Fourier-Domain Optical Coherence Tomography and Microperimetry Findings in Retinitis Pigmentosa

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• PURPOSE: To investigate the relation between the optical coherence tomography (OCT) findings and retinal sensitivity in patients with retinitis pigmentosa (RP) by assessing the retinal thickness and retinal function using Fourier-domain OCT (FD-OCT) and microperimetry, respectively.
• DESIGN: Observational case series.
• METHODS: Fifty-nine patients (118 eyes) were enrolled, mean age 47 ± 14.8 years. Thirty-two healthy subjects (HS) were enrolled as a control group. Patients were assessed by means of FD-OCT and microperimetry. We analyzed the average foveal thickness (diameter of 1 mm centered on the point of fixation), the value of the retinal sensitivities corresponding to the 4 degrees centered on the fixation point, and logMAR visual acuity for regression analysis converted from Snellen chart.
• RESULTS: We distinguished 4 groups of RP patients according to the macular pattern seen on OCT images. The first group of 36 eyes, mean age of 33.5 ± 7.4 years, had no macular changes, mean best-corrected visual acuity (BCVA) of 0.95 ± 0.07, mean foveal thickness of 256.3 ± 9.14 μm, and mean retinal sensitivities inside the central 4 degrees of 19.27 ± 0.87 dB ($P > .05$ for all the values). The second group of 28 eyes, mean age 35.4 ± 6.3 years, showed clinical macular edema (CME) on OCT images with mean BCVA of 0.72 ± 0.22, mean foveal thickness of 363.5 ± 93.45 μm, and mean retinal sensitivity inside the central 4 degrees of 15.94 ± 3.6 dB ($P < .01$ for all the values). The third group of 26 eyes, mean age 50.8 ± 8.7 years, showed macular vitreoretinal traction on OCT images with a mean BCVA of 0.5 ± 0.2, mean foveal thickness of 337.1 ± 71.7 μm, and mean retinal sensitivity inside the central 4 degrees of 11.78 ± 3.09 dB ($P < .01$ for all the values). The last group of 28 eyes, mean age 52.1 ± 13.6 years, showed macular retinal thinning on OCT images with mean BCVA of 0.36 ± 0.15, mean foveal thickness of 174.2 ± 24.40 μm, and mean retinal sensitivity inside the central 4 degrees of 10.22 ± 3.82 dB ($P < .01$ for all the values).
• CONCLUSIONS: MP-1 and FD-OCT showed high sensitivity for identifying functional and structural macular abnormalities, respectively. Future studies should investigate the relationships among photoreceptor cell loss, retinal sensitivity, and fixation in patients with RP. (Am J Ophthalmol 2011;151:106–111. © 2011 by Elsevier Inc. All rights reserved.)

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THE TERM RETINITIS PIGMENTOSA (RP) COMPRISES A heterogeneous group of genetic retinal disorders that primarily affect the rod and cone photoreceptors and retinal pigment epithelium (RPE).[1–4] RP is a slowly progressive disease and typically affects the rods before the cones. RP can be an isolated finding, or it can be associated with other systemic conditions. Several genes are associated with RP, which can be inherited as an X-linked, autosomal dominant, or autosomal recessive condition. Cases of RP with no known family history, referred to as RP simplex, can also occur. RP can predispose patients to cystoid macular edema (CME), epiretinal membranes (ERM), and macular thinning.[1–4] Time-domain optical coherence tomography (TD-OCT) is a recognized method for determining retinal structure in vivo and is particularly useful and accurate for measuring retinal thickness.[5–10] Several OCT studies on RP have been reported, and most show the capability of OCT to recognize and follow CME in RP patients.[11–14] However, visualizing, quantifying, and following microstructural changes within the photoreceptor and RPE layers is difficult using TD-OCT, which lacks an eye-tracking system and has a low-definition image.

Recently, improvements in OCT technology have been introduced.[15,16] Fourier-domain optical coherence tomography (FD-OCT) provides increased axial resolution and scanning speed by recording the interferometric information using a Fourier-domain spectrometric method, instead of adjusting the position of a reference mirror. The resolution is up to 5 times that of conventional TD-OCT, and the imaging speed is up to 100 times the speed of conventional TD-OCT.[17,18] Several studies have shown that FD-OCT is capable of imaging retinal pathologies in great detail. Recently, Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) was introduced for retinal imaging.[19–23] The instrument features an eye-tracking device that corrects for eye movement during the scanning process. Implementation of eye tracking should lead to highly reproducible measurements of retinal thickness.

Many previous studies used the best-corrected visual acuity (BCVA) to evaluate retinal function. The introduction of fundus-related microperimetry allowed retinal sen-

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sitivity to be measured in maculopathy patients in order to assess macular function. The scanning laser ophthalmoscope (SLO; Rodenstock GmbH, Munich, Germany) has been the only commercial microperimeter available until recently, when a new instrument called Microperimeter 1 (MP-1, NIDEK Technologies, Padova, Italy) was introduced. With this instrument, the exact correlation between fundus disease and corresponding functional defects is determined by integrating real fundus imaging and computerized threshold perimetry.[24–29] In the present study, we investigated the relation between the FD-OCT findings and retinal sensitivity in patients with retinitis pigmentosa by assessing the retinal thickness and retinal function using FD-OCT and microperimetry, respectively.

MATERIALS AND METHODS

THIS STUDY WAS AN OBSERVATIONAL CASE SERIES. FIFTY-nine patients (118 eyes) were enrolled (mean age, 47 ± 14.8 years). The patients had retinitis pigmentosa and had been followed in the Department of Retinal Inherited Disease of the University of Rome "La Sapienza" for at least 3 years. Thirty-one patients were male and 28 were female. Of the 59 patients, 12 had autosomal dominant retinitis pigmentosa; 11, autosomal recessive retinitis pigmentosa; five, X-linked recessive retinitis pigmentosa; and 31, simplex retinitis pigmentosa. Thirty-two healthy subjects, 18 male and 14 female, were enrolled as a control group.

All subjects underwent a complete ophthalmologic examination, including BCVA with the Snellen method, Goldmann applanation tonometry, biomicroscopy of the anterior segment, indirect ophthalmoscopy of the retina, FD-OCT (Spectralis OCT, Heidelberg Engineering), microperimetry (MP-1; NIDEK Technologies), electroretinogram (ERG), and visual evoked potential (VEP).

The diagnosis of RP was based on the clinical findings, including compromised night and side vision, characteristic funduscopic findings, and reduced or nondetectable rod and cone a- and b-wave amplitudes as shown by electroretinography (ERG). Upon ophthalmoscopic examination, we found retinal pigmentary changes with arteriolar narrowing and a pale optic disc.

Patients younger than 18 years and those with any additional ocular disease, including glaucoma, ametropias of more than 6 diopters (D), severe opacities of the lens, and systemic diseases (particularly diabetes and hypertension), were excluded from the study.

• **SPECTRALIS OCT:** Patients underwent OCT performed with a Spectralis OCT (Heidelberg Engineering), in a pattern of 20 × 15-degree raster scans consisting of 19 high-resolution line scans, using a volumetric software protocol. Spectralis OCT allows up to 40 000 A-scans/s with a depth resolution of 7 μm in tissue and a transverse resolution of 14 μm by using a superluminescence diode with an 870-nm bandwidth. Furthermore, Spectralis OCT provides an automatic real-time (ART) function for increased image quality. With ART activated, multiple frames (B-scans) of the same location are performed during the scanning process, and the images are averaged to reduce noise. In our study, the number of frames was adjusted at 19 to improve image quality.

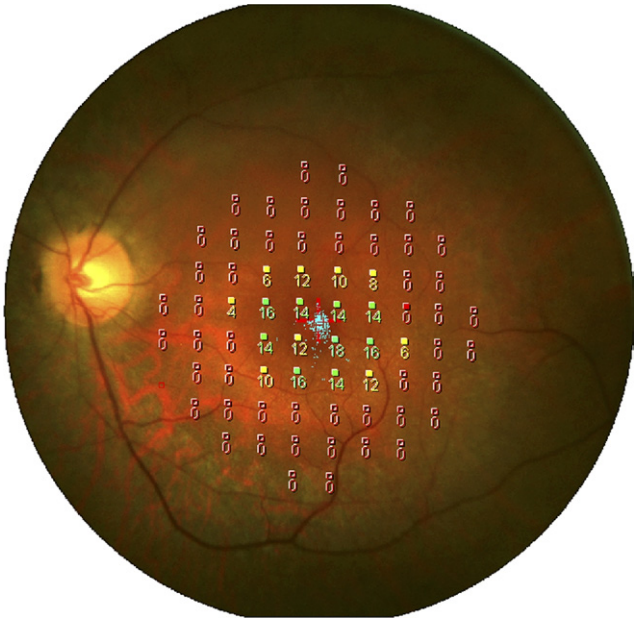

FIGURE 1. A picture of the fundus in a patient with retinitis pigmentosa is overlaid with microperimetry (MP-1) results, showing no retinal sensitivity in the peripheral visual field. The MP-1 examination was performed with a customized grid of 68 stimuli around 10 degrees centered on the fovea.

An eye tracker minimizes the effects of ocular movements. Retinal thickness (RT) was measured between the internal limiting membrane (ILM) and RPE. For statistical analysis, we used the average foveal thickness (1-mm diameter centered on the point of fixation). The CME, an intraregional hyporeflective area in the OCT images, was classified according to Otani and associates.[30] Vitreoretinal traction was defined as hyper-reflective lines at the ILM. According to Grover and associates,[31] we defined macular thinning as a fovea value ≤247.7 μm. We used the standardized method of Chan and associates for OCT image analysis.[32]

All subjects had their pupils dilated with tropicamide 1% before the examinations.

• **MICROPERIMETRY:** We used a MP-1 (NIDEK Technologies) for microperimetry, which was performed in all subjects with a red cross of 2 degrees as the fixation target, white background illumination of 4 apostilbs, Goldmann III stimuli with a projection time of 200 ms, and a customized grid of 68 stimuli around 10 degrees centered on the fovea (Figure 1). We used a 4-2 staircase strategy, and the initial projecting senility was fixed at 8 dB. We analyzed the value corresponding to 4 degrees centered on the fixation point. The fixation

TABLE 1. Clinical Data of Retinitis Pigmentosa Study Population and Healthy Subjects

Patient Group[a] (Number of Eyes; Mean Age; Male-Female Ratio)	BCVA (logMAR), Mean ± SD	Retinal Thickness (μm), Mean ± SD	Retinal Sensitivity (dB), Mean ± SD
Group I (36 eyes; 33.5 ± 7.4 years; 10M:8F)	0.03 ± 0.03[b]	256.3 ± 9.14[b]	19.27 ± 0.87[b]
Group II (28 eyes; 35.4 ± 6.3 years; 8M:6F)	0.17 ± 0.16	363.5 ± 93.45	15.94 ± 3.60
Group III (26 eyes; 50.8 ± 8.7 years; 6M:7F)	0.32 ± 0.20	337.1 ± 71.7	11.78 ± 3.09
Group IV (28 eyes; 52.1 ± 13.6 years; 7M:7F)	0.50 ± 0.24	174.2 ± 24.40	10.22 ± 3.82
HS (64 eyes; 52.1 ± 13.3 years; 18M:14F)	0.04 ± 0.03	276.3 ± 12.2	19.8 ± 0.1

BCVA = best-corrected visual acuity; F = female; HS = healthy subjects; logMAR = logarithm of minimal angle of resolution; M = male; SD = standard deviation.

[a]Retinitis pigmentosa (RP) study population was divided into 4 groups according to the macular pattern seen on optical coherence tomography (OCT) images. Group I: patients affected by RP with no abnormalities at OCT images; Group II: RP patients affected by macular edema; Group III: RP patients affected by vitreomacular traction; Group IV: RP patients affected by retinal thinning. All the groups were compared with the HS for statistical significance by means of 2-tailed *t* test.

[b]$P > .05$; for all the other data in the table $P < .01$.

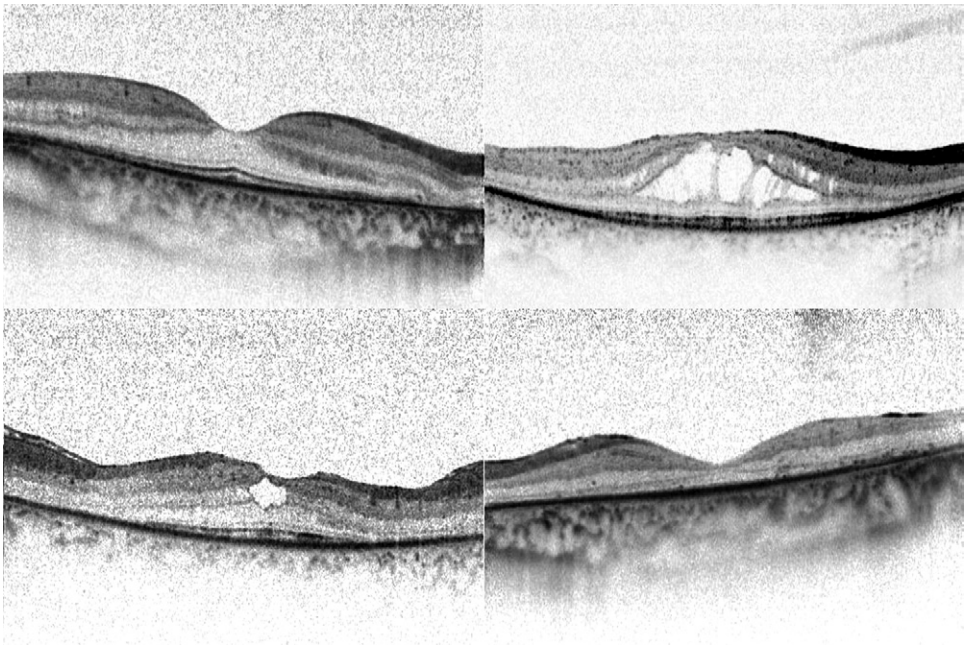

FIGURE 2. OCT images representative of each study group. (Top left) A retinitis pigmentosa (RP) patient with no abnormalities (Group I). (Top right) An RP patient with macular edema (Group II). (Bottom left) An RP patient with vitreomacular traction (Group III). (Bottom right) An RP patient with retinal thinning (Group IV).

pattern, stability, and fixation zone were classified according to Fujii and associates.[33]

• **STATISTICAL ANALYSIS:** The results are expressed as the mean ± standard deviation (SD). For the statistical analysis, we used SPSS ver. 14.0.1 for Windows (SPSS, Chicago, Illinois, USA). Statistical calculations were performed using individual logarithm of minimal angle of resolution (logMAR) acuity data, not decimal values, and the results were converted back, according to the procedure outlined by Holladay.[34] To compare values between the RP patients and the healthy control group, we used the Student 2-tailed *t* test. The Pearson correlation test and linear regression analysis were used to analyze the effect of mean foveal central thickness on the logMAR visual acuity and retinal sensitivity. A *P* value <.05 was considered statistically significant.

RESULTS

WE ENROLLED 59 PATIENTS (118 EYES), WITH A MEAN AGE OF 47.4 ± 14.8 years, who were affected by RP. As a control group, we enrolled 32 healthy subjects with a mean age of 52.1 ± 13.3 years, mean BCVA of 0.9 ± 0.06, mean foveal

TABLE 2. Correlation Coefficients of Logarithm of Minimal Angle of Resolution Visual Acuity Versus Retinal Thickness, and of Retinal Sensitivities Versus Retinal Thickness in Each Retinitis Pigmentosa Study Group

	BCVA (logMAR) vs Retinal Thickness (μm)			Retinal Sensitivity (dB) vs Retinal Thickness (μm)		
Group[a]	r	r^2	P^b	r	r^2	P^b
I	0.073	0.05	.781	0.329	0.108	.007
II	0.930	0.866	<.001	0.786	0.618	<.001
III	0.786	0.618	.02	0.840	0.705	<.001
IV	0.819	0.670	<.001	0.791	0.626	.021

BCVA = best-corrected visual acuity; logMAR = logarithm of minimal angle of resolution.

[a]Group I: retinitis pigmentosa (RP) patients with no abnormalities at optical coherence tomography images; Group II: RP patients affected by macular edema; Group III: RP patients affected by vitreomacular traction; Group IV: RP patients affected by retinal thinning.

[b]A *P* value <.05 was considered statistically significant.

thickness of 276.3 ± 12.2 μm, and mean sensitivity of 19.8 ± 0.1 dB.

We distinguished 4 groups of RP patients according to the macular pattern seen on OCT images (Table 1, Figure 2). The first group of 36 eyes (10 male subjects, 8 female; mean age, 33.5 ± 7.4 years) had no macular changes, a mean BCVA of 0.95 ± 0.07, mean foveal thickness of 256.3 ± 9.14 μm, no retinal sensitivity in the peripheral visual field, and mean retinal sensitivity inside the central 4 degrees of 19.27 ± 0.87 dB. We did not find any significant difference in BCVA, foveal thickness, or retinal sensitivity between Group I and the healthy subjects ($P > .05$). Linear regression of logMAR versus foveal thickness and retinal sensitivity versus foveal thickness gave r values of 0.073 and 0.329, respectively (Table 2).

The second group of 28 eyes (8 male subjects, 6 female; mean age, 35.4 ± 6.3 years) showed CME on OCT images and had a mean BCVA of 0.72 ± 0.22, mean foveal thickness of 363.5 ± 93.45 μm, and mean retinal sensitivity inside the central 4 degrees of 15.94 ± 3.60 dB. All of these values differed significantly from those in the control group ($P < .01$). Linear regression of logMAR versus foveal thickness and retinal sensitivity versus foveal thickness gave r values of 0.930 and 0.786, respectively.

The third group of 26 eyes (6 male subjects, 7 female; mean age, 50.8 ± 8.7 years) showed macular vitreoretinal traction on OCT with a mean BCVA of 0.5 ± 0.2, mean foveal thickness of 337.1 ± 71.7 μm, and mean retinal sensitivity inside the central 4 degrees of 11.78 ± 3.09 dB. All of these values differed significantly from those in the control group ($P < .01$). Linear regression of logMAR versus foveal thickness and retinal sensitivity versus foveal thickness gave r values of 0.786 and 0.840, respectively.

The last group of 28 eyes (7 male subjects, 7 female; mean age, 52.1 ± 13.6 years) showed macular retinal thinning on OCT with a mean BCVA of 0.36 ± 0.15, mean foveal thickness of 174.2 ± 24.40 μm, and mean retinal sensitivity inside the central 4 degrees of 10.22 ± 3.82 dB. All the values differed significantly from those in the control group ($P < .01$). Linear regression of logMAR versus foveal thickness and retinal sensitivity versus foveal thickness gave r values of 0.819 and 0.791, respectively.

DISCUSSION

OUR STUDY ASSESSED THE RELATIONSHIPS BETWEEN RETINAL structure and functional data obtained using microperimetry and Fourier-domain OCT, by comparing data between patients with RP and a healthy control group.

The functional and morphologic data for the patients with classic RP and without macular complications were not significantly different from those for healthy patients. Therefore, it is important to evaluate the progression of the disease using OCT and microperimetry in order to obtain more precise information about the changes in macular status.

Compared with the healthy subjects, patients affected by vitreomacular traction and macular thinning had greater reductions in retinal sensitivity and visual acuity than patients in the first 2 groups. Reductions in visual acuity and retinal sensitivity in patients with macular thinning and vitreomacular traction may reflect photoreceptor cell loss.

The relationships between retinal function and macular thickness differed among the different maculopathies. In patients with CME and vitreomacular traction, macular thickness was associated with the poorest BCVA and lowest retinal sensitivity, whereas in patients with macular thinning, greater thinning of the macula was associated with greater reductions in BCVA and retinal sensitivity.

Of the patients with CME, 9 young patients (mean age, 26.6 ± 2.4 years) showed CME with slight increases in foveal thickness and with no foveal depression. This type of CME, which is not easily recognizable by ophthalmologic examination, appears to reduce the BCVA and

retinal sensitivity to a lesser degree than the reductions associated with the other macular complications. Therefore, a reduction in retinal visual acuity may be related to other retinal structures, according to Sandberg and associates.[35,36]

Patients with macular thinning and vitreomacular traction (Groups III and IV) were older than the patients with CME and no macular abnormalities ($P < .05$), suggesting the progression of retinitis pigmentosa maculopathy from CME or no macular abnormalities to vitreomacular traction or macular thinning. Thus, macular thinning, vitreoretinal traction, and CME may be different stages of the same maculopathy.

The functional impact of retinitis pigmentosa maculopathy in clinical practice is usually quantified by BCVA, although this parameter is just 1 aspect of macular function. Further study is needed to evaluate the relationship between retinal sensitivity and perceived visual performance, as in the study by Hazel and associates[37] regarding low- and high-contrast visual acuity and contrast sensitivity.

Different OCT studies have examined RP patients to determine the macular morphologic changes, and several have analyzed the correlation between the inner segment/outer segment (IS/OS) line and visual acuity.[35,36,38] A significant correlation was found between the length of the IS/OS line and the retinal sensitivity using MP-1.[39] Microperimetry, particularly with MP-1, allows the quantification of macular sensitivity and fixation in an exact fundus-related fashion, adding detailed information about the degree and pattern of macular function alteration. Therefore, MP-1 is a useful tool for the evaluation of retinal function. MP-1 has been used successfully in the diagnosis and follow-up of various macular disorders, including age-related macular degeneration, myopic maculopathy, macular dystrophies, and diabetic macular edema.[25–30] We did not analyze the IS/OS line, because the retinal sensitivities were influenced by different macular complications and the IS/OS status was not repeatable between different groups.

This study has some limitations. The BCVA was measured on a Snellen chart, as opposed to the more standardized and better accepted Early Treatment Diabetic Retinopathy Study chart. In addition, genetic information was not obtained from all patients, and we did not study the relationship between mutations and macular complications. In our opinion, genetic analysis of macular complications may be the most important evolution of our research, as it may enable macular prognosis based on different mutations.

In conclusion, MP-1 and Spectralis OCT showed high sensitivity for identifying functional and structural macular abnormalities, respectively. Future studies should investigate the relationships among photoreceptor cell loss, retinal sensitivity, and fixation in patients with RP.

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