The Association between Visual Acuity and Central Retinal Thickness in Retinitis Pigmentosa

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PURPOSE. To determine whether visual acuity is related to central retinal thickness in patients with retinitis pigmentosa.

METHODS. Visual acuities were measured with Early Treatment Diabetic Retinopathy Study (ETDRS) charts and optical coherence tomography (OCT) was used to calculate retinal thicknesses and grade third high-reflectance band in 162 patients with the typical forms of retinitis pigmentosa who had Snellen visual acuities of 20/20 to 20/200, minimal to no cataracts, and no visible macular cysts. Sixty-five patients were retested within 2 months to estimate the intervisit variability of retinal thickness measurements.

RESULTS. ETDRS acuity was best related to retinal thickness measured at fixation and as the average value over the central 1 mm by a second-order polynomial (r² = 0.38 and P < 0.001 in both cases). Acuity was maximal for intermediate retinal thickness and appeared to decline for both lesser and greater retinal thicknesses. By linear regression, the decline in acuity for decreasing retinal thickness was steeper in eyes with an absent third high-reflectance band than for eyes with a partially distinct band. No decline was noted in eyes with an intact band. Assessment of intervisit variability of retinal thickness measurements showed 98% confidence limits of ±17 μm at fixation and ±11 μm for the central 1 mm.

CONCLUSIONS. Both retinal thinning (due to cell loss) and retinal thickening (due to presumed edema) appear to be associated with lower visual acuity in patients with typical retinitis pigmentosa. The definition of the OCT third high-reflectance band may help to predict which patients are more likely to lose visual acuity as retinal thickness declines. An increase or decrease in retinal thickness of more than 17 μm at fixation or 11 μm over the central 1 mm at follow-up can be considered a significant (P < 0.01) change in these patients. (Invest Ophtalmol Vis Sci. 2005;46:3349–3354) DOI:10.1167/iovs.04-1383

Optical coherence tomography (OCT) is a rapid, noninvasive method for obtaining cross-sectional images of the retina based on differential near-infrared light reflection at optical interfaces. OCT has shown progressive thinning of the retina and photoreceptor layer of rd/s/rd mice and of rd/rd/+ transgenic mice with photoreceptor degeneration. In the rd/s/rd mice the retinal thickness and photoreceptor layer thickness measured by OCT declined by about the same amount, suggesting that loss of photoreceptors is responsible for change in both thickness measurements. In the rd/rd/+ mice the retinal thickness quantified by OCT declined over time in parallel with retinal thickness measured by light microscopy, lending validity to the use of OCT to determine the stage of disease.

OCT has also been used to demonstrate retinal degenerative changes in patients with retinitis pigmentosa and allied diseases. A study of patients with typical retinitis pigmentosa or Usher syndrome found that macular pigment density measured psychophysically was significantly related to both central retinal thickness measured by OCT and to visual acuity, raising the possibility that some association also exists between central retinal thickness and visual acuity in this population. If retinal thickness measured by OCT were shown to be a surrogate measure of visual acuity in patients with retinitis pigmentosa, then it would have the potential of being an objective outcome measure in clinical trials of treatments designed to slow or halt loss of visual acuity.

The present study was undertaken to determine whether visual acuity is related to central retinal thickness as ascertained by OCT in a large cohort of patients with retinitis pigmentosa. We also quantified the intervisit variability of OCT thickness measurements in these patients to determine when change should be considered significant.

METHODS

Patients

The protocol was approved by the Institutional Review Boards of the Massachusetts Eye and Ear Infirmary and Harvard Medical School and conformed to the tenets of the Declaration of Helsinki and HIPAA (Health Insurance Portability and Accountability Act) regulations. Informed consent was obtained from all patients and normal control subjects in this study. The study population included 191 patients with typical forms of retinitis pigmentosa who had best corrected Snellen visual acuities of 20/20 to 20/200 and minimal to no cataracts. The patients had elevated dark adaptation thresholds, reduced and delayed full-field electroretinograms, retinal arteriolar narrowing, and, in most cases, bone spicule pigmentation around the periphery. Eight additional patients had also been tested but are not considered in this report, because their OCT images either were of insufficient intensity for retinal thicknesses to be quantified or could not be reliably centered on the fovea because of nystagmus.

Visual Acuity Measurements

In addition to Snellen visual acuity, we measured Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity with transilluminated charts. The ETDRS charts contain five letters of comparable difficulty on each line, and letters on each lower line decrease in size by 0.1 log unit (21%). Visual acuity was scored as the number of letters correctly read, each letter being valued at 0.02 log unit.

OCT Measurements

We used a high-resolution optical coherence tomographer (Stratus model 3000; Carl Zeiss Meditec, Dublin, CA) with software version 3.0 to measure retinal thickness and assess retinal structure after pupillary dilatation.
dilation. With this third-generation instrument (OCT3) we recorded from each eye six 6-mm (~20°) line scans in a radial spoke pattern intersecting at fixation. Each tomogram consisted of 512 A-scans, each A-scan comprising 1024 data points spanning a 2-mm depth. The examiner (MAS) asked each study participant to look at the internal fixation spot, which was kept in its central location, and confirmed that the image of the macula appeared to be approximately centered with respect to the spot’s image on the fundus monitor. He then used the OCT software to position on the screen a vertical line that designated the center of the scan image. During each scan, the examiner checked that the fovea in the scan image was centered with respect to the vertical line. If the foveal center was shifted to the left or right in a scan image, he instructed the patient on how to correct the error and saved the scan when the fovea was centered. We found that 28 (15%) of the 191 patients had macular cysts in both eyes by OCT and that one patient had cysts in the only eye with OCT recordings. The cysts ranged from rare discrete vacuoles as small as 50 μm in height at the level of the inner nuclear layer to multiple vacuoles of more than 400 μm in height that distorted the cytoarchitecture. We excluded these 29 patients, leaving 162 patients (91 men and 71 women; aged 18–68 years) who had one or both eyes that could be used for analysis. Twenty-two normal volunteers (13 men and 9 women, aged 25–56 years) served as control subjects. Each OCT radial scan group was analyzed as a retinal thickness map by the automated OCT software, which identified the vitreoretinal interface and retinal pigment epithelium (RPE)/choriocapillaris as regions of high reflectance. The software is designed to quantify retinal thickness as the separation of these boundaries in micrometers at fixation (the intersection of the radial lines) and as the average value for each of nine different areas, including the central 1 mm. In this report, we present retinal thickness data for fixation and for the central 1 mm average. The software also generated a two-dimensional pseudo-color map of retinal thickness for each eye, which we used to confirm that the foveal minimum was centered.

A third band of high reflectance has been reported to be visible in the tomograms of normal eyes and is selected by the OCT3 software in those eyes as the outer boundary of the retina. This third high-reflectance band has been hypothesized to represent the junction between the photoreceptor inner and outer segments. If this were true, then measurements made with respect to this band would underestimate central retinal thickness. We confirmed the presence of this third high-reflectance band in the tomograms from our 22 normal control subjects using the normalize + align image-processing protocol, although in 2 eyes (4.5%) the band appeared to be less distinct than in the other 42 eyes. One of us (MAS), who was masked to ETDRS acuity and retinal thicknesses, viewed the patients’ tomograms with the normalize + align image processing protocol and used a three-level indicator variable to code the third high-reflectance band within the central 1 mm as absent, 1; partially distinct, 2; or intact, 3 so as to be able to assess whether visual acuity or retinal thickness varied with band definition.

### Repeat OCT Measurements

We assessed the intervisit variability of retinal thickness measurements in the first 65 patients who were invited and able to return for follow-up within 2 months of their original visits and were without macular cysts at their first visit. These patients appear to be a representative sample, because at their first visit they did not differ significantly from the remaining 97 patients without macular cysts with respect to mean age (P = 0.41), gender distribution (P = 0.42), mean ETDRS acuity (P = 0.14), mean spherical equivalent refractive error (P = 0.19), mean retinal thickness at fixation (P = 0.59), or mean retinal thickness averaged over the central 1 mm (P = 0.75). The two groups also were not significantly different in mean acuity, mean refractive error, mean retinal thickness at fixation, or mean retinal thickness over the central 1 mm, after adjustment for age and gender (P = 0.14, P = 0.20, P = 0.53, and P = 0.69, respectively).

### Statistical Analyses

Data for each patient with retinitis pigmentosa and normal control subject used for analysis represented the test results from both eyes or for a single eye if results for the other eye were unavailable or censored (e.g., because of macular cysts in that eye). We used commercial software (PROC MIXED of SAS, ver. 6.12; SAS Institute, Cary, NC) for all eye-level analyses because of its capacity to handle unbalanced data (i.e., data missing for one eye) and because it can take into account the between-eyes intraclass correlation. The program uses maximum-likelihood estimation and does not directly calculate r² as a measure of goodness of fit. To estimate r² when regressing ETDRS acuity on retinal thickness, we obtained an output of the ETDRS acuities predicted by a given model, evaluated 1 – RSS/TSS for OD and OS (where RSS is the residual sum of squares and TSS is the total sum of squares), and then calculated the average value for the two eyes. We used another program (JMP, ver. 3.2; SAS Institute) for person-level analyses (e.g., age by category of repeated visit).

To quantify intervisit variability for retinal thickness measured at fixation and over the central 1 mm based on the patients who returned, we first subtracted the thickness at the first visit from the corresponding value at the second visit in each eye. Using the extreme Studentized deviate test, we next identified and excluded statistical outliers from the distributions of difference scores. Based on the remaining data, which approximated normal distributions, we then calculated the standard deviation of the difference scores for fixation and for the central 1 mm and multiplied these values by 2.326 to estimate the upper and lower 98% confidence limits.

### Results

#### Representative Tomograms

Figure 1 shows representative tomograms from a normal control subject, a patient with retinitis pigmentosa and good visual acuities, and a patient with retinitis pigmentosa and poor visual acuities. The tomograms at the top from the normal control subject show the low-reflectance outer nuclear layer peaking in thickness in the center beneath the foveal depression and visible from edge to edge. A third high-reflectance band is distinguishable just above a thicker high-reflectance RPE–choriocapillaris complex. The third high-reflectance band is slightly convex in the center, possibly reflecting longer cone outer segments in this region. The middle tomograms from a patient with retinitis pigmentosa and a Snellen visual acuity of 20/20 in each eye have a normal appearance in the center (with an intact third high-reflectance band) but show loss of the outer nuclear layer more peripherally. The tomograms at the bottom from a patient with a Snellen visual acuity of 20/200 OD and 20/80 OS show widespread loss of the outer nuclear layer with apparent thinning of the inner retina.

#### Mean Retinal Thicknesses

The 162 patients with retinitis pigmentosa had retinal thicknesses (mean ± SE) of 170 ± 3 μm at fixation and 204 ± 3 μm averaged over the central 1 mm. Thirty-one of these patients had a Snellen visual acuity of 20/20 in both eyes and retinal thicknesses of 185 ± 5 μm at fixation and 220 ± 5 μm in the central 1 mm. The corresponding thicknesses in the 22 normal control subjects were 167 ± 5 and 213 ± 5 μm, respectively. The age- and gender-adjusted differences in mean retinal thicknesses between the patients with normal acuities and the normal control subjects (i.e., patient mean –normal control mean), were 21 μm at fixation (P = 0.005) and 10 μm in the central 1 mm (P = 0.17).

#### Regression of Visual Acuity on Retinal Thickness

By linear regression, ETDRS acuity of the patients declined by 20/20 in each eye have a normal appearance in the center...
fixation ($r^2 = 0.27$, $P < 0.001$) and by 1.3 letters for each $10\mu m$ decrease in retinal thickness averaged over the central 1 mm ($r^2 = 0.32$, $P < 0.001$). These results are illustrated in Figures 2 and 3, respectively. Because the residual error for each of these linear models could be fitted to retinal thickness by a second-order polynomial in which the quadratic term was significant ($P < 0.001$), we repeated the regressions of ETDRS acuity on retinal thickness using a second-order polynomial. Both second-order models predicted acuity from retinal thickness with $r^2 = 0.38$ ($P < 0.001$). The predicted curves peak at an ETDRS acuity of 54 letters (Snellen equivalent = 20/25) for a retinal thickness of 218 $\mu m$ at fixation (Fig. 2) and 254 $\mu m$ averaged over the central 1 mm (Fig. 3), and both curves decline toward lower acuities to the left and right of the peak. For example, the curve based on retinal thickness measured at fixation (Fig. 2) shows that ETDRS acuity declines to 10 letters (Snellen equivalent, 20/200) for a retinal thickness of 34 $\mu m$ and to 43 letters (Snellen equivalent, 20/42) for a retinal thickness of 309 $\mu m$. Because ETDRS acuity is based on a logarithmic scale, we also evaluated the regression of ETDRS acuity on log10 retinal thickness. This model provided fits with $r^2 = 0.34$ ($P < 0.001$) for retinal thickness measured at fixation (Fig. 2) and $r^2 = 0.36$ ($P < 0.001$) for retinal thickness measured over the central 1 mm (Fig. 3), with these $r^2$ values falling between those for the linear and second-order polynomial models.
Visual Acuity and Retinal Thickness versus Definition of the Third High-Reflectance Band

Eighty-five (29.5%) of the eyes of the patients had an absent third high-reflectance band, 163 (56.6%) had a partially distinct band, and 40 (13.9%) had an intact band. Figures 2 and 3 illustrate that ETDRS acuity and retinal thickness varied by band definition, as the data based on eyes with less-defined bands tend to congregate at lower acuities and lower retinal thicknesses than the data based on eyes with better-defined bands. Table 1 shows that mean ETDRS acuity, retinal thickness at fixation, and retinal thickness averaged over the central 1 mm, adjusted for age and gender, all increased significantly with increasing band definition.

Figures 2 and 3 also show that ETDRS acuity was most related to retinal thickness for eyes with an absent third high-reflectance band and least related to retinal thickness for eyes with an intact band. Based on a multiple linear regression model including band definition, retinal thickness, their cross product, age, and gender as independent variables, we found from the cross-product term that the mean slope relating ETDRS acuity to retinal thickness varied significantly by band definition (Table 2; $P < 0.001$). For both fixation and the central 1 mm, the slope for eyes with an absent band was approximately four times that for eyes with a partially distinct band, whereas the slope for eyes with an intact band was not significantly different from zero. We also found with this model that mean ETDRS acuity varied significantly with band definition independent of retinal thickness. For example, by statistically adjusting for retinal thickness at fixation, we found that mean ETDRS acuity ranged from 48.2 letters for an absent band to 55.6 letters for an intact band ($P < 0.001$), although this range was less than that shown in Table 1 (i.e., without adjusting for retinal thickness).

For the 31 patients with a normal Snellen acuity in both eyes, 8.2% of eyes had an absent third high-reflectance band, 68.8% had a partially distinct band, and 23.0% had an intact band. Because only 23% of these eyes, compared with 95.5% of the normal control eyes (see the Methods section), had an intact band, we repeated our comparison of retinal thickness in patients versus control subjects, including only eyes from both groups with an intact band to remove any effect of band definition on the measurement of retinal thickness. These subset analyses showed that mean retinal thickness in the patients ($n = 12$) was 41 μm greater at fixation ($P < 0.001$) and 34 μm greater averaged over the central 1 mm ($P < 0.001$) than the corresponding thicknesses in the normal control subjects ($n = 22$).

Intervisit Variability of Retinal Thickness Measurements

Among the 65 patients who returned within 2 months for repeat OCT, we excluded the intervisit data of 1 patient who had macular cysts OU in her tomograms at the second visit that were not visible at the first visit. In each of three patients, we also excluded the data of one eye that was a statistical outlier for retinal thickness differences at fixation and also the data for one of these three eyes that was a statistical outlier for retinal thickness at fixation, and retinal thickness averaged over the central 1 mm.

<table>
<thead>
<tr>
<th>Third HRB Category*</th>
<th>ETDRS Acuity (Letters)</th>
<th>Retinal Thickness at Fixation (μm)</th>
<th>Retinal Thickness over Central 1 mm (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44.2 ± 0.9</td>
<td>151.0 ± 3.7</td>
<td>191.6 ± 3.4</td>
</tr>
<tr>
<td>2</td>
<td>50.8 ± 0.8‡</td>
<td>173.0 ± 3.0‡</td>
<td>204.7 ± 3.0‡</td>
</tr>
<tr>
<td>3</td>
<td>55.1 ± 1.4‡</td>
<td>191.0 ± 5.1†</td>
<td>220.3 ± 4.4‡</td>
</tr>
</tbody>
</table>

Acuity and retinal thickness are expressed as the mean ± SE adjusted for age and gender by PROC MIXED of SAS (Cary, NC).

* The third high-reflectance band (HRB), lying just above the RPE high-reflectance band, was coded as 1 (absent), 2 (partially distinct), or 3 (intact).

‡ The difference between the designated mean value and the mean value in the line above was significant at $P = 0.01$ with the Tukey-Kramer adjustment for multiple comparisons.

§ The difference between the designated mean value and the mean value in the line above was significant at $P = 0.001$ with the Tukey-Kramer adjustment for multiple comparisons.
thickness differences over the central 1 mm. Based on the remaining data, we found that the distributions of difference scores (i.e., second visit minus first visit) were approximately normal, with a mean of $0.4 \pm 7.2\, \mu m$ (SD) for retinal thickness at fixation and a mean of $-0.1 \pm 4.8\, \mu m$ for retinal thickness averaged over the central 1 mm. These standard deviations correspond to $98\%$ confidence limits of $\pm 16.7$ and $\pm 11.2\, \mu m$, respectively. The absolute values of the difference scores for fixation and the central 1 mm, converted from a skewed distribution to normalized ranks by a probit transformation, were not significantly related to retinal thickness at the first visit. The standard deviations of difference scores for retinal thicknesses averaged over the central 1 mm from 58 to 296 $\mu m$, and retinal thicknesses averaged over the central 1 mm at fixation from 41 to 273 $\mu m$, respectively.

## DISCUSSION

The present study of 162 patients with typical forms of retinitis pigmentosa shows that ETDRS acuity was significantly related to retinal thickness measured by OCT at fixation or as the average thickness over the central 1 mm by each of three different models: a linear function of retinal thickness, a logarithmic function (i.e., log retinal thickness), and a second-order polynomial (i.e., both linear and quadratic terms of retinal thickness). The second-order polynomial provided the best fits, accounting for both a marked decline in acuity for small retinal thicknesses and an apparent lesser decline in acuity for large retinal thicknesses. The logarithmic function provided better fits than the linear model, both models assuming that the relationship between acuity and retinal thickness was monotonic.

The marked decline in visual acuity for small retinal thicknesses, seen in all three models, undoubtedly reflects cell loss. A previous investigation suggested that the OCT third high-reflectance band may designate the photoreceptor inner segment–outer segment junction, with the implication that its prominence would be related to outer segment length and, thus, to visual acuity. Two earlier studies involving the use of OCT reported findings that raise the possibility that visual acuity in retinitis pigmentosa is related to the definition of the third high-reflectance band in the eyes of our patients with retinitis pigmentosa (see Table 1) outweighed the measurement bias. It will be of interest to see whether those patients whose retinas appeared to be thickened are at higher risk than others for development of visible macular cysts in the future.

The apparent, lesser decline in acuity for large retinal thicknesses could be indicative of edematous retinal thinning, even though we excluded tomograms with visible macular cysts. Retinal thinning may also occur in the absence of visual acuity loss, since our patients with a normal acuity in both eyes had a significantly greater mean retinal thickness at fixation than our normal control subjects. Because this difference could have been biased by the tendency of the OCT software to measure retinal thickness from the vitreoretinal interface to the third high-reflectance band in the eyes of our normal control subjects and to the RPE–choriocapillaris layer in the eyes of our patients (most of whom lacked an intact third high-reflectance band), we repeated the comparisons including only eyes with an intact third high-reflectance band. We found that patients in this subset had a significantly greater mean retinal thickness than did the control subjects, both at fixation and over the central 1 mm, differences that were larger than those found before limiting the analyses to eyes with an intact third high-reflectance band. Evidently, the positive relationship between retinal thickness and band definition in our patients with retinitis pigmentosa (see Table 1) outweighed the measurement bias. It will be of interest to see whether those patients whose retinas appeared to be thickened are at higher risk than others for development of visible macular cysts in the future.

The standard deviation of difference scores for retinal thickness measurements obtained at two visits within 2 months based on a subset of our patients with retinitis pigmentosa was $7.2\, \mu m$ at fixation and $4.8\, \mu m$ averaged over the central 1 mm. Each of these values was less than $2\, \mu m$ larger than the corresponding values ($5.6$ and $3.3\, \mu m$) based on a group of 10 normal subjects. We estimated the $98\%$ confidence limits for a given patient’s intervisit variability (rounded to the nearest integer) to be $\pm 17\, \mu m$ at fixation and $\pm 11\, \mu m$ for the central 1 mm. This means that an increase or decrease in retinal thickness of more than these values over follow-up should each occur by chance less than $1\%$ of the time in OCT3 measurements of patients with typical forms of retinitis pigmentosa without macular cysts. Because the intervisit variability was unrelated to visual acuity or to retinal thickness measured at the first visit, these figures should be applicable to patients whose visual acuities and retinal thicknesses are encompassed by those included in the intervisit variability analysis (i.e., Snellen visual acuities from 20/20 to 20/200, retinal thicknesses at fixation from 41 to 273 $\mu m$, and retinal thicknesses averaged over the central 1 mm from 58 to 296 $\mu m$).
By linear regression, we found that a 1.1-letter decline in ETDRS acuity corresponded to a 10-µm loss of retinal thickness at fixation based on our entire cohort of 162 patients with retinitis pigmentosa. We have reported that untreated patients with typical forms of retinitis pigmentosa lose 0.9 letter/year on the ETDRS chart, and we therefore project that the natural course of loss of retinal thickness at fixation would average 8.2 µm/year (i.e., 0.9 letter × 10 µm/1.1 letters). If a treatment were to cut this rate of retinal thinning in half to 4.1 µm/year, then based on the 38-µm SD in retinal thickness at fixation observed in the present study, we can estimate that for patients with visual acuities of 20/200 or better, a sample size of 85 patients/group would be needed to prove efficacy by comparing a treated group with a control group for change in mean retinal thickness with a two-tailed test at a 5% level of significance and power of 80% over 4 years of follow-up. OCT measurements of retinal thickness would complement visual acuity measurements by being an objective assessment of retinal architecture spanning the fovea.

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References


