Published in final edited form as:

Ophthalmology. 2010 August ; 117(8): 1512–1516. doi:10.1016/j.ophtha.2009.12.014.

A Proposed Method of Logarithmic Transformation of Optical Coherence Tomography Data for use in Clinical Research

Frederick L. Ferris III, M.D.¹, Kellee M. Miller, M.P.H.², Adam R. Glassman, M.S.², and Roy W. Beck, M.D., Ph.D. [on behalf of for the Diabetic Retinopathy Clinical Research Network]²

¹National Eye Institute, National Institute of Health, Bethesda, MD

²Jaeb Center for Health Research, Tampa, FL

Abstract

Purpose—To evaluate a logarithmic transformation of retinal thickness measurements from optical coherence tomography as a new approach to assess clinically meaningful changes in retinal thickness.

Design—Methodological evidence based review.

Participants—There were no participants.

Methods—Standard published approaches for assessing change in retinal thickness over time, as measured by optical coherence tomography (OCT), were compared with a new approach based on a logarithmic transformation of the retinal thickness data. Comparative examples were derived using published data from a clinical trial comparing intravitreal corticosteroid injections for diabetic macular edema with standard laser treatment.

Main Outcome Measures—Comparative examples using Diabetic Retinopathy Clinical Research Network data.

Results—Logarithmic transformation of retinal thickness data results in a more normalized distribution of OCT data and allows for data analyses assessing proportionate changes in retinal thickness during followup.

Conclusions—For analysis of grouped data, a logarithmic transformation of the OCT retinal thickness measurements (logOCT) provides several analytic advantages. Distributions of retinal thickness in groups of eyes with diabetic macular edema, and many other causes of macular thickening, tend to be skewed to the right, and the logOCT transformation tends to normalize these distributions, which has value for statistical comparisons. For assessing whether the observed OCT change in a patient is real (and not due to testing variability), a one step log scale change exceeds the measurement error for all degrees of retinal thickness in current instruments. In addition, this log scale is similar to the logarithm of the minimum angle of resolution (logMAR) scale used for visual acuity. Steps on the log scale for change in thickness seem better related to clinical importance than the actual change in microns because each step on the log scale is the

© 2009 American Academy of Ophthalmology, Inc. Published by Elsevier Inc. All rights reserved.

Corresponding Author: Kellee Miller, c/o Jaeb Center for Health Research, 15310 Amberly Drive, Suite 350, Tampa, FL 33647; Phone: (813) 975-8690, Fax: (800) 816-7601, drcrstat4@jaeb.org.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

same proportionate change in thickness, with a three step change equaling a halving or doubling of thickness, regardless of the baseline value. Transformation of OCT retinal thickness data to logOCT may assist in the assessment of clinically meaningful changes in retinal thickness just as use of the logMAR scale has helped assess clinically meaningful changes in visual acuity.

Introduction

The advent of optical coherence tomography (OCT) has provided a reproducible method for quantifying retinal thickness. The use of OCT measurements as outcome variables to assess the effects of various treatments in eyes with retinal thickening, from different disease processes, is now common. The ability to assess, quantitatively, changes in retinal thicknesses that are associated with various treatments has been helpful. However, there are a number of shortcomings to the current approaches.

Typically, authors have assessed change in retinal thickness between baseline measurements and measurements taken during follow-up. However, there are important differences in the clinical implication of a 50 micron change in retinal thickness for an eye starting with a central retinal thickness of 250 microns compared with that of an eye starting with a central retinal thickness of 500 microns. One approach to account for this important difference is to assess the percent change in retinal thickness. However, a 100% reduction in thickness would indicate that the retina has a follow-up thickness of zero. To address this problem within the Diabetic Retinopathy Clinical Research Network (DRCR.net), we have attempted to look at the percent change in retinal thickening (observed thickness minus an estimate of normal thickness) rather than retinal thickness. However, this approach was plagued with problems related to the variability of normal retinal thickness between individuals. Using the mean normal central retinal thickness of a population separately for men and women, and attempting to assess the percent change in retinal thickening for individuals, resulted in some individuals having more than a 100% reduction in thickening. In addition, when the baseline degree of retinal thickening was relatively small, measurement variability resulted in large percent changes. For example, an eye with central subfield thickness of 230 microns at baseline could have a measurement of 210 microns at follow up due to measurement variability and no real change in thickening.¹ If the “normal” retinal thickness is given a value of 200 microns, this patient would be reported to have over a 50% reduction in thickening even though there had been no real change. Additional details on the pros and cons of absolute and relative changes in retinal thickness and thickening have been reported previously.²

Methods

The desire to find improved analytical approaches for using OCT retinal thickness measurements was based on experience gained using these measurements in various clinical studies conducted by the DRCR.net as well as from evaluating approaches used in the literature. OCT data (Zeiss Stratus OCT3, Carl Zeiss Meditec, Dublin, CA.) for this paper is from the DRCR.net clinical trial of intravitreal triamcinolone vs. standard laser therapy for diabetic macular edema and was utilized to assess possible approaches to transform the OCT data for more clinically useful data analyses.³ DRCR.net protocol and Health Insurance Portability and Accountability Act (HIPAA)-compliant informed consent forms were approved by multiple institutional review boards. Each subject gave written informed consent. All DRCR.net protocols are available on the DRCR.net website (www.drcr.net Accessed September 25, 2009).

Statistical Methods

A logarithmic transformation of the OCT central retinal thickness measurements (logOCT) was calculated for the intravitreal triamcinolone vs. standard laser study baseline and follow-up visit scans by taking the log base 10 of the ratio of the central subfield thickness divided by 200 and rounding to the nearest hundredth. Change in logOCT from baseline was calculated for follow-up visits by subtracting the change in the baseline logOCT from the follow-up visit logOCT and rounding to the nearest hundredth.

Using this data treatment group comparisons were made using repeated-measures analysis of covariance models paralleling analyses reported for this study.³ All *P* values reported are two sided. SAS software version 9.1 (SAS Institute, Cary, NC) was used for all analyses.

Results

The frequency distribution of baseline central retinal thickness, as measured by OCT and the frequency distribution of the logarithmic transformations of these data (as seen in Figure 1) are reminiscent of frequency distributions of visual acuity and the logarithmic transformations of visual acuity data, where the transformed data are more normal in shape. Visual acuity charts developed for the Early Treatment Diabetic Retinopathy Study (ETDRS) have become the standard for use in clinical research over the last three decades. These charts provide an example of a logarithmic transformation system for measuring visual acuity that aids in the interpretation of clinically important changes.

A 3- step change on this log scale is a halving or doubling of the threshold visual angle regardless of the baseline value. A 2 or 3- step change in the logarithm of the minimum angle of resolution (logMAR) scale is generally considered clinically important at any level of visual acuity. This provides a method to assess the proportion of a study group with a clinically important change in visual acuity over time and to test for statistically significant differences between treatment groups. We believe a similar approach to OCT data will, in the same way, assist in assessing the proportion of study participants with important changes in OCT over time.

Given that there is extensive experience with the logMAR transformation of visual acuity in the ophthalmic research community, we developed an analogous system for evaluating retinal thickness. We took advantage of the fact that a Snellen visual acuity of 20/20 is near normal as is a central subfield thickness of 200 microns (some OCT machines being somewhat lower than 200 and some somewhat greater than 200).⁴⁻⁶ We transformed the OCT measurements to a log scale where 200 microns was set as the denominator of an OCT fraction, and the numerator was defined to be the observed OCT value for central retinal thickness. This provided a convenient analogy to the logMAR system and we defined this scale to be the logOCT system. As seen in Table 1, comparing logMAR with logOCT, the 20/20 Snellen fraction reduces to 1 and results in a logMAR score of zero ($\log(1) = 0$). Similarly, the OCT fraction at 200 microns retinal thickness is 200/200, which also results in a log score of 0. Each doubling of the denominator in the Snellen fraction or doubling of retinal thickness compared with 200 microns is a 3- step change on either scale. For convenience the table rounds the actual log values and shows a “log score”.

Another important feature of the logOCT scale is that one log step on that scale is approximately twice the error of measurement for any degree of retinal thickening, making it useful as a possible outcome variable for clinical research.¹ Thus, even a one step logOCT change is likely to be a real change and not a chance finding. As an additional convenience, the log steps on the logOCT scale are the same as the denominators of the Snellen fractions on the ETDRS charts times ten (160, 200, 250, 320, 400, 500, etc.).

Figures 2a and 2b demonstrate the mean change in central subfield retinal thickness and logOCT, respectively, for the 4 mg intravitreal triamcinolone group and the laser treated group at each of the study visits during the two year follow-up. As can be seen from the figures, the general appearance for mean change is similar, whether one uses the overall mean or the mean logOCT. The mean change indicates that the laser group had approximately a 40 micron reduction in retinal thickness at 4 months and this increased to 140 microns by 2 years. Although the mean change and the mean logOCT change are similar, the use of logOCT allows one to look at the proportion of the patient population with a log unit change in retinal thickness. In Figure 3 the proportion of patients with a two or more logOCT step improvement from baseline at each study visit is shown. A 1- step reduction of logOCT is approximately equivalent to a 20% reduction in thickness, a 2- step reduction is approximately equivalent to a 36% reduction and a 3- step reduction is equivalent to a 50% reduction in thickness. As can be seen in this figure, at four months there is an increase in the proportion of intravitreal triamcinolone patients with a two step reduction in thickness compared with the laser treated group, but this is reversed by two years.

Table 2 demonstrates statistical testing of treatment group differences between the 4 mg intravitreal triamcinolone group and the laser group using mean change from baseline to 2 years with and without the proposed logarithmic transformation. The statistical testing result of the difference in mean change using the logOCT transformation is similar to the result of the untransformed data. Table 2 also shows the statistical testing of the treatment group comparison (4 mg intravitreal triamcinolone group verse the laser group) using the proportion of subjects with a 2 or more step change in logOCT. The P-values for the treatment group proportional differences are similar to the P-values for the mean differences.

Discussion

Current systems for analyzing OCT data do not lend themselves readily to analyses of proportions of patients with clinically important changes in retinal thickness. Just as we look at the ETDRS visual acuity score to assess the proportion of patients with a 2 or 3 line (2 or 3 steps on the logMAR visual acuity scale) improvement in visual acuity, we could look to the logOCT score for a 1, 2 or 3- step improvement in logOCT. There continues to be debate over whether a 2 or 3- step logMAR change is clinically important and there will continue to be debate over what constitutes a clinically important change in logOCT. These mathematical principles will apply to distributions of retinal thickness obtained from any OCT instrument. However, only clinical experience with multiple types of OCT instruments will determine what will be considered a clinically important change in logOCT for different diseases and instruments. For an outcome to be considered clinically important it will have to be greater than reproducibility error for the instrument being used and greater than the random variation between patient visits. There will also be a judgment factor among ophthalmologists about what constitutes an important change in retinal thickness for the disease under study. These considerations are similar to those evaluated when deciding what constitutes a clinically important visual acuity change, with one important difference. Visual acuity is a measurement of a functionally important outcome, whereas OCT measures retinal thickness, which may or may not affect function.

Using current time domain OCT instruments, a 1- step improvement in logOCT might be considered analytically similar to a 2- step improvement in logMAR visual acuity based on measurement reproducibility. Also, a 1- step change in logOCT might be considered clinically important in some diseases. For example, reductions from 250 microns to 200 microns, 320 microns to 250 microns or 500 microns to 400 microns may be considered clinically important from a treatment effect perspective. A 2 step logOCT is a considerable

change, whatever the baseline value, and might be an appropriate outcome threshold for some studies. However, considering that some instruments include subretinal fluid in the assessment of thickness and others do not, clinical experience will be necessary to develop definitions of clinically important changes among different OCT machines.

We emphasize that our findings do not imply that the change in logOCT is correlated with a change in logMAR. It may be that correlations are better in some circumstances, simply because one is comparing two log transformed distributions, but it is the change in visual function that measures the importance of the treatment effect to the patient, not the change in OCT. Specifically in diabetic retinopathy, change in OCT is not well correlated with change in visual acuity, at least in part because a change in retinal thickness is only one of the reasons for change in visual acuity.⁷

To illustrate the way the logOCT system could be utilized analytically, we applied the logOCT approach to data published in the DRCR.net clinical trial of intravitreal triamcinolone vs. standard laser therapy for diabetic macular edema. This illustration is not limited to a diabetic retinopathy data set, and would be equally applicable to age-related macular degeneration or any other OCT distribution of diseased retinas that are skewed. Assessing statistical differences in mean change in OCT values, whether one uses logOCT or raw OCT values, is likely to yield a similar result. Although, the mean change over time in units of logOCT may provide a better sense of proportionate treatment effects across a wide variety of baseline retinal thicknesses than the actual mean change in microns. Because the use of logarithmic visual acuity charts is so prevalent in research, it is easy to forget that most published analyses of mean change in visual acuity actually represents a mean log change in visual acuity. Just as most analyses of visual acuity now use log visual acuity transformations, when using retinal thickness as a co variable in multivariable regression analyses, log transformation to “normalize” the OCT measurements may also be important.

The main advantage of the logOCT transformation lies in the ability to assess the proportion of patients with a potentially clinically important improvement (or worsening) in retinal thickness after treatment across the entire study group, regardless of baseline retinal thickness. If an absolute value such as a 50 micron improvement in OCT is used for analysis, this implies that such a change is important whatever the baseline retinal thickness is. With the transformation we can look at the proportion with a one or two step change in logOCT, where those with thicker retinas would have to demonstrate greater change than those with thinner retinas. This analysis is similar to an analysis where the outcome is a fixed percent reduction in retinal thickness from baseline.

Figure 3 shows the proportion of patients in the 4mg intravitreal triamcinolone group and the laser treated group with a two or greater step improvement in logOCT from baseline at each follow-up visit. As might be expected, the treatment differences are similar to those presented in Figures 2a and 2b, but these differences represent the proportion of patients who had a clinically important change in retinal thickness. Over the two year follow-up period, the proportion of patients in the laser treated group with a two-step improvement increased from approximately 13% at four months after treatment to almost 60% at two years, while in the steroid treated group there was an initial two-step improvement in approximately a third of the population with little change in that proportion during follow-up. In this case, the p-values for the treatment group differences are also similar to the *P* values for the mean differences (Table 2), with apparent statistically significant early benefit for the steroid group and a reversal by 2 years. This seems to be a useful way to provide a statistical test of the proportion of patients with a clinically important change in OCT central thickness.

LogOCT analyses are directly analogous to the logMAR analytic approaches, meaning that the same rationale for when to use mean differences to compare treatment groups and when to use log step differences applies.⁸ Using log scales for both visual acuity and OCT measurements also provides the opportunity to graphically indicate change over time for both variables in the same figure, with a 3-step change that equals a halving or doubling for both (Figure 4). As demonstrated in this figure, one can visually compare the change in logOCT with the change in logMAR visual acuity. This does not imply that logOCT is better correlated with logMAR than retinal thickness measurements, but only demonstrates that one can look at the change in retinal thickness in a similar manner to the way we often look at visual acuity data. In Figure 4, one can see that there was a larger log step change in retinal thickness than log step change in visual acuity over time.

Transformation of OCT retinal thickness data to logOCT will assist in the assessment of clinically meaningful changes in retinal thickness just as use of the logMAR scale has helped assess clinically meaningful changes in visual acuity.

Acknowledgments

Financial Support: Supported through a cooperative agreement from the National Eye Institute and the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services EY14231, EY14269, EY14229

References

1. Diabetic Retinopathy Clinical Research Network. Reproducibility of macular thickness and volume using Zeiss optical coherence tomography in patients with diabetic macular edema. *Ophthalmology* 2007;114:1520–5. [PubMed: 17353052]
2. Browning DJ, Glassman AR, Aiello LP, et al. Diabetic Retinopathy Clinical Research Network. Optical coherence tomography measurements and analysis methods in optical coherence tomography studies of diabetic macular edema. *Ophthalmology* 2008;115:1366–71. [PubMed: 18675696]
3. Diabetic Retinopathy Clinical Research Network. A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. *Ophthalmology* 2008;115:1447–59. [PubMed: 18662829]
4. Grover S, Murthy RK, Brar VS, Chalam KV. Normative data for macular thickness by high-definition spectral-domain optical coherence tomography (Spectralis). *Am J Ophthalmol* 2009;148:266–71. [PubMed: 19427616]
5. Kiernan DF, Hariprasad SM, Chin EK, et al. Prospective comparison of Cirrus and Stratus optical coherence tomography for quantifying retinal thickness. *Am J Ophthalmol* 2009;147:267–275. [PubMed: 18929353]
6. Bressler NM, Edwards AR, Antoszyk AN, et al. Diabetic Retinopathy Clinical Research Network. Retinal thickness on Stratus optical coherence tomography in people with diabetes and minimal or no diabetic retinopathy. *Am J Ophthalmol* 2008;145:894–901. [PubMed: 18294608]
7. Diabetic Retinopathy Clinical Research Network. Relationship between optical coherence tomography-measured central retinal thickness and visual acuity in diabetic macular edema. *Ophthalmology* 2007;114:525–36. [PubMed: 17123615]
8. Beck RW, Moke PS, Turpin AH, et al. A computerized method of visual acuity testing: adaptation of the Early Treatment of Diabetic Retinopathy Study testing protocol. *Am J Ophthalmol* 2003;135:194–205. [PubMed: 12566024]

Figure 1. Distributions of Optical Coherence Tomography (OCT) Central Subfield Thickness Measurements and the Log Transformation of Central Subfield Thickness Measurements (LogOCT) from Baseline Measurements Made in the Diabetic Retinopathy Clinical Research Trial of Intravitreal Triamcinolone vs. Standard Laser Therapy for Diabetic Macular Edema.

Figure 2. Mean Change in (a) Optical Coherence Tomography (OCT) Central Subfield Thickness (CST) and (b) the Log Transformation of Central Subfield Thickness (LogOCT) from Baseline for the 4mg Intravitreal Triamcinolone Acetonide Group and the Focal/Grid Laser Treated Group during 2 year Follow-up in the Diabetic Retinopathy Clinical Research Trial of Intravitreal Triamcinolone vs. Standard Laser Therapy for Diabetic Macular Edema.

Figure 3.

The Proportion of Subjects with a 2 or Greater Step Improvement in Log Transformation of Central Subfield Thickness (LogOCT) From Baseline in the 4mg Intravitreal Triamcinolone (IVT) Acetonide Group and the Focal/Grid Laser Treated Group during Two-year Follow-up in the Diabetic Retinopathy Clinical Research Trial of Intravitreal Triamcinolone vs. Standard Laser Therapy for Diabetic Macular Edema.

Figure 4. Mean Change from Baseline in Log Transformation of Central Subfield Thickness (LogOCT) and Mean Change in the Logarithm of the Minimum Angle of Resolution (LogMAR) in Patients Assigned to Focal/Grid Laser Treatment during 2-year Follow-up in the Diabetic Retinopathy Clinical Research Trial of Intravitreal Triamcinolone vs. Standard Laser Therapy for Diabetic Macular Edema.

Table 1

Logarithm of the minimum angle of resolution Scale and Log Transformation of Central Subfield Thickness Scale Equivalents

LogMAR*	VA (Snellen)	LogOCT**	OCT (μ)
0.1	20/16	-0.1	160
0	20/20	0	200
-0.1	20/25	0.1	250
-0.2	20/32	0.2	320
-0.3	20/40	0.3	400
-0.4	20/50	0.4	500
-0.5	20/64	0.5	640
-0.6	20/80	0.6	800
-0.7	20/100	0.7	1000

* LogMAR=Logarithm of the minimum angle of resolution Scale

** LogOCT=Log Transformation of Central Subfield Thickness Scale Equivalents

VA=visual acuity

OCT= optical coherence tomography

Table 2

Statistical Testing of Treatment Group Differences, Focal/grid Laser Group and the 4mg Intravitreal Triamcinolone Acetonide Group, With and Without Logarithm Transformation of Optical Coherence Tomography Central Subfield Measurements

Visit	Mean change in Central Subfield Thickness [†] P Value [*]	Mean Change in log of Central Subfield [‡] P Value [*]	2 or More Step Improvement in log of Central Subfield [‡] P Value [*]
4 Month N=546 eyes	<.001 ^{//}	<.001 ^{//}	<.001 ^{//}
1 Year N=491 eyes	0.99	0.54	0.25
2 Year N=457 eyes	<.001 [§]	<.001 [§]	<.001 [§]

* Repeated measures analysis controlling for baseline visual acuity, baseline optical coherence tomography (OCT), and prior focal/grid laser treatment

[†] OCT central subfield thickness

[‡] Logarithmic transformation of OCT central subfield thickness

^{//} = 4mg triamcinolone acetonide better

[§] = Focal/Grid Laser better