QUANTITATIVE OPTICAL COHERENCE TOMOGRAPHY REVEALS ROD PHOTORECEPTOR DEGENERATION in EARLY DIABETIC RETINOPATHY

DAVID LE, BS,* TAEYOON SON, PhD,* JENNIFER I. LIM, MD,† XINCHENG YAO, PhD*

Purpose: This study is to test the feasibility of optical coherence tomography (OCT) detection of photoreceptor abnormality and to verify that the photoreceptor abnormality is rod predominated in early diabetic retinopathy (DR).

Methods: OCT images were acquired from normal eyes, diabetic eyes with no DR, and mild nonproliferative DR (NPDR). Quantitative features, including thickness measurements quantifying band distances and reflectance intensity features among the external limiting membrane, inner segment ellipsoid, interdigitation zone, and retinal pigment epithelium were determined. Comparative OCT analysis of central fovea, parafovea, and perifovea were implemented to verify that the photoreceptor abnormality is rod predominated in early DR.

Results: Thickness abnormalities between the inner segment ellipsoid and interdigitation zone also showed a decreasing trend among cohorts. Reflectance abnormalities of the external limiting membrane, interdigitation zone, and inner segment ellipsoid were observed between healthy, no DR, and mild NPDR eyes. The normalized inner segment ellipsoid/retinal pigment epithelium intensity ratio revealed a significant decreasing trend in the perifovea, but no detectable difference in central fovea.

Conclusion: Quantitative OCT analysis consistently revealed outer retina, i.e., photoreceptor changes in diabetic patients with no DR and mild NPDR. Comparative analysis of central fovea, parafovea, and perifovea confirmed that the photoreceptor abnormality is rod-predominated in early DR.

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Diabetic retinopathy (DR) is the leading cause of blindness in working age adults and is predicted to significantly increase in prevalence worldwide.1 The number of people affected by diabetes mellitus (DM) is predicted to reach 552 million2 and nearly 45% of DM patients may develop DR-associated vision impairments.3 Typically, the early stages of DR progress asymptotically until the patient’s vision is affected; however, by this time, the condition may be irreversible.4 Therefore, early detection of DR is of utmost importance to enable prompt treatment to prevent vision loss.

Diabetic retinopathy encompasses retinal vascular and neural aspects. Previous studies have demonstrated the close correlation between retinal vascular abnormalities and DR severity,5,6 and quantitative vascular features of nonproliferative DR (NPDR) have been validated for computer-aided DR staging.7,8 Recent studies have also reported early retinal neurodegeneration in DR.9–11 Moreover, electrophysiologic features have provided evidence for photoreceptor changes in patients with DR,12,13 suggesting that outer
retinal alterations may be observed in optical coherence tomography (OCT).

OCT has enabled depth-resolved visualization of outer retinal changes, especially the external limiting membrane (ELM), photoreceptor inner segment ellipsoid (ISe), and retinal pigmented epithelium (RPE), as representative of photoreceptor status. Inner segment ellipsoid integrity has been demonstrated to affect visual acuity in retinal degenerative diseases.\(^\text{14,15}\) Stimulus-evoked ISe change has been also reported to reflect metabolic function of retinal photoreceptor.\(^\text{16}\) The ELM is also considered as a biomarker of photoreceptor integrity and could be an important predictor of visual function in DR.\(^\text{17}\) Although previous studies have revealed the outer retinal features as a DR predictor, these studies were limited to qualitative evaluation of ELM or ISe disruption, measuring outer retinal thickness changes and no consideration for early DR.\(^\text{18}\) We hypothesize that early subtle photoreceptor abnormalities can be quantified using OCT feature analysis. In this study, we evaluate outer retinal band features, thickness, and reflectance, to reveal early photoreceptor changes in early stages of DR.

**Methods**

This is a cross-sectional OCT study evaluating DR biomarkers in patients with DM. Patients with a history of no DR (NoDR) or mild NPDR were recruited from the University of Illinois at Chicago Retinal Clinic. This study was conducted in accordance with the ethical standards stated in the Declaration of Helsinki and approved by the institutional review board of the University of Illinois at Chicago. The inclusion criteria included subjects 18 years or older with a diagnosis of Type II DM. Exclusion criteria included presence of macular edema, NPDR higher than mild NPDR, previous vitrectomy surgery, history of other ocular diseases other than cataracts or mild refractive error, and ungradable OCT images. All patients underwent a complete anterior segment slit-lamp examination and dilated ophthalmoscopy using the biomicroscope and indirect ophthalmoscopy. The patients were classified as having NoDR or mild NPDR according to the Early Treatment Diabetic Retinopathy Study staging system (ETDRS) by a retina specialist (J.I.L.).\(^\text{19}\)

All patients underwent OCT imaging using spectral-domain OCT (ANGIOVUE spectral domain OCTA system; Optovue, Fremont, CA), with a wavelength of 850 nm, 70-kHz A-scan rate, an axial and lateral resolution of 5 \(\mu m\) and 15 \(\mu m\), respectively, and 6 \(\mu m\) \(\times\) 6 mm volumetric scan centered at the macula, for a total of 304 or 400 B-scans, were acquired. All the images were quantitatively examined and OCT images with severe motion or signal loss were also excluded. OCT volumes were exported into a custom-developed MATLAB (Mathworks, Natick, MA) software for further outer retinal analysis.

**Quantitative OCT Analysis**

Retinal regions for analysis were selected using OCT B-scans centered at the fovea, selection of points between 1.25 mm and 2.5 mm and 2.5 mm and 5.5 mm away from the center of the fovea were defined as parafoveal and perifoveal area, respectively (Figure 1A). A-lines were adjusted from selected areas to match each retinal layer in the same horizontal position and averaged, inner limiting membrane (ILM), ELM, ISe, interdigitation zone (IZ), RPE peaks, and the first and second hyporeflective troughs (T1 and T2) were manually detected (Figure 1B). In this study, we measured the thickness of six photoreceptor locations, L12, L23, L34, L13, DT1, and DT2, where L12 quantifies the distance between the ELM to ISe, L23 measures the distance from the ISe to IZ, L34 measures the distance from IZ to RPE, and L13 measures the distance from ELM to IZ. DT1 and DT2 measure the distance from the ELM to the first and second hyporeflective troughs, respectively. Examples of thickness measurements are illustrated in Figure 1B. Concurrently, the reflectance intensities of the ELM, ISe, IZ, and RPE were measured from the parafovea and perifovea retina. To reduce noise, the reflectance values were normalized to the inner plexiform layer intensity. In addition, we evaluated the ratio between the ISe and RPE intensity. At the central fovea, the boundary of the inner plexiform layer cannot be determined; therefore, intensity features at the central retina were not analyzed. Each feature was sampled from 10 adjacent A-lines in each retinal region, central fovea, parafovea, and perifovea, and the average value was reported.

**Statistical Analyses**

Statistical analysis was performed using OriginPro (OriginLab, Northampton, MA). All features were analyzed for normality using the Shapiro–Wilks test. If the feature was normally distributed, multiple group comparisons were performed using a one-way analysis of variance (ANOVA) test, and the individual pairwise comparisons were performed using an unpaired Student’s \(t\)-test. If the feature was not normally distributed, a Kruskal–Wallis one-way ANOVA was performed, and the individual pairwise comparisons were performed using a Mann–Whitney \(t\)-test. For this study, a \(P\) value of <0.05 was considered statistically significant.
Results

The image database used in this study included 14 control subjects (21 eyes) and 31 diabetic patients (20 NoDR eyes and 21 mild NPDR eyes) staged according to the ETDRS staging system. No statistically significant differences were observed among the controls and diabetic eyes with respect to age, sex, hypertension, or duration of diabetes (ANOVA, $P = 0.69$, chi-square test, $P = 0.85$). Furthermore, no significance in hypertension or insulin dependence among the diabetic groups was observed. A summary of the subject demographics used in this study are presented in Table 1.

In this study, we quantified 11 outer retinal features, namely 6 thickness measurements, $L_{12}$, $L_{23}$, $L_{13}$, $D_{T1}$, and $D_{T2}$, and five intensity features of the ELM, ISe, IZ, RPE, and ISe/RPE ratio. Examples of averaged A-line intensity plots in the central fovea, parafovea, and perifovea for healthy controls, NoDR, and mild NPDR eyes are illustrated in Figure 2. Qualitative observations of the example A-line intensity plots suggest an overall decreasing ISe intensity trend can be observed from control to mild NPDR eyes, whereas increasing in RPE intensity. Qualitative observations of thickness changes between cohorts did not reveal a discernible trend; therefore, quantitative feature analysis of thickness and intensity was performed.

For the thickness measurements, significant differences were observed for the $L_{23}$ thickness between mild NPDR and control eyes in the central fovea (Mann–Whitney $t$-test, $P = 0.005$), parafovea (Mann–Whitney $t$-test, $P = 0.044$), and perifovea (Mann–Whitney $t$-test, $P = 0.036$). Significant differences were also observed for the $L_{23}$ thickness between NoDR and mild NPDR in the parafovea (Mann–Whitney $t$-test, $P = 0.039$). Overall, the decreasing trend from no retinopathy to retinopathy can be seen in all three retinal eccentricities. The other thickness measurements did not reveal consistent statistically significant differences. All photoreceptor thickness measurements are summarized in Table 2.

Fig. 1. A. Representative OCT B-scan of healthy control subject, the dashed white lines are representative eccentricities for A-line analysis. The colored markers are representative retinal locations, the corresponding band location is summarized in the legend. B. Representative averaged A-line profile of the perifovea to illustrate individual retinal locations and outer retina thickness measurements. $D_{12}$, distance from the ELM to ISe; $D_{13}$, distance from the ELM to IZ; $D_{23}$, distance from the ISe to IZ; and $D_{14}$, distance from the ELM to RPE, $D_{T1}$, distance from the ELM to $T_1$; $D_{T2}$; Distance from the ELM to $T_2$. The scale bar represents 0.5 mm. ILM, inner limiting membrane; IPL, inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform layer; ONL, outer nuclear layer; $T_1$, first hyporeflective trough; $T_2$, second hyporeflective trough.
For the intensity features, the ELM intensity revealed statistically significant differences in the perifovea region between NoDR and control eyes (Student’s t-test, \(P = 0.011\)), and NoDR and mild NPDR eyes (Student’s t-test, \(P = 0.001\)). The IZ intensity revealed statistically significant differences between cohorts in the perifovea region between mild NPDR and control eyes (Student’s t-test, \(P = 0.038\)) and NoDR and mild NPDR eyes (Student’s t-test, \(P = 0.005\)). The ISe intensity features revealed statistically significant differences in the perifovea region between mild NPDR and control eyes (Student’s t-test, \(P = 0.001\)) and NoDR and mild NPDR eyes (Student’s t-test, \(P = 0.001\)). Overall, the trend for ISe intensity decreases with disease progression, whereas RPE intensity features revealed an increasing trend with disease progression. Because we observed an opposing trend between ISe and RPE intensity, to further highlight differences, we took the ISe/RPE intensity ratio. The ISe/RPE ratio revealed a clear decreasing trend with disease progression. There were statistically significant differences between all stages in the perifovea region (Student’s t-test, \(P < 0.05\)). However, there was no detectable difference in the central fovea. All intensity features are summarized in Table 3.

### Discussion

In summary, we evaluated outer retina alternations in early-stage DR using OCT photoreceptor thickness
and intensity features using clinical OCT, namely, we measured the thickness of the hyperreflective bands, L₁₂, L₂₃, L₃₄, L₁₃, and hyporeflexive troughs, DT₁, and DT₂, and the intensity of the hyperreflective bands in the central fovea, parafovea, and perifovea. The result of this study suggests that there may be metabolic abnormalities that occur in early DR, because of thickness and intensity changes associated with the ISe.

Previous OCT studies have primarily measured retinal thickness changes in DR. Goebel et al, evaluated retinal thickness in the parafovea retina and reported significant increase in the retinal thickness of diabetic eyes compared with healthy controls.¹⁸ However, that study was limited by absence of inclusion of analysis of DR stages, particularly NoDR and mild NPDR. In contrast, a study by Vujosevic et al, which performed retinal thickness measurements for healthy controls, NoDR, and NPDR groups reported no statistical differences in the outer retinal thickness.²⁰ Similarly, Dimitrova et al²¹ compared the differences in the outer retinal thickness of healthy controls and NoDR cohorts and reported no significant differences among the groups. A recent study by McAnany et al performed an analysis of the outer retinal thickness for healthy controls, NoDR, and mild NPDR cohorts.²² In these studies, there may be discrepancies in how they measure the outer retinal thickness. For instance, McAnany et al determined the outer retina thickness as the boundary between the inner nuclear layer and the outer plexiform layer, which may dilute the subtle thickness changes of the individual retinal bands. In these studies, the evaluation of OCT inner and outer retinal thicknesses alone may not provide the sensitivity for detection of early DR.

Further evaluation of individual retinal layers may provide better sensitivity for detection in DR. For the inner retina, Van Dijk et al found a selective loss of inner retinal layer thickness in type I diabetic patients with minimal DR.²³ In a follow-up study, they reported a statistically significant difference in the parafoveal ganglion cell layer and corresponding loss of the RNFL was a significant biomarker in a study of Type I diabetes compared with controls,²⁴ whereas for the outer retina, Mohammed et al used the probability density function to evaluate the thickness of the retinal layers by OCT in diabetics in various stages of retinopathy. They found that the outer plexiform layer was the most discriminative for classifying normal and diabetic patients with NPDR.²⁵ In a cross sectional study, Ozkaya et al²⁶ showed that the photoreceptor outer segment in the foveal center was thinner in

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**Table 2. Quantitative Analysis of OCT Thickness Measurements**

| Features | Control (I) | NoDR (II) | Mild NPDR (III) | P       |
|----------|-------------|-----------|-----------------|---------|
| L₁₂ (µm) |             |           |                 |         |
| Central  | 30.57 ± 2.04| 32.14 ± 4.15| 31.80 ± 3.69 | 0.253   |
| Parafovea| 25.86 ± 2.41| 24.86 ± 2.48| 24.60 ± 2.68 | 0.286   |
| Perifovea| 23.00 ± 2.57| 22.07 ± 2.79| 22.80 ± 2.26 | 0.350   |
| L₁₃ (µm) |             |           |                 |         |
| Central  | 70.71 ± 3.74| 71.57 ± 3.50| 68.40 ± 5.02 | 0.650   |
| Parafovea| 51.86 ± 4.46| 50.36 ± 3.75| 47.55 ± 5.44 | 0.298   |
| Perifovea| 46.00 ± 3.59| 45.43 ± 4.54| 43.80 ± 4.50 | 0.627   |
| L₂₃ (µm) |             |           |                 |         |
| Central  | 40.14 ± 3.21| 39.43 ± 4.54| 36.60 ± 3.84 | 0.651   |
| Parafovea| 26.00 ± 3.05| 25.50 ± 2.28| 22.95 ± 4.89 | 0.711   |
| Perifovea| 23.00 ± 2.74| 23.36 ± 2.92| 21.00 ± 3.64 | 0.943   |
| L₁₄ (µm) |             |           |                 |         |
| Central  | 13.29 ± 2.94| 13.07 ± 1.90| 15.00 ± 2.58 | 0.651   |
| Parafovea| 16.43 ± 3.50| 14.79 ± 2.49| 16.20 ± 3.82 | 0.148   |
| Perifovea| 17.14 ± 3.17| 15.21 ± 3.21| 16.50 ± 5.20 | 0.094   |
| DT₁ (µm) |             |           |                 |         |
| Central  | 12.86 ± 2.35| 13.93 ± 3.02| 13.20 ± 3.14 | 0.240   |
| Parafovea| 10.43 ± 2.44| 10.07 ± 1.90| 10.35 ± 2.28 | 0.713   |
| Perifovea| 8.86 ± 2.59 | 8.14 ± 1.83 | 8.55 ± 2.01  | 0.325   |
| DT₂ (µm) |             |           |                 |         |
| Central  | 47.57 ± 2.73| 49.29 ± 4.66| 48.75 ± 5.04 | 0.379   |
| Parafovea| 36.57 ± 5.09| 35.14 ± 2.98| 34.65 ± 3.15 | 0.161   |
| Perifovea| 32.71 ± 2.67| 31.71 ± 3.27| 32.10 ± 2.77 | 0.371   |

All values are presented as mean ± SD. Columns 5 to 7 are pairwise comparisons, and column 8 are multiple group comparisons. Kruskal–Wallis was used for multiple comparisons, One-versus-one comparisons were conducted using Mann–Whitney U-test.
patients with clinical retinopathy compared with normal subjects and diabetics without retinopathy. Yao et al. demonstrated the effect of retinal eccentricity on the thickness measurement of individual outer retina bands. Therefore, in this study, we similarly measured the individual outer retina bands, for the central fovea, parafovea, and perifovea, respectively. The observation in this study suggests that there is a subtle decrease in thickness with DR stage progression between the ISe and IZ bands.

Clinically, DR has been defined as a microvascular disease. Therefore, recent endeavors for early detection and objective classification of DR have primarily explored the retinal vasculature for the detection of early-stage DR using OCT angiography (OCTA).

However, there is a growing body of evidence that suggests that the photoreceptor cells play a role in the development of early stages of DR. Although the ELM and RPE are not neuronal cells, studies have shown that they do indicate the integrity of the photoreceptor. Recent studies have suggested alterations of the RPE in diabetes, in particular electron microscopy experiments have reported ultrastructural changes in early-stage DR.

To evaluate retinal function, recent studies have also explored the correlation between different imaging modalities and clinical features. Srinivasan et al. evaluated the correlation between retinal structure and function using modalities such as OCTA, multifocal electroretinogram, and contrast sensitivity among diabetic patients with and without retinopathy. In their multifocal electroretinogram analysis, they reported that significant differences in P1 implicit times were observed between NoDR and NPDR, and that P1 implicit times were significantly correlated with retinal perfusion. Similarly, Sener et al. evaluated the correlation between OCTA and multifocal electroretinogram in DM patients. They report that there were decreased amplitudes of multifocal electroretinogram waves, N1 and P1 in the circles of 2 and 5°. In their correlation analysis, they reported that the N1 and P1 amplitudes were correlated to the vascular density changes in the parafovea and perifovea regions. McAnany and Park evaluated contrast sensitivity, outer retina thickness in OCT, and visual acuity measurements. In their study,

### Table 3. Quantitative Analysis of OCT Intensity Features

| Features | Control (I) | NoDR (II) | Mild NPDR (III) | I vs. II | I vs. III | II vs. III | ANOVA |
|----------|-------------|-----------|-----------------|---------|----------|-----------|-------|
| ELM      |             |           |                 |         |          |           |       |
| Parafovea| 0.861 ± 0.054| 0.885 ± 0.042| 0.882 ± 0.029| 0.151  | 0.134    | 0.807     | 0.192* |
| Perifovea| 0.839 ± 0.044| 0.879 ± 0.042| 0.829 ± 0.038| 0.011  | 0.428    | 0.001     | 0.003* |
| ISe      |             |           |                 |         |          |           |       |
| Parafovea| 1.375 ± 0.064| 1.386 ± 0.085| 1.339 ± 0.060| 0.688  | 0.065    | 0.086     | 0.102* |
| Perifovea| 1.371 ± 0.071| 1.383 ± 0.065| 1.294 ± 0.065| 0.627  | 0.001    | 0.001     | <0.001*|
| IZ       |             |           |                 |         |          |           |       |
| Parafovea| 1.357 ± 0.085| 1.405 ± 0.113| 1.320 ± 0.093| 0.191  | 0.185    | 0.028     | 0.045* |
| Perifovea| 1.339 ± 0.072| 1.371 ± 0.078| 1.288 ± 0.080| 0.229  | 0.038    | 0.005     | 0.009* |
| RPE      |             |           |                 |         |          |           |       |
| Parafovea| 1.336 ± 0.061| 1.378 ± 0.054| 1.395 ± 0.061| 0.042  | 0.003    | 0.382     | 0.008* |
| Perifovea| 1.338 ± 0.050| 1.396 ± 0.059| 1.353 ± 0.074| 0.007  | 0.397    | 0.066     | 0.025† |
| ISe/RPE  |             |           |                 |         |          |           |       |
| Central  | 0.845 ± 0.069| 0.827 ± 0.046| 0.845 ± 0.036| 0.375  | 0.993    | 0.251     | 0.575* |
| Parafovea| 1.030 ± 0.041| 1.007 ± 0.059| 0.961 ± 0.049| 0.209  | <0.001   | 0.024     | <0.001*|
| Perifovea| 1.025 ± 0.040| 0.992 ± 0.051| 0.958 ± 0.040| 0.049  | <0.001   | 0.049     | <0.001*|

All values are presented as mean ± SD. Columns 5 to 7 are pairwise comparisons, and column 8 are multiple group comparisons. If one-way ANOVA was used for multiple comparisons, One-versus-one comparisons were conducted using Student’s t-test. If Kruskal-Wallis was used for multiple comparisons, One-versus-one comparisons were conducted using Mann-Whitney t-test.

*One-way ANOVA.
†Kruskal-Wallis.
they reported that visual acuity did not reveal significant differences between NoDR and NPDR groups, and that visual acuity did not correlate with the outer retinal thickness changes in NoDR and NPDR. Similarly, Srivinasan et al\(^\text{37}\) reported no significant differences in the logMAR between NoDR and NPDR. However, they did report that logMAR was significantly correlated with central subfoveal thickness in NoDR and NPDR. These studies suggest that functional changes may occur in early DR; however, clinical features such as visual acuity may not be sensitive for early DR detection. Better developments of quantitative imaging features, which may provide the sensitivity for early detection of DR, are desirable.

In this study, we assessed the reflectance intensity changes of the ELM, ISc, Iz, and RPE, and derived the ISc/RPE intensity ratio to evaluate photoreceptor abnormalities. The observations in this study suggest that the ISc intensity decreases with increased progression of early DR. A study by Toprak et al,\(^\text{10}\) similarly, observed a decrease in ISc intensity in mild NPDR compared with healthy eyes. Furthermore, we observed an increasing trend for the RPE intensity with increasing severity. Therefore, the relationship between two features with polarizing trends, the ISc/RPE intensity ratio, may enhance the subtle ISc and RPE abnormalities that occur in early DR. Significant differences in the ISc/RPE intensity ratio was observed in the parafovea and perifovea regions. However, there were no significant differences in the central fovea. Because the parafovea and perifovea regions are primarily rod-dominated, the observation in this study suggests rod abnormalities in early DR.

This study did have a few limitations, namely our sample size was modest for each cohort, and all the OCT data were acquired from one imaging device (ANGIOVUE spectral domain OCTA system) in a single location. For future study, we plan to expand the population and evaluate OCT data from different devices (e.g., Spectralis, Cirrus, etc).

In conclusion, quantitative OCT analysis consistently revealed photoreceptor abnormality in diabetic patients with NoDR and mild NPDR. The normalized ISc/RPE intensity ratio of perifoveal OCT is the most sensitive feature to differentiate all three cohorts. Comparative analysis of central fovea, parafovea, and perifovea confirmed the photoreceptor abnormality is rod-predominant in early DR.

**Key words:** optical coherence tomography, medical imaging, ophthalmology, diabetic retinopathy, neurodegeneration, macular, optical diagnostics for medicine, physiology, visual system, noninvasive assessment.

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