Alterations in Retinal Layer Thickness and Reflectance at Different Stages of Diabetic Retinopathy by En Face Optical Coherence Tomography

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Purpose. This article reports a method for en face optical coherence tomography (OCT) imaging and quantitative assessment of alterations in both thickness and reflectance of individual retinal layers at different stages of diabetic retinopathy (DR).

Methods. High-density OCT raster volume scans were acquired in 29 diabetic subjects divided into no DR (NDR) or non-proliferative DR (NPDR) groups and 22 control subjects (CNTL). A customized image segmentation method identified eight retinal layer interfaces and generated en face thickness maps and reflectance images for nerve fiber layer (NFL), ganglion cell and inner plexiform layers (GCLIPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL), photoreceptor outer segment layer (OSL), and retinal pigment epithelium (RPE). Mean thickness and intensity values were calculated in nine macular subfields for each retinal layer.

Results. En face thickness maps and reflectance images of retinal layers in CNTL subjects corresponded to normal retinal anatomy. Total retinal thickness correlated negatively with age in nasal subfields ($R \leq -0.31; P < 0.03, N = 51$). In NDR subjects, NFL and OPL thickness were decreased ($P = 0.05$), and ONL thickness was increased ($P = 0.04$) compared to CNTL. In NPDR subjects, GCLIPL thickness was increased in perifoveal subfields ($P < 0.05$) and INL intensity was higher in all macular subfields ($P = 0.04$) compared to CNTL.

Conclusions. Depth and spatially resolved retinal thickness and reflectance measurements are potential biomarkers for assessment and monitoring of DR.

Keywords: diabetic retinopathy, en face imaging, optical coherence tomography, reflectance, thickness

Diabetic retinopathy (DR) is currently the leading cause of vision loss in working-age adults. With anticipated growth of the diabetic population, the number of visually impaired diabetic people will continue to be a major public health concern. Diabetes is known to cause alterations in the retinal microvasculature and tissue that can progressively lead to visual impairment. Currently, prevention of vision loss due to DR requires early diagnosis, regular monitoring, and timely therapeutic intervention. However, a key impediment is identifying diabetic individuals who will develop retinopathy and progress to vision-threatening macular edema or proliferative DR.

Optical coherence tomography (OCT) imaging allows cross-sectional visualization of retinal layers and quantitative mapping of total retinal thickness. OCT technology is a standard of clinical care for detection of anatomical abnormalities within the retinal layers and the presence of retinal thinning in DR subjects. Several image segmentation methods have become available for measurement of thickness of individual retinal layers, and alterations in retinal layer thickness have been shown to occur in DR. Furthermore, alterations in the integrity of the inner segment ellipsoid layer, as shown by changes in continuity and reflectance, have also been reported in DR subjects. Methods for en face imaging have been developed and applied for visualizing pathologies due to various retinal conditions. We previously reported methods for generation of en face reflectance images of individual retinal layers from a high-density raster of images. In the current study, we report for the first time an en face OCT imaging method for quantitative measurements of both thickness and reflectance alterations in individual retinal layers and macular subfields at different stages of DR.

Methods

Subjects

The research study was approved by the Institutional Review Board at the University of Illinois at Chicago. Prior to subjects' enrollment, the research study was explained to them, and informed consent was obtained according to the tenets of the Declaration of Helsinki. Twenty-nine subjects with a clinical diagnosis of diabetes mellitus and 22 non-diabetic control subjects (CNTL) participated in the study. Exclusion criteria included high myopia (refractive error $> -6$ diopter [D]), active myocardial infarction (within 3 months of imaging), active antivascular endothelium growth factor treatment, stroke or myocardial infarction (within 3 months of imaging), active myocardial infarction (within 3 months of imaging).
En Face OCT Imaging

As shown in Figure 1, the eight retinal interfaces detected by the automated segmentation algorithm were the vitreous and nerve fiber layer (NFL), theNFL and combined ganglion cell/inner plexiform layers (GCLIPL), the GCLIPL and inner nuclear layer (INL), the INL and outer plexiform layer (OPL), the OPL and outer nuclear layer (ONL), the ONL and photoreceptor outer segment layer (OSL), the OSL and retinal pigment epithelium (RPE), and the RPE and choroid. To find a unique path for these eight retinal interfaces, image segmentation of the cell interfaces was performed in successive order. First, the interface between the vitreous and NFL was identified, because this interface was characterized by the largest dark-to-bright transition (largest positive vertical gradient) in the image and represented the lowest weighted path of the entire graph. Second, the interface between the ONL and OSL layers was found after restricting the graph search area to include only image regions external to the vitreous/NFL interface. Third, the path corresponding to the RPE/choroid interface was determined by restricting the graph search area to include only image regions external to the vitreous/NFL interface and finding a dark-to-bright transition. Sixth, the GCLIPL/INL interface was detected by limiting the graph search area to include only image regions external to the INL/OPL paths and designating lower weights of the graph for larger negative gradients (bright-to-dark transition). Seventh, the NFL/GCLIPL interface was determined by limiting the graph search area to include only image regions between the NFL/OPL and OPL/ONL cell interfaces and detecting a bright-to-dark transition. Eighth and finally, the OSL and RPE boundary was found by restricting the graph search area to include only image areas between the detected ONL/OSL and RPE/choroid interfaces and finding a dark-to-bright transition.

After the retinal interfaces were segmented, the operator was able to scroll through all 73 SD-OCT B-scans in the volume scan to review the segmentation results and, if necessary, manually correct errors in the detected interfaces. Such errors occurred with detached posterior hyaloid membranes, absence of inner retinal layers at the foveal center, and the presence of slightly irregular layer interfaces. Significant wrinkling of the inner limiting membrane was not observed, and cystoid changes that precluded confident identification of retinal layer interfaces were not present in this sample of images due to the exclusion criteria. To correct segmentation errors, the operator selected a segmentation path that required modification and then manually drew a revised line corresponding to the visualized cell layer interface. The search area of the graph was then restricted to include only a small vertical (depth) image region around the manually drawn line, and a revised path for the cell layer interface was obtained by determining a new graph cut solution. The error rate of the automated segmentation algorithm was determined in 5 CNTL and 5 NPDR subjects. For each of the eight retinal interfaces, an error rate was calculated as the percentage of length of the automated segmentation line that was manually modified. A mean error rate was calculated for each subject by averaging the error rates of all retinal interfaces.

En Face Thickness Mapping and Reflectance Imaging

En face thickness maps and reflectance images were generated for each of 7 retinal layers (NFL, GCLIPL, INL, OPL, ONL, OSL,
and RPE) based on segmentation of the 8 retinal interfaces in the SDOCT B-scans. Outer segment complex (OSC) thickness was calculated as the depth separation between the ONL/OSL and RPE/choroid interfaces (OSC = OSL + RPE). In addition, en face thickness maps and intensity images of the inner retina (IR), outer retina (OR), and total retina (TR) were generated. IR thickness was calculated as the depth separation between the vitreous/NFL and INL/OPL interfaces (IR = NFL + GCLIPL + INL). Outer retina thickness was calculated as the depth separation between the INL/OPL and RPE/choroid interfaces (OR = OPL + ONL + OSL + RPE). TR thickness was calculated as the depth separation between the vitreous/NFL and RPE/choroid interfaces (TR = sum of 7 layers). En face reflectance images of each of the seven retinal layers and the IR, OR, and TR were generated based on pixel values averaged vertically (in depth) within the segmented layers in each SDOCT B-scan to create rows of corresponding en face images. Mean thickness and intensity values were calculated in each of the 9 Early Treatment Diabetic Retinopathy Study (ETDRS) macular subfields for each of the 7 retinal layers and the IR, OR, and TR.

### Statistical Analysis

Mean thickness (T) measurements (NFLT, GCLIPLT, INLT, OPLT, ONLT, OSLT, RPET, IRT, ORT, TRT) and intensity (I) measurements (NFLI, GCLIPLI, INLI, OPLI, ONLI, OSLI, RPEI, IRI, ORI, TRI) were obtained in nine macular subfields in each subject. Data obtained in left eyes were transformed to orient all data to a right-eye configuration. Validity of the method was established by comparing TRT values at the central subfield provided by the automated segmentation software and the instrument's software using linear regression analysis. The relationship between TRT and age was determined using linear regression.

### RESULTS

#### Automated Segmentation Performance

Average error rates obtained by the automated segmentation algorithm were 3% ± 1% and 7% ± 6% in CNTL and NPDR subjects, respectively. The minimum lengths of manually modified segmentation lines were 7 pixels (41 μm) and 19 pixels (110 μm) in CNTL and NPDR subjects, respectively.

#### Control Subjects

**Thickness Maps.** Examples of thickness maps of seven retinal layers in the right eye of a CNTL subject are shown in Figure 2 (top row). As expected, the NFLT map displayed increased thickness in nasal subfields, decreased thickness in temporal subfields, and minimal thickness in the central subfield. GCLIPLT and INLT maps exhibited a parafoveal ring of increased thickness, with central thinning corresponding to the fovea. The OPLT map was relatively uniform in all subfields, except for the central subfield, which displayed minimal thickness. The ONLT map displayed increased thickness in the central subfield due to the longer and more densely packed cones. Similarly, the OSLT map showed increased thickness centrally, because of a greater separation between the ellipsoid of the inner segments and the RPE. The RPET map was relatively uniform.

Examples of IRT, ORT, and TRT maps in the same CNTL subject are shown in Figure 3 (top row). The IRT and TRT maps displayed a parafoveal ring of increased thickness surrounding a central depression corresponding to the fovea, whereas the ORT map showed increased thickness centrally due to longer cones near the fovea.

**En Face Reflectance Images.** Examples of reflectance images of seven retinal layers in the same CNTL subject are shown in Figure 2 (bottom row). Overall, reflectance images of all seven retinal layers displayed relatively uniform intensity indicating lack of pathological disruption. In NFL, GCLIPL, INL,
was increased in NPDR compared to that in CNTL in the y (macular subfields, and the correlation reached statistical measurements (/software and the instrument’s software (/central subfield provided by the automated segmentation from all subjects, there was a high correlation between TRT in and perifoveal temporal subfields, as anticipated. Based on data
the perifoveal subfields. Furthermore, TRT was larger in the parafoveal subfields than in the central subfield, whereas ORT had its highest value. TRT was larger in the parafoveal retina in the IR reflectance image due to the absence of inner retinal cell layers.

Examples of reflectance images of the IR, OR, and TR in the same CNTL subject are shown in Figure 3 (bottom row). All reflectance images were relatively homogeneous without significant intensity variations. Retinal vasculature can be visualized within the IR reflectance image but appears more prominently in OR reflectance image due to shadowing effects. The foveal center appeared darker, relative to the surrounding parafoveal regions due to the absence of inner retinal cell layers.

Validity
Mean IRT, ORT, and TRT in CNTL subjects stratified by macular subfield are shown in Figure 4. As expected, IRT and TRT had their lowest values in the central subfield, whereas ORT had its highest value. TRT was larger in the parafoveal subfields than in the parafoveal subfields. Furthermore, TRT was larger in the parafoveal and perifoveal nasal subfields than in the parafoveal and perifoveal temporal subfields, as anticipated. Based on data from all subjects, there was a high correlation between TRT in the central subfield provided by the automated segmentation software and the instrument’s software (R = 0.99; P < 0.001; N = 51). The slope of the best fit regression line was 1.03 and the y-intercept was −1.7 μm. Consistent with a previous study,35 a trend of lower TRT with increased age was observed in all macular subfields, and the correlation reached statistical significance in the parafoveal and perifoveal nasal subfields (R ≤ −0.31; P ≤ 0.03, N = 51).

Effect of Disease Stage (CNTL, NDR, NPDR)
Thicknless Measurements. The interaction effect between disease stage and location was significant for GCLIPLT (P = 0.001) and not significant for all other thickness measurements (P ≥ 0.07). As shown in Figure 5, GCLIPLT was increased in NPDR compared to that in CNTL in the perifoveal nasal, superior, and inferior subfields (P ≤ 0.05). The main effect of disease stage was significant for ONLT (P = 0.04), marginally significant for NFLT and OPLT (P = 0.06), and not statistically significant for INLT, ONLT, OSLT, RPET, and OSCI (P ≥ 0.2). As shown in Figure 5, ONLT was higher in NDR than in CNTL in all macular subfields (P = 0.04), whereasNFLT and OPLT were lower in NDR than in CNTL (P = 0.05). All thickness measurements had differences among macular subfields (P < 0.001), except for RPET (P = 0.1).

The interaction effect was not significant in ORT and TRT (P ≥ 0.08) and marginally significant in IRT (P = 0.06), IRT, ORT, and TRT were similar among disease stage groups (P ≥ 0.3) but differed among macular subfields (P < 0.001).

Intensity Measurements. There was no significant interaction effect between disease stage and location on intensity measurements (P ≥ 0.5). There was only a significant main effect of disease stage on INLI (P = 0.04). All other intensity measurements were similar among disease stage groups (P ≥ 0.1). As shown in Figure 5, INLI was higher in NPDR in all macular subfields than that in CNTL (P = 0.04). All intensity measurements showed differences among macular subfields (P ≤ 0.001).

There was no significant interaction effect between disease stage and location on IRI, ORI, and TRI (P ≥ 0.86). IRI, ORI, and TRI were similar among disease stage groups (P ≥ 0.19) but differed among macular subfields (P < 0.001).

Discussion
In the current study, we report an en face OCT imaging method to quantitatively assess thickness and reflectance alterations of individual retinal layers in non-diabetic control subjects and diabetic subjects with and without DR. The method allows spatial localization of both thickness and reflectance alterations in individual retinal layers, offering a comprehensive assessment of retinal anatomy that can potentially identify macular regions that are more susceptible to damage from DR. Alterations in thickness of individual retinal layers were detected among the disease stage groups in the current study. NFL thickness was found to be reduced in NDR subjects, in agreement with previous studies that reported peripheral NFL thinning in diabetics with no or minimal retinopathy, suggesting neuronal loss at early stages of retinopathy.10–13 However, the finding of GCLIPL thickening in NPDR subjects was different from previous studies that reported similar10 or reduced GCLIPL thickness.8,14 In the current study, ONL thickness was increased in NDR subjects, in agreement with the finding in a previous study,36 and different from that in another study that reported similar ONL thickness in NDR and CNTL subjects.10 Differences in the findings may be attributed to small sample size of the current study, technical and methodological differences, and variations in the study populations.

In the current study, increased INL reflectance was observed in NPDR subjects. This finding is consistent with that in a previous study that reported the presence of hyper-reflective spots in inner retinal layers of NPDR subjects, particularly the INL, which had the largest number of spots among inner retinal layers.57 As previously reported,58 alterations of en face retinal layer reflectance indicate pathological changes, including intraretinal fluid and hard exudates. For example, intraretinal fluid resulted in decreased layer reflectance, while hard exudates appeared as localized areas of hyperreflectivity. At early stages of diabetic retinopathy, the initial development of these intraretinal pathologies likely result in subtle reflectance changes in individual retinal layers by OCT imaging, which may not be evident by conventional retinal imaging due to light
reflectance from different layers. Future longitudinal studies are needed to substantiate the potential of intensity measurements as biomarkers for development of DR and progression from preclinical to clinical stage.

The study had certain limitations. Automated detection of retinal layer boundaries was limited by OCT B-scan image quality and retinal layer architecture integrity. In some instances, correction of the automated layer segmentation by manual intervention was implemented. However, subjective errors during this process were minimized by obtaining the new layer segmentation with the same graph theory framework applied to a narrow region of image defined by the user, and not from a manually specified line. The high correlation between thickness measurements obtained using two independent software algorithms further established data reliability. Nevertheless, automated image segmentation and identification of retinal layer interfaces may not be feasible for images obtained in subjects with advanced DR pathologies that cause gross disturbances in retinal layer integrity, such as may be seen in cystoid macular edema.

Retinal layer intensity measurements can be affected by variations in ocular opacity and focus depth of the OCT instrument and may limit comparison of measurements among subjects. One way to adjust for this variation is to normalize intensity measurements to the RPE intensity in each subject. However, RPEI averaged over nine macular subfields was nearly identical in CNTL ($204 \pm 6$), NDR ($204 \pm 4$), and NPDR subjects ($204 \pm 4$), such that there was no effect of disease stage on RPEI ($P = 1.0$). Furthermore, the mean RPE intensity variation among disease groups averaged over the 9 macular subfields was only 0.6%, indicating similar intensities among subjects. Therefore, differences in ocular opacity and focus depth did not likely affect comparison of intensity measurements among groups. Finally, despite the small sample size in some groups, statistically significant differences were detected in thickness and intensity measurements. Future studies with a larger sample size that account for potential confounding factors are needed to substantiate the current findings and reveal differences not discernable with this sample size.
Overall, depth and spatially-resolved measurements of retinal thickness and reflectance are potential biomarkers for monitoring DR development, progression, and response to therapeutic interventions.

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