Peripheral Refraction with Eye and Head Rotation with Multifocal Contact Lenses.** American Academy Meeting Seattle 2013;

Lopes-Ferreira D, Jorge J, Peixoto-de-Matos S, Faria-Ribeiro M, Queirós A, González-Méijome JM. **Peripheral Optical Quality with Two Different Multifocal Contact Lenses in Myopic Eyes**. American Academy Meeting Seattle 2013.

Award

Irvin M. Borish Student Travel Fellowship. **Peripheral optical quality with different multifocal contact lenses in myopes.** 92nd Annual Meeting of American Academy of Optometry Seattle 2013.

CHAPTER 1

Introduction

1.1. Introduction

Myopia is associated with ocular complications that can lead to permanent vision loss. Excessive axial elongation in high myopia increases the risk for cataract, glaucoma, chorioretinal degeneration, and idiopathic retinal detachment[1] and is a leading cause of permanent visual impairment.[2]

Then, several studies have been performed to determine the factors that could have some role in myopia progression and determine therapies that could have some potential in its retention.

1.2. Recent Evidences about Myopia Progression

Retinal shape is one of several factors that may be related with myopia progression, with many studies showing that the myopic eyes have a prolate retinal shape in comparison with emmetropic and hyperopic eyes that have an oblate retinal shape.[3-5] Myopic eyes manifests greater overall enlargement of the vitreous chamber.[3-5] Atchison and colleagues[6] observed that the peripheral refraction was relatively more hyperopic in myopic eyes than in emmetropic eyes along the horizontal visual field.

Conventional correction of myopia with spectacle lenses may result in an increase of peripheral relative hyperopic defocus[7-9] which will be worse in higher degree of myopia and with increase of eccentricity.[9] Modified peripheral optics at corrective devices can contribute to change the relative hyperopic defocus in myopic eyes into peripheral relative myopia. This is considered as one strategy to counterbalance the unknown stimulus that triggers the eye elongation and the subsequent myopia progression.

1.3. Foveal vs Peripheral Vision and Myopia Progression

1.3.1. Animal Studies: Different Stimulation with Different Species

Smith and colleagues dedicated many studies to understand the behaviour of central and peripheral refraction and its role in emmetropization and refractive errors development essentially in primates.[10, 11] Evidences from birds and mammals indicate that the effects of vision on ocular growth and refractive development are mediated, in large part, by local retinal mechanisms (i.e., mechanisms that integrate visual signals in a spatially restricted manner and exert their influence selectively on the underlying sclera).[12, 13] Recent studies have showed that peripheral refraction or defocus is capable to regulate the eye growth, and as consequence the development of refractive error (RE).[10, 14, 15] In chicks, diffusers[16, 17] or negative lenses[18] that cover only part of the visual field produce axial elongation and myopia that are restricted to the affected portion of the retina. It has subsequently been shown that hemiretinal form deprivation also alters ocular growth and refractive development in a regionally selective manner in tree shrews,[19] guinea pigs (McFadden SA. IOVS 2002;43: E-Abstract 189), and monkeys.[20] This suggests that the retina does not just compensate for the average amount of blur, but it can differentiate the sign of competing defocus and guide the growth of the eye towards the plane of myopic defocus,[21, 22] suggesting that there existed a homeostatic mechanism regulating of the RE.

1.3.2. Human Studies: Potential Mechanisms for Optical and Pharmacologic Control of Eye Growth

This homeostatic mechanism posed the difficult problem that it required that the eye or brain be able to distinguish hyperopic defocus (image behind the photoreceptors) from myopic defocus (image in front of the photoreceptors). Human are only able to focus a microscope or binoculars by trial and error, recalling whether the image is more in focus than it was a fraction of a second earlier; it seems impossible that the eye could use this method, especially as it seems implausible that the eye or brain could recall how sharp an image was days or months before — the time required for eye-growth to cause a detectible change in refractive status.[23]

1.4. Effect of Accommodation

During early 20th century, it was also accepted that excessive near work was the main environmental factor involved in the aetiology of myopia and as close work demanded extended periods of accommodation; then it was believed that excessive accommodation effort was the major factor not only to the development of myopia but also its progression.[24]

There are many reasons why excessive accommodation is unlikely to play a direct role in the aetiology of childhood myopia although, as has previously been suggested, the stimulus to accommodation from a blurred retinal image may be the same stimulus that leads to axial ocular growth and myopia. Recent study has demonstrated that illumination type[25] and also near work[26] induces transient induced myopia that can become a true myopia with repeated exposures to this situation. Normally, most of the methods that have been used clinically and or tested in research studies to prevent or reduce the magnitude of myopia are based on principle that accommodation is at least a part of the cause. The methods that have been explored include: (1) visual training and biofeedback (2) use of lenses (under-correcting the myopia or prescribing bifocals or progressive lenses) and (3) the use of pharmaceuticals.[24]

1.4.1. Under-Correction

For years, a handful of practitioners have advocated under-correcting avoid myopia progression inversely what happens if full-correction by spectacles. However two recent studies founded that under-correcting myopia actually increases myopic progression.[27, 28] Also could be seen a significant correlation between the myopic undercorrection magnitude and myopic progression.[29]

1.4.2. Bifocal Spectacles and Progressive Addition Lenses (PALs)

Among a variety of interventions, progressive addition lenses (PALs) are one option that has been evaluated across several populations.[30-32] The rationale for this intervention was based on the capacity of the PALs to decrease accommodative lag. Lag was presumed to be similar to hyperopic retinal defocus,[31, 33] that is known to induce experimental myopia in animals.[34]

Recent studies manifested small effect with PALs in children, higher results of effectiveness for children with baseline esophoria and accommodative lag,[33] and for children confirmed as progressing myopes pre-treatment.[35]

1.4.3. Pharmaceuticals: Cycloplegia

Atropine was largely used in several studies searching effect in myopia prevention.[36, 37] Atropine can reduce myopia progression, but not only due to paralysis of accommodation[38] but rather due a direct biochemical effect of atropine on axial eye growth.[39] A successful retention effect could be seen even with 0.01% and reduced visual side effects after 5 years, in children.[37] By the other hand is known that stop the treatment predicts a rebound effect that is more modulated and sustained in case of 0.01% concentration.[40]

1.4.4. Visual Training and Spherical Aberration Change

Previously were suggested that optical aberrations may be a cause of some of these accommodative anomalies.[41] Although some have found myopic eyes to have elevated higher order aberrations when compared to emmetropic eyes, others have found no correlation between refractive error group and spherical aberration or between refractive error magnitude and total root mean square higher order error and spherical aberrations.

Theagarayan et al[42] demonstrated that if change spherical aberration is possible to influence the slope of the accommodation response curve. Namely, addition of negative SA to the eye shows to improve the slope of the accommodation stimulus-response curve and decreases lag of accommodation, and positive addition of SA shows to depress the slope of the stimulus-response curve and increases lag.

The Cambridge Anti-Myopia Study was the more recent study testing effectiveness of improve two accommodation functions in myopia retention. As authors describe "treatment consisted of aberration control contact lenses to reduce lag of accommodation and vision training to increase accommodative facility".[43] While accommodative function can be improved through vision training[44] and manipulation of ocular aberrations,[42, 45] their effects on refractive error progression have not yet been established.

Allen and colleagues[46] tested aforementioned approaches allocating the participants in different treatment groups:(1) altered spherical aberration and vision training; (2) vision training only; (3) altered spherical aberration only; (4) no change to spherical aberration and no vision training. After 2 years, the study was unable to demonstrate that the progression of myopia can be reduced by either of the two treatments aimed at improving accommodative function with myopia progression of -0.33D on average over.

Additionally, Prince and collegues[43] found no significant difference in lag of accommodation at baseline between younger and older subjects (p = 0.09). AC/A ratio and lag of accommodation are significantly correlated to myopia progression confirming earlier observations by Mutti et al[47] and Gwiazda et al.[33]

1.4.5. Spherical Contact Lenses

Adolescent and Child Health Initiative to Encourage Vision Empowerment study (ACHIEVE), investigated if wearing spherical soft contact lenses affected myopic progression in children. Researchers found an average rate of myopic change of 0.06D per year more for contact lens wearers than spectacle wearers in children between the ages of eight and 11 with -1.00D to -6.00D myopia and less than 1.00D of astigmatism. After three years, the adjusted difference between contact lens wearers and spectacle wearers was not statistically significant, and there was no difference between the two groups regarding change in axial length or steepest corneal curvature.[48] Normally correction by spherical contact lenses is used at control groups when testing the effect of customized or multifocal contact lenses.

1.5. Multifocal Contact Lenses

Peripheral refraction of the eye might also be a factor influencing myopia progression.[49] It is possible that the contact lenses used to alter spherical aberration might have influenced the peripheral refractive error of the eye and therefore have had some undesirable effects on this factor. It is also possible that peripheral refractive errors may play a more significant role in refractive error development than central optical quality.[49] A recent study has shown significant changes in myopia progression when peripheral refractive errors are altered.[50]

Future studies controlling central and peripheral optical errors independently might be useful to understand these effects. It is also possible that peripheral refractive errors may play a more significant role in refractive error development than central optical quality.[49] Recent studies have shown significant changes in myopia progression when peripheral refractive errors are altered,[50, 51] as already seen in orthokeratology.

Previous research[27] pointed that it is significant that a full distance correction for myopia, taken in conjunction a progressive reading addition, to reduces the progression of myopia.[32] Evidences of these works indicate that the presence of blurred vision at any distance may stimulate the progression of myopia regardless of the sign of defocus. The table 1.1 describes some examples of publications of effect of multifocal contact lenses (MFCL) at peripheral refraction of young subjects.

Table 1.1. Review of recent studies that stated effect of MFCL to modify peripheral relative RE.

Author (year)	Multifocal CL used	Ages of subjects (N eyes)	Technical method	Axial RE	Peripheral Relative RE (N and T)
Lopes-Ferreira (2011) [52]	Proclear MF D (+1; +2;+3;+4D)	21,6 ± 2,3 (20)	Grand-Seiko WAM-5500 open-field autorefractor. Rotating the eye.	Emmetropes (-0,06±0,54 D)	Add+1 (-0.49 ± 0.58 and -1.78 ± 1.4) Add+2 (-0.54 ± 0.61 and -2.15 ± 1.10) Add+3 (-0.78 ± 1.66 and -3.15 ± 1.85 Add+4 (-0.39 ± 2.44 and -3.43 ± 2.29)
Sankaridurg (2011) [50]	Center-distance (CIBA Vision, Duluth, GA) +2.00D power in treatment zone	11.6±1.5 (treatment) 10.8 ±1.9 (spectacle group)	Modified open-field autorefractor (NVision-K5001; Shin-Nippon,Tokyo, Japan). Rotating the eye.	2.24±0.79D (treatment) 1.99±0.62D(spectacle group)	Less hyperopic/more myopic relative peripheral refractions (p<0.001) at 20°, 30°, and 40° eccentricities in the nasal field and at the 30° and 40° eccentricities in the temporal field, comparing with spectacles
Rosen (2012)[53]	Purevision spherical Proclear MF D (+1; +2D) Proclear MF N (+1; +2D)	25-39 (4)	Scanning Hartmann–Shack wavefront sensor eye stationed	-0.7D (+0.50 to -2.75 D)	Spherical (0.9±0.3D; 0.3±0.4D) Proclear N (0.4±0.6; 0.4±0.5D) Proclear D (1.3±0.6; 0.2±0.5)
Berntsen (2013)[54]	Biofinity MF D (+2.50)	22-27 (25)	Grand-Seiko WAM-5500 open-field autorefractor Rotating the head	-3.62±1.56 D	Biofinity D; 30 and 40 degrees (-0.77 and -0.82 D) and (-1.11 and -1.04 D)
Radhakrishnan (2013)[55]	Custom designed CL which control spherical aberration and accommodative effort	16.75±2.05 (113)	Shin-Nippon SRW-500 Autorefractor. Rotating the eye.	-3.37±1.84 D	No evaluated

Several studies suggested multifocal contact lenses as efficient devices to change peripheral refraction (peripheral myopization or peripheral myopic defocus) and to allow myopia retention. [50, 52-54, 56]

1.6. Orthokeratology

Corneal reshaping treatment (CRT) is hypothesized to inhibit myopia progression by inducing peripheral retinal myopic defocus.[57, 58] The treatment consists in controlled corneal changes by wear of a gas permeable lens of inverse geometry that eliminate myopic refractive error in the central area, there is probably an increase in myopia in intermediate peripheral areas caused by the annular ridge of epithelial and stromal thickening.[58] The most dramatic higher aberration changes were considerable increases in positive spherical aberration in the central visual field and reversals of the signs of coma slope across the visual field.[59] Spherical aberration allows the central image to focus on the fovea, while the peripheral image field is focused in a significantly shorter focal distance.

1.7. Modulation of Accommodation Response with Multifocal Optics Systems

Few studies have addressed the relationship between aberrations, accommodation, and refractive error, and their findings have been inconsistent. He et al. (IOVS 2003;44:ARVO E-Abstract 2122) found that in a group of young adults, ocular aberrations decreased with accommodation in emmetropic eyes, but in myopic eyes, aberrations increased or did not change. This suggests that, at near, those with myopia have greater amounts of higher order aberrations than emmetropic persons.

Three studies in humans suggested that increases in accommodative lag occur before the onset of myopia.[33, 60, 61] However, a recent more controlled study evaluating accommodative lag before onset, during the year of onset, and after the onset of myopia and comparing with accommodative lag in emmetropic children (over an extended period in a large sample of ethnically diverse children) founded no association between accommodative lag and the myopia onset, suggesting that the increased hyperopic defocus from accommodative lag may be a consequence rather than a cause of myopia.[62] In addition, there was no evidence of excess tension on the crystalline lens in myopes; post saccadic crystalline lens oscillations were unrelated to refractive error.[63]

Day et al[64] founded that mid- and high-frequency microfluctuations during accommodation were increased in late-onset myopes compared with emmetropes, possibly from accommodative plant noise, but poorer neurologic control and increased blur threshold were other possible sources. Therefore no clear line of evidence points to the crystalline lens itself as a source of internal tension. Alterations in ciliary muscle might also explain the increase in the response AC/A ratio before the onset of myopia.[47] Then, the process of becoming myopic appears to be more than just one of excess axial elongation. The myopic eye is certainly elongated relative to the emmetropic eye, but the elongation is accompanied compensatory optical changes in the crystalline lens likely in place from infancy up to the time of myopia onset.[65] Multifocal contact lenses have been constructed in first place to gives an accommodative replication by power changes in surface of lens; different optical devices could induce changes in accommodative effort and in peripheral refractive pattern. It has been assumed that multifocal lenses reduce the lag of accommodation based on work with single vision lenses;[66] however, there is evidence that a near addition can produce a lead of accommodation in both spectacles[67] and bifocal soft contact lenses,[68] resulting in myopic retinal defocus. The static accommodative response to targets at real distances was increased by the altered SA contact lenses and also the rates of accommodative facility improved with vision training.[45]

1.8. Hypothesis, Aims of the Thesis

The hypotheses to this work are that the multifocal contact lenses induce changes in accommodative effort as induces changes in peripheral refractive pattern, in young subjects. Different geometries of multifocal contact lenses eventually produce different changes in peripheral refraction and in accommodative effort.

Considering all previous authors contributions about multifocal contact lenses and its effectiveness on prevention of myopia and considering the several designs available in market that could replicates others that were used in experimental trials, (1) to determine objectively what are the changes at level of accommodative effort (accommodative lag and microflutuations) and in peripheral refraction produced by multifocal contact lenses.

Knowing technical limitations founded previously to obtain peripheral refractive pattern (PRP) of multiconcentric contact lenses, other aim of these work is (2) to study a method to measure more precisely and reliably the PRP in this type of MFCL. (3) To characterize the effect of MFCL on accommodative lag according the central refractive error, and understand the better addition for each value of central myopia or each peripheral refractive pattern.

Chapter 2.

Strategies to Control Myopia Progression with Contact Lenses: A Review.

The purpose of Chapter 2 is to review our understanding of the rationale(s) and success of contact lenses (CL) used to reduce myopia progression.

Chapter 3.

Peripheral refraction with dominant design multifocal contact lenses in young myopes.

Chapter 3 had as purpose to show the potential of a commercial center-distance multifocal soft contact lens to induce relative peripheral myopic defocus in myopic eyes

Chapter 4.

Peripheral Refraction with Eye and Head Rotation with Contact Lenses.

To evaluate the effect of ocular and head rotation on the peripheral refraction measurements obtained with an open-field autorefractor in myopic eyes using two different center-distance designs of MFCLs comprising an aspheric multifocal design and a concentric multifocal design.

Chapter 5.

Relative Peripheral Refraction across 4 meridians after Orthokeratology and LASIK surgery.

To characterize the axial and off-axis refraction across the horizontal, vertical and 2 oblique meridians of the retina in myopic eyes before and after Orthokeratology (OK) and LASIK surgery.

Chapter 6.

Astigmatic Peripheral Defocus with Different Contact Lenses: Review and Metaanalysis.

Chapter 6 has two specific aims:

1. To review the amount of relative peripheral defocus measured with different devices with potential use in myopia retention.
2. To present comparative data of the change in astigmatic peripheral refraction with different contact lenses evaluated in different studies conducted in the same laboratory and with the following same methodology in myopic human eyes.

Chapter 7.

Combined Effect of Ocular and Multifocal Contact Lens Induced Aberrations on Visual Performance: Dominant vs Non-Dominant Design.

Chapter 7 has as aim evaluate the combined effects of inherent ocular aberrations and induced aberrations by the multifocal contact lens (MFCL) of dominant and non-dominant design on visual performance at distance and near under high and low contrast.

Chapter 8.

Peripheral Optical Quality with Two Different Multifocal Contact Lenses in Myopic Eyes

To evaluate the feasibility of measuring the peripheral refraction and peripheral high order ocular aberrations (HOA) with an adapted Hartmann-Shack aberrometer and to report the peripheral HOA induced by two commercially available silicone hydrogel multifocal contact lenses (MFCL) with dominant design and multi-concentric design in myopic eyes.

Chapter 9.

Changes in Accommodative Response in Young Subjects Using Multifocal Contact Lenses

Chapter 9 have a purpose of to evaluate influence of use of commercial available multifocal contact lenses (MFCL) of different optic designs in accommodative function and accuracy of young emmetropic subjects.

1.9. References

1. Xu L, Wang Y, Wang S, Wang Y, Jonas JB. High Myopia and Glaucoma Susceptibility: The Beijing Eye Study. *Ophthalmology.* 2007;114:216-220.
2. Lin LL, Shih YF, Tsai CB, et al. Epidemiologic study of ocular refraction among schoolchildren in Taiwan in 1995. *Optom Vis Sci.* 1999;76:275-281.
3. Mutti DO, Sholtz RI, Friedman NE, Zadnik K. Peripheral Refraction and Ocular Shape in Children. *Invest Ophthalmol Vis Sci.* 2000;41:1022-1030.
4. Atchison DA, Pritchard N, Schmid KL, Scott DH, Jones CE, Pope JM. Shape of the Retinal Surface in Emmetropia and Myopia. *Invest Ophthalmol Vis Sci.* 2005;46:2698-2707.
5. Atchison DA, Jones CE, Schmid KL, et al. Eye Shape in Emmetropia and Myopia. *Invest Ophthalmol Vis Sci.* 2004;45:3380-3386.
6. Atchison DA, Pritchard N, Schmid KL. Peripheral refraction along the horizontal and vertical visual fields in myopia. *Vision Res.* 2006;46:1450-1458.
7. Bakaraju RC, Ehrmann K, Ho A, Papas EB. Pantoscopic tilt in spectacle-corrected myopia and its effect on peripheral refraction. *Ophthalmic Physiol Opt.* 2008;28:538-549.
8. Tabernero J, Vazquez D, Seidemann A, Uttenweiler D, Schaeffel F. Effects of myopic spectacle correction and radial refractive gradient spectacles on peripheral refraction. *Vision Res.* 2009;49:2176-2186.
9. Lin Z, Martinez A, Chen X, et al. Peripheral Defocus with Single-Vision Spectacle Lenses in Myopic Children. *Optom Vis Sci.* 2010;87:4-9.
10. Smith IIIEL, Kee C-s, Ramamirtham R, Qiao-Grider Y, Hung L-F. Peripheral Vision Can Influence Eye Growth and Refractive Development in Infant Monkeys. *Invest Ophthalmol Vis Sci.* 2005;46:3965-3972.
11. Kee CS, Ramamirtham R, Qiao–Grider Y, Hung LF, Ward M, Iii ELS. The Role of Peripheral Vision in the Refractive–Error Development of Infant Monkeys (Macaca mulatta). *Invest Ophthalmol Vis Sci.* 2004;45:1157-1157.
12. Wallman J, Winawer J. Homeostasis of Eye Growth and the Question of Myopia. *Neuron.* 2004;43:447-468.

13. Norton TT, Siegwart JT, Jr. Animal models of emmetropization: matching axial length to the focal plane. *J Am Optom Assoc.* 1995;66:405-414.

14. Smith IIIEL, Ramamirtham R, Qiao-Grider Y, et al. Effects of foveal ablation on emmetropization and form-deprivation myopia. *Invest Ophthalmol Vis Sci.* 2007;48:3914-3922.

15. Smith IIIEL, Hung L-F, Huang J. Relative peripheral hyperopic defocus alters central refractive development in infant monkeys. *Vision Res.* 2009;49:2386-2392.

16. Hodos W, Kuenzel WJ. Retinal-image degradation produces ocular enlargement in chicks. *Invest Ophthalmol Vis Sci.* 1984;25:652-659.

17. Wallman J, Gottlieb M, Rajaram V, Fugate-Wentzek L. Local retinal regions control local eye growth and myopia. *Science.* 1987;237:73-77.

18. Diether S, Schaeffel F. Local Changes in Eye Growth induced by Imposed Local Refractive Error despite Active Accommodation. *Vision Res.* 1997;37:659-668.

19. Metlapally S, McBrien NA. The effect of positive lens defocus on ocular growth and emmetropization in the tree shrew. *J Vis.* 2008;8:1-1.

20. Smith IIIEL, Huang J, Hung L-F, Blasdel TL, Humbird TL, Bockhorst KH. Hemiretinal Form Deprivation: Evidence for Local Control of Eye Growth and Refractive Development in Infant Monkeys. *Invest Ophthalmol Vis Sci.* 2009;50:5057-5069.

21. Liu Y, Wildsoet C. The Effect of Two-Zone Concentric Bifocal Spectacle Lenses on Refractive Error Development and Eye Growth in Young Chicks. *Invest Ophthalmol Vis Sci.* 2011;52:1078-1086.

22. Diether S, Wildsoet CF. Stimulus Requirements for the Decoding of Myopic and Hyperopic Defocus under Single and Competing Defocus Conditions in the Chicken. *Invest Ophthalmol Vis Sci.* 2005;46:2242-2252.

23. L.Nickla. JWaD. The Relevance of Studies in Chicks for Understanding Myopia in Humans. In: Roger W.Beuerman S-MS, Donald T.H.Tan, Tien-Yin Wong., ed. *Myopia: Animal Models to Clinical Trials.*: World Scientific; 2010.: 239-266.

24. Sivak J. The cause(s) of myopia and the efforts that have been made to prevent it. *Clin Exp Optom.* 2012;95:572-582.

25. Zhang CW, Xu JH, Wang YL, Xu W, Li K. Survey and analysis of visual acuity of Kazakhs in different lighting environments. Genet Mol Res. 2014;13:2451-2457.

26. Ciuffreda KJ, Vasudevan B. Effect of nearwork-induced transient myopia on distance retinal defocus patterns. *Optometry.* 2010;81:153-156.

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

28. Adler D, Millodot M. The possible effect of undercorrection on myopic progression in children. *Clin Exp Optom.* 2006;89:315-321.

29. Vasudevan B, Esposito C, Peterson C, Coronado C, Ciuffreda KJ. Under-correction of human myopia – Is it myopigenic?: A retrospective analysis of clinical refraction data. *J Optom.* 2014;7:147-152.

30. Edwards MH, Li RW-h, Lam CS-y, Lew JK-f, Yu BS-y. The Hong Kong Progressive Lens Myopia Control Study: Study Design and Main Findings. *Invest Ophthalmol Vis Sci.* 2002;43:2852-2858.

31. Gwiazda J, Hyman L, Hussein M, et al. A Randomized Clinical Trial of Progressive Addition Lenses versus Single Vision Lenses on the Progression of Myopia in Children. *Invest Ophthalmol Vis Sci.* 2003;44:1492-1500.

32. Leung JT, Brown B. Progression of myopia in Hong Kong Chinese schoolchildren is slowed by wearing progressive lenses. *Optom Vis Sci.* 1999;76:346-354.

33. Gwiazda J, Thorn F, Held R. Accommodation, Accommodative Convergence, and Response AC/A Ratios Before and at the Onset of Myopia in Children. *Optom Vis Sci.* 2005;82:273-278.

34. Norton TT. Animal Models of Myopia: Learning How Vision Controls the Size of the Eye. *ILAR J.* 1999;40:59-77.

35. Cheng D, Schmid KL, Woo GC, Drobe B. Randomized trial of effect of bifocal and prismatic bifocal spectacles on myopic progression: Two-year results. *Arch Ophthalm.* 2010;128:12-19.

36. Chia A, Chua W-H, Cheung Y-B, et al. Atropine for the Treatment of Childhood Myopia: Safety and Efficacy of 0.5%, 0.1%, and 0.01% Doses (Atropine for the Treatment of Myopia 2). *Ophthalmology.* 2012;119:347-354.

37. Chia A, Lu Q-S, Tan D. Five-Year Clinical Trial on Atropine for the Treatment of Myopia 2. *Ophthalmology.* 2016;123:391-399.

38. McBrien NA, Stell WK, Carr B. How does atropine exert its anti-myopia effects? *Ophthalmic Physiol Opt.* 2013;33:373-378.

39. Smith IIIEL, Hung L-F, Huang J, Blasdel TL, Humbird TL, Bockhorst KH. Effects of Optical Defocus on Refractive Development in Monkeys: Evidence for Local, Regionally Selective Mechanisms. *Invest Ophthalmol Vis Sci.* 2010;51:3864-3873.

40. Chia A, Chua W-H, Wen L, Fong A, Goon YY, Tan D. Atropine for the Treatment of Childhood Myopia: Changes after Stopping Atropine 0.01%, 0.1% and 0.5%. *Am J Ophthalm.* 2014;157:451-457.e451.

41. Radhakrishnan H, Pardhan S, Calver RI, O'leary DJ. Unequal Reduction in Visual Acuity with Positive and Negative Defocusing Lenses in Myopes. *Optom Vis Sci.* 2004;81:14-17.

42. Theagarayan B, Radhakrishnan H, Allen PM, Calver RI, Rae SM, O'Leary DJ. The effect of altering spherical aberration on the static accommodative response. *Ophthalmic Physiol Opt.* 2009;29:65-71.

43. Price H, Allen PM, Radhakrishnan H, et al. The Cambridge Anti-Myopia Study: Variables Associated with Myopia Progression. *Optom Vis Sci.* 2013;90:1274-1283.

44. Ciuffreda KJ, Ordonez X. Vision therapy to reduce abnormal nearwork-induced transient myopia. *Optom Vis Sci.* 1998;75:311-315.

45. Allen PM, Radhakrishnan H, Rae S, et al. Aberration Control and Vision Training as an Effective Means of Improving Accommodation in Individuals with Myopia. *Invest Ophthalmol Vis Sci.* 2009;50:5120-5129.

46. Allen PM, Radhakrishnan H, Price H, et al. A randomised clinical trial to assess the effect of a dual treatment on myopia progression: The Cambridge Anti-Myopia Study. *Ophthalmic Physiol Opt.* 2013;33:267-276.

47. Mutti DO, Jones LA, Moeschberger ML, Zadnik K. AC/A Ratio, Age, and Refractive Error in Children. *Invest Ophthalmol Vis Sci.* 2000;41:2469-2478.

48. Walline JJ, Jones LA, Sinnott L, et al. A Randomized Trial of the Effect of Soft Contact Lenses on Myopia Progression in Children. *Invest Ophthalmol Vis Sci.* 2008;49:4702-4706.

49. Charman NW, Radhakrishnan H. Peripheral refraction and the development of refractive error: a review. *Ophthalmic Physiol Opt.* 2010;30:321-338.

50. Sankaridurg P, Holden B, Smith IIIE, et al. Decrease in Rate of Myopia Progression with a Contact Lens Designed to Reduce Relative Peripheral Hyperopia: One-Year Results. *Invest Ophthalmol Vis Sci.* 2011;52:9362-9367.

51. Walline JJ, Greiner KL, McVey ME, Jones-Jordan LA. Multifocal Contact Lens Myopia Control. *Optom Vis Sci.* 2013;90:1207-1214.

52. Lopes-Ferreira D, Ribeiro C, Maia R, et al. Peripheral myopization using a dominant design multifocal contact lens. *J Optom.* 2011;4:14-21.

53. Rosén R, Jaeken B, Lindskoog Petterson A, Artal P, Unsbo P, Lundström L. Evaluating the peripheral optical effect of multifocal contact lenses. *Ophthalmic Physiol Opt.* 2012;32:527-534.

54. Berntsen DA, Kramer CE. Peripheral Defocus with Spherical and Multifocal Soft Contact Lenses. *Optom Vis Sci.* 2013;90:1215-1224.

55. Radhakrishnan H, Allen PM, Calver RI, et al. Peripheral Refractive Changes Associated with Myopia ProgressionAssociated Changes with Myopia Progression. *Invest Ophthalmol Vis Sci.* 2013;54:1573-1581.

56. Lopes-Ferreira D, Ribeiro C, Neves H, et al. Peripheral refraction with dominant design multifocal contact lenses in young myopes. *J Optom.* 2013;6:85-94.

57. Queirós A, González-Méijome JM, Jorge J, Villa-Collar C, Gutiérrez AR. Peripheral Refraction in Myopic Patients After Orthokeratology. *Optom Vis Sci.* 2010;87:323-329.

58. Charman WN, Mountford J, Atchison DA, Markwell EL. Peripheral Refraction in Orthokeratology Patients. *Optom Vis Sci.* 2006;83:641-648.

59. Mathur A, Atchison DA. Effect of Orthokeratology on Peripheral Aberrations of the Eye. *Optom Vis Sci.* 2009;86:E476-E484.

60. Goss DA. Clinical Accommodation and Heterophoria Findings Preceding Juvenile Onset of Myopia. *Optom Vis Sci.* 1991;68:110-116.

61. Drobe B, De Saint-André R. The pre-myopic syndrome. *Ophthalmic Physiol Opt.* 1995;15:375-378.

62. Mutti DO, Mitchell GL, Hayes JR, et al. Accommodative Lag before and after the Onset of Myopia. *Invest Ophthalmol Vis Sci.* 2006;47:837-846.

63. Manns F, Parel J-M, Denham D, et al. Optomechanical Response of Human and Monkey Lenses in a Lens Stretcher. *Invest Ophthalmol Vis Sci.* 2007;48:3260-3268.

64. Day M, Strang NC, Seidel D, Gray LS, Mallen EAH. Refractive group differences in accommodation microfluctuations with changing accommodation stimulus. *Ophthalmic Physiol Opt.* 2006;26:88-96.

65. Mutti DO, Mitchell GL, Sinnott LT, et al. Corneal and Crystalline Lens Dimensions Before and After Myopia Onset. *Optom Vis Sci.* 2012;89:251-262.

66. Seidemann A, Schaeffel F. An evaluation of the lag of accommodation using photorefraction. *Vision Res.* 2003;43:419-430.

67. Rosenfield M, Carrel MF. Effect of near-vision addition lenses on the accuracy of the accommodative response. *Optometry.* 2001;72:19-24.

68. Tarrant J, Severson H, Wildsoet CF. Accommodation in emmetropic and myopic young adults wearing bifocal soft contact lenses. *Ophthalmic Physiol Opt.* 2008;28:62-72.

CHAPTER 2

Strategies to Control Myopia Progression with Contact Lenses: A Review

2.1. Abstract

Purpose: Higher myopic refractive errors are associated with serious ocular complications that can put at risk the visual function. As a consequence there is an interest to slow-down and if possible stop myopia progression before it reaches pathological levels. The purpose of this report was to review our understanding of the rationale(s) and success of contact lenses (CL) used to reduce myopia progression.

Method: A review has been done by searching in Pubmed database. The results from clinical trials evaluating the efficacy of contact lenses in myopia progression based on axial length measurements as a primary outcome, and published in peer-review journals have been reviewed.

Results: The mechanisms that presently support myopia control with CL are mainly based on the change of relative peripheral defocus and changing the foveal image quality signal to potentially interfere with the accommodative system. Ten clinical trials addressing myopia control with CL have been reviewed including orthokeratology, peripheral gradient lenses, bifocal (dual-focus) and multifocal lenses. The use of spectral filters to balance the stimulation of medium (M-cones) and long wavelength (L-cones) activity have also been considered as a potential application of CL's to control myopia progression.

Conclusions: CL's have shown to be well accepted, consistent and safe methods to address myopia retention in children. Orthokeratology is so far the method with the larger demonstrated efficacy in myopia retention across different ethnic groups. However, considering other factors such as patient convenience or the degree of initial myopia and other treatments could also be considered. Furthermore, the combination of different principles (i.e. central defocus, peripheral defocus and/or spectral filters) in a single device might present further testable hypotheses to evaluate how different mechanisms can reinforce or compete with each other to improve or reduce myopia progression control with CLs.

Key Words: Myopia progression— Contact lens— Peripheral defocus— Accommodation— Spectral filter —Refractive error regulation— Refractive therapy— Orthokeratology.

2.2. Introduction

There is increasing interest in actively interfering with the progression of myopia rather than simply compensating for the refractive deficit associated with the condition. Refractive therapeutic intervention addresses myopia not only as a refractive anomaly that can be optically compensated but also a condition that can be treated (or at least managed), as Rubin and Milder suggested in 1976.[1] However, those authors still advocated for conservative (compensatory) treatments based on the lack of evidence to support other treatments portending to address myopia progression.

An interesting report from Kelly et al.[2] in 1975 compared the myopia progression in several cohorts of patients using spectacles alone (control), spectacles plus atropine, contact lenses (CLs) alone, and CLs plus atropine. They concluded that CLs alone were the least effective method to regulate myopia progression. The first reports on the potential beneficial role of CLs as treatments to reduce myopia progression were published in the early 70s. However, little information is available from studies by German researchers Küster[3] and Volckmar.[4] Later reports in the 80s by Kerns,[5] Drobec,[6] Andreo,[7] and Goldschmidt[8] reported the potential of CL to reduce myopia progression. Although pharmacological and spectacle-based optical treatments were the object of extensive review works,[9-12] no updated information is available in the CL field, despite the numerous advances in the last half of that decade.[13]

In the 90s, Singaporean researchers Heng and Khoo published a review article with a suggestive title, "Can contact lenses control the progression of myopia?" in which they discussed the potential role of strategies such as regular wearing of rigid gas-permeable lenses and orthokeratology lenses to regulate myopia progression. The authors concluded that more research in the Asian eye was necessary, as most of the evidence reported early in the 70s had been with Caucasian eyes.[14] Since then, a great deal of new scientific knowledge and clinical evidence has been presented and will be discussed in this review. The question today may be rephrased as "Which contact lenses are more effective to regulate the progression of myopia?" Thus, the aim of this review is to present a summary of the evidence published in peer-reviewed journals related to CL strategies to regulate myopia progression. Other treatments not involving CL wear are out of the scope of this report.

The authors of this report choose the terms "refractive therapy" and "refractive error regulation" as the most accurate terms for the future therapeutic management of refractive errors. The animal studies to date support the ability to influence scleral growth in either direction; hence, the terminology will apply in the event there is interest or need beyond the present discussion of myopia to regulate hyperopia and astigmatism toward emmetropization. The refractive therapy efforts described here are only a part of the overall research in regulating myopia. The following discussion is limited to CL refractive therapy in contrast to pharmaceutical refractive therapy. Heretofore, the term myopia control has been used by some. The authors prefer the term regulate instead of control consistent with other medical therapeutic interventions.

2.2.1. Socioeconomic Burden and Risks of Myopia Progression

The increase in the prevalence of myopia and the complications associated with the condition have a large socioeconomic impact. Costs associated with myopia can be classified as direct costs, related to spending on eyeglasses, ophthalmic lenses, CLs, and health care office visits, or indirect costs, associated with surgical interventions and treatment of retinal detachment, glaucoma, or lack of productivity derived from visual impairment or blindness.[15, 16] A study conducted in Singapore with 301 subjects between the ages of 12 and 17 years revealed that the mean annual direct cost of myopia for each subject in Singapore dollars was $221.76313.7 (US $1486$209.1). Based on age-specific prevalence of myopia, the authors estimated that costs of $37.5 million would be required to correct myopia for only Singaporean teenagers.[17] In 2006, Vitale et al.[18] conducted a study for the National Health and Nutrition Examination Survey (NHANES) in the United States and estimated the annual direct cost of correcting myopia to be between $3.9 and $7.2 billion. Ocular diseases such as cataract, glaucoma, maculopathy, and retinal detachment are often associated with high myopia increasing the risk of blindness. These sequelae establish myopia as a major public health problem in some countries in East Asia and in certain ethnic groups such as the Chinese.[19-23] The definition of pathological myopia is not clear in the literature, and a single definition is complicated because patients with lower myopia also exhibit pathological ocular findings.[24] However, it is accepted that the higher the myopia, the greater is the risk of pathological changes. In the Blue Mountains Eye Study, the risk for myopic maculopathy increased from ·2.2 for myopia below 3.00 diopter (D) to ·41 for myopia between 25.00 and 27.00 D and to ·350 for myopia over 29.00 D.[25] The risk for retinal detachment shifts from ·5 to ·10 for myopia under 23.00 D to myopia over 23.00 D, according to a Japanese study.[26]

Table 2.1. Summary of Studies Evaluating the Annual Progression of Myopia Derived With Cycloplegic Refraction and/or Axial Length Elongation in Children Aged 6 to 12 Years from Different Ethnicities

Author (Year)	Sample (n, Eyes)	Ethnicity	Age	Method	D/year	Elongation (mm/year)
Pointer (2001)[27]	60 (41)	Caucasian	7-13	Static dry retinoscopy + Sx	-0.09 D/yr (stable from 11-13)	NR
Xiang et al. (2012)[28]	607	Chinese	7-15	Autorefraction cycloplegic	-0.7 D/yr	0.21 mm/yr
Fan et al. (2004)[29]	255	Chinese	2-6	Cycloplegic Autorefraction / Ultrason Biometry	-0.24 D/yr	0.344mm/y
Zhao et al. (2002)[30]	4662 myopes	Chinese	5-13	Cycloplegic autorefraction	-0.18D/y (-0.37)	NR
Anderson et al. (2011)[31]	114 myopes	8 Asians, 19 Blacks, 29 whites, 51 Hispanics, and 7 individuals of mixed ethnicity.	7-13	Noncycloplegic autorefraction	-0.23D/y	NR
Shih et al. (2010)[32]	Aggregate from different studies	Urban Chinese population	7-12	Different methods	Boys: 20.20; girls: 20.27	NR

NR, not reported

Table 2.1 exemplifies the average myopia progression per year in different studies for periods ranging from 4 to 8 years. Most of these studies evaluated the general population; of course, the rates of progression are expected to be faster in the becoming myopic or myopic population. This risk differential highlights the relevance of treatments directed to keeping myopia at lower levels. Therapeutic intervention is even more relevant considering the evidence that points to higher prevalence of myopia in the younger populations, even in western countries, as has been reported in the U.S. NHANES.[33, 34]

2.2.2. Contact Lenses and Pathways to Reduce Myopia Progression

It is very important for clinicians to be aware of the rationale that supports the application of optical treatments to regulate myopic progression. We will discuss the role of peripheral myopic defocus, the role of near add power to compensate for the higher accommodative demand, the role of accommodative lag, and very briefly will comment on the recently proposed role of modulation of the activity of different visual pathways by means of spectral filters.

2.2.2.1. Relative Peripheral Defocus

Results from several animal species including young chickens[35] and monkeys[36] have demonstrated that their eyes are capable of responding to myopic or hyperopic defocus by altering their posterior chamber shape. Asymmetrical ocular elongation results when defocus is only imposed in one half of the retina or when different sign defocus is imposed in both hemifields.[37] Troilo and Wallman were able to demonstrate that the supposed visually guided eye growth mechanism in chickens tends to recognize defocus and adjust axial growth according to its signal even with a sectioned optic nerve. The authors concluded that the mechanism behind the defocus sign recognition and eye growth modulation must be located within the eye and be somehow independent from central neural system, while brain activity must be maintained for emmetropia to succeed.[38] When infant rhesus monkeys were raised with central opening diffusers that deprived the animal's peripheral vision allowing only clear foveal vision, an accelerated axial elongation resulted.[39] The monkeys were then submitted to another experience where their central vision was deprived by foveal ablation and only clear peripheral vision was allowed. The authors concluded that foveal vision is not essential for the emmetropization to occur in primates and that peripheral retina visual experience may be responsible for the regulation of ocular growth. A recent study reported by Liu and Wildsoet concluded that myopic peripheral defocus with refractive-corrected central vision (concentric multifocal CLs) results in an inhibitory effect on axial eye growth in young chickens, but the contrary effect occurred when myopic defocus was restricted only to central vision with a focused peripheral area.[40] Whether by design or default, most of the currently available treatments for myopia regulation with CL can be viewed as owing their success to their propensity to change the relative peripheral defocus. Several patents have been issued for this purpose. Commercially available and investigational devices falling in this category will be discussed further in the Discussion section.

2.2.2.2. Accommodative Lag and Phoria at Near

Different studies have linked myopia onset and myopia progression with increased levels of near-vision work,[41] and a link to the activity of the accommodative system has been established.[42, 43] Eyes after the onset of myopia are observed to have greater accommodative lag (under-accommodation for a given target distance) compared with emmetropic eyes.[44] The same study suggests that higher accommodative lag seems to be a consequence instead of a cause of myopia. Considering the higher lag, myopic eyes are exposed to hyperopic defocus and respective poor image quality[45, 46] during near-work, and these optical effects may have a role in the myopia progression mechanism. Weizhong et al.[47] could not demonstrate a higher myopia progression in myopic eyes having higher accommodative lag. This contradiction leads to some controversy regarding the role of accommodative lag alone in myopia progression. The use of bifocals or progressive addition ophthalmic lenses for slowing the progression of myopia has been reported to result in small therapeutic regulation of myopia. Myopia showed 0.15 to 0.50 D slower progression in the treatment groups when compared with control groups over a period of 1.5 to 3 years.[48-50] Despite the positive effect of the intervention with bifocal and progressive addition lenses, the low annual regulation may not be clinically relevant for the general population of patients with myopia. Other studies showed a greater effectiveness with bifocal and progressive addition ophthalmic lenses in children with esophoria and high accommodative lag.[51] Moreover, some authors have reported that high myopia is related to higher esophoria.[52] The link between esophoria and accommodative lag might provide a working hypothesis based on the relationship between the accommodative and convergence systems.[53] A hypothesis in patients with esophoria suggests that the accommodative lag is higher to prevent the increase of the esophoria at near. Thus, providing a near add will warrant that the visual effects in the form of hyperopic defocus at near associated with a higher lag will be minimized. Concentric bifocal CLs might also provide myopia regulation by imposing some degree of peripheral myopic defocus. This has been postulated by Smith[54] and suggests a synergistic effect by interfering simultaneously with the foveal vision partially compensating the negative effects of accommodative lag and simultaneously inducing peripheral myopic defocus. However, our evaluations using an open-field autorefractometer failed to detect any significant effect on peripheral refraction or relative peripheral defocus by concentric annular multifocal CLs.[55] The autorefractometer measures covered an area of 2.3 mm in diameter. The measurement zone might be too large to detect the power differences between 6 concentric rings of alternating near and distance power. Aberrometric evaluation for smaller pupil sizes may bring more detailed information on the sign of the local peripheral defocus with concentric bifocal CLs. Even so, measurement of such lenses may not be accurate with Hartmann-Shack sensors because of the overlapping and duplication of the microarray spots formed by light passing through the distance and near power rings. Instead of solely compensating for accommodative lag using a positive add at near, another alternative is to improve the accommodative response in the myopic eye. Allen et al.[56] reported a reduction in accommodative lag of myopic eyes by fitting soft CLs to induce 20.1 mm of fourth-order spherical aberration at a pupil diameter of 5.0 mm. For the average eye with positive spherical aberration,[57] this intervention will push the best image focus backwards and the eye will need to accommodate more efficiently to bring it forward to the retinal plane. Contact lens devices falling in this kind of intervention include the use of refractive and diffractive bifocal CLs, near-center multifocal CLs, and single vision lenses with induced negative spherical aberration to improve accommodative function[56] without the purpose of multifocal vision. CLs with negative spherical aberration will induce relative peripheral hyperopic defocus.[58] This is in opposition to the desired myopic peripheral defocus previously described. Both mechanisms within the same device could interact in an antagonistic way. Commercially available and investigational devices falling in this category will be discussed further in the Discussion section.

2.3. Methods

A search was performed in PubMed (www.pubmed.com) using the following combination of keywords "myopia progression contact lens" by June 2014; this was the combination that produced the most sensitive and specific outcome. The primary outcome of interest in this search was to find the peer-reviewed publications addressing the potential effect of CLs on myopia progression, with particular interest in clinical trials conducted in the field. Selection criteria were original articles or case reports published in peer reviewed journals from 2004 to 2014 reporting clinical and biometric data of eye growth and myopia progression with CLs; no conference abstracts nor review articles were considered. A total of 107 citations were retrieved. Of them, 49 were related to generic topics and not directly related to the use of CL in myopia research, 19 were review articles, 9 were investigating the effect of CL on peripheral refraction, and 4 were related to animal studies. Of the remaining 26 articles reporting clinical trials, 9 were related to single vision contact lenses (SVCL), 8 to orthokeratology or corneal refractive therapy, 2 to non-orthokeratology gas-permeable CLs, 3 to bifocal soft CLs, 1 to multifocal dominant design CL, and 1 to peripheral gradient CLs. There was one case report related to the use of orthokeratology and one related to bifocal CLs. For the purpose of this review, the results of the last eight studies with orthokeratology/corneal refractive therapy, six studies describing the use of other CLs, one study reporting the results of a dominant design multifocal CL for presbyopia, and two studies on the effect of SVCL have been tabulated and subjective to more detailed analysis and discussion.

2.4. Results

The main characteristics of the CL designed with the primary purpose of regulating myopia progression and their reported effectiveness are discussed here. Other CLs that have been reported in isolated case reports or in systematic clinical trials with their respective effectiveness as myopia regulation treatments are included. Table 2.2 presents a summarized overview of the main outcomes of the clinical case reports and clinical trials. Considering the strong body of literature arising in the recent years for orthokeratology/corneal refractive therapy treatments, Table 2.3 addresses specifically the outcomes of these studies. A graphical overview of these interventions is shown in Figure 2.1 for an approximate simulated pupil size of 6 mm.

2.5. Discussion

2.5.1. Refractive Bifocal and Multifocal CLs

Goldschmidt,[8] in a review article published in 1990, described the results of a Danish study conducted in the 80s, which was reported to show evidence of the beneficial effect of bifocal CLs on myopia progression. To our knowledge, this is one of the first results reported in the peer-reviewed literature (although indirectly) on the potential effect of CL in preventing myopia progression.

2.5.2. Bifocal and Dual-focus Contact Lenses

Bifocal lenses used with the purpose of reduction of myopia progression included ACUVUE Bifocal lens (Johnson & Johnson, Jacksonville, FL) made of etafilcon A (ionic, 58% water content) with a total diameter of 14.0 mm and a base curve radius of 8.5 mm. The optical design of the lens comprises a central distance zone with a diameter of 2 mm surrounded by a 0.6 width near addition ring, a 0.6 mm width distance ring, a 0.35 near addition ring, and a fifth 1.45-mm wide distance ring (approximate design shown in Fig. 2.1C).

The use of bifocal CLs to prevent myopia progression with modern CLs was initiated by Aller and Wildsoet who reported on the case of two identical twin sisters in a cross-over clinical fitting during 2 years. They found that bifocal CLs were able to reduce the ocular growth in the twin sisters alternatively fitted with ACUVUE Bifocal.[59] Furthermore, the authors reported in 2006 on a 1-year clinical trial testing the efficacy of ACUVUE Bifocal CL in myopic endophoric patients. They reported a 71% reduction in refractive change as measured with cycloplegic autorefraction and a 79% reduction in axial length with the bifocal CL.[60]

Table 2.2. *Summary of Studies Evaluating the Myopia Regulation Effect With Single Vision, Multifocal, Dual-Focus, Gradient Power*

Author (Year)	**Ethinicity (Age)**	**Study Design (duration*)**	**Test (n eyes) (Rx Range)**	**Control (nº eyes) [Rx Range]**
Aller & Wildsoet (2008)	Caucasian	Case report	Acuvue Bifocal (n=2)	Acuvue 2 (n=2)
Aller & Wildsoet (2006)[60]	Various (8-18)	Randomized (12 months)	Acuvue Bifocal (n=38)	Acuvue 2 (n=40)
Sankaridurg (2011)[61]	Chinese (7-14)	Parallel, controlled, randomized (6 months) Parallel, controlled, randomized (12 months)	Peripheral gradient (45) (-2.24±0.79) Peripheral gradient (43) (-0.75, -3.50)	Spectacles (40) (-1.99±0.62)
Walline and McVey (2010)[62]	NR (10-11)	24 months	Multifocal CL (n=14) (–2.31 ± 1.05)	Spherical CL (14) (–2.22 ± 0.97)
Horner et al. (1999)[63]	NR (11-14)	3 years	SV SCL (n=62) (-3.01±0.22)	SV SCL (68) (-3.10±0.21)
Walline et al. (2008)[64]	47.1% white, 21.5% black, 21.5% Hispanic, 6.6% Asian or	3 years	SV SCL (237) (-2.38±0.98)	SV SCL (247) (-2.43±1.10)

	Pacific Islander (8-11)			
Marsh-Tootle et al. (2009)[65]	Ethnically diverse (5-6)	2years	Spectacles (106) (-4.32±1.40)	SV SCL (77) (-4.25±1.52)
Anstice and Phillips (2010)[66]	Various (11-14)	Cross-over controlled randomized (20 months)	Dual-focus (n=35) (-1.25, 4.00)	Dual-focus (n=35) [-1.25, 4.00]
Lam et al. (2011)[67]	Chinese (8-13)	Controlled randomized (24 months)	DISC (n=65) (-2.90±1.05)	SVCL (n= 32) [-1.00,-5.00]

Author (Year)	**Refraction Method**	**Biometric Method**	**Dioptric Progression in Test Group vs. Control (Regulation Effect, %)**	**Axial Growth in Test Group vs. Control (Regulation Effect, %)**
Aller & Wildsoet (2008)[59]	Noncycloplegic refraction	IOLMaster	0.00 vs. 21.25 (100%)	NR (at baseline)
Aller & Wildsoet (2006)[60]	Cycloplegic autorefraction	IOLMaster	-0.22 vs. -0.78 (71.8%)	0.05 vs. 0.24; 0.19 mm (79.2%)
Sankaridurg (2011)[61]	Cycloplegic open-field autorefraction		-0.28 vs. -0.57 (50.9%) -0.54 vs. -0.84 (37.5%)	0.09 vs. 0.26; 0.17 mm (65.4%) 0.24 vs. 0.39; 0.15 mm (38.5%)
Walline and McVey (2010)[62]	Cycloplegic open-field autorefraction	A-scan ultrasonography	-0.55 vs. -1.10 (50.0%)	0.32 vs. 0.47; 0.15 mm (31.9%)
Horner et al. (1999)[63]	Noncycloplegic subjective examination	NR	14.7%	NR
Walline et al. (2008)[64]	Cycloplegic autorefraction	A-scan ultrasonography	-1.30 vs. -1.12 (-16.1%)	0.62 vs. 0.59; 20.03 mm (25.1%)
Marsh-Tootle et al. (2009)[65]	Cycloplegic autorefraction	A-scan ultrasonography	47.1%	11.1%

Anstice and Phillips (2010)[66]	Cycloplegic autorefraction	IOLMaster	-0.17 vs. -0.38 (55.3%)	0.03 vs. 0.15; 0.15 mm (80.0%)
Lam et al. (2011)[67]	Cycloplegic autorefraction	IOLMaster	-0.59 vs. -0.80 (26%)	0.25 vs. 0.36 (31%)

SV SCL, single vision soft contact lenses; NR, not reported; DISC, defocus incorporated soft contact lenses.
*Report from interim results before study completion.

The only human randomized controlled clinical trial with this category of lenses was conducted by Anstice and Phillips[66] with refractive bifocal (dual-focus) CLs in the Dual-focus Inhibition of Myopia Evaluation in New Zealand study. Dual-focus CLs consist of a hydrophilic soft CL made of hioxifilcon A, nonionic 49% water content material (Benz Research and Development, Sarasota, FL), with a total diameter of 14.2 mm and a base curve of 8.5 mm. The optical design consists of a series of concentric areas starting with a 3.36-mm central distance area, surrounding by a 0.71-mm width treatment zone (near zone), a 0.99 distance zone ring, and a 0.78 with second treatment zone. A graphical representation of the lens design is shown in Figure 2.1G over a 6-mm diameter. In this study, either eye of 40 young children between 11 and 14 years of age was randomly fitted with a dual-focus lens or with a single vision lens and replaced bimonthly.

After a period of 10 months with the first prescription, the treatments were switched between right and left eyes. In this clinical trial, right eye lenses were blue-tinted to avoid confusion. At the end of the study, data from the 2 parts of the study (up to a total of 20 months) were combined to obtain the progression effect during dualfocus and single vision lens wearing. The spherical equivalent refraction increased by -0.44±0.33 D in the dual-focus group and -0.69±0.38 D in the single vision lens group ($P<0.001$). Axial length increased by 0.11±0.09 mm for the eyes during the dualfocus lens wearing and 0.22±0.10 mm during the single vision lens wearing ($P<0.001$).

Table 2.3. Summary of Studies Evaluating Myopia Regulation Effect With Corneal Refractive Therapy (Orthokeratology)

Author (Year)	**Cheung et al. (2004)**[68]	**Cho et al. (2005)**[69]	**Walline et al. (2009)**[70]	**Kakita et al. (2011)**[71]	**Santodomingo-Rubido et al. (2012)**[72]
Test Group (n eyes, M/F) (Average SER)	Ortho-k (n=1, male) (-2.50-0.50x170)	Ortho-k (n=34, 16/19) (-2.27±1.09)	CRT (n=28, 16/19)[a]	Ortho-k (n=28, 21/21) (-2.55±1.82)	Ortho-k (n=31, 15/16) (-2.35)
Ethnicity Age range Mean age (years)	Chinese 13 —	Chinese 7-12 9.6	Caucasian 8-11 10.5	Japanese 8-16 12.0	Caucasian 6-12 9.7
Range SER	-2.50	-0.25 to -4.00	-0.75 to -4.00	-0.50 to -10.00	-0.75 to -4.00
Max. cylinder, D	-0.50	-2.00	-1.00	-1.50	-1.00
Refraction baseline	Noncycloplegic refraction	Noncycloplegic refraction	Cycloplegic autorefraction	Non-cycloplegic autorefraction	Cycloplegic autorefraction
Duration of study, years	3	2	2	2	2
Randomization	Case Report	Nonrandomized	Historic Data	Nonrandomized	Nonrandomized
Control Group (n eyes, M/F) (Average Rx)	Emmetrope (n=1, male) (-0.25-0.75x168)	SVSL (n=34, 16/19) (-2.55±0.98)	SVSL	SVSL (n=50, 22/28) (-2.59±1.66)	SVSL (n=30, 15/15) (-2.53)
Refraction	Non-cycloplegic refraction	Cycloplegic refraction, retinoscopy	Cycloplegic autorefraction	Noncycloplegic autorefraction	Cycloplegic autorefraction
Biometry (outcome measures)	US A-Scan (VCD, AL)	US A-scan 5500, (VCD, AL	US A-scan (ACD, LT, VCD, AL)	PCI (AL)	PCI (AL)
Dioptric regulation (D) effect, %	+3.25 vs. -0.75, -118% vs. 150%	+2.09±1.34 vs. -1.20±0.61, -92% vs. 47%	[a]	+1.87±1.34 vs. -1.24±1.71, -73% vs. 48%	+1.86 vs. -1.27, -80% vs. 50%
Increase AL treated vs. control, mm	0.13 vs. 0.34	0.29±0.27 vs. 0.54±0.27	0.25±0.72 vs. 0.57±0.74	0.39±0.27 vs. 0.61±0.24	0.47 vs. 0.69

Mean growth retention effect per year (%)	-0.11 mm (62%)	-0.12 mm (46%)	-0.16 mm (56%)	-0.11mm (36%)	-0.11 mm (32%)
Contact Lenses Material Dk* Central thickness Overall diameter Optic Zone diameter	WAVE lens NR NR 0.22 mm 10.6 mm 6.0 mm	Boston XO / Paragon HDS $100x\ 10^{-11}$ NR NR NR	Paragon CRT Paragon HDS 100 NR NR NR	Emerald Boston XO $100x\ 10^{-11}$ NR NR NR	Menicon Z Night Tisilfocon A $163x10^{-11}$ NR NR NR

Author (Year)	**Hiraoka et al. (2012)**[73]	**Chen et al. (2012)**[74]	**Cho et al. (2012)**[75]	**Charm and Cho (2012)**[76]
Test Group (n eyes, M/F) (Average SER)	Ortho-k (n=22, 10/12) (-1.89±0.82)	Ortho-k (n=25, –/–) (-2.64±0.82)	Ortho-k (n=37, 19/18) (-2.16±0.77)	Ortho-k (n=12, -/-) (26.38)
Ethnicity Age range Mean age (years)	Japanese 8-12 10.0	Chinese 9-14 11.2	Chinese 7-10 9.0	Chinese 8–11 10.0
Range SER	-0.50 to -5.00	-1.00 to -4.50	-0.50 to -4.50	-5.00 to -8.30
Max. cylinder, D	-1.50	-1.50	-1.50	-1.50
Refraction baseline	Noncycloplegic refraction	Noncycloplegic refraction	Noncycloplegic refraction	Cycloplegic refraction
Duration of study, years	5	2	2	2
Randomization	Nonrandomized	Nonrandomized	Randomized	Randomized, single asked
Control Group (n eyes, M/F) (Average Rx)	SVSL (n=21, 8/13) (-1.83±1.06)	SVSL (n=22, NR/NR) (-2.40±0.86)	SVSL (n=41, 22/19) (-2.36±0.86)	SVSL (n=16, —/—) (-6.00)
Refraction	Noncycloplegic autorefraction	NR	Cycloplegic refraction	Cycloplegic autorefraction
Biometry (outcome measures)	PCI (AL)	PCI (AL)	PCI (AL)	AL
Dioptric regulation (D) effect, %	+1.19 vs. -3.20 -63% vs. 175%	NR	NR	-0.13 vs. -1.00, 0.87 D (87.0%)
Increase AL treated vs. control, mm	0.99±0.47 vs. 1.41±0.68	0.55 vs. 0.50[b]	0.36±0.24 vs. 0.63±0.26	0.19 vs. 0.51
Mean growth retention effect per year (%)	-0.13 mm, 37% (2 years) -0.08mm, 30% (5 years)	+0.05 mm, -10%[b]	-0,14mm (43%)	NR

Contact Lenses	Emerald	Hiline	Menicon Z Night	Procornea
Material	Boston XO	Boston XO	Tisilfocon A	Boston XO
Dk[c]	100x10^{-11}	100x10^{-11}	163x10^{-11}	100x10^{-11}
Central thickness	0.22 mm	NR	NR	0.22 mm
Overall diameter	10.6 mm	10.6 – 10.8 mm	NR	10.5 mm
Optic Zone diameter	NR	6.0 mm	NR	6.0 mm

Positive values of dioptric regulation effect and negative values of axial growth regulation effect mean a lower ocular elongation in the orthokeratology group.

[a] Refractive error and corneal curvature are temporarily altered by orthokeratology, so they are not compared in this investigation.

[b] Authors do not report the increment in AL for the whole sample in the orthokeratology group or SVL group, so an average of the data presented by the authors for their different subgroups is displayed in the table.

[c] Barrer (cm2/s) (mL · O_2/mL x mm Hg).

AL, axial length; Average Rx, average Rx at baseline; NR, not reported; PCI: partial coherence interferometry (IOLMaster, Carl Zeiss, Dublin, CA); SVCL, single vision contact lenses; SVSL, single vision spectacle lenses; US, ultrasound; VCD, vitreous chamber depth.

Another recent approach to regulate myopia progression with CL is represented by the defocus incorporated soft contact lens (DISC). This is a refractive concentric bifocal soft CL comprising 10 to 12 rings of alternating power over the optic zone. A graphical representation of the lens design is shown in Figure 2.1H. In the lens description presented by the authors in the animal studies conducted with pigmented guinea pigs, the authors describe the lenses as Fresnel lenses designed to minimize spherical aberration.[77] The 2-year clinical trial in humans was completed by 65 children wearing the DISC lenses bilaterally and 63 children wearing single vision CLs.[67] The clinical group using the DISC lenses showed a 31% lower axial elongation compared with the SVCL group over the 2-year period. Apparently, the retention effect was positively correlated with the number of hours of lens wear, varying from 25% for the subjects wearing the lenses for shorter periods during the day to 60% for those wearing the lenses 8 or more hours. However, the authors only provided this analysis in terms of spherical equivalent refraction rather than axial elongation, so blur adaptation in those wearing the lenses for longer periods might confound this analysis. Additionally, the authors do not report the average age of subjects in each group of wearing time, which might also be a confounding factor, as older children tend to progress at a slower rate than younger children.

Although this fact might not be relevant, some recent developments supporting the use of blue-tinted lenses to provide myopic regulation effect might bring a possible additional source of variability in myopia regulation effect, although this observation is merely speculative.[76]

2.5.3. Multifocal Center-Distance Contact Lenses

Center-distance multifocal CLs are used for presbyopia correction. Their optical design has been proposed as a viable way to induce myopic peripheral defocus,[78] which may be inhibitory for axial elongation similar to the refractive effect created with corneal refractive therapy. Center-distance multifocal CLs used in myopia progression studies were Proclear (CooperVision, Pleasanton, CA) dominant "D" design lens made of omafilcon A (nonionic, 62% water content), with an overall diameter of 14.2 mm and a base curve radius of 8.6 mm. The optical design consists of a spherical central zone of 2.3 mm in diameter dedicated to distance vision, surrounded by an annular aspheric zone of 5.0 mm (1.35-mm width) of increasing addition power and a spherical annular zone of 8.5 mm (1.50 mm width) reaching the maximum add power. This design is presently available also in the Biofinity multifocal (comfilcon A, 48% water content silicone hydrogel material). The amount of relative peripheral refractive error is correlated with the add power chosen from +1 to +3 D.[78, 79] Figure 2.1D represents the in vitro power profile for a 22.00 D distance powered with +2.00 D add Proclear D lens; Figure 2.1E,F represent the on-eye corneal topography power map over a plano lens at distance with add power of +3 and +4 D. Walline and McVey reported on the potential benefit of using Proclear multifocal dominant "D" design as a method to regulate myopia progression in children. The Bifocal Lens Inhibition of Myopia Progression study was a 2-year study comparing the progression of myopia between children wearing single vision CLs and age-matched children wearing multifocal dominant design lenses. Two-year outcome reported was a regulation effect in axial length growth of 29% in the children who used Proclear D (add power +2.00 D) when compared with the cohort wearing conventional single vision CLs. The authors claimed a 50% regulation effect in the progression of refractive error. A statistically significant, though weak correlation existed between baseline myopia and axial length regulation.[80]

2.5.4. Peripheral Gradient Lenses

Similar to center-distance multifocal lenses, custom rigid gas permeable and soft CLs can be designed to compensate for central myopic errors, and at the same time, they impose peripheral positive defocus.[81] A special soft CL with these features was used in a clinical trial to assess its effectiveness in myopia regulation.[61] The treatment CLs made of a silicone hydrogel lens material (8.6-mm base curve, 14.2-mm diameter, lotrafilcon B; CIBA Vision, Duluth, GA) had a clear central zone that corrected for the eye's central refractive error (1.5-mm semichord and

1.5 mm within a relative plus of +0.25 D). Outside the central zone, the refracting power of the lens increased progressively in relative positive power to reach a relative positive power of +1.00 D at 2 mm semichord and +2.00 D at a semichord of 4.5 mm. Approximate design is shown in Figure 2.1I.

Sankaridurg et al. performed a randomized and controlled clinical trial in China with a cohort of 43 Chinese children aged from 7 to 14 years, with baseline spherical refractive error ranging between -0.75 and -3.50 D and -1.00 D or less of astigmatism, and who were treated with the special design CLs for a period of 12 months. The control group consisted of 39 Chinese children with similar baseline ocular characteristics and age range who were treated with single vision spectacle lenses during the same period.

At the end of the 12 months, the eyes treated with the special contact lens showed a 33% slower axial elongation compared to the control group treated with single vision lenses. Although the regulation effect of myopia progression is still below the expected, it demonstrates the effectiveness of this category of CL for the regulation of myopia.

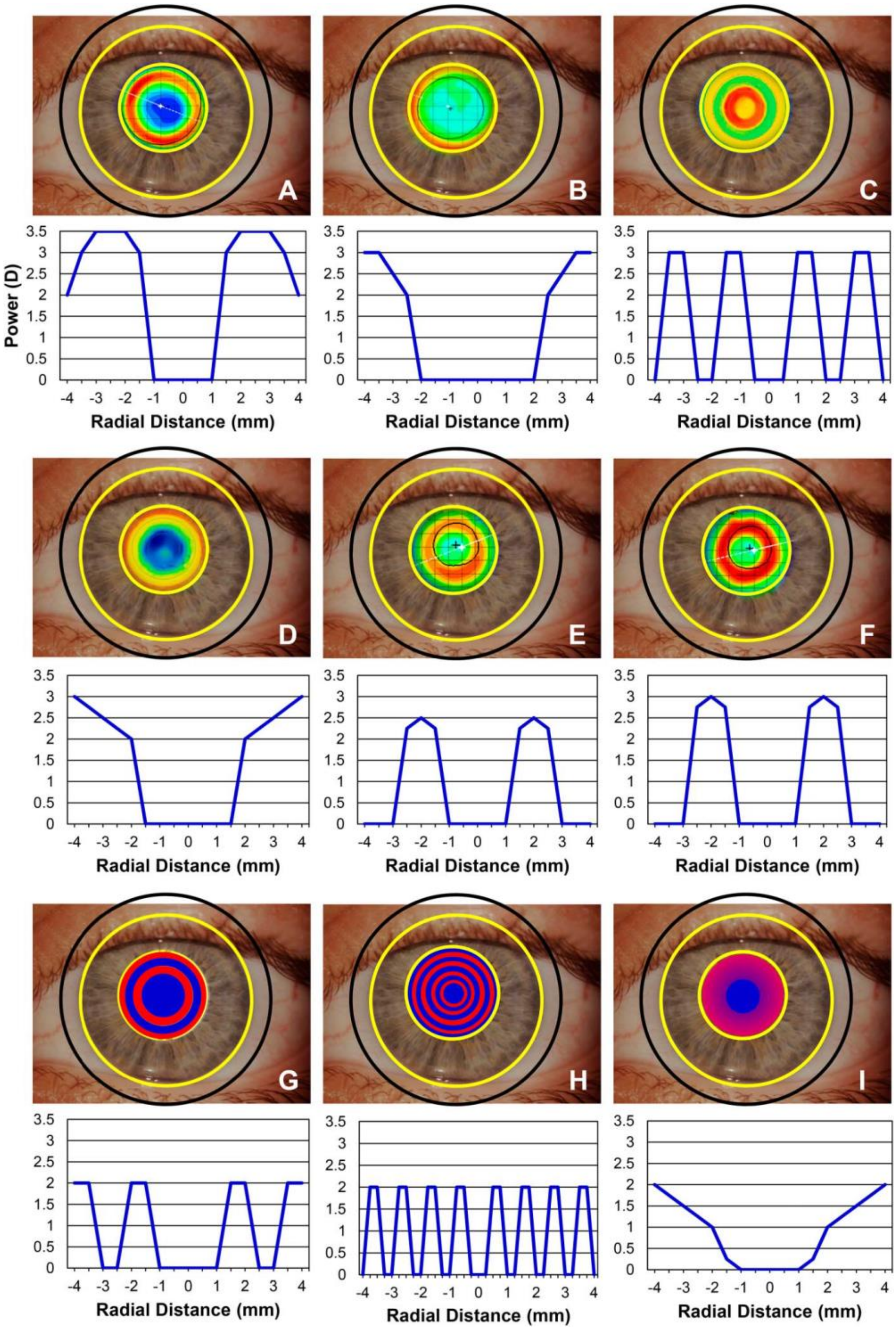


Figure 2.1. *Representation of the optical design of different contact lenses with potential to retain myopia progression over the 6 mm of the pupil and graphs representing the approximate power profile over the central 8 mm: (A) corneal refractive therapy for an axial myopia of 23.5 D; (B) corneal refractive therapy for axial myopia of +1.5 D; (C) bifocal annular design; (D) power profile of a multifocal center-distance soft contact lens as measured in vitro; (E) and (F) power profile of a multifocal center-distance soft contact lens on-eye with +3.00 and +4.00 D of addition for near, respectively, as measured with a corneal topographer; (G) dual-focus as described by Anstice and Phillips[66]; (H) defocus incorporated special contact lens (DISC)[67]; and (I) peripheral gradient design as described by Sankaridurg et al.[61] Note: Drawings might not be a true representation of the lens design; some lens designs might be different for different patients depending on their*

pupil size, refractive error, or other clinical parameters. Graphs do not represent the actual profiles reflected in the maps. Red areas represent maximum positive power, whereas blue or green areas represent distance refractive correction (plano for the purpose of this comparison). All graphs are drawn to represent a maximum power addition of 3 D over a base of plano power except for A (+3.50), B (+1.50), (+4.00), and G (+2.00).

2.5.5. Single Vision Contact Lenses

Conventional single vision soft CLs are largely used to correct refractive errors. It has been described recently that undercorrection, full correction, and overcorrection with single vision soft CL causes hyperopic shifts in the peripheral visual field.[82] In another study, Shen et al.,[83] using commercially available spherical CLs, reported the ability to decrease the amount of relative peripheral hyperopia. This seems to be more effective in high myopia (manifest spherical equivalent=-8.31±2.10 D), where central refractive correction with spherical CLs can result in significant absolute myopic peripheral defocus.[84]

Other studies performed to evaluate myopia progression reported that single vision CLs do not produce an effect on the change of refractive development in a test group when compared with a control group wearing spectacle lenses.[63, 64] When children switched from spectacle lenses to CLs, Marsh-Tootle et al.[65] found a significant but clinically irrelevant increase in myopia. Fulk et al.[85] reported an increase in the amount of myopia three times faster in children who switched to single vision CLs than those who remained in spectacles (mean difference, -0.74 D; P<0.001). Nevertheless, no differences were observed in the vitreous chamber depth, and the refractive change between both groups was related with the change verified in corneal curvature (mean difference, 0.189 D, P=0.007), probably related with molding effects or slight edema.

An additional form of single vision intervention in myopia progression has been tested in the context of the Cambridge Antimyopia Study (CAMS). Allen et al.[56] used CLs to induce negative spherical aberration to improve the accommodative function and reduce the accommodation lag in myopic eyes. The CAMS evaluated the role of accommodative visual therapy and negative spherical aberration CL, alone or combined in myopia progression, in adolescents and young adults from 14 to 22 years of age in a 2-year randomized controlled clinical trial. The results of the CAMS clinical trial were recently published and concluded that there was no effect of improving accommodative function either through vision training alone, negative spherical aberration lenses alone, or the combination of both on myopia progression. It is necessary to consider that these CLs will probably induce relative peripheral hyperopia as a result of their aspheric design as has been observed in multifocal CLs using center-near designs.[58] Thus, there is a possibility that the potential benefit of improving the accommodative function could be somewhat counterbalanced by the negative effect of induced hyperopic peripheral defocus.

2.5.6. Corneal Refractive Therapy and Orthokeratology

In the last decade, several clinical studies evaluated the effect of overnight corneal reshaping for the temporary correction of myopia in the regulation of myopia progression. Cheung et al. reported the case of an 11 year old child treated with orthokeratology in one eye with full undercorrection in the contralateral eye. This case showed a reduction in myopia progression of 62% compared with the contralateral eye not wearing an orthokeratology lens.[68]

Between 2005 and 2012, the results of 6 different clinical trials have been reported in 7 peer-reviewed publications. All of them agreed that treatment with overnight corneal reshaping lenses demonstrated regulation of myopia progression by 30% to 50% in children of different ethnicities aged 8 to 12 years.

Lenses used in these studies were tetracurve and pentacurve reverse geometry lenses and proximity control lenses made of paflufocon D (Paragon HDS 100), hexafocon A (Boston XO), and tisilfocon A (Menicon Z). A graphical representation of the power profile of the cornea over a 6-mm pupil diameter after overnight corneal reshaping for a moderate (-3.5 D) and low (-1.5 D) myopic correction is presented in Figure 2.1A and 2.1B, respectively. Four of the most recently published studies report on East Asian populations,[69, 75] one report results from the United States,[70] and the second reports on Caucasian patients living in Spain.[72] A summary of these and other studies and their characteristics and outcomes are reported in Table 2.3. Only studies including vitreous chamber or axial length measurement as a primary outcome were included in this analysis. With the exception of the U.S. study, all studies included a control population of spectacle wearers. The U.S. study included a control population of soft CL wearers. The follow-up time was 2 years with the exception of the Japanese study presented by Hiraoka et al.[73] Hiraoka et al. reported on the 5-year outcomes showing an average myopia regulation effect of 30% over the 5 years compared with the 37% regulation effect presented previously by Kakita et al.[71] in the same population. This might suggest that the therapeutic regulation effect of orthokeratology might decline over time. The apparent decline might also be related to a slower myopia progression in the control population, as the children became older. Santodomingo-Rubido et al. in 2012 reported a regulation effect of 32% over 2 years in children aged 6 to 12 years.

More recently, the results of the only randomized clinical trial (Retardation of Myopia in Orthokeratology study) conducted in Hong Kong confirmed the results of previous studies with an average axial growth regulation effect of 43% at a consistent rate of 20.14 mm per year in children wearing orthokeratology lenses compared with spectacle wearers who experienced an average growth of 0.63 mm per year.[75]

Considering the consolidated evidence of the role of corneal refractive therapy on regulating myopia progression, there is a growing interest in evaluating the potential factors associated with a higher or lower efficacy of the treatment. Baseline myopia was considered as a potential candidate to predict the efficacy of the treatment, considering the linear relationship between baseline myopia and the relative peripheral refractive error induced by the corneal refractive therapy treatment. However, only Cho et al. in the LORIC study have been able to demonstrate a moderate and statistically significant direct correlation between the amount of baseline myopia and the effect on myopia regulation.[69] More recently, Chen et al. demonstrated that pupil size might have a significant impact on myopia regulation. In their study, larger pupils were associated with a greater efficacy of the treatment, whereas smaller pupil size was related to no regulation effect[74] as Figure 2.1 A,B illustrate. Previous studies using orthokeratology for myopia regulation did not report on the potential effect of pupil size on the degree of myopia regulation.

Despite the apparent susceptibility of East Asian ethnic groups to suffer myopia, corneal refractive therapy has shown to be effective in all ethnic groups including Asian, Caucasian, and African ethnic groups.

A closer observation to information displayed in Table 2.3 shows that the lenses used in different studies are made of different materials and using different designs. Despite the differences in overall lens diameter and optical zone diameter, all studies are consistently showing similar myopia regulation of approximately 40%. Considering the recently observed relationship between pupil size and the myopia regulation effect, one might expect that the smaller treatment zones might be associated to higher myopia regulation. However, Kang et al. have recently reported that the peripheral refraction pattern was not significantly different between lenses with different treatment zones.[86]

It is presently accepted that the mechanism to explain lower myopia progression with corneal refractive therapy is the relative peripheral myopization optical effect resulting from flattening the central cornea and steepening the mid peripheral cornea.[87-90] The effect of the treatment on foveal vision as a result of the higher order aberrations induced[91] may also have a therapeutic effect and is a worthwhile outcome to observe in future studies to evaluate if there is a synergistic effect between the manipulation of the peripheral refraction and the induction of bifocality/multifocality in the foveal region. The authors are aware of current developments in this field, but no current report is available in the peer-review literature so far.

The report of the effect of pupil size on treatment efficacy and the apparent role of the retinal area and location of the defocus raise issues for the role of the lens registration with regard to the center of the pupil or visual axis. Displacement of a multifocal CL or a corneal refractive therapy treatment induces on-axis coma while also shifting the peripheral defocus and generating an asymmetric peripheral defocus circumferentially. Future studies might benefit from the inclusion of measurement of lens registration and evaluation of its impact on treatment efficacy.

2.5.7. Safety of Contact Lenses for Myopia Regulation

Refractive therapy in the form of CLs for the regulation of myopia is targeted to be prescribed for children and adolescents. Safety must be a primary goal. In the context of the present review, two different safety issues or risks are raised, as the two modalities of CL wearing raise their respective safety concerns. The first one is the safety of overnight wearing of corneal refractive therapy lenses, and the second is the safety of daily wearing of soft CLs with multifocal optics. The safety of overnight corneal refractive therapy has been questioned, particularly after the cases of microbial keratitis presented mainly in Asian children in the early years of the past decade.[92] Most of these reports showed positive cultures for microorganisms that were potentially related to poor compliance. Indeed, the rate of reporting of adverse events in orthokeratology patients has decreased for the last 5 to 7 years, whereas the number of children fitted in this modality has increased as a consequence of the higher evidence of efficacy as a myopia regulation modality. Despite a significant part of contact lens–related corneal infections in children was related with corneal refractive therapy in a recent study in Hong Kong, those cases responded well to treatment and recovered without visual loss.[93] Recently, Bullimore et al. reported the rates of microbial keratitis in orthokeratology patients. A trend for higher indices of adverse events in children compared with adults was reported.[94] The reported risk was significantly lower than the numbers reported risk for overnight wear of soft CLs in extended or continuous modalities.[95] Overall, corneal refractive therapy is now considered an effective and safe alternative to correct and regulate myopia progression.[96] Other less severe complications of overnight corneal refractive therapy are important to understand. Early work by Walline et al. in the context of the COOKI study showed that children wearing orthokeratology lenses for 6 months did not reported serious complications. The most frequent finding reported was central superficial punctate staining.[97] These findings have been confirmed by most of the subsequent longitudinal 2 to 5-year studies with orthokeratology presented in the next section. Santodomingo-Rubido et al.,[98] in the context of the Myopia Control with Orthokeratology in Spain study, reported the rate of adverse events and discontinuations in the orthokeratology clinical arm compared with the spectacles control arm. They reported 16 adverse events in children wearing orthokeratology, including 11 related with the CL (5 corneal erosions, 2 clinically significant corneal staining, 2 papillary conjunctivitis, 1 CL peripheral ulcer, and 1 dimple veiling). Most of the events occurred between the 6 and 12 months of treatment over the 2 years of the study, and none of them compromised visual function. Studies were reviewed of daily wearing of soft CLs by children and adolescents. Jones-Jordan et al. in the context of the Adolescent and Child Health Initiative to Encourage Vision Empowerment (ACHIEVE) study reported that children are able to safely wear CLs.[99] Studies of the safety of daily disposable CLs are useful to estimate the risks.[66, 100, 101] Unfortunately, none of the studies reported, including soft CLs designed specifically for myopia regulation, had adequate statistical power for a safety analysis or provided information regarding the complications or adverse events.[61, 66, 80] At present, there is no evidence that younger CL wearers are at a higher risk than adults for the occurrence of adverse events or even minor complications. Chalmers et al. have recently shown that age is a significant risk factor for infiltrative events in young CL wearers, this risk was the lowest for the age range from 8 to 15 years,[102] which is consistent with the age range for CL prescribing for myopia regulation as shown by the age profiles in the studies presented in this review.

2.6. Conclusions

Regulating myopia progression might provide substantial benefits in lowering the risks of several sight threatening complications linked to moderate and high myopia. Contact lenses are convenient optical devices for the purpose of regulating myopia progression for several reasons: (1) they maintain near alignment with the optics of the eye, providing a more consistent effect than spectacle plane ophthalmic lenses; (2) they are well accepted aesthetically, which is particularly important with children and teens; and (3) they have acceptable levels of safety[96, 97] in terms of side effects. Presently, different strategies are available that differ in their principle of action and also in their wearing modality. We are faced with the possibility and probability that the ethical/professional responsibility is to therapeutically intervene to regulate the rate of progression of the disease instead of following the traditional standard of prescribing a spectacle or CL refractive corrective. From the clinical point of view, there are several conclusions that can be derived. First, CLs demonstrate greater efficacy over spectacles for eyes with higher myopia because of their inherent ability to reduce the peripheral hyperopic defocus induced by spectacle lenses.[83] Second, corneal refractive therapy (orthokeratology) is at present the modality with the largest volume of accumulated evidence relating to the efficacy to regulate myopia progression in children.[69, 70, 72, 73] To date, the effect of treatment interruption and the presence or absence of subsequent myopia progression has not been adequately evaluated. Third, soft multifocal CLs are available and design refinements will become available to regulate myopia progression, and multifocal CLs have been reported to have promising preliminary results.[61, 66] Long-term randomized controlled clinical trials with multifocal CLs with methods including pupil size measures, vitreous chamber depth increase, and peripheral refraction are needed. This could eventually elucidate the potential cumulative effect over time and the effect of treatment interruption. In summary, CLs are ideal platforms for incorporating peripheral defocus, imposed foveal defocus, and specific aberration structures, independently or in combination with each other. The combination of several different utilities might potentially reinforce the effectiveness of the currently available approaches.

2.7. References

1. Rubin ML, Milder B. Myopia-A treatable "disease"? *Surv Ophthalmol* 1976;21:65-69.

2. Kelly TS, Chatfield C, Tustin G. Clinical assessment of the arrest of myopia. *Br J Ophthalmol* 1975;59:529-538.

3. Kuster A. The progression of myopia in wearers of contact lenses and spectacles. 400 cases [in German]. Klin Monbl Augenheilkd 1971;159:213-219.

4. Volckmar H. Fitting of contact lenses in children and juveniles with progressive myopia (author's transl) [in German]. *Klin Monbl Augenheilkd* 1975;166:528-532.

5. Kerns RL. Contact lens control of myopia*. Am J Optom Physiol Opt* 1981;58:541-545.

6. Drobec P. Effect of hard contact lenses on the progression of myopia [in German]. *Klin Monbl Augenheilkd* 1982;181:355-356.

7. Andreo LK. Long-term effects of hydrophilic contact lenses on myopia. *Ann Ophthalmol* 1990;22:224-227, 229.

8. Goldschmidt E. Myopia in humans: Can progression be arrested? *Ciba Found Symp* 1990;155:222-229.

9. Sankaridurg PR, Holden BA. Practical applications to modify and control the development of ametropia. *Eye (Lond)* 2014;28:134-141.

10. Gwiazda J. Treatment options for myopia*. Optom Vis Sci* 2009;86:624-628.

11. Walline JJ, Lindsley K, Vedula SS, et al. Interventions to slow progression of myopia in children. *Cochrane Database Syst Rev* 2011:CD004916.

12. Saw SM, Shih-Yen EC, Koh A, et al. Interventions to retard myopia progression in children: An evidence-based update*. Ophthalmology* 2002;109:415-421.

13. Choo JD, Holden BA. The prevention of myopia with contact lenses. *Eye Contact Lens* 2007;33:371-372.

14. Heng LS, Khoo CY. Can contact lenses control the progression of myopia*? Singapore Med J* 1994;35:367-370.

15. Berdeaux G, Alio JL, Martinez JM, et al. Socioeconomic aspects of laser in situ keratomileusis, eyeglasses, and contact lenses in mild to moderate myopia. *J Cataract Refract Surg* 2002;28:1914-1923.

16. Rose K, Smith W, Morgan I, et al. The increasing prevalence of myopia: Implications for Australia. *Clin Exp Ophthalmol* 2001;29:116-120.

17. Lim MC, Gazzard G, Sim EL, et al. Direct costs of myopia in Singapore. *Eye (Lond)* 2009;23:1086-1089.

18. Vitale S, Cotch MF, Sperduto R, et al. Costs of refractive correction of distance vision impairment in the United States, 1999-2002. *Ophthalmology* 2006;113:2163-2170.

19. Kobayashi K, Ohno-Matsui K, Kojima A, et al. Fundus characteristics of high myopia in children*. Jpn J Ophthalmol* 2005;49:306-311.

20. Karlin DB, Curtin BJ. Peripheral chorioretinal lesions and axial length of the myopic eye. Am J Ophthalmol 1976;81:625-635.

21. Silva R. Myopic maculopathy: A review*. Ophthalmologicam* 2012;228:197-213.

22. Saw SM. How blinding is pathological myopia*? Br J Ophthalmol* 2006;90:525-526.

23. Saw SM, Gazzard G, Shih-Yen EC, et al. Myopia and associated pathological complications. *Ophthalmic Physiol Opt* 2005;25:381-391.

24. Flitcroft DI. The complex interactions of retinal, optical and environmental factors in myopia aetiology*. Prog Retin Eye Res* 2012;31:622-660.

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

26. Ogawa A, Tanaka M. The relationship between refractive errors and retinal detachment-Analysis of 1,166 retinal detachment cases. *Jpn J Ophthalmol* 1988;32:310-315.

27. Pointer JS. A 6-year longitudinal optometric study of the refractive trend in school-aged children. *Ophthalmic Physiol Opt* 2001;21:361-367.

28. Xiang F, He M, Morgan IG. Annual changes in refractive errors and ocular components before and after the onset of myopia in Chinese children. *Ophthalmology* 2012;119:1478-1484.

29. Fan DS, Cheung EY, Lai RY, et al. Myopia progression among preschool Chinese children in Hong Kong. *Ann Acad Med Singapore* 2004;33:39-43.

30. Zhao J, Mao J, Luo R, et al. The progression of refractive error in school-age children: Shunyi district, China. *Am J Ophthalmol* 2002;134:735-743.

31. Anderson H, Stuebing KK, Fern KD, et al. Ten-year changes in fusional vergence, phoria, and nearpoint of convergence in myopic children. *Optom Vis Sci* 2011;88:1060-1065.

32. Shih YF, Chiang TH, Hsiao CK, et al. Comparing myopic progression of urban and rural Taiwanese schoolchildren. *Jpn J Ophthalmol* 2010;54:446-451.

33. Sperduto RD, Seigel D, Roberts J, et al. Prevalence of myopia in the United States. *Arch Ophthalmol* 1983;101:405-407.

34. Vitale S, Sperduto RD, Ferris FL III. Increased prevalence of myopia in the United States between 1971-1972 and 1999-2004. *Arch Ophthalmol* 2009;127:1632-1639.

35. Zhu X, Park TW, Winawer J, et al. In a matter of minutes, the eye can know which way to grow*. Invest Ophthalmol Vis Sci* 2005;46:2238-2241.

36. Smith EL III, Hung LF, Kee CS, et al. Effects of brief periods of unrestricted vision on the development of form-deprivation myopia in monkeys. *Invest Ophthalmol Vis Sci* 2002;43:291-299.

37. Diether S, Schaeffel F. Local changes in eye growth induced by imposed local refractive error despite active accommodation*. Vision Res* 1997;37:659-668.

38. Troilo D, Wallman J. The regulation of eye growth and refractive state: An experimental study of emmetropization. *Vision Res* 1991;31:1237-1250.

39. Smith EL III, Kee CS, Ramamirtham R, et al. Peripheral vision can influence eye growth and refractive development in infant monkeys*. Invest Ophthalmol Vis Sci* 2005;46:3965-3972.

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

41. Saw SM, Chua WH, Hong CY, et al. Nearwork in early-onset myopia*. Invest Ophthalmol Vis Sci* 2002;43:332-339.

42. Bullimore MA, Reuter KS, Jones LA, et al. The Study of Progression of Adult Nearsightedness (SPAN): Design and baseline characteristics. *Optom Vis Sci* 2006;83:594-604.

43. Goss DA, Rainey BB. Relationship of accommodative response and nearpoint phoria in a sample of myopic children. *Optom Vis Sci* 1999;76:292-294.

44. Mutti DO, Mitchell GL, Hayes JR, et al. Accommodative lag before and after the onset of myopia. *Invest Ophthalmol Vis Sci* 2006;47:837-846.

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

46. He JC, Gwiazda J, Thorn F, et al. The association of wavefront aberration and accommodative lag in myopes. *Vision Res* 2005;45:285-290.

47. Weizhong L, Zhikuan Y, Wen L, et al.. A longitudinal study on the relationship between myopia development and near accommodation lag in myopic children. *Ophthalmic Physiol Opt* 2008;28:57-61.

48. Edwards MH, Li RW, Lam CS, et al. The Hong Kong progressive lens myopia control study: Study design and main findings. *Invest Ophthalmol Vis Sci* 2002;43:2852-2858.

49. Gwiazda J, Hyman L, Hussein M, et al. A randomized clinical trial of progressive addition lenses versus single vision lenses on the progression of myopia in children. *Invest Ophthalmol Vis Sci* 2003;44:1492-1500.

50. Hasebe S, Ohtsuki H, Nonaka T, et al. Effect of progressive addition lenses on myopia progression in Japanese children: A prospective, randomized, double-masked, crossover trial. *Invest Ophthalmol Vis Sci* 2008;49:2781-2789.

51. Gwiazda JE, Hyman L, Norton TT, et al. Accommodation and related risk factors associated with myopia progression and their interaction with treatment in COMET children. *Invest Ophthalmol Vis Sci* 2004;45:2143-2151.

52. Chung KM, Chong E. Near esophoria is associated with high myopia. *Clin Exp Optom* 2000;83:71-75.

53. Schor C. The influence of interactions between accommodation and convergence on the lag of accommodation. *Ophthalmic Physiol Opt* 1999;19:134-150.

54. Smith EL III. Optical treatment strategies to slow myopia progression: Effects of the visual extent of the optical treatment zone. *Exp Eye Res* 2013;114:77-88.

55. Lopes-Ferreira DP, Ferreira-Neves HI, Faria-Ribeiro M, et al. Peripheral refraction with eye and head rotation with contact lenses. *Cont Lens Anterior Eye*. [published online ahead of print December 16, 2014]. doi: 10.1016/j.clae.2014.11.201.

56. Allen PM, Radhakrishnan H, Rae S, et al. Aberration control and vision training as an effective means of improving accommodation in individuals with *myopia. Invest Ophthalmol Vis Sci* 2009;50:5120-5129.

57. Salmon TO, van de Pol C. Normal-eye Zernike coefficients and root-mean-square wavefront errors. *J Cataract Refract Surg* 2006;32:2064-2074.

58. Rosen R, Jaeken B, Lindskoog PA, et al. Evaluating the peripheral optical effect of multifocal contact lenses. *Ophthalmic Physiol Opt* 2012;32:527-534.

59. Aller TA, Wildsoet C. Bifocal soft contact lenses as a possible myopia control treatment: A case report involving identical twins. *Clin Exp Optom* 2008;91:394-399.

60. Aller TA, Wildsoet C. Results of a one-year prospective clinical trial (CONTROL) of the use of bifocal soft contact lenses to control myopia progression. *Ophthalmic Physiol Opt* 2006;26:8-9.

61. Sankaridurg P, Holden B, Smith E III, et al. Decrease in rate of myopia progression with a contact lens designed to reduce relative peripheral hyperopia: One-year results. *Invest Ophthalmol Vis Sci* 2011;52:9362-9367.

62. Walline JJ, McVey L. Myopia control with a soft bifocal contact lens (ABSTRACT) in myopia: Proceedings of the 13th International Conference. *Optom Vis Sci* 2010;88:395-403.

63. Horner DG, Soni PS, Salmon TO, et al. Myopia progression in adolescent wearers of soft contact lenses and spectacles. *Optom Vis Sci* 1999;76:474-479.

64. Walline JJ, Jones LA, Sinnott L, et al. A randomized trial of the effect of soft contact lenses on myopia progression in children. *Invest Ophthalmol Vis Sci* 2008;49:4702-4706.

65. Marsh-Tootle WL, Dong LM, Hyman L, et al. Myopia progression in children wearing spectacles vs. switching to contact lenses*. Optom Vis Sci* 2009;86:741-747.

66. Anstice NS, Phillips JR. Effect of dual-focus soft contact lens wear on axial myopia progression in children. *Ophthalmology* 2011;118:1152-1161.

67. Lam CS, Tang WC, Tse DY, et al. Defocus Incorporated Soft Contact (DISC) lens slows myopia progression in Hong Kong Chinese schoolchildren: A 2-year randomised clinical trial. *Br J Ophthalmol* 2014;98:40-45.

68. Cheung SW, Cho P, Fan D. Asymmetrical increase in axial length in the two eyes of a monocular orthokeratology patient. *Optom Vis Sci* 2004;81:653-656.

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

70. Walline JJ, Jones LA, Sinnott LT. Corneal reshaping and myopia progression. *Br J Ophthalmol* 2009;93:1181-1185.

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

72. Santodomingo-Rubido J, Villa-Collar C, Gilmartin B, et al. Myopia control with orthokeratology contact lenses in Spain: Refractive and biometric changes*. Invest Ophthalmol Vis Sci* 2012;53:5060-5065.

73. Hiraoka T, Kakita T, Okamoto F, et al.. Long-term effect of overnight orthokeratology on axial length elongation in childhood myopia: A 5-year follow-up study*. Invest Ophthalmol Vis Sci* 2012;53:3913-3919.

74. Chen Z, Niu L, Xue F, et al. Impact of pupil diameter on axial growth in orthokeratology. *Optom Vis Sci* 2012;89:1636-1640.

75. Cho P, Cheung SW. Retardation of myopia in Orthokeratology (ROMIO) study: A 2-year randomized clinical trial. *Invest Ophthalmol Vis Sci* 2012;53:7077-7085.

76. Charm J, Cho P. High myopia-partial reduction ortho-k: A 2-year randomized study. *Optom Vis Sci* 2013;90:530-539.

77. McFadden SA, Tse DY, Bowrey HE, et al.. Integration of defocus by dual power Fresnel lenses inhibits myopia in the mammalian eye. *Invest Ophthalmol Vis Sci* 2014;55:908-917.

78. Lopes-Ferreira D, Ribeiro C, Maia R, et al. Peripheral myopization using a dominant design multifocal contact lens. *J Optom* 2011;4:14-21.

79. Lopes-Ferreira D, Ribeiro C, Neves H, et al. Peripheral refraction with dominant design multifocal contact lenses in young myopes. *J Optom* 2013;6:85-94.

80. Walline JJ, Greiner KL, McVey ME, et al. Multifocal contact lens myopia control. *Optom Vis Sci* 2013;90:1207-1214.

81. Paune J, Queiros A, Quevedo L, et al. Peripheral myopization and visual performance with experimental rigid gas permeable and soft contact lens design. *Cont Lens Anterior Eye* 2014;37:455-460.

82. Kang P, Fan Y, Oh K, et al. Effect of single vision soft contact lenses on peripheral refraction. *Optom Vis Sci* 2012;89:1014-1021.

83. Shen J, Clark CA, Soni PS, et al. Peripheral refraction with and without contact lens correction. *Optom Vis Sci* 2010;87:642-655.

84. Kwok E, Patel B, Backhouse S, et al. Peripheral refraction in high myopia with spherical soft contact lenses. *Optom Vis Sci* 2012;89:263-270.

85. Fulk GW, Cyert LA, Parker DE, et al. The effect of changing from glasses to soft contact lenses on myopia progression in adolescents. *Ophthalmic Physiol Opt* 2003;23:71-77.

86. Kang P, Gifford P, Swarbrick HA. Can manipulation of orthokeratology lens parameters change the peripheral refraction profile? 2012. *American Academy of Optometry E-abstract* #120992.

87. Lu F, Simpson T, Sorbara L, et al. The relationship between the treatment zone diameter and visual, optical and subjective performance in corneal refractive therapy lens wearers. *Ophthalmic Physiol Opt* 2007;27:568-578.

88. Queiros A, Gonzalez-Meijome JM, Villa-Collar C, et al. Local steepening in peripheral corneal curvature after corneal refractive therapy and LASIK. *Optom Vis Sci* 2010;87:432-439.

89. Queiros A, Gonzalez-Meijome JM, Jorge J, et al. Peripheral refraction in myopic patients after orthokeratology. *Optom Vis Sci* 2010;87:323-329.

90. Charman WN, Mountford J, Atchison DA, et al. Peripheral refraction in orthokeratology patients. *Optom Vis Sci* 2006;83:641-648.

91. Queiros A, Villa-Collar C, Gonzalez-Meijome JM, et al. Effect of pupil size on corneal aberrations before and after standard laser in situ keratomileusis, custom laser in situ keratomileusis, and corneal refractive therapy. *Am J Ophthalmol* 2010;150:97-109.

92. Watt KG, Swarbrick HA. Trends in microbial keratitis associated with orthokeratology. *Eye Contact Lens* 2007;33:373-377.

93. Young AL, Leung KS, Tsim N, et al. Risk factors, microbiological profile, and treatment outcomes of pediatric microbial keratitis in a tertiary care hospital in Hong Kong. *Am J Ophthalmol* 2013;156:1040-1044.

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

95. Keay L, Stapleton F, Schein O. Epidemiology of contact lens-related inflammation and microbial keratitis: A 20-year perspective. *Eye Contact Lens* 2007;33:346-353, discussion 362-363.

96. Koffler BH, Sears JJ. Myopia control in children through refractive therapy gas permeable contact lenses: Is it for real? *Am J Ophthalmol* 2013;156:1076-1081.

97. Walline JJ, Rah MJ, Jones LA. The Children's Overnight Orthokeratology Investigation (COOKI) pilot study. *Optom Vis Sci* 2004;81:407-413.

98. Santodomingo-Rubido J, Villa-Collar C, Gilmartin B, et al. Orthokeratology vs. spectacles: Adverse events and discontinuations. *Optom Vis Sci* 2012;89:1133-1139.

99. Jones-Jordan LA, Chitkara M, Coffey B, et al. A comparison of spectacle and contact lens wearing times in the ACHIEVE study. *Clin Exp Optom* 2010;93:157-163.

100. Sankaridurg PR, Sweeney DF, Holden BA, et al. Comparison of adverse events with daily disposable hydrogels and spectacle wear: Results from a 12-month prospective clinical trial. *Ophthalmology* 2003;110:2327-2334.

101. Solomon OD, Freeman MI, Boshnick EL, et al. A 3-year prospective study of the clinical performance of daily disposable contact lenses compared with frequent replacement and conventional daily wear contact lenses. *CLAO J* 1996;22:250-257.

102. Chalmers RL, Wagner H, Mitchell GL, et al. Age and other risk factors for corneal infiltrative and inflammatory events in young soft contact lens wearers from the Contact Lens Assessment in Youth (CLAY) study. *Invest Ophthalmol Vis Sci* 2011;52:6690-6696.

CHAPTER 3

Peripheral Refraction with Dominant Design Multifocal Contact Lenses in Young Myopes

3.1. Abstract.

Purpose: The purpose of this study was to show the potential of a commercial center-distance multifocal soft contact lens to induce relative peripheral myopic defocus in myopic eyes.

Methods: Twenty-eight myopic right eyes from 28 patients (mean age: 22.0 ±2.0 years) were evaluated. The measurements of axial and off-axis refraction were made using a Grand-Seiko WAM-5500 open-field autorefractometer without lens and with multifocal contact lenses (Proclear Multifocal D® Design) of +2.00 D and +3.00 D add power applied randomly. Central mean spherical equivalent refraction was −2.24±1.33 D. Ocular refraction was measured at center and at eccentricities between 35° nasal and 35° temporal (in 5° steps).

Results: Baseline relative peripheral refractive error (RPRE) as spherical equivalent (M) was −0.69 ±1.14 D and −0.46±1.38 D at 35° in the nasal and temporal degrees of visual field, respectively. Both add powers increased the relative peripheral myopic defocus up to −0.82 ± 1.23 D ($p = 0.002$) and −1.42±1.45 D ($p < 0.001$) at 35° in the nasal field; and −0.87 ±1.42 D ($p = 0.003$) and −2.00±1.48 D ($p < 0.001$) at 35° in the temporal retina with +2.00 D and +3.00 D add lenses, respectively. Differences between +2.00 and +3.00 D add lenses were statistically significant beyond 20° in the nasal visual field and 10° in the temporal visual field.

Conclusion: It is possible to induce significant changes in the pattern of relative peripheral refraction in the myopic direction with commercially available dominant design multifocal contact lenses. The higher add (+3.00 D) induced an significantly higher effect than the +2.00 D add lens, although an increase of 1 D in add power does not correspond to the same amount of increase in RPRE.

Keywords: Peripheral refraction; Multifocal contact lenses; Myopization

3.2. Introduction

Retinal shape is one of several factors that may be related with myopia progression with many studies showing that the myopic eye has on average a more prolate retinal shape in comparison with emmetropic eyes.[1-3] This probably reflects the result of stretching induced by posterior ocular elongation as modern techniques of magnetic resonance imaging and low coherence biometry have shown.[4, 5] Atchison et al.[6] observed that the peripheral refraction was relatively more hyperopic in myopic eyes than in emmetropic eyes along the horizontal visual field. Smith's studies have shown that peripheral retina alone is capable to regulate the emmetropization process,[7-9] and not the fovea as previously thought, thereby showing the relevance of peripheral retina in ocular development.

Conventional correction of myopia with spectacle lenses may result in an increase of peripheral relative hyperopic defocus[10, 11] which worsens with higher degree of myopia and with increase of eccentricity.[12] By changing the peripheral optics of corrective devices it is now possible to invert the relative hyperopic defocus in myopic eyes into peripheral relative myopia.[11] This is considered one possible strategy to counterbalance the unknown stimulus that triggers the eye elongation and the subsequent myopia progression.

There are several options to change the relative peripheral refractive error (RPRE) pattern, for example corneal refractive therapy (CRT)[13-15] or laser in situ keratomileusis (LASIK) surgery.[16] Special designs of spectacle lenses,[17] and contact lenses[18] are also produced with the aim of increasing the peripheral relative myopic defocus and to slow-down myopia progression. Some commercially available multifocal contact lenses (MFCL) (dominant-design) might afford a similar effect by means of a peripheral add power area primarily intended to increase spherical aberration and depth of focus in presbyopic patients. Dominant design multifocal contact lenses have been previously demonstrated to induce significant changes to the peripheral refractive error profile of the eye. Lopes-Ferreira et al. using an open-field auto-refractor found a more effective peripheral myopization with a +3.00 D add dominant design Proclear Multifocal lens in a setting of 20 emmetropic eyes.[19] More recently, Rosén et al. using an experimental Hartman-Shack sensor showed that the same lens was able to induce about 0.50 D of relative peripheral myopia at 30° using a +2.00 D lens in 3 emmetropic and 1 myopic patients.[20] However, the potential effect of these lenses on myopic eyes that could be potentially treated with these lenses, is not well described in a larger sample size. The goal of this study was to use commercially available center-distance multifocal soft contact lenses (Proclear® Multifocal dominant design) to evaluate their impact in the peripheral optics of the myopic eye.

3.3. Methods

In this study, we measured 28 eyes of 28 myopic patients (24 females and 4 males) aged 19-26 years (mean age: 22.0 ± 2.0 years) with central spherical equivalent refraction (MSE ±SD) of −2.24 ±1.33 D. The experiments were conducted at the Clinical and Experimental Optometry Research Lab (CEORLab, University of Minho, Braga, Portugal). All volunteers were fully informed of the purpose and all the procedures of this study, and they gave written consent following the tenets of the Declaration of Helsinki.

The refractive error of the patients was assessed through a complete optometric examination, including noncycloplegic objective and subjective refraction. Central and peripheral refraction without any correction (baseline) was measured using an open-view autorrefractometer/ keratometer Grand-Seiko WAM-5500 (Grand Seiko Co., Ltd., Hiroshima, Japan).[21, 22] Subjects are instructed to fixate a target located at 2.5 m consisting of a row of LEDs arranged horizontally. Measurements were made in straight-ahead viewing (in fovea) and in the positions corresponding to eccentricities between 35° nasal and 35° temporal, in 5°steps. The patient rotated the eye to fixate different LED targets,[23, 24] while the fellow eye was occluded. This technique has been used also to evaluate the effect of single vision soft contact lenses on peripheral refraction.[25]

Inclusion criteria required that patients had myopia lower than −6.00 D, astigmatism lower than −1.00 D and should be free of any current eye disease or injury, did not undergo refractive surgery and not being under effect of any ocular or systemic medication.

Proclear® Multifocal with Dominant design (Coopervision, Pleasanton, CA, USA) were fitted only to the right eye of all patients. The lens comprises a central spherical 2.3 mm area targeted to compensate the refractive error of each patient, surrounded by an annular aspheric zone of increasing power reaching the maximum add power at 5 mm chord area. Second spherical zone with the maximum near add covers the area from the 5 to 8 mm chord (either +2.00 or +3.00 D of add has been used in this study). Further technical details of the lens are presented in Table 3.1.

Table 3.1. *Technical details of Proclear Multifocal Contact Lens.*

Parameter	**Value**
Material	Omafilcon A
Equilibrium Water Content	62%
Base Curve Radius	8.6 mm
Overall Diameter	14.2 mm
Distance Power	Distant correction of each patient
Near Add Power	+2.00D and +3.00 D
Spherical Distance Zone Diameter	2.3 mm
Aspheric Multifocal Zone Width/Diameter	1.35 mm/5.0 mm
Spherical Near Zone Width/Diameter	1.75 mm/8.5 mm

Lenses with the two add powers were fitted in random order and in independent sessions, in different days. Lens fit was checked for lateral centration on primary gaze and lag on lateral gaze as this are the main factors that will potentially affect our measures. Only patients with less than 0.5 mm of lateral decentration on primary gaze and less than 0.25 mm of lag compared to primary gaze position at the maximum eye rotation (35°) to ensure minimal effect of lens lag upon eye rotation on the measures of peripheral refraction. We used a caliper attached to the ocular of the slit lamp to be able the measure this small effects of lag (0.1 mm resolution). The illumination on examination room was adjusted to obtain sufficiently large pupil size to allow peripheral measurements without artificial pupil dilatation, which was achieved in all cases. Five measures of refraction (sphere, cylinder and axis) were obtained at each central or eccentric location. Individual data were converted to vector components of refraction as recommended by Thibos[26]: M, J0 and J45 according to Fourier analysis,

$$M = \mathrm{Sph} + \frac{\mathrm{Cyl}}{2},$$

$$J0 = \left(-\frac{\mathrm{Cyl}}{2}\right)\cos(2\alpha) \quad \text{and}$$

$$J45 = \left(-\frac{\mathrm{Cyl}}{2}\right)\sin(2\alpha)$$

where Sph, Cyl and represent sphere, cylinder and axis, respectively. Data were stored automatically in Microsoft Excel spreadsheet using custom software (DRRE, CEORLab, Portugal) and treated statistically using SPSS v.19 for Windows (SPSS Inc., IL, USA). Kolmogorov-Smirnov Test was applied in order to evaluate the normality of data distribution. When normality could not be assumed, Wilcoxon Signed Ranks Test was used for paired comparison between baseline and lens adds power and Paired Samples T-Test was used when normality could be assumed. For statistical purposes, a p value lower than 0.05 was considered statistically significant.

3.4. Results

Table 3.2 presents the mean values of refractive error and standard deviations of all eyes without lens (WL), and wearing each one of two tested multifocal soft contact lens Proclear® multifocal D (dominant design) of near addition +2.00 D (Add2) and +3.00 D (Add3).

Figs. 3.1-3 represent the RPRE expressed as M, J0 and J45, respectively, in each case were represented values that corresponds to the situation without lenses and with each one of the contact lenses used in the study. According to Fig. 3.1, Add2 multifocal lens shows statistically significant differences in the peripheral visual field from N25 and from T10 compared to baseline. Add3 multifocal lens can induce significant myopization effect from N25 and T5 toward the more peripheral locations.

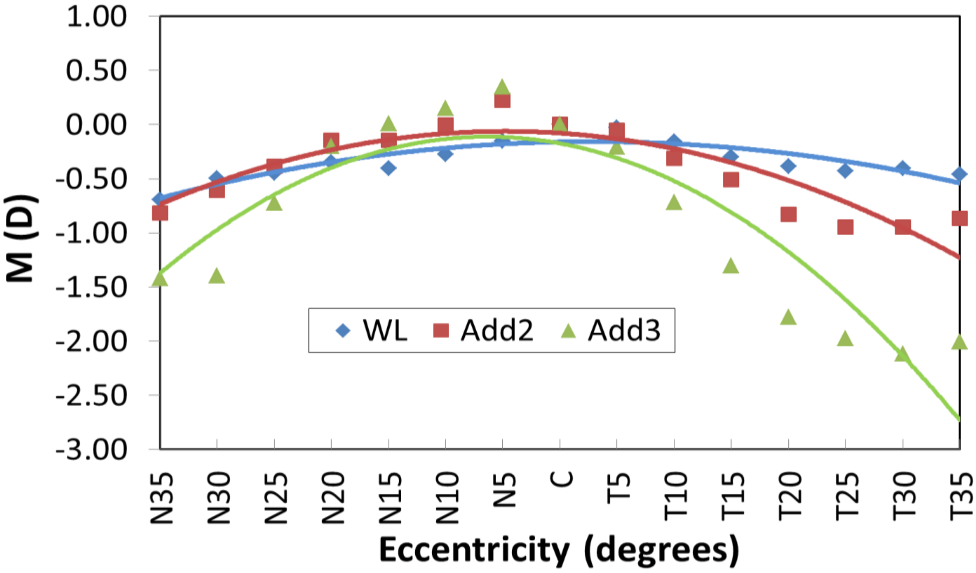


Figure 3.1. *Relative peripheral refractive error (eccentricity minus center) in mean spherical equivalent values (M) as a function of angle in temporal field (T) and nasal field (N), across 70° of horizontal visual field. One polynomial function of 2nd degree was adapted for each experimental situation and refractive components analysed: for without lens condition (WL -◆): y = −0.009x2 + 0.156x −0.826; with multifocal contact lens add +2.00 D (Add2 -■): y = −0.018x2 + 0.259x −0.976 and with MFCL addition +3.00 D (Add3 -▲): y = −0.038x2 + 0.516x −1.850. *Wilcoxon Signed Ranks Test and +Paired Sample T-Test. Only those locations with statistically significant differences (p < 0.05) compared to center are illustrated (top symbols for Add2 and bottom symbols for Add3).*

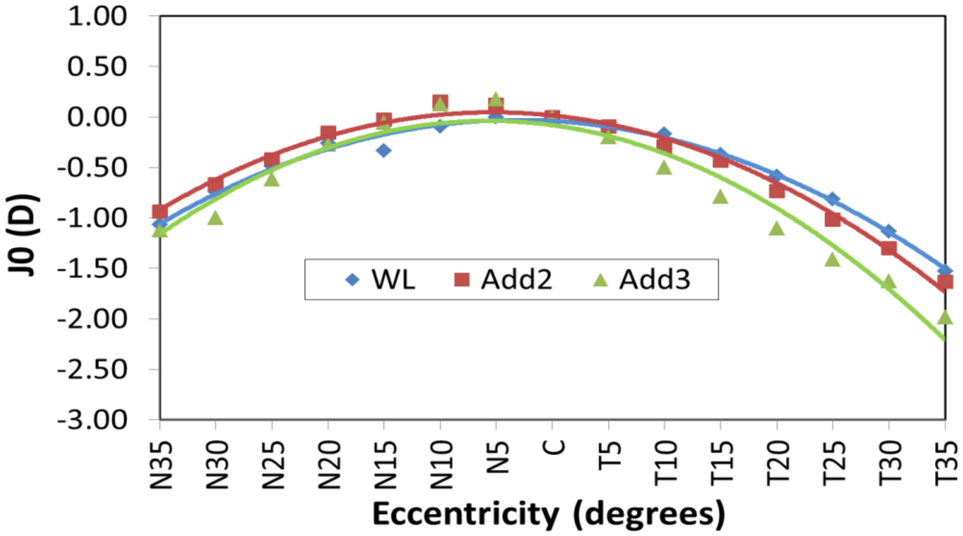


Figure 3.2. *Relative peripheral refractive error (eccentricity minus center) in horizontal astigmatism component values (J0) as a function of field angle the temporal (T) and nasal (N) retinal area, across central 70° of horizontal visual field. One polynomial function of 2nd degree was adapted for each experimental situation and refractive components analysed: for without lens condition (WL -◆): y = −0.025x² + 0.373x − 1.406; with multifocal contact lens add +2.00*

*D (Add2 -■): $y = -0.027x^2 + 0.379x - 1.270$ and with MFCL addition +3.00 D (Add3 -▲): $y = -0.032x^2 + 0.448x - 1.577$. *Wilcoxon Signed Ranks Test and +Paired Sample T-Test. Only those locations with statistically significant differences ($p < 0.05$) compared to center are illustrated (top symbols for Add2 and bottom symbols for Add3).*

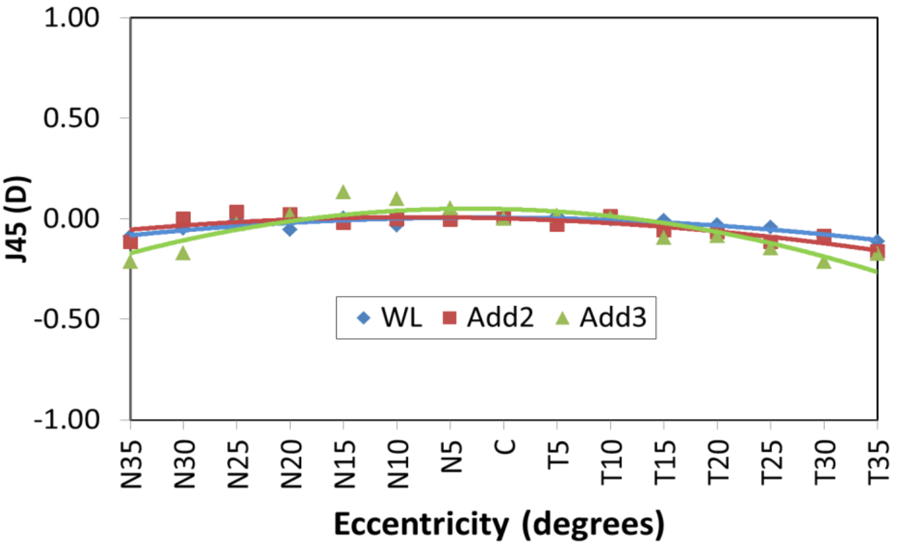


Figure 3.3. *Relative peripheral refractive error (eccentricity minus center) in oblique astigmatism component values (J45) as a function of field angle the temporal (T) and nasal (N) retinal area, across 70º of horizontal visual field. One polynomial function of 2nd degree was adapted for each experimental situation and refractive components analysed: for without lens condition (WL -◆): $y = -0.002x^2 + 0.030x - 0.111$; with multifocal contact lens add +2.00 D (Add2 -■): $y = -0.002x^2 + 0.027x - 0.079$ and with MFCL addition +3.00 D (Add3 -▲): $y = -0.005x^2 + 0.080x - 0.245$. *Wilcoxon Signed Ranks Test and +Paired Sample T-Test. Only those locations with statistically significant differences ($p < 0.05$) compared to center are illustrated (top symbols for Add2 and bottom symbols for Add3).*

Fig. 3.2 shows that differences against baseline in J0 significantly increase with eccentricity of the visual field and the changes are also higher for Add3 multifocal lens. In Fig. 3.3, it is shown that J45 values do not change significantly, along the horizontal visual field, with any of the lenses used.

Table 3.2. *Mean spherical equivalent values (MSE±SD), horizontal astigmatism component (J0 ± SD) and oblique astigmatism component (J45 ± SD) for the whole sample (n = 28 eyes) at different eccentricities under different conditions: without lens, MFCL addition +2.00 D (Add2) and MFCL addition +3.00 D (Add3). Values are expressed in diopters (D). N: nasal visual field; T: temporal visual field; C: center.*

	M			J0			J45		
Point	**WL**	**Add2**	**Add3**	**WL**	**Add2**	**Add3**	**WL**	**Add2**	**Add3**
N35	-2.93±1.68	-1.92±1.32	-2.92±1.62	-1.04±0.46	-0.99±0.34	-1.21±0.60	-0.08±0.32	-0.12±0.38	-0.20±0.40
N30	-2.73±1.63	-1.71±1.22	-2.90±1.25	-0.71±0.29	-0.72±0.35	-1.09±0.48	-0.04±0.26	-0.01±0.32	-0.16±0.48
N25	-2.68±1.43	-1.49±0.84	-2.23±1.02	-0.46±0.21	-0.47±0.40	-0.71±0.49	0.00±0.23	0.03±0.30	-0.02±0.46
N20	-2.58±1.46	-1.25±0.81	-1.70±0.84	-0.23±0.30	-0.21±0.40	-0.36±0.45	-0.05±0.31	0.02±0.29	0.03±0.38
N15	-2.64±1.46	-1.25±0.59	-1.50±0.86	-0.31±0.42	-0.08±0.45	-0.14±0.60	0.01±0.26	-0.03±0.42	0.14±0.46
N10	-2.51±1.33	-1.10±0.52	-1.35±0.74	-0.07±0.22	0.10±0.26	0.04±0.46	-0.03±0.24	-0.01±0.32	0.11±0.44
N5	-2.39±1.38	-0.88±0.47	-1.15±0.68	0.03±0.22	0.07±0.26	0.09±0.26	0.02±0.17	-0.01±0.27	0.07±0.32
C	-2.24±1.33	-1.10±0.53	-1.50±0.62	0.03±0.20	-0.05±0.33	-0.09±0.35	0.00±0.14	-0.01±0.34	0.01±0.43
T5	-2.26±1.42	-1.15±0.71	-1.71±0.76	-0.08±0.16	-0.14±0.34	-0.29±0.30	0.02±0.15	-0.04±0.35	0.03±0.50
T10	-2.39±1.49	-1.41±0.75	-2.22±0.69	-0.14±0.22	-0.34±0.30	-0.59±0.29	0.00±0.16	0.00±0.41	0.02±0.49
T15	-2.53±1.50	-1.61±0.67	-2.81±0.76	-0.34±0.23	-0.48±0.31	-0.88±0.33	0.00±0.16	-0.07±0.35	-0.08±0.56
T20	-2.62±1.58	-1.93±0.92	-3.28±0.73	-0.56±0.24	-0.78±0.34	-1.19±0.27	-0.02±0.19	-0.08±0.34	-0.07±0.57
T25	-2.66±1.66	-2.05±1.12	-3.48±0.76	-0.79±0.31	-1.07±0.35	-1.50±0.31	-0.04±0.18	-0.12±0.27	-0.13±0.40
T30	-2.64±1.82	-2.05±1.30	-3.62±1.01	-1.11±0.40	-1.35±0.40	-1.71±0.42	-0.09±0.26	-0.09±0.29	-0.20±0.30
T35	-2.70±2.08	-1.97±1.52	-3.51±1.12	-1.50±0.50	-1.68±0.52	-2.07±0.53	-0.11±0.27	-0.17±0.33	-0.16±0.33

The numerical values of differences between refractive components at each eccentricity and center are shown in Table 3.3 for values of M, J0 and J45 along with all the statistical comparisons against baseline and between both contact lenses used. It is evident that the differences between extreme peripheral points (35°) either nasal or temporal and the center became significant with Add2 multifocal contact lens reaching values of RPRE for *M* component of −0.82 ± 1.23 D and −0.87 ± 1.42 D; these differences are greater with Add3 reaching −1.42 ±1.45 D and −2.00 ± 1.48 D in the nasal and temporal visual fields, respectively. Differences against baseline for each Add power were statistically significant beyond 25° N and 10° T, with Add2 and out of 25° N and 5° T in case of Add3. Differences between Add2 and Add3 were statistically significant beyond eccentricities of 25° in the nasal visual field and beyond 10° in the temporal visual field ($p < 0.05$).

Table 3.3. *Relative peripheral refractive error (eccentric points minus center) as spherical equivalent values (M±SD), horizontal astigmatism component (J0±SD) and oblique astigmatism component (J45±SD) for the situation without lens, with MFCL addition +2.00D (Add2) and with MFCL addition 3.00D (Add3). Values are expressed in diopters (D). N: nasal side of retina; T: temporal side of retina; C: Center. p represents the value of statistical significance according to: +Paired Sample T-Test or *Wilcoxon Signed Ranks Test.; Bold indicates statistically significant power difference compared with central point (95% confidence).*

	M				J0			
Point	WL±SD Sig. (p)	Add2±SD Sig. (p)	Add3±SD Sig. (p)	Diff. Add2 vs Add3 Sig. (p)	WL±SD Sig. (p)	Add2±SD Sig. (p)	Add3±SD Sig. (p)	Diff. Add2 vs Add3 Sig. (p)
N35	-0.69±1.14 0.001*	-0.82±1.23 0.002*	-1.42±1.45 <0.001*	0.60±1.16 0.011*	-1.07±0.51 <0.001*	-0.94±0.38 <0.001*	-1.12±0.55 <0.001*	0.19±0.65 0.127+
N30	-0.50±0.98 0.008*	-0.61±1.14 0.009+	-1.40±1.23 <0.001*	0.79±0.73 <0.001*	-0.74±0.30 <0.001*	-0.67±0.38 <0.001*	-1.00±0.37 <0.001*	0.33±0.46 <0.001*
N25	-0.45±0.80 0.002*	-0.39±0.83 0.032*	-0.73±1.01 0.001+	0.34±0.69 0.016*	-0.49±0.23 <0.001*	-0.42±0.40 <0.001*	-0.62±0.39 <0.001*	0.20±0.43 0.022*
N20	-0.35±0.69 0.007*	-0.14±0.80 0.348*	-0.20±0.90 0.249+	0.06±0.85 0.801+	-0.26±0.30 <0.001*	-0.16±0.43 0.139*	-0.27±0.42 0.003*	0.12±0.43 0.194+
N15	-0.40±0.57 0.001*	-0.15±0.65 0.288*	0.01±0.87 0.966+	- 0.15±0.88 0.368*	-0.34±0.40 <0.001*	-0.03±0.50 0.692*	-0.06±0.43 0.657*	0.03±0.44 0.561+
N10	-0.27±0.47 0.007*	0.00±0.49 0.914*	0.15±0.77 0.291*	- 0.15±0.70 0.418+	-0.10±0.25 0.047*	0.15±0.31 0.021*	0.13±0.38 0.072*	0.02±0.45 1.000+
N5	-0.15±0.20 <0.001+	0.22±0.42 0.009+	0.35±0.45 0.001*	- 0.13±0.61 0.605+	0.00±0.16 0.732*	0.12±0.26 0.023*	0.18±0.33 0.013*	- 0.05±0.37 0.657+
T5	-0.03±0.28 0.586+	-0.05±0.42 0.515+	-0.21±0.47 0.029*	0.15±0.66 0.285+	-0.11±0.15 0.002*	-0.09±0.25 0.060*	-0.20±0.22 <0.001*	0.11±0.34 0.07
T10	-0.15±0.40 0.054+	-0.31±0.40 <0.001+	-0.72±0.56 <0.001*	0.41±0.62 <0.001*	-0.17±0.17 <0.001*	-0.29±0.22 <0.001*	-0.50±0.29 <0.001*	0.21±0.33 <0.001*
T15	-0.30±0.51 0.004+	-0.51±0.47 <0.001+	-1.31±0.71 <0.001*	0.80±0.66 <0.001*	-0.37±0.18 <0.001*	-0.43±0.32 <0.001*	-0.79±0.30 <0.001*	0.36±0.34 <0.001*
T20	-0.38±0.63 0.003+	-0.83±0.72 <0.001+	-1.78±0.79 <0.001*	0.94±0.68 <0.001*	-0.59±0.23 <0.001*	-0.73±0.30 <0.001*	-1.10±0.32 <0.001*	0.37±0.37 <0.001*
T25	-0.43±0.86 0.013+	-0.95±0.94 <0.001+	-1.98±0.94 <0.001*	1.03±0.71 <0.001*	-0.82±0.29 <0.001*	-1.02±0.33 <0.001*	-1.41±0.29 <0.001*	0.39±0.27 <0.001*
T30	-0.40±1.13 0.071+	-0.94±1.09 <0.001*	-2.11±1.27 <0.001*	1.17±0.93 <0.001*	-1.13±0.42 <0.001*	-1.30±0.41 <0.001*	-1.63±0.43 <0.001*	0.33±0.57 <0.001*
T35	-0.46±1.38 0.088+	-0.87±1.42 0.003*	-2.00±1.48 <0.001*	1.13±1.00 <0.001*	-1.53±0.51 <0.001*	-1.63±0.59 <0.001*	-1.99±0.52 <0.001*	0.36±0.61 0.01*

Table 3.4. (Continuated)

	J45			
Point	**WL±SD Sig. (p)**	**Add2±SD Sig. (p)**	**Add3±SD Sig. (p)**	**Diff. Add2 vs Add3 Sig. (p)**
N35	-0.09±0.31 0.019+	-0.12±0.52 0.386+	-0.21±0.73 0.274+	0.10±0.63 0.187*
N30	-0.05±0.25 0.015+	0.00±0.54 0.406+	-0.17±0.83 0.227+	0.17±0.75 0.219*
N25	-0.01±0.24 0.085+	0.03±0.49 0.084+	-0.03±0.81 0.873+	0.06±0.59 0.946*
N20	-0.05±0.24 0.071+	0.02±0.49 0.283+	0.02±0.70 0.692+	0.00±0.61 0.964*
N15	0.01±0.25 0.239+	-0.02±0.50 0.685+	0.13±0.73 0.298+	- 0.15±0.65 0.227*
N10	-0.03±0.23 0.218+	0.00±0.25 0.214+	0.10±0.43 0.181+	-0.10±0.50 0.419*
N5	0.01±0.20 0.678+	0.00±0.26 0.479+	0.05±0.34 0.091+	-0.06±0.44 0.855*
T5	0.01±0.12 0.653+	-0.03±0.22 0.812+	0.02±0.28 0.672+	- 0.04±0.35 0.399*
T10	0.00±0.11 0.484*	0.01±0.25 0.097+	0.00±0.33 0.918*	0.01±0.41 0.585*
T15	-0.01±0.14 0.699+	-0.06±0.23 0.768+	-0.09±0.33 0.144+	0.04±0.39 0.393*
T20	-0.03±0.15 0.500+	-0.07±0.24 0.649+	-0.08±0.48 0.306+	0.02±0.46 0.682*
T25	-0.04±0.19 0.290*	-0.11±0.30 0.574+	-0.15±0.39 0.091*	0.03±0.41 0.350*
T30	-0.09±0.24 0.110+	-0.09±0.30 0.850*	-0.21±0.39 0.037*	0.13±0.32 0.031*
T35	-0.11±0.28 0.075*	-0.16±0.35 0.251+	-0.17±0.52 0.253*	0.01±0.40 0.495*

3.5. Discussion

In this study it was evaluated the relative peripheral refractive error (RPRE) along the horizontal field between 35° nasal and 35° temporal, with dominant design MFCL of two near add powers (+2.00 and +3.00 D) in myopic eyes.

In a previous study we demonstrated that this multifocal design can induce significant peripheral myopic shift in emmetropic patients.[19] As expected, with increasing of add power (from +1.00 to +4.00 D) the myopization effect also increased in the peripheral visual field. However, there was not a linear relationship between the relative peripheral myopia induced and the add power such that there was no significant gain in fitting +1.00 lenses when compared with plano lenses made of the same material. There was also no significant improvement in the relative peripheral myopia induced by the +4.00 lens compared to the +3.00 lens. When it comes to choose a fitting add for myopes with the purpose of inducing significant peripheral myopia it is necessary to bear in mind this preliminary information. According to our previous results, a minimum add of +2.00 is necessary to induce significant effects in terms of peripheral myopization, while the +4.00 D add MFCL would not seem to add significant advantages. Higher near add powers increase significantly the effect of visual distortion due to the expected increase in positive spherical aberration.

From the present study, it seems that the results obtained in emmetropes are reproducible in myopic patients. Furthermore, there is a significant increase in the peripheral myopization effect with the +3.00 Add compared to the +2.00 Add of 1.00 D and 1.54 D in nasal and temporal more eccentric points, respectively (Table 3.2). These findings, eventually will allow customizing the treatment to each particular eye considering its baseline peripheral refractive pattern and the desired level of change, to more conveniently interfere with the mechanism of refractive error development.

Since the refractive error was corrected by the lenses, we should expect to obtain central measurements near plano and the refractive change symmetrically distributed to both sides of the central line of sight. However, we obtain an average refractive error along the central line of sight of −1.10 with the Add2 MFCL and −1.40 with the Add3 MFCL. In this study we have controlled the effect of centration and lag effect on lateral gaze. However, the infrared light that measures refractive status of eye in the open-view autorefractor used[27] is about 2.3 mm in diameter and therefore may have influenced the amount of refractive power. With a center distance area of the same size, small misalignment of the lens (<0.5 mm) will make the autorefractor to read a small part of the addition power, thus increasing the myopic value given for the central point. Although this might be considered a methodological limitation, in this particular study we are interested in analysing the refractive profile across the center and the periphery and then derive the RPRE change induced by the lenses. By using the same procedure (area sampled) to measure all points the aperture-dependant issue is balanced between all the measured points. Thus, we are confident that the profiles we obtain are still valid and representative of the ‘‘relative’’ refractive change along the 70° visual field in the horizontal direction. The small decentration effect might be also reflected on the slight asymmetry of 0.50 D between the nasal and temporal visual field RPRE for the Add3 lens.

The amount of RPRE change induced by each lens does not match the value of the add power placed by the manufacturer in the peripheral area of the optic zone. In this sample the change in RPRE was −0.87 D for the Add2 lens and −2.00 D for the Add3 lens. This is in agreement with our previous work in emmetropic eyes[19] and with the measures of Rosén et al. who found a RPRE change of −0.50 D at 30° using a different measuring technique.[20] Two reasons might explain this effect. The peripheral add power is formed by an aspheric zone. Thus, the maximum add might be beyond the 35° we measure in this study. Second, the actual power of the surface might change slightly when the hydrophilic lens is coupled with the corneal surface so that part of the power might be masked. In our previous study, the lens Add3 was preferred because it produced a greater effect of significant relative peripheral myopization in a wider range of peripheral eccentricities like in our previous clinical trial.[19] If MFCL design described in this trial eventually will apply for therapeutic purposes, there will be a necessity to expand central optical distance zone of the MFCL as a means of improving peripheral effect and quality of vision, once MFCL with high add and center distance design, as MFCL used, decreases the peripheral image quality at optimal defocus.[20]

In the present study we did not measure the peripheral refraction with plano contact lenses (non-multifocal design). However, considering the lack of significant changes in peripheral refractive profile observed with the +1.00 Add lens in our previous work with these lenses,[19] we did not expect to obtain a significantly different result between baseline and spherical plano lens in this population either. Kang et al.[25] found recently a significant difference between baseline and full correction of the refractive error with Proclear single vision contact lenses. They found a trend to measure higher hyperopic values at 20°, 30° and 40° of eccentricity with full correction in single vision contact lenses than at baseline. Although we do not have a control measure with plano lenses, the possibility of finding slightly higher hyperopic trends with single vision lenses will make our results to become even more relevant when it comes to the quantification of the peripheral myopization effect of the Add2 and Add3 lenses.

Other authors already conducted longitudinal studies evaluating axial growth and myopia progression in Chinese,[28] Japanese[29] and in American[30] children wearing orthokeratology lenses during 24 month. It is believed that the effect of retention of myopia progression is related with the peripheral myopization induced by orthokeratology.[13, 14] Despite the benefits of orthokeratology, the effect of peripheral myopization is so far limited to the amount of central myopia to be compensated[14] and also affect significantly the quality of vision due to increased aberrations.[31] More recently some authors[17] tried to produce peripheral myopization with newly designed spectacle lenses for myopia, the best lens from the three that were tested was optimized to achieve reduced astigmatism in the horizontal meridian while attaining a positive additional peripheral power of 1.9 D at 25 mm from the axis in that meridian. However, their results suggest that this approach was not able to reduce the rate of myopia progression, because in comparison with control group after 12 months, the lens showed a small and no statistical significant reduction of axial elongation. Spectacle lenses mounted in frames at certain vertex distance do not warrant are not likely to induce the therapeutic effect afforded by contact lenses. Compared to spectacle lenses, contact lenses have the advantage of following the eye in its vergence movements, thus allowing that the optical effect pretended with these optic solutions will be continuously centered with the optical system of the eye. Recently, Shen et al.[32] have observed that even non-multifocal, non-customized rigid gas permeable lenses might have a significant effect to induce relative peripheral myopic blur. However, this effect might be insufficient to play a significant role in retarding myopia progression as a clinical study conducted by Walline et al[33] came to show in 2004.

Within the contact lens field, custom-made contact lenses have also been developed to change purposely the relative peripheral refractive error patterns. Some lenses are intended to create a similar refractive effect to that induced in the dominant design multifocal contact lenses[34] evaluated here. Indeed, the optical performance of other designs in terms of relative peripheral refractive error changes have already been tested, demonstrating a significant effect to create relative peripheral myopization.[35] Peripheral gradient lenses[34] have shown to be effective in decrease myopia progression in myopic children.[18] Soft contact lenses visual correction was associated with more clarity of vision than orthokeratology,[36] what could be an additional benefit. However, it is expected that these multifocal lenses with small center distance apertures, induce significant visual distortions.

In summary, it is possible to modify the pattern of peripheral refraction in the periphery with the wear of Dominant Design Multifocal Contact Lenses, preferably with +3.00 D add power that has demonstrated to be more effective to produce the peripheral myopization effect.

3.6. References

1. Mutti DO, Sholtz RI, Friedman NE, Zadnik K. Peripheral Refraction and Ocular Shape in Children. *Invest Ophthalmol Vis Sci.* 2000;41:1022-1030.
2. Atchison DA, Jones CE, Schmid KL, et al. Eye Shape in Emmetropia and Myopia. *Invest Ophthalmol Vis Sci.* 2004;45:3380-3386.
3. Atchison DA, Pritchard N, Schmid KL, Scott DH, Jones CE, Pope JM. Shape of the Retinal Surface in Emmetropia and Myopia. *Invest Ophthalmol Vis Sci.* 2005;46:2698-2707.
4. Singh KD, Logan NS, Gilmartin B. Three-Dimensional Modeling of the Human Eye Based on Magnetic Resonance Imaging. *Invest Ophthalmol Vis Sci.* 2006;47:2272-2279.
5. Mallen EAH, Kashyap P. Technical Note: Measurement of retinal contour and supine axial length using the Zeiss IOLMaster. *Ophthalmic Physiol Opt.* 2007;27:404-411.
6. Atchison DA, Pritchard N, Schmid KL. Peripheral refraction along the horizontal and vertical visual fields in myopia. *Vision Res.* 2006;46:1450-1458.
7. Smith Iii EL, Hung L-F, Huang J. Relative peripheral hyperopic defocus alters central refractive development in infant monkeys. *Vision Res.* 2009;49:2386-2392.
8. Smith EL, 3rd, Ramamirtham R, Qiao-Grider Y, et al. Effects of foveal ablation on emmetropization and form-deprivation myopia. *Invest Ophthalmol Vis Sci.* 2007;48:3914-3922.
9. Smith IIIEL, Kee C-s, Ramamirtham R, Qiao-Grider Y, Hung L-F. Peripheral Vision Can Influence Eye Growth and Refractive Development in Infant Monkeys. *Invest Ophthalmol Vis Sci.* 2005;46:3965-3972.
10. Bakaraju RC, Ehrmann K, Ho A, Papas EB. Pantoscopic tilt in spectacle-corrected myopia and its effect on peripheral refraction. *Ophthalmic Physiol Opt.* 2008;28:538-549.
11. Tabernero J, Vazquez D, Seidemann A, Uttenweiler D, Schaeffel F. Effects of myopic spectacle correction and radial refractive gradient spectacles on peripheral refraction. *Vision Res.* 2009;49:2176-2186.
12. Lin Z, Martinez A, Chen X, et al. Peripheral Defocus with Single-Vision Spectacle Lenses in Myopic Children. *Optom Vis Sci.*2010;87:4-9.

13. Charman WN, Mountford J, Atchison DA, Markwell EL. Peripheral Refraction in Orthokeratology Patients. *Optom Vis Sci.*2006;83:641-648.

14. Queirós A, González-Méijome JM, Jorge J, Villa-Collar C, Gutiérrez AR. Peripheral Refraction in Myopic Patients After Orthokeratology. *Optom Vis Sci.* 2010;87:323-329.

15. Kang P, Swarbrick H. Peripheral Refraction in Myopic Children Wearing Orthokeratology and Gas-Permeable Lenses. *Optom Vis Sci..* 2011;88:476-482.

16. Ma L, Atchison DA, Charman WN. Off-axis refraction and aberrations following conventional laser in situ keratomileusis. *Journal of Cataract & Refractive Surgery.* 2005;31:489-498.

17. Sankaridurg P, Donovan L, Varnas S, et al. Spectacle Lenses Designed to Reduce Progression of Myopia: 12-Month Results. *Optom Vis Sci.* 2010;87:631-641.

18. Sankaridurg P, Holden B, Smith IIIE, et al. Decrease in Rate of Myopia Progression with a Contact Lens Designed to Reduce Relative Peripheral Hyperopia: One-Year Results. *Invest Ophthalmol Vis Sci.* 2011;52:9362-9367.

19. Lopes-Ferreira D, Ribeiro C, Maia R, et al. Peripheral myopization using a dominant design multifocal contact lens. *J Optom.* 2011;4:14-21.

20. Rosén R, Jaeken B, Lindskoog Petterson A, Artal P, Unsbo P, Lundström L. Evaluating the peripheral optical effect of multifocal contact lenses. *Ophthalmic Physiol Opt.* 2012;32:527-534.

21. Queirós A, Jorge J, González-Méijome JM. Influence of Fogging Lenses and Cycloplegia on Peripheral Refraction. *J Optom.* 2009;2:83-89.

22. Queiros A, Gonzalez-Meijome J, Jorge J. Influence of fogging lenses and cycloplegia on open-field automatic refraction. *Ophthalmic Physiol Opt.* 2008;28:387-392.

23. Radhakrishnan H, Charman WN. Peripheral refraction measurement: does it matter if one turns the eye or the head? *Ophthalmic Physiol Opt.* 2008;28:73-82.

24. Mathur A, Atchison DA, Kasthurirangan S, et al. The influence of oblique viewing on axial and peripheral refraction for emmetropes and myopes. *Ophthalmic Physiol Opt.* 2009;29:155-161.

25. Kang P, Fan Y, Oh K, Trac K, Zhang F, Swarbrick H. Effect of Single Vision Soft Contact Lenses on Peripheral Refraction. *Optom Vis Sci.*2012;89:1014-1021.

26. Thibos LN, Horner D. Power vector analysis of the optical outcome of refractive surgery. *Journal of cataract and refractive surgery.* 2001;27:80-85.

27. Fedtke C, Ehrmann K, Holden BA. A Review of Peripheral Refraction Techniques. *Optom Vis Sci.* 2009;86:429-446.

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

29. Kakita T, Hiraoka T, Oshika T. Influence of Overnight Orthokeratology on Axial Elongation in Childhood Myopia. *Invest Ophthalmol Vis Sci.* 2011;52:2170-2174.

30. Walline JJ, Jones LA, Sinnott LT. Corneal reshaping and myopia progression. *Br J Ophthalmol.* 2009;93:1181-1185.

31. Queirós A, Villa-Collar C, González-Méijome JM, Jorge J, Gutiérrez AR. Effect of Pupil Size on Corneal Aberrations Before and After Standard Laser In Situ Keratomileusis, Custom Laser In Situ Keratomileusis, and Corneal Refractive Therapy. *Am J Ophtalmol.* 2010;150:97-109.e101.

32. Shen J, Clark CA, Soni PS, Thibos LN. Peripheral Refraction with and without Contact Lens Correction. *Optom Vis Sci.* 2010;87:642-655.

33. Walline JJ, Jones LA, Mutti DO, Zadnik K. A randomized trial of the effects of rigid contact lenses on myopiaprogression. *Arch Ophtalmol.* 2004;122:1760-1766.

34. Holden BA, Ho A SP, Aller TA, EL. SI. Mean for controlling the progression of myopia 2007. Mean for controlling the progression of myopia. US Patent 0296916 A1. 2007.

35. Paune J, Lopes-Ferreira D, Queirós A, González-Méijome J. Performance of a new special GP lens design for myopia control to produce peripheral myopization. *Global specialty lens symposium*. Las Vegas2011.

36. Queirós A, Villa-Collar C, Gutiérrez AR, Jorge J, González-Méijome JM. Quality of Life of Myopic Subjects With Different Methods of Visual Correction Using the NEI RQL-42 Questionnaire. Eye Contact Lens. 2012;38:116-121.

CHAPTER 4

Peripheral Refraction with Eye and Head Rotation with Contact Lenses

4.1 Abstract

Purpose: To evaluate the impact of eye and head rotation in the measurement of peripheral refraction with an open-field autorefractometer in myopic eyes wearing two different center-distance designs of multifocal contact lenses (MFCLs).

Methods: Nineteen right eyes from 19 myopic patients (average central M ± SD = −2.67 ± 1.66 D) aged 20–27 years (mean ± SD = 23.2 ± 3.3 years) were evaluated using a Grand-Seiko autorefractometer. Patients were fitted with one multifocal aspheric center-distance contact lens (Biofinity Multifocal D®) and with one multi-concentric MFCL (Acuvue Oasys for Presbyopia). Axial and peripheral refraction were evaluated by eye rotation and by head rotation under naked eye condition and with each MFCL fitted randomly and in independent sessions.

Results: For the naked eye, refractive pattern (M, J0 and J45) across the central 60° of the horizontal visual field values did not show significant changes measured by rotating the eye or rotating the head ($p>0.05$). Similar results were obtained wearing the Biofinity D, for both testing methods, no obtaining significant differences to M, J0 and J45 values ($p>0.05$). For Acuvue Oasys for presbyopia, also no differences were found when comparing measurements obtained by eye and head rotation ($p>0.05$). Multivariate analysis did not showed a significant interaction between testing method and lens type neither with measuring locations (MANOVA, $p>0.05$). There were significant differences in M and J0 values between naked eyes and each MFCL.

Conclusion: Measurements of peripheral refraction by rotating the eye or rotating the head in myopic patients wearing dominant design or multi-concentric multifocal silicone hydrogel contact lens are comparable.

Key words: Peripheral refraction; Myopia; Multifocal contact lens; Eye rotation; Head rotation

4.2. Introduction

Peripheral refraction has been studied extensively since it was suggested that it might play a role in the refractive development ofthe eye, particularly, in myopia progression.[1, 2] Researchers have observed that the peripheral refraction was relatively more hyperopic in myopic eyes than in emmetropic eyes along the horizontal visual field.[3] There are also differences in the peripheral refraction and retinal contour between progressing and stable myopes.[4] A previous animal study reported that peripheral hyperopic defocus (behind the retina) could induce central myopic development.[5]

Myopia correction with conventional spectacles may increase relative peripheral hyperopic defocus,[6, 7] especially in high degrees of myopia and at larger eccentricities of the visual field.[8] Considering the evidence that orthokeratology slows myopia progression[9-14] and that this treatment induces a substantial change in the peripheral refractive error[15] of the myopic eye toward high degrees of peripheral myopic defocus and astigmatism, a link has been suggested between relative peripheral hyperopic defocus and myopia progression in humans.[9-11] Some ophthalmic lenses[7] and contact lenses[16] have been designed specifically to arrest myopia progression based on this hypothetical mechanism. The main goal of the commercially available center-distance design multifocal contact lenses (MFCLs) is to compensate for presbyopia. However, considering the similar change in the peripheral refractive pattern induced by these lenses,[17-19] it has been hypothesized that such designs can be useful to slow myopia progression.[20] Bifocal contact lenses for presbyopia have previously been used to slow myopia progression.[21, 22] Recently, a dual-focus contact lens has been proved to be effective in reducing myopia progression by up to 34% in children over a 10 month period.[23] Kollbaum et al. recently evaluated the quality of vision of center-distance design and bifocal contact lenses for presbyopia and compared them to dual-focus lenses to determine the potential use of such lenses to control myopia.[24] Although not all of these devices are intended to induce peripheral myopic defocus, it might be of interest to evaluate the potential contribution of this factor with each lens design. However, when evaluating the potential of different multifocal devices for changing the peripheral myopic refractive pattern with contact lenses on the eye, ocular and head rotation might be a concern. Seidemann et al.[25] hypothesized that pressure exerted by the extraocular muscles and the eyelids on eye rotation might distort the shape of the eyeball and alter refraction across the visual field. However, Radhakrishnan and Charman reported that for the naked eye this might not be relevant.[26] This might be potentially different with a contact lens in place considering the effect of decentration during peripheral gaze. However, this effect remains controversial, and several authors have preferred to measure the peripheral refraction by rotating the head,[16, 27, 28] while others performed such measurements with eye rotation.[29, 30] The current study was conducted to evaluate the effect of ocular and head rotation on the peripheral refraction measurements obtained with an open-field autorefractor in myopic eyes using two different center-distance designs of MFCLs comprising an aspheric multifocal design and a concentric multifocal design.

4.3. Methods

The experiments were conducted at the Clinical and Experimental Optometry Research Lab (CEORLab, Minho University, Braga, Portugal). All participants were fully informed about the purposeand procedures of this study and provided written consent. The study followed the tenets of the Declaration of Helsinki; the Scientific Committee of the School of Sciences of Minho University (Portugal) approved the research protocol. Nineteen healthy young subjects were recruited from a university population. Inclusion criteria required that patients had 20/20 monocular visual acuity, myopia lower than –8.00 diopters (D), astigmatism lower than –1.00 D as measured by subjective refraction, no ocular disease or injury, no history of refractive surgery, and no use of ocular or systemic medication.

4.3.1. MFCLs

The right eyes of the participants were fitted randomly in independent sessions with two MFCLs that included a distance vision zone with their foveal refractive correction. The Biofinity® Multifocal D (Comfilcon A, Coopervision, Pleasanton, CA, USA) is a new multifocal contact lens with an optical design and fitting procedure similar to those of the Proclear Multifocal D (OmafilconA, Coopervision, Pleasanton, CA, USA). The Biofinity D lens has an aspheric center-distance multifocal design with more positive power in the outer zone of the lens. The optical design consists of aspherical central zone of 2.3 mm in diameter dedicated to distance vision, surrounded by an annular aspheric zone of 5.0 mm (1.35 mm width) of increasing addition power and a spherical annular zone of 8.5 mm (1.50 mm width) reaching the maximum add power. The second lens, the Acuvue® Oasys for Presbyopia (Senofilcon A, Johnson & Johnson, Jacksonville, FL, USA), has a multi-concentric design with center-distance area of about 2.0 mm followed by multiple alternating near and distance concentric zones (between 0.5 and1.0 mm width) from the center to the end of the optical zone at 8.0 mm. The maximal add power in both

MFCLs was +2.50 D to guarantee that equivalent add powers were available in both lenses, and the add power was closer to the one that yielded the best peripheral myopic defocus effect with the Proclear D lens in our previous study.[19] After a previous fitting session during which the optimum centration (less than 0.5 mm of lateral displacement against the limbal area) and movement (lag < 0.5 mm on lateral and upgaze) were assessed.

4.3.2. Central and Peripheral Refraction

The non-cycloplegic objective refraction was obtained in the right eye using an open-field autorefractor/keratometer Grand-Seiko WAM-5500 (Grand Seiko Co., Ltd., Hiroshima, Japan) previously used to measure the central and peripheral refractions.[31, 32] The illumination in the examination room was adjusted to obtain sufficiently large pupils to facilitate peripheral measurements. The central and peripheral non-cycloplegic refractions were evaluated for the naked eye and with both MFCLs. The left eyewas always occluded during measurements. Head and eye rotation measurements were performed randomly during the same session 5 min apart from each other. The peripheral refraction was obtained using an array of light-emitting diodes (LEDs) with a diameter of 5 mm located at 2.5 m along the horizontal visual field at eccentricities between 30° nasally and 30° temporally, in 10° steps. For the eye rotation measurements, the patient was instructed to fixate on the LEDs as previously described.[26, 33] For the head rotation measurements, we used a previously reported method,[26, 28] during which a laser pointer positioned on top of the patient's head was oriented toward the primary gaze position. Room light was kept at low intensity (about 20 cd/m^2, low photopic level) in order to avoid pupil miosis. Under these conditions, the pupil size was large enough to allow measures to be obtained through the elliptical pupil when the eye or head rotated. The patient rotated his or her head, avoiding lateral displacement, until the pointer reached the desired eccentric LED while the eyes remained in the primary gaze position. Individual data were transposed into vector components according to Fourier analysis.[34, 35] Five refractive measurements were performed and averaged after transposition into the vector components (M, J0 and J45) for each eccentricity. The refractive data were saved automatically in Microsoft Excel spreadsheets using custom software (DRRE,CEORLab).

4.3.3. Statistical Analysis

The data were analyzed using SPSS for Windows, version 20 (SPSS Inc., New York, USA). The Shapiro–Wilk test was applied to evaluate the normality of the data distribution. Relative peripheral refractive error was obtained by subtracting the central refractive error to the refractive component (M, J0 or J45) at each eccentric location (10, 20, 30° nasal or temporal). The behaviors between the relative peripheral refractive patterns between ocular and head rotation were evaluated for each condition (naked eye, Acuvue Oasys lens for presbyopia, and Biofinity Multifocal D lens). The effect of factors such as measurement location (eccentricities), lens type (naked eye, Acuvue Oasys lens for presbyopia, or Biofinity D lens), and testing method (eye or head rotation) on the mean values of the dependent variables (M, J0, and J45) were evaluated using multivariate analysis of variance (MANOVA). When MANOVA detected the statistically significant effects ($p < 0.05$) of a certain factor, we performed an individual ANOVA for each dependent variable, followed by the Bonferroni post hoc test. A *p* value lower than 0.05 was considered statistically significant.

4.4. Results

We evaluated right eyes of 19 young students (13 women, 6men) (mean age ± standard deviation [SD], 23.2 ± 3.3 years), mean central refractive error (M ± SD) of −2.67 ± 1.66 D. Fig. 4.1A–C shows the average relative peripheral (eccentric values minus central value) values of M, J0, and J45 obtained by testing methods evaluated (eye and head rotation) in naked eyes. The M component showed greater differences at 30° nasally (−0.12 ± 0.30 D; $p < 0.001$) and 30° temporally (0.19 ± 0.59 D; $p = 0.002$), but neither achieved statistical significance.

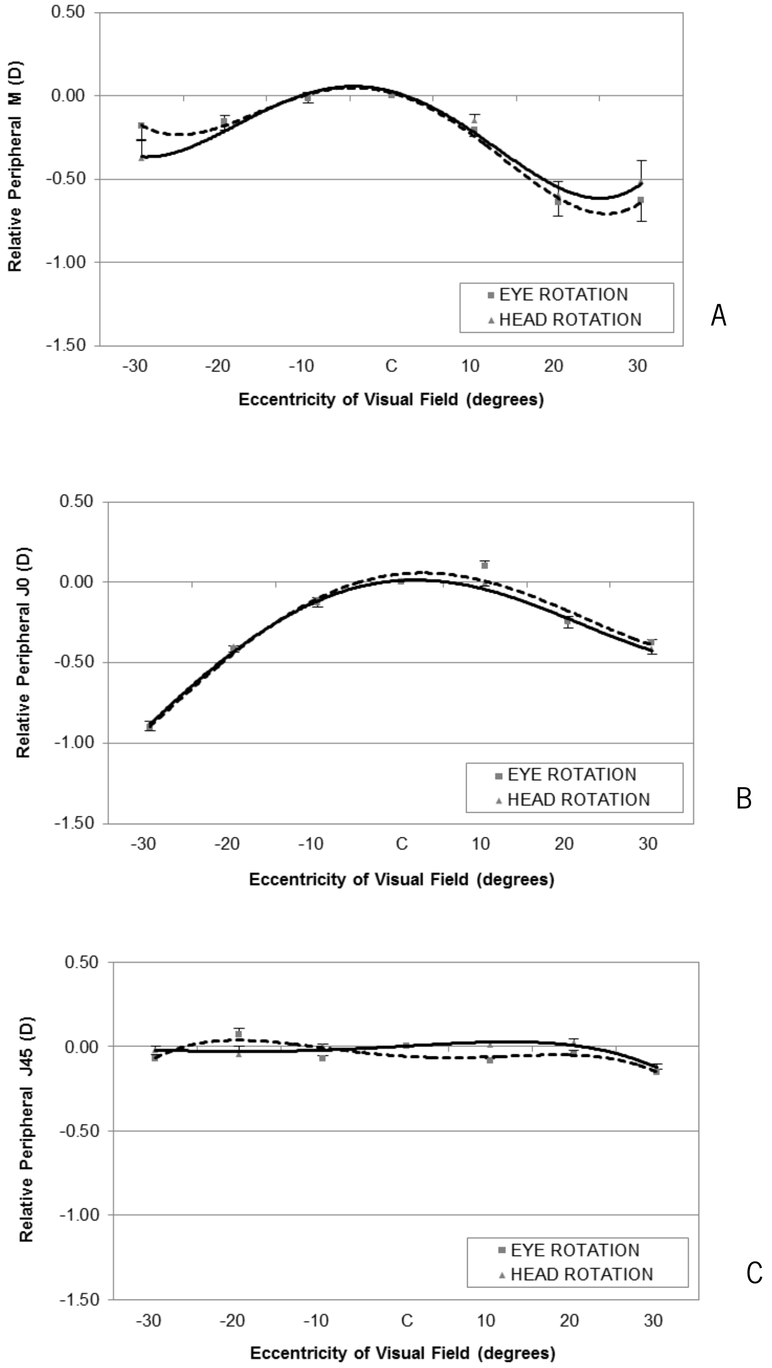


Figure 4.1. *Relative peripheral refractive error measured in naked eyes (eccentric location minus center) by eye rotation (squares, dashed line) and head rotation (triangles, solid line). (A) Spherical equivalent values (M); (B) horizontal component of astigmatism (J0) and (C) oblique component of astigmatism (J45) across the central 60° of the horizontal visual field (nasal visual field eccentricities as positive). The error bars represent the standard error of the mean.*

Fig. 4.2A–C shows the comparison of the peripheral refractive errors between testing methods in eye fitted with the Acuvue Oasys lens for presbyopia. The values obtained by rotating the eye were slightly more myopic than those obtained with head rotation but neither statistically difference were found to M values (p = 0.761).

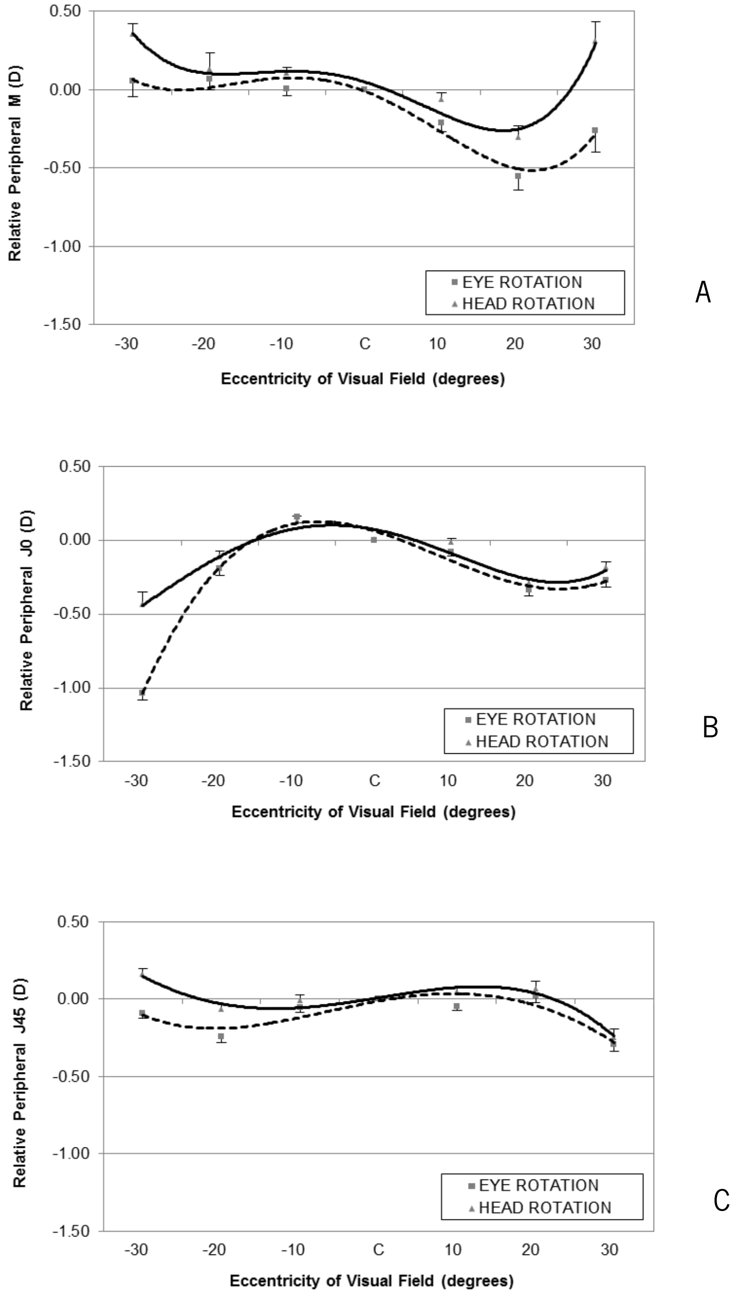


Figure 4.2. *Relative peripheral refractive errors measured with Acuvue Oasys for presbyopia (eccentric location minus center) by rotating the eye (squares, dashed line) and rotating the head (triangles, solid line). (A) Spherical equivalent values (M); (B) horizontal component of astigmatism (J0) and (C) oblique component of astigmatism (J45) across the central 60° of the horizontal visual field (nasal visual field eccentricities as positive). The error bars represent the standard error of the mean.*

Similar results were found with the J0 and J45 component; measuring by eye rotation the values manifested more myopia for all eccentricities, however differences did not reach to the statistical significance ($p = 0.050$ and $p = 0.479$, respectively).

Finally, the peripheral refractive changes induced by the Biofinity Multifocal D lens are shown in Fig. 4.3A–C. The relative peripheral M values were similar between the two testing methods used, no statistically differences were found ($p = 0.345$). The J0 component was more myopic at the more eccentric temporal points (20 and 30°) measured by head rotation, and the J45 component showed lower hyperopic values by eye rotation method. However, differences between head and eye rotation were not statistically significant for both astigmatic components ($p= 0.777$ and $p= 0.255$, respectively).

No significant interactions were found between the testing method and location or between the testing method and lens type for M, J0, and J45 ($p> 0.05$ in all comparisons by MANOVA analysis). Significant interaction was observed between location and lens type ($p<0.001$, MANOVA analysis). Between subjects effects also showed that this interaction was significant for all dependent variables M, J0, and J45 ($p<0.005$ for all comparisons). After adjusting for multiple comparisons analysis followed by ANOVA analysis and Bonferroni post hoc test, the results indicated that peripheral relative M was significantly different between naked eyes and the same eyes fitted with each MFCL; the differences were were significant for all point-to-point comparisons between the naked eye and the Acuvue Oasys lens for presbyopia ($p<0.001$, ANOVA with the Bonferroni post hoc test) and the naked eye and the Biofinity D Multifocal lens, being less myopic with the naked eyes; statistically less myopic in all points in case of first comparison and except for 20 and 30° temporally for the second ($p = 0.092$ and $p = 0.840$ respectively). However, in the comparisons of the two MFCLs studied, the M values did not differ significantly ($p = 0.969$). Peripheral relative J0 values also differed significantly between the naked eyes and the MFCLs ($p < 0.001$), and between the lens Acuvue Oasys for presbyopia and the Biofinity D ($p<0.001$). In contrast, J45 did not show significant differences between naked eyes and the MFCL conditions or between the MFCLs ($p = 0.076$).

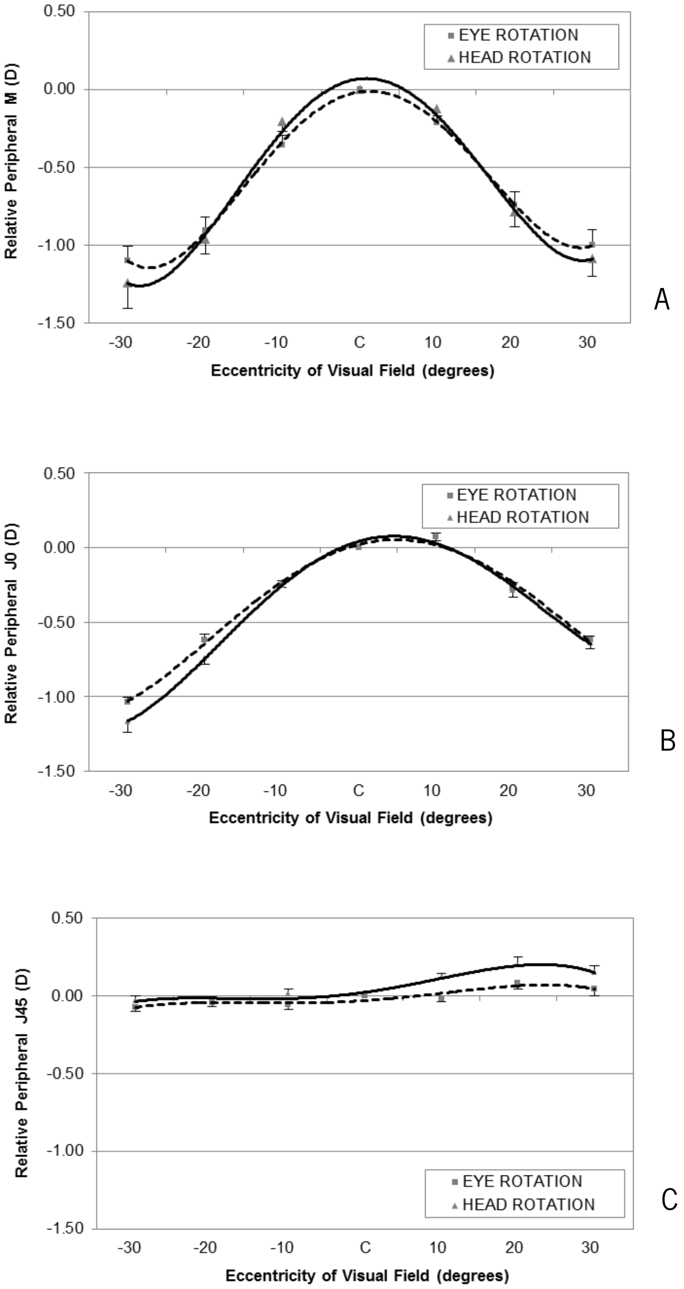


Figure 4.3. *Relative peripheral refractive errors measured with Biofinity Multifocal D design (eccentric location minus center) by rotating the eye (squares, dashed line) and rotating the head (triangles, solid line). (A) Spherical equivalent values (M); (B) horizontal component of astigmatism (J0) and (C) oblique component of astigmatism (J45) across the central 60° of the horizontal visual field (nasal visual field eccentricities as positive). The error bars represent the standard error of the mean.*

4.5. Discussion

The current study aimed to investigate if peripheral refraction (PR) measurements using an open-field autorefractor were different between head rotation and eye rotation in myopic eyes while they were without lenses or wearing 2 different brands of MFCLs. Comparisons between the eye rotation and head rotation methods in the assessment of peripheral refraction[26] and ocular shape[36] have already been performed but only for naked eyes. According to the current results and independent of the method that was performed, the peripheral refractive pattern was similar in the naked eye as Radhakrishnan and Charman[26] previously described using an autorefractor and by Mathur et al.[33] using an aberrometer. Considering the interest in the effectiveness of optical devices, such as MFCLs, to produce relative peripheral myopic defocus orto modulate the accommodative effort of the eye, it is relevant to understand if reliable results can be obtained when measuring peripheral refraction in eyes wearing a soft contact lens. Ocular rotation may induce contact lens displacement by mechanical interaction with the eyelids. Thus, some authors have used the head rotation method in experiments in which patients were fitted with a contact lens.[27, 28] However, recently Kang et al.[30] measured the peripheral refraction with a contact lens by rotation of the eyeto evaluate the effect of under-correction, full-correction, and over-correction in the peripheral refraction of young subjects. Ticak and Walline also measured the peripheral refraction with Proclear Multifocal D Soft Contact Lenses by rotating the eye.[29] The current results supported this approach, in that we did not find significant differences in M, J0, or J45 obtained by rotating the eye or the head. This might be supported by the small movement of modern soft contact lenses on the average eye. Young et al.[37] previously estimated the lag of soft contact lenses on up gaze and versions to be about 1–1.5 (on a scale of 0–4), which represents between 0.5 and 0.75 mm, respectively. However, these values can be lower when considering modern silicone hydrogel CL because these lenses previously were fitted tighter than older low-Dk lenses and therefore moved less. Indeed, more recently Wolffsohn et al.[38] used video recordings to observe that the version lags of soft contact lenses might be an average of about 0.5 mm. The Acuvue Oasys lens for presbyopia showed higher variability than the Biofinity D lens, which might be explained by the aspheric nature of the Biofinity D lens with smooth transition of power and the multiconcentric nature of the Acuvue Oasys lens for presbyopia with abrupt changes in power. In other words, while 0.5mm displacement in an aspheric lens might have less of an impact on the outcomes of peripheral refraction reading, this impact might be higher for lenses with rapid and/or alternating changes of power. The lens design differences also might explain the lack of changes in refraction across the eccentricities of the visual field compared with the center with the Acuvue Oasys lens for presbyopia. The diameter of the measurement area with the Grand-Seiko autorefractor/keratometer is larger than the size of the individual concentricrings of approximate uniform power. As a result, each single measurement might include information from two adjacent portions of the lens and produce an aliasing effect. Thus, the absence of changes in the peripheral refractive pattern across the visual field with the Acuvue Oasys lens for presbyopia might not be discarded, but also cannot be measured with this methodology. As recently suggested, the center-distance design MFCL (Proclear D lens) can induce peripheral myopic defocus[17, 18] and the same behavior was verified in this work using two different measuring methods to determine peripheral refraction with an open-field autorefractor and aberrometer. The differences between values obtained by ocular and head rotation did not manifest significant difference both statistically and clinically. The analysis with MANOVA considered all factors that could influence refrac-tion obtained across the horizontal visual field. But as many factors were put together in same test and under same statistical analysis this could minimize the importance/significance of the differences and for this reason some substantial differences that could be seen in the charts did not archieve statistical significance. However, regarding research and particularly if we attempt to compare the outcomes of different lens designs and fitting strategies, the influence of each measuring method on peripheral refraction should be considered carefully. Measuring method by head rotation was performed in previous studies using contact lenses[27, 28] to limit potential translocation of the contact lenses associated with large eye turn. However, considering the current data, refraction measured with eye rotation may provide results which are comparable with head rotation in eyes fitted with a MFCL. Ticak and Walline[29] did not obtain peripheral myopic defocus in patients wearing Proclear D lenses, which is very unlikely considering the previous research. A limitation of our results is that we represent the amount of change that is being induced. However this does not consider the actual position of the peripheral foci regarding the retina. Such information would be essential in clinical trials where the potential effect of peripheral defocus might be relevant to interpret the outcomes in terms of myopia progression. But the purpose of our study is to evaluate the change induced by the lenses as measured with either method (eye rotation and head rotation). The authors argued that lens movement on eye rotation might be responsible for this. In our previous studies[17, 19] and in a study of Rosén et al.[18] a significant change toward higher peripheral myopic defocus was found with the Proclear D lens. In the current work, the Biofinity D lens showed a trend toward induction of peripheral myopic defocus of about −1.00 D at 30° of eccentricity. The fact that Ticak and Walline did not find similar results, but rather an opposite trend with peripheral relative hyperopia, might be explained by a different dynamic behavior of the lens on peripheral eye versions in their population or by differences in the methodology used to control ocular fixation. Same amount of myopic shift may have beeninduced in the current study as by Ticak and Walline,[29] but if baseline data is not the same, this could be a possible explication for different effect of these MFCL at relative PR in present work. By this reason we considered important represent present results as relative peripheral refractive error to can visualize the real shift of refractive error at each peripheral location respectively to baseline. However, our results do not support this hypothesis as our results for a lens with a similar optical design was not different rotating the head where potential lens displacement on lateral versions is not present. However, their measures showed large standard deviation on the peripheral measurements which suggests a heterogeneous behavior of the lens centration or the effect of the +2.00 add indifferent subjects; both factors could justify their results against the expected according to present study and previous research mentioned above. Additional justifications might be found on the different polymers used in Proclear D (Omafilcon A) and BiofinityD (Comfilcon A) with different modulus and different potential fit-ting behavior. Furthermore, in their study, Ticak and Walline used a +2.00 Add while we used a +2.50. The current study cannot ensure that the same results could be obtained if applied to other lens material of different modulus, front and back surface designs, or even for lenses with the same design and material using different add powers. Non-cycloplegic evaluation of axial and peripheral refractive errors might eventually be considered a limitation of the current study once refractive error could vary with accommodative demand. However, we guaranteed at least a distance of 2.5 m between the corneal apex and the fixation targets, which might minimize the effects of accommodation on our refractive error measurements. Another limitation must be considered: we only measured refraction along the horizontal visual field, which means that other future works has needed to evaluate the refractive pattern at vertical visual field. In summary, we did not find differences in peripheral refraction measurements between eye rotation and head rotation methods using the Grand-Seiko autorefractor/keratometer in eyes wearing two different MFCLs. The differences did not reach any statistical or clinical significance. The Grand-Seiko autorefractor seems to not be sufficiently sensitive to detect the changes between distance and near power areas with the Acuvue Oasys lens for presbyopia. Despite the fact that we could not detect a relative peripheral myopic defocus generated by the near vision zones across the horizontal visual field relatively to the center, we cannot eliminate the possibility that this lens changes the pattern of the peripheral refractive error.

4.6. Acknowledgements

The authors thank the companies that donated the contact lenses used in the study. The authors declare that they do not have any proprietary or financial interests in any of the materials mentioned in this article. This work was funded in part by FEDER through the COMPETE Program and by the Portuguese Foundation for Science and Technology (FCT) in the framework of projects PTDC/SAU-BEB/098391/2008, PTDC/SAU-BEB/098392/2008 and the Strategic Project PEST-C/FIS/UI607/2011. This study has been presented at American Academy of Optometry, Seattle 2013 October 24th to 27th.

4.7. References

1. Charman NW, Radhakrishnan H. Peripheral refraction and the development of refractive error: a review. *Ophthalmic Physiol Opt.* 2010;30:321-338.
2. Wallman J, Winawer J. Homeostasis of Eye Growth and the Question of Myopia. *Neuron.* 2004;43:447-468.
3. Atchison DA, Pritchard N, Schmid KL. Peripheral refraction along the horizontal and vertical visual fields in myopia. *Vision Res.* 2006;46:1450-1458.
4. Faria-Ribeiro M, Queirós A, Lopes-Ferreira D, Jorge J, González-Méijome JM. Peripheral Refraction and Retinal Contour in Stable and Progressive Myopia. *Optom Vis Sci..* 2013;90:9-15.
5. Smith IIIEL, Hung L-F, Huang J. Relative peripheral hyperopic defocus alters central refractive development in infant monkeys. *Vision Res.* 2009;49:2386-2392.
6. Bakaraju RC, Ehrmann K, Ho A, Papas EB. Pantoscopic tilt in spectacle-corrected myopia and its effect on peripheral refraction. *Ophthalmic Physiol Opt.* 2008;28:538-549.
7. Tabernero J, Vazquez D, Seidemann A, Uttenweiler D, Schaeffel F. Effects of myopic spectacle correction and radial refractive gradient spectacles on peripheral refraction. *Vision Res.* 2009;49:2176-2186.
8. Lin Z, Martinez A, Chen X, et al. Peripheral Defocus with Single-Vision Spectacle Lenses in Myopic Children. *Optom Vis Sci..* 2010;87:4-9.
9. Cho P, Cheung SW, Edwards M. The longitudinal orthokeratology research in children (LORIC) in Hong Kong: a pilot study on refractive changes and myopic control. *Current eye research.* 2005;30:71-80.
10. Hiraoka T, Kakita T, Okamoto F, Takahashi H, Oshika T. Long-Term Effect of Overnight Orthokeratology on Axial Length Elongation in Childhood Myopia: A 5-Year Follow-Up StudyLong-Term Effect of Orthokeratology on Axial Length. *Invest Ophthalmol Vis Sci.* 2012;53:3913-3919.
11. Walline JJ, Jones LA, Sinnott LT. Corneal reshaping and myopia progression. *Br J Ophthalmol* 2009;93:1181-1185.
12. Santodomingo-Rubido J, Villa-Collar C, Gilmartin B, Gutiérrez-Ortega R. Myopia Control with Orthokeratology Contact Lenses in Spain: Refractive and Biometric Changes

Orthokeratology in Myopia Progression Control. *Invest Ophthalmol Vis Sci.* 2012;53:5060-5065.

13. Cho P, Cheung S-W. Retardation of Myopia in Orthokeratology (ROMIO) Study: A 2-Year Randomized Clinical TrialRetardation of Myopia in Orthokeratology Study. *Invest Ophthalmol Vis Sci.* 2012;53:7077-7085.

14. Kakita T, Hiraoka T, Oshika T. Influence of Overnight Orthokeratology on Axial Elongation in Childhood Myopia. *Invest Ophthalmol Vis Sci.* 2011;52:2170-2174.

15. Queirós A, González-Méijome JM, Jorge J, Villa-Collar C, Gutiérrez AR. Peripheral Refraction in Myopic Patients After Orthokeratology. *Optom Vis Sci.* 2010;87:323-329.

16. Sankaridurg P, Holden B, Smith IIIE, et al. Decrease in Rate of Myopia Progression with a Contact Lens Designed to Reduce Relative Peripheral Hyperopia: One-Year Results. *Invest Ophthalmol Vis Sci.* 2011;52:9362-9367.

17. Lopes-Ferreira D, Ribeiro C, Maia R, et al. Peripheral myopization using a dominant design multifocal contact lens. *J Optom.* 2011;4:14-21.

18. Rosén R, Jaeken B, Lindskoog Petterson A, Artal P, Unsbo P, Lundström L. Evaluating the peripheral optical effect of multifocal contact lenses. *Ophthalmic Physiol Opt.* 2012;32:527-534.

19. Lopes-Ferreira D, Ribeiro C, Neves H, et al. Peripheral refraction with dominant design multifocal contact lenses in young myopes. *J Optom.* 2013;6:85-94.

20. Walline J, McVey L. Myopia control with a soft bifocal contact lens in myopia: Proceedings of the 13th International Conference. *Optom Vis Sci.* 2010;88:395–403.

21. Aller TA, Wildsoet C. Bifocal soft contact lenses as a possible myopia control treatment: a case report involving identical twins. *Clin Exp Optom.* 2008;91:394-399.

22. Aller T, Wildsoet C. Results of a one-year prospective clinical trial (CONTROL) of the use of bifocal soft contact lenses to control myopia progression. *Ophthalmic Physiol Opt.* 2006;26:8–9.

23. Anstice NS, Phillips JR. Effect of Dual-Focus Soft Contact Lens Wear on Axial Myopia Progression in Children. *Ophthalmology.* 2011;118:1152-1161.

24. Kollbaum PS, Jansen ME, Rickert ME. Comparison of patient-reported visual outcome methods to quantify the perceptual effects of defocus. *Cont Lens Anterior Eye.* 35:213-221.

25. Seidemann A, Schaeffel F, Guirao A, Lopez-Gil N, Artal P. Peripheral refractive errors in myopic, emmetropic, and hyperopic young subjects. *J Opt Soc Am A Opt Image Sci Vis.* 2002;19:2363-2373.

26. Radhakrishnan H, Charman WN. Peripheral refraction measurement: does it matter if one turns the eye or the head? *Ophthalmic Physiol Opt.* 2008;28:73-82.

27. Shen J, Clark CA, Soni PS, Thibos LN. Peripheral Refraction with and without Contact Lens Correction. *Optom Vis Sci.* 2010;87:642-655.

28. Kwok E, Patel B, Backhouse S, Phillips JR. Peripheral Refraction in High Myopia with Spherical Soft Contact Lenses. *Optom Vis Sci.* 2012;89:263-270.

29. Ticak A, Walline JJ. Peripheral Optics with Bifocal Soft and Corneal Reshaping Contact Lenses. *Optom Vis Sci.* 2013;90:3-8.

30. Kang P, Fan Y, Oh K, Trac K, Zhang F, Swarbrick H. Effect of Single Vision Soft Contact Lenses on Peripheral Refraction. *Optom Vis Sci.* 2012;89:1014-1021.

31. Queirós A, Jorge J, González-Méijome JM. Influence of Fogging Lenses and Cycloplegia on Peripheral Refraction. *J Optom.* 2009;2:83-89.

32. Queiros A, Gonzalez-Meijome J, Jorge J. Influence of fogging lenses and cycloplegia on open-field automatic refraction. *Ophthalmic Physiol Opt.* 2008;28:387-392.

33. Mathur A, Atchison DA, Kasthurirangan S, et al. The influence of oblique viewing on axial and peripheral refraction for emmetropes and myopes. *Ophthalmic Physiol Opt.* 2009;29:155-161.

34. Harris WF. Dioptric power: its nature and its representation in three- and four-dimensional space. *Optom Vis Sci.* 1997;74:349-366.

35. Thibos LN, Horner D. Power vector analysis of the optical outcome of refractive surgery. *J Cataract Refract Surg.* 2001;27:80-85.

36. Macfadden LA, Gray LS, Strang NC, Seidel D. Peripheral retinal shape measurements, using the IOLMaster, in myopia and hyperopia. *Ophthalmic Physiol Opt.* 2008;28:101-101.

37. Young G, Holden B, Cooke G. Influence of soft contact lens design on clinical performance. *Optom Vis Sci.* 1993;70:394-403.

38. Wolffsohn JS, Hunt OA, Basra AK. Simplified recording of soft contact lens fit. *Cont Lens Anterior Eye.2008;* 32:37-42.

CHAPTER 5

Relative Peripheral Refraction across 4 Meridians after Orthokeratology and LASIK Surgery

5.1. Abstract

Purpose: To characterize the axial and off-axis refraction across the horizontal, vertical and 2 oblique meridians of the retina in myopic eyes before and after Orthokeratology (OK) and LASIK surgery.

Methods: Sixty right eyes of 60 myopic patients underwent LASIK (n=26), or OK (n=34) to treat myopia with a spherical equivalent (M) between –0.75 to –5.25D. Horizontal meridian up to 35° of eccentricity in the nasal and temporal retinal area, vertical meridian up to 15° of eccentricity in the superior and inferior retina; and 2 oblique directions (45-225° and 135-315°) up to 20° of eccentricity in 5° steps using an open-field autorefractometer before and at least 3 months after treatments. Results were presented as relative peripheral refractive error (RPRE).

Results: OK and LASIK post-treatment results showed an increase of myopic relative refraction at several eccentric locations. RPRE post treatment for M component within the 30° of central visual field after LASIK, and 20° after OK at the 4 meridians evaluated was not statistically different from RPRE pretreatment values ($p>0.05$) demonstrating that the treatment zone warrants a central optimally corrected field of vision.

Conclusions: Present study give an overview of RPRE after refractive corneal reshaping treatments (OK and LASIK) across vertical, horizontal and 2 oblique meridians together allowing a 3D representation of RPRE at retina and showing that myopic shift induced by both treatments is more relevant at horizontal direction.

Keywords: LASIK surgery; orthokeratology, peripheral refraction; myopia progression.

5.2. Introduction

The scientific knowledge on the development of the human eye has evolved dramatically during the last decades from the embryologic, physiological and functional viewpoints, from the ocular surface to the neural pathway and visual cortex. Myopia is a public health concern affecting about 70% of the general population in East Asia and about 30% in the America or Europe.[1-4] On the last decade several risk factors and protector factors have been identified.[5,6]

Current knowledge suggests that the pattern of peripheral refraction could be involved in the progression of the refractive error. Although the biological process behind this behavior is not fully understood, the results of Smith et al. showed in animal models that the optical defocus in the peripheral retina is able to regulate the ocular growth and the emmetropization process.[7] According to their results, hyperopic peripheral defocus stimulates ocular growth while myopic peripheral defocus could prevent ocular growth and reduce myopia progression.

Some optical treatments can change the peripheral defocus and refractive profile in myopic eyes, from relative peripheral hyperopia to a relative peripheral myopia.[8,9] The myopic changes in the relative peripheral refractive error (RPRE) after orthokeratology (OK) have been well documented along the horizontal visual field by Queirós et al[9] and Mathur et al[10] also evaluated the peripheral ocular aberrations after the treatment. OK treatment induces an increase of corneal thickness at periphery of treatment/central area increasing the optical power in this zone, which results in a paracentral myopization effect.[11] This changes in corneal surface induced by OK has been pointed as the mechanism to slow down axial eye growth associated to this treatment in case reports[12] and also in controlled clinical trials in Hong Kong, Japan, USA and Spain,[13-16] thought a cause-effect relationship is still lacking.

Furthermore, clinical studies have also proved that the peripheral refractive profile along the horizontal meridian could also play a role in the onset and progression of myopia in children, with the pre-myopic eyes showing hyperopic or less myopic peripheral refractive patterns.[17]

Over the last two decades, corneal refractive surgery has emerged as an attractive corrective option to people with low-to-moderate refractive errors, particularly in myopic patients. Laser-Assisted in Situ Keratomileusis (LASIK) has allowed millions of people worldwide to reduce or to over their dependence on spectacles or contact lenses.

Although LASIK is not applied with the purpose of myopia regulation, as orthokeratology, but is expected to move towards a customization of the transition between the central treatment and the peripheral cornea similarly to LASIK treatment in order to reduce the induced optical aberrations. It is important to evaluate the behavior of the optics of the eye between both treatments. Queirós et al[18] using the auto-refraction technique studied the changes in peripheral refraction of a same clinical population before and after LASIK surgery. The characterization of peripheral refraction after LASIK surgery has previously been addressed by a work of Ma et al,[19] where the authors showed that myopic refractive surgery procedures alter the pattern of peripheral focusing towards a more myopic profile beyond the central 20° of eccentricity. Additionally, other studies evaluated the impact of the treatment changes in peripheral anterior corneal topography after myopic LASIK, and the impact of corneal first surface aberration after LASIK surgery, with the increase of pupil diameter.[20] More recently, Mathur and Atchison[21] also evaluated the peripheral aberrations after LASIK surgery.

Our goal in present study was to measure the changes in relative peripheral refractive pattern across the horizontal, vertical and oblique meridians of subjects before and after have undergone LASIK surgery and OK treatment. To our knowledge this is the first study evaluating the relative peripheral refraction in OK and LASIK patients across different orientations of the visual field.

5.3. Methods

5.3.1. Subjects and Inclusion Criteria

This is a prospective study in which patients undergoing LASIK surgery or Orthokeratology to correct low-to-moderate myopia were evaluated before and at 3 months after treatment.

The inclusion criteria required that the subjects did not suffer from any current eye disease or injury and were not taking any ocular or systemic medication. No patient had any history of ocular disease or had undergone previous ocular surgery. Refractive error must have been stable within the last two years to be considered for surgery. A complete optometric and ophthalmological examination was performed before surgery or adaptation of OK lenses. All patients had satisfactory results after treatments (surgery or OK) with respect to residual refractive error, visual acuity, regularity and centering of the treatment zone. The study was approved by the School of Science (University of Minho, Braga, Portugal) and followed the tenets of the Declaration of Helsinki.

The study was approved by the School of Science (University of Minho, Braga, Portugal) and followed the tenets of the Declaration of Helsinki. Measurements were obtained from twentysix eyes of 26 subjects undergoing LASIK using non-customized corneal ablations at the ophthalmological clinic Novovision, (Madrid, Spain) and thirty-four right eyes of 34 university students that were adapted with OK contact lenses to treat myopia between −0.75 and −5.25D (M). After the nature of the study was explained, each patient signed a consent form before enrollment.

Subjective non-cycloplegic refraction was performed monocularly. The criterion of maximum plus for best visual acuity was used to arrive to the end point of refraction. The intraocular pressure was checked with a non-contact tonometer before and after treatment (Nidek Model NT-4000, non-contact tonometer).[22]

5.3.2. Central and Off-Axis Refraction

The measurement of central and off-axis refraction was obtained with the open-field Grand Seiko Auto-Refractometer/Keratometer WAM-5500 (Grand Seiko Co., Ltd., Hiroshima, Japan). This instrument has been previously used and validated to measure refraction in the central[23] and peripheral visual field.24 While the process has been previously described by the authors, it is presented here again as the present protocol involves additional orientations in addition to the horizontal visual field usually considered. The system was attached to custom software developed to automatically record data from the autorefractometer thus avoiding errors in data collection and allowing rapid acquisition to be processed in an Excel spreadsheet for later statistical analysis.

The illumination of the room was adjusted to obtain a pupil size greater than 4mm required to allow off-axis measurements with the Grand Seiko, which was achieved in all cases. The fixation target was placed at a distance of 2.5 meters from the corneal vertex (0.50D accommodative demand) and consisted of 37 LEDs: horizontal meridian up to 35° of eccentricity in the nasal and temporal retinal area (15 LEDs in the horizontal direction: one central, seven to the right and seven to the left side, the LEDs were separated from each other by an angular distance of 5° at the patient's position), vertical meridian up to 15° of eccentricity in the superior and inferior retina (5° steeps) and oblique directions (45-225° and 135-315°) up to 20° of eccentricity in 5° steps. Results are presented as relative peripheral refractive error (RPRE). Five readings were taken and averaged only on the right eye of each individual in all positions. The subject was seated with the head stabilized in a chin-rest so that the eye was aligned with the central LED. For the right eye (the left eye was occluded), the fixation of an object positioned on the right side of the central point (nasal visual field in the eye primary position in horizontal direction) matches the temporal retina measures. Patients kept their head stationary during the preceding, only rotating their right eyes to view LED targets that were illuminated one by one. Five readings were averaged for each position. The axis of the autorefractor was aligned with the center of the entrance pupil during all measurements.

Descriptive statistics (mean±SD) were obtained for the refraction vector components, $M = Sph + Cyl/2$, $J0 = -Cyl \cdot \cos(2\Theta)/2$ and $J45 = -Cyl \cdot \sin(2\Theta)/2$, according to Fourier analysis, as recommended by Thibos,[25] where Sph, Cyl and Θ are the manifest sphere, cylinder and axis, respectively.

5.3.3. Orthokerathology: Lens Characteristics

Paragon CRT™ (paflufocon D, Dk=100 barrer) sigmoid reverse geometry rigid gas permeable lenses were used (Paragon Vision Sciences, Mesa, AZ, USA). Trial lenses were derived from sliding table nomograms provided by the manufacturer and which have shown high levels of predictability in terms of first trial success.[26] The fitting was evaluated according to the recommendations of the manufacturer regarding fluorescein pattern, topographical evaluation, refractive and visual outcomes.

A minimum treatment period of one month was required to guarantee that the treatment was completely stable.[27] The time between pre and post treatment measures was 37.0±3.0 days. During that period, lenses were worn overnight for 7.82±1.02 hours. After the first night of treatment where the patients attended the clinic wearing their lenses, they were asked to insert the lenses ten minutes before sleep along with a drop of artificial tear. The patients removed the lenses within ten minutes after waking-up in the following morning after applying again a drop of artificial tear solution. The measurements were performed between 9:00 and 11:00 A.M. and at least 2 hours after lens removal, to minimize the influence of treatment regression[28] and diurnal variations in corneal thickness that might influence anterior corneal topography.[29;30]

5.3.4. LASIK Procedure

In all cases the ablation was central, with an optic zone of 6.5 mm for all LASIK treatments. Surgical routine for LASIK surgery was held according to international standards, and the commonly accepted criteria for refractive surgery procedures were observed regarding predictability, efficacy and safety. After creating a 120 µm, 9.5 mm diameter flap with a

Hansatome microkeratome (Chiron Vision, model 2765; Bausch & Lomb, Claremont, California, USA), Standard LASIK (Munnerlyn based)[31] ablation profiles were produced using the Allegretto Wave Eye-Q - 400 Hz (Wavelight, Erlangen, Germany). All surgical procedures were uneventful and successful. A minimum of 3 months after treatment was required to guarantee that the topography was completely stable.[32]

5.3.5. Statistical analysis

The SPSS software package v.19 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Shapiro-Wilk Test was applied in order to evaluate the normality of the data distribution. When normality could not be assumed, the Wilcoxon Signed Ranks Test was used for paired comparison between baseline and post-treatment values; reversely Paired Samples t-test was used in cases that normality could be assumed. P values lower than 0.05 were considered statistically significant. Changes in relative peripheral refraction across vertical, horizontal and 2 oblique meridians (3D) were evaluated for statistical significance after both treatments and the locations across the visual field showing statistically significant changes were identified.

5.4. Results

5.4.1. Orthokeratology

Measurements in the OK group were made on thirty-four right eyes of 34 university students with a mean age of 25.2±3.7 years (ranging from 20 to 41), of which 13 were female (38.2%) and 21 were male (61.8%). Average pretreatment spherical equivalent was -1.95±1.27D ranging from -0.88 to -5.25D. The time between pre and post-treatment measures was 37.0±3.0 days.

A 3D representation of the relative peripheral refraction in the OK group (as M) is shown in Figure 5.1. Analyzing pretreatment condition in Figure 5.1A it is observed that the refractive pattern manifests little variation comparing peripheral locations and central location (Central M: -1.99±1.07D), being the greater difference of -0.82D at 15°superior retinal location (vertical meridian).

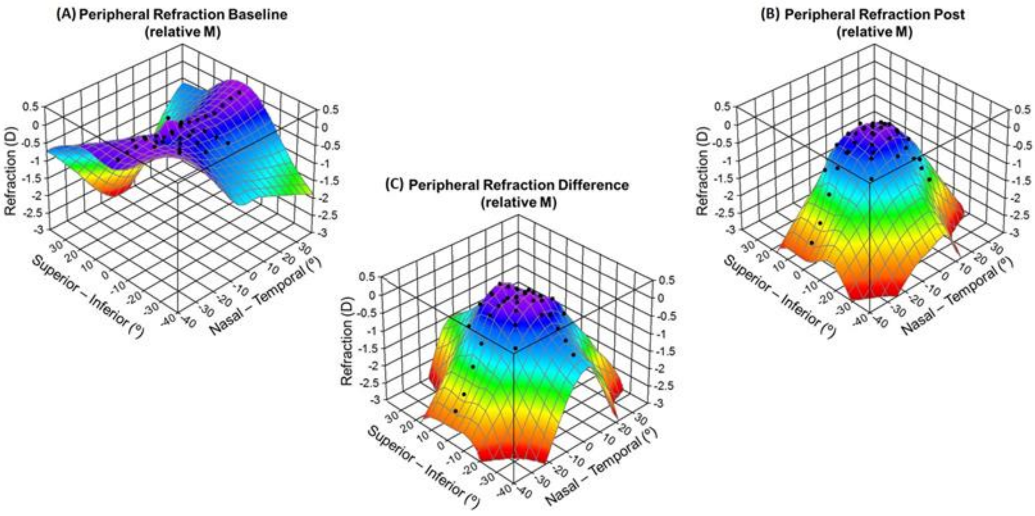


Figure 5.1. Three-dimensional representation of axial and peripheral RPRE (relative M) across horizontal (70° central in 5° steps), vertical (30 central in 5° steps) and 2 oblique (40° central in 5° steps) meridians in myopic healthy eyes before (A) and after (B) OK treatment and respective differences (C).

Post-treatment results however showed an increase of myopic relative refraction at several eccentric locations as shown in Figure 5.1B. M differences between pre vs post-treatment were represented schematically in Figure 5.1C. As could be seen at Figure 5.3A there were statistically significant differences ($p<0.001$, grey) vertically only at location of 15° superior. Across horizontal meridian significant differences could be observed above 20°N (including) and above 15°T (including). Obliquely there were differences at more eccentric location of 20° at all meridians and also at 15° at temporal side. Greater M differences obtained at horizontal meridian: -2.30±1.79 (35° nasal) and -2.54±1.32 (35° temporal), at central 30 degrees locations differences were very reduced and without statistical relevance (differences inferior to 0.46D – Figure 5.3A). J0 and J45 differences could be seen at Figure 5.3 (B and C, respectively).

5.4.2. LASIK

The right eyes of 26 subjects with mean age of 30.4±4.8 years (ranging from 20 to 37 years) were included in the LASIK group of which 11 were female (42.3%) and 15 were male (57.7%). Average preoperative spherical equivalent was -2.12±0.92D ranging from -0.75 to -3.88D. The time between surgery and post-surgery measures was 124.3±12.8 days.

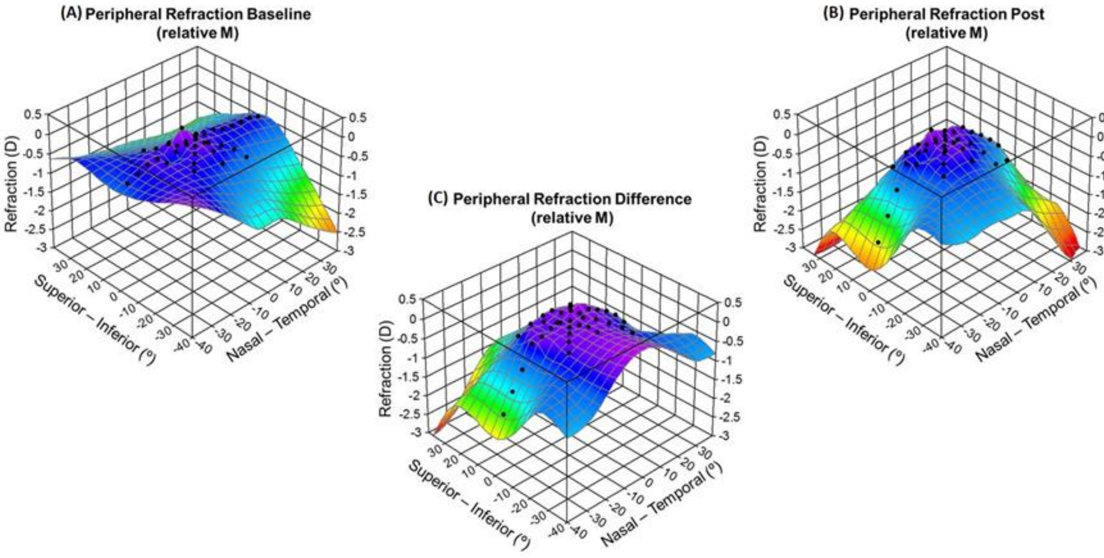


Figure 5.2. Three-dimensional representation of axial and peripheral RPRE (relative M) across horizontal (70° central in 5° steps), vertical (30 central in 5° steps) and 2 oblique (40° central in 5° steps) meridians in myopic healthy eyes before (A) and after (B) LASIK surgery and respective differences (C).

A 3D representation of the RPRE in the LASIK group is presented in Figure 5.2 Analyzing pretreatment condition in Figure 5.2A, the refractive pattern show little variation comparing peripheral locations with central location (Central M=-2.12±0.92D), being the greater difference of -0.64D at 20° oblique meridian retinal superior/temporal. Post-LASIK treatment results manifest an increase of myopic relative refraction at eccentric locations as observed in Figure 5.2B.

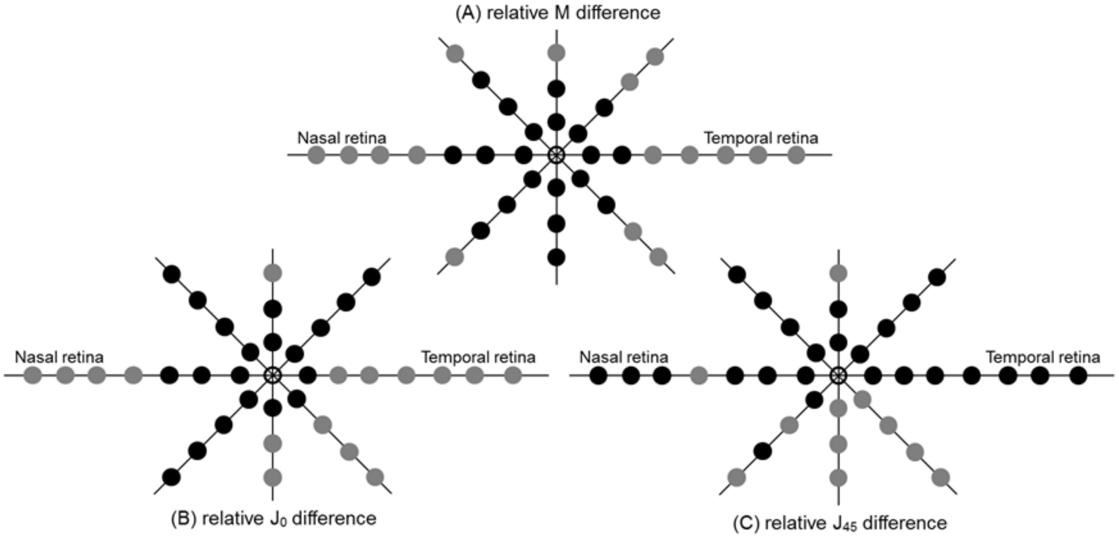


Figure 5.3. Schematic representation of statistical significance at retinal eccentric locations. No existence of differences between pre and post OK treatment RPRE related to M (A), J0 (B) and J45(C) were represented as black spots in respective evaluated locations.

There were no differences between values of RPRE (M) comparing before and after LASIK surgery over the central 30 degrees across horizontal meridian and also at point 20 degrees nasal, as seen at Figure 5.2C. Statistically significant differences were found in the vertical orientation at 20° superior point (diff=-0.24±0.29, p=0.001). Across oblique meridians we found statistically significant differences in the M component in the superior hemi-field (retina superior temporal/ superior nasal). Greater M differences obtained at horizontal retina were of -1.52±1.06 and -1.17±0.97 at 35° nasal and temporal respectively; remaining differences were inferior to 1D being inferior to 0.25D at central 40°. J0 values as M does not revealed differences at central 30° (horizontal meridian) excepting point of 10° nasal (diff=-0.12±0.26, p<0.01). Remaining vertical and oblique meridians significance differences for J0 and J45 values could be seen in detail at Figure 5.4B and 5.4C respectively.

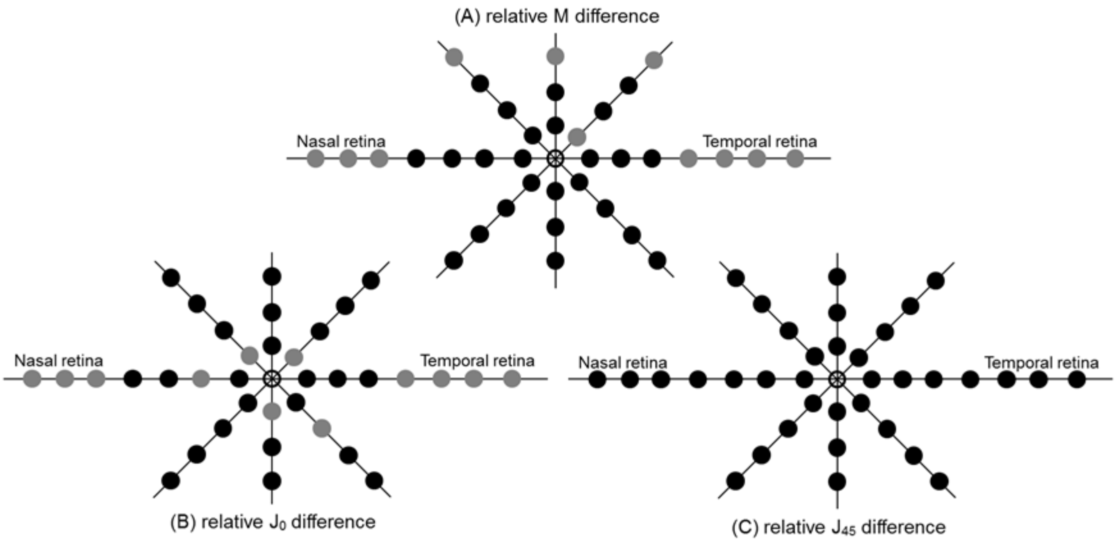


Figure 5.4. Schematic representation of statistical significance at retinal eccentric locations. No existence of differences between pre and post LASIK surgery RPRE related to M (A), J0 (B) and J45(C) were represented as black spots in respective evaluated locations.

5.5. Discussion

This study shows that the pattern of peripheral refraction changes significantly after LASIK surgery across the entire visual field. This change in peripheral focusing of the post-surgical eye is statistically significant beyond the central 35° of the central visual field in the orthokeratology group. This behavior has been well described in the literature in the form of spherical aberration induced by central ablations for myopic treatments as measured with wavefront sensors.[20,33,34] However, no previous studies have addressed the clinical measurement of the peripheral refraction before and after LASIK treatments and in so extended eccentricities, excepting our previous work, evaluating pre and post only in horizontal direction.[18] Despite these outcomes has proved negative in terms of optical quality of the eye, there is a rationale to think that it could be beneficial preventing myopia progression. Previous results from Ma et al.19 showed that myopic LASIK procedures can alter the pattern of peripheral refraction towards a more myopic profile beyond the central 20° of eccentricity (about 40° of the central visual field). Ma's pioneering work[19] showed that myopic LASIK surgery renders similar results to those observed more recently with orthokeratology in terms of change in peripheral refractive profile refraction and it is believed that this effect contributes to a certain extent to the reduction of myopia progression.[8,9,35] A similar effect could also see in patients that were fitted with dominant design multifocal contact lenses, that induce a relative peripheral myopia,[36,37] and this could also be related with the recently demonstrated myopia retention.[35]

Present results show that LASIK induces a change in the relative peripheral refractive error such that the peripheral visual field will be myopic after the procedure, while the central visual field within the optic zone created by the laser will become emmetropic. Present results also show that relative peripheral myopization occurs at all meridians studied nevertheless the more notorious effect could be seen at horizontal visual field direction because is where more eccentric locations are evaluated. This correlates well with previous results reported in terms of central and peripheral (horizontal) corneal curvature after refractive surgery.[11]

While orthokeratology treatment results in a more relative myopic peripheral refraction, LASIK manifests the same tendency of peripheral myopic shift, however the value of relative peripheral refractive error was more reduced at more peripheral locations across all directions9 (Figure 5.1C and 5.2C). Previously were demonstrated in orthokeratology,[9] and also in LASIK patients that the change towards peripheral relative myopization is strongly correlated with baseline myopia.[18,38] Although the average baseline myopia in LASIK group was slightly higher than in OK group, peripheral relative myopia after LASIK was lower than in the orthokeratology group. These results are consistent with previous findings reporting lower levels of steepening of the front corneal surface at the edge of the treatment zone after LASIK compared to orthokeratology.[11] The tissue redistribution in orthokeratology, as opposed to the ablation of central tissue in LASIK, is the main reason for the greater increase in paracentral corneal power observed with orthokeratology.[11] Additionally, larger optical zone and smoother transition area contributes to lower relative peripheral myopia after LASIK as it has been previously shown by Queirós et al.[18]

It is known the controversy around the application of refractive surgery in children.[39,40] The implantation of intraocular lens in cases of congenital cataract is fully accepted by the clinical and scientific community to perform in children, the same is not true to refractive corneal surgery with cosmetic purposes. Several studies reported the therapeutic applications of radial keratotomy in teenagers,[41] and laser-assisted procedures in high bilateral myopia[42,43] as well as myopic and hyperopic anisometropia[44,45] in order to prevent refractive and anisometropic amblyopia, respectively.

Considering LASIK potential to prevent myopia progression, numerous reports could show refractive error stability after LASIK surgery. Present results, might be argued that the profile of refractive focalization after the procedure might be involved. Nevertheless, previous studies as present have been carried out in adult patients and this could be pointed as main limitation to understand such a potential in progression, considering that myopia expected stable in adults.

Mathur et al, already studied the optical quality after both: CRT[10] and LASIK[21,46] observed an increase of high order aberration at peripheral locations after both treatments, measurements were across the 42° × 32° central visual field, however in samples of 3 and 6 subjects, respectively. Also Ehsaei et al[47] studied refractive error across four meridians, in healthy myopic subjects and emmetropes, obtaining to the overall eccentricities studied comparable results with eccentricity-dependent profile also shown by Shen et al[48] in 2010. Majority of previous reports about refractive profile pre and post refractive treatments as addressed in this study only reported results from horizontal meridian[18,38] or horizontal x vertical.[10,21,35] Autorefractometers were used in most of works10,[11,18,38] but COAS[10,21] and other wavefront sensors are also introduced in these kind of evaluation, considering good correlation between autorefractometers and Hartmann-Shack aberrometer values already proved.[49] More recently a new device was introduced, capable to measure measurements from -50 to +50 degrees in 10 degree steps in less than half a second.[50] This new device allow measures refractive error and also ocular aberrations along horizontal, vertical, and five oblique (i.e.,15, 30, 45, 60, and 75 degrees) visual field meridians, to distance and to near distance. Moreover, the preliminary results were presented to a sample of 26 healthy myopic eyes, along only horizontal visual field under unaccommodated and accommodated eye status. Results indicated that there is refraction relatively hyperopic in the periphery for distance that changed to being relatively myopic at accommodative demand of 5.00 D.

Present study represents an overview of RPRE after refractive corneal reshaping treatments (OK and LASIK) across vertical, horizontal and 2 oblique meridians using a commercially available open-field autorefractor. The technique used seams rudimental comparing with other automatic and faster methods;[50] however the complete comparison between treatments and in overall directions reveals that as we could observe at literature differences will be more pronounced at horizontal direction. If incorporated in future myopia progression studies, this methodology could bring new information to the role of focalization at different retinal areas in myopia progression.

Future studies are needed in order to characterize more completely tridimensional refractive error and also peripheral aberrations. Recent developments in eccentric autorefractometers and aberrometers, faster and more accurate promise a better understand of mechanisms that could be involved in myopia onset and progression. A complete knowledge of overall RPRE across eccentric visual field gives important information to plan customization of treatments as OK and LASIK and also to build and designing new optics of multifocal soft contact lenses in order to further myopia retention in children.

5.6. References

1. Jorge J, Almeida JB, Parafita MA. Refractive, biometric and topographic changes among Portuguese university science students: a 3-year longitudinal study. *Ophthalmic Physiol Opt* 2007;27:287-294.

2. Saw SM, Katz J, Schein OD, Chew SJ, Chan TK. Epidemiology of myopia. *Epidemiol Rev* 1996;18:175-187.

3. Morgan I, Rose K. How genetic is school myopia*? Prog Retin Eye Res* 2005;24:1-38.

4. Vitale S, Sperduto RD, Ferris FL, III. Increased prevalence of myopia in the United States between 1971-1972 and 1999-2004. *Arch Ophthalmol* 2009;127:1632-1639.

5. Mehdizadeh M, Nowroozzadeh MH. Outdoor activity and myopia. *Ophthalmology* 2009;116:1229-1230.

6. Rose KA, Morgan IG, Ip J et al. Outdoor activity reduces the prevalence of myopia in children. *Ophthalmology* 2008;115:1279-1285.

7. Smith EL, III, Kee CS, Ramamirtham R, Qiao-Grider Y, Hung LF. Peripheral vision can influence eye growth and refractive development in infant monkeys. *Invest Ophthalmol Vis Sci 2005*;46:3965-3972.

8. Charman WN, Mountford J, Atchison DA, Markwell EL. Peripheral refraction in orthokeratology patients. *Optom Vis Sci* 2006;83:641-648.

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

10. Mathur A, Atchison DA. Effect of orthokeratology on peripheral aberrations of the eye. *Optom Vis Sci* 2009;86:476-484.

11. Queiros A, Gonzalez-Meijome JM, Villa-Collar C, Gutierrez AR, Jorge J. Local steepening in peripheral corneal curvature after corneal refractive therapy and LASIK. *Optom Vis Sci* 2010;87:432-439.

12. Cheung SW, Cho P, Fan D. Asymmetrical increase in axial length in the two eyes of a monocular orthokeratology patient. *Optom Vis Sci* 2004; 81:653-656.

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

14. Walline JJ, Jones LA, Sinnott LT. Corneal reshaping and myopia progression. *Br J Ophthalmol* 2009; 93:1181-1185.

15. Santodomingo-Rubido J, Villa-Collar C, Gilmartin B, Gutierrez AR. Myopia control with Orthokeratology contact lenses in Spain (Mcos): Design, Baseline Findings and 18 month refractive & Biometric Data. *Optom Vis Sci* 2010; 88:1-44.

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

17. Mutti DO, Hayes JR, Mitchell GL et al. Refractive error, axial length, and relative peripheral refractive error before and after the onset of myopia. *Invest Ophthalmol Vis Sci* 2007;48:2510-2519.

18. Queiros A, Villa-Collar C, Jorge J, Gutierrez AR, Gonzalez-Meijome JM. Peripheral refraction in myopic eyes after LASIK surgery. *Optom Vis Sci* 2012; 89:977-983.

19. Ma L, Atchison DA, Charman WN. Off-axis refraction and aberrations following conventional laser in situ keratomileusis. *J Cataract Refract Surg* 2005;31:489-498.

20. Queiros A, Villa-Collar C, Gonzalez-Meijome JM, Jorge J, Gutierrez AR. Effect of pupil size on corneal aberrations before and after standard laser in situ keratomileusis, custom laser in situ keratomileusis, and corneal refractive therapy. *Am J Ophthalmol* 2010;150: 97-109.

21. Mathur A, Atchison DA. Influence of spherical intraocular lens implantation and conventional laser in situ keratomileusis on peripheral ocular aberrations. *J Cataract Refract Surg* 2010;36:1127-1134.

22. Queiros A, Gonzalez-Meijome JM, Fernandes P, Jorge J, Almeida JB, Parafita MA. Non-contact tonometry synchronized with cardiac rhythm and its relationship with blood pressure. *Ophthalmic Physiol Opt* 2006;26:384-391.

23 Queiros A, Gonzalez-Meijome J, Jorge J. Influence of fogging lenses and cycloplegia on open-field automatic refraction. *Ophthalmic Physiol Opt* 2008;28:387-392.

24. Queiros A, Jorge J, Gonzalez-Meijome JM. Influence of fogging lenses and cycloplegia on peripheral refraction. *J Optom* 2009; 2:83-89.

25. Thibos LN, Wheeler W, Horner D. Power vectors: an application of Fourier analysis to the description and statistical analysis of refractive error. *Optom Vis Sci* 1997;74:367-375.

26. Gonzalez-Meijome JM, Villa-Collar C. Nomogram, corneal topography, and final prescription relations for Corneal Refractive Therapy. *Optom Vis Sci* 2007;84:59-64.

27. Lu F, Simpson T, Sorbara L, Fonn D. The relationship between the treatment zone diameter and visual, optical and subjective performance in Corneal Refractive Therapy lens wearers. *Ophthalmic Physiol Opt* 2007;27:568-578.

28. Villa-Collar C, Gonzalez-Meijome JM, Queiros A, Jorge J. Short-term corneal response to corneal refractive therapy for different refractive targets. *Cornea* 2009;28:311-316.

29. Handa T, Mukuno K, Niida T, Uozato H, Tanaka S, Shimizu K. Diurnal variation of human corneal curvature in young adults. *J Refract Surg* 2002;18:58-62.

30. Du TR, Vega JA, Fonn D, Simpson T. Diurnal variation of corneal sensitivity and thickness. *Cornea* 2003;22:205-209.

31. Munnerlyn CR, Koons SJ, Marshall J. Photorefractive keratectomy: a technique for laser refractive surgery. *J Cataract Refract Surg* 1988;14:46-52.

32. Holladay JT, Dudeja DR, Chang J. Functional vision and corneal changes after laser in situ keratomileusis determined by contrast sensitivity, glare testing, and corneal topography. *J Cataract Refract Surg* 1999;25:663-669.

33. Anera RG, Villa C, Jimenez JR, Gutierrez R. Effect of LASIK and contact lens corneal refractive therapy on higher order aberrations and contrast sensitivity function. *J Refract Surg* 2009;25:277-284.

34. Kohnen T, Mahmoud K, Buhren J. Comparison of corneal higher-order aberrations induced by myopic and hyperopic LASIK. *Ophthalmology* 2005;112:1692.

35. Ticak A, Walline JJ. Peripheral optics with bifocal soft and corneal reshaping contact lenses. *Optom Vis Sci* 2013;90:3-8.

36. Lopes-Ferreira D, Ribeiro C, Maia R et al. Peripheral myopization using a dominant design multifocal contact lens. *J Optom* 2011;4:14-21.

37. Lopes-Ferreira D, Ribeiro C, Neves H et al. Peripheral refraction with dominant design multifocal contact lenses in young myopes. *J Optom* 2013;6:85-94.

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

39. Fecarotta CM, Kim M, Wasserman BN. Refractive surgery in children. *Curr Opin Ophthalmol* 2010;21:350-355.

40. Daoud YJ, Hutchinson A, Wallace DK, Song J, Kim T. Refractive surgery in children: treatment options, outcomes, and controversies. *Am J Ophthalmol* 2009;147:573-582.

41. O'Dell LW, Wyzinski P. Radial keratotomy in teenagers. I. A practical approach*. Refract Corneal Surg* 1989;5:315-318.

42. Tychsen L, Hoekel J. Refractive surgery for high bilateral myopia in children with neurobehavioral disorders: 2. Laser-assisted subepithelial keratectomy (LASEK). *J AAPOS* 2006;10:364-370.

43. Astle WF, Huang PT, Ingram AD, Farran RP. Laser-assisted subepithelial keratectomy in children. *J Cataract Refract Surg* 2004;30:2529-2535.

44. Astle WF, Rahmat J, Ingram AD, Huang PT. Laser-assisted subepithelial keratectomy for anisometropic amblyopia in children: outcomes at 1 year. *J Cataract Refract Surg* 2007;33:2028-2034.

45. Yin ZQ, Wang H, Yu T, Ren Q, Chen L. Facilitation of amblyopia management by laser in situ keratomileusis in high anisometropic hyperopic and myopic children. *J AAPOS* 2007;11:571-576.

46. Moreno-Barriuso E, Lloves JM, Marcos S, Navarro R, Llorente L, Barbero S. Ocular aberrations before and after myopic corneal refractive surgery: LASIK-induced changes measured with laser ray tracing. *Invest Ophthalmol Vis Sci* 2001;42:1396-1403.

47. Ehsaei A, Mallen EA, Chisholm CM, Pacey IE. Cross-sectional sample of peripheral refraction in four meridians in myopes and emmetropes. *Invest Ophthalmol Vis Sci* 2011;52:7574-7585.

48. Shen J, Clark CA, Soni PS, Thibos LN. Peripheral refraction with and without contact lens correction. *Optom Vis Sci* 2010;87:642-655.

49. Atchison DA. Comparison of peripheral refractions determined by different instruments. *Optom Vis Sci* 2003;80:655-660.

50. Fedtke C, Ehrmann K, Falk D, Bakaraju RC, Holden BA. The BHVI-EyeMapper: peripheral refraction and aberration profiles. *Optom Vis Sci* 2014;91:1199-1207.

CHAPTER 6

Astigmatic Peripheral Defocus with Different Contact Lenses: Review and Metaanalysis

6.1. Abstract

Purpose: To review the level of relative peripheral defocus measured with different devices with potential use for myopia retention. To present comparative data of the change in astigmatic peripheral refraction with different contact lenses evaluated in different studies conducted in the same laboratory following the same methodology in myopic human eyes

Methods: A joint analysis of work, carried out at the same laboratory (CEORLab) in 137 myopic subjects with different types of contact lenses (CL), was performed to obtain the tangential (FT = M − J0), sagittal (FS = M + J0), and mean (M) power refractive errors (M and J0 are the refraction vector components). Orthokeratology, standard aspheric rigid gas-permeable (RGP), experimental RGP, experimental soft CL, and different multifocal soft CL were used to induce peripheral myopic defocus (236 peripheral refraction measures).

Results: Compared with values obtained in naked eye condition (baseline), only three of the eight approaches tested show statistically significant peripheral myopic defocus induction ($p < 0.001$) in both temporal and nasal retina (orthokeratology, experimental RGP, and Proclear multifocal CL with Add: +3.00 D). Standard aspheric RGP also produced a significant increase in myopic defocus for the FT, of about −2.00 D. The experimental soft CL, designed to mimic the peripheral performance of the experimental RGP, induced a similar effect to the standard aspheric CL.

Conclusion: Orthokeratology, multifocal soft CL, and custom-designed RGP CL were able to generate a significant relative peripheral myopia in myopic eyes. Conversely, standard and experimental soft CL were not able to induce significant peripheral myopic and astigmatic defocus values.

Keywords: Astigmatism; myopia progression; peripheral defocus; peripheral refraction

6.2. Introduction

Peripheral refraction has been widely studied since it was suggested that it might play a role in the refractive development of the eye, more specifically in myopia progression.[1, 2] Previous animal studies reported that peripheral hyperopic defocus (light focused “behind” the retina) seems to act as a stimulus for central myopic development.[3] It has been observed that peripheral refraction is relatively more hyperopic in myopic eyes than in emmetropic along the horizontal visual field.[4] There is also evidence of differences in peripheral refraction between Asian and Caucasian eyes[5] and between progressing and stable myopes.[6]

However, there is controversy over the potential benefit of manipulating peripheral defocus to interfere with the emmetropization mechanism of the eye. This is because the relative peripheral hyperopia appears to exert little consistent influence on the risk of the onset of myopic refractive error, on the rate of myopia progression, or on axial elongation in children,[7] as observed in other clinical studies.[8, 9] While a previous report had assigned a supplementary risk of onset of myopia to adult subjects who manifested hyperopic peripheral refraction,[10] others suggested that hyperopic blur is a risk factor for myopia progression only when the eye has a negative spherical aberration, because that is the combination leading to relatively low contrast in the defocused retinal image.[11] Despite this it is not well understood how the eye distinguishes signs of defocus. A potential explanation could be the use of the relative position of both astigmatic focal surfaces (sagittal and tangential), as previously suggested by Howland and further elaborated upon by Charman.[12] According to this theory, Howard Holland has suggested that the retinal circuitry involving cells sensitive to different orientations might be involved in detecting the relative position of the tangential and sagittal image planes. The peripheral retina is less likely to be involved in defocus sensitivity due to its lack of resolution. However, it is argued that it might be much more sensitive to radially and tangentially oriented gratings.[12] The mechanisms by which the eventual detection of the stimulus results in an action to elongate or not to elongate the eyeball are still elusive. Several treatments addressing changes in the peripheral refraction issue are now available.[13, 14] Some of these treatments were specifically designed for the purpose of inducing peripheral myopic defocus, while others that are commercially available to correct central myopia and presbyopia also shown successful results in preventing myopia progression.[15, 16]

Single-vision (SV) soft contact lenses (SCLs) have been reported to potentially change the state of relative peripheral defocus. However, Shen et al. study revealed that visual correction with SVCLs did not provide significant change in relative peripheral hyperopia, although could be expected to slightly decrease in peripheral hyperopia with both soft and rigid CLs.[17] On the other hand, another study showed that full correction of central myopia with Proclear SCLs resulted in an increase in relative peripheral hyperopia in both low and moderate myopes. Opposite reports were related with differences in design of each specific SV SCL studied.[18]

Orthokeratology (OK) is considered a corrective treatment that also allows myopia retention.[19] Previous studies on OK observed retention rates of about 40% in children of different ethnicities.[20-22] Also, aspheric center-distance multifocal contact lenses (MFCLs) demonstrated retention rates of about 40–50% in recent clinical trials[23] and also axial elongation reduction of 20%, after 2 years. Both treatments have in common the production of a relative peripheral myopia reversely comparing with baseline condition in which could be seen a relative hyperopia. After OK, the expected relative myopia induced is correlated 1:1 with central myopia,[24, 25] being almost symmetrical across horizontal and vertical meridians of the peripheral retina.[26]

Center-distance MFCL predictably induces peripheral myopia,[27, 28] which might be expected knowing that increasing the additional power of MFCL also increases the induction of peripheral myopia. A study has shown that center-distance aspheric multifocal soft contact lenses with +3.00 and +4.00 add power induced more peripheral myopia than +1.00 and +2.00 D add lenses. However, there were no differences between +3.00 and +4.00 and the off-axis myopia induced was less symmetric between nasal and temporal retina with the higher add powers.[27] Recently, Flitcroft highlighted the impact of different corneal and retinal shapes on the relative position of the sagittal and tangential image shells.[29] Our results indeed suggested that this pattern is significantly different between progressing and stable myopes in a cross sectional study involving 60 ethnic, age, foveal refraction, and axial length-matched stable and progressive myopes.[6]

Some earlier attempts to measure peripheral refraction were performed in the context of studies evaluating night vision and night myopia, with the justification that vision at very low brightness involves the parafoveal area up to 10–15°. As early as 1918, Ogata and Weymouth measured refraction at various angles and found that 40% of the sample measured showed increasing relative peripheral myopia until 4° of eccentricity, where the value became constant at about −0.37 D (−0.30 to −0.50 D). They justified this finding with the parafoveal cupping of the retina.[30] The importance of the pattern of astigmatic refraction was originally attributed to the early works of Ferree and his definition of different patterns and their role in emmetropization (1931–33).[31] Ames and Proctor, in a review paper published in 1921, reported that the retina is located between the primary (tangential) and secondary (sagittal) foci.[32] Results from animal studies provided evidence of a significant correlation effect between the relative astigmatic defocus (sagittal and tangential power errors) and the emmetropization process of rhesus monkeys.[33] Despite this, most previous studies addressing the changes in peripheral refraction concentrated on spherical equivalent changes and vectorial decomposition of astigmatism (J0 and J45). Table 6.1 shows the outcomes of different studies reporting the changes in relative peripheral defocus with different contact lenses[14, 17, 18, 24, 26-28, 34-39] Conversely, information about the relative position of the sagittal and tangential components of refraction regarding the retinal plane across the visual field is lacking in the literature published on this topic. Therefore this study looks at peripheral refraction in the tangential and sagittal planes.

The goal of the present study is to report aggregated data showing the changes induced by different contact lenses on peripheral astigmatic defocus. With this work we intend to summarize the results of different studies and provide a comparative view of all the results obtained from the same center with the same methodology using different optical devices.

6.3. Methods

6.3.1. Subjects and Lenses

The present study gather the results of different clinical trials conducted at the Clinical and Experimental Optometry Research Lab (CEORLab, Minho University, Braga, Portugal) between January 2008 and December 2012. The results of those studies, comprising a total of 137 eyes, are published in previous works (see Table 6.2).[24, 27, 40-42] However, the information provided here has not previously been reported.

A total of eight different contact lens types tested in 137 subjects resulted in 236 peripheral refraction measures. Those included orthokeratology[24] (n = 28), standard aspheric rigid gas permeable (RGP, n = 52),[41] experimental RGP (n = 52),[41] and experimental soft CL[40] (n = 10) to facilitate induction of peripheral myopic defocus, concentric MFCL (Oasys, n = 19),[42] aspheric center-distance silicone hydrogel soft MFCL with Add: +2.00 D (Biofinity multifocal D, n = 19)[42] and aspheric center-distance MFCL with add: +2.00 D (Proclear Multifocal D, n = 28), and +3.00 D (Proclear multifocal D, n = 28).[28] Table 6.2 summarizes the characteristics of all the contact lenses involved in the experiments reported.

With the exception of orthokeratology, all the remaining studies were non-dispensing. All studies included a young Caucasian university student population with the same inclusion and exclusion criteria. In brief, subjects were required to have myopia, without any eye disease or injury, no previous history of refractive surgery, and not being under the effect of any ocular or systemic medication. Table 6.3 summarizes the demographic data for the different samples evaluated for each treatment. As defined in the respective publications, the participants were fully informed about the purpose, all the procedures of each study were approved by the Scientific Committee of the School of Sciences of Minho University (Portugal), and all participants gave their written agreement following the tenets of the Declaration of Helsinki Research protocol. The data obtained under naked eye condition (baseline) from the same subjects, as peripheral refractive error, were collected and analyzed as baseline data for comparison purposes.

Table 6.1. *Summary of studies comparing the relative peripheral myopic defocus with single vision (SV) contact lenses (CL), Center-distance multifocal (MF) soft contact lenses (SCL), gradient power CL, orthokeratology CL (OK) and single vision or peripheral gradient spectacles (for comparison purposes) in human myopic eyes.*

Author (Year)	Sample (n° eyes)	Refractive Error [Max M, Min M, Max cyl]	Methods	Type of Correction	Change at center	M RPRE (post - pre)
Kang et al (2011)[35]	16 Asia — [11-16 years]	-2.37±1.17 D [-1.00,-4.00,-1.00] vs -2.43±0.91 D [-1.00,-4.00,-1.00]	Non-cycloplegic Shin-Nippon open-field AR Eye rotation Horizontal (±35°) 20°, 30° and 40°	OK (BE or BE-A, Capricornia Contact Lens) vs SV RGP (J-Contour, Capricornia)	+1.83±1.18 vs -0.15±0.45	35°N:-1.55 35°T:-2.69 vs 35°N:-0.20* 35°T:-0.10*
Kang et al (2012)[18]	34 Asia — [18-29]	-1.41±0.60 D [-0.75,-2.00,-0.75] vs -3.25±0.80 D [-2.25,-6.00,-0.75]	Non-cycloplegic Shin-Nippon open-field AR Eye rotation Horizontal (±35°) 10°, 20°, 30° and 35°	Low myope SV Proclear Sphere SCL vs Moderate Myope SV Proclear Sphere SCL	+1.71 vs +3.49	35°N:+0.29* 35°T:+0.29* vs 35°N:+0.51* 35°T:+0.36*
Kang et al (2013)[34]	34 Asia — [18-29]	-1.41±0.60 D [-0.75,-2.00,-0.75]	Non-cycloplegic Shin-Nippon open-field AR Eye rotation Horizontal (±35°) 10°, 20°, 30° and 35°	SCL Proclear Sphere vs MF SCL Proclear	+1.71 vs +1.00	35°N:+0.23* 35°T: +0.30* vs 35°N: -0.16* 35°T:-0.55*
		-3.25±0.80 D [-2.25,-6.00,-0.75]		SCL Proclear Sphere vs MF SCL Proclear	+3.54 vs +2.66	35°N:+0.45* 35°T:+0.34* vs 35°N:+0.41* 35°T:-0.16*
Kwok et al (2012)[36]	10 New Zealand 22±0	-8.31±2.10 D [-6.50,-12.50,-1.50]	Cycloplegic Shin-Nippon open-field AR Head rotation	SV SCL	—	20°N:-1.07 20°T:-1.92

	[20-26]		Horizontal (±20°) 5°, 10°, 15° and 20°			
Lopes-Ferreira et al. (2011)[27]	20 Portuguese 21.6±2.3 [20-26]	Emmetropic eyes -0.06±0.54 D	Non-cycloplegic Grand-Seiko open-field AR Eye rotation Horizontal (±35°) Angular distance of 5°	Center-distance MF SCL Proclear Multifocal D	Add1:-0.44 Add2:-0.89 Add3:-1.64 Add4:-2,69	Add1:-0.49vs-1.78 Add2:-0.54vs-2.15 Add3:-0.78vs-3.15 Add4:-0.39vs-3.43 (35N vs 35T)
Lopes-Ferreira et al. (2013)[28]	28 Portuguese 22.0±2.0 [19-26]	-2.24±1.33 D [-0.50,-5.25,-1.00]	Non-cycloplegic Grand-Seiko open-field AR Eye rotation Horizontal (±35°) Angular distance of 5°	Proclear multifocal D Addition +2.00 D (Add2) and +3.00 D (Add3).	Add2:+1.44 Add3:+0.74	Add2:-0.13vs-0.73 Add3:-0.41vs-1.54 (35N vs 35T)
Sankaridurg et al. (2011)[14]	40/45 Chinese 11.2 [7-14]	-1.99±0.62 D -2.24±0.79 D [-0.75,-3.50,-1.0]	Cycloplegic Grand-Seiko open-field AR Head rotation Horizontal (±40°) 10°, 20°, 30° and 40°	SV spectacle lenses (C) vs SV SCL	—	40°N:+0.39 40°T:+0.72 vs 40°N:-0.47 40°T:-1.60
Lin et al. (2010)[37]	28 Chinese — [9-15]	-2.30±0.42 D [-1.48,-2.89,-1.00] vs -4.27±0.65 D [-3.27,-5.27,-1.00]	Cycloplegic Shin-Nippon open-field AR Eye rotation Horizontal (±40°) 10°, 20°, 30° and 40°	Low myope Spectacles vs Moderate myope Spectacles	+2.20 vs +4.18	40°N:+0.27 40°T:+0.48 vs 40°N:+0.96 40°T:+1.26
Queirós et al. (2010)[24]	28 Portuguese 24.6±6.3 [20-41]	-1.95±1.27 D [-0.88,-5.25,-1.50]	Non-cycloplegic Grand-Seiko open-field AR Eye rotation Horizontal (±35°) Angular distance of 5°	OK, Paragon CRT (paflufocon D)	+1.57±0.77	35°N:-2.30 35°T:-2.53
Shen et al. (2010)[17]	9 USA — [23-30]	— [-1.00,-6.50,-2.00]	Non-cycloplegic COAS wavefront aberrometer Head rotation Horizontal (±35°) Angular distance of 5°	SV SCL vs SV RGP	—	35°N:-0.12* 35°T:-0.17* Vs 35°N:-0.25* 35°T:-0.35*
Sankaridurg et al. (2010)[38]	210 Chinese 11.0±2.3 [6-16]	-1.87±0.68 D -1.82±0.62 D -1.81±0.67 D -1.82±0.66 D [-0.75,-3.50,-1.50]	Cycloplegic Grand-Seiko open-field AR Head rotation Horizontal (±40°) 10°, 20°, 30° and 40°	SV spectacle lenses (C) and 3 novel types spectacle lens designs	C:+1.95* T1:+1.85* T2:+1.85* T3:+1.80*	C:+0.40vs+0.65* T1:+0.20vs+0.50* T2:-0.40vs-0.35* T3:+0.00vs+0.30*
Tikat and Walline	14 Asian,	2.88±1.22D	Cycloplegic Grand-Seiko open-	OK Paragon CRT CL (HDS	OK +2.42D	30°T +1.88 vs-0.50*

(2013)[26]	Black, and White 26.6±2.8-		field AR Eye rotation and mirror system	100 material) vs Proclear Multifocal D add+2.00D		30°N +1.22vs-1.06*
Mathur and Atchison (2009)[39]	2 myopes	-2.00 -3.50	Non-cycloplegic Grand-Seiko open-field AR Eye rotation	RGP CL (Capricornia, Brisbane, Australia)	Subject 1: +2.00D Subject 2: +2.50D	34°T +2,25 vs +2.50* 34°N +2.63 vs+3.37*

SVSCL: single vision soft contact lenses; SVRGP: single vision rigid gas permeable
* The numerical information was not provided by the authors; approximate values were obtained from the graphs.
RPRE (M): relative peripheral refractive error (M component). Negative and positive values reflect an increase in myopic or hyperopic defocus, respectively, with the given treatment.

Table 6.2. *Characteristics of the contact lenses used in the studies reported*

Type of contact lenses	**Ortho-K**	**Center-distance Multifocal**		**Concentric Multifocal**	**Experimental Soft CL**	**Aspheric RGP**	**Experimental RGP**
Previous Report	Queirós et al. 2010[24]	Lopes-Ferreira et al. 2013[28]	Lopes-Ferreira et al. 2015[42]	Lopes-Ferreira et al. 2015[42]	Pauné et al. 2014[40]	Pauné et al. 2015[41]	
Brand	Paragon CRT	Proclear Multifocal D	Biofinity Multifocal D	Acuvue Oasys for Presbyopia	Amiopik Soft	Aspheric	Amiopik
Material	Paflufocon D	Omafilcon A (62%)	Comfilcon A (48%)	Senofilcon A (38%)	Polymacon (38%)	Boston EO	Boston EO
Dk		27	128	103			
Base Curve	variable	8.6	8.6	8.4	8.7	variable	variable
Overall Diameter	10.5	14.4	14.4	14.3	10.5	10.8	10.8
Optic Zone	6.0	8.7	8.6	8.4	8	8	8
Geometry	Ortho-k	Aspheric Center Distance	Aspheric Center Distance	Multiconcentric	Bicurve	Aspheric	Center Distance
Other specifica-tions	Sigmoid Geometry Overnight Wear	Add: +2.00D and +3.00D	Add: +2.50D	Add: +2.50D	Add: +1.50 @ 30°	Distance Correction Only	Add: +1.50 @ 30°

6.3.2. Peripheral Refraction Measurements

Objective central and peripheral refraction was measured in the right eye by a non-cycloplegic examination using an open-field autorefractor/keratometer (Grand-Seiko WAM-5500, Grand-Seiko Co., Ltd., Hiroshima, Japan). The illumination in the examination room was adjusted to obtaining sufficiently large pupil size to allow peripheral measurements, which were achieved in all cases without pharmacological mydriasis. The left eye was always occluded during measurements. Peripheral refraction was taken at known eccentricities presented in a static target, located at 2.5 m and consisting of an offset of LEDs arranged on a horizontal flat rail implying eccentricities between 30o nasal and 30o temporal, in intermediate 5° or 10° steps, depending on the study. As the targets used in studies were small LED lights and were located at 2.5 m distance, the expected accommodative demand would be about 0.5 D. However, measurements at distance using an open-field autorefractor did not significantly change the axial refractive error, in comparison with cycloplegic refractive values, in young subjects.[43] All measurements reported were obtained by rotating the eye to rectify fixation of the peripheral LED targets. The objective refraction was averaged from five measures taken on- and off-axis, at each retinal eccentricity (α). Individual data were converted to vector components according to Fourier analysis, as recommended by Thibos.[44] M, J0, and J45 are only presented as descriptive values for the sample characterization. For statistical analysis only the tangential (FT = M + J0) and sagittal (FS = M − J0) power errors were considered. We have previously published data on astigmatic peripheral defocus, decomposed in sagittal and tangential power errors for myopic eyes undergoing orthokeratology treatment.[45]

6.3.3. Statistical Analysis

Refraction data were treated statistically using SPSS (for Windows, version 20, New York, USA). The Shapiro–Wilk Test was applied to evaluate the normality of data distribution. When normality could not be assumed, the Wilcoxon signed-rank test was used for paired comparison (between baseline and post-treatment values; nasal and temporal symmetry of the refractive profile; and relative peripheral myopia with eccentricity/center), and paired-sample t-testing was used when normality could be assumed. The concept of relative peripheral refractive error (RPRE) was used to define the degree of myopia/hyperopia at baseline or induced by the treatment for each eccentric location, normalized to the axial refraction off-axis minus on-axis. For statistical purposes, p-values lower than 0.05 were considered statistically significant.

6.4. Results

Figure 6.1 shows RPRE (M) as a function of field angle with and without (naked eye) each type of CL in the temporal (T) and nasal (N) retinal area.

6.4.1. Relative Peripheral Myopia

The concept of RPRE was used to define the degree of myopia/hyperopia existing or induced by the CL at each eccentric location compared to the axial refraction (at 0°). For a given eccentric location of angle = α, RPREα = PREα (post-CL) – RPREα (pre-CL), with M or J0 as previously defined. This section reports the change in relative peripheral defocus from the center towards the periphery with different optical design devices (CL). We are particularly interested in reporting at which eccentricity (α) the RPRE becomes significantly myopic. In the OK treatment the nasal retina becomes significantly myopic beyond 15° (i.e., $p < 0.05$ for $\alpha > 20°$) and in the temporal retina beyond 10° (i.e., $p < 0.05$ for $\alpha > 15°$). Regarding changes in FT power error, all points except those located between 15° nasal and 5° temporal show statistically significant differences compared to changes in axial refraction, and for the FS component all points except the central ones (α = 15° nasal to 15° temporal). This follows experimental RGP showing myopic RPRE from 10° in the nasal retina to 5° in the temporal retina. The third approach, showing a significant RPRE myopic defocus is Proclear multifocal with +3.00 D near add. On the other hand, Acuvue Oasys multifocal presents a “flat” pattern with no significant change in RPRE for peripheral eccentricities ($p > 0.05$, for all eccentricities). Table 6.4 presents the average values of RPRE for M, FS, and FT measured for each treatment at 30° of eccentricity.

Table 6.3. *Demographic baseline parameters of the subjects sampled in each study and significance for comparisons among them.*

	Ortho-K	**Aspheric RGP + Experimental RGP**	**Experimental Soft CL**	**Oasys and Biofinity Multifocal**	**Multifocal Proclear**	**p$^{a)}$**
	Queiros et al. 2010[24]	Paune et al, 2015[41]	Pauné et al, 2014[40]	Lopes-Ferreira et al. 2015[42]	Lopes-Ferreira et al. 2013[28]	
Gender (M/F)	17 / 11	52	0 / 10	6 / 13	4 / 24	
Age (years)	20-41 24.6±6.3	18-25 23.4±1.8	21-26 23.4±1.8	20-27 23.2±3.3	19-26 22.0±2.0	
Ethnicity	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	
Sphere (D)	-1.73±1.22	-2.92±1.61	-3.15±1.29	-2.16±1.31	-2.04±1.32	0.001
Cylinder (D)	-0.43±0.33	-0.58±0.39	-0.49±0.30	-0.46±0.32	-0.45±0.25	0.305
M (D)	-1.95±1.27	-3.22±1.66	-3.39±1.31	-2.67±1.66	-2.24±1.33	<0.001
J0 (D)	0.05±0.21	-0.02±0.29	0.10±0.22	0.01±0.24	0.03±0.19	0.478
J45 (D)	0.01±0.16	-0.02±0.20	0.09±0.14	0.02±0.17	0.00±0.14	0.546
FT (D)	-1.89±1.25	-3.24±1.52	-3.29±1.26	-2.38±1.30	-2.21±1.30	<0.001
FS (D)	-2.00±1.33	-3.19±1.84	-3.49±1.40	-2.41±1.27	-2.26±1.32	0.001

a) Kruskal Wallis Test

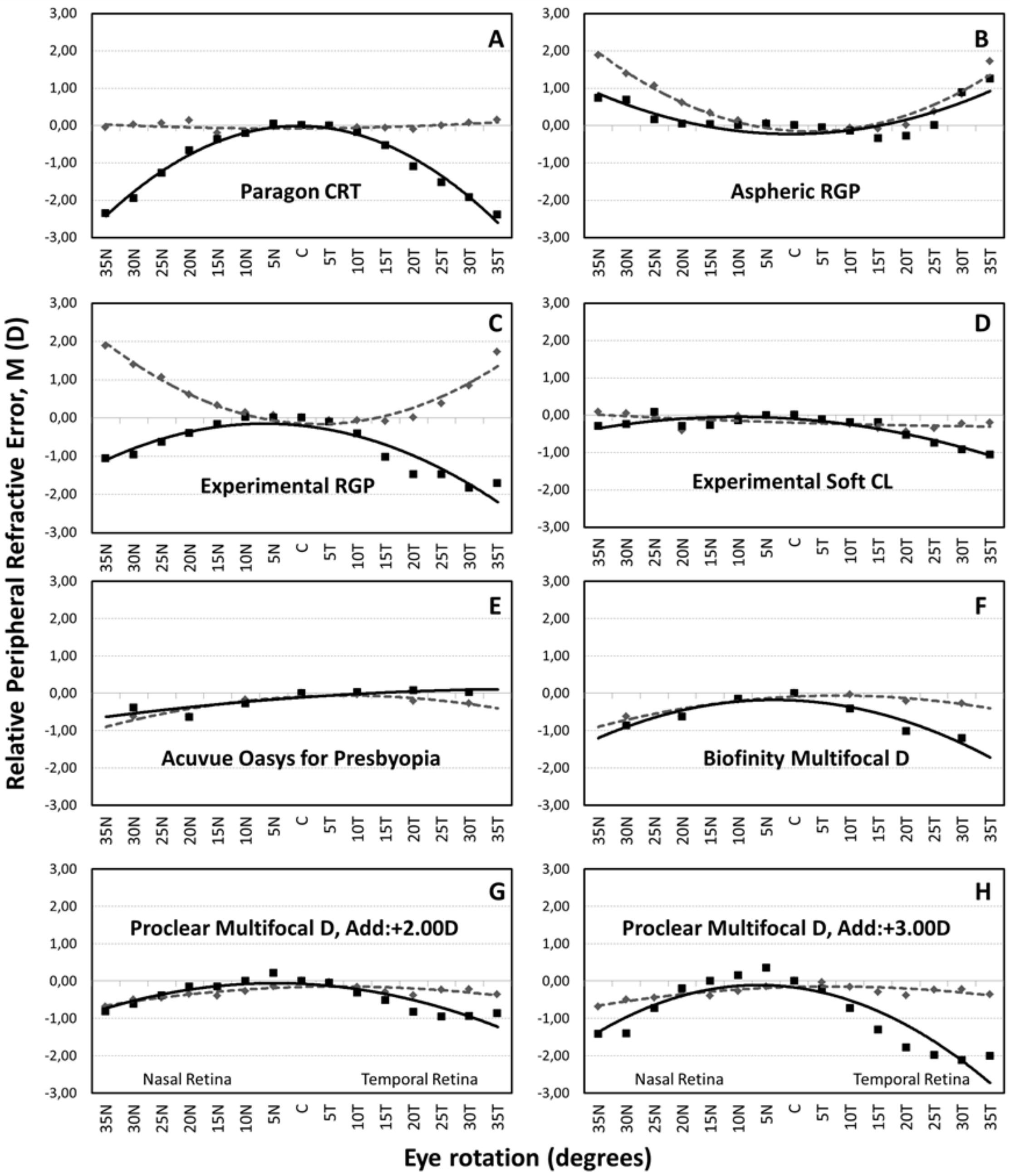


Figure 6.1. Relative peripheral refractive error (M) as a function of field angle with and without each type of contact lens in the temporal (T) and nasal (N) retinal area. Lines represent second-order polynomial fits to the data from: orthokeratology (A), aspheric RGP (B), experimental RGP (C), experimental soft CL (D), Acuvue Oasys multifocal (E), Biofinity multifocal D (F), Proclear multifocal D add: +2.00 D (G), Proclear multifocal D add: +3.00 D (H). Gray dashed line denotes under naked-eye condition (baseline) and black solid line denotes contact lenses.

6.4.2. Symmetry of Refractive Profile vs. Eccentricity

This section reports the symmetry between the relative peripheral defocus, comparing the nasal and temporal areas for each given eccentricity (10°, 20°, 30°). Figure 6.2 shows the average peripheral refractive patterns obtained with each treatment. Plots represent relative peripheral defocus, with all curves normalized to set the central refractive value at “zero.” This provides an enhanced view of the relative changes in peripheral refraction compared to central measurement. For the FT component there were no statistically significant differences between nasal and temporal corresponding eccentricities of the retina for aspheric RGP (B) and experimental sSCL (D); for the FS component there were no statistically significant differences for orthokeratology (A), aspheric RGP (B), and experimental RGP (C). The treatments that induced a more marked increase in myopic RPRE were experimental RGP and orthokeratology lenses. Additionally, orthokeratology was the treatment that produced the least asymmetrical refractive pattern comparing nasal and temporal retina at 30° eccentricity: difference in FT = 0.05 ± 2.48 D (p = 0.266) and difference in FS = 0.01 ± 1.08 D (p = 0.962).

Table 6.4. Relative peripheral difference between center and at 30° of eccentricity in the nasal and temporal retina

	M		FT		FS	
	Nasal	Temporal	Nasal	Temporal	Nasal	Temporal
Paragon CRT[24]	**-1.96±1.86; 0.000+**	**-1.99±1.34; 0.000***	**-2.98±2.63; 0.000+**	**-3.03±1.89; 0.000***	**-0.94±1.19; 0.000***	**-0.95±0.95; 0.000***
Aspheric RGP[41]	**-0.71±2.12; 0.001+**	0.05±2.84; 0.410+	**-1.05±2.79; 0.009***	-0.17±3.99; 0.759*	**-0.37±1.64; 0.003+**	0.26±2.02; 0.917+
Experimental RGP[41]	**-2.36±1.95; 0.000***	**-2.67±1.81; 0.000***	**-3.46±2.85; 0.000***	**-4.02±3.07; 0.000***	**-1.25±1.26; 0.000+**	**-1.32±0.85; 0.000***
Experimental Soft CL[40]	-0.29±0.53; 0.121*	**-0.69±0.46; 0.001***	**-0.56±0.75; 0.043***	**-0.88±0.70; 0.003***	-0.02±0.66; 0.944*	**-0.50±0.55; 0.018***
Acuvue Oasys for Presbyopia[42]	0.23±0.63; 0.133*	0.31±0.72; 0.091*	0.33±0.84; 0.114*	0.15±0.83; 0.444*	0.14±0.66; 0.382*	**0.46±0.86; 0.039***
Biofinity Multifocal D[42]	-0.25±0.69; 0.149*	**-0.93±0.58; 0.000***	**-0.50±0.84; 0.022***	**-1.05±0.62; 0.000***	0.01±0.62; 0.958*	**-0.80±0.66; 0.000***
Proclear Multifocal D 2.00D[28]	-0.11±0.75; 0.442*	**-0.72±1.00; 0.000+**	-0.04±1.08; 0.856*	**-0.98±1.42; 0.000+**	-0.18±0.56; 0.092*	**-0.46±0.77; 0.003+**
Proclear Multifocal D 3.00D[28]	**-0.90±0.96; 0.000***	**-1.89±1.34; 0.000***	**-1.16±1.21; 0.000***	**-2.47±1.85; 0.000+**	**-0.64±0.88; 0.001***	**-1.31±1.10; 0.000***

Bold for statistically significant differences against center.

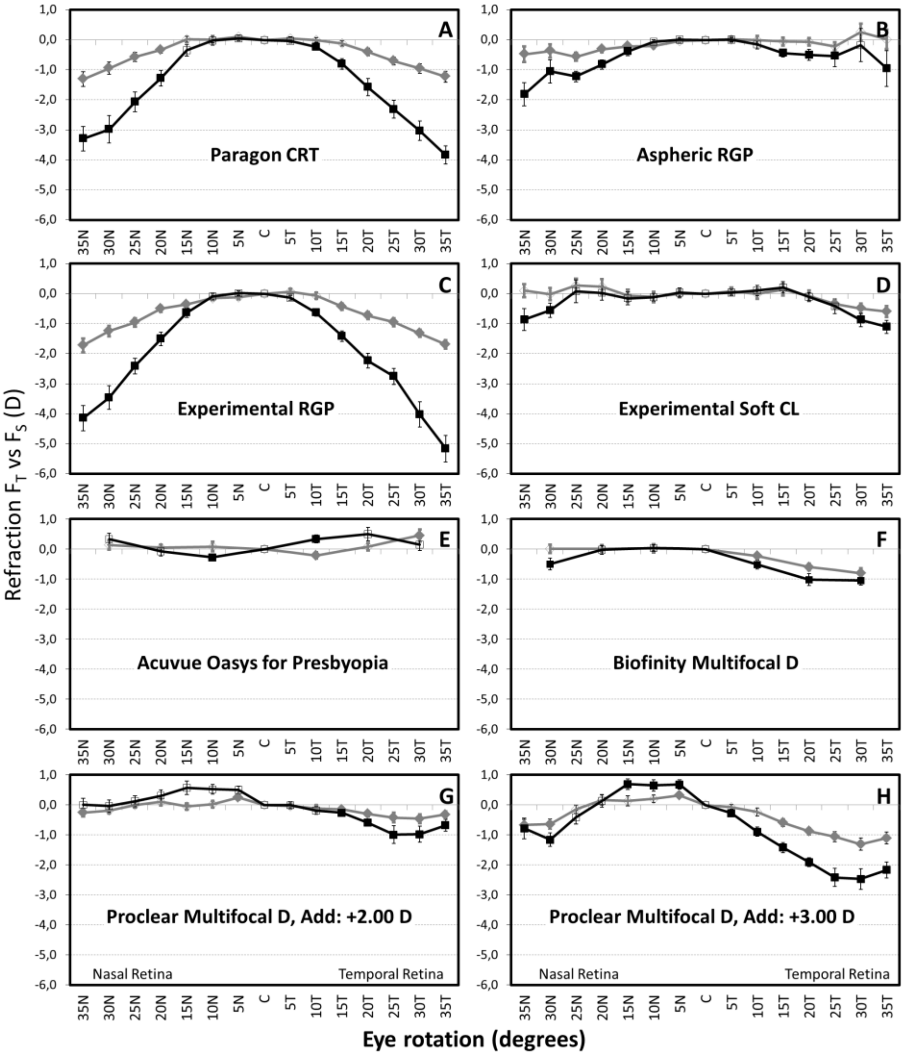


Figure 6.2. Relative differences (treatment minus baseline) between components refraction FT (black line) and FS (gray line) as a function of field angle across the nasal (N) and temporal (T) retinal area. The filled squares represent the points where the changes in off-axis refraction are significantly more myopic ($p < 0.05$) than those induced in the central visual axis. Orthokeratology (A), aspheric RGP (B), experimental RGP (C), experimental soft CL (D), Acuvue Oasys multifocal (E), Biofinity multifocal D (F), Proclear multifocal D add: +2.00 D (G), Proclear multifocal D add: +3.00 D (H). Error bars represent standard error of the mean (SEM).

6.5. Discussion

The present study provides a meta-analysis of peripheral refraction data obtained from different contact lenses used or with the potential to be used in myopia progression studies. Using the same methodology at the same research center we have shown that their effect on peripheral refraction varies significantly.

Peripheral refraction has become an important issue in the evaluation of myopia progression, as it can provide an explanation for the effectiveness in myopia retention of certain treatments such as orthokeratology.

However, it is not well understood how the eye distinguishes signs of defocus that triggers ocular growth. Several theories have been proposed, one of which is related to the oblique astigmatism of the eye.[46, 47] It has been hypothesized that the ocular growth mechanism in the peripheral retina might use orientation cues to assess the "positions" of the two astigmatic image shells and thus compensate for axial elongation whenever the relative peripheral sagittal focal line "stands behind" the retina. In this domain, the limits of Sturm's interval (distance between tangential and sagittal focal lengths) and their orientations might provide the necessary cue to stimulate or slow the growth of the posterior pole of the eyeball.

Potential explanations for this mechanism are found in the radial orientation of some photosensitive cells that show preferential orientation, maximizing grating contrast in the periphery. Nevertheless, the mechanism by which the detection of the relative position of the astigmatic foci, which result in a stimulating or protective effect on ocular growth, is not known.[12] This is partly supported by results from Hung et al.[48], who found differences in the pattern of eye growth in rhesus monkeys dependent on the relative positions of the tangential and sagittal focal lengths with respect to the retinal plane. In the presence of mixed astigmatism, the primates' eyes tended to grow in order to reposition the retina with the most posterior focal shell position (FS).[49]

When analyzing the data from the eight different optical devices reported in this study, there is evidence that both OK lenses and peripheral gradient RGP lenses are able to provide a greater degree of peripheral myopia induction for both limits of Sturm's interval. Rather, treatments such as concentric MFCL (Acuvue Oasys for Presbyopia) did not show potential in producing peripheral myopic defocus, as observed in Figure 6.1E, despite previous studies having shown to be partly effective in myopia retention.[13-15] The results suggest that the effectiveness of myopia regulation with lenses of this type[13-15] cannot be exclusively assigned to peripheral myopic defocus or peripheral astigmatic defocus and other factors may be involved, including changes in both the accommodative activity of the eye and the focusing properties at the foveal area.[50, 51] Recently, Smith et al. suggested that the efficacy of bifocal concentric addition designs used in myopia progression trials[13] might be explained by a certain effect of peripheral myopic defocus in addition to other potential mechanisms affecting the foveal vision. Although our methodology does not support such an assumption, we have to recognize that due to the sudden power changes between distance and near zones in these MFCL, measuring methods such as autorefractometry or even aberrometry might not be sensitive enough to detect such a hypothetical peripheral myopic defocus, and it is a limitation of this study. Another limitation of the methodology followed might be in the fixation stimulus used. When looking at a LED source of light, the accuracy of consistency of the response may change over time. However, we consider that this is relatively well-controlled source of error by virtue of averaging the five measurements obtained over a short period of time. Finally, the fact that we used a flat target instead of a curved one creates minor changes in the accommodative demand for the eye of 0.054 D when looking at the peripheral LEDs. However, this source of bias is not relevant for the purposes of the study and might have marginally affected the results presented in Figure 6.1. Soft peripheral refractive gradient CLs designed for myopia regulation do not seem to be as effective as their rigid counterparts or orthokeratology in changing the peripheral refractive pattern. Their effect on reduction of peripheral hyperopia is limited and only noticed at the most eccentric retinal locations. This is agreement with the results of a recent 2-year longitudinal study evaluating the efficacy of a soft radial gradient contact lens to control myopia progression.[52] The authors compared the soft lens against orthokeratology and found a lower myopia retention effect compared with orthokeratology, but a significant effect of retention compared with the SV spectacle lens wearers acting as controls. In fact, SCLs are preferred platforms for this kind of device because of their disposability and immediate comfort, which makes them ideal for children. Good centration and dynamical stabilization is fundamental to obtaining a good and required adjustment of peripheral myopic shift. Previous studies a showed lack of effect on reduction of relative peripheral hyperopia at one side of the retina, presumably because the lens was decentered from the visual axis.[14] Sankaridurg et al. showed that a specially designed MFCL was able to reduce myopia progression by about 30%.[14] It seems that the induction of myopic defocus in both the nasal and temporal visual fields could improve the efficacy.[53] The conventional aspheric RGP designs provide a certain degree of myopic defocus for the peripheral tangential focal length, but almost no effect on the peripheral sagittal foci. This is in agreement with the results of Shen et al.[17] Then, the peripheral myopic defocus would be negligible from the perspective of myopia control treatments. This partly agrees with the absence of effect of conventional (excepting orthokeratology) RGP lenses on myopia progression as previously reported in two different clinical trials.[54, 55]

Biofinity and Proclear MFCL with +2.00 add powers showed minimal effect on myopic peripheral defocus induced. However, it has been observed that center-distance aspheric MFCL presents increasing peripheral myopic defocus as the peripheral add power increases,[27] and higher add powers would be expected to induce more myopic defocus. Conversely, the Proclear with +3.00 add power induced a higher level of relative peripheral myopic defocus. In light of the potential effect of relative peripheral myopic defocus on myopia regulation, we could argue that a +3.00 add might be more effective than a +2.00 add center-distance aspheric multifocal contact lens. This is in agreement with the limited results in myopia retention found by Walline et al. in a clinical trial involving the use of Proclear multifocal with add +2.00 D.[23] The level of peripheral myopia is probably not the only factor involved in the peripheral induction of defocus. Evidence of the OK myopia retention effect can be seen in Cho21, and was expected to be almost 2 D, and in Kakita[22] almost 2.50 D of peripheral myopia induction was found.[24] Nevertheless, the optimal results for induction of peripheral myopic defocus, peripheral FT, and FS were seen with the CRT OK lens, experimental RGP lens, and with MFCL Proclear +3.00 D add (Table 6.4).

Beyond the amount of peripheral myopic defocus induced, the asymmetry between the nasal and temporal visual fields is evident for some treatments (center-distance multifocal contact lens) while others show a fairly symmetric effect (orthokeratology, experimental RGP). These effects might be relevant to the efficacy of myopia control considering the asymmetries shown between the nasal and retinal anatomy of progressive and non-progressive myopes.[6] We might also hypothesize that the degree of efficacy in myopia control of these treatments could be enhanced if personal approaches that could account for inter-subject variation and asymmetry in the peripheral refraction patterns were considered. Again, though some authors have found in prospective clinical trials that the sign of peripheral defocus does not predict the axial elongation of the eye during myopia development, those studies analyzed only the spherical equivalent components rather than the astigmatic defocus.[7, 56] Furthermore, the fact that the sign of peripheral defocus does not predict myopic progression does not directly imply that addressing treatments based on changing the peripheral defocus cannot be effective for myopia control. Indeed, several animal studies and clinical trials in humans seem to point towards the efficacy of such treatments. While the ultimate causative factors are still to be clarified, the potential role of peripheral defocus treatments cannot be ruled out, but considered carefully either per se or in association with other potential mechanisms.

In summary, in a young university Caucasian population, the present results may provide some clarification on the potential role of different devices in interfering with myopia progression based on the impact of relative peripheral myopic defocus and the potential role of astigmatism in acting as a critical cue for this mechanism.

6.6. Acknowledgment

The authors thank the companies that donated the contact lenses used in the study. This study was supported by Fundação para Ciência e Tecnologia, Portugal through projects PTDC/SAU-BEB/098392/2008 and PTDC/ SAU-BEB/098391/2008.

6.7. References

1. Charman NW, Radhakrishnan H. Peripheral refraction and the development of refractive error: a review. *Ophthalmic Physiol Opt* 2010;30:321-338.
2. Wallman J, Winawer J. Homeostasis of Eye Growth and the Question of Myopia. *Neuron.* 2004;43:447-468.
3. Smith Iii EL, Hung L-F, Huang J. Relative peripheral hyperopic defocus alters central refractive development in infant monkeys. *Vision Res.* 2009;49:2386-2392.
4. Atchison DA, Pritchard N, Schmid KL. Peripheral refraction along the horizontal and vertical visual fields in myopia. *Vision Res.* 2006;46:1450-1458.
5. Kang P, Gifford P, McNamara P, et al. Peripheral refraction in different ethnicities. *Invest Ophthalmol Vis Sci.* 2010;51:6059-6065.
6. Faria-Ribeiro M, Queirós A, Lopes-Ferreira D, Jorge J, González-Méijome JM. Peripheral Refraction and Retinal Contour in Stable and Progressive Myopia. *Optom Vis Sci.* 2013;90:9-15.
7. Mutti DO, Sinnott LT, Mitchell GL, et al. Relative peripheral refractive error and the risk of onset and progression of myopia in children. *Invest Ophthalmol Vis Sci.* 2011;52:199-205.
8. Gwiazda J, Hyman L, Hussein M, et al. A Randomized Clinical Trial of Progressive Addition Lenses versus Single Vision Lenses on the Progression of Myopia in Children. *Invest Ophthalmol Vis Sci.* 2003;44:1492-1500.
9. Mutti DO, Mitchell GL, Hayes JR, et al. Accommodative Lag before and after the Onset of Myopia. *Invest Ophthalmol Vis Sci.* 2006;47:837-846.
10. Hoogerheide J, Rempt F, Hoogenboom WP. Acquired myopia in young pilots. *Ophthalmologica.* 1971;163:209-215.
11. Thibos LN, Bradley A, Liu T, Lopez-Gil N. Spherical aberration and the sign of defocus. *Optom Vis Sci.* 2013;90:1284-1291.
12. Charman WN. Myopia, posture and the visual environment. *Ophthalmic Physiol Opt* 2011;31:494-501.
13. Anstice NS, Phillips JR. Effect of Dual-Focus Soft Contact Lens Wear on Axial Myopia Progression in Children. *Ophthalmology.* 2011;118:1152-1161.

14. Sankaridurg P, Holden B, Smith IIIE, et al. Decrease in Rate of Myopia Progression with a Contact Lens Designed to Reduce Relative Peripheral Hyperopia: One-Year Results. *Invest Ophthalmol Vis Sci.*. 2011;52:9362-9367.

15. Aller TA, Wildsoet C. Bifocal soft contact lenses as a possible myopia control treatment: a case report involving identical twins. *Clin Exp Optom.* 2008;91:394-399.

16. Walline JJ, Lindsley K, Vedula SS, Cotter SA, Mutti DO, Twelker JD. Interventions to slow progression of myopia in children. *The Cochrane database of systematic reviews.* 2011:Cd004916.

17. Shen J, Clark CA, Soni PS, Thibos LN. Peripheral Refraction with and without Contact Lens Correction. *Optom Vis Sci.* 2010;87:642-655.

18. Kang P, Fan Y, Oh K, Trac K, Zhang F, Swarbrick H. Effect of Single Vision Soft Contact Lenses on Peripheral Refraction. *Optom Vis Sci.* 2012;89:1014-1021.

19. Gonzalez-Meijome JM, Peixoto-de-Matos SC, Faria-Ribeiro M, et al. Strategies to Regulate Myopia Progression With Contact Lenses: A Review. *Eye Contact Lens.* 2016;42:24-34.

20. Walline JJ, Jones LA, Sinnott LT. Corneal reshaping and myopia progression. *British Journal of Ophthalmology.* 2009;93:1181-1185.

21. Cho P, Cheung SW, Edwards M. The longitudinal orthokeratology research in children (LORIC) in Hong Kong: a pilot study on refractive changes and myopic control. *Current eye research.* 2005;30:71-80.

22. Kakita T, Hiraoka T, Oshika T. Influence of Overnight Orthokeratology on Axial Elongation in Childhood Myopia. *Invest Ophthalmol Vis Sci.* 2011;52:2170-2174.

23. Walline JJ, Greiner KL, McVey ME, Jones-Jordan LA. Multifocal Contact Lens Myopia Control. *Optom Vis Sci.* 2013;90:1207-1214.

24. Queirós A, González-Méijome JM, Jorge J, Villa-Collar C, Gutiérrez AR. Peripheral Refraction in Myopic Patients After Orthokeratology. *Optom Vis Sci.* 2010;87:323-329.

25. Mathur A, Atchison DA. Effect of Orthokeratology on Peripheral Aberrations of the Eye. *Optom Vis Sci.* 2009;86:E476-E484.

26. Ticak A, Walline JJ. Peripheral Optics with Bifocal Soft and Corneal Reshaping Contact Lenses. *Optom Vis Sci.* 2013;90:3-8.

27. Lopes-Ferreira D, Ribeiro C, Maia R, et al. Peripheral myopization using a dominant design multifocal contact lens. *J Optom.* 2011;4:14-21.

28. Lopes-Ferreira D, Ribeiro C, Neves H, et al. Peripheral refraction with dominant design multifocal contact lenses in young myopes. *J Optom.* 2013;6:85-94.

29. Flitcroft DI. The complex interactions of retinal, optical and environmental factors in myopia aetiology. *Prog Retin Eye Res.* 2012;31:622-660.

30. Ogata D, Weymouth FW. Refractive Differences in Foveal and Parafoveal Vision. *Am J Ophthalmol.* 1918;1:630-644.

31. Ferree CE, Rand GG, Hardy CC. Refraction for the peripheral field of vision. *Arch Ophthalmol.* 1931;5:717-731.

32. Koomen M, Scolnik R, Tousey R. A Study of Night Myopia. *J. Opt. Soc. Am.* 1951;41:80-90.

33. Smith EL, 3rd, Hung LF. The role of optical defocus in regulating refractive development in infant monkeys. *Vision Res.* 1999;39:1415-1435.

34. Kang P, Fan Y, Oh K, Trac K, Zhang F, Swarbrick HA. The effect of multifocal soft contact lenses on peripheral refraction. *Optom Vis Sci.* 2013;90:658-666.

35. Kang P, Swarbrick H. Peripheral Refraction in Myopic Children Wearing Orthokeratology and Gas-Permeable Lenses. *Optom Vis Sci.* 2011;88:476-482.

36. Kwok E, Patel B, Backhouse S, Phillips JR. Peripheral Refraction in High Myopia with Spherical Soft Contact Lenses. *Optom Vis Sci.* 2012;89:263-270.

37. Lin Z, Martinez A, Chen X, et al. Peripheral Defocus with Single-Vision Spectacle Lenses in Myopic Children. *Optom Vis Sci.* 2010;87:4-9.

38. Sankaridurg P, Donovan L, Varnas S, et al. Spectacle Lenses Designed to Reduce Progression of Myopia: 12-Month Results. *Optom Vis Sci.* 2010;87:631-641.

39. Mathur A, Atchison DA, Charman WN. Effect of accommodation on peripheral ocular aberrations. *J Vis.* 2009;9:20-20.

40. Paune J, Queiros A, Quevedo L, Neves H, Lopes-Ferreira D, Gonzalez-Meijome JM. Peripheral myopization and visual performance with experimental rigid gas permeable and soft contact lens design. *Cont Lens Anterior Eye.* 2014;37:455-460.

41. Pauné J, Queiros A, Lopes-Ferreira D, Faria-Ribeiro M, Quevedo L, Gonzalez-Meijome JM. Efficacy of a Gas Permeable Contact Lens to Induce Peripheral Myopic Defocus. *Optom Vis Sci.* 2015;92:596-603.

42. Lopes-Ferreira DP, Neves HIF, Faria-Ribeiro M, Queirós A, Fernandes PRB, González-Méijome JM. Peripheral refraction with eye and head rotation with contact lenses. *Cont Lens Anterior Eye.* 2015;38:104-109.

43. Queiros A, Gonzalez-Meijome J, Jorge J. Influence of fogging lenses and cycloplegia on open-field automatic refraction. *Ophthalmic Physiol Opt.* 2008;28:387-392.

44. Thibos LN, Wheeler W, Horner D. Power vectors: an application of Fourier analysis to the description and statistical analysis of refractive error. *Optom Vis Sci.* 1997;74:367-375.

45. Gonzalez-Meijome JM, Faria-Ribeiro MA, Lopes-Ferreira DP, Fernandes P, Carracedo G, Queiros A. Changes in Peripheral Refractive Profile after Orthokeratology for Different Degrees of Myopia. *Curr Eye Res.* 2016;41:199-207.

46. Smith IIIEL, Kee C-s, Ramamirtham R, Qiao-Grider Y, Hung L-F. Peripheral Vision Can Influence Eye Growth and Refractive Development in Infant Monkeys. *Invest Ophthalmol Vis Sci.* 2005;46:3965-3972.

47. Kee C-S, Hung L-F, Qiao-Grider Y, Roorda A, Smith IIIEL. Effects of Optically Imposed Astigmatism on Emmetropization in Infant Monkeys. *Invest Ophthalmol Vis Sci.* 2004;45:1647-1659.

48. Hung L-F, Ramamirtham R, Huang J, Qiao-Grider Y, Smith EL. Peripheral refraction in normal infant rhesus monkeys. *Invest Ophthalmol Vis Sci.* 2008;49:3747-3757.

49. Smith I. I. I EL, Greeman N, Ho A, BA H. Methods and apparatuses for altering relative curvature of field and positions of visual extent of the peripheral off-axis focal positions. Vol 7.025.460 B2. USA2006.

50. Paune J, Thivent S, Armengol J, Quevedo L, Faria-Ribeiro M, Gonzalez-Meijome JM. Changes in Peripheral Refraction, Higher-Order Aberrations, and Accommodative Lag With a Radial Refractive Gradient Contact Lens in Young Myopes. *Eye Contact Lens.* 2016.

51. Gonzalez-Meijome JM, Carracedo G, Lopes-Ferreira D, Faria-Ribeiro MA, Peixoto-de-Matos SC, Queiros A. Stabilization in early adult-onset myopia with corneal refractive therapy. *Cont Lens Anterior Eye.* 2016;39:72-77.

52. Paune J, Morales H, Armengol J, Quevedo L, Faria-Ribeiro M, Gonzalez-Meijome J. Myopia Control with a Novel Peripheral Gradient Soft Lens and Orthokeratology: A 2-Year Clinical Trial. *Biomed Res Int.* 2015;2015:10.

53. Smith IIIEL. Optical treatment strategies to slow myopia progression: Effects of the visual extent of the optical treatment zone. *Exp. Eye Res.* 2013;114:77-88.

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

55. Katz J, Schein OD, Levy B, Cruiscullo T, Saw SM, Rajan U, Chan TK, Yew Khoo C, Chew SJ. A randomized trial of rigid gas permeable contact lenses to reduce progression of children's myopia. Am J Ophthalmol. 2003 Jul;136(1):82-90.

56. Atchison DA, Li S-M, Li H, et al. Relative Peripheral Hyperopia Does Not Predict Development and Progression of Myopia in ChildrenRelative Peripheral Hyperopia and Myopia in Children. *Invest Ophthalmol Vis Sci.* 2015;56:6162-6170.

CHAPTER 7

Combined Effect of Ocular and Multifocal Contact Lens Induced Aberrations on Visual Performance: Dominant vs Non-Dominant Design

7.1. Abstract

Purpose: To evaluate the combined effects of inherent ocular aberrations and induced aberrations with a multifocal contact lens (MFCL) after 15 days of lens wear in presbyopic participants and their influence in visual performance at distance and near under high and low contrast conditions.

Methods: Forty presbyopic participants (mean age 48.7±3.4) presenting a mean addition of 1.53± 0.58D were fitted with Biofinity Multifocal (Cooper-Vision, Fairport, NY) and included in the study. Measurements comprised distance and near monocular high (100%) and low-contrast (10%) logMAR Visual Acuity (VA). Ocular aberrations were obtained with Hartmann-Shack aberrometer (IRX3, Imagine Eyes) and analyzed for 2mm and maximum round natural pupil.

Results: Distance VA was significantly better in dominant eye while near VA was significantly better in the non-dominant eye ($p<0.05$ in all conditions). For a 2mm pupil In the Dominant eye, for the 2 mm pupil, Spherical-like aberration significantly increased ($p=0.027$) as well higher order aberrations (HOA) ($p=0.002$). Similarly, a significant increase was observed in Spherical-like ($p=0.001$), coma-like ($p=0.006$) and HOA ($p=0.004$) in Non-Dominant eye. For the maximum round natural pupil size, a significant decrease in vertical coma was observed ($p=0.018$) in Dominant eye, while a significant increase in Spherical-like ($p<0.001$) and Coma-like ($p=0.007$) was observed in Non-Dominant eye. A negative significant correlation was found between Vertical coma and high-contrast near VA (Rho=-0.405, $p=0.011$) in Dominant eye, while in Non-Dominant eye a significant correlation was found between induced Secondary Astigmatism and distance VA under high (Rho=0.556, $p<0.001$) and low-contrast (Rho=0.448, $p=0.005$).

Conclusions: On-eye higher-order aberrations induced by MFCLs are dependent on Dominant and Non-dominant design and coupling of the wearer's ocular spherical aberration with the aberration profiles provided by MFCLs differently affects their visual performance.

Key words: Multifocal Contact lenses, Optical Aberrations, Vision, center-distance design, center-near design.

7.2. Introduction

In recent years the contact lens industry has produced a remarkable range of patented presbyopic contact lens designs. Although, a survey across 38 countries between 2005 and 2009 revealed that the majority of presbyopic contact lens participants (63%) were fitted with non-presbyopic corrections, simultaneous vision designs represents only 29% of all fits.[1] Another survey of contact lens prescribing trends in US conducted between 2002 and 2014 revealed that multifocal soft contact lenses (MFCL) are prescribed more frequently (12.3% of soft lens fits) than monovision corrections (5.0% of soft lens fits).[2]

Multifocality is accomplished in soft aspheric contact lenses by variation of zonal power incorporating controlled spherical aberration (SA): theoretically negative in center-near and positive in center-distance designs. A recent study revealed that negative SA, measured with a Hartmann–Shack based technique, occurred for almost all of the multifocal contact lenses, including the center-distance designs in vitro,[3] and has been reported that negative SA leads to an increase in relative peripheral hyperopia and additionally improve vision performance in high and low contrast conditions.[4]

Recent studies have shown that MFCL increases the measured high-order ocular aberrations (HOA).[5-11] Although the 'best' image on the retina is degraded by the induced spherical aberration, this is outweighed by the increase in the vergence range over which there is no apparent deterioration in retinal image quality, i.e. depth of focus (DoF) is increased.[6, 12] However, DoF enhancements involves some deterioration in the level of vision, namely in the contrast sensitivity function (CSF)[13] or visual acuity (VA), although clinical studies revealed that CSF is mostly unaffected by centre-near MFCL comparing with single vision contact lens.[8] Also, a combination of 4th order SA and 6th order SA with opposite signs has proved to increase DoF in a factor of 3.6 and by this increase the range of near vision,[14, 15] while trefoil and coma appears to not significantly modify the DoF.[16]

Previous clinical trials showed good performance of centre-near MFCL17 and simultaneous asymmetrical design MFCL17,[18] providing acceptable visual acuity in distance, but not satisfactory at near for early presbyopes. Martin and Roorda have shown that visual quality with bifocal soft CLs can be predicted based on CL induced ocular aberrations.[19] However, there is a great inter-individual variability in subjective acceptance which may be attributed to inherent optical factors, such as pupil size,[20] inherent ocular HOA,[10, 12] binocular summation[21] and personality characteristics such as tolerance to blur and anxiety.[22]

The purpose of this study was to investigate the influence of center-near and center-distance MCLs on vision using commercially available multifocal CL designs (Biofinity Multifocal), specifically the combined effects of inherent ocular aberrations and induced aberrations by the different MFCL design on visual performance at distance and near under high and low contrast conditions.

7.3. Methods

7.3.1. Subjects and Inclusion Criteria

Forty-three participants were enrolled in the study at the Clinical and Experimental Optometry Research Lab of University of Minho. The inclusion criteria were a minimal age of 45 years; maximal spectacle astigmatism of 0.75 diopter (D) in either eye, best-corrected distance VA of at least 0.00 logMAR in each eye, no binocular vision anomaly, no evidence of ocular disease or previous ocular surgery and no topical or systemic medication need that might interfere with or contraindicate contact lens wear. Participants with refractive error higher than ± 4.00D were excluded. All subjects gave informed written consent after they received an explanation of the nature, procedures, and consequences of the study, and were screened before enrolment to ensure that they met study eligibility criteria. The study was conducted in accordance with the tenets of the Declaration of Helsinki and followed a protocol approved by the Institutional Review Board. All measurements were performed by the same operator.

7.3.2. Contact Lenses

Participants were fitted with Biofinity® Multifocal contact lens (Cooper Vision, Fairport, NY) made by silicone hydrogel material (Comfilcon A) with water content of 48%, diameter of 14.0 mm and a base curve of 8.60 mm.

Subjects received the MF contact lenses, according to the manufacturer's fitting guidelines for the initial lens selection. Ocular dominance was identified using the sensory dominance method in which the participant looked to a line immediately below the best VA (high contrast logMAR VA chart at 4 m), and a +1.50-D lens was placed alternately in front of each eye for a few seconds and the subject described which eye had more blurred vision under binocular conditions.

The balanced presbyopic design combines MF optics with one lens for distance viewing and the other lens for near viewing. This design combines spherical, aspheric optics and unique zone sizes to yield a "distance" (D design) lens for the dominant eye (center-distance design), which emphasizes distance vision, and a "near" (N lens) lens for the non-dominant eye (center-near design), which optimizes near vision. The distance lens has a spherical central zone 2.3 mm in diameter for distance vision, surrounded by a 5.0 mm annular aspheric zone and an 8.5 mm spherical annular zone both increasing in add power. In contrast, the near lens has a 1.7 mm spherical central zone dedicated to near vision followed by a 5.0 mm aspheric annular zone and an 8.5 mm spherical annular zone both with decreasing add power. In this study, the lens fitting was assessed for proper centration and reduced lag (<0.25mm) of the lens on lateral gaze.

7.3.3. CSF Evaluation and Stereoacuity

The CSF was recorded at 40 cm using the Functional Acuity Contrast Test (F.A.C.T) incorporated in a Functional Visual Analyzer (StereoOptical Co. Inc., Chicago, IL) for spatial frequencies of 1.5, 3, 6, 12, and 18 cycles/ degree. This device allows fine control of the distance of the examination and luminance conditions and provides comparable values to the Vision Contrast Test System VCTS 6500 (Vistech Consultants, Dayton, OH).[13] The results correspond to the binocular distance CSF in logarithmic units. The near stereoacuity was recorded at 40 cm using the Stereo Fly SO-001 (StereoOptical Co.).

7.3.4. Vision Assessment

With multifocal contact lenses, the optimal distance and near VA and on-eye lens fit were ensured for each eye using standard optometric techniques and if needed, the contact lens was replaced by the one that would provide better binocular vision results. All clinical measurements of visual function were conducted monocularly and binocularly under consistent room illumination and natural pupil sizes were used for comparing the effect of the different designs on vision function.

The distance VA was recorded at 4 meters with a Logarithmic Visual Acuity Chart "ETDRS" Precision Vision, IL) under high (100%) (CAT No. 2110) and low (10%) contrast (CAT No. 2153) conditions with a Cabinet Illuminator No. 2425 (Precision Vision, IL). The near VA was recorded at a distance of 40 centimeters using the Logarithmic Visual Acuity Chart 2000 "New ETDRS" (Chart "1"- CAT No. 2106), as recommended, for high (100%) contrast and with "Chart "2" (CAT No 2117) for low-contrast (10%) conditions. All VA values reported refer to high (HCDVA) or low (LCDVA) contrast distance VA while HCNVA and LCNVA will be used for high-or low-contrast near

VA. The visual acuity was evaluated at two experimental conditions: at baseline that correspond the best corrected refraction condition and with MFCL after 15 days of wear.

7.3.5. HOA Assessment

A commercially available Hartman-Shack aberrometer (IRX3, ImaginEyes, France) was used to determine higher-order aberrations in unaided eyes (baseline) and in subjects' eyes fitted with MFCL after 15 days of adaptation. For averaged, three measurement were performed with subject observing the instrument's internal fixation target (6/12 Snellen "E") against a background luminance of 85cd/m2. To evaluation, it was asked to participant to blink and taken the measure approximately between 4-6 seconds after blink.[23] Zernike polynomials were used to describe the wavefront aberrations of the eye up to the 6th order. To comparison purposes, pupil size was adjusted to 2mm and to maximum round pupil size of each participant using resizing calculation from apparatus software.

7.3.6. Analysis

Pupil size was adjusted to maximum round pupil size of each participant using resizing calculation from apparatus software to comparison purposes. Statistical power analysis performed before the start of the study showed that an estimated final sample size of 20 subjects required a power ranging from 0.88 to 0.92 (to detect differences of 0.08 logMAR unit, i.e.,-4 letters- in HCDVA with a SD of 0.1, -1 whole line), for a level of statistical significance of 0.05. Statistical analysis was performed using SPSS for Windows software (version 19, SPSS, Inc.). The normality of the data was checked using the Kolmogorov-Smirnov test. The nonparametric Friedman test was used to evaluate the statistical significance of VA, and when significant differences were indicated a paired Wilcoxon signed rank-sum test was performed, while Kruskal-Wallis test was used to explore differences between binocular, dominant and non-dominant eye. For CSF comparisons, the repeated measures analysis of variance, with post hoc correction (Bonferroni), for multiple comparisons was used. Pearson's or Spearman's correlations were used to explore the relationship between visual function and induced aberrations by the MFCL. Differences were considered statistically significant when the p value was less than 0.05.

7.4. Results

From 43 participants enrolled, three were lost across follow-up, with no data at the 15th day, and were excluded from the study. Of the 40 subjects who completed the study (mean age, 48.8±3.6 years; range, 45-57 years), 20 (50%) were women and seventeen (42.5%) were myopic. All except two participants were new wearers of CL. Of them, 35% had progressive-add spectacle lenses; 30% had near glasses; and 25% were single-vision spectacle wearers and did not use any near vision correction despite their presbyopic complains. The mean (±SD) distance manifest refraction (as M) was -0.66 ±1.97D (range, -4.00D to 1.63D) in the dominant eye and -0.54± 2.15 D (range -7.38 to +2.00) in the non-dominant eye. The mean add power was +1.58± 0.43 D, ranged by +0.75D to +2.50.

7.4.1. Visual Acuity

The results comparing visual function with the best corrected refraction (baseline) and at the 15 days visit with the MFCL are shown in Table 1. Results were disposed by Dominant and Non-Dominant eye. There were no significant differences in high contrast binocular VA at distance and near with MFCL compared to best correction ($p>0.05$, in both comparisons); there were, however, a significant VA reduction at low contrast with MFCL at both distance and near ($p=0.008$ and $p=0.042$ respectively).

As expected, the monocular distance VA was significantly better with MF correction in the dominant eye compared to non-dominant eye at high contrast (-0.07 vs. 0.09 logMAR, $p<0.01$) and at low contrast (0.13 vs. 0.28 logMAR, $p<0.01$). Similarly, the near VA was significantly better with the MF lens in the non-dominant eye compared with dominant eye in high- (0.06 vs. 0.20 logMAR, $p<0.01$) and low- (0.24 vs. 0.36 logMAR, $p<0.01$) contrast conditions.

Table 7.1. Binocular and Monocular LogMAR Visual Acuity measured in dominant and in non-dominant eye at distance and at near using high contrast (HCDVA and HCNVA respectively) and also low contrast (LCDVA and LCNVA) optotypes. Measurements in two conditions: with best correction in spectacles and after 15 days of Biofinity MFCL wear.

		Mean ± Standard Deviation		
		Best Corrected w/spectacles (Baseline)	MFCL after 15 days	p value
HCDVA	Binocular	-0.12±0.10*	-0.11±0.07*	0.668¥
	Dominant eye	-0.09±0.09*	-0.07±0.11*	0.356¥
	Non Dominant eye	-0.06±0.13*	0.09±0.18*	**<0.001¥**
	p value	0.053&	**<0.001&**	
LCDVA	Binocular	0.04±0.08*	0.07±0.07*	**0.008¥**
	Dominant eye	0.09±0.09*	0.13±0.12*	0.079¥
	Non Dominant eye	0.13±0.15*	0.28±0.15*	**<0.001¥**
	p value	**0.001&**	**<0.001&**	
HCNVA	Binocular	-0.02±0.10*	0.00±0.10*	0.164¥
	Dominant eye	0.05±0.13*	0.20±0.17*	**<0.001¥**
	Non Dominant eye	0.04±0.14*	0.06±0.13*	0.475$
	p value	**0.047&**	**<0.001&**	
LCNVA	Binocular	0.15±0.10*	0.18±0.10*	**0.042¥**
	Dominant eye	0.23±0.14*	0.36±0.17*	**0.001$**
	Non Dominant eye	0.22±0.12*	0.24±0.14*	0.343$
	p value	**0.010&**	**<0.001&**	

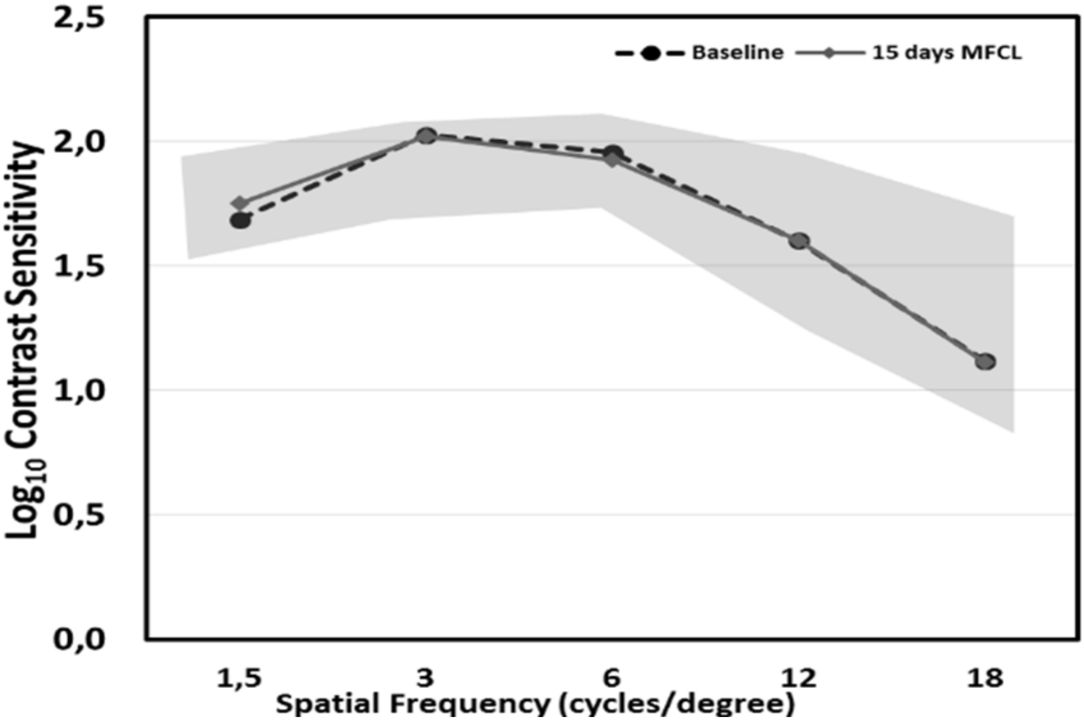
HCDVA= High contrast distance visual acuity; LCDVA= Low contrast distance visual acuity; HCNVA= High contrast near visual acuity; LCNVA= Low contrast near visual acuity

* Friedman test; ¥ WilcoxonSigned Rank test; $ Paired Sample T-Test; & Kruskal-Wallis test. Significant differences are highlighted in bold

7.4.2. CSF and Stereoacuity

There were no significant changes in the distance CSF with MF correction compared with baseline (p>0.05 for all spatial frequencies) and all the values remained within the normal range for CSF (Figure 1). The mean stereoacuity was 79±106 (range, 20-400) seconds of arc at baseline and it was 71±76 (range, 20-400) seconds of arc with the MF lens at day 15 (p=0.777).

Figure 7.1. *Binocular Log Contrast Sensitivity measured at 1.5, 3, 6, 12, and 18 cycles per degree at Baseline (best corrected vision with spectacles) and after 15 days corrected by Biofinity Multifocal Soft Contact Lenses.*

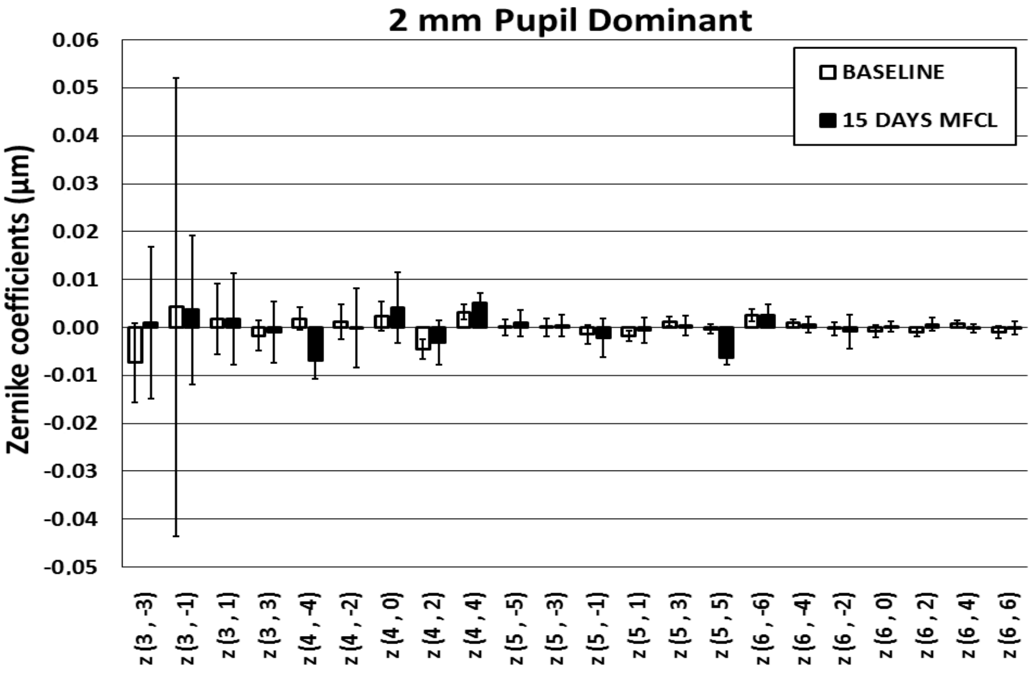


7.4.3. Pupil Size Differences

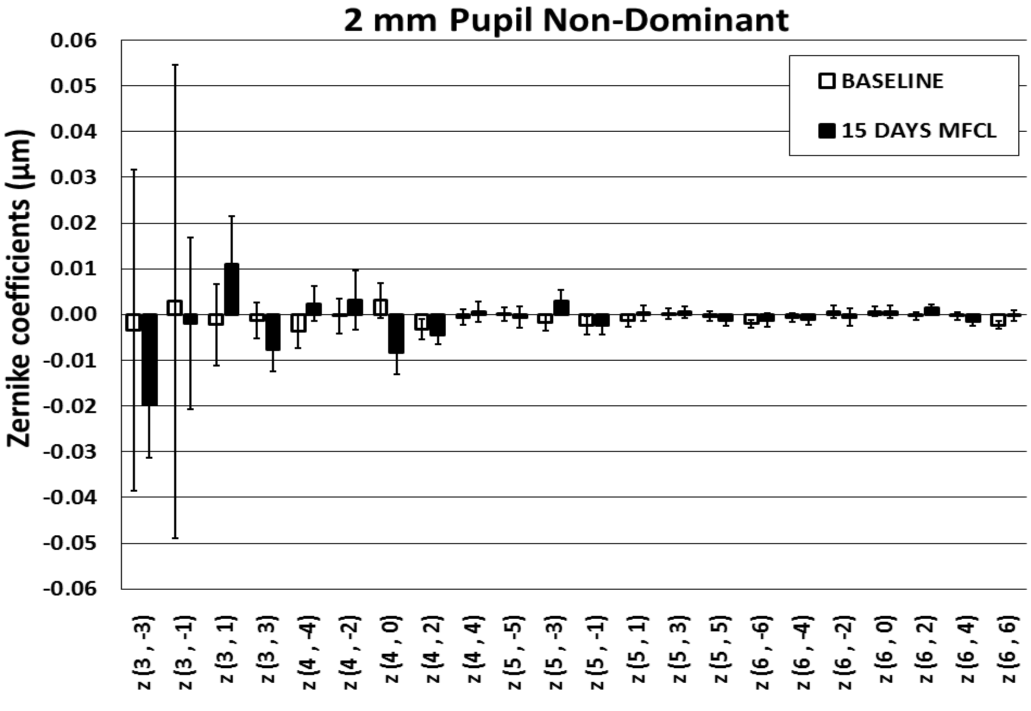
With regards to the max round pupil size, there were no significant differences comparing pupil size between dominant and non-dominant eye, neither in unaided condition (5.30±0.75 vs 5.33±0.79, Anova, F=0.007, p= 0.933) or with MFCL after 15 days of wear (n (5.32±0.77 vs 5.28±0.81,Anova, F=0.002, p= 0.962). There is a strong and significant correlation between pupil size at unaided condition and pupil size with MFCL (Rho=0.950, p<0.001)

7.4.4. Induced Aberrations by MFCL – 2mm Pupil

Figure 7.2 shows the difference between the monochromatic aberrations for the eye measured with and without the contact lens with a 2-mm pupil diameter and for dominant (a) and non-dominant eye (b). Fig 7.2c represents the main induced higher order aberrations (HOA) by the worm MFCL.



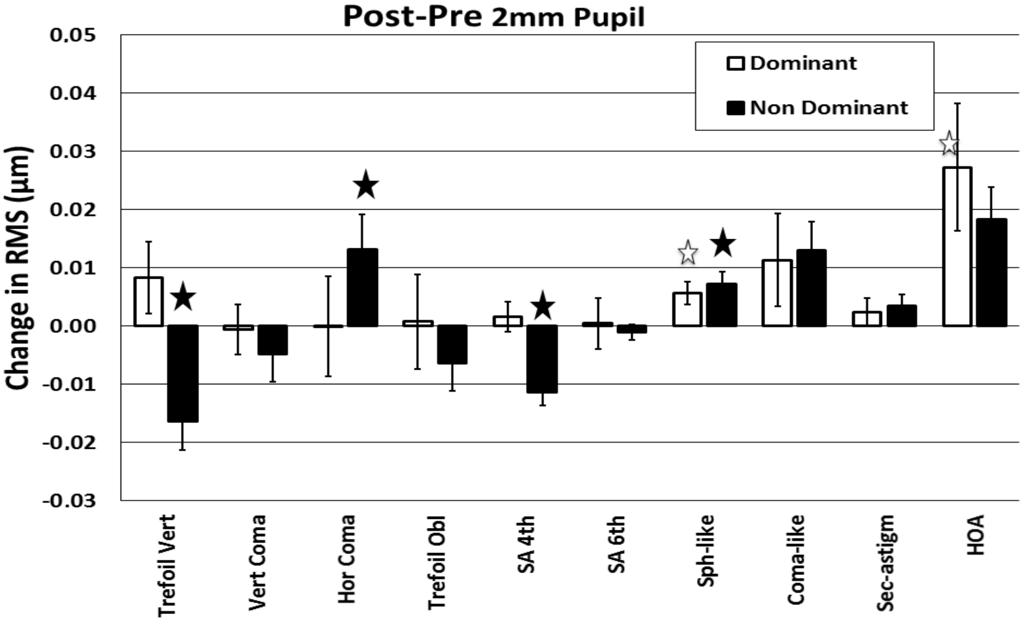
(a)



(b)

In the Dominant eye with wear of MFCL and for 2mm pupil there is small increase in almost all Zernike coefficient comparing with baseline (Figure 7.2a), being significant the changes seen to Spherical-like RMS aberration (p=0.010) and HOA (p=0.019) as well (Figure 7.2c). In Non-Dominant eye, with MFCL and for 2mm pupil size there is a significant increase in negative trefoil (Z6) (p=0.002); a significant increase at positive horizontal coma (Z8) (p=0.034) and a significant increase of negative 4th order spherical aberration (Z12) (p<0.001) (Figure 7.2b).

Additionally, there are also significant changes in Spherical-like RMS (p=0.001), Coma-like RMS (p=0.013) and HOA (p=0.003) with MFCL (Figure 7.2c).

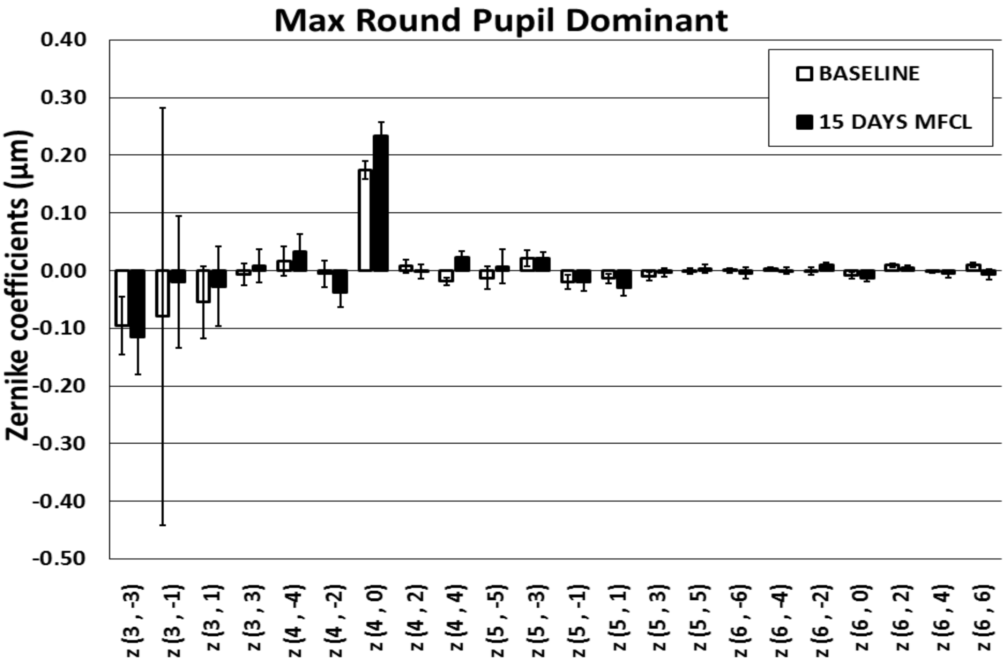


(c)

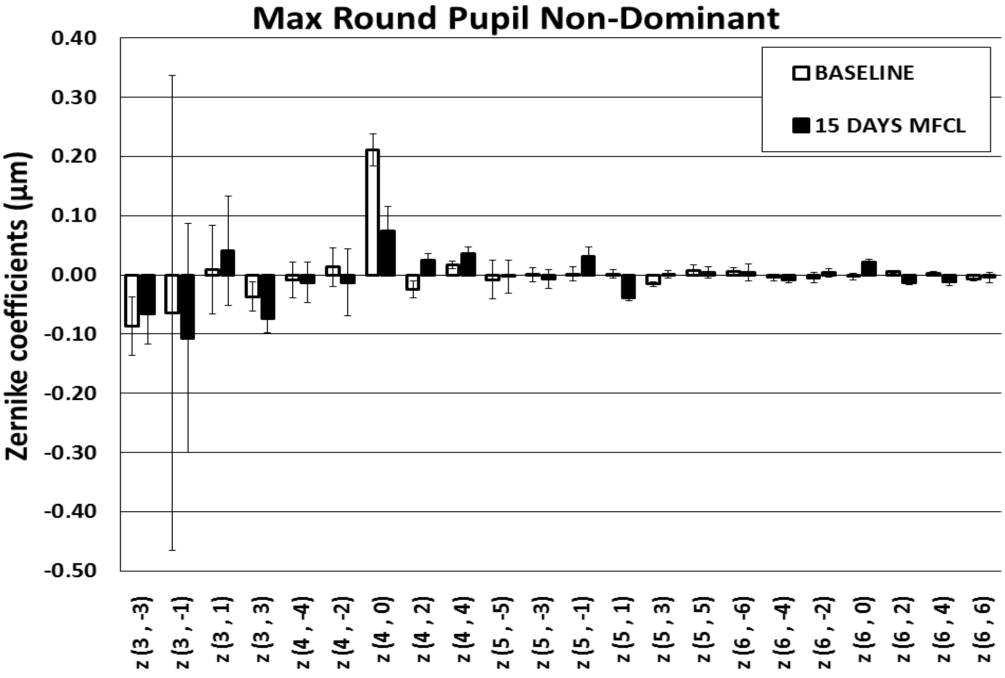
Figure 7.2. Aberrations (Zernike coefficients up to 6th order) measured for a 2mm pupil for the naked eye (baseline) and the eye wearing the Biofinity Multifocal (15 days MFCL) for Dominant (center-distance) (a) and for Non-Dominant eye (center-near) (b). (c) Absolute difference of aberrations between the naked eye and the eye wearing the contact lens averaged for Dominant and Non-dominant eye. Error bars indicate standard error of the mean. Stars represent cases of statistically significant differences (p<0.05).

7.4.5. Induced Aberrations by MFCL –Max Round Pupil

Figure 7.3 shows the difference between the monochromatic aberrations for the eye measured with and without the contact lens with a max-round pupil diameter and for dominant (a) and non-dominant eye (b). Fig 7.3c represents the main induced higher order aberrations (HOA) by the worm MFCL.



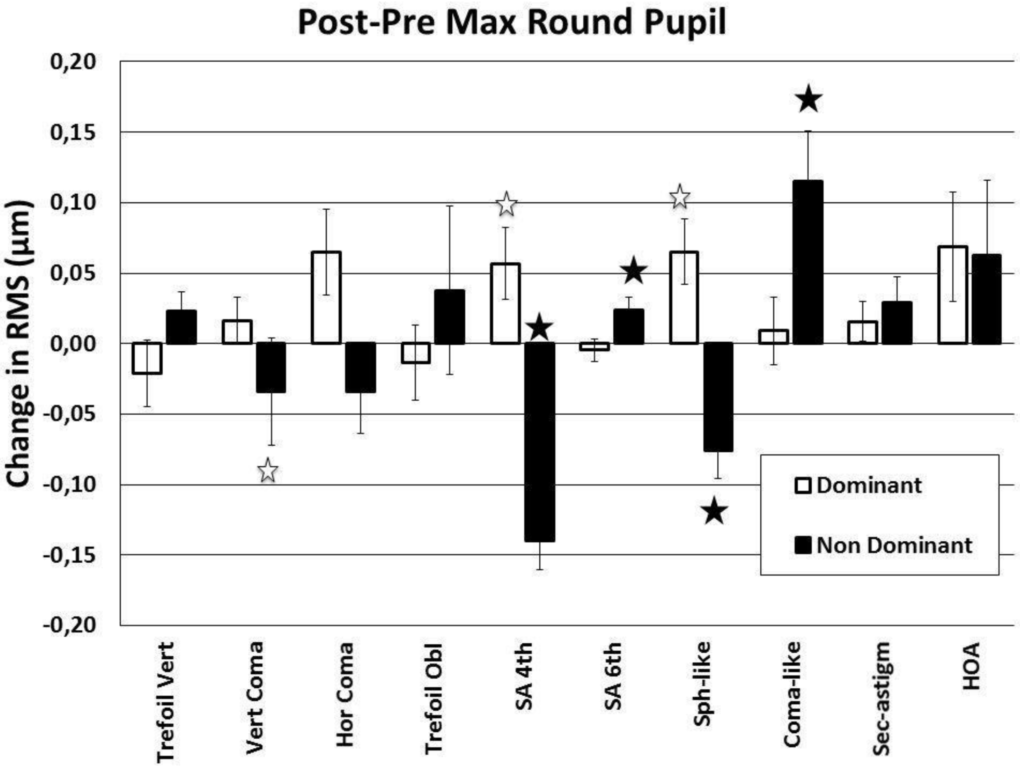
(a)



(b)

In the Dominant eye, there is a positive increase in almost all Zernike coefficients (Figure 7.3a) being significant in Vertical-Coma (p=0.021), SA 4th (p=0.038) and Spherical-like RMS (p=0.014) (Figure 7.3c). A significant positive correlation was found between induced Trefoil RMS and high-contrast distance VA (Rho=0.354, p=0.031) i.e. the more positive trefoil RMS the worse (i.e. more positive) the HCVA.

In Non-Dominant eye, with MFCL there is a significant increase in negative SA 4th ($p<0.001$) as seen at Figure 7.3b and 7.3c; a significant positive increase in SA 6th ($p=0.002$). Additionally, the induced aberrations were also significant in Spherical-like RMS ($p<0.001$) and Coma-like RMS ($p=0.007$) (Figure 7.3c). A significant positive correlation was found between induced Secondary-Astigmatism RMS and high-and low-contrast distance VA (Rho=0.556, $p<0.001$ and Rho=0.448, $p=0.005$) and between induced HOA and low contrast distance VA (Rho=0.350, $p=0.031$).



(c)

Figure 7.3. Aberrations (Zernike coefficients up to 6th order) measured for Max-Round pupil for the naked eye (baseline) and the eye wearing the Biofinity Multifocal (15 days MFCL) for Dominant (center-distance) (a) and for Non-Dominant eye (center-near) (b). (c) Absolute difference of aberrations between the naked eye and the eye wearing the contact lens averaged for Dominant and Non-dominant eye. Error bars indicate standard error of the mean. Stars represent cases of statistically significant differences ($p<0.05$).

7.5. Discussion

On-eye high-order aberrations induced by MFCL in presbyopic subjects are dependent on each multifocal optical design and correlate differently with visual performance as we observed in current study.

Recent studies have confirmed MFCLs as a valuable option in presbyopia correction once it provides good visual acuity at distance and near range of clear vision, better patient satisfaction[24, 25] as well as patient preference over another options to compensate presbyopia.[26] Regarding visual performance, in the present study there were no significant differences in binocular distance and near VA at high-contrast wearing MFCL comparing with best subjective refraction, while binocular vision at distance and near under low contrast conditions was slightly reduced when wearing MFCL (Table7.1). These results are comparable to those obtained in previous studies using a different MFCL similar to the Biofinity MF design (Proclear MF lens)[27] or with studies that used the same design (Biofinity MF) .[7, 9, 28, 29] Additionally, stereopsis and the CSF did not reveal a significant difference (all $p > 0.05$) by the wear of the Biofinity MF. These data were measured binocularly, and it was not possible to correlate with monocular visual performance or with monocular induced aberrations and only give us the assurance that globally the binocular CSF was not significantly altered by the MFCL. There are however, significant differences in VA at high- and low-contrast when compared monocularly. Those differences were expected, since we used a MF contact lens that combines different spherical and aspheric optics for the dominant and non-dominant eyes while different studies used a center-near aspheric MF lens in the dominant and non-dominant eyes.[7] The asymmetric nature of the current design somewhat limits the distance vision in the non-dominant eye and the near vision in the dominant eye, which is directly related to the central spherical 1.7 mm near or 2.3 mm distance areas, respectively.

It is of knowledge that patient satisfaction is an important data to evaluate multifocal adaptation. In present study we did not evaluate participant satisfaction across 15 days of wear being it a limitation of the study, however a recent study using the same MFCL reported good subjective visual satisfaction concerns to comfort and handling, subjective visual performance, and subjective task performance such as and wearing success after 15 days of MFCL wear.[28]

Different visual performance of MFCL depends on various factors, including the power of addition, lens zone geometry design and material and pupil size.[8, 10, 12, 30, 31]

Lopez-Gil et al.[32] reported that the wave aberration measurement of eyes while wearing a contact lens can be considered as the sum of eye's aberrations and lens aberrations and consequently, the aberrations of a contact lens can be obtained by subtraction of eye's aberrations while wearing the contact lens and eye's aberrations without the contact lens, as we performed in the current study. Spherical aberration is one of the high-order ocular aberrations that are particularly important in relation MFCL performance since, depending upon its sign; it may enhance or reduce the effects of multifocality.[10, 12] Any variation of zonal power is equivalent to change in spherical aberration. In soft aspheric contact lenses, multifocality is enhanced by incorporating controlled spherical aberration: negative in center-near and positive in center-distance designs.

Most recent studies have shown that wear MFCL induces an increase in high-order ocular aberrations.[5-11] The most significant increase was noted for the SA 4th Zernike coefficient and central-near multifocal contact lenses induce large amounts of negative SA while center-distance contact lenses induce an increase in positive SA. Peyre et al.[5] reported that Proclear D (add +2.00) and Proclear N (add +2.00) were the soft contact lenses designs with the most significant increase in total HOA (increase of 29% and 43%, respectively) among eight different multifocal contact lenses studied. Legras et al.[6] studied monochromatic aberrations when wearing center-distance Proclear multifocal and with a center-near Proclear multifocal add +2.00 contact lens and showed that the worn MFCL mainly induced in average 0.31 µm of astigmatism, 0.28 µm of coma and 0.11 µm of SA (for a 5mm pupil size). Similar results were observed in the current study. For a 2mm pupil, the changes in ocular aberrations induced by the worm MFCL were more pronounced in the center-near design probably caused by transition of near central zone and aspheric distance zone that starts out of central 1.7mm, in which it was observed a significant increase in negative trefoil (Z6, p=0.002) and positive horizontal coma (Z8, p=0.034) while 4th order SA became significantly more negative (Z12, p<0.001).

7.5.1. Pupil Size

Pupil diameter plays an important role in determining the impact of optical aberrations on the eye, in addition to altering the depth of focus. In the current study, a pupil diameter of 2 mm was chosen to ensure that we measure aberrations induced mainly by the portion of the MFCL that corresponds exactly to the near power, in the case of center-near design, or distance power in the case of center-distance design. On the other hand we choose max-round pupil to observe the induced aberrations when the maximum pupil is reached, to simulate in the changes in aberrations induced by the MFCL over a wide range of pupil size that represents an average of pupil size in dim and bright illumination. Gifford et al.[8] reported a significant effect of pupil size on SA 4th and SA 6th Zernike coefficients, measured with the multifocal designs (Purevision and Airoptix) particularly for the high add designs. The increase in pupil size from 4 to 6 mm lead to greater negative SA 4th for high add, while SA 6th increased in line with pupil size from 4 mm to 6 mm pupil diameters within each lens design. Similar results were observed in the present study for the center-near design; SA 4th significantly increased negatively in both 2mm and max round pupil in the non-dominant design, while SA 6th showed a significant increase. Some authors[6, 15, 33] have explored the positive effect of SA 4th on the DoF and showed a significant increase in DoF when adding different amounts of SA 4th. In addition they also studied some combinations of SA 4th and SA 6th and observed that a combination of the same signs of SA 4th and SA 6th did not change the DoF obtained with only SA 4th, whereas inducing certain SA 6th with opposite sign than SA 4th increases the DoF obtained with only SA 4th. Similar results were observed at present study with non-dominant optic design at max round pupil condition.

Best visual performance was achieved with binocular compared to monocular vision at all conditions tested. It has recently been shown that binocular viewing improves visual perception of out-of-focus images to a much greater extent than it does for in-focus images.[10] It seems that by wearing de MFCL during the 15 days[28] perceptual processes, such as binocular summation and the neural adaptation phenomena to aberration changes, enhance the interpretation of superimposed multiple images on the retina, as expected. Although in present study was measured binocular VA, comparisons and correlations only have been performed in monocular condition. Plainis et al.[34] observed advantage of binocular over monocular vision under spherical positive defocus induction in young subjects, in which only 0.02 units of logMAR difference were caused by reduction of pupil size at binocular condition comparing with monocular (dominant eye). Authors explain binocular facilitation as caused by activation of a larger population of neurons closer-to-threshold. Applegate et al.[35] observed that The RMS wavefront error and equivalent defocus are not good predictors of visual performance for low levels of optical aberration poiting the Strehl ratio as a good predictive measure of visual performance. In the present study, in majority supports that aberrations induced by the MFCL did not compromises a reasonable VA in a clinical setting.

7.5.2. Coma, Trefoil, Spherical Aberration and Secondary Astigmatism

The Astigmatism induced by the MFCL may amplified the multifocal behavior of the lenses, that could be defined by an enlarged depth-of-field with a worse peak performance.[6] Additionally, differences in ocular and lens design parameters, i.e. base curve and diameter, and material properties can affect the fit of MFCLs and thereby the lens centration. It has been reported that some MFCLs decentered more than others and increase odd higher-order aberrations such as coma and, also that decentration of MFCLs reduced objective visual performance.[36-38] Thus, the reduction observed in the current study for low-contrast VA may be justified by the values of coma, trefoil and astigmatism induced by the MFCL. A recent study on non-presbyopes,[37] compared measured on-eye HOA and lens decentration among several commercial single vision contact lenses and MFCL. Out of all MFCLs, only the Proclear MFCL lenses exhibited a significant difference in coma when compared to a single vision control and were also the only MFCLs that were significantly decentered. In the present study, despite efforts to guarantee satisfactory lens centration and no excessive movement, the decentration of the MFCL was not measured, we can presume that some of the changes observed at 3rd order HOA could be due to small decentering of the MFCL. Applegate et al.[39] found that secondary astigmatism and SA affects more VA. This may be the cause of the worsen distance VA at high- and low- contrast observed in present study with center-near MFCL which induce more secondary astigmatism, independently of pupil size.

A limitation of present study was the fact that measured HOA was performed in the unaided eye and a single vision CL rather than uncorrected control should be chosen to specifically investigate how MFCLs differ from a single vision soft CL design. The impact of multiple refractive zones across the pupillary zone can lead to the cancelling out of aberrations across the measured pupil, making a direct comparison of induced aberrations of different MFCL lens designs difficult as well as their influence in VA. However, in present case, the majority of the participants had good distance and near vision with their habitual correction or in some cases with the absence of any type of refractive correction before the contact lens trial, secondly, one of the aims of the study was to explore how the induced HOA of center-near and center-distance MFCL designs can influence differently the visual performance of presbyopic patients in a more real wear situation.

7.6. Conclusions

On-eye higher-order aberrations induced by tested MFCLs were dependent of design (Dominant and Non-dominant) and coupling of the wearer’s inherent ocular aberrations differently affects their visual performance. Aberrations that were induced by MFCL allow preserving binocular distance visual acuity of presbyopes similar to that achieved with spectacles.

7.7. References

1. Morgan PB, Efron N, Woods CA. An international survey of contact lens prescribing for presbyopia. *Clin Exp Optom*. 2011;94:87-92.

2. Efron N, Nichols JJ, Woods CA, et al. Trends in US Contact Lens Prescribing 2002 to 2014. *Optom Vis Sci* 2015;92:758-67.

3. Wagner S, Conrad F, Bakaraju RC, et al. Power profiles of single vision and multifocal soft contact lenses. *Cont Lens Anterior Eye* 2015;38:2-14.

4. Rae SM, Allen PM, Radhakrishnan H, et al. Increasing negative spherical aberration with soft contact lenses improves high and low contrast visual acuity in young adults.*Ophthalmic Physiol Opt* 2009;29:593-601.

5. Peyre C, Fumery L, Gatinel D. Comparison of high-order optical aberrations induced by different multifocal contact lens geometries. *J Fr Ophtalmol* 2005;28:599-604.

6. Legras R, Benard Y, Rouger H. Through-focus visual performance measurements and predictions with multifocal contact lenses. *Vision Res* 2010;50:1185-93.

7. Vasudevan B, Flores M, Gaib S. Objective and subjective visual performance of multifocal contact lenses: pilot study. *Cont Lens Anterior Eye* 2014;37:168-74.

8. Gifford P, Cannon T, Lee C, et al. Ocular aberrations and visual function with multifocal versus single vision soft contact lenses. *Cont Lens Anterior Eye* 2013;36:66-73.

9. Pinero DP, Carracedo G, Ruiz-Fortes P, et al. Comparative analysis of the visual performance and aberrometric outcomes with a new hybrid and two silicone hydrogel multifocal contact lenses: a pilot study. *Clin Exp Optom* 2015;98:451-8.

10. Plainis S, Ntzilepis G, Atchison DA, et al. Through-focus performance with multifocal contact lenses: effect of binocularity, pupil diameter and inherent ocular aberrations. *Ophthalmic Physiol Opt* 2013;33:42-50.

11. Ruiz-Alcocer J, Madrid-Costa D, Radhakrishnan H, et al. Changes in accommodation and ocular aberration with simultaneous vision multifocal contact lenses. *Eye Contact Lens* 2012;38:288-94.

12. Bakaraju RC, Ehrmann K, Ho A, Papas E. Inherent ocular spherical aberration and multifocal contact lens optical performance. *Optom Vis Sci* 2010;87:1009-22.

13. Piers PA, Fernandez EJ, Manzanera S, et al. Adaptive optics simulation of intraocular lenses with modified spherical aberration. *Invest Ophthalmol Vis Sci* 2004;45:4601-10.

14. Benard Y, Lopez-Gil N, Legras R. Optimizing the subjective depth-of-focus with combinations of fourth- and sixth-order spherical aberration. *Vision Res* 2011;51:2471-7.

15. Benard Y, Lopez-Gil N, Legras R. Subjective depth of field in presence of 4th-order and 6th-order Zernike spherical aberration using adaptive optics technology. *J Cataract Refract Surg* 2010;36:2129-38.

16. Rocha KM, Vabre L, Chateau N, et al. Expanding depth of focus by modifying higher-order aberrations induced by an adaptive optics visual simulator. *J Cataract Refract Surg* 2009;35:1885-92.

17. Madrid-Costa D, Garcia-Lazaro S, Albarran-Diego C, et al. Visual performance of two simultaneous vision multifocal contact lenses. *Ophthalmic Physiol Opt* 2013;33:51-6.

18. Sanders E, Wagner H, Reich LN. Visual acuity and "balanced progressive" simultaneous vision multifocal contact lenses. *Eye Contact Lens* 2008;34:293-6.

19. Martin JA, Roorda A. Predicting and assessing visual performance with multizone bifocal contact lenses. *Optom Vis Sci* 2003;80:812-9.

20. Bakaraju RC, Ehrmann K, Falk D, et al. Optical performance of multifocal soft contact lenses via a single-pass method. *Optom Vis Sci* 2012;89:1107-18.

21. Plainis S, Petratou D, Giannakopoulou T, et al. Binocular summation improves performance to defocus-induced blur. *Invest Ophthalmol Vis Sci* 2011;52:2784-9.

22. Woods RL, Colvin CR, Vera-Diaz FA, et al. A relationship between tolerance of blur and personality. *Invest Ophthalmol Vis Sci* 2010;51:6077-82.

23. Montes-Mico R. Role of the tear film in the optical quality of the human eye. *J Cataract Refract Surg* 2007;33:1631-5.

24. Llorente-Guillemot A, Garcia-Lazaro S, Ferrer-Blasco T, et al. Visual performance with simultaneous vision multifocal contact lenses. *Clin Exp Optom* 2012;95:54-9.

25. Gispets J, Arjona M, Pujol J, et al. Task oriented visual satisfaction and wearing success with two different simultaneous vision multifocal soft contact lenses. *J Optom* 2011;04:76-84.

26. Richdale K, Mitchell GL, Zadnik K. Comparison of multifocal and monovision soft contact lens corrections in patients with low-astigmatic presbyopia. *Optom Vis Sci* 2006;83:266-73.

27. Ferrer-Blasco T, Madrid-Costa D. Stereoacuity with balanced presbyopic contact lenses. *Clin Exp Optom* 2011;94:76-81.

28. Fernandes PRB, Neves HIF, Lopes-Ferreira DP, et al. Adaptation to Multifocal and Monovision Contact Lens Correction. *Optom Vis Sci* 2013;90:228-35.

29. Lopes-Ferreira DP, Neves HI, Faria-Ribeiro M, et al. Peripheral refraction with eye and head rotation with contact lenses. *Cont Lens Anterior Eye* 2015;38:104-9.

30. Bennett ES. Contact lens correction of presbyopia. Clin Exp Optom 2008;91:265-78.

31. Bradley A, Nam J, Xu R, et al. Impact of contact lens zone geometry and ocular optics on bifocal retinal image quality. *Ophthalmic Physiol Opt* 2014;34:331-45.

32. Lopez-Gil N, Castejon-Mochon JF, Benito A, et al. Aberration generation by contact lenses with aspheric and asymmetric surfaces. *J Refract Surg* 2002;18:603-9.

33. Rocha KM, Vabre L, Chateau N, et al. Enhanced visual acuity and image perception following correction of highly aberrated eyes using an adaptive optics visual simulator. *J Refract Surg* 2010;26:52-6.

34. Plainis S, Petratou D, Giannakopoulou T, et al. Binocular Summation Improves Performance to Defocus-Induced Blur. *Invest Ophthalmol Vis Sci* 2011;52:2784-9.

35. Applegate RA, Marsack JD, Ramos R, et al. Interaction between aberrations to improve or reduce visual performance *J Cataract Refract Surg* 2003;29:1487-95.

36. Bakaraju RC, Fedtke C, Ehrmann K, et al. Comparing the relative peripheral refraction effect of single vision and multifocal contact lenses measured using an autorefractor and an aberrometer: A pilot study. *J Optom* 2015;8:206-18.

37. Fedtke C, Bakaraju RC, Ehrmann K, et al. Visual performance of single vision and multifocal contact lenses in non-presbyopic myopic eyes. *Cont Lens Anterior Eye* 2016;39:38-46.

38. Fernandez-Sanchez V, Ponce ME, Lara F, et al. Effect of 3rd-order aberrations on human vision. *J Cataract Refract Surg* 2008;34:1339-44.

39. Applegate RA, Sarver EJ, Khemsara V. Are all aberrations equal? *J Refract Surg* 2002;18:556-62.

CHAPTER 8

Peripheral Optical Quality with Two Different Multifocal Contact Lenses in Myopic Eyes

8.1. Abstract

Purpose: To evaluate the feasibility of measuring the peripheral refraction and peripheral high order ocular aberrations (HOA) with an adapted Hartmann-Shack aberrometer and to report the peripheral HOA induced by two commercially available silicone hydrogel multifocal contact lenses (MFCL) with dominant design and multi-concentric design in myopic eyes.

Methods: Sixteen right eyes from 16 myopic patients aged 20 to 32 years (23.2±3.3 years) were evaluated (mean non-cycloplegic central refractive error M±SD= -2.38±1.34D). Peripheral refraction was evaluated without cycloplegia using an open-field autorefractor (G-S, Grand-Seiko, Hiroshima, Japan) and under cycloplegia using a Hartmann-Shack aberrometer (IRX3, ImaginEyes, France) adapted with an experimental peripheral fixation system along the path of light of the instrument. Peripheral refraction with both devices was assessed across the central 80° of the horizontal visual field and ocular aberrations were also evaluated. Procedure was performed in myopic eyes and also in same eyes fitted with two different silicone hydrogel MFCL, both with near add power of 2.5 D: Biofinity Multifocal D and Acuvue Oasys for presbyopia. MFCL were fitted in random order and evaluated in different sessions.

Results: The measures of refraction and HOA obtained with and without the experimental peripheral fixation system were not significantly different. M, J0 and J45 components of refraction were not significantly different between G-S and IRx3 either axially or in different peripheral locations of naked eyes. Differences detected were equal or lower than 0.31±0.29D (J45±SD, at 20N). Both MFCL induced different changes in HOA across horizontal visual field, but greater amount of aberrations were induced by Acuvue Oasys for presbyopia and principally at peripheral locations.

Conclusions: Measures of refraction by G-S and adapted IRX3 showed similar values at center and in all eccentricities evaluated. Interestingly, despite Acuvue Oasys for presbyopia maintained almost unchanged the pattern of M along the horizontal visual field increased significantly the level of HOA induced in the peripheral visual field.

Key-words: peripheral refraction; peripheral optical quality; multifocal contact lenses; peripheral ocular aberration.

8.2. Introduction

Myopia development is usually related with abnormal axial elongation of the eye and can result from deprivation associated with highly aberrated blurred axial retinal image, or as result of relative peripheral hyperopia.[1-4] Recent findings suggested that axial aberrations of the eye might be related with myopia development, although this theory seems to lack some inconsistence when other studies are analyzed.[55-7] Despite controversy about relationship between axial aberrations and myopia, this does not reject the possibility that abnormal axial growth could be caused by the retinal image blur in the periphery where high levels of aberrations are present.[5]

Recent studies conducted with animals[6-8] suggest that alternating hyperopic defocus (supposed to be a strong myogenic stimulus) with periods of myopic defocus, significantly reduces eye growth rates and prevents myopia progression. Some researchers also suggested that the retina recognizes the signal of peripheral defocus and can react through a compensatory eye growth mechanism towards the plane of myopic defocus.[9-11] Benavente-Perez et al[12] studied the impact of positive and negative defocus induced through a multi-concentric contact lens in marmosets. They verified that imposing simultaneously negative and positive defocus resulted in relatively smaller and less myopic eyes, similarly to results previously reported in chicks following similar experimental procedures.[10;11]

In humans, Aller and Wildsoe[13] evaluated the effect of multi-zone bifocal contact lenses in two identical twin girls, and observed that by wearing these lenses the rate of myopia progression was slower. A more recent clinical trial[14] was performed in children wearing Dual Focus contact lenses that also produced a significant myopic retention effect. Other treatments for myopia retention were used in humans such as orthokeratology (OK) or center distance dominant design multifocal contact lenses. Dominant design multifocal contact lenses and orthokeratology are intended to shift the peripheral field curvature from hyperopic to myopic, but are also to be associated with a significant increase in ocular aberrations.[15-17] In order to better understand the mechanisms behind these myopia control treatments, the central and peripheral image quality needs to be better understood. Axial and peripheral aberrations have already been determined in eyes fitted with single vision soft contact lenses (SVCL) and rigid gas permeable contact lenses (RPG).[18] In attempt to investigate the peripheral optical effect of commercially available multifocal contact lenses (MFCL), Bakaraju et al,[19] as well as Rosén et al,[20] have also evaluated peripheral aberrations in a limited sample of eyes fitted with MFCL, however this data have not yet been reported for a larger sample of myopic eyes.

The goals of this study were firstly to evaluate the feasibility of measuring axial and peripheral refraction in naked eyes using an adapted commercial Hartman-Shack aberrometer comparing with open-field autorefractometer. Secondly, to compare peripheral refractive pattern and peripheral optical quality changes induced in the same myopic eyes by two optically different MFCL: an aspheric center distance lens and a multizone concentric lens.

8.3. Methods

8.3.1. Subjects and Inclusion Criteria

All measurements were performed at the Clinical and Experimental Optometry Research Lab (CEORLab, University of Minho, Braga, Portugal). Subjects with ocular disease, undergoing ocular medication or that have undergone ocular surgery were excluded from the study. The patient's refractive error was assessed through a complete optometric examination, including non-cycloplegic objective and subjective refraction. Only patients with myopia between -0.75 and -6.00 and with astigmatism under -1.00D were enrolled. The protocol was reviewed and approved by the institutional review board at the School of Science of the University of Minho. After full explanation of all the procedures in the study, every participant gave their written consent following the tenets of the Declaration of Helsinki.

Twenty-two eyes from 11 young subjects participated in the validation experiments while 16 right eyes from 16 young subjects participated in the experiment measuring the different MFCL.

8.3.2. Axial and Peripheral Autorefraction

An open-field autorefractometer Grand-Seiko (G-S) WAM-5500 (Grand Seiko Co., Ltd., Hiroshima, Japan)[21;22] was used to measure peripheral refraction along horizontal visual field and a custom software (DRRE; CEORLab, University of Minho, Braga, Portugal) provided automatically export of all measurements to an Excel spreadsheet for later statistical analysis. Measuring procedure by eye rotation has already been described[23-25] to obtain axial and peripheral readings; in present work were performed measures at 20° and 40° in the temporal and nasal visual field eccentricities. We have previously demonstrated that as long as appropriate fitting of the lenses is warranted, eye rotation and head rotation provides equivalent results for peripheral refraction measurements. In this study, the lens fitting was assessed for proper centration and reduced lag (<0.25mm) of the lens on lateral gaze.[26]

8.3.3 Axial and Peripheral Aberrometry Setup and Validation

A commercially available Hartman-Shack aberrometer (IRX3, ImaginEyes, France) was adapted with an experimental device for eccentric fixation, in order to allow peripheral optical quality assessment (Figure 8.1). Nine small light emitting diodes (LED) (1.6x0.8mm) were mounted, in an array on top of the instrument to match with eccentricities between 40° nasal and 40° temporal of visual field in 10° steeps. Each LED could be fixated by reflection in a glass plate acting as beam-splitter (B-S) set at 45 degrees across the light path of the aberrometer. A distance of 30±1.5mm between corneal apex and the center of the B-S was maintained through the focusing system of the aberrometer. Axial measurement was performed with the patient fixating the instrument's internal fixation target (6/12 Snellen "E") against a background luminance of 85cd/m^2. Peripheral targets (LED lights) were activated in random order. Only eccentric positions corresponding to 20° and 40° in nasal and temporal visual field were evaluated. The patient rotated the eye to fixate the peripheral targets along the horizontal visual field. Zernike polynomials were used to describe the wavefront aberrations of the eye up to the 6th order.[27] All results refer to 780nm wavelength infrared laser light that is used by IRX3 aberrometer. Despite the slightly differences in wavelength used by the both devices, previous studies have shown that another aberrometer using also 780 nm and autorefraction provide interchangeable measures of refraction.[28] Three measurements were averaged for each position with each instrument.

In order to evaluate the effect of the experimental setup (B-S) along the light path of the aberrometer, a preliminary study was conducted. Refractive measurements and evaluation of the ocular aberrations were performed axially and peripherally at 40° in the nasal and temporal visual field with and without the B-S, in 22 eyes of 11 subjects (mean age 29.6 ± 9.0years). Differences between measurements performed 'with B-S' and 'without B-S' were compared for M, J0, J45, as well as for the Zernike coefficients; Z(3,-1), Z(3,1) (horizontal and vertical coma); and Z(4,0) (4th order spherical aberration), measured axially for a pupil size of 3 and 5 mm and at 40° in the temporal and nasal visual fields only for a circular pupil size of 3 mm. Individual Zernike polynomials and spherical-like, coma-like and total root mean square (RMS) were evaluated). No significant differences were observed between the condition with B-S or without B-S for all parameters under evaluation ($p>0.05$, Paired T-Test and Wilcoxon Ranks Test).

In order to prevent the effect of accommodation provoked for the near targets used, aberrometry were performed in 16 right eyes of 16 subjects (mean age: 23.2±3.3 years; M±SD= -2.38±1.34D) under cycloplegia using Tropicamide 1% (Tropicil®, Edol laboratory, Portugal).

Measurements were performed 30 minutes after instillation of two drops, separated by 5 minutes interval and using peripheral fixation setup in aberrometer IRX3. Non-cycloplegic peripheral refraction was also measured in the same subjects with the Grand Seiko open-field autorefractometer.

8.3.4. Multifocal Contact Lenses

Two commercially available MFCL were used. Both multifocal contact lenses have optical design similar to others CL previously described as potential myopia retention devices: center distance aspheric multifocal29 and multi-concentric lenses.[13] The technical details of the lenses are presented in Table 8.1. Sixteen right eyes from 16 subjects were fitted with both types of MFCL in two different visits in random order. The lenses where chosen according to the best distance spherical correction (M) and with a maximum add power of +2.50D.

Table 8.1. Technical details of the contact lenses used

Parameter	Biofinity Multifocal D	Acuvue Oasys for Prebyopia
Material	Comfilcon A	Senofilcon A
Equilibrium Water Content	48%	38%
Base Curve Radius	8.60 mm	8.40 mm
Overall Diameter	14.00 mm	14.30 mm
Distance Power	Vertexed patient distance refraction	
Near Add Power	+2.50D	High (until +2.50D)
Spherical Central Distance Zone Diameter	3.0 mm	2.0 mm
Aspheric Multifocal Zone Width/Diameter	0.5 mm / 4.0mm	Distance and near power in concentric alternating zones until 8.0 mm of diameter (center-distance)
Spherical Near Zone Width/Diameter	1.50 mm / 8.0 mm	

8.3.5. Data Analysis

Data were treated statistically using SPSS Software, version 20 (SPSS Inc., Chicago, IL). The Shapiro-Wilk Test was applied in order to evaluate the normality of data distribution.

The effect of factors such as measurement location [eccentricities], lens type [Naked eye, Acuvue Oasys for presbyopia or Biofinity D] and device of measure [IRX3 or G-S] on dependent variables M, J0, J45, spherical aberration, coma, secondary astigmatism, total high order aberrations (HOA) and 4th order spherical aberration has been evaluated using multivariate analysis of variance (MANOVA). When MANOVA detected statistically significant effects of a certain factor, we performed an individual ANOVA to each dependent variable, followed by Bonferroni post hoc test. For statistical purposes, a p value lower than 0.05 was considered statistically significant.

8.4. Results

8.4.1. Axial and Peripheral Refraction with MFCL

Axial and peripheral refractive pattern obtained with auto-refractometer (G-S) and aberrometer (IRX3) are presented in figures 8.2, 8.3 and 8.4 as M, J0 and J45 refractive components along the horizontal visual field for naked right eyes (Figure 8.2), eyes fitted with Biofinity Multifocal D lens (Figure 8.3) and fitted with Acuvue Oasys for presbyopia (Figure 8.4). Differences between IRX3 and G-S across horizontal visual field are presented in Table 8.2.

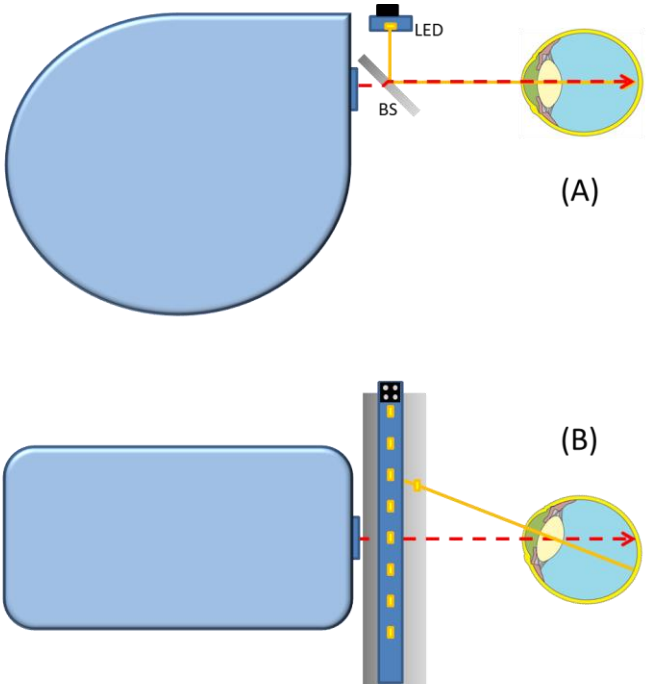


Figure 8.1. *Schematic representation of peripheral fixation device attached to the IRX3 aberrometer in lateral view (A) and sagittal view while fixating a peripheral stimulus at 20° of eccentricity in the temporal visual field for a right eye (B). Draw not to scale. BS: beam splitter; LED: light emitting diodes array.*

Table 8.2. *Summary of difference values of axial and peripheral refractive error in naked eyes and in eyes fitted with Biofinity Multifocal D and Acuvue Oasys for presbyopia represented as M, J0 and J45 measured by IRX3 compared G-S.*

Refractive Vectorial Component	Eccent (degrees)	Naked Eye	Biofinity D	Acuvue Oasys for presbyopia
		Mean Difference ±SD (D)	Mean Difference ±SD (D)	Mean Difference ±SD (D)
M (D)	40N	0.09±1.05	0.32±1.05	0.27±1.53
	20N	0.06±1.03	0.15±1.29	-0.30±1.12
	C	-0.25±0.35	-0.17±0.44	-0.26±0.47
	20T	0.17±0.71	1.01±1.08	-0.31±1.09
	40T	-0.15±0.99	-0.52±1.40	-1.07±2.69
J0 (D)	40N	0.17±0.26	0.29±0.39	0.28±0.74
	20N	0.00±0.29	-0.13±0.29	-0.06±0.36
	C	0.06±0.17	0.22±0.21	0.12±0.28
	20T	0.23±0.25	0.54±0.38	0.15±0.67
	40T	-0.04±0.76	-0.30±1.03	-0.25±1.81
J45 (D)	40N	0.31±0.24	0.81±0.25	0.05±0.46
	20N	0.31±0.29	0.35±0.26	0.46±0.29
	C	0.08±0.19	0.05±0.25	0.13±0.32
	20T	-0.08±0.35	-0.52±0.27	-0.37±0.50
	40T	-0.14±0.37	-0.26±0.50	0.24±1.01

Positive sign of difference means that values obtained in IRX3 in referred eccentricities (Eccent) was more myopic than obtained at G-S. Eccentricities are represented by numerical value followed by N and T that means Nasal and Temporal side of horizontal visual field, respectively. C means central point of fixation (fovea).

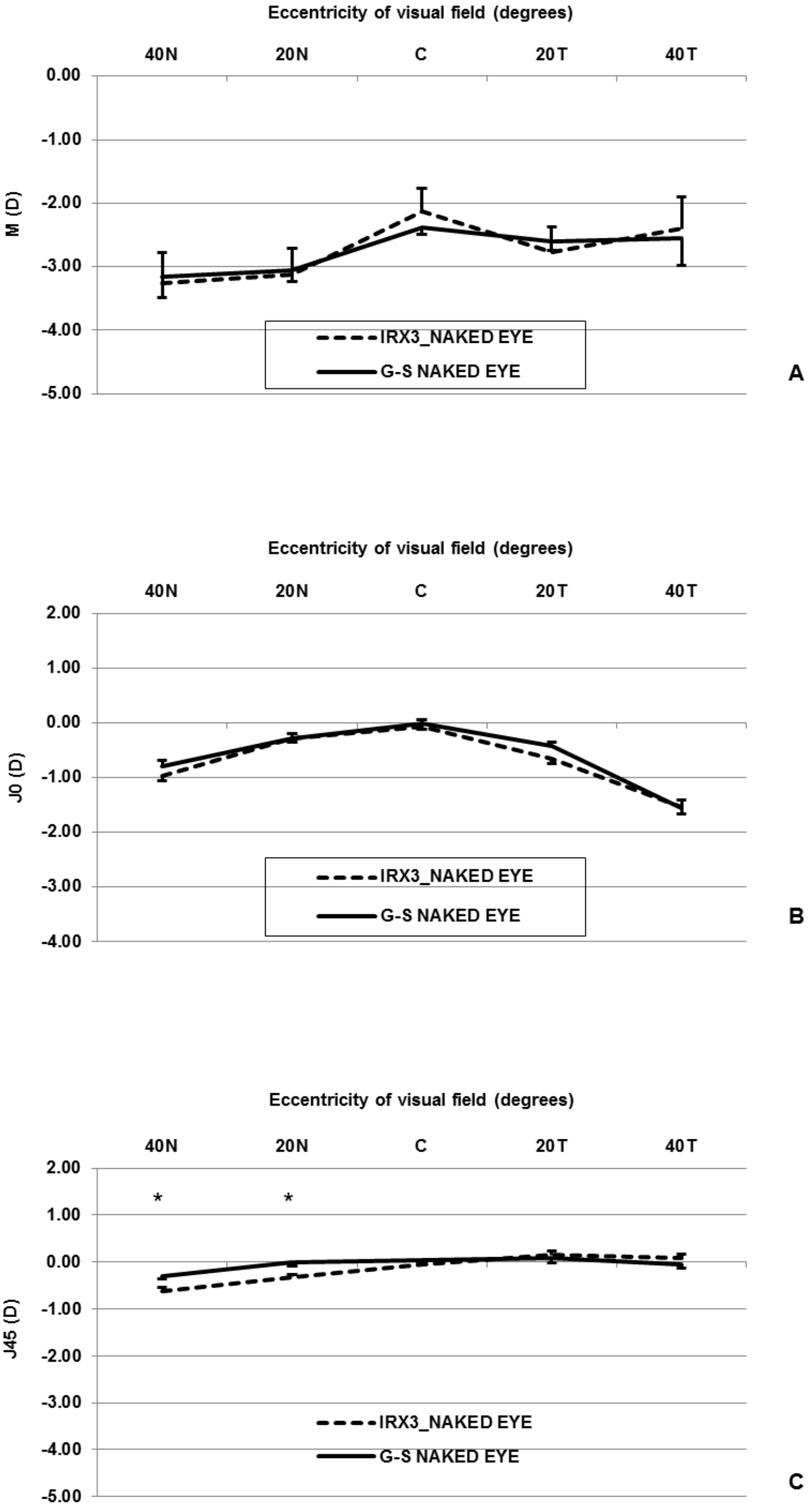


Figure 8.2. Mean refractive error of naked eyes obtained with auto-refractometer (G-S NAKED EYE) and obtained with aberrometer under cycloplegia (IRX3 NAKED EYE) represented as M (A), J0 (B) and J45 (C) along the nasal (N) and temporal (T) visual fields. Error bars represent Standard Error of Mean (SEM). Statistical significant differences (p<0.05) were calculated by one-way ANOVA analysis (*) after ANOVA analysis considering all factors.

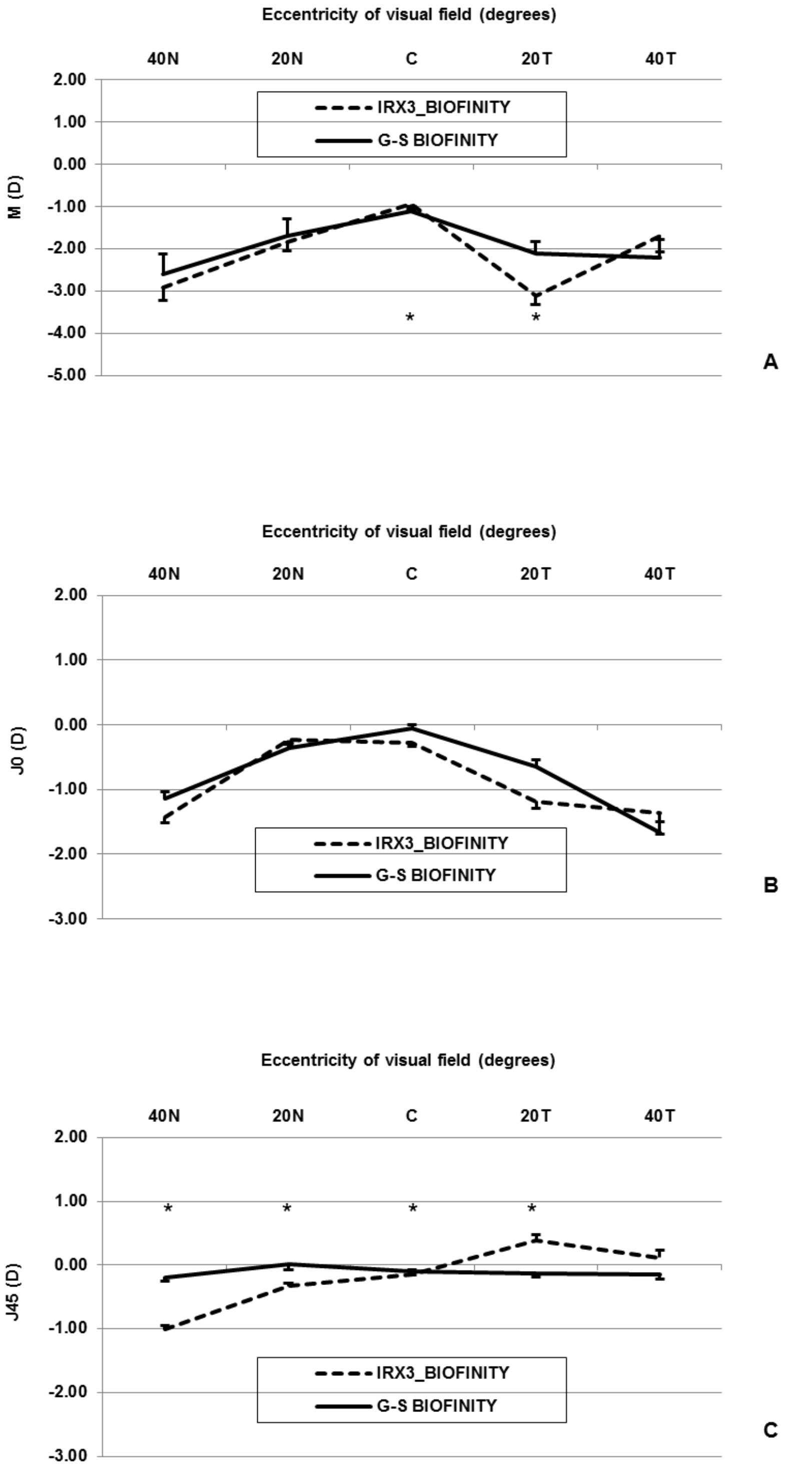


Figure 8.3. *Mean refractive error along the nasal (N) and temporal (T) visual fields of eyes fitted with Biofinity Multifocal D (add=+2.50D) obtained with auto-refractometer (Biofinity G-S) and with aberrometer under cycloplegia (Biofinity IRX3) represented as M (A), J0 (B) and J45 (C). Error bars represent Standard Error of Mean (SEM). Statistically significant differences (p<0.05) were calculated by one-way ANOVA analysis (*) after ANOVA analysis considering all factors.*

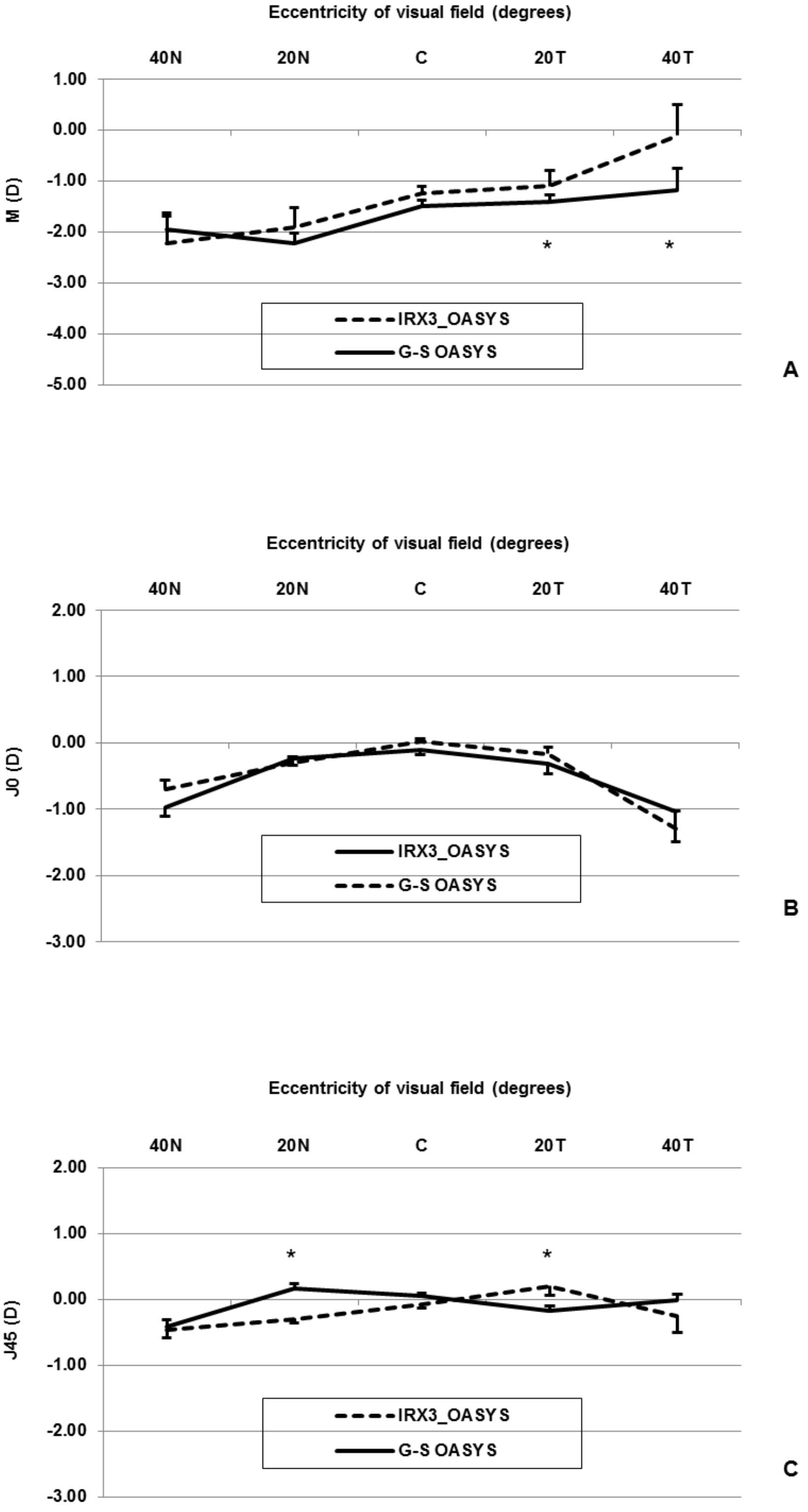


Figure 8.4. *Mean refractive error of eyes along the nasal (N) and temporal (T) visual fields fitted with Acuvue Oasys for presbyopia (add=High) obtained with autorefractometer (Oasys G-S) and with aberrometer under cycloplegia (Oasys IRX3) represented as M (A), J0 (B) and J45 (C). Error bars represent Standard Error of Mean (SEM). Statistically significant differences (p<0.05) were calculated by one-way ANOVA analysis (*) after ANOVA analysis considering all factors.*

G-S measures were similar to aberrometer (IRX3) under cycloplegia. The largest differences detected between devices were -0.25±0.35D (center), 0.23±0.25D (20° temporal) and 0.31±0.29D (20° nasal) for M, J0 and J45, respectively. MANOVA analysis revealed that factors 'lens type', 'location' and 'device' were statistically significant factors for M and J45 components of refraction. However, posterior analysis with ANOVA test showed that M values of Naked eyes are not statistically different between IRX3 and G-S in either point. For J45 only nasal field points (20N and 40N) showed to be significantly different between both instruments.

Cycloplegic IRX3 values of M with Biofinity D (Figure 8.3a) were very similar compared with G-S with the exception of location 20T, in which the difference between devices achieved 1.01±1.08D ($p<0.001$, ANOVA analysis). As referred above there were no significant differences for J0 (Figure 8.3b) but J45 (Figure 8.3c) showed statistically significant differences at all points evaluated with the exception of 40T.

Contrary to the results obtained for Biofinity D, Acuvue Oasys for presbyopia did not induce peripheral myopic defocus (figure 8.4). The horizontal refractive pattern produced was almost flat, comparing eccentric points with the center. Greater differences between both devices were detected with this lens, for M, at 20 and 40° in the temporal field: -0.31±1.09D ($p=0.010$) and -1.07±2.69D ($p=0.008$), respectively. The J45 values were significantly different between devices at 20N (0.46±0.29D, $p=0.005$) and 20T (-0.37±0.50D, $p=0.042$*).*

8.4.2. Axial and Peripheral Optical Quality with MFCL

Figure 8.5 shows the value of different RMS computed for the naked eye and with each one of the MFCL studied. To compare constant round pupils among experimental conditions, in this case for a 2 mm pupil size as this was the minimum value of round pupil size in the peripheral locations. This 2 mm pupil is also comparable to the 2.3 mm circular area measured with the autorefractometer.

Biofinity D does not induce significant changes in secondary astigmatism across the central 80° of visual field compared to the naked eye. The values of coma-like, spherical-like and HOA RMS with Biofinity also were not significantly affected by the MFCL compared to the naked eye. Values of differences are listed in Table 8.3.

Table 8.3. *Summary of mean difference values of RMS calculated by spherical aberration, coma, secondary astigmatism and total HOA and absolute values of 4th order spherical aberration obtained across horizontal visual field under experimental conditions (Naked eye; Biofinity and Oasys).*

		Naked eye - Biofinity	Naked eye - Oasys	Biofinity - Oasys	
Aberration Component	Ecc. (°)	Mean Difference ±SD (µm)	Mean Difference ±SD (µm)	Mean Difference ±SD (µm)	P
Spherical Aberration	40N	-0.004±0.005	-0.016±0.014	0.002±0.001	**<0.001***
	20N	-0.007±0.007	-0.014±0.010	-0.007±0.011	**<0.001***
	C	-0.003±0.006	-0.008±0.009	-0.005±0.009	**<0.001***
	20T	-0.003±0.007	-0.026±0.015	-0.023±0.017	**<0.001***
	40T	-0.006±0.013	-0.039±0.034	-0.033±0.041	**<0.001***
Coma	40N	-0.013±0.030	-0.057±0.034	-0.044±0.046	**<0.001***
	20N	-0.004±0.010	-0.036±0.020	-0.031±0.021	**<0.001***
	C	-0.018±0.027	-0.038±0.036	-0.021±0.039	**<0.001***
	20T	-0.010±0.013	-0.065±0.060	-0.055±0.062	**<0.001***
	40T	-0.030±0.058	-0.126±0.086	-0.096±0.129	**<0.001***
Secondary Astigmatism	40N	-0.008±0.010	-0.032±0.014	-0.024±0.016	**0.001**
	20N	-0.001±0.003	-0.009±0.014	-0.008±0.014	**0.003**
	C	-0.003±0.006	-0.021±0.010	-0.018±0.013	**<0.001***
	20T	-0.004±0.008	-0.034±0.022	-0.030±0.023	**<0.001***
	40T	-0.014±0.019	-0.064±0.051	-0.049±0.062	**<0.001***
HOA Total	40N	-0.027±0.024	-0.093±0.028	-0.066±0.039	**<0.001***
	20N	-0.006±0.010	-0.044±0.025	-0.038±0.023	**<0.001***
	C	-0.014±0.026	-0.057±0.043	-0.043±0.046	**<0.001***
	20T	-0.031±0.016	-0.119±0.073	-0.089±0.079	**<0.001***
	40T	-0.049±0.078	-0.220±0.162	-0.171±0.213	**<0.001***
4th order Spherical Aberration	40N	-0.004±0.015	0.007±0.026	0.011±0.029	0.152
	20N	-0.004±0.007	-0.010±0.014	-0.006±0.014	**0.008**
	C	-0.003±0.009	0.007±0.011	0.008±0.014	**0.012**
	20T	-0.001±0.013	-0.007±0.037	-0.006±0.037	0.702
	40T	0.014±0.012	0.011±0.048	0.003±0.052	0.392

p values were calculated by one-way ANOVA (*), after MANOVA analysis proved interaction between factors 'lens type' and 'location'. Bold values represent differences that were statistically significant, at confidence level of 95%. Eccentricities are represented by numerical value followed by N and T that means Nasal and Temporal side of horizontal visual field, respectively. C means central point of fixation (fovea).

Acuvue Oasys for Presbyopia induced higher values of HOA compared to Biofinity D. There were statistically significant differences for all points and for all aberration components analyzed, when comparing with naked eye condition and also when comparing with aberrations induced by Biofinity D.

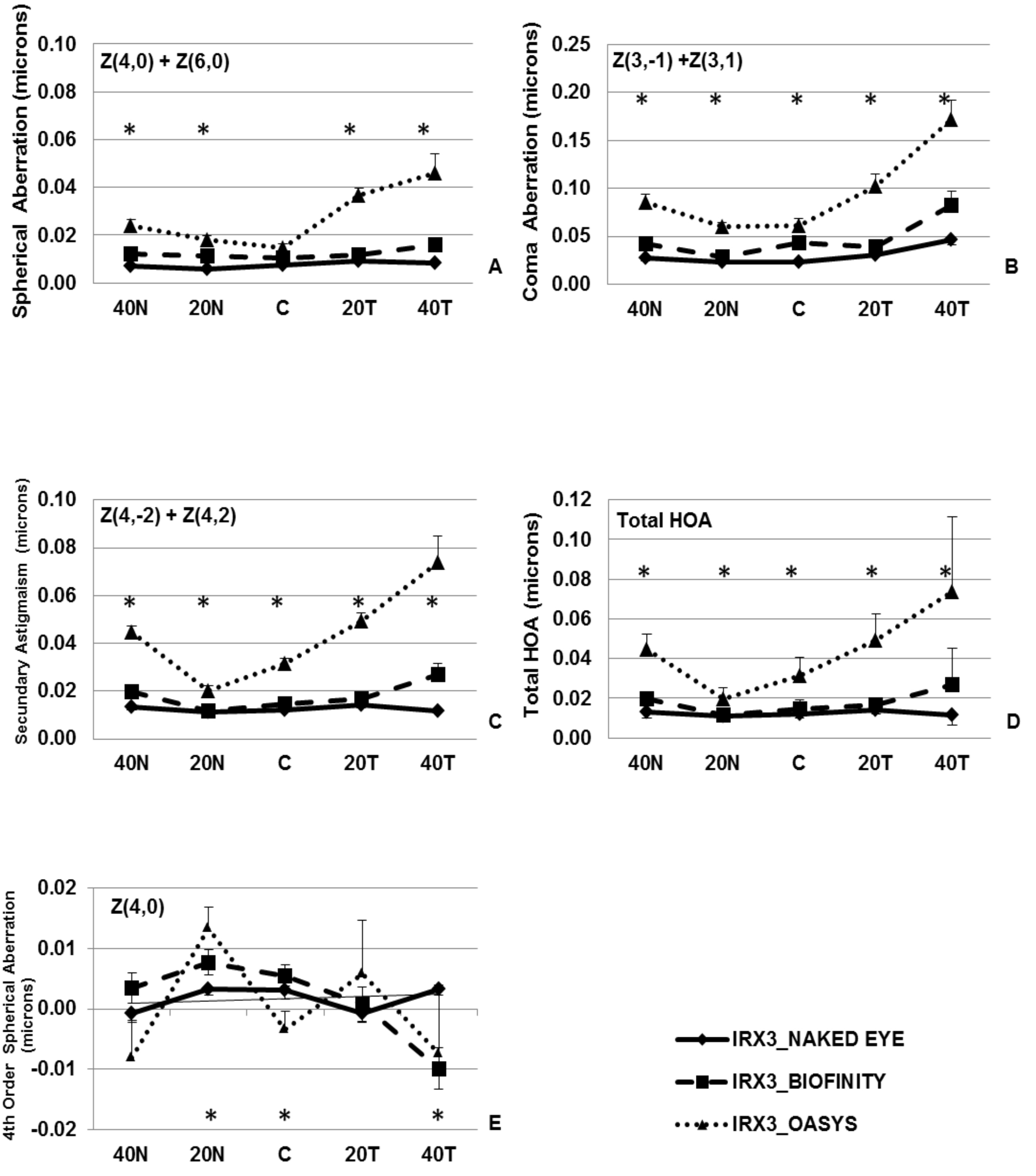


Figure 8.5. *Average RMS wavefront error measured along the nasal (N) and temporal (T) visual fields for 4th and 6th order spherical aberrations (A), horizontal and vertical comas (B), secondary astigmatism (C) total higher-order aberrations up to 6th order (D) and absolute values of 4th order spherical aberration (E). Error bars represent Standard Error of Mean (SEM). Statistically significant differences (p<0.05) were calculated by one-way ANOVA analysis (*) after ANOVA analysis considering all factors.*

However, 4th order spherical aberration were not statistically different with any of MFCL used relatively to naked eye, except for differences between naked eye and Acuvue Oasys for presbyopia at central measurement. There were no differences in 4th order spherical aberration between both MFCL.

8.5. Discussion

8.5.1. Axial and Peripheral Aberrometry Setup and Validation

Peripheral HOA have been previously evaluated along the horizontal visual field in naked eyes and with limited samples of contact lens wearers.[30] Atchison and Schott[30] have measured the peripheral ocular aberrations of naked eyes using a Hartmann-Shack wavefront sensor across central 80° of visual field, in 5° steeps. More recently Mathur, Atchison and Scott[31] also described the trend of HOA across vertical and horizontal meridians of visual field.

Compared to other devices, the experimental setup presented in this study could have two potential limitations, at least, which might be the short distance of targets used to eccentric fixation that make cycloplegia needed and the need to have a B-S in the path of measuring light. Previous researchers[31] have measured peripheral refractive error and peripheral ocular aberrations using a B-S along the instrument's light path to align subject's eye. We have found no effects of the B-S on refractive measurements and also in eye aberrations determination, either in central or peripheral fixation. To overcome the proximity of the targets, cycloplegia was needed in our system and the results were compared to autorefraction using distant targets. Despite it was not expected that the peripheral astigmatism (J0 and J45) components change with accommodative demand for narrower angles,[32] large changes with accommodation might be expected at field angles of 30° and beyond.[33]

8.5.2 Axial and Peripheral Refraction with MFCL

Present results showed similar spherical equivalent values (M) at center (differences between devices of -0.25±0.35, -0.13±0.42 and -0.26±0.48) for Naked eyes, Biofinity D and Acuvue Oasys for presbyopia, respectively. In peripheral locations were found differences between devices that seem to be more relevant at 20° T eccentricity in case of Biofinity D, being about 1.01±1.08D and 0.54±0.38D for M and J0 respectively. These larger differences might be an artifact caused by the transition aspheric zone between distance and near zones, for which the IRX3 seems to be more sensitive than the G-S. However we did not found the same trend at 20° N. Considering that we have ensured proper centration and reduced lag of the lens on lateral gaze, this might be attributed to the natural asymmetry between both retinal hemi-fields, caused by the temporal location of the fovea.[34]

8.5.3 Axial and Peripheral Optical Quality with MFCL

Axial optical quality in subjects wearing contact lenses has been already meticulously evaluated through theoretical calculation and experimental measurements.[35;36] Subjects that wear rigid-gas-permeable (RGP) CL presented lower levels of axial aberration than the ones wearing soft contact lenses (SCL).[35;37] Our baseline data shows that spherical aberration (Z4,0) measured axially in the naked eye was slightly positive (0.003±0.006 microns), which is consistent with results found in previous studies.[5;31] Also were determined in recent studies5 that mean values of Z4,0 were almost constant along horizontal central 40° of visual field, and the signal of central Z4,0 is more positive in emmetropic eyes than in myopes (M±SD= -3.67±1.91D), where it becomes slightly negative (-0.007±0.045μm). A significant correlation between 4th order spherical aberration and mean of spherical equivalent refraction (r^2=0.51, p=0.03) was also reported,[5] indicating that more negative refraction (myopia) implies a more negative spherical aberration. The transition from positive to negative takes place about -3.00D.[5]

Both studied MFCL caused a significant increase in central coma (Z3,-1+Z3,1), spherical aberration (Z4,0+Z6,0), secondary astigmatism (RMS for Z4,-2+Z4,2) and total HOA (Table 8.3), however changes were more evident in the periphery. Oasys MFCL was the one which caused greater increase to all Zernike terms under study. Gifford et al.[38] reported that designs with front aspheric surfaces, namely Purevision Multifocal (Baush&Lomb) and AirOptix Multifocal (CibaVision) increased significantly the amount of on-axis spherical aberration RMS obtained, and these changes increased with increase in add power and with increase of pupil size.[10] Similar findings were also found by Bakaraju et al[19] with aspheric center-near and center-distance MFCL, multizone bifocal contact lenses with center-near and center-distance.

A center-near design (high add) showed to change of Z4,0 from positive to negative,[38;39]as theoretical simulations already indicated by multi-concentric bifocal (center-near) design.[19]

It has been suggested that if is present a lack of correspondence between the demand and the accommodative system response (LAG), the near work may contribute to myopia progression, due to central hyperopic blur. It was also recently determined that increasing accommodation demand in about 4 D causes a significant negative shift in axial Z4,0 (0.10μm)[16;38] and also across the central 40° of visual field.[32] As previousl stated, non-accommodated myopic eyes above -3.00D manifests already negative Z4,0.[5]

The Biofinity D have produced positive shift of Z4,0 in all points evaluated except at 40° in temporal visual field. The Oasys multi-concentric optics showed higher change of HOA at all points particularly at peripheral locations, namely in spherical aberration, however Z4,0 had a negative mean value at central point and also in 40° of eccentricity nasal and temporal. Interestingly, despite Acuvue Oasys for presbyopia maintained almost unchanged the pattern of M along the horizontal visual field increased significantly the level of HOA induced in the peripheral visual field.

Recent study with chinese children found no link between change in peripheral innerent optical quality and the progression of axial myopia. On other hand there was a significant correlation between myopia progression and hyperopic changes occurred at peripheral defocus.[40]

Multi-zone concentric contact lenses, in marmosets caused hyperopic and myopic defocus simultaneously resulting in relatively smaller and less myopic eyes, despite being exposed to a greater percentage of hyperopic defocus. Considering results of similar optic devices[13;14] in humans can be hypothesized that, the overall changes in ocular aberrations induced in myopic eyes wearing the multi-zone concentric lenses could provide a justification for their apparent efficacy in decreasing myopia progression.

In summary, our study showed that a commercial aberrometer could be easily modified to allow peripheral measures of refraction, similarly as was obtained by the auto-refractometer. We have also found that different designed MFCL similar to others used to obtain myopia retention can change peripheral refraction and peripheral optical quality in significantly different ways. The combination of modifications in axial and peripheral refraction and optical quality might involve different paths for myopia retention, with different multifocal or multi-zone/dual-focus optical systems.

8.6. References

1. Diether S, Schaeffel F. Local changes in eye growth induced by imposed local refractive error despite active accommodation. *Vision Res* 1997;37:659-668.

2. Smith EL, III, Hung LF, Ramamirtham R, Huang J, Qiao-Grider Y. Optically Imposed Hyperopic Defocus in the Periphery Can Produce Central Axial Myopia in Infant Monkeys. *Invest Ophthalmol Vis Sci* 2007;48:1533.

3. Smith EL, III, Ramamirtham R, Qiao-Grider Y et al. Effects of foveal ablation on emmetropization and form-deprivation myopia*. Invest Ophthalmol Vis Sci* 2007;48:3914-3922.

4. Smith EL, III, Kee CS, Ramamirtham R, Qiao-Grider Y, Hung LF. Peripheral vision can influence eye growth and refractive development in infant monkeys*. Invest Ophthalmol Vis Sci* 2005;46:3965-3972.

5. Mathur A, Atchison DA, Charman WN. Myopia and peripheral ocular aberrations. *J Vis* 2009;9:15-12.

6. Schmid KL, Wildsoet CF. Effects on the compensatory responses to positive and negative lenses of intermittent lens wear and ciliary nerve section in chicks. *Vision Res* 1996;36:1023-1036.

7. Smith EL, III, Hung LF, Kee CS, Qiao Y. Effects of brief periods of unrestricted vision on the development of form-deprivation myopia in monkeys. *Invest Ophthalmol Vis Sci* 2002;43:291-299.

8. Kee CS, Hung LF, Ying QG et al. Temporal constraints on experimental emmetropization in infant monkeys. *Invest Ophthalmol Vis Sci* 2007;48:957-962.

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

10. Diether S, Wildsoet CF. Stimulus requirements for the decoding of myopic and hyperopic defocus under single and competing defocus conditions in the chicken. *Invest Ophthalmol Vis Sci* 2005;46:2242-2252.

11. Tse DY, Lam CS, Guggenheim JA et al. Simultaneous defocus integration during refractive development*. Invest Ophthalmol Vis Sci* 2007;48:5352-5359.

12. Benavente-Perez A, Nour A, Troilo D. The effect of simultaneous negative and positive defocus on eye growth and development of refractive state in marmosets. *Invest Ophthalmol Vis Sci* 2012;53:6479-6487.

13. Aller TA, Wildsoet C. Bifocal soft contact lenses as a possible myopia control treatment: a case report involving identical twins. *Clin Exp Optom* 2008;91:394-399.

14. Anstice NS, Phillips JR. Effect of dual-focus soft contact lens wear on axial myopia progression in children. *Ophthalmology* 2011;118:1152-1161.

15. Plainis S, Ntzilepis G, Atchison DA, Charman WN. Through-focus performance with multifocal contact lenses: effect of binocularity, pupil diameter and inherent ocular aberrations. *Ophthalmic Physiol Opt* 2013;33:42-50.

16. Madrid-Costa D, Ruiz-Alcocer J, Radhakrishnan H, Ferrer-Blasco T, Montes-Micó R. Changes in Accommodative Responses with Multifocal Contact Lenses: A Pilot Study. *Optom Vis Sci* 2011;88.

17. Mathur A, Atchison DA. Effect of orthokeratology on peripheral aberrations of the eye. Optom Vis Sci 2009;86:476-484.

18. Shen J, Thibos LN. Peripheral aberrations and image quality for contact lens correction. *Optom Vis Sci* 2011;88:1196-1205.

19. Bakaraju RC, Ehrmann K, Ho A, Papas E. Inherent ocular spherical aberration and multifocal contact lens optical performance*. Optom Vis Sci* 2010;87:1009-1022.

20. Rosen R, Jaeken B, Lindskoog PA, Artal P, Unsbo P, Lundstrom L. Evaluating the peripheral optical effect of multifocal contact lenses*. Ophthalmic Physiol Opt* 2012;32:527-534.

21. Queiros A, Gonzalez-Meijome J, Jorge J. Influence of fogging lenses and cycloplegia on open-field automatic refraction. *Ophthalmic Physiol Opt* 2008;28:387-392.

22. Queiros A, Jorge J, Gonzalez-Meijome JM. Influence of fogging lenses and cycloplegia on peripheral refraction. *J Optom* 2009;2:83-89.

23. Lopes-Ferreira D, Ribeiro C, Maia R et al. Peripheral myopization using a dominant design multifocal contact lens. *J Optom* 2011;4:14-21.

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

25. Queiros A, Villa-Collar C, Jorge J, Gutierrez AR, Gonzalez-Meijome JM. Peripheral refraction in myopic eyes after LASIK surgery. *Optom Vis Sci* 2012;89:977-983.

26. Young G, Holden B, Cooke G. Influence of soft contact lens design on clinical performance. *Optom Vis Sci* 1993;70:394-403.

27. Thibos L, Applegate RA, Schwiegerling JT, Webb R. Standards for reporting the optical aberrations of eyes. *J Refract Surg* 2002;18:S652-S660.

28. Atchison DA. Comparison of peripheral refractions determined by different instruments. *Optom Vis Sci* 2003;80:655-660.

29. Walline JJ ML. Myopia Control With a Soft Bifocal Contact Lens (ABSTRACT) in Myopia: Proceedings of the 13th International Conference [abstract]Walline JJ ML. *Optom Vis Sci* 2010;88:395-403

30. Atchison DA, Scott DH. Monochromatic aberrations of human eyes in the horizontal visual field. *J Opt Soc Am A* 2002;19:2180-2184.

31. Mathur A, Atchison DA, Scott DH. Ocular aberrations in the peripheral visual field. *Opt Lett* 2008;33:863-865.

32. Mathur A, Atchison DA, Charman WN. Effect of accommodation on peripheral ocular aberrations. *J Vis* 2009;9:20-11.

33. Whatham A, Zimmermann F, Martinez A et al. Influence of accommodation on off-axis refractive errors in myopic eyes. *J Vis* 2009;9:14-13.

34. Faria-Ribeiro M, Queiros A, Lopes-Ferreira D, Jorge J, Gonzalez-Meijome JM. Peripheral refraction and retinal contour in stable and progressive myopia. *Optom Vis Sci* 2013;90:9-15.

35. Hong X, Himebaugh N, Thibos LN. On-eye evaluation of optical performance of rigid and soft contact lenses. *Optom Vis Sci* 2001;78:872-880.

36. Lu F, Mao X, Qu J, Xu D, He JC. Monochromatic wavefront aberrations in the human eye with contact lenses. *Optom Vis Sci* 2003;80:135-141.

37. Dorronsoro C, Barbero S, Llorente L, Marcos S. On-eye measurement of optical performance of rigid gas permeable contact lenses based on ocular and corneal aberrometry. *Optom Vis Sci* 2003;80:115-125.

38. Gifford P, Cannon T, Lee C, Lee D, Lee HF, Swarbrick HA. Ocular aberrations and visual function with multifocal versus single vision soft contact lenses. *Cont Lens Anterior Eye* 2013;36:66-73.

39. Ruiz-Alcocer J, Madrid-Costa D, Radhakrishnan H, Ferrer-Blasco T, Montes-Mico R. Changes in accommodation and ocular aberration with simultaneous vision multifocal contact lenses. *Eye Contact Lens* 2012;38:288-294.

40. Yamaguchi T, Ohnuma K, Konomi K, Satake Y, Shimazaki J, Negishi K. Peripheral optical quality and myopia progression in children. *Graefes Arch Clin Exp Ophthalmol* 2013 ;251(10):2451-61

CHAPTER 9

Changes in Accommodative Response in Young Subjects Using Multifocal Contact Lenses

9.1. Abstract

Purpose: To evaluate influence of use of commercial available multifocal contact lenses (MFCL) of different optic designs in accommodative function of young emmetropic subjects.

Methods: The accommodative monocular response of sixteen eyes from 8 emmetropic young volunteers (mean age: 21.25 ± 2.38 years) initially was evaluated to fixation at 50, 33 and 20 cm distance. Three different targets were used: a Maltese Cross, text calibrated for a constant distance of 33 cm and text calibrated for each given distance. Grand Seiko WAM-5500 open-field autorefractor was used, linked to automatic recording data software. An automatic custom hardware allowed movement of the visual stimulus along a rail and acquisition of position data, pupil size, and refractive error that were measured directly to an excel sheet. Accommodative response was recorded at 3Hz rate during 20 seconds at each position. In a second experiment accommodative monocular response of fourteen right eyes of 14 young subjects (mean age 21 ± 2.38 years) was evaluated to the same distances but under different experimental conditions: to naked eye and eye fitted with different types of MFCL.

Results: No differences for accommodative response for viewing of different stimuli at evaluated distances (ANOVA to 50 cm: $p=0.381$; 33 cm: $p=0.616$; 20 cm: $p=0.493$). High correlations for accommodative response were observed at all comparisons of targets at evaluated distances. Accommodative curve obtained to naked eye condition did not correspond to expected but similar at 50 cm target, major difference could be seen at 33 cm and 20 cm target (accommodative lag), similarly as seen with all MFCL. There were no differences between accommodative efforts measured with different MFCL ($p>0.05$ to all comparisons at all distances) with exception to comparison between baseline and Proclear N at 50 cm ($p<0.001$), and between Proclear N and Oasys at 33 cm ($p=0.002$). Fluctuations of accommodation detected differences only between Baseline and Proclear N at 20 and 50 cm.

Conclusions: Accommodative response did not varied significantly across different target stimuli and for different distances. Present results reveal no effect of MFCL to allow change in amount or reliability of accommodative effort of young subjects.

Key-words: Fluctuations of accommodation, Multifocal contact lenses, Lag of accommodation.

9.2. Introduction

Myopia promotes axial elongation of the eye, causing eyes longer than emmetropes. Axial elongation could lead to pathological issues as earlier cataract,[1] glaucoma[2] and retinal detachment[3] deserving some concern across optometric and ophthalmologic community.

Abnormal accommodation function has been identified as myopigenic, possibly by producing hypermetropic retinal image defocus.[4, 5] There is also a suggestion from a previous study that could be seen differences in accommodation fluctuation between myopes and emmetropes,[6] that was not associated with typically myopic lack of contrast sensitivity at high frequencies, caused by post receptors loss.[7] By other hand, referred reduction at level of CS could explain the fact of myopes have manifested larger depth of focus than emmetropes, and less accurate accommodative response (larger accommodative lag). Depending of the study could be found an increased lag of accommodation in both myopic children and adults when compared to other refractive groups[4, 5, 8, 9] or not.[10, 11] Accommodative responses were reduced before the onset on myopia as Goss et al[12] and Gwiazda et al[13] studied although Mutti et al[9] found increased lag was only present after the onset of myopia, being a consequence, contradicting the idea that accommodative lag is a cause for myopia development.

As several studies documented, myopes may show larger amounts of high-order aberrations than emmetropes.[14-16] The presence of high-order aberrations may result a change of accuracy of accommodation, as referred, mainly when spherical and coma is handle;[17] normally could be seen reduction of accuracy with add of positive spherical aberration (SA) and coma[17] and an improvement with add of negative SA.[18]

Some authors suggested that the increase of accommodative lag found in myopes comes from naturally increased aberration in these eyes, however only strehl ratio were significantly correlated with accommodative lag in myopes.[19] As aberrations affects depth of focus, it is likely that it also play a role in the fluctuation of accommodation,[6, 20] having significantly found larger microfluctuations in myopes comparing with emmetropes.[6] The magnitude of the fluctuations of accommodation has been shown to depend also on different factors that also affect depth of focus, such pupil size[6, 21] or luminance.[6, 22]

Several studies indicated that wear of multifocal contact lenses could retain myopia progression,[23-25] nevertheless is not currently clear the mechanism that leads to myopia retention. The retention effect seen with center distance multifocal contact lenses as well as orthokeratology was linked with changes induced at peripheral refraction namely myopic shift respecting baseline condition,[26-29] however other different optic designed contact lenses[30] presented equally effect at level of retention but did not were also proved that could induce changes in peripheral refractive error.

Previously Purevision Multifocal, AirOptix Multifocal and Proclear Multifocal showed to induce different amounts of aberration, essentially negative spherical aberration[31-34] as mean to increase depth of focus. Theoretically, with slightly lens decentration could be induced coma,[35] even if, did not found it testing induced aberrations with Focus Progressive.[34] Single vision contact lenses have been shown not to influence the fluctuations of accommodation measurements using an open field autorefractometer in myopes.[36] Lopez-Gil et al.[20] also not found any statistically significant variation in the accommodative gain for low sphere contact lenses through a COAS aberrometer comparing with naked eyes.[35]

As aberration inducted with modern multifocal contact lenses is “favorable” to enhance accommodative function, the goal of present study was to know accommodative response (lag and fluctuations) of emmetropic healthy subjects that wearing different commercially available multifocal contact lenses with high add.

9.3. Methods

The experiment were divided in two phases, firstly were tested different target stimulus to determine target that induces more reliable responses. Inclusion criteria included astigmatic error ≤ 0.50D, no ocular or systemic disease including binocular or accommodative dysfunction and 0.00 logMAR visual acuity or better. The study followed the tenets of the Declaration of Helsinki and informed consent was obtained from all participants after explanation of the nature and procedures of this study. Accommodative responses were recorded using the Grand Seiko WAM-5500 (Hiroshima, Japan) open-field autorefractor linked to automatic recording data software that convert refractive results automatically in a excel sheet as M (sphere+1/2 cylinder) in function of time and position of target.

9.3.1. ‘Best Target’ Experiment

Firstly to determine best target, sixteen eyes from eight emmetropic young (mean age: 21.3 ± 2.38 years) adult volunteers were evaluated. The accommodative response was measured monocularly for the natural photopic pupil for three different distances i.e. 50, 33 and 20 cm and fixing different high contrast targets under a random order: Maltese cross, text calibrated for a constant distance of 33 cm and text calibrated for each given distance (50 cm, 33 cm and 20 cm). The automatic custom hardware implemented consists to move the stimulus along a rail. Target movement and corresponding position and data acquisition were synchronized through custom software facilities. At each target distance the test remained stable for 20 seconds while the accommodative response was recorded at a rate of 3Hz (3 readings/second). Basically, the procedure was as follows, beginning with the stimulus to 50 cm and after giving information to the system to start, there remained 20 seconds in each position while the accommodative response was being recorded, starts always in more distant target. Stimulus moves to each position in a velocity of 20 cm/ second. Subjects were instructed to maintain focused the center of the target. Also pupil diameter at each accommodative demand was obtained as average of individual measurements. The mean accommodative responses value of these recordings was calculated and standard deviation was used as magnitude of the fluctuations of accommodation.[37] The accommodative lag was defined as the difference between theoretical accommodative demand and subject accommodative response.

9.3.2. Variation of Accommodation with MFCL

In a second experiment the accommodative response was newly evaluated to right eye of other sample of 15 young emmetropes with mean age of 21.9±1.77 years respecting same inclusion/exclusion criteria, procedure but using only Malta cross as target.

9.3.3. Multifocal Contact Lenses

Follows a short description of different multifocal contact lenses used in this study: (1) Acuvue Oasys for presbyopia is a multiconcentric based optics, manufactured by senofilcon A, with a 38% of water content. Despite some individual differences in power transitions across surface, it were used three different aspheric centre-near MFCL: (2) Airoptix, lotrafilcon A, 33% of water content; (3) Proclear N design multifocal, omafilcon A, 67% of water content and (4) Purevision Multifocal, balafilcon A, 36% of water content. Distance power was zero diopters and near power used was for all a high add and in case of Proclear Multifocal N was used add +3.00D. Measurements were performed after 15 minutes of fitting the lenses to archive tear film stabilization. Centration and movement of all lens fitted were evaluated to guarantee convenient centration and avoid excessive movement of the lens.

Statistical analysis in this study was performed using SPSS version 21 and all graphs were produced using Microsoft Excel version 2010.

9.4. Results

Accommodation responses to each target could be seen at Figure 9.1, there were no differences in mean monocular accommodative response of subjects using different stimuli at different tested distances ($p>0.05$ to all). At all distances could be seen accommodative lag, that was reduced at 50 cm, almost 1D at 33 cm and more notorious at 20 cm.

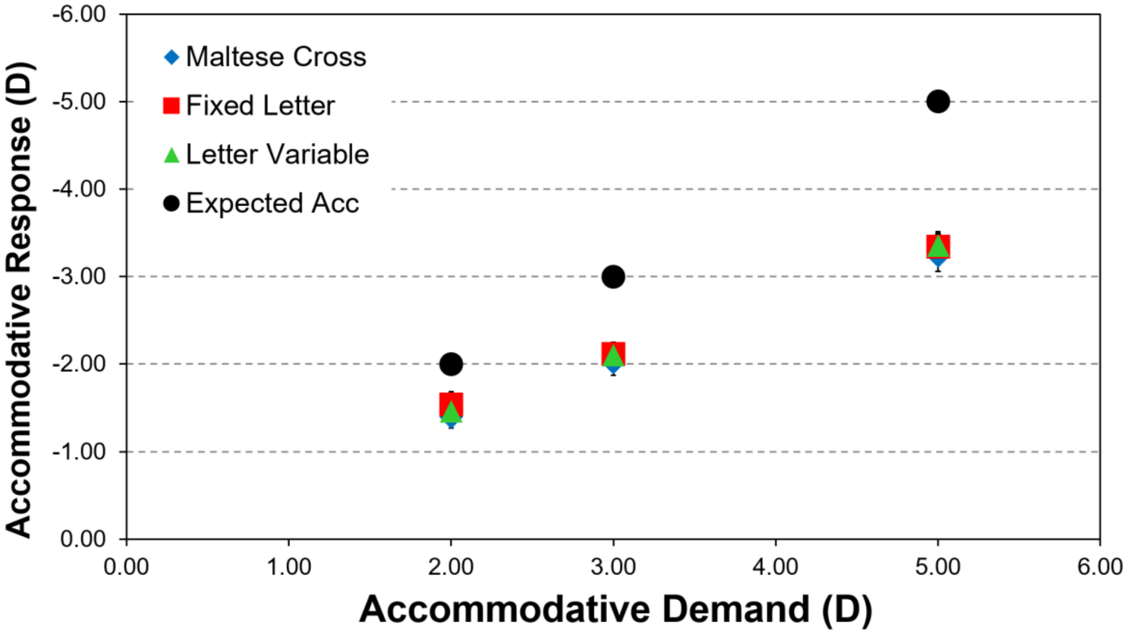


Figure 9.1. *Accommodative response of subjects to 2.00D, 3,00D and 5.00D demand. Values obtained to fixation of Maltese cross were represented by lozenges (◊), to fixed size letters by squares (■) and to variable size letters by triangles (Δ). Values of expected accommodation response were also represented by x symbol (×).*

Generally, could be observed in figure 9.2, 9.3 and 9.4 that to different accommodative distances (50, 33 and 20 cm respectively) and for different targets comparisons a high correlation between accommodation results. The highest correlation was registered for comparison between variable letter vs fixed letter (r^2=0.966), to 33 cm while the lowest (r^2=0.815) was fixed letter vs Maltese cross to 20 cm.

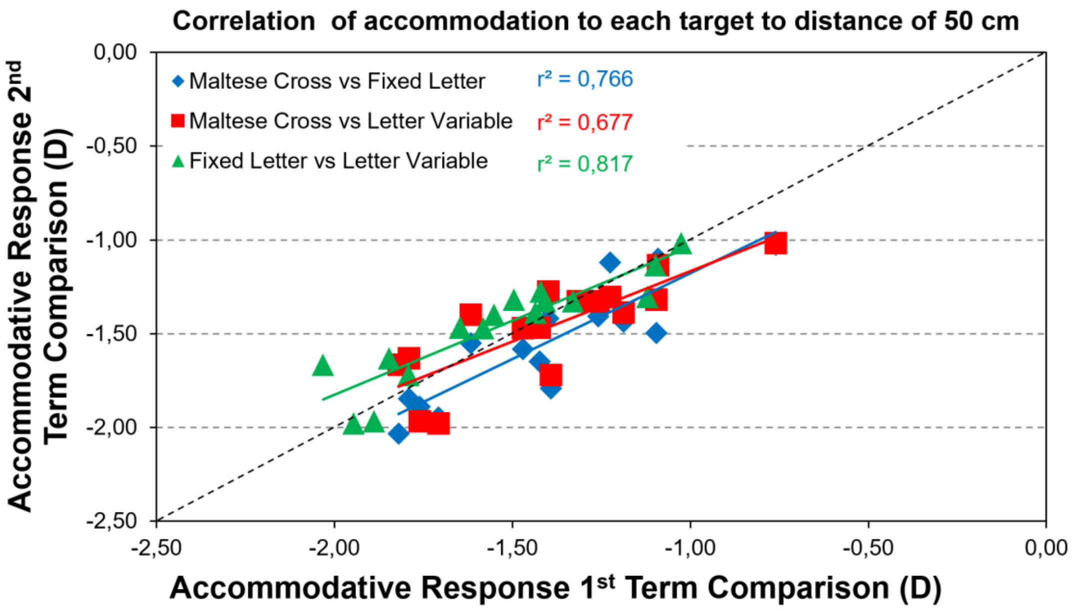


Figure 9.2. Correlation of accommodation response registered with different stimulus used at 50 cm distance. Comparison between Maltese cross and fixed size letters was represented as lozenges (◊), Maltese cross vs variable size letters as squares (■) and fixed size letters vs variable size letters as triangles (Δ).

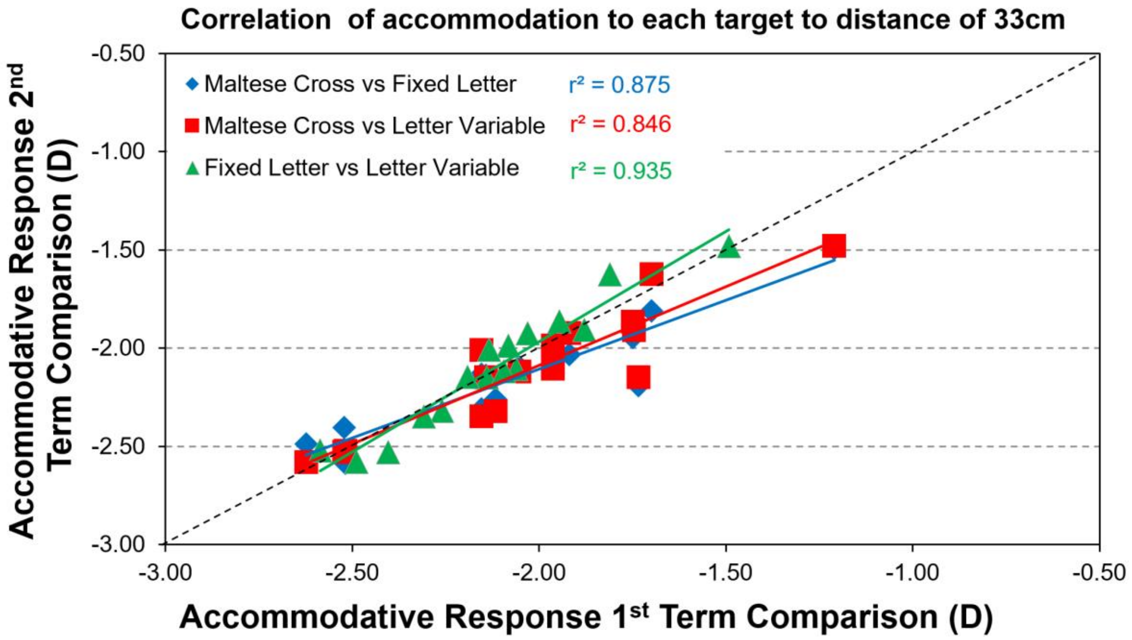


Figure 9.3. Correlation of accommodation response registered with different stimulus used at 33 cm distance. Comparison between Maltese cross and fixed size letters was represented as lozenges (◊), Maltese cross vs variable size letters as squares (■) and fixed size letters vs variable size letters as triangles (Δ).

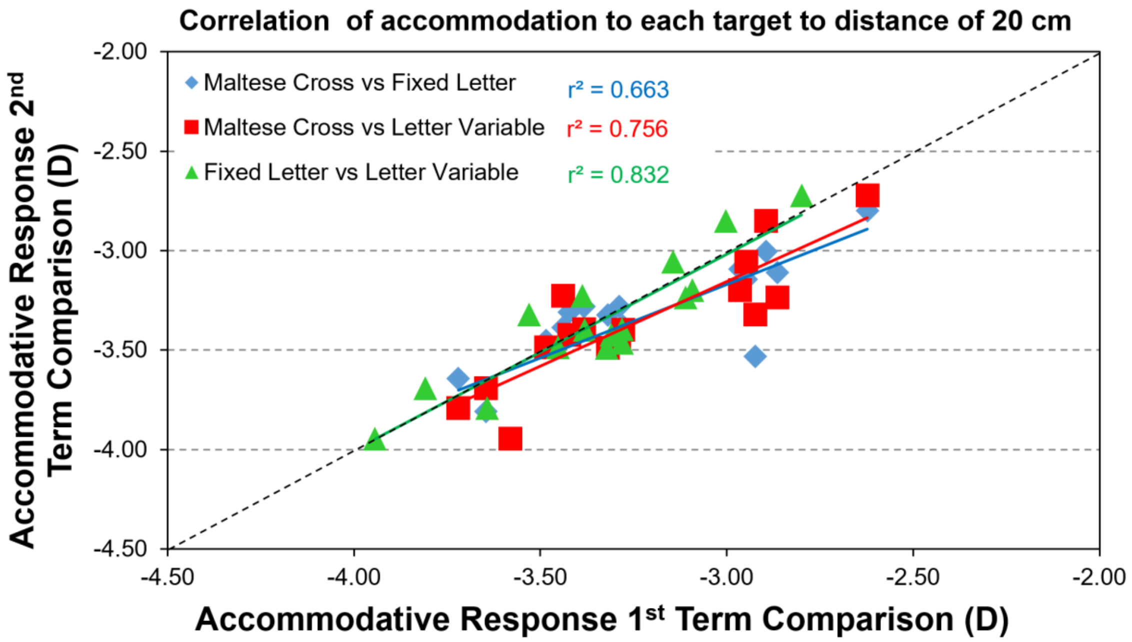


Figure 9.4. Correlation of accommodation response registered with different stimulus used at 20 cm distance. Comparison between Maltese cross and fixed size letters was represented as lozenges (◊), Maltese cross vs variable size letters as squares (■) and fixed size letters vs variable size letters as triangles (Δ).

At Figure 9.5 could be seen the mean accommodative response of subjects under different experimental conditions: Naked eye (baseline), and fitted with 4 different multifocal contact lenses, also were been represented the accommodative values expected to each distance of target. Similarly, as preliminary experiment, could be seen accommodative lag to all distances tested. At 50 cm, to baseline condition, accommodative lag was low (average accommodative lag= 0.56±0.17D), but statistically reduced at condition with Proclear N, that presenting accommodative leads to more than half of subjects tested (average accommodative lag= 0.13±0.36, $p<0.001$ Bonferroni test). More considerable accommodative lag could be seen to 33 cm distance for all conditions, in average 0.95±0.23D at Baseline, 0.79±0.22D with Airoptix, 0.93±0.21D with Purevision, 0.67±0.37D with Proclear, and 1.09±0.33D with Oasys, statistically differences only were found between accommodative lag measured under the last two conditions ($p=0.002$, Bonferroni test). At nearest position tested of 20 cm, the accommodative lag exceeds 1.50D to all conditions: 1.72±0.32D, 1.84±0.32D; 1.61±0.31D; 1.76±0.56D and 1.71±0.24D at baseline, wearing Airoptix Multifocal, AcuvueOasys for Presbyopia, Proclear N and Purevision Multifocal, respectively. There were no differences in lag of accommodation value between conditions at 20 cm.

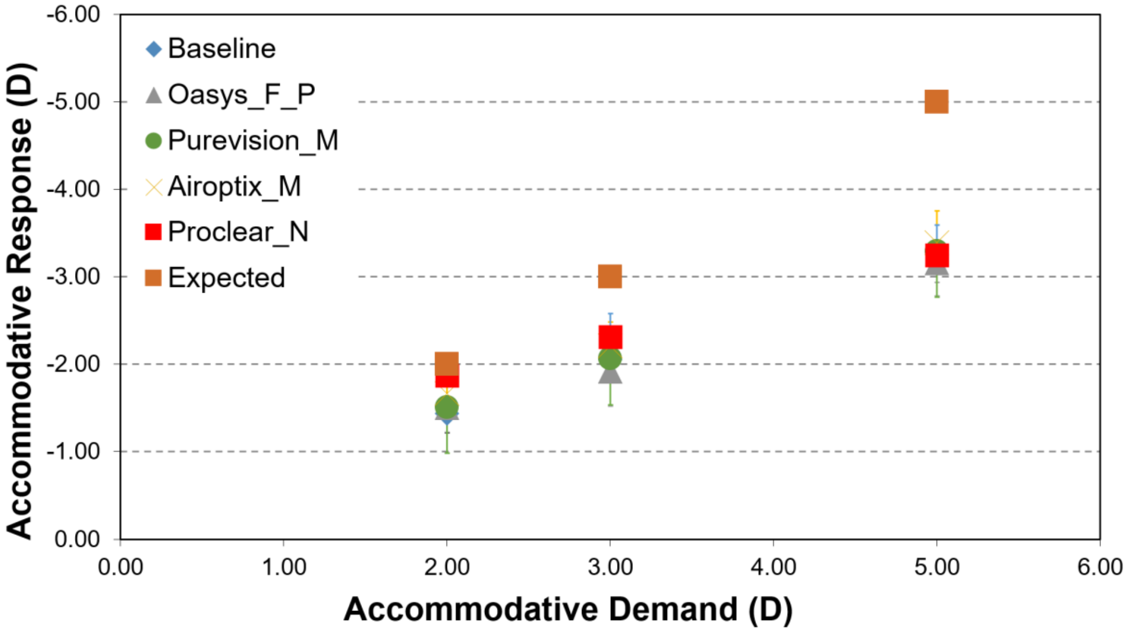


Figure 9.5. Accommodative response of subjects to 2.00D, 3,00D and 5.00D demand. Values obtained to condition naked eye (baseline) were represented with lozenges (◊), values to eyes fitted with Acuvue Oasys for Presbyopia as triangles (Δ), with Purevision Multifocal as circles (●), with Airoptix Multifocal were represented as x symbols (×) and with Proclear N as blue squares (■). Values of expected accommodation response were also represented by dark red squares (■). Error bars represent SD.

Pupil diameter was also automatically and simultaneously recorded with accommodative effort and was represented to each condition at Figure 9.6. In each distance, were not seen differences between pupil sizes measured under experimental conditions ($p \geq 0.05$, to all comparisons). However, the condition baseline was which present more induction of change at pupil size across accommodation stimulation, whose larger and significant variation registered was to comparison between 50 and 20 cm with difference value of 0.489±188 mm, $p=0.031$. The lower variation was with Proclear N (difference= 0.262±0.186 mm, $p=0.346$). There were no differences with statistical significance in pupil sizes along accommodative distances, for neither condition in which wearing MFCL.

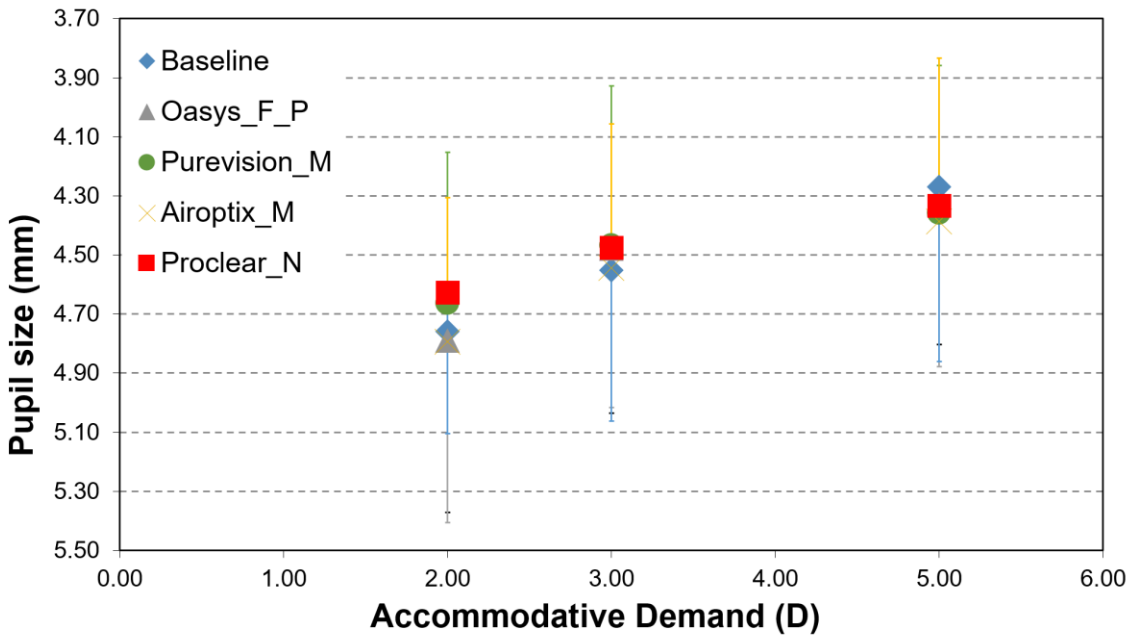


Figure 9.6. *Pupil size measured at moment of refraction (Grand-Seiko WAM-5500) to 2.00D, 3,00D and 5.00D demand. Values obtained to condition naked eye (baseline) were represented with lozenges (◊), values to eyes fitted with Acuvue Oasys for Presbyopia as triangles (Δ), with Purevision Multifocal as circles (●), with Airoptix Multifocal were represented as x symbols (×) and with Proclear N as blue squares (■).Error bars represent SD.*

Fluctuations of accommodation (Figure 9.7) registered lower values to all distances in baseline condition, being more 'instable' at 20 cm. Values of fluctuation of accommodation were higher to conditions with MFCL respecting to naked eye and specially with Proclear Multifocal N, whose differences were statistically significant at 50 cm distance ($p<0.001$, Bonferroni test) and also at 20 cm ($p<0.001$, Bonferroni test). Generally to all conditions, the short distance of fixation of target induces higher amount of fluctuations in accommodation effort along the 20 seconds that was the duration of evaluation, however no statistically significant differences were detected to neither other comparison.

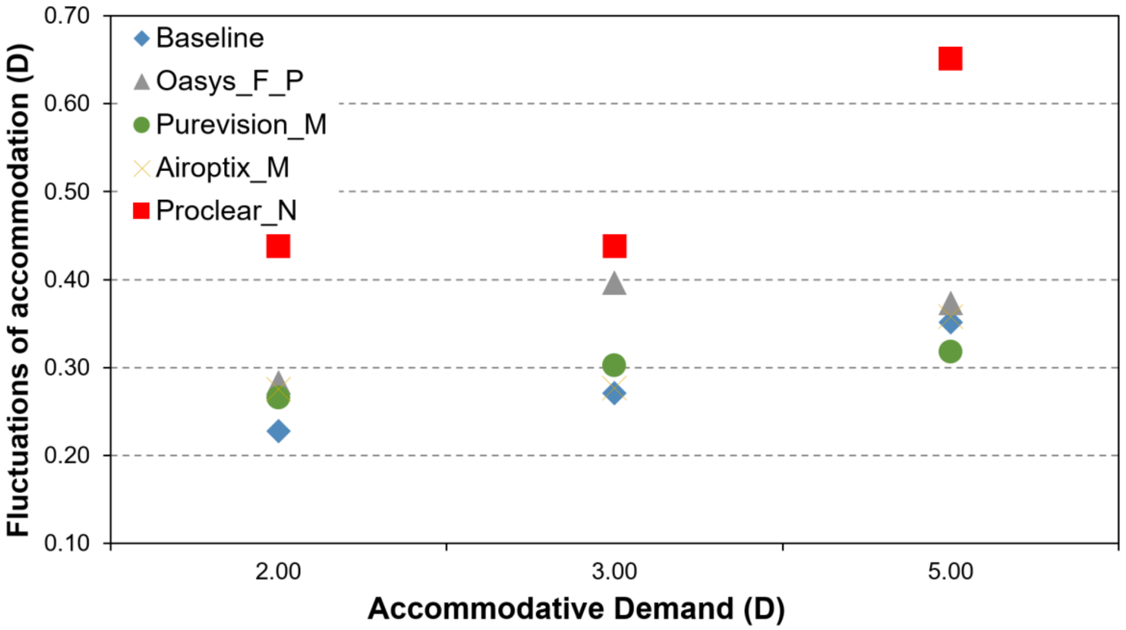


Figure 9.7. Fluctuations of accommodation measured from subjects to 2.00D, 3.00D and 5.00D demand. Values obtained to condition naked eye (baseline) were represented with lozenges (◊), values to eyes fitted with Acuvue Oasys for Presbyopia as triangles (Δ), with Purevision Multifocal as circles (●), with Airoptix Multifocal were represented as x symbols (×) and with Proclear N as blue squares (■).

9.5. Discussion

Previous study[38] indicated that accommodative accuracy are affected by differences in text design as contrast and size, in this study different targets (letters and Maltese cross) and sizes (fixed and variable) were tested using an open field autorefractor, as referred study, there were no differences in accommodation effort for neither of three distances evaluated.

In this study was evaluated simultaneously pupil size (diameter) and refractive evaluation. There is well known that pupil size contributes to the induction/correction of aberrations and to the relative change of high-order aberrations with accommodation to the accommodative response. Recently Gambra et al.[17] found decrease of pupil size with accommodative response at a rate of 0.35 mm/D (under natural condition), as other previous that founded 0.45 mm/D[39] and 0.18 mm/D,[37] our results pointed to 0.16mm/D rate in baseline, and lightly reduced about 0.15 mm/D, 0.14 mm/D, 0.10 mm/D and 0.10 mm/D to Acuvue Oasys for Presbyopia, Airoptix Multifocal, Proclear N and Purevision Multifocal conditions. Greater pupillary constriction may reduce optical blur caused by accommodative error and other higher-order aberrations, thus allowing for a better image quality,[40] present results reveals a poorer pupillary constriction wearing multifocal optical devices comparing to baseline by induction of aberration, that did not represent statistical significance. A reduction of pupillary constriction mechanism could be seen to all lenses comparing to baseline, however neither significant difference of pupil size was found between conditions at each distance. Gifford et al.[33] previously shown a significant effect of pupil size on aberration-derived M refraction measured with the multifocal designs, that were non-depending of add. The shift in focus caused by optics of multifocal contact lenses should help to compensate for the reducing benefit from spherical aberration that would occur as pupil diameter constricts.

Changes in inherent aberrations of the eye could be induced by wear of custom contact lenses,[18] also a changing in accommodative response could be expected, namely by induction of spherical aberration.[37] Theagarayan et al[18] pointed as major finding of theirs paper the induction of spherical aberration be capable of influence the slope of the accommodation response curve, independently of its effect on RMS aberration inducted. By induction of positive spherical aberration they proved significantly depression of response slope function, and by induction of negative spherical aberration (at least up to 0.2 µm), enhances it, as correcting natural aberrations of eye.[17]

As in present study, others[19] also founded accommodative lag in healthy emmetropic sample, however the lag of accommodation expected by induction of negative and positive SA is greatly different.[18] Normally myopic subject's reveals higher lag of accommodation than emmetropes,[5] one explanation possible is that myopic eyes have more aberrations.[14, 41, 42] Recently was confirmed that age, lag of accommodation, and AC/A ratio were significantly associated with myopia progression.[43]

Most designs of multifocal CLs use the concept of simultaneous focus, that is, the CL simultaneously provides retinal images set at distance and near. To do that, these CLs combine multiple powers positioned within the pupil and an aspheric design, which alters the spherical aberration of the eye. Aspheric profiles as Purevision multifocal, Airoptix multifocal and Proclear Multifocal N used in this work have a flatter zone in the periphery that becomes more curved toward the center of the lens. This change in the CL profile looks for inducing an inversion in spherical aberration toward negative values and then obtaining near add in the center of the lens contributing to increase near vision and may contribute to the depth of focus. Recent report[44] reveals that as in present study Purevision Multifocal (low and high add) did not provide a reduction in accommodation in young subjects comparing to naked emmetropic eye (in this study) or compared with single-vision contact lenses (as cited study), probably because did not produced clear-enough near images. Reversely, a bifocal contact lenses (+1.50 D near addition), also was tested in myopes and emmetropes and conducted to a reduction of accommodation lag in both.[45] Although of recognized benefits of negative spherical aberrations induction at reliability of accommodative response, did not be seen myopia retention effect in children at 2-years study.[46]

In this work we found an increase of fluctuations of accommodation systematically with accommodative response. For baseline condition, we have obtained that fluctuations varied from 0.228 D to 0.352 D in the 2– 5 D stimulus range with a slope of 0.041 D/D, this is consistent with previous studies,[7, 37] however in this work we did not evaluated the accommodative response in far distance (relaxed accommodation) as referred authors to can completely compare. Also could be expected an increase in accommodation fluctuations when spherical aberration and coma is induced, reversely it was found a reduction for baseline condition or at condition of adaptative optics corrected aberrations.[17] This finding indicates that retinal image quality plays an active role in the fluctuations of the accommodative response,[37, 47] likely due to the increased depth-of-focus when aberrations are increased.

In future this study must to be repeated but in myopic subjects. The results presented allow to concluding that commercially available multifocal contact lenses tested in monocular condition did not produced changes in accommodative lag or in the accommodative fluctuations across different amounts of accommodative effort.

9.6. References

1. Wang JJ, Mitchell PG, Cumming RG, Lim R. Cataract and age-related maculopathy: the Blue Mountains Eye Study. *Ophthalmic Epidemiol*. 1999;6(4):317-26.

2. Mitchell P, Hourihan F, Sandbach J, Wang JJ. The relationship between glaucoma and myopia: the Blue Mountains Eye Study. *Ophthalmology*. 1999;106(10):2010-5.

3. Morita H, Ideta H, Ito K, Yonemoto J, Sasaki K, Tanaka S. Causative Factors of Retinal Detachment in Macular Holes. *Retina.* 1991;11(3):281-4.

4. Gwiazda J, Thorn F, Bauer J, Held R. Myopic Children Show Insufficient Accommodative Response to Blur. *Invest Ophthalmol Vis Sci*. 1993;34(3):690-4.

5. Allen PM, O'Leary DJ. Accommodation functions: Co-dependency and relationship to refractive error. *Vision Res.* 2006;46(4):491-505.

6. Day M, Seidel D, Gray LS, Strang NC. The effect of modulating ocular depth of focus upon accommodation microfluctuations in myopic and emmetropic subjects. *Vision Res.* 2009;49(2):211-8.

7. Atchison DA, Schmid KL, Pritchard N. Neural and optical limits to visual performance in myopia. *Vision Res.* 2006;46(21):3707-22.

8. McBrien NA, Millodot M. Amplitude of accommodation and refractive error. *Invest Ophthalmol Vis Sci*. 1986;27(7):1187-90.

9. Mutti DO, Mitchell GL, Hayes JR, Jones LA, Moeschberger ML, Cotter SA, et al. Accommodative Lag before and after the Onset of Myopia. *Invest Ophthalmol Vis Sci.* 2006;47(3):837-46.

10. Bullimore MA, Gilmartin B, Royston JM. Steady-state accommodation and ocular biometry in late-onset myopia. Documenta Ophthalmologica. 1992;80(2):143-55.

11. Seidel D, Gray LS, Heron G. The Effect of Monocular and Binocular Viewing on the Accommodation Response to Real Targets in Emmetropia and Myopia. *Optom Vis Sci.* 2005;82(4):279-85.

12. Goss DA. Clinical Accommodation and Heterophoria Findings Preceding Juvenile Onset of Myopia. *Optom Vis Sci.* 1991;68(2):110-6.

13. Gwiazda J, Thorn F, Held R. Accommodation, Accommodative Convergence, and Response AC/A Ratios Before and at the Onset of Myopia in Children. *Optom Vis Sci.* 2005;82(4):273-8.

14. Collins MJ, Buehren T, Iskander DR. Retinal image quality, reading and myopia. *Vision Res.* 2006;46(1–2):196-215.

15. Charman WN. Aberrations and myopia. Ophthalmic Physiol Opt. 2005;25(4):285-301.

16. Marcos S, Moreno E, Navarro R. The depth-of-field of the human eye from objective and subjective measurements. *Vision Res.* 1999;39(12):2039-49.

17. Gambra E, Sawides L, Dorronsoro C, Marcos S. Accommodative lag and fluctuations when optical aberrations are manipulated. *J Vis.* 2009;9(6):4-.

18. Theagarayan B, Radhakrishnan H, Allen PM, Calver RI, Rae SM, O'Leary DJ. The effect of altering spherical aberration on the static accommodative response. *Ophthalmic Physiol Opt.* 2009;29(1):65-71.

19. He JC, Gwiazda J, Thorn F, Held R, Vera-Diaz FA. The association of wavefront aberration and accommodative lag in myopes. *Vision Res.* 2005;45(3):285-90.

20. López-Gil N, Rucker FJ, Stark LR, Badar M, Borgovan T, Burke S, et al. Effect of third-order aberrations on dynamic accommodation. *Vision Res.* 2007;47(6):755-65.

21. Stark LR, Atchison DA. Pupil size, mean accommodation response and the fluctuations of accommodation. *Ophthalmic Physiol Opt.* 1997;17(4):316-23.

22. Gray LS, Winn B, Gilmartin B. Effect of target luminance on microfluctuations of accommodation. *Ophthalmic Physiol Opt.* 1993;13(3):258-65.

23. Walline JJ, Greiner KL, McVey ME, Jones-Jordan LA. Multifocal Contact Lens Myopia Control. *Optom Vis Sci.* 2013;90(11):1207-14.

24. Aller TA, Wildsoet C. Bifocal soft contact lenses as a possible myopia control treatment: a case report involving identical twins. *Clin Exp Optom.* 2008;91(4):394-9.

25. Sankaridurg P, Holden B, Smith IIIE, Naduvilath T, Chen X, de la Jara PL, et al. Decrease in Rate of Myopia Progression with a Contact Lens Designed to Reduce Relative Peripheral Hyperopia: One-Year Results. *Invest Ophthalmol Vis Sci.* 2011;52(13):9362-7.

26. Ticak A, Walline JJ. Peripheral Optics with Bifocal Soft and Corneal Reshaping Contact Lenses. *Optom Vis Sci.* 2013;90(1):3-8.

27. Berntsen DA, Kramer CE. Peripheral Defocus with Spherical and Multifocal Soft Contact Lenses. *Optom Vis Sci.* 2013;90(11):1215-24.

28. Lopes-Ferreira D, Ribeiro C, Maia R, García-Porta N, Queirós A, Villa-Collar C, et al. Peripheral myopization using a dominant design multifocal contact lens. *J Optom.* 2011;4(1):14-21.

29. Lopes-Ferreira D, Ribeiro C, Neves H, Faria-Ribeiro M, Queirós A, Villa-Collar C, et al. Peripheral refraction with dominant design multifocal contact lenses in young myopes. *J Optom.* 2013;6(2):85-94.

30. Anstice NS, Phillips JR. Effect of Dual-Focus Soft Contact Lens Wear on Axial Myopia Progression in Children. *Ophthalmology.* 2011;118(6):1152-61.

31. McAlinden C, Moore JE, McGilligan VE, Moore TC. Spherical aberration and higher order aberrations with Balafilcon A (PureVision) and Comfilcon A (Biofinity). *Graefes Arch Clin Exp Ophthalmol.* 2011;249(4):607-12.

32. Legras R, Benard Y, Rouger H. Through-focus visual performance measurements and predictions with multifocal contact lenses. *Vision Res.* 2010;50(12):1185-93.

33. Gifford P, Cannon T, Lee C, Lee D, Lee HF, Swarbrick HA. Ocular aberrations and visual function with multifocal versus single vision soft contact lenses. *Cont Lens Anterior Eye.* 2013;36(2):66-73.

34. Patel S, Fakhry M, Alió JL. Objective Assessment of Aberrations Induced by Multifocal Contact Lenses In Vivo. *Eye Contact Lens*. 2002;28(4):196-201.

35. Lopez-Gil N, Castejon-Mochon JF, Benito A, Marin JM, Lo-a-Foe G, Marin G, et al. Aberration generation by contact lenses with aspheric and asymmetric surfaces. *J Refract Surg.* 2002;18(5):S603-9.

36. Day M, Strang NC, Seidel D, Gray LS. Technical Note: Effect of contact lenses on measurement of the accommodation microfluctuations. *Ophthalmic Physiol Opt.* 2008;28(1):91-5.

37. Plainis S, Ginis HS, Pallikaris A. The effect of ocular aberrations on steady-state errors of accommodative response. *J Vis.* 2005;5(5):7-.

38. Schmid KL, Hilmer KS, Lawrence RA, Loh S-Y, Morrish LJ, Brown B. The Effect of Common Reductions in Letter Size and Contrast on Accommodation Responses in Young Adult Myopes and Emmetropes. *Optom Vis Sci.* 2005;82(7):602-11.

39. Alpern M, Mason GL, Jardinico RE. Vergence and accommodation. V. Pupil size changes associated with changes in accommodative vergence. *Am J Ophthalmol.* 1961;52:762-7.

40. López-Gil N, Iglesias I, Artal P. Retinal image quality in the human eye as a function of the accommodation. *Vision Res.* 1998;38(19):2897-907.

41. He JC, Sun P, Held R, Thorn F, Sun X, Gwiazda JE. Wavefront aberrations in eyes of emmetropic and moderately myopic school children and young adults. *Vision Res.* 2002;42(8):1063-70.

42. Buehren T, Collins MJ, Carney LG. Near work induced wavefront aberrations in myopia. *Vision Res.* 2005;45(10):1297-312.

43. Price H, Allen PM, Radhakrishnan H, Calver R, Rae S, Theagarayan B, et al. The Cambridge Anti-Myopia Study: Variables Associated with Myopia Progression. *Optom Vis Sci.* 2013;90(11):1274-83.

44. Ruiz-Alcocer J, Madrid-Costa D, Radhakrishnan H, Ferrer-Blasco T, Montés-Micó R. Changes in Accommodation and Ocular Aberration With Simultaneous Vision Multifocal Contact Lenses. *Eye Contact Lens.* 2012;38(5):288-94.

45. Tarrant J, Severson H, Wildsoet CF. Accommodation in emmetropic and myopic young adults wearing bifocal soft contact lenses. *Ophthalmic Physiol Opt.* 2008;28(1):62-72.

46. Allen PM, Radhakrishnan H, Rae S, Calver RI, Theagarayan BP, Nelson P, et al. Aberration Control and Vision Training as an Effective Means of Improving Accommodation in Individuals with Myopia. I*nvest Ophthalmol Vis Sci.* 2009;50(11):5120-9.

47. Cheng X, Bradley A, Hong X, Thibos LN. Relationship between Refractive Error and Monochromatic Aberrations of the Eye. *Optom Vis Sci.* 2003;80(1):43-9.

CHAPTER 10

General Overview of Results, Conclusions and Future Work

10.1. General Overview of Results

Present work provides an overview across different approaches used in previous years to modulate peripheral refractive pattern, peripheral aberrations in the eye and accommodative effort as well accuracy of accommodation in a perspective that studying the changes of these factors will provide a better understand the mechanisms behind myopia progression.

First two chapters focus mainly on the state of art and review several strategies adopted in last decade to retain myopia progression using contact lenses (search of publications between 2004 and 2014). The perspective of use of orthokeratology as refractive therapy to retain myopia was also addressed and as could be seen this modality have the largest volume of accumulated evidence relating to the efficacy in myopia progression regulation in children. As second best approach appear soft multifocal CLs that have been reported to show promising preliminary results. Across the studies evaluated, at review, is clear that CL have acceptable levels of safety to be wear by children, age group that will be largest recipient with myopia retention therapeutics.

However it is not clear what influence or change certain type of multifocal contact lenses does to retain myopia progression. Chapter 3 addresses, therefore, the study the influence of dominant design (or centre-distance) MFCL across peripheral refraction of young myopes. Despite the effect of this type of MFCL already has been studied in emmetropes, it is necessary confirm behavior on myopic eyes, knowing the differences on retinal contour between myopes and emmetropes. In this study could be seen the relative myopization induced by Proclear D with add+3.00 at myopic eyes about -1.42D (at 35° nasal side of retina vs -1.21D in emmetropes) and about -2.00D (at 35° temporal side of retina vs -2.78D in emmetropes). The difference between myopic shift at periphery, induced in myopes and emmetropes, was higher in temporal side. Also could be seen that the effect of myopization was superior to 1D with add +3.00, in both sides, and was more centered at case of myopic eyes, using similar methodology (eye rotation).

The question of eye rotation along horizontal viewing was several times placed at previous literature, and pointed as limitation of studies that evaluated eyes wearing contact lenses. However, it was not known the effect of rotating the eye with a contact lens in place which is necessary for several clinical trials and experimental studies. In Chapter 4 were evaluated the influence of rotating the eyes in peripheral refraction evaluation wearing MFCL, comparing with measurements in same eyes but rotating the head, as suggested previously as an alternative method. Despite multiconcentric MFCL seems to be more difficult of measure, considering fast transitions of power across the surface, there were not found differences between peripheral refractive results founded in same subjects evaluated by different methods (i.e. rotating the eye or head). However some concern respecting to centration of CL must be considered.

The refraction along the horizontal visual field was more frequently studied by several purposes. Despite this fact, treatments as orthokeratology (OK) and LASIK induce changes at all 360° of mid periphery of cornea and by consequence at retinal peripheral defocus at all directions and not only at horizontal meridian. Therefore in Chapter 5 we studied two samples of myopes that underwent these two treatments and were evaluated peripheral refraction across vertical, horizontal and 2 oblique meridians. Results of this evaluation shows that both treatments induce peripheral myopization at all 4 meridians evaluated, however could be noted that myopic shift induced by both treatments was more relevant at horizontal direction out of 25° of central retina in case of OK, and out of 35°central retina in case of LASIK (post/pre-treatment M values and also astigmatism components).

In Chapter 6, several approaches were compared respecting power of peripheral myopization at review/ metanalysis: Orthokeratology, a standard aspheric rigid gas-permeable (RGP), an experimental RGP, an experimental soft CL, and different multifocal soft CL. The experimental soft CL, designed to induce similar defocus effect at periphery of the experimental RGP, induced a similar effect to the standard aspheric CL. Only orthokeratology, experimental RGP, and Proclear multifocal CL with Add: +3.00 D showed high effect of peripheral myopization. This metanalysis represents a useful reference to comparison purposes of efficacy of treatments.

In chapter 7, MFCL were evaluated from presbyopia compensation perspective, not only were evaluated ocular aberrations induced by two types of MFCL, but also evaluated visual acuity in presbyopic subjects. Two different designs of MFCL were evaluated: Dominant design (centre-distance) and Non-dominant design (centre-near). Centre-distance optics favors distance vision as already was postulate reversely centre-near optics favors near vision. As optics presents different distribution of power at lens surface also induce different amounts of aberration in presbyopic eyes, being higher to maximum round pupil analysis. Dominant design induced positive increase of 4th order spherical aberration and consequently spherical-like, reversely non-dominant design induced negative increase of coma and 4th order spherical aberration and positive increase of 6th order SA and coma-like. Changes at on-eye aberration depending of optical design and has related with monocular visual performance.

Considering that peripheral refraction could influence myopia progression, peripheral aberrations eventually also exert influence on myopic eye that could trigger myopia progression or slow-down effect. Chapter 8 presents a study that evaluated peripheral aberrations measured in myopic eyes fitted with 2 different designs of MFCL. An experimental peripheral fixation system was linked along the path of light of a commercial Hartmann-Shack aberrometer to allow peripheral evaluations. Results reveal that multiconcentric optic induced higher amounts of aberration at periphery comparing with centre-distance MFCL. As both multifocal optic designs already are seen as myopia retention devices, this work clarify that centre-distance optics induces mainly peripheral myopic defocus, whereas multiconcentric optic induces mainly peripheral aberration.

The changing of aberrations on-eye could induce changes in accuracy of accommodation or it will be changed after myopia onset. This aspect was studied in Chapter 9. The accommodative function was evaluated in young subjects wearing 4 different multifocal contact lenses across different accommodative demands and results revealed that neither of tested MF optics of CLs was capable to change significantly accommodative function. Also fluctuations of accommodation and pupil size were evaluated not variate significantly with accommodative demand, despite center-near MFCL revealed a tendency to induce higher values of fluctuation mainly at higher vergence.

In conclusion, Multifocal Contact Lenses presented in this work as one of most powerful approaches to myopia retention in children, by safety, convenience and reversibility of treatment. Several authors studied longitudinally its efficacy in myopia retention. In this work shows that depending the design of MFCL this will be capable to induce changes at peripheral refraction (defocus) or in peripheral aberrations of the eye, however accommodation amount and accuracy did not be changed by MFCL, independently the design.

10.2. Conclusions

Present work addressed the influence of multifocal contact lenses and other optic treatments in healthy eyes to enumerate effects on-eye capable to justify its efficacy in myopia retention. The main outcomes of this work can be summarized as follow:

1. In a review of the literature on different methods to control myopia with contact lenses, orthokeratology arose as the method with the more robust evidence in several controlled randomized and non-randomized clinical trials.
2. It is possible to induce significant changes in the pattern of relative peripheral refraction in the myopic direction with commercially available dominant design multifocal contact lenses. When comparing the effect of multifocal lenses of different add, we concluded that the +3.00 lens were the most effective in changing the peripheral refractive error in myopia patients. This should be considered in the design of future clinical trials involving these devices to test their efficacy in slowing down myopia progression.
3. Eye rotation while wearing multifocal contact lenses does not affect the measures of peripheral refraction with the open field autorefractometer compared with the situation in which the head is rotated. These results allow us to adopt the same strategies used with the naked eye and therefore simplify the experimental setup in this kind of studies.
4. RPRE after refractive corneal reshaping treatments (OK and LASIK) show changes at periphery across horizontal and 2 oblique meridians, however 3D representation of RPRE at retina and showing that myopic shift induced by both treatments is more relevant at horizontal direction.
5. Orthokeratology, multifocal soft CL, and custom-designed RGP CL were able to generate a significant relative peripheral myopia in myopic eyes. Conversely, standard and experimental soft CL was not able to induce significant peripheral myopic and astigmatic defocus values.
6. Aberrations induced by MFCLs on-eye are dependent of design of multifocal contact lens and coupling of the wearer’s ocular spherical aberration with the aberration profiles provided by MFCLs and differently affects their visual performance.

7. Measures of refraction by autorefractometer and adapted H-S aberrometer showed similar values at center and in all eccentricities evaluated, Showing to future possible to use the same apparatus to evaluate peripheral refractive pattern and peripheral aberrations. Multiconcentric MFCL was the MFCL that more HOA are induced and mainly at peripheral locations of visual field.
8. Accommodative response did not varied significantly across different target stimuli and for different distances. Present results reveal no effect of MFCL to allow change in amount or reliability of accommodative effort of young subjects.

10.3. Future Work

After conclusions and outcomes listed from work executed above, some other aspects could be explored as continuation and improvement of the findings and knowledge acquired at present Thesis. Some future works could include:

- Construction of aberrometry system to measure accurately peripheral aberrations in the eye fitted with Multifocal Contact Lens.
  - Digital and automatic recording of contact lens position at ocular surface along measurements that require eccentric viewing;
  - Implementation of virtual eccentric targets at distance to avoid cycloplegia need;
- Evaluate retinal cells response to induced different defocus at retina.
  - Study the axial and eccentric response in retina to axial and peripheral signs of defocus and to different multifocal optics;
- Protocol measurement of peripheral optical quality and peripheral refraction at longitudinal clinical studies testing different optical devices.