Universidad de Valladolid

Máster en Rehabilitación Visual

Functional Asymmetry in Macular Area in Patients with Pathological Myopia Using Microperimetry

Final Project of the Master

Medicine Faculty

Zeyad A. Alzaben

Directed by:

Dr. Miguel J. Maldonado

Dr. Ahmad Zaben Omran

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ioba
Instituto Universitario de Oftalmobiología Aplicada

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AUTORIZACIÓN DEL TUTOR PARA LA EXPOSICIÓN PÚBLICA DEL TRABAJO DE FIN DE MÁSTER

(Art. 6.2 del Reglamento del la UVA sobre la Elaboración y Evaluación del Trabajo Fin de Máster)

D. Dr. Miguel J. Maldonado **en calidad de Tutor / a del alumno**

D. Zeyad A. Alzaben

Del Máster en: Rehabilitación Visual

Curso académico: 2013/2015

CERTIFICA haber leído la memoria del Trabajo de Fin de Máster titulado "**Functional Asymmetry in Macular Area in Patients with Pathological Myopia Using Microperimetry**" y estar de acuerdo con su exposición pública en la convocatoria de julio

En Valladolid, 14 de julio de 2015

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To all,

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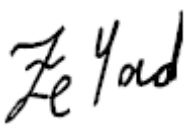


ABSTRACT

Introduction: Microperimetry is a clinical innovation to evaluate the retinal sensitivity. In this study, we explored the inter-ocular retinal variations of retinal sensitivity in the macular area in patients with pathological myopia.

Methods: A transversal study was designed in which the macular sensitivity (Expert exam protocol) of MAIA^{TM} microperimeter was employed to evaluate the functional variations of 10° in macular areas in patients affected by pathological myopia using 37 points strategy, in a sample of 36 persons aged between 13 and 60 years (spherical equivalent from -6.00 to -16.00 diopters). Inter-ocular asymmetry values were determined and compared with previous published tolerance values by means of a paired t test, and the interocular differences were calculated as the 2.5th and the 97.5th percentiles.

Results: The interocular difference tolerance limits for central sensitivity of the macula was 5.45 dB in patients affected by pathological myopia. Statically significant differences were found between males and females in the asymmetry of the central ring and the second ring of retinal sensitivity (SC and S2). There was a significant positive correlation between the retinal sensitivity and the spherical equivalent, and a weak correlation between the retinal sensitivity and the fixation level. Also we encountered significant positive correlation in retinal sensitivity between the central ring and the third ring (SC and S3).

Conclusions: A general reduction in the central and average retinal sensitivity in eyes with pathological myopia is expected to be more marked with increasing ametropia. Considering inter-ocular asymmetry in central and average retinal sensitivity should help understand better the retinal features of patients with pathological myopia, for which establishing normative percentile values should prove a useful tool.

RESUMEN

Introducción: la microperimetría es una innovación clínica para evaluar la sensibilidad de la retina. En este estudio, se evaluó las variaciones de la sensibilidad de la retina en el área macular entre ambos ojos en pacientes con miopía patológica.

Métodos: se diseñó este estudio transversal para evaluar la sensibilidad de la retina, en los que se empleó examen *expert test* y estrategia 37 puntos dentro de los 10° del microperímetro MAIA^{TM}, para evaluar las variaciones funcionales en áreas maculares en pacientes con miopía patológica, en una muestra de 36 personas con edades comprendidas entre (13 y 60 años) equivalente esférico (-6,00 y 16,00 Dioptrias). Los valores de asimetría Intraoculares se determinaron y se compararon como se realizó en estudios previos, los valores de tolerancia por medio de una prueba t pareada y las distribuciones porcentuales de las diferencias entre los ojos derecho e izquierdo, se calcularon para 2.5^{th} y 97.5^{th}.

Resultados: El límite de tolerancia de las diferencias entre los ojos derechos e izquierdos de sensibilidad central de la mácula fue de 5,45 dB en pacientes afectados por la miopía patológica. Estáticamente se encontraron diferencias significativas entre los hombres y las mujeres y asimetría en el anillo central y el segundo anillo de la sensibilidad retiniana (SC y S2). Existe una correlación positiva significativa entre la sensibilidad de la retina y el equivalente esférico, y la correlación débil entre la sensibilidad de la retina y el nivel de fijación. También nos encontramos correlación positiva significativa en la sensibilidad retiniana entre la región central y el tercer anillo (SC y S3).

Conclusiones: Hay una reducción general de la sensibilidad retiniana central y media en ojos con miopía patológica y su valor aumenta con la cantidad de la ametropía. Teniendo en cuenta la asimetría inter-ocular en la sensibilidad retiniana central y media, y los valores de los percentiles es una herramienta útil que debe ayudar a comprender mejor las características de la retina de los pacientes con miopía patológica.

Contents

1. Introduction

1.1 Pathological Myopia

It is evident that, impaired vision can be caused by various diseases, accidents or congenital malformations; in all cases it is a chronic, irreversible condition, thus, it is essential to know how to evaluate patients presenting these visual alterations, ocular diseases, how visual function is altered, and the treatment options (Maduka Okafor et al., 2009)(Saw, 2006).

Within this context, we are talking about the pathological myopia, which is a chronic, irreversible disease with great social and economic burden. It is one of the leading causes of blindness in industrialized countries and their effects affect young people, within the working age. In Spain, is the first reason to get the membership of the National Organization of Spanish Blind (in Spanish, Organizaciόń Nacional de Ciegos Españoles or ONCE) (Wong et al., 2015) (Saxena et al., 2015).

We must recognize that, this pathological myopia is characterized by a progressive elongation of the anteroposterior axis of the eye (which does not stop at the end of the growth age), usually has high refractive power of -6.00 diopters and ocular axial length of 26 mm. Therefore, various changes occur in the optic nerve, sclera, choroid, and retina, being significantly thinner than normal (Flores-Moreno et al., 2013).

Degenerative changes that occur in eyes affected by pathological myopia in the macular region and outside the macula, have no clear pathogenesis, but it is believed that, according to different theories, they are secondary to biomechanical alterations or hereditary (degenerative) factors with the presence of some signs as myopic cone, tigroid fundus appearance, lacquer cracks, focal chorioretinal atrophy, etc. (McBrien et al., 2009).

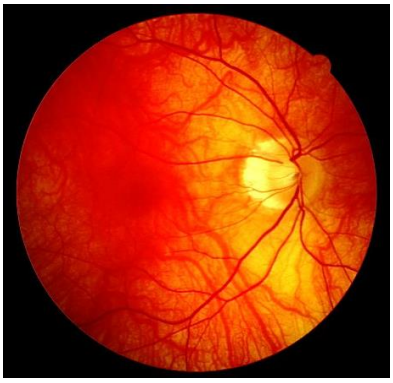


Figure 1.1 Myopic crescent with focal chorioretinal atrophy (From: www1.appstate.edu)

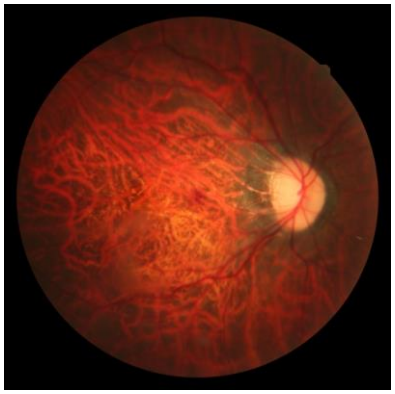


Figure 1.2 Tigroid fundus in degenerative myopia (From: usa.nidek.com)

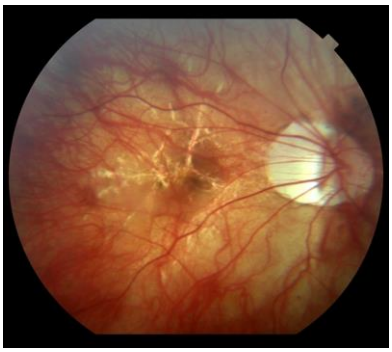


Figure 1.3 Lacquer cracks (From: imagebank.asrs.org)

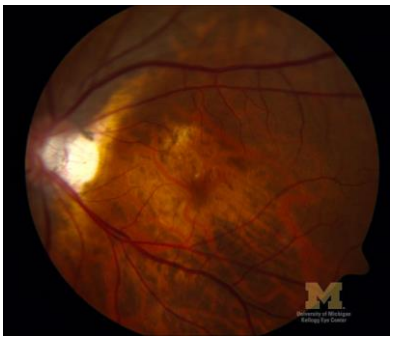


Figure 1.4 Posterior staphyloma (From: www.kellogg.umich.edu)

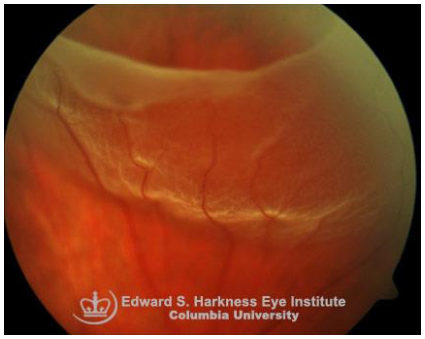


Figure 1.5 Rhegmatogenous retinal detachment (From: dro.hs.columbia.edu)

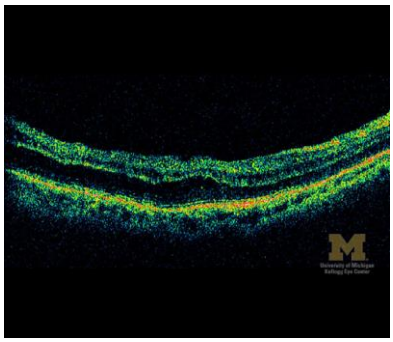


Figure 1.6 Retinoschisis (From: www.kellogg.umich.edu)

Also, there are some ocular complications, including the staphyloma, rhegmatogenous retinal detachment, retinoschisis, etc. Associated with symptoms of decreased visual acuity (VA), and it is often correlated with the presence of cataract and glaucoma (Alkabes et al., 2013) (Zaben et al., 2015).

The objective of its treatment is to prevent the development of posterior staphyloma with its syndicated loss of vision, but there is not any solution to achieve that. In children, topical atropine may delay efficiently the growth of the axial length, or slowing the axial growth of the globe using a peripheral defocus technique (Benavente-Pérez et al., 2014) (Atchison, 2014).

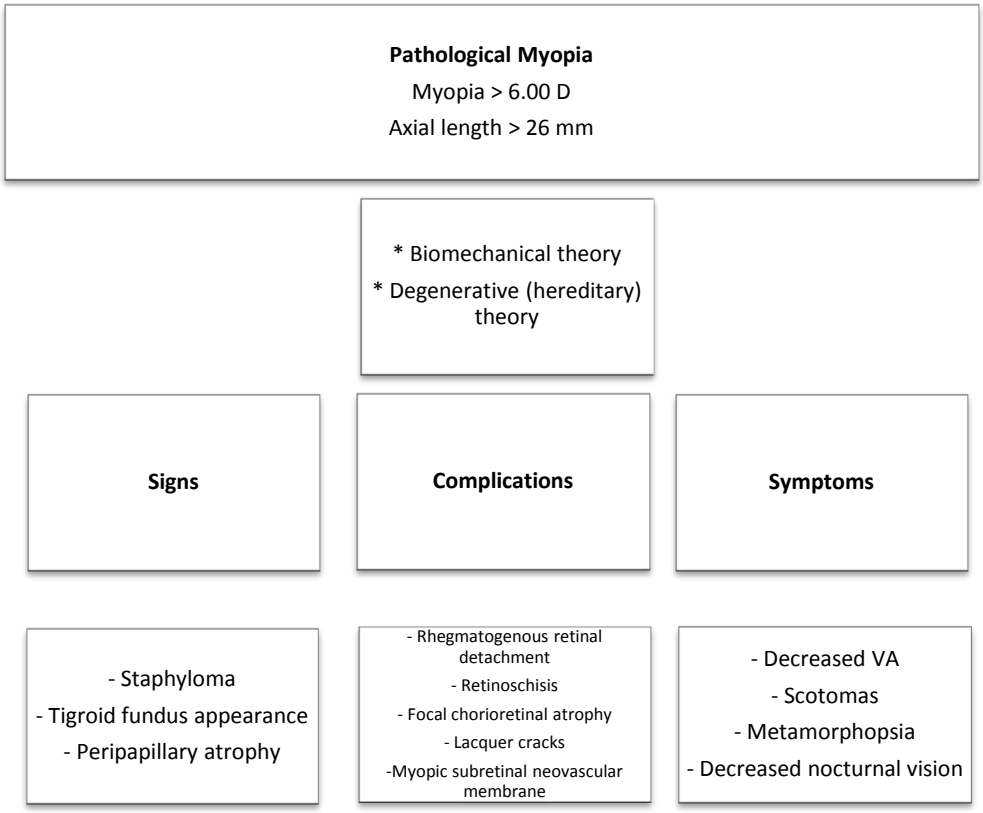


Figure 1.7 Summary about pathological myopia

1.2 Microperimetry

In order to assess the functional vision of the macula, various tests were used like visual acuity test, Amsler grid test, speed reading test, and contrast sensitivity test. Microperimeter has become more advanced than all of these, in which there are stimuli projected on the retinal surface precisely using eye tracking technology. Microperimetry is a subjective psychophysiological test to measure the retinal sensitivity using simultaneous imaging technique to track the retina, in order to calculate the correlation between the structure and the function of the macula (Virgili et al., 2015) (Chui et al., 2014) (Markowitz and Reyes, 2013).

The subject is placed away, while wave front correction is adjusted, then collimated laser passes through, and thus it reflected on a mirror (beam splitter). While this procedure takes place, the light should go through vertical and horizontal scanning mirror before/after the eye is being scanned, to align the scanning beam. This way, the light will be reflected on a deformable mirror to diffuse the light aberrations (**Figure 1.8**), and the laser will enter the eye, highlighting the selected region of the retina before getting out from the same way, using Charge Coupled Device (CCD) camera to detect any optical aberrations, and another Shark-Hartmann wave front sensor in the evaluation, utilizing a phase-stabilized optical frequency domain imaging (OFDI) system and Tracking Scanning Laser Ophthalmoscope (TSLO) to overcome the ocular movements (Vienola et al., 2012).

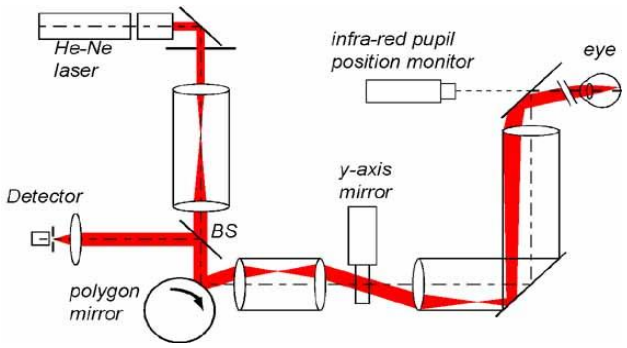


Figure 1.8 SLO (From: www.roorda.vision.berkeley.edu)

After the loss of the macular function, the remaining visual function is defined by the scotomal characteristics, preferred retinal loci (PRLs), and oculomotor control, therefore, using microperimeter permits us to circumscribe accurately the PRLs, and to

estimate the consequences of some diseases or interventions on the retinal surface (Nguyen et al., 2007).

The main categories of its functions are to evaluate:

- The glaucomatous damage of the residual visual function
- The visual function

Standard automated perimetry (SAP) is a commonly used method in our Ophthalmological assessments, but it has clinical limitations, where we can find the grey grid has little reliability, and patients with cataracts could present shades that do not mean always a glaucomatous damage (Alencar and Medeiros, 2011).

Beyond, in addition to the SAP, different clinical methods were applicable to assess the functional vision, like confrontational visual field test, Amsler grid test, and Tangent screen test.

In patients with central visual field loss, it is better to analyse the functional central vision using the appropriate test, while monitoring the retina at the same time to get precise measurements, like so, this property is available using fundus related perimetry, in order to know the stimulus presented in each specific retinal point, letting us to correct the instable fixation or the instable central vision (Nguyen et al., 2009).

We can apply visual acuity test at the maximum contrast level, or other conventional test to check the functional central vision, but they are limited in the existence of macular diseases or in the elderly. Even though, speed reading test and contrast sensitivity test enable us to evaluate the improved visual function after the medical intervention.

Microperimeter provides the examiner a retinal sensitivity map to confirm the patient's capacity to see luminance stimuli of different levels of intensity, and in various positions in the examined retinal area.

The first fundus related microperimeter was Scanning Laser Ophthalmoscope (SLO-101) microperimeter (Rodenstock, Munich) to evaluate the functional vision in the macular region, using a fixation protocol of foveal or extrafoveal, and the stability of stable/instable fixation. Then Nidek MP1 microperimeter was commercially available,

which allows automated eye tracking at the same retinal loci, using an infrared camera of the fundus with a resolution of 768 x 576 pixels, and 45° of visual field (Dunbar et al., 2010).

Also, there are physical features of the automated microperimetry, such as extreme resolution (until 10 stimuli / degree), short duration of the examination (microperimetry, retinography, and analysis of the fixation occur simultaneously), quantification of the retinal sensitivity, automated eye tracking, scotometry, and peripapillary microperimetry (to follow-up glaucomatous cases).

1.2.1 Types of Microperimetry

Microperimetry is a non-invasive, in-vivo, functional test, allows us to analyse the retinal sensitivity with special extreme resolution, regardless of any ocular movements during the examination, using a controlled projected method of the stimuli.

In this research, we are reviewing briefly the advantages of the microperimeter in the detection and follow-up of various macular pathologies, using MAIA^{TM} (Macular Integrity Assessment) – CenterVue, Padova, Italia.

a. MP-1 Microperimeter

The first microperimeter was integrated from Nidek Technologies in 2002, Italy. This type uses infrared (IR) camera in order to image the retina, and the stimuli are projected on a LCD screen inside the device, performing the retinal follow-up automatically. This conventional camera gives coloured image of the retina, and this type involves various visual field patterns including a grid 10-2, macular grids, and optimized patterns in the retina.

This type could be individualized by reflecting off each stimulus at a certain area, changing the size of the stimulus, and the fixation points. It allows the examiner to do the conventional kinetics perimetry, selecting manually the exact retinal area, and by selecting the follow-up mode, we can perform longitudinal studies to do easily test-retest of variability, as well as the range of retinal sensitivity using this instrument is (0-20 dB) which equals to (14-34 dB) using Humphrey perimeter (Wu et al., 2014). Vujosevic et al. find that the microperimetry is relatively good in patients with retinal

fixation impairment due to the existence of diabetic macular oedema, showing the location of the fixation and its stability (Vujosevic et al., 2008).

Using this instrument, we should dilate the pupil, despite of it is difficult to capture a clear retinal image (the maximum luminance of 130 cd/m^2), but it overcomes the artefacts of SLO-101, and in comparison with Humphrey perimeter (the maximum luminance of 3183 cd/m^2), in addition due to the low dynamic range of the screen, the dimmest stimulus is only 1% of the brightest target's intensity (Crossland et al., 2012)(Rohrschneider et al., 2008).

b. OCT – SLO (OPKO, Miami, Florida, USA)

It combines OCT with the analysis of microperimeter based on laser ophthalmoscope principle, which means, that there is no need to dilate the pupil, giving higher quality of the retinal image. The maximum intensity of the stimulus is similar to MP-1 (137 cd/m^2) having a low dynamic range of screen too (2%).

c. MAIA^{TM} Microperimeter

Utilizing this type of microperimeter permits us to capture a retinal image of 36° X 36° field of view, with a resolution of 1024 X 1024 pixels, penetrating 25 microns of the retina using the light source of infrared superluminance of about 850 nm wavelength.

The projection of the image occurs in 25 femtosecond, with a working distance of 30 mm using a standard perimetry test of macular protocol of 10° over a visual field of macular area, which equals to 20° X 20°. The follow-up velocity equals to 25 Hz, performing the assessment with stimulus size of Goldmann III, a background luminance of 4 asb (or apostilb, which is an old unit of luminance), dynamic range of its stimuli of 36 dB, and a maximum luminance of 1000 asb.

The utility of MAIA^{TM} requires a minimum diameter of the pupil of 2.5 mm, with a focus range from -15.00 to +10.00 D, which can focus and recognize the eye (right / left) automatically. It uses a laser scan to capture the retinal image projecting a light LED stimulus.

Examination types of this device are:

1. Fast exam: Doing a rapid evaluation of the macular sensitivity and the fixation stability, figuring out if the results are within the normal range or not, taking 2-3 minutes for each eye.

2. Expert exam: Realizing a complete assessment in order to determine the macular sensitivity and the fixation stability, notifying the examiner if the results are within normal limits or not, taking 4-7 minutes for each eye.

3. Follow-up exam: This test is only available if we did one of the previous tests, repeating the test of the expert type of examinations, while reading the same points, as a reference.

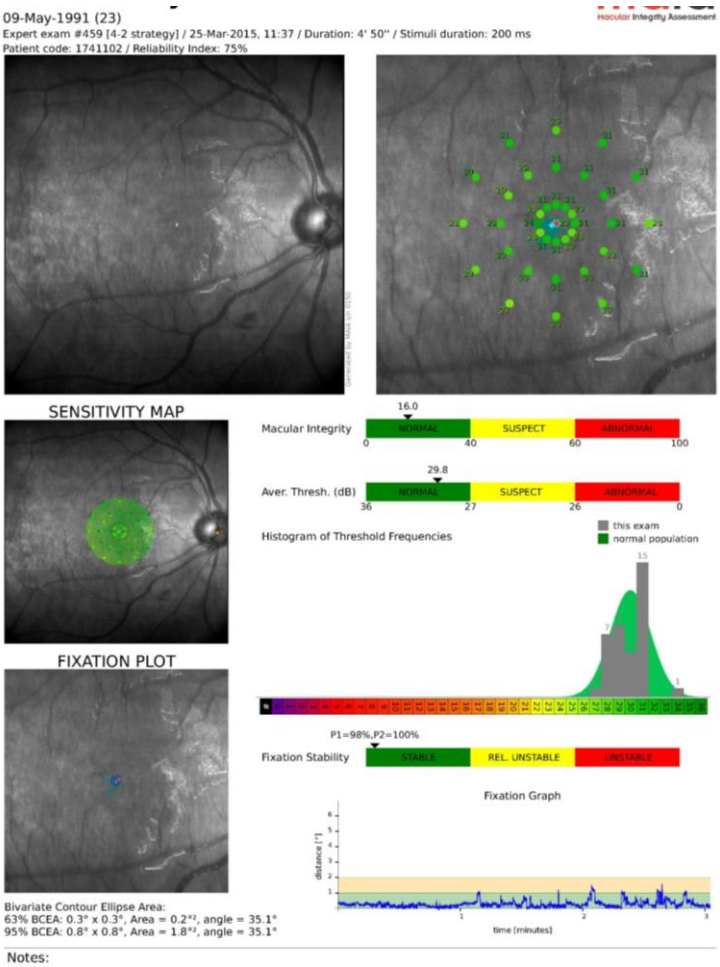


Figure 1.9 Expert exam microperimetry's (MAIA^{TM}) printout in normal subject; the top left represents SLO image of the fundus, the top right represents sensitivity values and PRL, the histogram represents threshold values in grey compared with normal distribution in green.

The colour coded scale:

- Green: seen to 27 dB (27 dB represents 90 percentile of normal values)
- Yellow: seen to 25 dB (25 dB represents 97 percentile of normal values)
- Red: Did not see to 25 dB

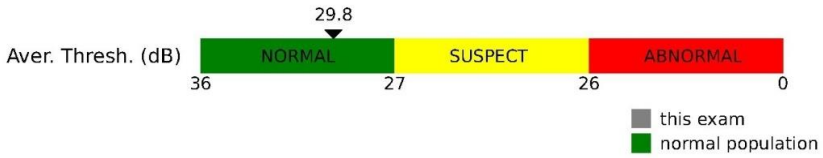


Figure 1.10 Retinal sensitivity in normal macula (or SM)

Fixation stability index: it is stabilized about the base, of which the left part contains analysis of fixation stability, thus the fixation would be classified as:

- Stable: if there are more than 75% of the fixation points within the inner circle of 2° in diameter.
- Relatively stable: if there are more than 75% of the fixation points within the outer circle of 4° in diameter and less than 75% in the inner circle of 2° in diameter.
- Instable: if less than 75% of the fixation points' contents are within the circle of 4° in diameter.

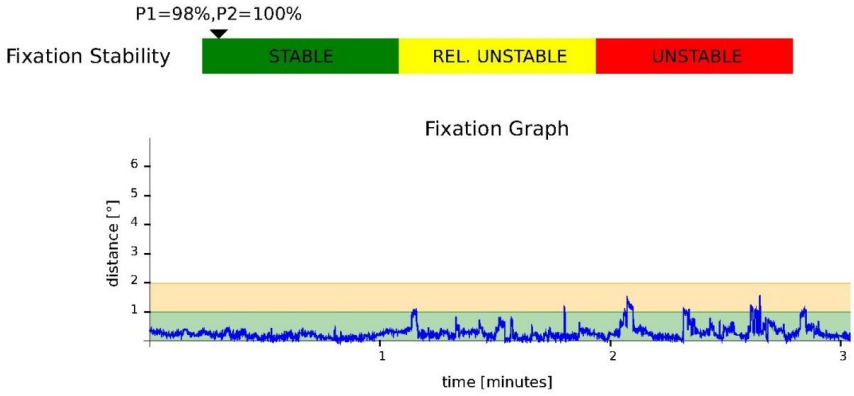


Figure 1.11 Fixation stability graph representing P1 (2° ring), and P2 (4° ring) in normal subject, where the fixation was maintained on the central 1° during 98 percent of examination time.

Therefore, more than 25% of the fixation points' contents are within the circle of 2° in diameter when the fixation considered poorly centred.

Fixation plot: A quantitative measurement of fixation stability and the position of each fixation point is represented and calculated in an elliptical area, using Bivariate Contour Ellipse Area (BCEA) method, that provides a value of fixation stability, in which the lesser values indicate stable fixation. MP-1 microperimeter does not calculate the elliptical area in order to quantify the fixation stability automatically, in contrast to MAIA^{TM} (Crossland et al., 2004).

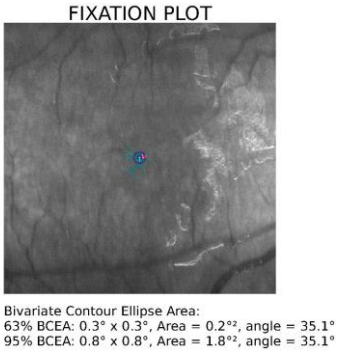


Figure 1.12 Fixation point of the test of 2° in diameter, and 4° in diameter in normal subject

Macular integrity index: It indicates if the threshold values are normal, suspicious, or abnormal (**Figure 1.13**). This indication is obtained by a comparison of paired-normative data in relative to age, and is based on the statistical analysis of point number observed in:

- Green colour: normal intensity
- Yellow colour: perceived intensity, which corresponds to 2 standard deviations
- Red colour: perceived intensity, which corresponds to 3 standard deviations

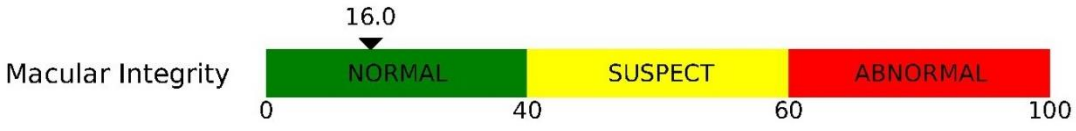


Figure 1.13 Macular integrity index in normal subject

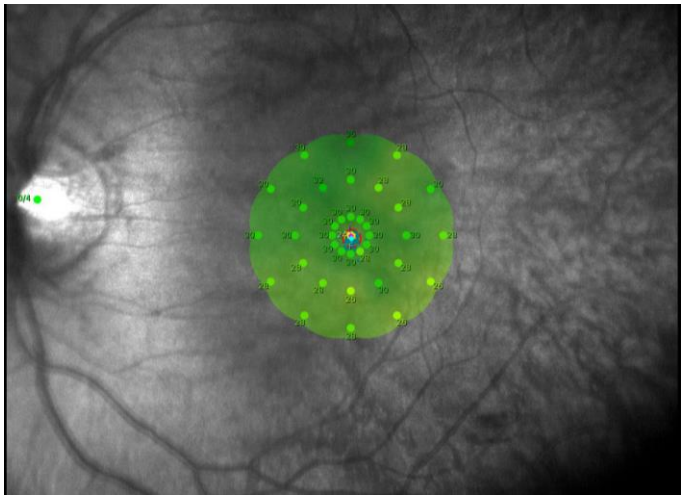


Figure 1.14 Retinal sensitivity at normal macula, the red circle represents the fixation point to which the patient is looking during the test, with a number at the centre which represents the central sensitivity (SC), the first ring represents the sensitivity at 1° (its average equals to S1), the second ring represents the sensitivity at 3° (its average equals to S2), and the third ring represents the sensitivity at 5° (its average equals to S3). This figure can detect the scotoma, and the green dot at the centre of the optic nerve represents the blind spot.

1.2.2 Clinical Implications

Microperimeter is a subjective psychophysiological test that is used to measure the retinal sensitivity using simultaneous imaging technique to track the retina, in order to calculate the correlation between structure and function of the macula.

Microperimeter has the potential in our clinic to do the following:

- Analyse any central retinopathy
- Monitoring the functional vision of a patient with ARMD or diabetic maculopathy
- Detecting reduced functional areas or complete scotomas
- Serial assessments provide a prognosis of these ocular conditions

The main artefact of this instrument is that, the maximum field of view limits its utility for farther peripheral evaluations, or in glaucomatous examination.

The innovation of the advanced technological techniques provides detailed information about the morphological characteristics of the retina in patients with pathological myopia, with respect to the structural aspects such as OCT (Zaben et al., 2015).

The clinical implication of microperimetry is to provide detailed information about the retina with respect to functional vision, especially in patients with pathological myopia, where encountered that myopic maculopathy is directly proportion to the extent of pathological alterations in macular area, therefore, the early diagnosis of the degenerative myopia is based on the detection of retinal pigmented epithelium atrophy, and choroidal thinning. The atrophic areas are associated with the presence of dense scotoma, best detected with microperimeter, due to the stable extrafoveal fixation which they have.

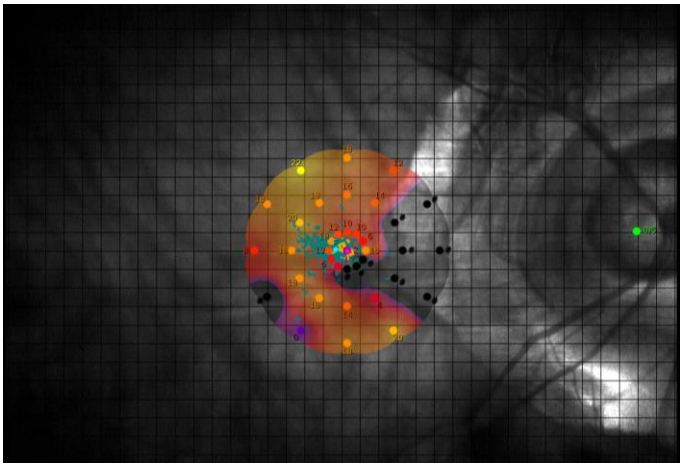


Figure 1.15 Retinal sensitivity at the macula of a patient with pathological myopia, in which the black dots represent his scotomas

1.2.3 Microperimetry in Pathological Myopia

Patients with pathological myopia should be associated with a lower average and regional sensitivity, even if they do not present outstanding fundus alterations, similar to the case of a patient in our study, a woman of 39 years old, and the degree of her myopia is (OD: -13.50 D / OS: -11.75 D). Also, she has been diagnosed in our clinic with a small myopic crescent in both eyes without any clinical complications, and the blood vessels of her eyes were normal, shows arterioles and venules in the posterior pole, and the macula with a regular morphology in both eyes, as well as, she presents lower SM = 26 dB average sensitivity.

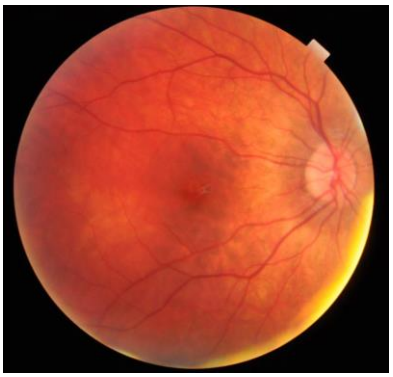


Figure 1.16 Right fundus

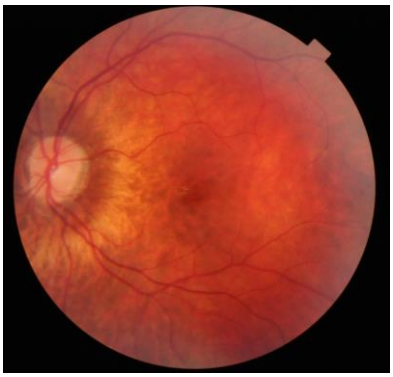


Figure 1.17 Left fundus

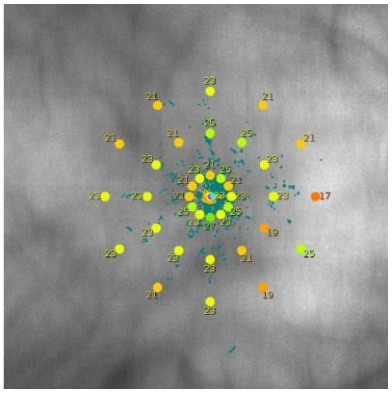


Figure 1.18 Macular sensitivity of the right eye

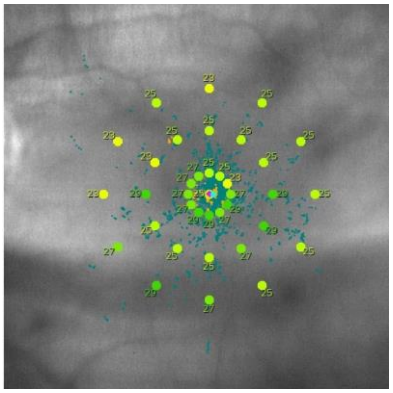


Figure 1.19 Macular sensitivity of the left eye

In this context, the areas with chorioretinal atrophy are observed in the posterior pole, always associated with a dense scotoma detected by posterior microperimetry; however, in these patients, they have a stable extrafoveal fixation, and with a presence of advanced atrophic changes. In contrast, in the eyes that have lacquer cracks associated with absorbed subretinal hemorrhages, the retinal sensitivity suffers from a significant reduction and absolute scotoma. We noticed this in one of our cases, of a woman (40 years old), with a myopia of (OD: 24.00 D / OI -23.50 D), that the sensitivity was (SM OD = 12 dB, SM OI = 14 dB), and a fixation stability of (P1 95%, P2 100%).

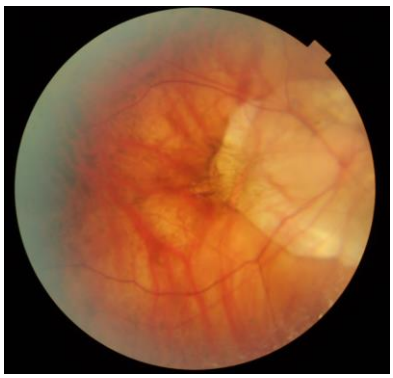


Figure 1.20 Right fundus

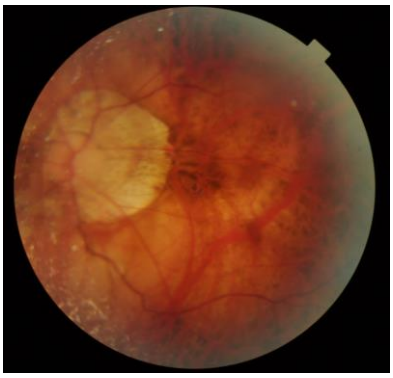


Figure 1.21 Left fundus

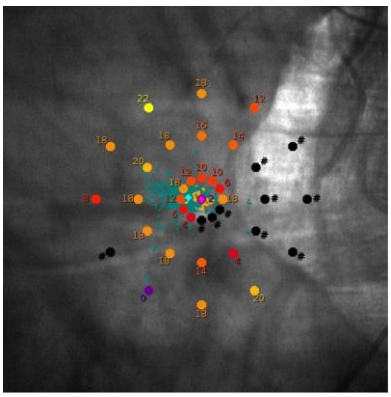


Figure 1.22 Macular sensitivity of the right eye

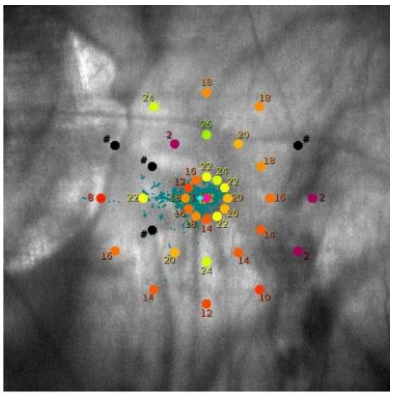


Figure 1.23 Macular sensitivity of the left eye

2. Justification

Pathological myopia and its complications, such as glaucoma, cataracts, retinal detachment and macular degeneration are some of the leading causes of blindness and low vision in industrialized countries. However, it is not entirely clear how it affects the thinning process that occurs in the structures of the eye in pathological myopia, specifically the retina, and the associated effects to functional vision, so understanding the behaviour of these structural and functional changes is a key to describe correctly the retina of the eye with pathological myopia, in order to help the low vision rehabilitator to evaluate any retinal alterations and well-define the proper treatment. On the other hand, it supposed that the asymmetry of the retinal sensitivity is not explored yet. This information could be relative to the supervision of the conditions and the treatments that can lead to asymmetry, thus the functional alterations would result in structural changes.

Therefore, this study aims to conduct an evaluation that allows better understanding of the functional information of the retina in impaired vision patients, due to the pathological myopia, through a precise retinal sensitivity analysis, in term of asymmetry.

3. Hypothesis

The retinal sensitivity in low vision patients with pathological myopia is reduced in the macular region, and also there is an asymmetry and regional variations in macular function in patients affected by pathological myopia.

4. Objectives

1. Determining the variations of retinal sensitivity in the macular region in low vision patients with pathological myopia using microperimeter.

2. Evaluate the asymmetry of retinal sensitivity of macular region in patients with high myopia.

3. Investigate the correlations between the refractive power, age, best corrected visual acuity for distance vision, and retinal sensitivity of the macular area.

5. Methods

5.1 Study Design

Transversal study

5.2 Patients

Data collection was conducted in the period between December 2014, and May 2015. Patients are part of the population that goes spontaneously to the optometry clinic for a visual assessment, as well as patients who have it, in our database, agree with our inclusion criteria for this research.

The study design was carried out following the guidelines of the Declaration of Helsinki. All participants were asked for permission to be included in the study through informed consent in which exploration and complementary tests that were undergoing, as well as the possible consequences of the results that may appear are explained.

All met the inclusion criteria (patients with pathological myopia of ≥ -6.00 D), while the exclusion criteria were any disease that causes an alteration of macular area, ocular media opacity of the crystalline lens or the cornea, existence of glaucoma, patients who have choroidal neovascularization secondary to myopia, amblyopia, and who did not sign the informed consent. The patient should understand what requires the test, and be able to respond.

5.3 Examination

A *case history* was realized, including name, sex, date of birth (age), general diseases (diabetes mellitus, hypertension or hypotension, cardiovascular disease, etc.), *family history* of glaucoma, a history of frequent headaches, previous or current systemic treatments, a *general anamnesis* was performed (steroids, etc.) and an *ophthalmological history* of previous surgeries, trauma, uveitis, previous ophthalmic medications or current treatments.

In the optometric examination, objective and subjective examination were performed; the spherocylindrical refraction was obtained as a result (in diopters) of each patient.

The spherical equivalent was used in the formula for calculating the correlations. Refractive errors were found in myopia of more than 6.00 diopters.

The visual acuity in logMAR was recorded in the ETDRS chart (Early Treatment Diabetic Retinopathies). Ocular examination with a slit-lamp biomicroscope of the anterior segment of the eye in general, in order to assess the optical media and to discard the eye that represents any pathology in the anterior segment, such as cataract.

Measurement of intraocular pressure (in mmHg) was performed using a non-contact, air-puff tonometer, to exclude any eye over 21 mmHg of intraocular pressure.

The protocol of microperimetry examination of the macular sensitivity was used by MAIA^{TM} microperimeter (Macular Integrity Assessment), where the examination was held in the dark without cycloplegia, all subjects was exposed to a Fast test of 2 minutes in duration, to become familiar with the instrument and to minimize the learning impacts.

Then we did further exploration using Expert test to perform a full assessment, determining the threshold of macular sensitivity and the stability of fixation, which was held in the centre of 10 ° (in diameter) of the macular area (1° = 300 microns, therefore 10 ° = 3000 microns encompassing the macular area) using a strategy of 36 stimuli in a duration of the stimulus of 200 ms, and a duration of the test of 5 minutes for each eye.

Before starting the test, we give some information to our patients about: the test that is meant to study the patient's ability to perceive the light, and he must look at a stationary target, the test is non-invasive, in particular, the device never touches the eye and he only will see a tiny red-white light, he should not move, he must stay focused throughout the test, which will last about 5 minutes for each eye, getting comfortable rest by keeping the chin and the forehead pressed firmly against the remnants, look for the small red circle as a target inside the instrument and always keep his eyes fixed on the centre of the target during the test, he can blink, he will be given a button so that he can press it with the thumb when he sees, or thinks that he sees a small bright spot that appears anywhere on the background.

The test began after the subject was comfortable with the procedure. Above, a threshold stimulus (superthreshold) is projected onto the blind spot of the instrument

for controlling false positives. This retinal configuration is manually identified in the machine before the test as the region of the optic nerve. Any test that produced false positives was excluded. The outpatient spherical equivalent was added to the focus, to adjust the clearance of the image as the MAIA allows automatic recognition and adjustment range in focus from -15.00 D to +10.00 D (automatic) for OD / OS.

The fixation target used for all subjects was a dyne to 1°. The software automatically calculated the percentage of fixations remained within 2° and 4° in diameter.

Fixation pattern was evaluated as the location and the stability of the fixation. The stability of fixation is classified into three categories: stable, relatively unstable, or unstable according to our criteria that were developed in the theoretical part. We got the printout as it shown in the figure (Figure 1.9) when the exam was finished, where we proceed to register the mean sensitivity (MS), central sensitivity (SC), fixation stability P1, P2 and the average of 12 points from the concentric centre of the macula to 1 degree (1 = 300 microns) or S1, three degrees (3 ° = 900 microns) or S2, and 5 degrees (5 ° = 1500 microns) or S3, respectively. We proceed to record data on our paper sheets, and then rewrite down the data on an excel table for further analysis.

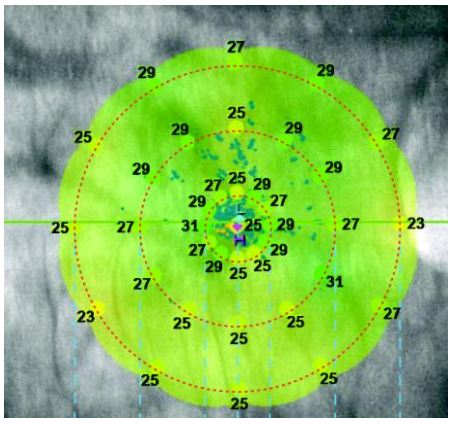


Figure 5.1 Macular area represented in the printout of

5.4 Statistical Analysis

All statistical analyses were performed using SPSS software (IBM, Inc.) version 17.00 for Windows 7 and Analysis-it for Microsoft Excel 3.90.7. Before conducting the statistical analysis, we evaluated our data for normality with the Kolmogorov-Smirnov test, revealing several instances of non-normal distribution.

Therefore, we opted to present our results for each eye, as well as the differences between eyes, as median and range (minimum and maximum), although mean values and standard deviation (±SD) are also summarized to allow comparison with previous studies.

In order to explore the statistical significance of the differences between non-paired data (such as between males and females) the Mann-Whitney U-test was used, whereas when data was paired (comparing right with left eye), the Wilcoxon signed ranks test was used.

The Spearman correlation test was employed to explore possible associations between the variables under evaluation. For this test, and given the clinical nature of the present study, we considered a rho coefficient ≥ ±0.4 as an indicator of either a positive or negative weak correlation between variables, a rho value between 0.6 and 0.8 as an indicator of moderate correlation and any rho ≥±0.8 as an indicator of strong correlation. A p value <0.05 denoted statistical significance throughout the study.

Finally, Inter-ocular asymmetry values were determined and compared with previous published tolerance values by means of a paired t test, and the interocular differences were calculated as the 2.5^{th} and the 97.5^{th} percentiles.

6. Results

6.1 Descriptive Statistics of Controlled Variables

After the exclusion of 14 subjects who did not comply with the inclusion and exclusion criteria or who presented insufficiently clear retinal fundus images, a total of 36 subjects (n = 36) participated in this research, *i.e*., 72 eyes. 13 subjects were males (age range: 17 – 60 years old) and 23 were females (13-57 years old).

	N	Mean	Median	SD	Minimum	Maximum
Age F	23	34.39	36.00	11.85	13.00	57.00
Age M	13	38.92	43.00	15.09	17.00	60.00

F: females, M: males, SD: standard deviation
Table 6.1 Descriptive statistics of the age (female, male)

6.2 Descriptive Statistics of Controlled Variables (Macular Sensitivity)

In order to figure out the normality of our sample, we have used the Shapiro-Wilk test, as a rule of thumb, if the p-value is less than 0.05, then the data tested are not from a normally distributed sample.

Relative Interocular Differences

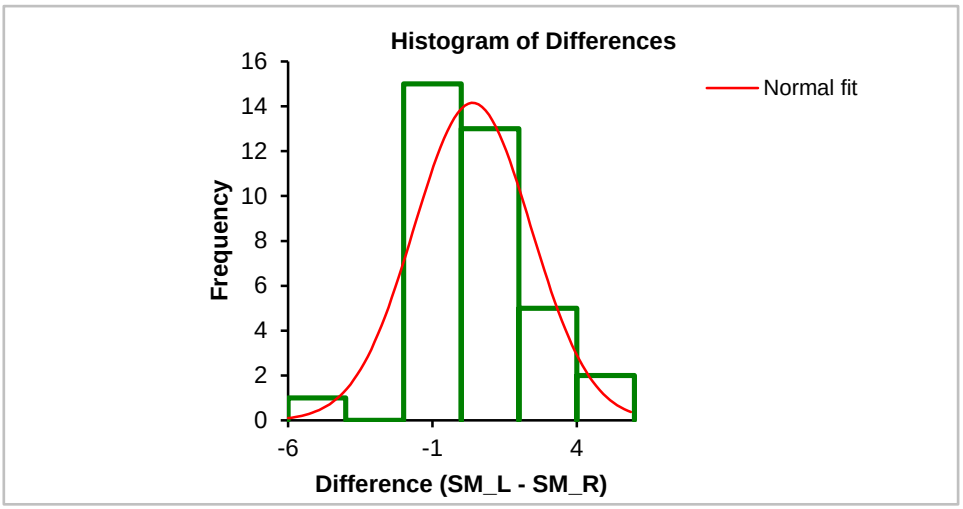
Descriptive statistics of the relative interocular differences, between both eyes, represented, as we mentioned above, by the calculations of the mean, standard deviation, median, minimum, and maximum in the 3 rings (S1, S2, and S3), the central sensitivity (SC), fixation stability (P1. and P2), refractive power (SphE), and visual acuity (VA). (Table 6.2)

Also, we have demonstrated that the distribution of the deferential frequencies of SM between both eyes. It is lightly distributed towards the left, which has slightly positive differences towards the right side (Histogram 6.1).

		R .EYE (dB)					L. EYE (dB)					
	N	Mean	SD	Median	Min.	Max.	Mean	SD	Median	Min.	Max.	r
Age.	36	36.03	13.09	38.00	13.00	60.00	36.03	13.09	38.00	13.00	60.00	
SM.	36	27.86	2.23	28.50	22.90	33.00	28.25	1.31	28.50	24.90	30.30	0.48
SC.	36	25.61	2.76	25.50	18.00	31.00	26.50	2.68	27.00	19.00	32.00	0.26
S1.	36	27.97	2.65	28.50	21.70	32.10	28.62	1.54	29.17	24.00	30.20	0.39
S2.	36	27.90	1.92	28.42	23.80	31.30	28.51	1.27	28.66	25.50	31.20	0.56
S3.	36	27.21	1.10	27.66	23.30	30.40	27.75	1.25	28.12	24.50	29.90	0.49
P1.	36	91.08	10.10	93.50	53.00	100.00	92.22	9.02	96.00	61.00	100.0	0.77
P2.	36	97.69	3.96	100.00	86.00	100.00	98.14	3.25	100.00	86.00	100.0	0.71
SphE.	36	8.58	2.51	8.13	6.00	16.00	8.57	2.24	8.13	6.00	15.00	0.93
VA.	36	0.03	0.04	.022	-0.02	0.12	0.034	0.04	0.022	-0.02	0.12	0.95

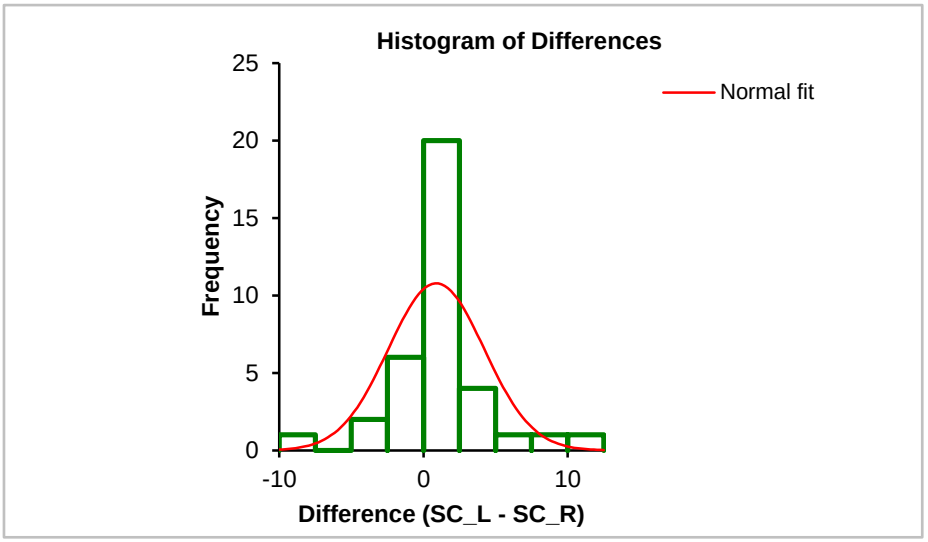
SM: mean sensitivity, SC: central sensitivity, S1: sensitivity 1°, S2: sensitivity 2°, S3: sensitivity 3°, P1: fixation stability to 1°, P2: fixation stability to 2°, SphE: Spherical equivalence, logMARCDVA: corrected distance visual acuity. r: correlation coefficient

Table 6.2 Variation values and relative interocular differences in (S1, S2, S3), (P1, P2), SphE, and VA



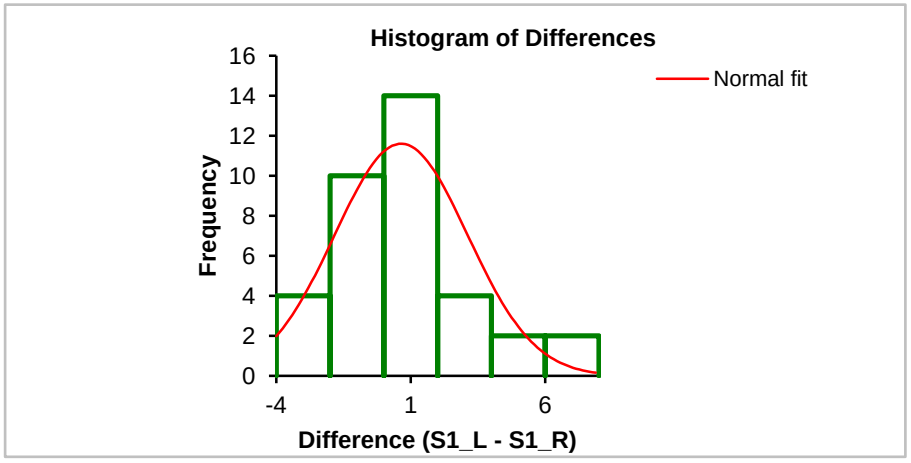
Histogram 6.1 Histogram of Differences for SM

Accordingly, we demonstrated in the histogram 6.2 the distribution of the deferential frequencies of SC between both eyes, and we noticed as well, the distribution to the right of zero value was higher (i.e. the left eye's sensitivity is higher than the right).



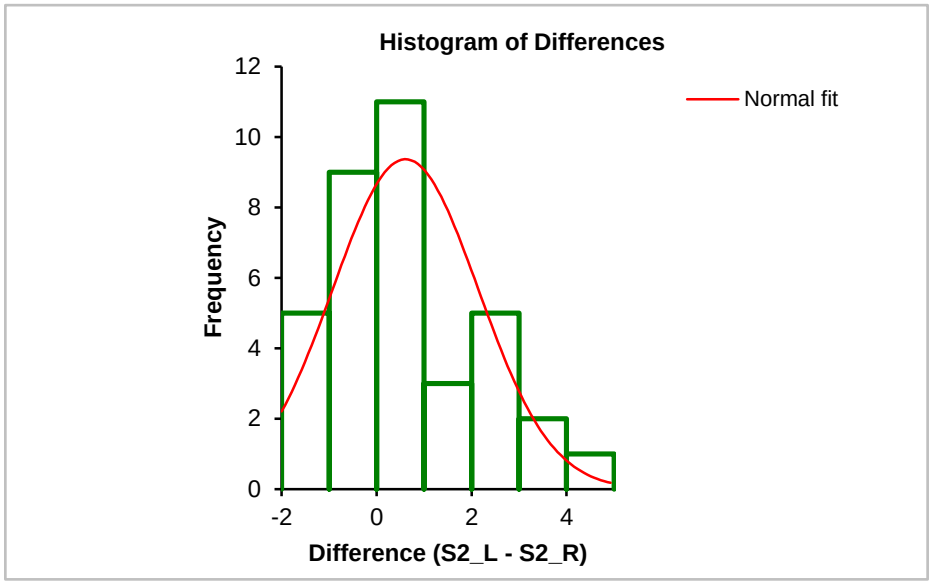
Histogram 6.2 Histogram of Differences for SC

Likewise, in the histogram below, we noticed the distribution of deferential frequencies of S1, which is the first ring (300 microns or 1 degree away from the centre of the fovea).



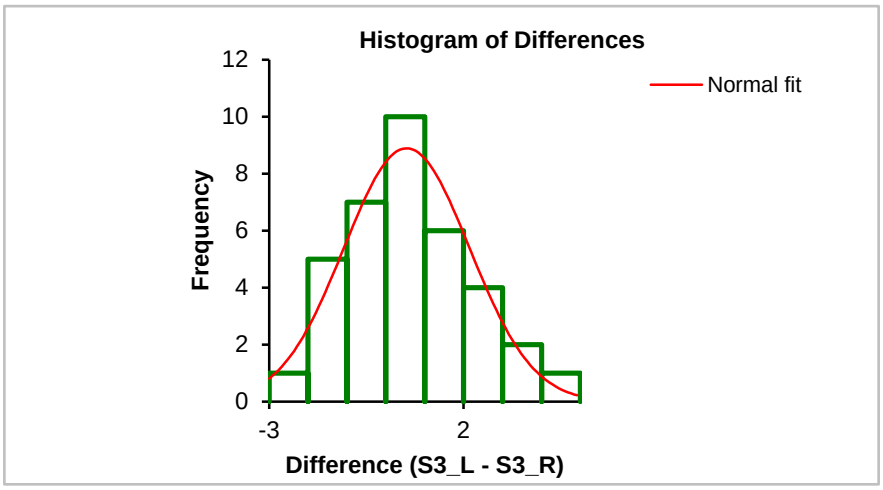
Histogram 6.3 Histogram of Differences for S1

Moreover, in the histogram 6.4 we reported the distribution of the deferential frequencies of S2 between both eyes, which is the second ring (900 microns of 3 degrees away from the center of the fovea).



Histogram 6.4 Histogram of Differences for S2

Meanwhile, the distribution of the deferential frequencies of S3 between both eyes was explored in the histogram 6.5, where the third ring was located 1500 microns or 5 degrees away from the centre of the fovea.



Histogram 6.5 Histogram of Differences for S3

Non-Parametric Tests

Otherwise, in the table 6.3 we have compared the differences between the right and left eyes of the all parameters, as we used non-parametric test to compare paired-data in the same patient. According to Wilcoxon test, nothing appeared different to be statistically significant between both eyes, but SC and S2 are approximately different without reaching the level of the significance, however, the age and the spherical equivalent were equalled.

Difference between pairs		N	Mean rank	Rank sum	Hypothesis	Z statistic	*p*
SM.L - SM.R	Negative rank Positive rank Equal Total	16[a] 20[b] 0[c] 36	16.53 20.08	264.50 401.50	a. SM.L < SM.R b. SM.L > SM.R c. SM.L = SM.R	-1.077[a]	0.282
SC.L - SC.R	Negative rank Positive rank Equal Total	9[d] 19[e] 8[f] 36	14.33 14.58	129.00 277.00	d. SC.L < SC.R e. SC.L > SC.R f. SC.L = SC.R	-1.704[a]	0.088
S1.L - S1.R	Negative rank Positive rank Equal Total	14[g] 22[h] 0[i] 36	18.04 18.80	252.50 413.50	g. S1.L < S1.R h. S1.L > S1.R i. S1.L = S1.R	-1.265[a]	0.206
S2.L - S2.R	Negative rank Positive rank Equal Total	14[j] 21[k] 1[l] 36	14.79 20.14	207.00 423.00	j. S2.L < S2.R k. S2.L > S2.R l. S2.L = S2.R	-1.770[a]	0.077
S3.L - S3.R	Negative rank Positive rank Equal Total	13[m] 20[n] 3[o] 36	14.96 18.33	194.50 366.50	m. S3.L < S3.R n. S3.L > S3.R o. S3.L = S3.R	-1.538[a]	0.124
P1.L - P1.R	Negative rank Positive rank Equal Total	14[p] 17[q] 5[r] 36	14.21 17.47	199.00 297.00	p. P1.L < P1.R q. P1.L > P1.R r. P1.L = P1.R	-0.965[a]	0.335
P2.L - P2.R	Negative rank Positive rank Equal Total	7[s] 9[t] 20[u] 36	8.00 8.89	56.00 80.00	s. P2.L < P2.R t. P2.L > P2.R u. P2.L = P2.R	-0.629[a]	0.530

Table 6.3 Wilcoxon Signed Ranks Test and Contrast Statistics

Absolute Interocular Differences

Consequently, asymmetry of retinal sensitivity in pathological myopia was measured with MAIA^{TM}, and the Percentile distribution of interocular differences (right eye minus left eye) in the same subject was explored taking into account the 2.5th, 5th, 25th, 50th, 75th, 95^{th,} and 97.5th. Also the absolute differences of mean, standard deviation, minimum and maximum were explored (Table 6.4).

	Differences			**Percentile** (dB)								
	N	Mean	SD	Min.	2.5	5	25	50	75	95	97.5	Max.
SM.	36	-0.39	2.03	-4.90	-4.71	-4.22	-1.32	-0.30	0.70	2.50	4.93	5.90
SC.	36	-0.89	3.33	-10.00	-9.52	-8.30	-2.00	-1.00	0.58	5.45	7.28	8.00
S1.	36	-0.65	2.47	-6.90	-6.86	-6.73	-1.89	-0.38	1.17	2.95	3.57	3.83
S2.	36	-0.59	1.61	-4.50	-4.24	-3.56	-1.27	-0.50	0.59	1.50	1.50	1.51
S3.	36	-0.54	1.62	-4.00	-3.96	-3.83	-1.26	-0.25	0.85	1.87	2.22	2.34
P1.	36	-1.14	6.67	-21.00	-21.00	-17.60	-4.58	0.00	1.58	12.45	15.00	100.00
P2.	36	-0.44	2.57	-10.00	-10.00	-8.30	-0.58	0.00	0.00	2.45	5.00	100.00

SM: mean sensitivity, SC: central sensitivity, S1: sensitivity 1°, S2: sensitivity 2°, S3: sensitivity 3°, P1: fixation stability to 1°, and P2: fixation stability to 2°. SD: standard deviation, Min: minimum, Max: maximum, and N: number of sample.

Table 6.4 Absolute interocular differences in (S1, S2, S3), and (P1, P2)

Total Correlations

Therefore, we assessed the total correlation between all parameters and the spherical equivalent, age, and best corrected visual acuity of logMAR for distance vision (Table 6.5). This correlation was explored using Spearman correlation test, giving the p-value of the Rho of Spearman.

N		SphE		Age		logMARCDVA	
		r	*p*	*r*	*p*	*r*	*p*
SM.	72	-0.50	< 0.001	-0.37	0.002	-0.47	<0.001
SC.	72	-0.29	< 0.012	-0.29	0.012	-0.27	0.02
S1.	72	-0.43	< 0.001	-0.40	0.001	-0.45	<0.001
S2.	72	-0.44	< 0.001	-0.45	< 0.001	-0.41	<0.001
S3.	72	-0.47	< 0.001	-0.36	0.002	-0.38	0.001
P1.	72	-0.17	0.16	-0.06	0.56	-0.04	0.76
P2.	72	-0.19	0.11	0.09	0.46	0.06	0.60

SM: mean sensitivity, SC: central sensitivity, S1: sensitivity 1°, S2: sensitivity 2°, S3: sensitivity 3°, P1: fixation stability to 1°, P2: fixation stability to 2°, SphE: Spherical equivalence, logMARCDVA: corrected distance visual acuity, p: Rho of Spearman, r: correlation coefficient

Table 6.5 Spearman correlation test

Correlations between the Right and Left Eyes

Finally, in the table (Table 6.6) we explored the total correlations between the paired-data in our patients for right and left eyes, using Spearman correlation test, giving the p-value of Spearman.

N		SphE		SM.R-L		SC. R-L		S1. R-L		S2. R-L		S3. R-L	
		r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
SM.R-L	36	-0.26	0.13	0.76**	0.00	0.15	0.38	0.73**	0.00	0.63*	0.00	0.56**	0.00
SC. R-L	36	-0.32	0.06	0.44**	0.01	0.57**	0.00	0.49**	0.00	0.44**	0.01	0.52**	0.00
S1. R-L	36	-0.30	0.08	0.66**	0.00	0.19	0.26	0.82**	0.00	0.66**	0.00	0.64**	0.00
S2. R-L	36	-0.34*	0.04	0.62**	0.00	0.22	0.20	0.73**	0.00	0.72**	0.00	0.69**	0.00
S3. R-L	36	-0.47**	0.004	0.57**	0.00	0.19	0.28	0.69**	0.00	0.66**	0.00	0.70**	0.00
P1. R-L	36	-0.10	0.57	0.17	0.31	0.23	0.17	0.15	0.39	0.08	0.64	0.19	0.27
P2. R-L	36	-0.05	0.76	0.22	0.21	0.19	0.26	0.10	0.56	0.14	0.42	0.23	0.19

**. Correlation is significant at the 0.01 level (2-tailed). , *. Correlation is significant at the 0.05 level (2-tailed).

SM: mean sensitivity, SC: central sensitivity, S1: sensitivity 1°, S2: sensitivity 2°, S3: sensitivity 3°, P1: fixation stability to 1°, P2: fixation stability to 2°, p: Rho of Spearman, r: correlation coefficient

Table 6.6 Spearman correlation test

7. Discussion

The microperimetry (fudus related perimetry) evaluate the macular sensitivity and provide almost an exact correlation between the fundus pathology and the corresponding functional defects, taking into account the fixation pattern and stability, allowing us to assess the retina in some ocular conditions, like macular oedema, age-related macular degeneration, and diabetes retinopathy.

In the present study, we conducted an analysis of the macular sensitivity using MAIA^{TM} microperimeter throughout confocal laser assessment, which covers the central 10° of the macula in patients with pathological myopia.

The results provide information regarding the regional variations in the macular function, in patients affected by pathological myopia, in which, after the best corrected visual acuity for distance vision, the macular sensitivity is reduced.

When the central sensitivity is compared, which is reduced in subject with normal foveal fixation, due to the absence of rod photoreceptors in the fovea, therefore increasing the brightness of the stimulus was required to achieve the umbral detection (Notaroberto *et al., 2012).*

Even though, the mean of the retinal sensitivity in the third ring was significantly reduced in comparison with the first and second rings in patients with pathological myopia. The macular sensitivity correlates significantly with the age and spherical equivalent (Chen et al., 2009), and the measuring protocol is similar to the recent study of A. Zaben (Zaben et al., 2015) in which he investigates the retinal sensitivity in the macular region exploring the mean sensitivity. Conversely, in our study we investigated the retinal sensitivity in three rings, in the macular region.

In this study, the mean of the retinal sensitivity was higher in the 1st ring S1 (27.97 dB for the right eye, and 28.62 dB for the left eye) in comparison with other regions SC, S2, and S3. As well as, the left eye has higher retinal sensitivity than the right eye (Table 6.2).

This way, these differences in the retinal sensitivity between the right and left eyes could be due to the test-learning factor, and the darkness adaptation (hence, we started with the right eye), thus, the left eye was appearing more sensible than the right one.

Besides, the Table 6.4 demonstrates the absolute interocular differences of the mean, as well as, the maximum and minimum. The difference between both eyes in the same subject of the SC and SM, moreover the three concentric rings of sensitivity from the fovea, S1, S2, and S3. We also obtained the percentiles of 5%, 25%, 50%, 75%, 95%, and 97.5% to determine the physiological ranges of the interocular asymmetry in the functionality of the retina, which is essential to detect abnormal values.

Furthermore, the major absolute interocular difference of SM gave a mean of 0.39 dB in high myopic patients, with a minimum of -4.90 dB and a maximum of 5.90 dB, ranged (22.90 - 33.00 in the right eye, and 24.90 – 30.30 in the left eye). Our study revealed that, 95% of patients with pathological myopia could have interocular differences limit of 2.50 dB, which is considered normal. In contrary, the absolute interocular differences in S2, and S3 (0.54 dB, 0.59 dB) respectively, with a range of (-4.50 to 1.51 dB for S2), and (-4.00 to 2.34 dB for S3). Moreover, the 97.5th percentile in our results has 95% of the population with myopia, which may have a difference of the retinal sensitivity in the 2nd, and the 3rd rings up to (1.50 dB, 2.22 dB) respectively, in this case it is considered normal too.

In our research, we obtained a higher difference of retinal sensitivity of the central region of 5.45 dB, and a lower difference in the 2nd ring 3° away from the centre of the fovea of 1.51 dB, in which it is considered that 95% of our population could have a difference in the central sensitivity up to 5.45 dB.

The correlation coefficient using Wilcoxon test indicated significant asymmetry in retinal sensitivity in SC (Z= -1.704 dB), and S2 (Z= -1.770 dB) i.e. the retinal sensitivity is higher in the left eye among these regions than the right eye (Table 6.3).

In the study of Gella, she was comparing the retinal sensitivity using microperimeter and the morphological changes in the retinal layers using SD-OCT between myopic and emmetropic patients; she found a reduction in the retinal sensitivity in patients with myopia. There was a positive correlation between the refractive error and the medium of retinal sensitivity (r = 0,725, p = <0,001) (Gella et al., 2011). Also in our study, we have got similar results, in which we found a significant negative correlation between the refractive power and the retinal sensitivity of the macular area, and a negative correlation between the visual acuity (logMAR) and the retinal sensitivity (see Table 6.5),

which goes hand in hand with the study of Zaben`s research group, as they concluded the correlation between the retinal sensitivity and the low visual acuity associated with high degree of myopia (Zaben et al., 2015).

As though, Zhou et al. according to our study, he found similar results in which the retinal sensitivity differs from the centre of the macula towards the peripheral retina; even he was using MP-1 microperimeter among normal subjects of different middle and advanced ages, where he did not get any correlation between the retinal sensitivity and the age (Zhou et al., 2011). In our study, we found a correlation between the age and the retinal sensitivity.

The present study has demonstrated the correlation between both eyes (72 eyes) in table 6.5. We noticed that, SM and S3 are correlated with the refractive power, while the S1 and S2 are correlated with the age, whereas, the SM and S1 are correlated with the logMAR VA, without any correlation with the fixation points P1 and P2.

Nevertheless, the correlation between the 3 rings were not evaluated before, which still as an interesting consideration, where we found the correlation between the retinal sensitivity of the 3 rings and the refractive power, by which with higher refractive power there is a lower retinal sensitivity. This relationship is powerful in SM, and the three rings, with higher correlation of the exterior one towards the centre, it conforms the reality of the recent investigation of A. Zaben (Zaben et al, 2015).

We recognize that it’s necessary to perform additional studies with a larger sample to support our conclusions in the future.

Accordingly, to determine the physiological ranges of interocular asymmetry in retinal functions among patients with pathological myopia, it is essential to detect abnormal values. Our study is the first to detect the physiological asymmetry of retinal sensitivity in patients affected by pathological myopia, and we suggest that, it should not exceed 5.45 dB in the centre of the macula, and 2.50 in SM, if measured with MAIA^{TM} microperimeter (see Figure 7.1).

The results of our study have been provided new vision about the relation between the fixation, retinal sensitivity, age, and best corrected visual acuity of distance vision in patients with pathological myopia (compare Table 6.2 and Table 6.5).

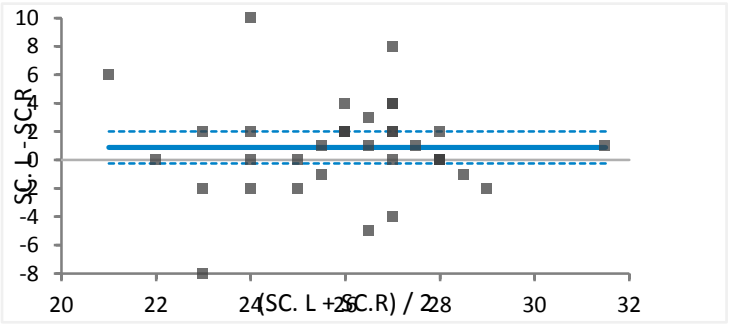


Figure 7.1 Significant functional asymmetry in (SC) macular area in patients with pathological myopia

The present study has been conducted using MAIA^{TM} microperimeter, which does not indicate the refractive error into account, despite the diagnosis of the functional integrity of the macula could be modified depending on the refractive power, small size of our sample, and the absence of a control group were considered of the main limitations of our study.

In the future, we could overcome the darkness adaptation taking the first eye to be examined randomly, instead of starting always with the right eye. Although, we have got statistical correlations between the age and retinal sensitivity in our transversal study, but it would be more accurate if it was a longitudinal study.

8. Conclusions

1. Interocular differences exceeding 5.45 dB in the foveal region and 2.50 dB in SM may indicate asymmetrical macular decline typical of pathological myopia, if measured with MAIA^{TM} microperimeter.
2. The interocular asymmetry of retinal sensitivity may be an effective approach to understand better the physiological variations of the macula in patients affected by pathological myopia.
3. There are significant correlations between the refractive power, age, best corrected visual acuity for distance vision, and retinal sensitivity of the macular area.

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10. Annexes:

ANNEX I. INFORMED CONSENT

HOJA DE CONSENTIMIENTO INFORMADO

En cumplimiento de los artículos 8 y siguientes de la Ley 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica le ofrecemos por escrito y de manera comprensible la descripción de las características de riesgo y beneficios de participar en el proyecto de investigación cuyo objetivo es **determinar la asimetría de sensibilidad retiniana en el área macular mediante micropermetría (MAIA^{TM}).**

Nombre del informador: **Zeyad Alzaben** **(BCH, MSc)** Firma:_____

Descripción

Este proyecto de investigación está siendo realizado por **Zeyad A. Alzaben**, estudiante del máster de rehabilitación visual de la universidad de Valladolid.

El propósito de esta investigación es **determinar la asimetría de sensibilidad retiniana en el área macular en pacientes con miopía alta mediante micropermetría (MAIA^{TM}).**

Usted es candidato para participar en este proyecto de investigación por miopía alta.

Si acepta participar en este proyecto de investigación se le solicitará la realización de un conjunto de pruebas y la recolección de datos como su **refracción ocular, agudeza visual, parámetros de la retina estructural** mediante la tomografía de coherencia óptica y parámetros funcionales mediante la microperimetría para determinar su sensibilidad a la luz en diferentes zonas de su retina central. La participación en este estudio le tomará aproximadamente unos 30 min.

Riesgos y beneficios

No existen riesgos a nivel ocular durante la realización de este estudio dado que las pruebas que se realizan son empleadas en las consultas de optometría y oftalmología de manera cotidiana y todas ellas en este caso se realizan de manera NO invasiva.

Los beneficios esperados de esta investigación son su aportación a la ciencia, y la realización de distintas pruebas de tipo optométrico-oftalmológicas sin coste alguno.

Confidencialidad

La identidad del participante será protegida ya que todo este proceso será totalmente anónimo, solo se conocerá la edad y el sexo. Toda información o datos que pueda identificar al participante serán manejados confidencialmente.

Solamente el optometrista de este trabajo y los facultativos implicados en esta investigación tendrán acceso a los datos que puedan identificar directa o indirectamente a un participante, incluyendo esta hoja de consentimiento.

Estos datos serán almacenados en expedientes confidenciales con la finalidad única de esta investigación y se conservarán por un periodo de 2 años máximo después de que concluya este estudio.

Derechos

Si ha leído este documento y ha decidido participar, por favor entienda que su participación es completamente voluntaria y que usted tiene derecho a abstenerse de participar o retirarse del estudio en cualquier momento, sin ninguna penalidad. También tiene derecho a no participar en alguna prueba en particular. Además, tiene derecho a recibir una copia de este documento.

Si tiene alguna pregunta o desea más información sobre esta investigación, por favor comuníquese al Tel. 972506386

Su firma en este documento significa que ha decidido participar después de haber leído y discutido la información presentada en esta hoja de consentimiento y que ha recibido copia de este documento.

Nombre de el/la participante	Firma	Fecha

Ha discutido el contenido de esta hoja de consentimiento con el/la arriba firmante

Nombre de el/la participante	Firma	Fecha