Logarithmic Transformation of Spectral-Domain Optical Coherence Tomography Data in Uveitis-Associated Macular Edema

John F. Payne,1 Beau B. Bruce,1,2 Lyndon B. K. Lee,1 and Steven Yeh1

PURPOSE. To determine the utility of logarithmic transformation of spectral-domain optical coherence tomography (logSD-OCT) retinal thickness data for assessment of clinically meaningful changes in uveitis-associated macular edema.

METHODS. Patients with noninfectious uveitis-associated macular edema at our institution between August 2010 and March 2011 were identified. Only those with SD-OCT imaging were included. The clinical diagnoses, visual acuities, and central subfield thickness (CST) measurements were recorded. Logarithmic transformation of the retinal thickness was performed and frequency histograms plotted. A linear mixed-effects model of the logarithm minimum angle of resolution (logMAR) visual acuity on logSD-OCT was created to account for Within-patient correlation among visits and between eyes.

RESULTS. A total of 98 SD-OCT images from 34 patients were analyzed. The mean age at examination was 40 years (range, 11–69 years). Anatomic diagnoses included anterior/intermediate uveitis (23%), intermediate uveitis (21%), posterior uveitis (12%), and panuveitis (44%). LogSD-OCT data provided a more normal distribution than standard CST. Skewness and kurtosis of CST data were 1.04 and 0.37, respectively, and skewness and kurtosis of logSD-OCT data were 0.40 and −0.48, respectively. There was a positive correlation between logSD-OCT and logMAR visual acuity. Specifically, for each 0.1-unit increase in logSD-OCT, the logMAR visual acuities increased (worsened) by 0.082 units (95% CI: 0.057–0.107, P < 0.001).

CONCLUSIONS. Logarithmic transformation of SD-OCT measurements provided a more normal distribution and positively correlated with logMAR visual acuity. This transformation of retinal thickness may be valuable for assessing clinically significant changes in SD-OCT measurements in future uveitis studies.

Optical coherence tomography (OCT) technology has revolutionized the field of ophthalmology and is commonly used today to diagnose and assess treatment effects of various conditions of the retina, optic nerve, and anterior segment. The axial resolution of most spectral-domain OCT (SD-OCT) instruments approaches 5 μm, which allows for detailed characterization of specific retinal layers and provides insight into structural variation in pathologic processes. Although many clinical trials use OCT data as outcome measures, there has been little information published about the possible ways to analyze OCT numerical data, and in which situations one analysis method might be preferred to another.

Recently, Ferris et al.4 reported the clinical usefulness of transforming retinal thickness measurements into a logarithmic format in a subset of patients from the Diabetic Retinopathy Clinical Research Network. The authors concluded that this logarithmic transformation of the retinal thickness measurements from time-domain OCT (logOCT) was advantageous because it provided a more normal distribution of measurements and because changes in logOCT were more associated with clinical importance than the absolute change in micrometers. Furthermore, they concluded that logOCT was relevant to the assessment of clinically meaningful changes in retinal thickness, just as the logMAR visual acuity scale has helped to assess clinically meaningful changes in visual acuity. Although this report provides a possible methodology for evaluating retinal thickness measurements in clinical research, its potential utility for other disease conditions warrants further study. The purpose of this study was to evaluate the utility of logarithmic transformation of spectral-domain OCT (logSD-OCT) in evaluating clinically relevant changes in macular edema secondary to uveitis. In this report, we describe our assessment of logarithmic transformation of SD-OCT data, its relationship to logMAR visual acuity changes, and the potential clinical utility of this conversion tool in uveitis-associated macular edema.

METHODS

The Emory University School of Medicine Institutional Review Board approved this study, and all work was conducted in accordance with Health Insurance Portability and Accountability Act regulations and complied with the Declaration of Helsinki. This is a retrospective chart review of patients with noninfectious uveitis-associated macular edema at the Emory Eye Center who were evaluated between August 2010 and March 2011. Only those who underwent SD-OCT imaging were included for analysis. Exclusion criteria included patients with subfoveal fibrosis or retinal pigment epithelial atrophy and those with optic disc edema.

The anatomic locations of uveitis, according to Standardization of Uveitis Nomenclature criteria, and Snellen visual acuities were recorded. All patients underwent SD-OCT imaging with the Cirrus-HD OCT-4000 system; Carl Zeiss Meditec; Dublin, CA). Topographic surface maps were constructed with the automated software algorithms and displayed with numeric averages of the thickness measurements for each of the nine map sectors as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS).5 The central subfield thickness (CST) was recorded for each patient.
Logarithmic transformation of the CST was calculated by taking the log base 10 of the ratio of CST divided by 250 and rounding to the nearest hundredth, according to the following formula:

\[ \log_{10}(\text{CST}/250) \]

Frequency histograms were plotted for CST and logSD-OCT, and skewness and kurtosis of both data sets were determined. A linear mixed-effects model of the logarithm of the minimum angle of resolution (logMAR) visual acuity on logSD-OCT was created to account for within-patient correlation among visits and between eyes. R: A language and environment for statistical computing (ver. 2.11.1; R Foundation for Statistical Computing, Vienna Austria, http://www.R-project.org) was used for linear mixed-effects modeling.

RESULTS
A total of 98 SD-OCT images from 34 patients were analyzed. Eight male patients and 26 female patients were included, and the mean age at examination was 40 years (range, 11–69 years). Anatomic diagnoses included anterior/intermediate uveitis (23%), intermediate uveitis (21%), posterior uveitis (12%), and panuveitis (44%).

LogSD-OCT Scale
A scale for logSD-OCT was created by assuming a normal CST of 250 μm (Table 1). This table shows that a three-step change on the logSD-OCT scale is equivalent to either doubling or halving of the CST. The logOCT score, which was first created by Ferris et al., is always one step greater than the logSD-OCT score. The reason for this 0.1-unit shift is the increase in baseline CST as measured by the manufacturer’s software on currently marketed SD-OCT machines (i.e., Cirrus; Carl Zeiss Meditec, Dublin, CA, and Spectralis HRA OCT; Heidelberg Engineering, Heidelberg, Germany). The logSD-OCT scale is analogous to the logMAR scale, which has been used extensively in clinical research.

Frequency Histograms, Skewness, and Kurtosis
The frequency distributions of both CST data and logSD-OCT data are shown in Figure 1. Logarithmic transformation of SD-OCT data provided a more normal distribution than CST.

Skewness and kurtosis of CST data were 1.04 and 0.37, respectively; whereas skewness and kurtosis of logSD-OCT data were 0.40 and −0.48, respectively.

LogSD-OCT and LogMAR Visual Acuity Correlation
A linear mixed-effects model was used to assess correlation between logSD-OCT thickness and logMAR visual acuity, accounting for multiple measurements on each eye of individual patients. There was a significant positive correlation between logSD-OCT and logMAR visual acuity. Figure 2 graphically displays the positive correlation between logSD-OCT and logMAR visual acuity for individual eyes of patients with four or more measurements (to allow for adequate degrees of freedom for plotting). Overall, for each 0.1-unit increase in the logSD-OCT the logMAR visual acuities increased (worsened) by 0.082 units (95% CI: 0.057–0.107, \( P < 0.001 \)). Figure 3 displays the representative SD-OCT images, as well as the logSD-OCT and logMAR visual acuity data for two eyes from two different patients in this study. In both of these examples, there is a positive correlation between logSD-OCT and logMAR visual acuity.

DISCUSSION
The purpose of this study was to use logarithmic transformation of SD-OCT retinal thickness measurements to assess cystoid macular edema secondary to uveitis. This statistical transformation provided a more normal distribution and also positively correlated with logMAR visual acuity. Using a mixed linear effects model, we were able to account for intra- and interpatient correlations and identified a significant relationship between logSD-OCT and logMAR visual acuity.
numerous clinical trials have used logMAR visual acuity to compare treatment effects, logSD-OCT has potential in retinal and uveitis clinical trials where the assessment of clinically meaningful changes in retinal thickness is particularly relevant. As Ferris et al.4 noted, debate over what constitutes a clinical significant change in logSD-OCT is likely. Nonetheless, there are statistical advantages of using logSD-OCT over standard CST measurements.

One major benefit of the logarithmic transformation is that it provides a more normal distribution of retinal thickness measurements across a study population. When plotting measurements on the logSD-OCT scale, an assumption of normal retinal thickness is required to calibrate the 0 on the scale. This same assumption was made for logMAR visual acuity when logMAR 0.0 was made equivalent to Snellen visual acuity of 20/20. When considering normal central retinal thickness, several studies have reported that measurements vary depending on the type of OCT machine used.1,6,7 These differences occur because the different machines have varying outer retinal boundaries for their measurements. Specifically, the Stratus time-domain OCT (Carl Zeiss Meditec, Inc.) measures retinal thickness to the inner segment/outer segment (IS/OS) junction of photoreceptors, whereas the Cirrus HD-OCT (Carl Zeiss Meditec, Inc.) and RTVue-100 (Optovue, Fremont, CA) include the outer segments. These measures more closely approach the thickness from inner retina to retinal pigment epithelium.1 The outer boundary of the 3D OCT-1000 (Topcon America, Oakland, NJ) includes the photoreceptor outer segment tips, which is between the RPE and the IS/OS junction.1

A recent study comparing retinal thickness measurements in normal subjects on five different SD-OCT instruments showed that the overall mean central retinal thickness for all five machines was 260 μm.6 Another study comparing three SD-OCT instruments showed that mean central retinal thickness measurements in normal subjects ranged between 227 and 267 μm.1 Legaretta et al.7 also reported that central retinal thickness measurements on the Cirrus HD-OCT system were approximately 50 μm greater than those on the time-domain Stratus OCT system. Considering that Ferris et al.4 used 200 μm as an estimation of normal when converting to logOCT, it is reasonable to assume 250 μm as the normal retinal thickness for calculating logSD-OCT. One recent study assessing the treatment effect of laser photocoagulation for diabetic macular edema used logarithmic transformation of SD-OCT measurements, but assumed 200 μm as normal retinal thickness.8 Although the precise absolute number for central retinal thickness may differ between populations and vary slightly between SD-OCT machines, 250 μm is a reasonable approximation for normal retinal thickness when absolute values of logSD-OCT are calculated based on currently available SD-OCT measurement algorithms.

Moreover, the principal advantage of using logSD-OCT is that a difference identified by logSD-OCT is a quantifiable and clinically meaningful measure of improvement or worsening of
retinal thickness after an intervention across an entire study population, regardless of baseline retinal thickness. The following mathematical formula illustrates how the baseline retinal thickness (b) is irrelevant when measuring the change in retinal thickness (t) for a given individual, assuming that the patient is measured on the same OCT machine across two time points (t1 and t2).

\[ \log(t_1/b) - \log(t_2/b) = \log(t_1/t_2) \]

One theoretical advantage of this key principle, because the baseline retinal thickness is irrelevant when evaluating change in logSD-OCT, is that different OCT machines (i.e., TD-OCT and SD-OCT) may be used to measure retinal thickness, and the difference in logOCT or logSD-OCT calculations would be equivalent. Provided that the same OCT machine and settings are used for a given patient, transformation of retinal thickness data into a logarithmic format would allow clinicians to compare clinically meaningful changes for patients across multiple OCT machines, which is extremely valuable for multicenter trials in which various OCT machines may be used.

In addition, the logarithmic transformation provides an improved assessment of clinically meaningful changes in retinal thickness instead of absolute values. For example, a 50-μm reduction in central retinal thickness is likely to be clinically significant if a patient has a baseline retinal thickness of 300 μm but may be less relevant if the baseline retinal thickness is 500 μm. By using a given change in logSD-OCT as a clinically significant threshold (e.g., 0.2 logSD-OCT change from baseline), patients with thicker baseline retinal thickness measurements will need to show a greater absolute reduction in thickness compared with those with thinner baseline retinal thickness measurements. Furthermore, because linear regression relies on a normally distributed outcome for valid statistical inferences (e.g., confidence intervals), logarithmic transformation of retinal thickness measures are preferred over untransformed data.

Logarithmic transformation of SD-OCT may be particularly useful in assessing clinically meaningful differences in retinal thickness in uveitis patients. A recent study by Gupta et al.\(^9\) showed that the Cirrus HD-OCT system was superior to the time-domain Stratus OCT system in analyzing both normal retinal structures and pathologic macular features in patients with uveitis. The authors found that the SD-OCT provided better scan quality and retinal detail for a given degree of media haze. Roesel et al.\(^10\) and Monnet et al.\(^11\) confirmed these findings and asserted that SD-OCT is a superior tool because of its ability to more accurately image the IS/OS junction, which correlates with visual acuity in patients with posterior uveitis, such as birdshot retinochoroidopathy.

In this study, logSD-OCT positively correlated with logMAR visual acuity. Specifically, for every 0.1 unit increase in the logSD-OCT, the logMAR visual acuity increased (worsened) by 0.082 units. Recently, Thorne et al.\(^12\) demonstrated that a 20% change in retinal thickness by time-domain CST measures correlates with a 10-letter change in visual acuity (i.e., 2-line ETDRS change) with a sensitivity of 75%. In the present study, the magnitude of the logMAR visual acuity change was not as great; specifically, a change in 0.08 logMAR VA (approximately 4 ETDRS letters) was observed for an approximately 20% change in retinal thickness. Other studies have demonstrated a correlation between retinal thickness measurements and visual acuity in uveitis associated macular edema. Tran et al.\(^13\) showed that visual acuity correlated well with retinal thickness measurements in uveitis patients with cystoid macular edema but not in those with diffuse macular edema. Markomichelakis et al.\(^14\) found that, in patients with uveitis and a clear media, the morphologic features edema and macular thickness correlated with visual acuity. The results in the present study compare well with those in these prior studies, and it would be interesting to apply a logarithmic transformation to the retinal thickness data to other large uveitis databases to determine whether the findings in this study could be more broadly applied.

Although the present study and the evidence above suggests that retinal thickness measurements correlate with visual acuity, prior clinical experience in a variety of retinal diseases has shown us OCT or SD-OCT measures may not correlate with vision because of other concomitant pathologies. In diabetic retinopathy, prior studies have shown that changes in OCT retinal thickness measurements do not correlate with changes in visual acuity.\(^14\) Factors that may contribute to a greater degree in patients with diabetes include macular ischemia and cataract. Similar to patients with diabetes, uveitis patients may develop visual loss from causes other than macular edema, including cataract, vitreous opacity, secondary glaucoma, and band keratopathy, which would not be visualized by SD-OCT. The contribution of other retinal pathologies including macular atrophy,\(^15\) epiretinal membrane, vitreomacular traction, and foveal ischemia in patients with vasculitis also should be further assessed in a controlled, prospective manner with pre-defined anatomic structures assessed and analysis of their contribution to visual acuity.

In summary, logarithmic transformation of SD-OCT central retinal thickness data provides a more normal distribution than central retinal thickness data alone, which is valuable for hypothesis testing in outcomes research that assess uveitic macular edema. Moreover, the correlation of logSD-OCT with logMAR visual acuity in this setting suggests that changes in logSD-OCT are clinically meaningful, objective, and potentially a useful measure for the evaluation of therapies targeting uveitic macular edema. Although there are other factors that contribute to visual acuity outcomes, further assessment of logSD-OCT for uveitis outcomes research is warranted.

References


