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Relationship between Optical Coherence Tomography Retinal Parameters and Visual Acuity in Diabetic Macular Edema

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Abstract

Purpose—To investigate the relationship between optical coherence tomography (OCT)-derived measurements of retinal morphology and visual acuity in patients with diabetic macular edema.

Design—Retrospective cross-sectional study.

Participants—A total of 67 consecutive patients (67 eyes) with diabetic macular edema (DME) who underwent Stratus OCT imaging.

Methods—Best-corrected Snellen visual acuity was recorded for each patient. Raw exported Stratus OCT images for each patient were analyzed using custom software entitled “OCTOR”, which allows the precise positioning of prespecified boundaries on individual B-scans. Thickness, volume, and intensity were calculated for neurosensory retina and subretinal fluid. In addition, photoreceptor outer segment (POS) thickness was quantified.

Main Outcome Measures—OCT-derived measurements of retinal morphology and visual acuity.

Results—The Spearman coefficient values (r) of the correlation between OCTOR-derived measurements of central subfield thickness, intensity, subretinal fluid (SRF) volume, POS thickness and logMAR visual acuities (logarithm of the minimum angle of resolution) were 0.3428 ($p=0.005$), -0.2658 ($p=0.03$), -0.2683 ($p=0.38$), -0.3703 ($p=0.002$) respectively. Multivariate models with stepwise selection revealed a cumulative R^2 of 0.4305 in the total study population, with R^2 of 0.4999 and 0.7628 in the untreated and prior focal laser groups, respectively.

Conclusions—Subanalysis and quantification of OCT features in eyes with DME appears to be of value. In particular, photoreceptor outer segment thickness appears to be an important predictor of function and visual acuity in patients with DME.

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Introduction

Diabetic macular edema (DME) has been well established as an important cause of visual loss in diabetic patients.¹⁻⁴ Although stereophotography was previously considered the gold standard for identifying macular edema, it has recently been supplanted by optical coherence tomography (OCT) as the preferred method for quantification and monitoring of macular edema in diabetic eyes, both in clinical trials and clinical practice.⁵⁻⁷ OCT has also proven more sensitive for the detection of mild DME, although it remains unclear whether treatment is indicated in such cases.⁸

Despite the significant advantages offered by OCT, the automated measurements provided by the instrument software are not always reliable, as several studies have documented segmentation errors with misidentification of the inner and outer retinal boundaries.^{9,10} Despite these segmentation errors, Glassman et al. observed that the error introduced by using automated Stratus OCT center point measurements in DME was sufficiently small that results were not likely to be affected if scans were not routinely sent to a reading center, provided adequate quality control measures were in place.¹¹

A topic of great interest to many clinicians and investigators conducting clinical trials is the correlation between OCT-measured retinal thickness and visual function. Previous studies have shown large variability in the strength of the association with correlation coefficients ranging from 0.28 to 0.73. Moreover, some investigators have observed a paradoxical change in visual acuity in response to changes in OCT-measured thickening.^{5,7,12-19}

Although some previous studies have suggested that assessment of macular thickness using OCT is a clinically useful correlate of visual function, it is important to recognize that macular thickness is just one of several variables which can affect visual acuity.⁷ For example, several recent studies have correlated the integrity of the photoreceptor inner segment/outer segment (IS-OS) junction with visual acuity in patients with different retinal diseases including retinitis pigmentosa, birdshot chorioretinopathy, and age-related macular degeneration.²⁰⁻²⁴⁻²³ The usefulness of quantifying this structure in eyes with DME, however, has not been studied, nor has the clinical utility of OCT-derived measurements, other than retinal thickness, been determined.

We previously described the use of custom OCT grading software (entitled "OCTOR") to manually segment and quantify structures of interest on a set of B-scans to generate thickness and volume maps of these structures. In this report, we evaluate the relationship between automated and manually-derived quantitative OCT parameters and visual acuity in a cohort of patients with DME.

Materials and Methods

Data Collection

We retrospectively reviewed the clinical and imaging records of 89 consecutive patients referred to the Doheny Ophthalmic Imaging Unit with a diagnosis of DME, who underwent OCT imaging on a single Stratus OCT machine (Carl Zeiss Meditec, Inc., Dublin, CA).

From this initial set, six patients were excluded because they had received previous intravitreal injections and seven were excluded for previous vitreo-retinal surgery. Since a large majority of patients had prior laser therapy, patients with focal laser were not excluded. However, the inclusion criteria of the pretreated group was established to include eyes at least six months after laser therapy in order to have a homogenous cohort. Additionally, the effect of a prior history of laser was evaluated in subsequent multivariable analysis. In patients with bilateral DME, the eye with better OCT image quality (generally those with better signal strength) was selected for the analysis. Using these criteria, a total of 67 eyes of 67 patients were selected for inclusion the study analyses. Approval for data collection and analysis was obtained from the Institutional Review Board of the University of Southern California. The research adhered to the tenets of the Declaration of Helsinki for research involving human subjects.

All patients were scanned utilizing the Radial Lines protocol of 6 high-resolution B-scans (512 A-scans per 6 mm B-scan) on a single Stratus OCT machine. Best-corrected visual acuities were obtained using Snellen charts, and converted to logMAR (logarithm of the minimum angle of resolution) for the purposes of statistical analysis.

Automated Stratus OCT Analysis

OCT images from all patients were analyzed with Stratus OCT Software Version 4.0. Measurement of retinal thickness by this software depends on identification of the internal limiting membrane and the inner hyper-reflective band [now believed to correspond to the photoreceptor inner segment-outer segment (IS-OS) junction]. The distance between the inner and outer retinal boundaries is then calculated across all sampled points, with interpolation of values in unsampled areas. The presence of morphologic features, such as fluid between the retina and the retinal pigment epithelium (RPE), may confuse the segmentation algorithms and lead to inaccurate identification of the retinal boundaries. Stratus OCT provides a measurement of average retinal thickness in the central 1-mm area of the fovea – termed the foveal central subfield (FCS) – that corresponds to Early Treatment Diabetic Retinopathy Study (ETDRS) subfield 9.¹⁹ StratusOCT also measures average retinal thickness at a single point at the center of the fovea – foveal center point (FCP).²⁵

Manual OCT Analysis

Raw exported Stratus OCT images for each patient were analyzed using custom software entitled “OCTOR”, which was written by Doheny Image Reading Center software engineers to facilitate viewing and manual grading. OCTOR is publicly accessible at <http://www.diesel.la> (accessed March 8, 2010) and has been described and validated in previous reports.²⁵⁻²⁹ OCTOR allows the precise positioning of prespecified boundaries on individual B-scans. Using the OCTOR software, on each B-scan for every case, the grader manually drew a line at (a) the inner retinal boundary [(at the location of internal limiting membrane (ILM)], (b) the IS-OS junction line, (c) the outer border of the neurosensory retina (outer border of the photoreceptor outer segments --- also corresponds to the inner surface of the RPE in cases without subretinal fluid), and (d) in cases with subretinal fluid, the inner surface of the RPE.²⁵ By drawing these lines, the grader was able to define several compartments (based on combinations of these lines as inner and outer boundaries of the

compartment). Thickness, volume, and intensity values were then computed for the compartments of interest: neurosensory retina, subretinal fluid, and photoreceptor outer segments (Figure 1). To compute the intensity value for a compartment, the intensity of all pixels in the compartment was summed.

Each set of OCT scans was reviewed independently by two authors certified in OCT grading by the Doheny Image Reading Center (TA and YO) using a standard protocol to identify commonly graded OCT features. Disagreement regarding the detection of features was resolved by open adjudication.

Retinal thickness was defined as the distance between the vitreoretinal interface (ILM) and the outer border of the photoreceptor outer segments. Serous retinal detachment (SRD) was defined as the accumulation of the subretinal fluid beneath a highly reflective and dome-like elevation of the detached retina without elevation of retinal pigment epithelium. An epiretinal membrane (ERM) was defined as a highly reflective tissue membrane occurring on the inner retinal surface on OCT images. Exudates were defined as focal areas of hyperreflectivity with posterior shadowing located within the neurosensory retina. Photoreceptor outer segment (POS) thickness was defined as the distance between the outer border of the neurosensory retina and the IS-OS junction line. Any interruption in the integrity of POS was considered as disturbance on OCT qualitative analysis. In order to evaluate the effects of DME on POS thickness in the setting of total retinal edema, the ratio of POS thickness to retinal thickness was examined. Cystoid changes were defined as round or oval hyporeflective areas that are located internal to the IS-OS junction line.

Statistical Methods

Analyses were performed to assess the association between visual acuity and automated and manually-derived measurements of central retinal thickness from the OCT. Wilcoxon rank sum tests were used to compare visual acuity between eyes, with and without associated SRF, ERM, exudates, POS disturbance and cystoid changes. OCT-derived measurements of retinal morphology were correlated with visual acuity using Spearman correlation coefficients. Multivariate regression models were created using stepwise selection to determine which of the OCT measurements were independently associated with visual acuity. SAS V 9.1 (SAS Inst., Cary NC) programming language was used for all analyses. P values < 0.05 were considered statistically significant.

Results

Patient Enrollment and Baseline Characteristics

The 67 subjects included in the study had an average age of 65+/-13 years, 33 (49%) were women, 28 (42%) were Hispanic, 14 (21%) Caucasian, 8 (12%) Asian, 2 (3%) African-American, and 15 (22%) other races. Four (6%) subjects had Type 1 diabetes mellitus, while the remaining 63 (94%) subjects had Type 2 diabetes mellitus. The average duration of diabetes was 18 +/- 8 years. Among the 67 subjects, 45 patients (67%) had no prior history of focal laser treatment for DME, whereas 22 patients (33%) had received focal laser treatment more than six months prior.

Automated OCT analysis results

The Spearman coefficient values of the correlation between automated (StratusOCT machine-generated) OCT measurements of retinal parameters and logMAR visual acuities are summarized in Table 1. LogMAR visual acuity was positively correlated with the mean retinal thickness for FCS, FCP, and the whole grid (subfields 1-9) for the total cohort ($p=0.01$, 0.02 , and 0.02 respectively). Total macular volume was also correlated with logMAR visual acuity ($r = 0.2958$, $p=0.02$ for the total cohort). Interestingly, the prior laser subgroup did not show a statistically significant correlation between retinal thickness and visual acuity except for FCP ($r= 0.4465$, $p= 0.04$).

Manually-derived OCT analysis results

OCT qualitative analysis of 67 eyes revealed serous retinal detachments in 10 eyes (15%), epiretinal membranes in 10 eyes (15%), exudates in 44 eyes (66%), cystoid changes in 22 eyes (33%), and POS disturbances in 22 eyes (34%). The association between qualitative parameters and logMAR visual acuities is summarized in Table 2. Tables 3 and 4 present the associations in the previously untreated and prior laser subjects respectively. In the combined cohort, the presence of either POS disturbance or cystoid change was associated with reduced visual acuity ($p<0.001$ and $p=0.008$ respectively).

The Spearman coefficient values of the correlation between OCTOR-derived measurements of different retinal parameters and logMAR visual acuities are summarized in Table 5, for previously treated and untreated subjects. Retinal thickness (Figure 2) and retinal volume were positively correlated with logMAR visual acuity. POS thickness (Figure 3) and volume were negatively correlated with logMAR visual acuity. Thus, OCTOR analysis showed that visual acuity worsened with increased retinal thickness and volume, and with decreased POS thickness and volume.

We evaluated the POS thickness as a fraction of total retinal thickness, and we found a significant correlation with logMAR visual acuity in the central subfield (Figure 4) and all ETDRS subfields ($p<0.001$).

Since we studied multiple retinal parameters in a cohort where a group of patients had received focal laser treatment, we performed multivariate models with stepwise selection, the results of which are summarized in Table 6. The best-model cumulative R^2 for the entire study cohort was 0.4305, with R^2 of 0.4999 and 0.7628 for previously untreated and treated eyes, respectively. Photoreceptor outer segment thickness was an important contributor for all models.

Discussion

In this retrospective study, we performed manual grading of OCT images to examine the difference between automated and manually derived measurements of central retinal thickness, and to elucidate the relationship between different retinal parameters and visual acuity in patients with DME.

Stratus OCT includes image analysis software that generates a number of retinal parameters, including thickness measurements corresponding to each of the 9 ETDRS subfields. In addition, a value for FCP is calculated as an average of the center points from individual radial line scans. FCP measurement may be more subject to decentration errors in patients with poor fixation.^{7, 11, 30} FCS includes contributions from the parafoveal region, and is thought to be a better indicator of visual function than the FCP.³¹ In our analysis we evaluated FCS, all the ETDRS subfields, and FCP.

Errors have been documented to occur in automated segmentation of OCT.³¹ To address this issue, many clinical trials now use image-reading centers to obtain manual measurements of central retinal thickness in the case of automated segmentation error.¹¹ The OCTOR software has the advantage of not only correcting these errors, but also allowing further study of a wide variety of retinal parameters including different disease compartments (e.g., SRF, POS) and different measures (e.g., thickness, volume, intensity). Many of these parameters have not been evaluated in previous studies.

On OCT, DME is generally seen as an area of retinal thickening that is often accompanied by loss of the foveal depression.³³ In areas of long-standing edema, lipid and protein may precipitate in the outer retina forming hard exudates that appear on OCT as focal areas of hyperreflectivity with posterior shadowing.¹⁴ Our qualitative analysis of the OCTs in the study revealed the presence of focal areas of hyperreflectivity (i.e., likely hard exudates) in 66% of DME patients, but no correlation with visual acuity was observed. We did not, however, specifically study the location of the exudates relative to the foveal center.

While the automated Stratus OCT FCP thickness value revealed no significant correlation with visual acuity in previously untreated DME patients, several OCTOR-derived parameters showed significant correlation between FCP thickness and visual acuity in previously untreated DME patients. The correlations were not statistically significant, however, in eyes which had received prior focal laser. Previous studies of laser treatment in DME observed an initial transient increase in retinal thickness. However, findings from a recent clinical trial conducted by the Diabetic Retinopathy Clinical Research (DRCR) Network suggested that laser treatment may be more effective than intravitreal triamcinolone in reducing retinal thickening over the longer term.³⁴ A possible explanation for our findings may be that despite the reduction in retinal thickness, there was a loss of retinal function as a result of the retinal edema which was not fully captured even when accounting for outer segment thickness.

We detected serous retinal detachment on OCT as an optically hyporeflective space between the outer layer of photoreceptors and the highly hyperreflective RPE band in 15 % of our DME study group. The presence of this feature or quantitative parameters derived from this feature did not seem to strongly correlate with visual acuity. This is consistent with previous studies, which have demonstrated OCT-evidence of serous retinal detachment in 15 to 30 % of patients with DME, and found no indication of poor visual prognosis despite its presence.^{17,18,35,36}

Previous histological studies of human retina have demonstrated photoreceptor outer segment length of 25-63 μm in the macula.^{37,38} Srinivasan et al. utilized an ultra high-speed OCT to measure a mean cone outer segment length of 40.6 μm in the fovea of healthy subjects.³⁹ Our results revealed POS thickness of 34 $\pm$ 14 μm at the foveal center point and 31 $\pm$ 10 μm in the foveal central subfield of DME patients. Additionally, we found a significant correlation between the integrity of POS and visual acuity in patients with DME. Furthermore, a statistically significant correlation was found between visual acuity and POS thickness (Figure 3) and volume. A significant correlation was also appreciated when the POS thickness was evaluated as a fraction of retinal thickness (Figure 4). Our findings are consistent with other retinal diseases including retinitis pigmentosa, birdshot chorioretinopathy, and age-related macular degeneration.²⁰⁻²⁴

Gibran et al. hypothesized that the level of reflectivity from inner retinal layers on OCT may provide objective criteria in predicting the visual outcome in DME patients.⁴⁰ In our study, we evaluated the reflectivity of the retinal layers by quantifying the intensity of the various quantified layers. The observed correlations between intensity parameters and visual acuity were somewhat inconsistent. While the correlation between intensity and visual acuity was not significant in general, the retinal intensity was significantly correlated with visual acuity when looking at the FCS and the entire grid (ETDRS subfields 1-9) in the previously untreated group. The POS intensity was not significantly correlated with visual acuity. These inconsistent findings suggest that investigation of other, novel, OCT-derived parameters may be warranted to allow the construction of models that show stronger correlations with visual function in patients with diabetic macular edema. Such OCT-derived models might include parameters such as inner retinal thickness and integrity, RPE thickness and integrity, and lesion eccentricity. In addition, we used unnormalized intensity parameters in this study. The intensity/reflectivity of the OCT signal may be affected by a variety of factors (such as media opacity) which may not always correlate with visual acuity in a predictable fashion.

Approximately 50 % of patients with DME demonstrate evidence of round or oval hyporeflective areas on OCT that are consistent with intraretinal cystoid space formation.³⁶ Detection of cystoid macular edema (CME) on OCT of patients with DME is associated with a more severe reduction in visual acuity and a poorer response to treatment than OCTs displaying sponge-like retinal thickening alone.⁴¹ Our study supports these prior observations by demonstrating a significant correlation between the existence of cystoid changes on OCT and visual acuity in the untreated patients with DME. CME was detected in only 33 % of our DME patients.

Our study has a number of strengths: in particular, the utilization of manual grading with specialized software, performed in a dedicated OCT image reading center. The subjects included in this study were diverse and probably representative of subjects with DME seen throughout the United States. The demographics of this study population were similar to those of other large studies of diabetic macular edema both in the United States and Great Britain.

Our study also has a number of limitations related to its retrospective nature. The sample size is relatively small, and there was variability in the duration between laser treatment and

the OCT in the treated group. However, patients who received laser therapy within 6 months were excluded. There may also be additional unknown confounders between the treated and untreated groups. In addition, this study used data from Stratus OCT only. As a time-domain OCT instrument, Stratus OCT is limited by a relatively slow scanning speed and is dependent on interpolation algorithms to generate retinal thickness maps.

In summary, several OCT-derived parameters, in particular photoreceptor outer segment thickness, were observed to correlate with visual acuity in patients with diabetic macular edema. Despite the observed correlations, much of the variability still remains and should be the target of future studies.

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Figure 1.

Optical coherence tomography (OCT) morphologic patterns of diabetic macular edema in the left eye of a 24-year-old woman with type I diabetes mellitus. The patient received focal laser treatment in the past and visual acuity (VA) was 20/60. (A) OCT B-scan demonstrates sponge-like retinal thickening, cystoid macular edema (thin arrow), serous retinal detachment (star), and an interruption in the photoreceptor outer segments (POS) (thick arrows). (B) Manual drawing (white lines) of four boundaries (internal limiting membrane, inner segment – outer segment junction, outer retinal border, and inner retinal pigment epithelium (RPE) border) allows various compartments to be defined. In this case, foveal central subfield (FCS) mean retinal thickness measured 515.2 μm , total subretinal fluid volume measured 0.38 mm^3 , and mean photoreceptor outer thickness measured 35.2 μm .

Figure 2. Figure 2 illustrates a comparison of foveal central subfield (FCS) thickness and logMAR (logarithm of the minimum angle of resolution) visual acuity (VA). The slope is 0.002.

Figure 3. Figure 3 illustrates a comparison of foveal central subfield (FCS) photoreceptor outer segment (POS) thickness and logMAR (logarithm of the minimum angle of resolution) visual acuity (VA). The slope is -0.0239.

Figure 4. Figure 4 illustrates a comparison of foveal central subfield (FCS) photoreceptor outer segment thickness/total retinal thickness ratio and logMAR (logarithm of the minimum angle of resolution) VA. The slope is -4.2981.

Table 1
Automated Stratus Optical Coherence Tomography measurements

	Correlation with logMAR Visual Acuity r (n=67)	Not pretreated r (n=45)	Pretreated r (n=22)
Retinal Thickness, FCS	0.3057 p=0.01	0.3243 p=0.03	0.3596 p=0.10
Retinal Thickness, Entire Grid (Subfields 1-9)	0.2791 p=0.02	0.3564 p=0.02	0.1483 p=0.51
Retinal Thickness FCP	0.2913 p=0.02	0.2661 p=0.08	0.4465 p=0.04
Total Macular Volume	0.2958 p=0.02	0.3981 p=0.007	0.1322 p=0.56

FCP = Foveal center point

FCS = Foveal central subfield

logMAR = logarithm of the minimum angle of resolution

r = Spearman correlation coefficient

P ≤ 0.05 is considered to be statistically significant

Table 2
Qualitative Analysis

	logMAR visual acuity			p-value*
	N	Mean (SD)	Median	
SRF				0.32
Yes	10	0.675 (0.552)	0.477	
No	57	0.499 (0.461)	0.398	
ERM				0.43
Yes	10	0.534 (0.339)	0.544	
No	57	0.523 (0.498)	0.398	
Exudates				0.52
Yes	44	0.592 (0.563)	0.398	
No	23	0.396 (0.180)	0.398	
POS disturbance				<0.001
Yes	23	0.866 (0.647)	0.544	
No	44	0.346 (0.193)	0.349	
Cystoid changes				0.008
Yes	22	0.758 (0.665)	0.544	
No	45	0.411 (0.295)	0.398	
Treatment group				0.71
Previous treatment	22	0.470 (0.268)	0.438	
No previous treatment	45	0.552 (0.550)	0.398	

* Wilcoxon rank sum test p-value.

ERM = Epiretinal membrane

POS = Photoreceptor outer segment

SRF = Subretinal fluid

SD = Standard deviation

logMAR = logarithm of the minimum angle of resolution

Table 3
Qualitative Analysis – Previously untreated subjects

	logMAR visual acuity			p-value*
	n	Mean (SD)	Median	
SRF				0.25
Yes	9	0.706 (0.576)	0.477	
No	36	0.513 (0.545)	0.398	
ERM				0.87
Yes	8	0.474 (0.336)	0.471	
No	37	0.568 (0.588)	0.398	
Exudates				0.36
Yes	28	0.661 (0.662)	0.398	
No	17	0.371 (0.189)	0.398	
POS disturbance				<0.001
Yes	15	0.986 (0.744)	0.744	
No	30	0.334 (0.211)	0.300	
Cystoid changes				0.04
Yes	14	0.869 (0.808)	0.511	
No	31	0.408 (0.303)	0.398	

* Wilcoxon rank sum test p-value.

ERM = Epiretinal membrane

POS = Photoreceptor outer segment

SRF = Subretinal fluid

SD = Standard deviation

logMAR = logarithm of the minimum angle of resolution

Table 4
Qualitative Analysis – Previously treated subjects

	logMAR visual acuity			p-value*
	n	Mean (SD)	Median	
SRF				0.81
Yes	1	0.398	0.398	
No	21	0.474 (0.274)	0.477	
ERM				0.11
Yes	2	0.772 (0.322)	0.772	
No	20	0.440 (0.251)	0.398	
Exudates				0.69
Yes	16	0.471 (0.306)	0.438	
No	6	0.469 (0.139)	0.438	
POS disturbance				0.03
Yes	8	0.641 (0.347)	0.544	
No	14	0.373 (0.150)	0.398	
Cystoid changes				0.07
Yes	8	0.563 (0.212)	0.544	
No	14	0.417 (0.288)	0.398	

* Wilcoxon rank sum test p-value.

ERM = Epiretinal membrane

POS = Photoreceptor outer segment

SRF = Subretinal fluid

SD = Standard deviation

logMAR = logarithm of the minimum angle of resolution

Table 5
OCTOR-derived measurements (n=67, for SRF variables n=13)

	Correlation with logMAR Visual Acuity r	Not pretreated r	Pretreated r
Retinal Thickness, FCS	0.3428 p=0.005	0.3786 p=0.01	0.3240 p=0.14
Retinal Thickness, Entire Grid (Subfields 1-9)	0.2699 p=0.03	0.3595 p=0.02	0.0510 p=0.82
Retinal Thickness, FCP	0.3960 p<0.001	0.4234 p=0.004	0.4397 p=0.04
Retinal Volume, FCS	0.3432 p=0.005	0.3836 p=0.009	0.3292 p=0.13
Retinal Volume, Entire Grid (Subfields 1-9)	0.2690 p=0.03	0.3595 p=0.02	0.0510 p=0.82
Retinal Intensity, FCS	-0.2658 p=0.03	-0.3222 p=0.03	-0.1079 p=0.63
Retinal Intensity, Entire Grid (Subfields 1-9)	-0.2566 p=0.04	-0.3237 p=0.03	-0.0590 p=0.79
Retinal Intensity FCP	-0.2338 p=0.06	-0.2997 p=0.05	0.0149 p=0.95
SRF Volume, FCS	-0.2683 p=0.38	-0.2326 p=0.49	-----
SRF Volume, Entire Grid (Subfields 1-9)	0.2667 p=0.38	0.1445 p=0.67	-----
SRF Intensity, FCS	-0.2156 p=0.50	-0.1162 p=0.75	-----
SRF Intensity, Entire Grid (Subfields 1-9)	-0.3498 p=0.27	-0.2752 p=0.44	-----
SRF Intensity FCP	0.1659 p=0.63	0.0253 p=0.95	-----
POS Thickness, FCS	-0.3703 p=0.002	-0.3259 p=0.03	-0.5025 p=0.02
POS Thickness, Entire Grid (Subfields 1-9)	-0.2876 p=0.02	-0.2469 p=0.10	-0.4122 p=0.06
POS Thickness FCP	-0.3879 p=0.001	-0.3515 p=0.02	-0.5154 p=0.01
POS Intensity, FCS	0.1212 p=0.33	0.0909 p=0.56	0.2439 p=0.27
POS Intensity, Entire Grid (Subfields 1-9)	-0.1018 p=0.41	-0.1567 p=0.30	0.0321 p=0.89
POS Intensity, FCP	0.1651 p=0.19	0.1588 p=0.30	0.2462 p=0.27
POS Volume, FCS	-0.3687 p=0.002	-0.3286 p=0.03	-0.5329 p=0.01
POS Volume, Entire Grid (Subfields 1-9)	-0.2883 p=0.02	-0.2459 p=0.10	-0.4211 p=0.05

----- Unable to calculate correlation coefficient for pretreated group (n=2 for SRF variables).

r = Spearman correlation coefficient

P ≤ 0.05 is considered to be statistically significant

FCP = Foveal center point

FCS = Foveal central subfield

POS = Photoreceptor outer segment

SRF = Subretinal fluid

logMAR = logarithm of the minimum angle of resolution

Table 6

Multivariate models with stepwise selection.

	Partial R ²	p-value [*]
All subjects R ² =0.4305		
POS Thickness, Entire Grid (Subfields 1-9)	0.1570	.001
POS Intensity FCP	0.1152	0.002
Retinal Thickness FCP	0.0713	0.01
POS Thickness FCP	0.0315	0.08
POS thickness/Retinal thickness ratio, FCS	0.0555	0.02
Previously untreated subjects R ² =0.4999		
POS Intensity, FCP	0.1573	0.008
POS Thickness, FCS	0.1095	0.02
Retinal Thickness, FCP	0.0432	0.12
POS thickness/Retinal thickness ratio, FCS	0.1490	0.002
POS thickness/Retinal thickness ratio, Entire Grid	0.0409	0.09
Previously treated subjects R ² =0.7628		
POS Thickness, Entire Grid (Subfields 1-9)	0.4579	<0.001
POS Intensity, FCP	0.1455	0.02
Retinal Thickness, FCS	0.1156	0.01
Retinal Volume, FCS	0.0438	0.09

^{*} Improvement chi-square p-value

FCP = Foveal center point

FCS = Foveal central subfield

POS = Photoreceptor outer segment