

Significant Relationship of Visual Field Sensitivity in Central 10° to Thickness of Retinal Layers in Retinitis Pigmentosa

Akira Sayo, Shinji Ueno, Taro Kominami, Satoshi Okado, Daiki Inooka, Shiori Komori, and Hiroko Terasaki

Department of Ophthalmology, Nagoya University Graduate School of Medicine, Nagoya, Japan

Correspondence: Shinji Ueno, Department of Ophthalmology, Nagoya University Graduate School of Medicine, 65 Tsuruma-cho, Showa-ku, Nagoya 466-8550, Japan; ueno@med.nagoya-u.ac.jp.

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PURPOSE. To determine the relationship between the sensitivity of the retina in the central 10° and the thickness of the retinal layers in patients with retinitis pigmentosa (RP).

METHODS. Fifty-two RP patients were studied. All of the patients had been examined by the Humphrey Field Analyzer 10-2 program (HFA10-2) and spectral-domain optical coherence tomography (SD-OCT). The thicknesses of the photoreceptor outer segment (OS), outer nuclear layer (ONL), inner nuclear layer (INL), and the retinal nerve fiber layer (RNFL) were measured at 1°, 3°, 5°, 7°, and 9° from the fovea. The same measurements were made on the SD-OCT images of 40 healthy subjects and used as controls. The relationships between the retinal sensitivities and retinal layer thicknesses were determined.

RESULTS. The thicknesses of the OS and ONL and their product were significantly and positively correlated with the retinal sensitivities. The thickness of the INL was significantly and negatively correlated with the sensitivity. The strongest correlation with the sensitivity was with the OS thickness (marginal R^2 [mR^2] = 0.525, $P < 0.001$), followed by the product of the OS and ONL thicknesses ($mR^2 = 0.420$, $P < 0.001$), ONL thickness ($mR^2 = 0.416$, $P < 0.001$), and the INL thickness ($mR^2 = 0.014$, $P = 0.044$). The thickness of the RNFL was not correlated with the sensitivity ($mR^2 = 0.005$, $P = 0.331$).

CONCLUSIONS. In contrast to previous reports, the thickness of the OS reflected the retinal sensitivity better than the product of OS and ONL.

Keywords: retinitis pigmentosa, OCT, Humphrey

Retinitis pigmentosa (RP) is an inherited retinal disease that is characterized by a constriction of the visual fields due to the degeneration of primarily the rods.¹ In advanced stages, the cones degenerate, which leads to a reduction of the central vision, and with time, complete blindness. The natural course of the visual field constriction in RP patients is important for counseling patients, and the course of the constriction has been extensively studied by Goldmann perimetry.²⁻⁴

More recently, the Humphrey field analyzer (HFA) has been shown to be useful in assessing the residual central visual field of patients with RP.⁵⁻⁸ HFA is useful because it can not only determine the extent of the visual field but can also quantify the visual sensitivity of different regions of the retina.

Optical coherence tomography (OCT) has been used to determine the overall morphologic features of the retina in healthy and diseased eyes. OCT analyses have shown that there is a shortening of the ellipsoid zone (EZ) length, a thinning of the outer retinal layers, and thickening of the inner retinal layers in eyes with RP.^{9,10} Relevant to the current study, a number of studies have examined the relationships between the OCT findings and the visual field sensitivity of RP patients.¹¹⁻¹⁵ Determining these correlations between the retinal structure and visual function enables clinicians to quantify the status of the RP and counsel RP patients more accurately, and it is also important for treatment trials.

Among the numerous studies comparing the structure and function of patients with RP, one study that examined the visual fields with the HFA 30-2 program found that the thickness of the outer segment (OS) was proportional to the retinal sensitivity, and that the product of the OS thickness and the outer nuclear layer (ONL) thickness had an even stronger linear correlation with the sensitivity than the OS thickness.¹² The results suggested that examining this linear correlation in a more limited region would be more informative.

Thus, the purpose of this study was to determine whether there is a significant linear relationship between the retinal layer thickness and the retinal sensitivity in the more central areas of the retina using HFA10-2 and SD-OCT. We also investigated which retinal thickness parameter best reflected the retinal sensitivity, and the relationship between structure and sensitivity at different retinal eccentricities.

METHODS

All of the procedures conformed to the tenets of the Declaration of Helsinki, and the institutional review board (IRB)/Ethics Committee of the Nagoya University Hospital approved this study. The IRB waived the need for a written informed consent because the study design was a retrospective chart review.



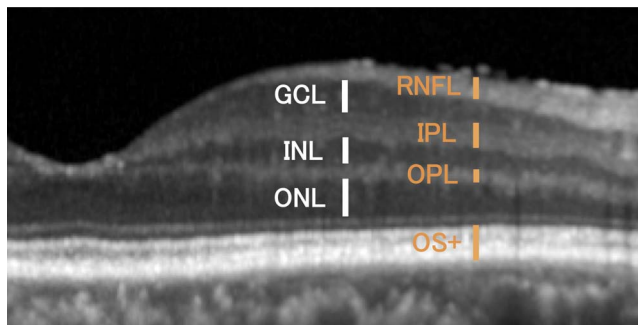


FIGURE 1. Segmentation of a SD-OCT image of a healthy eye.

Subjects

We reviewed the medical records of 315 RP patients who were examined by one of the authors (SU) at the Nagoya University Hospital between January 2007 and December 2017. The diagnosis of RP was based on the presence of night blindness, visual field constriction, typical fundus appearance, such as bone spicule pigmentation, and a reduced (<50 μV) or extinguished full-field scotopic flash electroretinograms (PE-300; TOMEY, Nagoya, Japan). Of the 315 patients, 122 had been examined by HFA10-2 and SD-OCT on the same day, and 66 of these had mean deviations (MD) of the HFA -15 dB or greater because the photoreceptors were preserved to some extent. This then allowed us to determine the relationship between the sensitivity and structure of the retina. Eyes with other ocular diseases such as cystoid macular edema and epiretinal membrane severe enough to affect the visual fields or the measurements of the thickness of retinal layers were excluded. In addition, eyes with HFA10-2 fixation loss scores more than 10% were also excluded. If both eyes of an individual met the inclusion criteria, the findings in the eye with the better MD was chosen for the statistical analyses. When a subject was examined more than once, the most recent data were used. In the end, 52 eyes of 52 RP patients were studied.

To determine the thickness of the different retinal layers in healthy eyes, 40 age-matched controls were evaluated by SD-OCT. These control eyes were those of patients who had undergone surgery on the contralateral eye due to a unilateral disorder such as epiretinal membrane or trauma.

Spectral-Domain Optical Coherence Tomography (SD-OCT)

Horizontal scans of 30° that were centered on the fovea were obtained from all the subjects by SD-OCT (Heidelberg Engineering, Heidelberg, Germany). All images were the average of 100 scans with the eye tracking system functioning. The thickness of the OS plus (OS+) was measured as the distance between the EZ and choroid/Bruch's membrane, the thickness of the ONL was measured as the distance between the outer plexiform layer (OPL) and the external limiting membrane (ELM), the thickness of the inner nuclear layer (INL) was measured as the distance between the inner plexiform layer (IPL) and the outer plexiform layer (OPL), and the thickness of the retinal nerve fiber layer (RNFL) was measured as the distance between the inner limiting membrane (ILM) and the ganglion cell layer (GCL). The measurements were made with the built-in caliper. The measurements were made perpendicular to the RPE at 1° , 3° , 5° , 7° , and 9° from the fovea along the horizontal meridian in both nasal and temporal retina. The segmentation of the retinal layers is shown in Figure 1.

Humphrey Field Analyzer (HFA) 10-2

All of the RP patients but not control subjects underwent HFA 10-2 measurements. The procedures were carried out with the SITA standard test strategy after correction of the refractive error. The visual field test assessed 68 points, and the points were located 2° apart. We used the total deviation (TD) values, which represented the deviation of the patient's sensitivity from age-matched controls at each location. We averaged the two values 1° from either side of the horizontal meridian to calculate the sensitivities at 1° , 3° , 5° , 7° , and 9° from the fovea along the horizontal meridian on both the nasal and temporal sides (Fig. 2). Because the decibel values are on a logarithmic scale, we converted the two values to 1/Lambert (1/L) linear scale using the following equation^{12,14}:

$$\text{TD (1/L)} = 10^{\text{TD (dB)}/10} \quad (1)$$

The averaged values were then converted back to decibel units.

Definition of Normalized Thickness of Retinal Layers

As in previous reports, the OS+ thickness included the following two main components¹²: the OS length that decreases with the loss of visual field sensitivity (s), and base level (b) that is not influenced by the reduction of sensitivity.^{12,14} The thicknesses of the RPE, Bruch's membrane, and blood vessels contribute to b in this case. We estimated the value of b by averaging the OS+ thickness of all the patients' test points below -20 (dB).¹² Thus, the normalized thickness of OS of each RP patient at each location was determined as,

$$[\text{OS} + - b] / [\text{average OS} + \text{of controls at each location} - b] \quad (2)$$

The base level of the thickness of the ONL (b'), which included the glial cells, blood vessels, and any residual tissues, was also defined as the average thickness of the ONL of all the points below -20 (dB). For the INL and RNFL, we did not assume the base level. Therefore, the normalized thickness of the ONL, INL, RNFL, and the normalized product of OS and ONL were determined as follows:

$$\begin{aligned} & [\text{ONL} - b'] / [\text{average ONL of controls at each location} - b'] \\ & \text{INL} / \text{average INL of controls at each location} \\ & \text{RNFL} / \text{average RNFL of controls at each location} \\ & \text{normalized OS} \times \text{normalized ONL} \end{aligned} \quad (3)$$

Statistical Analyses

Linear mixed-models were used with one of the retinal thickness parameters, that is, normalized OS, ONL, INL, RNFL or product, as an outcome, TD (1/L) as fixed effect, and each patient identification (ID) and eccentricities as random effects. Random slopes were added to the models in addition to random intercepts when they lower the Akaike information criterion. The marginal R^2 (mR^2) was calculated to measure the proportion of variance explained by only the fixed effects.¹⁵ This index takes a value between 0 and 1, and a large mR^2 means a strong association between each datum and the mean trend line. To examine whether the slopes of regression lines varied by eccentricities or locations (nasal or temporal), an interaction between sensitivity and the factor in question was tested. Student's *t*-tests were used to compare the individual

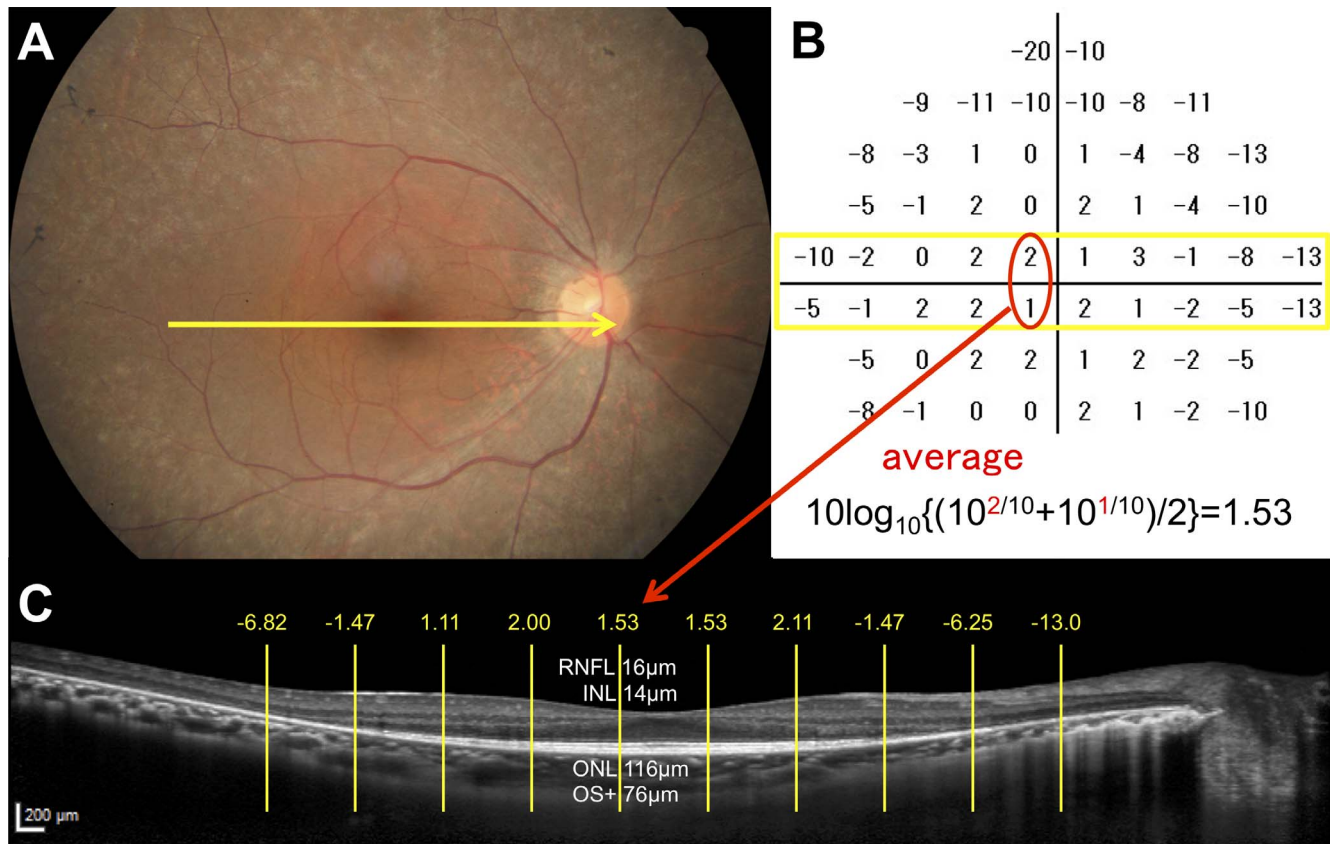


FIGURE 2. Superimposition of the visual field sensitivities on a fundus photograph. (A) Fundus photograph of a representative RP patient showing the extent of the 30° SD-OCT scan line. (B) TD plot of HFA 10-2 with an example of how the average sensitivity was calculated at 1°. (C) SD-OCT image with measured retinal thicknesses for that eccentricity. The two values at 1° from both sides of the horizontal meridian were averaged to calculate the sensitivities at 1°, 3°, 5°, 7°, and 9° from the fovea.

retinal layer thickness between RP patients and controls. All statistical analyses were performed with the R version 3.2.3 (R Statistics, Vienna, Austria).

RESULTS

Clinical Data

The average age was 44.7 ± 15.6 (range, 16–75) years for the 52 RP patients (19 men, 33 women). The mean visual acuity was 0.036 ± 0.16 (range, -0.78 to 0.52) logMAR units. The mean false-positive errors in the HFA 10-2 measurements were $0.92 \pm 1.28\%$ (range, 0%–5%), and the mean false-negative errors were $2.58 \pm 4.42\%$ (range, 0%–18%). The mean fixation loss score was $0.91 \pm 2.04\%$ (range, 0%–6.67%). The median MD was -8.31 dB (range, -15.0 to 1.51 dB).

Comparison of Each Layer Thickness Between RP Patients and Controls

The mean retinal layer thickness was calculated for each individual by averaging all the 10 values (1°–9°, nasal and temporal sides), and they were compared between RP patients and controls. The average OS (22.3 ± 10.8 μm) and ONL (44.5 ± 16.4 μm) of the RP patients were significantly thinner than those of the controls (OS: 42.6 ± 2.98 μm, ONL: 66.5 ± 7.00 μm; $P < 0.001$). On the other hand, the INL thickness (36.5 ± 7.01 μm) and RNFL (35.3 ± 6.57 μm) of the RP patients were significantly thicker than those of the controls (INL: 32.0 ± 3.52 μm, RNFL: 27.3 ± 2.68 μm; $P < 0.001$).

Relationship Between Retinal Layer Thickness and Sensitivity

Plots of the normalized thicknesses of the OS, ONL, product of OS and ONL, INL, and RNFL as a function of the TD (dB) at all the test locations of all the 52 patients are shown in Figure 3. The plots indicate that the photoreceptors thickness is reduced in eyes with a reduction of retinal sensitivity. Because the structural damage has been reported to be proportional to functional alterations on a linear scale (1/L),¹² we converted the dB values to 1/L and plotted the normalized thickness of each retinal layer against the TD (1/L) in Figure 4. The red line is the predicted change in the retinal thickness with a change in the visual field sensitivity.¹⁴ The linear model for the OS, ONL, and their product fits our data reasonably well as did the data reported by Rangaswamy et al.¹²

The data shown in Figures 3 and 4 are not independent of each other because some of the data were obtained from the same subject or at the same eccentricity. Thus, a linear mixed-model was used to examine the relationship between retinal structure and function. The analysis was first performed with only the data with retinal sensitivities of 1 (1/L) or less where the thickness of photoreceptors is reduced as is depicted by the red line in Figure 4. All of the retinal thickness parameters, except for the RNFL, were significantly correlated with the sensitivity. The normalized OS, ONL, and their products were positively and significantly correlated. On the other hand, the INL was significantly and negatively correlated with the visual field sensitivity, although the correlation was very weak (Table). Among these retinal thickness parameters, the

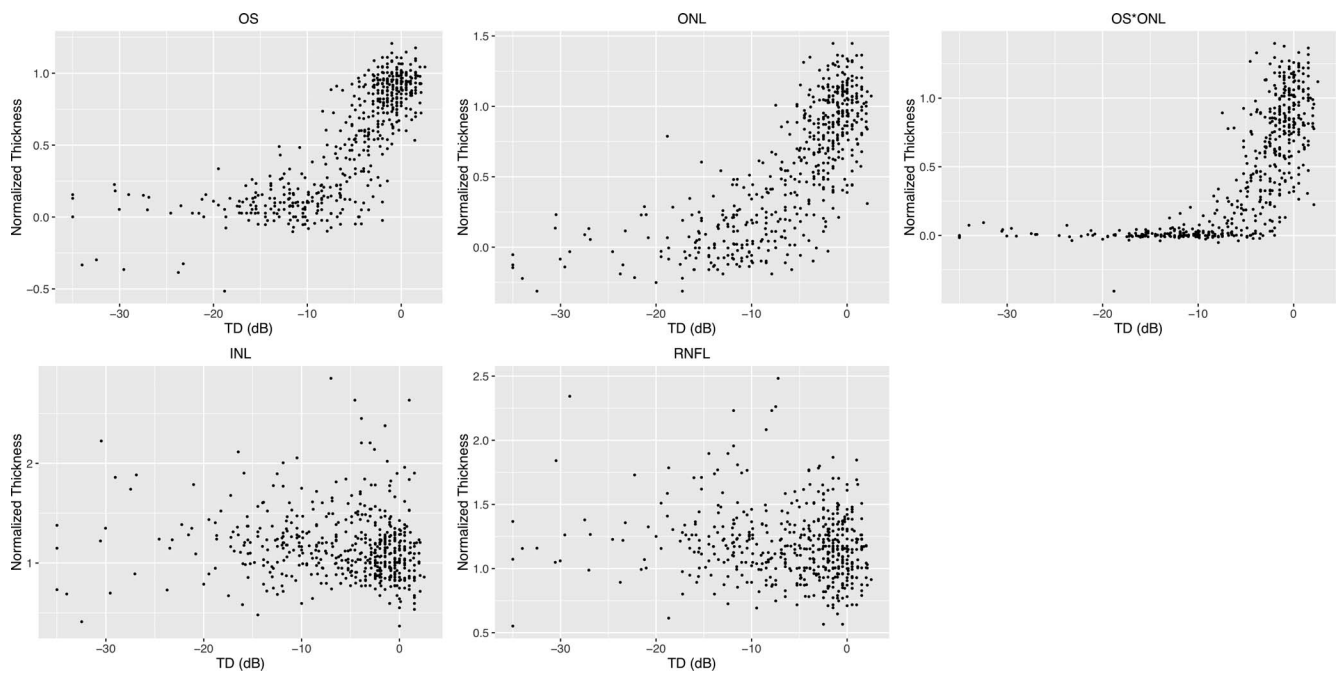


FIGURE 3. Plots of the normalized thickness of the OS, ONL, product of OS and ONL, INL, and RNFL as a function of TD (dB) at all test locations of all the 52 patients.

strongest correlation with the sensitivity was with the normalized OS thickness ($mR^2 = 0.525$, $P < 0.001$), followed by the product of the OS and ONL ($mR^2 = 0.420$, $P < 0.001$), ONL ($mR^2 = 0.416$, $P < 0.001$), and the INL ($mR^2 = 0.014$, $P = 0.044$). The thickness of the RNFL was not correlated with the sensitivity ($mR^2 = 0.005$, $P = 0.331$).

The results of the sensitivity more than 1 (1/L) were also analyzed, and there were no significant correlations between

the sensitivity and thickness for all the retinal thickness parameters ($P > 0.05$).

The results for the OS in Figure 4 are replotted in Figure 5 for the different eccentricities at the nasal or temporal hemispheres with a regression line for each cluster. Only the data with sensitivity of 1 (1/L) or less are shown. The linear relationship between the relative thickness and the relative sensitivity appears to exist at all eccentricities for both the nasal and temporal sides. Adding random slopes for each

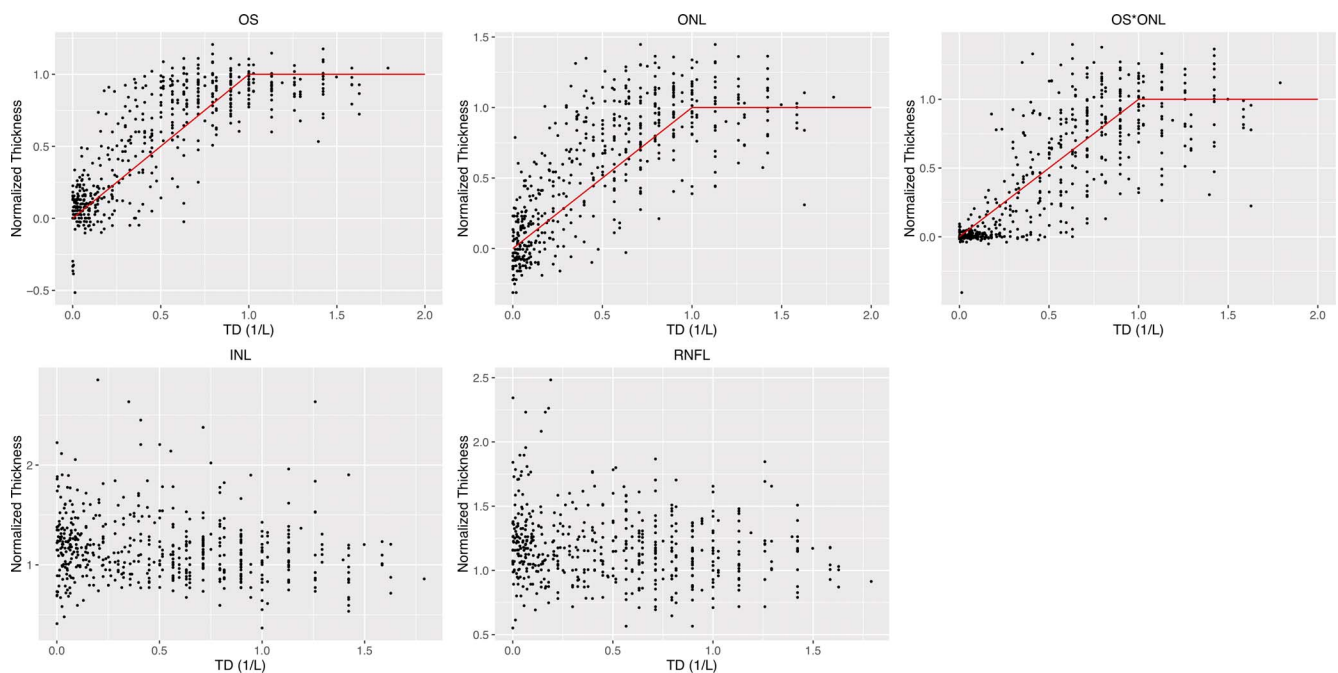


FIGURE 4. Plots of the normalized thickness of the OS, ONL, product of OS and ONL, INL, and RNFL as a function of TD (1/L) at all the test locations of all the 52 patients. The same data in Figure 3 are used with the conversion of dB to 1/L. The red line is the predicted change in the retinal thickness with a change in the visual field sensitivity.

TABLE. Sensitivity With Normalized Thickness of Retinal Layers. The Analysis was Performed With Only the Data With Retinal Sensitivities

Retinal Layers	Regression	mR ²	P Value
OS	0.191 + 0.772 × TD (1/L)	0.525	<0.001
ONL	0.207 + 0.780 × TD (1/L)	0.416	<0.001
OS × ONL	0.051 + 0.758 × TD (1/L)	0.420	<0.001
INL	1.219 - 0.126 × TD (1/L)	0.014	0.044
RNFL	1.217 - 0.063 × TD (1/L)	0.005	0.331

Linear mixed-models were used with one of the retinal thickness parameters as an outcome, TD (1/L) as fixed effects, and each patient ID and eccentricities as random effects.

eccentricity significantly improved the model fit ($P = 0.003$), which indicates that the slopes of the regression lines of OS at different eccentricities were not the same. The slopes of the OS length at different eccentricities were calculated by adding each random slope to the fixed slope (0.772; Table). They were 0.581 at 1°, 0.737 at 3°, 0.851 at 5°, 0.799 at 7°, and 0.889 at 9°. By testing the interaction between the eccentricities and sensitivities, we found out that the slope at 1° was statistically significantly less steep than that at 3°, 5°, and 9° ($P < 0.005$) but not at 7° ($P = 0.049$) with the Bonferroni correction. There was no significant difference between the other two eccentricities. The findings in the nasal or temporal locations did not have a significant interaction between the sensitivities ($P = 0.868$).

DISCUSSION

HFA has been extensively used to assess the central visual field changes of glaucoma patients.^{16,17} Using HFA and OCT, Hood et al.¹⁸ proposed a simple linear model to predict the relationship between the RNFL thickness and the retinal sensitivity in eyes with glaucoma. They reported that the reduction of the RNFL thickness was proportional to the decrease in the sensitivity.¹⁸ Interestingly, that relationship exists when the sensitivity is less than 1 (1/L), and there is no significant correlation between the two in healthy eyes.¹⁴

Rangaswamy et al.¹² examined whether this linear model can be applied to the relationship between photoreceptors and sensitivity in RP patients using the findings of the OCT and HFA 30-2. They verified that the thickness of photoreceptor layer decreased linearly with a reduction in retinal sensitivity. They also showed that the product of OS and ONL thicknesses was

correlated slightly better ($R^2 = 0.36$) with the sensitivity loss than the thickness of the OS alone ($R^2 = 0.30$). They suggested that this relationship was possibly because the ONL thickness represented the number of photoreceptors, and the OS length represented the quantal catch of the photoreceptors. Therefore, the product of them would be a better index of the quantum absorption than either alone.

There was another study done by Machida et al.¹⁹ to support these finding. They investigated the correlation of retinal function with the histology in rhodopsin transgenic rats.¹⁹ They found that the product of OS and ONL thickness had a strong linear correlation with the electroretinogram a-wave amplitude.

Our results are consistent with these earlier studies in that the thicknesses of the OS and ONL and the product of them decreased with a reduction in the visual field sensitivity. However, the strongest correlation with the sensitivity reduction was found in the OS thickness ($mR^2 = 0.525$), followed by the product of OS and ONL ($mR^2 = 0.420$). This could be because accurate ONL measurements were difficult to make due to the Henle fiber layer around the fovea. The thickness of Henle fiber layer in the OCT imaging is reported to depend on the entry position of the OCT beam through the pupil, and the layer is thinner in more peripheral areas than in the fovea.^{20,21} We used the HFA 10-2 findings while Rangaswamy et al.¹² used HFA 30-2. The beam entry position is generally displaced to some extent and focusing on the more central area might have produced greater variance in the ONL measurements. This should then lower the mR^2 of the ONL and the product of OS and ONL. On the other hand, the EZ and RPE are hyperreflective lines that can be easily distinguished in the OCT images, and the integrity of the EZ line has been described as an important marker of retinal function by numerous reports.^{11,22-24} These are the possible reasons for the OS thickness having the highest mR^2 . In addition, the statistical methods used in this study are different from those of the previous report with HFA 30-2; the past report used simple linear regression while we applied linear mixed-effects regression. We constructed linear mixed-models on the assumption that the data obtained from each subject or each eccentricity is not independent of each other. Actually, the slopes of the regression lines of the OS at different eccentricities were significantly different ($P = 0.003$). This might be due to the differences of the cone densities, which depend on the distance from the fovea. The cone density reduction at the most central area may precede the thinning of the OS, which could contribute to the less steep slope at 1°

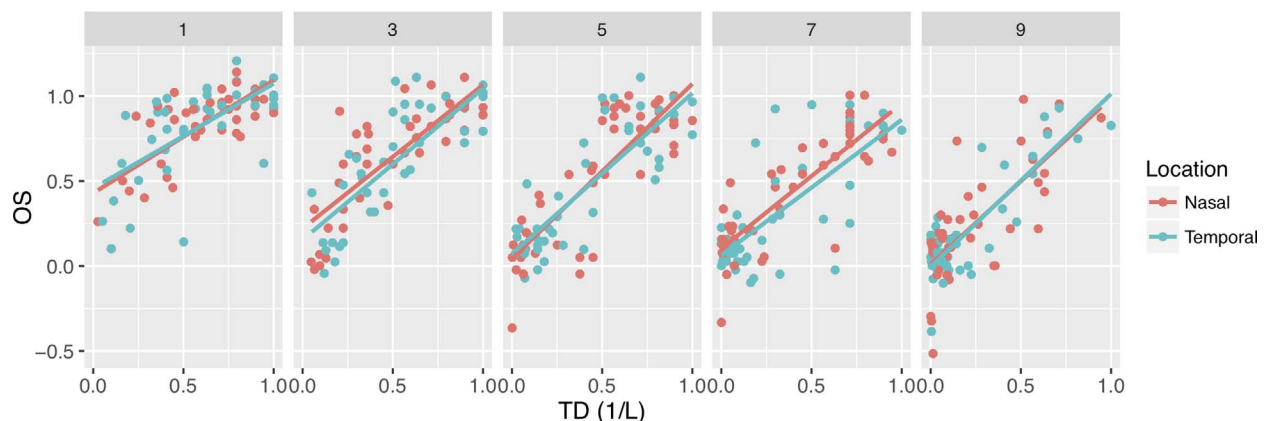


FIGURE 5. Plots of the normalized OS as a function of TD (1/L) for the different eccentricities for the different locations (*red* = nasal, *blue* = temporal) with a regression line for each cluster. Only the data with sensitivity less than or equal to 1 (1/L) are shown.

than most of the other eccentricities. Further investigation with adaptive optics fundus camera is needed.

Another possible explanation is that the difference of the slopes simply reflects the differences in the degree of damage to the retina. The more peripheral regions are usually more affected in RP, and the regression line may be steeper in the more severely damaged areas. This means that the relationship between the thickness and sensitivity is not completely linear. Investigating RP patients with MD less than -15 dB would help elucidate this matter.

We used mR^2 to assess how well the fixed effects of the model can explain the variance in the data, which is not the same as the conventional R^2 . The use of different statistical techniques may have contributed to the different results from the finding by Rangaswamy et al.¹²

As has been reported, the retina of RP patients is characterized by a thinning of the photoreceptors and the outer layers.^{25,26} In contrast, the inner layers thicken as the disease progresses.²⁵ Our results are consistent with these findings and showed that the INL and RNFL of the RP patients were significantly thicker than those of the controls. In addition, the thickness of the INL was negatively correlated with the sensitivity ($mR^2 = 0.014$, $P = 0.044$). However, the correlation was very weak so the INL thickness was not a good parameter to predict the visual field sensitivity loss. The RNFL thickness was not even correlated with the sensitivity reduction ($mR^2 = 0.005$, $P = 0.331$), which might suggest that the thickening of the RNFL could be affected by the global intraocular environment as well as by the local photoreceptor death. Although the pathophysiology of the inner retinal thickening is still unclear, some morphologic remodeling of the retina of RP including gliosis, cell body migration, and sprouting of ectopic processes may be responsible.²⁷ Because the status of the inner layer is critical for RP patients to receive treatments such as artificial or induced-pluripotent stem cell (iPSC)-derived retinas, further investigations of how the thickened inner retina affects the synapses with an implanted retina would be informative.

There are several limitations in this study. HFA10-2 may cause more measurement errors due to eye movements compared to a microperimeter.¹³ The device enables researchers to detect the exact location of the retina stimulated, and Birch et al.²⁸ showed its usefulness in a study with RP patients. Another limitation could be that the distance from the fovea was determined by only 30° horizontal scans of the SD-OCT and its built-in caliper. It is possible that each location (1°–9°) on the OCT scans does not accurately correspond to that of HFA10-2. Further analysis by microperimetry is needed.

In conclusion, we evaluated the relationship between the thicknesses of the retinal layers and visual field sensitivities. The thickness of OS, ONL, and the product of the OS and ONL decreased with a decrease in retinal sensitivities, but the thickness of the INL increased as the sensitivity decreased. The RNFL of the RP patients was thicker than that of the controls, but it was not significantly correlated with the sensitivity loss. We found that the thickness of OS is a better parameter to reflect the retinal function than the product of OS and ONL in the OCT imaging.

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