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ORIGINAL RESEARCH ARTICLE

High myopic patients with and without foveoschisis: morphological and functional characteristics

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Abstract

Purpose Myopic foveoschisis (MF) is characterized by the splitting of the retinal layers in the fovea of patients with high myopia (HM). MF may progress into foveal detachment or macular hole formation with consequent loss of central vision. The aim of this study is to investigate morphological and functional changes of the macular region in myopic subjects with and without foveoschisis.

Design Observational, cross-sectional, comparative study.

Methods Forty-eight patients with HM and 24 healthy controls were evaluated by spectral domain-optical coherence tomography (SD-OCT), multifocal electroretinography (mfERG) and microperimetry (MP-1) tests to assess macular thickness, functionality and sensitivity values, respectively. The results of the diagnostic examinations were compared between three groups: HM patients with MF ($N = 24$), HM patients without MF ($N = 24$) and control group (CG) ($N = 24$). All statistical analyses were performed with STATA 14.0 (Collage Station, Texas, USA). One-way analysis of variance (ANOVA) followed by Tukey's post hoc test was used to analyze differences between groups unless specified; p values < 0.05 were considered as statistically significant. Gender distribution was compared by the Chi square test.

Results The statistical analysis with one-way ANOVA followed by Tukey's post hoc test showed a significant increase in macular thickness in HM patients with MF when compared to both HM patients without MF and CG. Morphological changes were associated with functional impairment as demonstrated by the significant decrease in amplitude of the P1 wave and MP-1 sensitivity ($p < 0.05$), according to the anatomical landmarks.

Conclusions This study showed that the morphological changes observed in the central retina of HM patients with MF are associated with functional alterations. High-tech diagnostic tests such as SD-OCT, mfERG and MP-1 could be useful for management in complications of MF.

Keywords High myopia · Microperimetry (MP-1) · Multifocal electroretinography (mfERG) · Myopic foveoschisis · Pathological myopia · Retinoschisis · Spectral domain-optical coherence tomography (SD-OCT)

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Introduction

The prevalence of myopia is increasing throughout the world, becoming a prominent public health issue, particularly in Taiwan, Japan, Hong Kong, Singapore and the USA [1–3]. To date, myopia is one of the ocular conditions classified as priorities by the World Health Organization's Global Initiative for the Elimination of Avoidable Blindness [4]. High myopia (HM), in particular, is characterized by a refractive error greater than − 6.00 diopters (DS) and/or by an axial length exceeding 26.5 mm [3–5]. This condition is a major risk factor for the development of cataract, glaucoma, retinal detachment (RD) and myopic retinopathy [3–5]. In addition, patients with HM may develop pathological changes of the fundus, namely pathological myopia (PM), caused by the progressive stretching and thinning occurring in the posterior section of the eye [3–5]. These changes include peripapillary intrachoroidal cavitations, choroidal neovascular membranes, paravascular inner retinal cysts, tractional internal limiting membrane detachment, macular holes, posterior retinal detachment and dehiscence of retinal layers (retinoschisis) [5–7]. Moreover, patients with HM and posterior staphyloma are prone to develop myopic foveoschisis (MF), which is characterized by the splitting of the inner foveal layers [3–5]. In 1958, Phillips was the first to notice a lifting of the neurosensory retina in the absence of macular holes or RD in HM patients [8]. In 1999, Takano and Kishi, using optical coherence tomography (OCT) technology, objectively evaluated the retinal status of patients with PM and confirmed Phillips's findings, coining the term MF [9]. Currently, the use of spectral domain-OCT (SD-OCT) scans allows the evaluation of morphological changes associated with MF. It has been described that the progressive confluence of intraretinal cysts leads to the thickening of the MF and the accumulation of subretinal fluid, which may be complicated by the development of a macular hole, with or without RD, and loss of central vision [10, 11]. The natural course and progression of MF are unpredictable, mainly because the disease is initially asymptomatic and progresses slowly. Hence, MF is often underdiagnosed, and its incidence is considerably underestimated. Epidemiological studies show a prevalence of MF ranging from 9 to 34% in PM eyes [3–5, 10, 11]. Early diagnosis and monitoring of MF are crucial to identify complications such as the development of vitreoretinal interface traction, epiretinal membrane, macular hole, limiting membrane detachment, paravascular microholes and RD [5, 10, 11]. In fact, up to 50% of highly myopic eyes with MF have been reported to develop RD or macular hole within a few years of diagnosis [6, 12–16].

Although many studies have investigated structural and functional changes in myopia, few have focused on the correlation between structural and functional changes, especially in healthy high myopia and with macular foveoschisis. Further on, we have also analyzed retinal function using objective (mfERG) and psychophysical (MP-1) tests in patients with high myopia and macular schisis.

Therefore, the aim of this study was to evaluate macular morphological and functional changes in patients affected by HM. In particular, data obtained using SD-OCT, multifocal electroretinography (mfERG) and microperimetry (MP-1) in HM patients with and without MF were compared with healthy control subjects.

Materials and methods

In this study, we recruited 48 HM subjects (24 with MF and 24 without MF) from the Retina and Electrophysiology Unit, Department of Sense Organs, Umberto I Policlinico of Rome. We included 24 healthy subjects as control group (CG). The research was carried out over three months. A comprehensive eye examination, including best-corrected visual acuity (BCVA) measured using the early treatment diabetic retinopathy study (ETDRS) charts at 4 m, slit lamp biomicroscopy, intraocular pressure measurement with Goldmann applanation tonometry, ocular biometric measurement and dilated fundus examination, was performed in all the subjects participating in the study. The indications for the study and inclusion criteria of 48 HM patients were: refractive defect > -8.00 DS and ocular axial length > 26 mm; visual acuity with BCVA $>$ 20/50 Snellen ($+$ 0.4 logMAR); age from 47 to 55 years; and macular retinoschisis shown by OCT in MF group. The exclusion criteria were: patients with ≤ -8.00 DS; lamellar or complete macular holes; chorioretinal neovascularization; history of macular photocoagulation; paravascular retinal cysts; cystoid macular

edema; RD; amblyopia; glaucoma; ocular media opacities; uveitis; chorioretinitis; neuritis; and patients who underwent any previous ocular surgery. Were also excluded from the study those affected by systemic diseases that could invalidate our tests, such as diabetes mellitus, cardiovascular disorders, cancer, connective disease and dysthyroidism. Inclusion criteria of the healthy group were: age from 48 to 55 years, BCVA > 20/25 Snellen (+ 0.1 logMAR), refractive condition of prevalent emmetropia, no abnormality in SD-OCT, mfERG and MP-1 exams, and no vitreoretinal diseases, or neuritis, glaucoma, cataract, or previous ocular surgery, etc.

One eye from each healthy subject was randomly chosen for instrumental evaluation of the macular area between 0 and 20 degrees, according to the anatomical landmarks, and to the chronological order of arrival of the participants starting from the right eye. Furthermore, 24 of the 48 patients with HM were chosen in the absence of macular foveoschisis and 24 with macular foveoschisis.

In accordance with the Helsinki Declaration and Good Clinical Practice guidelines, all the patients and controls were informed about the use of their data and signed an informed consent. The study protocol was approved by the Ethics Committee of the Sapienza University of Rome.

All patients and controls were evaluated by SD-OCT, a non-contact imaging technology that provides a detailed cross-sectional view of the retinal profile using an infrared laser probe and confocal scanning laser ophthalmoscopy, mfERG, a technique that provides an objective assessment of macular functionality, MP-1 tests, a psychophysical examination that quantifies central retinal sensitivity in different areas and evaluates the fixation characteristics, allowing the correlation of this information with the fundus.

We evaluated all three tests in one setting: retinal sensitivity in decibel (dB) by MP-1 microperimetry; macular thickness in micrometers (μm) by SD-OCT, retinal function with amplitude in microvolts/squared degree (μV/deg2) and the implicit time in milliseconds (ms) of the P1 wave of mfERG.

OCT measurement

SD-OCT data were obtained using the Spectralis OCT (Spectralis® HRA/OCT Heidelberg Engineering, Heidelberg Germany). A macular thickness map was obtained for each eye, using the raster 25° × 15°, 25-line horizontal raster scan protocol, centered on the fovea, with up to 10 frames averaged for each scan. Retinal thickness and macular volume (Fig. 1) within 1 mm (central area), 3 mm (2°–5° ring) and 6 mm (5°–10° ring) diameter area centered on the fovea - were automatically calculated by the software (Fig. 2). Retinoschisis on the SD-OCT images was classified according to the extent of the outer schisis: no macular retinoschisis, partial and/or entire macular retinoschisis.

Electrophysiological testing

MfERG data were obtained using the Optoelectronic Stimulator Vision Monitor MonPak 120 by Metrovision, (Pérenchies, France) according to the standard guidelines of the International Society for Clinical Electrophysiology of Vision (ISCEV) [17]. Before examination, pupils were dilated with tropicamide 1% eye drops. All subjects were left to adapt to ordinary room light for 30 min before testing. MfERG recording was performed using an ERG-Jet corneal contact lens active electrode; the cornea was previously anaesthetized with proparacaine hydrochloride 0.5% eye drops. A skin reference or inactive electrode was

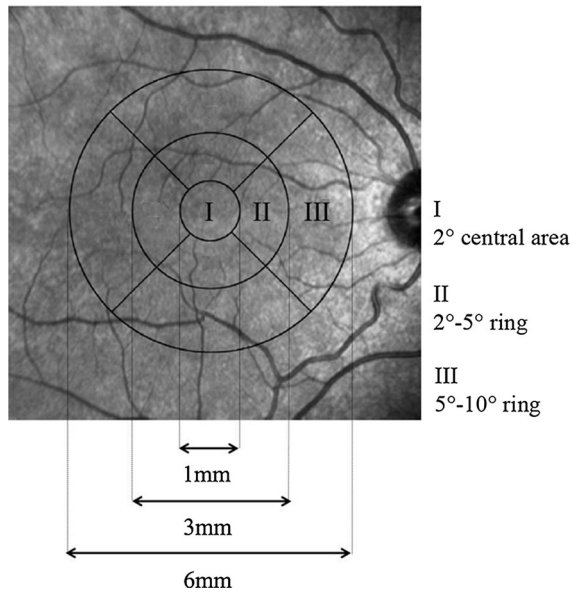


Fig. 1 Grid used for evaluation of retinal thickness, functionality and sensitivity values of the macular areas using spectral domain-optical coherence tomography (SD-OCT), multifocal electroretinography (mfERG) and microperimetry (MP-1) tests

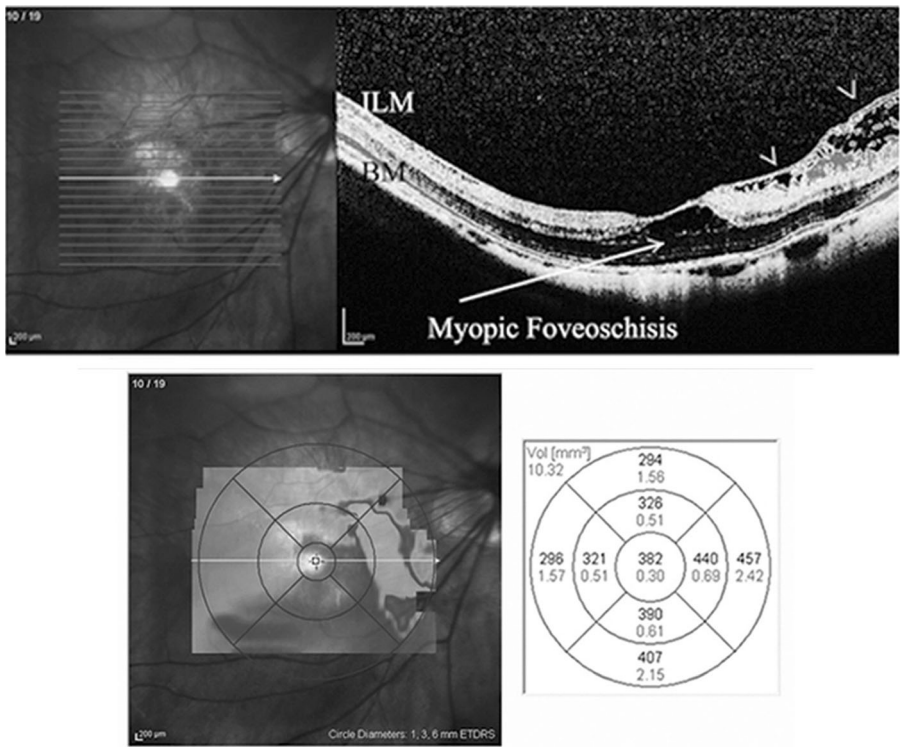


Fig. 2 Patient X.Y. with high myopia (HM) and foveoschisis. Spectral domain-optical coherence tomography (SD-OCT) shows macular schisis and outer retinal layer dehiscence in the fovea (white arrow). The topographic retinal map of the SD-OCT reveals localized retinal elevation in the area of foveoschisis. Bruch's membrane (BM), internal limiting membrane (ILM)

placed at the outer canthus of the corresponding eye. A ground electrode was placed on the patient's earlobe. The active, inactive and ground electrodes were connected with a junctional box, from which signals were delivered to additional recording components for amplification and display. MfERG was evaluated on the computerized Optoelectronic Stimulator (Table 1) [17]. The standard display was a hexagonal stimulus pattern scaled in size to produce mfERG responses of approximately equal amplitude across the healthy retina. Roughly half of the elements were illuminated at any one time. Thus, the central hexagons were smaller than the more peripheral ones. The stimulus field consisted of a hexagonal array with the fixation point at the center. The field contained either 61 hexagons within a diameter of 20°–25° radius from the fixation point to edge of display. Amplitudes and implicit times of three peaks named N1, P1 and N2 were extrapolated using the first-order Kernel. The average responses were over a group of up to three rings from zero to 10 degrees of eccentricity relative to fixation (Fig. 3a). The P1 peak includes the activity of the cells contributing to the light-adapted b-wave and oscillatory potentials of the full-field ERG [17].

Perimetric examinations with MP-1

MP-1 was performed in a dedicated psychophysics dark room. All subjects had a pupil diameter wider than 4 mm, required for the MP-1 Nidek measurement (Nidek Technologies Padua, Italy). A Goldmann III size white stimulus with a luminance of 1.0 cd/m^2 and duration of 200 ms was projected onto a white background. The stimulus intensity ranged from 0 to 34 dB, and the light threshold was determined by a 4–2 staircase strategy. The MP-1 test is based on a 4–2 full threshold staircase strategy using a Goldmann III stimulus size. The measured test points in the MP-1 are shown in Fig. 3b. The fixation target is a 1° diameter red circle, and the background luminance is set at 31.4 asb. The maximum luminance of the MP-1 is 10,000 asb, and the stimulus dynamic range is

Table 1 Type of analysis of multifocal electroretinography (mfERG)

Six minutes per analysis	MfERG photopic response 61B
Optical correction	As required at 30 cm
Stimulated fields	Thirty degrees horizontally and 23 degrees vertically
Modes of stimulation and zones	Areas covering the central 25° of the retina and scaled eccentrically to simulate an array of 61 hexagons. Zones of size 3.4° centrally
Hexagons modulated	Between a high luminance of stimulations set at 200 cd/mq for the bright flashes and 1 cd/m^2 for the dark flashes according to a binary pseudo-random m-sequence
Standard stimulation	Black/white monochrome cathode ray tube monitor with blue
	Background: rod and cone responses
Frame frequency	120 Hz to provide higher temporal resolution
Band-pass filtering	High pass cutoff 10 Hz; low pass cutoff 300 Hz; amplified with a gain of 100,000
Stimulus screen	Surrounded by uniformly illuminated background cover with a luminance set at 30 cd/m^2 to eliminate the rod responses
Stimulus frequency	Set at 17 Hz to optimize the amplitude of responses
Fixation stability	Monitored with an infrared refractor camera
Cutoff of amplitude P1-N1 in μV/deg2	Ring 1: 104; Ring 2: 78; Ring 3: 57.6; Ring 4: 42.9; Ring 5: 41.7

Parameters used on the computerized Optoelectronic Stimulator Vision Monitor MonPack 120 Metrovision (Pérenchies, France). The analysis generates a histogram for each of the extended zones indicating the average amplitude of the peaks, and of the root mean square (RMS) in microvolts/deg2 (μV/deg2). The RMS characterizes the energy content of each response. Several visualization modes were obtained with 2-D and 3-D maps. Different types of ring display allow the measurement of P1–N1 amplitude and implicit time, which can be compared to normative data to evaluate the general size and timing of signals in a given patient

between 0 and 34 dB. Only reliable visual fields were used in the analyses, defined as a fixation loss (FL) rate $< 20\%$ and a false-positive (FP) rate $< 15\%$. Using the retinal sensitivities obtained, the mean sensitivity in the fovea, within 2 degrees, 2–5 degrees and 5–10 degrees were calculated. To assess fixation stability, movements of the fundus were tracked during the examination while the patient stared at the fixation target.

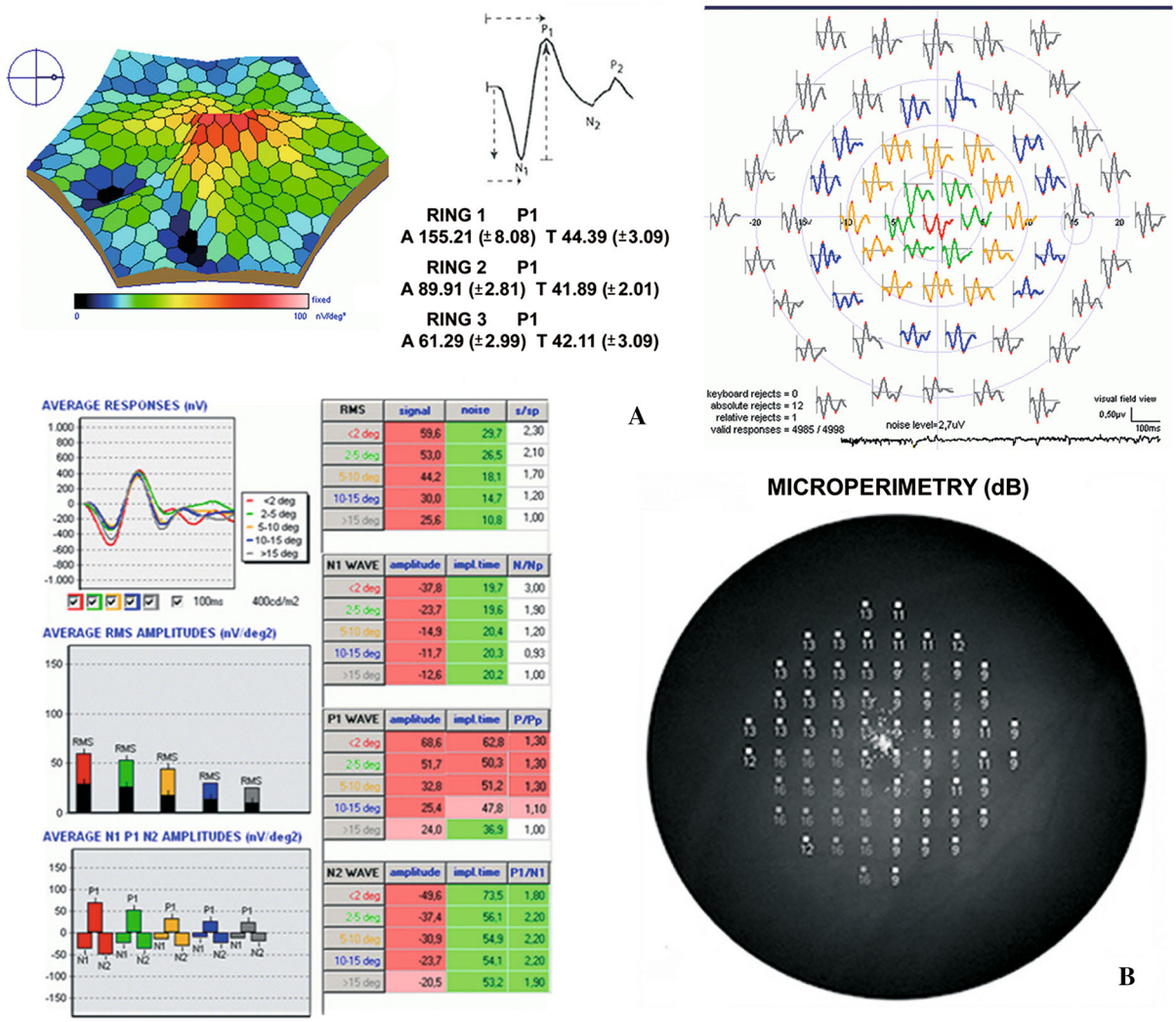
Statistical analysis

Statistical analysis was performed using the STATA 14.0 (Collage Station, Texas, USA). Results were presented as mean value ± SD. One-way analysis of variance (ANOVA) followed by Tukey's post hoc test was used to analyze differences between groups unless specified. The ANOVA test was also used to compare mean age between study groups. Gender distribution was compared by the Chi square test; p values < 0.05 were considered as statistically significant.

Results

In the present study, we enrolled 48 eyes of 48 HM patients with a mean age of 54.1 ± 2.3 years (ranging from 47 to 55 years). Twenty-four HM eyes with MF had a mean refractive error of − 14.23 DS and a mean BCVA of 20/40 Snellen or + 0.3 logarithm of the minimum angle of resolution (logMAR). An additional group of 24 HM patients without foveoschisis was included. They had a mean refractive error of − 12.09 DS, and a mean BCVA of 20/20 (0.0 logMAR). Twenty-four healthy, emmetropic subjects were also included as the control group (CG), they had a mean age of 53.2 ± 1.9 years SD (ranging from 48 to 54 years of age) and a mean BCVA of 20/20 (0.0 logMAR). We checked for the normality of our data and ANOVA assumptions were tested and met. The mean age and gender distribution between the three groups was not statistically significant (p values < 0.05).

We examined a 10° macular area with SD-OCT, mfERG and MP-1 to assess macular thickness, amplitude and implicit time of the P1 wave and retinal sensitivity. No abnormality in SD-OCT, mfERG and



RMS	signal	noise	s/sp
<2 deg	59,6	29,7	2,30
2-5 deg	53,0	26,5	2,10
5-10 deg	44,2	18,1	1,70
10-15 deg	30,0	14,7	1,20
>15 deg	25,6	10,8	1,00

N1 WAVE	amplitude	impl.time	N/Np
<2 deg	-37,8	19,7	3,00
2-5 deg	-23,7	19,6	1,90
5-10 deg	-14,9	20,4	1,20
10-15 deg	-11,7	20,3	0,93
>15 deg	-12,6	20,2	1,00

P1 WAVE	amplitude	impl.time	P/Pp
<2 deg	68,6	62,8	1,30
2-5 deg	51,7	50,3	1,30
5-10 deg	32,8	51,2	1,30
10-15 deg	25,4	47,8	1,10
>15 deg	24,0	36,9	1,00

N2 WAVE	amplitude	impl.time	P1/N1
<2 deg	-49,6	73,5	1,80
2-5 deg	-37,4	56,1	2,20
5-10 deg	-30,9	54,9	2,20
10-15 deg	-23,7	54,1	2,20
>15 deg	-20,5	53,2	1,90

Fig. 3 Patient X.Y. the figure shows lower values of retinal functionality with delay in the implicit time and reduction in the amplitude of the mfERG P1 waves registered in the area affected by myopic foveoschisis (MF) (**a**). P1 average waveform and standard deviation (±) of amplitude (A) and implicit time (T) from the three rings (1, 2 and 3). These values indicate that the patient responses are reduced. The microperimetry (MP-1) shows lower values of retinal sensitivity in the same area as well (**b**)

MP-1 examinations was recorded in the CG. In HM patients with MF, SD-OCT showed an increase in macular thickness (Fig. 2) associated with a reduction in the amplitude and a delay in the implicit time of the P1 wave recorded by mfERG. Lower values of retinal sensitivity, as assessed by MP-1, were also found in these subjects (Fig. 3).

Patients with MF showed an increased macular thickness, assessed by SD-OCT, when compared with both the HM patients without MF and the CG (ANOVA, $p < 0.001$) (Table 2). The morphological changes observed in patients with MF were associated with a functional impairment as demonstrated by the decreased P1 wave amplitude evaluated by mfERG ($p < 0.001$) (Table 2), and the decreased macular sensitivity in the three areas assessed with MP-1 (ANOVA, $p < 0.001$) (Table 2). The values of implicit time in the mfERG were statistically significant only between 5° and 10° (Table 2). Furthermore, HM and CG did not show significant difference, in the variables analyzed, except for the third ring of SD-

Table 2 Data obtained using spectral domain-optical coherence tomography (SD-OCT), multifocal electroretinography (mfERG), and microperimetry (MP-1) in high myopia (HM) patients with and without myopic foveoschisis (MF) compared to the control group (CG)

Area	MF SD-OCT mean ± SD	HM SD-OCT mean ± SD	CG SD-OCT mean ± SD	*p*			
				ANOVA	MF versus HM*	MF versus CG*	HM versus CG*
2°	406.29 ± 25.59	276.08 ± 8.33	271.32 ± 9.61	< 0.001	< 0.001	< 0.001	NS
2°–5°	420.19 ± 41.01	342.70 ± 19.92	300.87 ± 10.01	< **0.001**	< **0.001**	< **0.001**	NS
5°–10°	382.10 ± 12.09	298.11 ± 6.04	283.48 ± 8.68	< **0.001**	< **0.001**	< **0.001**	< **0.001**
	MF mfERG A	HM mfERG A	CG mfERG A				
2°	51.24 ± 15.01	90.33 ± 19.61	155.21 ± 8.08	< **0.001**	< **0.001**	< **0.001**	**<0.001**
2°–5°	31.00 ± 12.71	59.32 ± 8.00	89.91 ± 2.81	< **0.001**	< **0.001**	< **0.001**	**<0.001**
5°–10°	29.91 ± 10.00	40.30 ± 4.51	61.29 ± 2.99	< **0.001**	< **0.001**	< **0.001**	< **0.001**
	MF mfERG T	HM mfERG T	CG mfERG T				
2°	44.21 ± 2.98	44.05 ± 3.02	44.39 ± 3.09	NS	NS	NS	NS
2°–5°	46.08 ± 7.31	39.89 ± 2.09	41.89 ± 2.01	NS	NS	NS	NS
5°–10°	45.68 ± 4.01	42.05 ± 1.97	42.11 ± 3.09	< **0.05**	< **0.05**	< **0.05**	NS
	MF MP-1	HM MP-1	CG MP-1				
2°	11.90 ± 3.15	19.11 ± 2.03	20.00 ± 0.00	< **0.001**	< **0.001**	< **0.001**	NS
2°–5°	12.09 ± 2.90	19.09 ± 1.09	19.04 ± 1.20	< **0.001**	< **0.001**	< **0.001**	NS
5°–10°	12.31 ± 2.99	18.08 ± 1.06	19.00 ± 1.30	< **0.001**	< **0.001**	< **0.001**	NS

A one-way analysis of variance (ANOVA) followed by Tukey's post hoc test was applied for analysis of differences between groups. Macular area thickness (in μm) through SD-OCT. Retinal functional amplitude (A) expressed as microvolts/deg2 (μV/deg2) and implicit time (T) in milliseconds (ms) of the P1 wave with mfERG. Retinal functionality expressed as sensitivity values in dB measured by MP-1

Values are expressed as mean ± standard deviation (SD). The statistical significance was attested at a probability of $p < 0.05$. Value significantly higher by one-way ANOVA and Tukey's post hoc test (in bold)

NS not significant

*After Tukey correction

OCT and the mfERG amplitude in all the rings (Table 2).

Discussion

The purpose of our study was to evaluate the morphological and functional retinal changes in patients affected by HM with and without MF using SD-OCT, mfERG and MP-1. We demonstrated that significant retinal functional changes occur in MF subjects with SD-OCT anatomical alterations. To the best of our knowledge, we evaluated two groups of patients with HM, those affected and not affected by macular foveoschisis [18]. Moreover, the decreased sensitivity to MP-1 tests, probably related to the stretching of the photoreceptor outer segments, is also useful in the evaluation of myopia-related retinal foveoschisis. Several studies have been carried out to describe MF in HM patients; however, functional changes associated with the morphological characteristics of these subjects have not yet been reported. In 1938, Rochon-Duvigneaud observed a histological description of foveoschisis in a highly myopic eye that appears to be very similar to our SD-OCT results [19]. Using OCT scans, it has been clearly demonstrated that MF in PM patients is characterized by a detachment of the neuroretina at the level of the plexiform layer [19, 20]. It has been hypothesized that the main causes of retinal delamination in myopic macular retinoschisis could be the posterior myopic staphyloma, and incomplete vitreous detachment that exerts excessive traction on a previously stretched posterior pole [12, 14, 21]. It has been also demonstrated that the presence of vitreous pre-retinal membranes represents a risk factor for MF progression, while the role of axial

length and chorioretinal atrophy in the progression of the disease has not been clearly established yet [9, 22–26].

Polito et al. and Lai et al. reported some cases of foveoschisis with incomplete vitreous detachment that recovered after vitreo-retinal adhesion release with increased visual function and normalization of OCT scans. This observation supports the hypothesis that an incomplete vitreous detachment, with less severe traction on the retina, may represent a cause of MF in highly myopic eyes, which could resolve spontaneously [26, 27]. Shimada et al. investigated morphological changes occurred during the development of early RD in HM patients with MF performing a series of OCT scans in five patients. This longitudinal research highlighted that the progression from MF to RD goes through four stages, and the formation of an outer lamellar hole predisposes to RD [9]. In addition, Lai et al. found that foveal detachment can also spontaneously resolve in patients with high myopic traction maculopathy without evidence of posterior vitreous detachment [27].

In our study, we evaluated retinal function and morphological changes in patients with HM and MF through three hi-tech examinations, SD-OCT, mfERG and MP-1. We demonstrated that the macular central area in highly myopic eyes affected by MF showed functional alterations associated with anatomical changes. These findings are in line with previous studies showing retinal thickening at the posterior pole and separation between the less reflective external retina and the more reflective internal one, in HM patients with MF [9, 14, 20, 22–26].

Notably, in our research, MF was mainly confined to the 10° scanning area, and no disruption of any detached internal limiting membrane was noted. Nevertheless, the macular sensitivity analysis performed by mfERG and MP-1 detected a significant alteration of the retinal function in patients with HM and MF. Previous studies demonstrated that microperimetry shows an adequate reproducibility, greater than conventional perimetry, to evaluate mean retinal sensitivity in patients with macular diseases [28]. Sugiura et al. showed that retinal sensitivities, measured by microperimetry, declined with the increase in retinal thickness, assessed by SD-OCT [28]. In addition, Park and colleagues showed that, especially in patients with HM, the correlation between structural (thickness) and functional (amplitude/implicit time) changes should be considered when interpreting retinal structure and function using SD-OCT and mfERG [10].

In our study, in order to minimize the impact of age on the results, only subjects aged between 47 and 55 years were included. Moreover, it is well known that mfERG can be used for the quantitative and objective detection of abnormal macular areas [29]. In fact, the first-order kernel mainly reflects the function of the outer retina, especially of the cones [29]. The differences of P1 implicit time among the three groups of patients were statistically significant in ring 5°–10°, but only for HM patients with MF versus HM patients without MF, and HM patients with MF versus CG. We can therefore assert that amplitude of the mfERG is more sensitive than implicit time. The reasons for the increased macular thickness caused by the schisis associated with the thinning in the retinal morphological profile (SD-OCT) and the decreased retinal sensitivity (mfERG/MP-1) are probably related to the stretching of the photoreceptor outer segments. The phenomenon of abnormal axial elongation could explain the enlargement of the subretinal space with consequent decreased foveal cellular density caused by ischemia and retinal circulation disturbances [10]. In our study, we described a positive correlation between TROL in retinal macular areas and mfERG and MP-1 tests. Consequently, a thicker retina outer layer may imply an improved photoreceptor metabolism and better visual function, as also demonstrated in another study using mfERG and SD-OCT [30]. There are two key pathological factors that are deemed to be responsible for this retinal dysfunction. One is the mechanical stretching related to posterior staphyloma and vitreous traction of the inner retina associated with the elongation of the globe in myopic eyes. The other is the metabolic distress of the photoreceptor layer caused by a decrease in blood supply of the thinned HM choroid [30]. Ultimately, both the mechanical and vascular factors may contribute to the derangements of the retinal functional responses [15].

It has also been suggested that other factors, such as the dysfunction of the dopaminergic system, may play a role in the pathogenesis of the functional decline in myopic eyes [30, 31]. Experimental studies in animal models have demonstrated that an increase in retinal levels of dopamine activates D1 and D2 dopaminergic receptors present throughout the retina generating a

signal that inhibits axial growth once the eye has reached a normal length [31–34].

Currently, OCT scans and BCVA are the most commonly used tools to define MF progression, especially because of the lack, in many clinics, of more sophisticated techniques such as MP-1 and mfERG [9, 14]. Nevertheless, the clinical work-up and follow-up of HM patients with MF should include hi-tech diagnostic tests such as SD-OCT, mfERG and MP-1, which could be useful not only for the detection of macular modifications in MF, but also to assess the relationship between functional variations and structural degeneration. These methods may allow predicting the disease's progression providing, especially in the presence of complications, an objective basis for the management of surgical treatment and the prevention of loss of sight in MF patients. In order to fully understand the processes involved in retinal damage, a further study aiming to longitudinally evaluate the results of these examinations in a larger population of HM patients with MF will be carried out at our clinic.

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Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership or other equity interest; and expert testimony or patent-licensing arrangements) or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Statement of human rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Statement on the welfare of animals No animals were used in this research.

Informed consent Informed consent was obtained from all individual participants included in the study.

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