Optical Coherence Tomography Measurements and Analysis Methods in Optical Coherence Tomography Studies of Diabetic Macular Edema

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Objective: To evaluate optical coherence tomography (OCT) measurements and methods of analysis of OCT data in studies of diabetic macular edema (DME).

Design: Associations of pairs of OCT variables and results of 3 analysis methods using data from 2 studies of DME.

Participants: Two hundred sixty-three subjects from a study of modified Early Treatment of Diabetic Retinopathy Study (mETDRS) versus modified macular grid (MMG) photocoagulation for DME and 96 subjects from a study of diurnal variation of DME.

Methods: Correlations were calculated for pairs of OCT variables at baseline and for changes in the variables over time. Distribution of OCT measurement changes, predictive factors for OCT measurement changes, and treatment group outcomes were compared when 3 measures of change in macular thickness were analyzed: absolute change in retinal thickness, relative change in retinal thickness, and relative change in retinal thickening.

Main Outcome Measures: Concordance of results using different OCT variables and analysis methods.

Results: Center point thickness correlated highly with central subfield mean thickness (CSMT) at baseline (0.98–0.99). The distributions of changes in CSMT were approximately normally distributed for absolute change in retinal thickness and relative change in retinal thickness, but not for relative change in retinal thickening. Macular thinning in the mETDRS group was significantly greater than in the MMG group when absolute change in retinal thickness was used, but not when relative change in thickness and relative change in thickening were used. Relative change in macular thickening provides unstable data in eyes with mild degrees of baseline thickening, unlike the situation with absolute or relative change in retinal thickness.

Conclusions: Central subfield mean thickness is the preferred OCT measurement for the central macula because of its higher reproducibility and correlation with other measurements of the central macula. Total macular volume may be preferred when the central macula is less important. Absolute change in retinal thickness is the preferred analysis method in studies involving eyes with mild macular thickening. Relative change in thickening may be preferable when retinal thickening is more severe. *Ophthalmology 2008;115:1366–1371 © 2008 by the American Academy of Ophthalmology.*

In the past decade, optical coherence tomography (OCT) has progressed from a research tool to a commonly available office procedure for managing patients with macular disease and obtaining measurements used in clinical trials.[1–3] The analysis of data obtained from groups of patients in OCT studies has received less attention than correlations between retinal morphology and OCT scan features,[4,5] the recognition of OCT artifacts,[6–9] and OCT patterns associated with various disease states.[10] No consensus exists regarding the relative value of the variables measured in OCT scans, or the circumstances in which one variable

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might better be emphasized rather than another. Little information has been published about the possible ways to analyze OCT numerical data, and under what circumstances one analysis method might be preferred to another.[11] In the current report, we address these topics with reference to diabetic macular edema (DME), and not other conditions, based on experience with analyzing >16 000 scans with OCT in clinical research protocols over 4 years.

Materials and Methods

The specific objectives of this report are (1) to identify the optimal OCT measurement for central macular thickening in DME; (2) to identify roles for paracentral and global macular OCT measurements and explore correlations between these measurements and their changes in DME and treatments for DME; and (3) to identify limitations and advantages in 3 methods of analysis of OCT measurement changes—namely, (a) absolute change in thickness, (b) relative change in thickness, and (c) relative change in thickening.

Data reported from 2 studies performed by the Diabetic Retinopathy Clinical Research Network (DRCR.net): a randomized trial comparing modified Early Treatment of Diabetic Retinopathy Study (ETDRS)-style focal laser photocoagulation with mild macular grid laser photocoagulation for DME (modified ETDRS [mETDRS] vs modified macular grid [MMG] trial),[12] and an observational study of diurnal variation in DME (diurnal variation study).[2] In each study, various OCT measurements were end points for analysis. Experience in analyzing OCT data in these studies led to preferred variables and methods of analysis with associated rationales for the preferences resulting from exploratory and comparative analyses. We report the current network preferences with examples from our data sets that motivated the preferred choices and provide plausibility.

The preponderance (>99%) of data collected in DRCR.net studies has been from the OCT3 machine (Zeiss, Jena, Germany). Although the data can be displayed in either 3.45- or 6.0-mm formats, by convention all OCT tests for DRCR.net protocols have used the 6.0-mm format. The OCT tests were analyzed at the reading center of the University of Wisconsin, Madison. For OCT tests requiring manual grading, central subfield macular thickness (CSMT) was imputed from the manually graded center point thickness (CPT) by using a regression equation: CSMT = CPT*0.84 + 63.6.[12]

Because of the variable terminology in OCT studies, we define several terms. Table 1 (available at http://aaojournal.org) cross-references these terms to synonyms in the literature.

- *Retinal thickness:* value in microns of the distance between the OCT layers assumed to be the retinal pigment epithelium and the internal limiting membrane. This ignores artifactitious designation of the outer segment–inner segment junction as the retinal pigment epithelium in scans obtained with the OCT3.[9]
- *Retinal thickening:* calculated value equal to the thickness minus the population mean for the variable under consideration (either CPT or CSMT). The normative value chosen should be specified as these values differ according to source.[13–15]
- *Center point* (CP): the intersection of the 6 radial scans of the fast macular thickness protocol of the OCT.
- *Center point thickness* (CPT): average of the thickness values for the 6 radial scans at their point of intersection.
- *Central subfield* (CS): circular area of diameter 1 mm centered around the center point; 128 thickness measurements are made in this circular area in the fast mac protocol.
- *Central subfield mean thickness* (CSMT): mean value of the 128 thickness values obtained in the central subfield.
- *Absolute change in thickness*: difference in the thickness between 2 measurements made at different times. For example, if measurements M_1 and M_2 are made at 2 different times, then the absolute change in thickness equals M_2-M_1. The absolute change in thickness is equal to the absolute change in thickening, which is the first of 3 methods of analyzing OCT changes listed above.
- *Relative change in thickness*: absolute change in thickness divided by the baseline thickness. Using the symbols introduced previously, relative thickness equals $[(M_2-M_1)/M_1] \cdot 100\%$, which is the second of 3 methods of analyzing OCT changes.
- *Relative change in thickening*: absolute change in thickness (or thickening) divided by the baseline thickening. Using the symbols introduced previously, relative change in thickening equals $[(M_2-M_1)/(M_1-\text{normative mean})]$ 100%, which is the third of 3 methods of analyzing OCT changes.

In comparing the methods of data analysis for change in OCT measurements, 3 approaches were used. The first was to visually inspect the distribution of the OCT measurement changes recorded using the 3 different methods to ascertain normality and the extent of outliers. This approach was used for the data sets from both studies. The second was to perform parallel analyses of eye- and subject-specific factors associated with OCT measurement changes recorded under the 3 methodologies to determine concordance or discordance of the predictive factors of the 3 methods. The third was to determine whether statistical comparisons of treatment group outcomes gave meaningfully different results according to which of the 3 methods was used. The second and third approaches could be applied only to the mETDRS versus MMG trial. We used the entire dataset from the mETDRS versus MMG trial for the second and third approaches, and did not exclude the eyes with CSMT<250 microns as was done in an earlier publication from this trial.[12]

Results

Optical Coherence Tomography Outcomes for the Center of the Macula

Center point thickness and central subfield mean thickness are 2 measures of the central portion of the macula printed on the Zeiss OCT Retinal Map Analysis. For the 2 studies, the correlation between these 2 measures at baseline was 0.98, and 0.99, respectively.[2,3] The correlation coefficients for change in CPT and change in CSMT in the mETDRS versus MMG trial and the diurnal variation study at their primary follow-up end points were 0.98 and 0.87, respectively.

As a result of these high correlations, conclusions derived from analyses based on center point and central subfield should be equivalent. It seems, therefore, unnecessary to analyze both measures. In choosing which of the 2 measures to emphasize, we prefer central subfield mean thickness over CPT because the central subfield is composed of an average of 128 data points whereas the center point is an average of 6. In addition, center point values are more dependent on centration of the scan; these advantages for CSMT have been noted previously.[11]

An advantage for preferring CPT to CSMT is that it can be salvaged from lower quality scans more often. When a reading center is involved in the grading of the OCT images, the center point of scans with incorrect placement of algorithm lines can be graded manually. In contrast, there is no commercial software available that can manually adjust inaccurate boundary lines for

the central subfield. Manual grading was required in 14% of OCTs in the 2 DRCR.net studies.

The coefficients of repeatability for CSMT and CPT in DME have been reported to be 11% and 17%, respectively.[16] Primarily because of the difference in coefficient of repeatability, our preferred outcome for statistical analysis and clinical evaluation of the center of the macula is CSMT and not CPT.[11] To overcome the problem of missing data for OCT images needing manual grading, the central subfield can be imputed for analysis from the manually determined CPT using a regression equation.[12]

Paracentral and More Global Macular Optical Coherence Tomography Measurements

There are several OCT outcomes that can be used when paracentral or global macular assessment of thickening is desired. The outcome of choice depends on the goals of the study. Paracentral subfields and retinal volume (the average of the central subfield, 4 inner subfields, and 4 outer subfields weighted by the area of the subfields and converted to cubic millimeters), can be obtained directly from the OCT Retinal Map Analysis and represent more global measures of macular edema. Average thickness within the grid is also a global measure of the macula, and is calculated by dividing total macular volume by grid area (28.275 mm^2). Maximum retinal thickening in the inner zone or maximum retinal thickening within the grid can also be used for OCT analyses. Maximum retinal thickening in the inner zone is the largest thickening value among the central and each of the 4 inner subfields. Similarly, maximum retinal thickening within the grid is the largest thickening value among the central subfield, 4 inner subfields, and 4 outer subfields.

There is a strong correlation between these noncentral OCT measures and CSMT. For the mETDRS versus MMG trial and the diurnal variation study, the correlations between maximum retinal thickening in the inner zone and CSMT were 0.97 and 0.95, respectively. The correlation between maximum retinal thickening within the grid and CSMT was 0.94 in both studies. The correlation between total macular volume and CMST was 0.75 and 0.77 for the mETDRS versus MMG trial and the diurnal variation study, respectively. As a result of the strong relationships, the conclusions for the treatment effect in the mETDRS versus MMG trial were similar for each of these additional outcomes (data not shown).

Methods of Optical Coherence Tomography Data Analysis for Change in Optical Coherence Tomography Measurements

Absolute Change in Thickness. In both DRCR.net studies, the absolute changes in CSMT induced by diurnal variation or intervention were approximately normally distributed (Fig 1 [available at http://aaojournal.org]). Outliers were rare as determined by visual inspection. For the data set of change in CSMT at 12 months from the mETDRS versus MMG trial, the predictive factors in multivariable analyses were baseline CSMT and sensory subretinal fluid on OCT. In the 2 data sets, there were 47% of eyes with thickness <300 microns. These maculas with small degrees of thickening have less room to improve after any intervention, making it more difficult to determine the efficacy of any treatment compared with samples in which the maculas are thicker.

Relative Change in Thickness. The relative change in thickness for each of these studies was approximately normally distributed (Fig 2 [available at http://aaojournal.org]). Outliers were rare as determined by visual inspection. For this outcome, a ceiling exists for the maximal relative decrease in thickness. Because all maculas have a thickness, even after a treatment designed to reduce macular thickening, the relative decrease in thickness is always <100%. The maximal value for the relative change in thickness depends on the characteristics of the baseline distribution of the macular thicknesses. Samples with greater macular thicknesses have larger maximal values. In the DRCR.net studies, the maximal decreases ranged from 26% in the diurnal variation study to 79% for the mETDRS versus MMG study.

The data from the mETDRS versus MMG trial were analyzed as absolute change in CSMT and not relative change in CSMT (estimated difference: mETDRS group 30 microns thinner compared with MMG; 95% confidence interval, 8–53; $P = 0.01$). We have reanalyzed the data using the relative change in thickness methodology. The predictive factors for change in CSMT at 12 months did not change. The comparison of the 2 treatment groups had borderline statistical significance (estimated difference: 6%; 95% confidence interval, 0%–12%; $P = 0.05$).

Relative Change in Thickening. The relative change in thickening in both studies was nonnormally distributed. Figure 3 shows the distribution of the relative change in thickening of the maculas for the eyes in the diurnal variation and mETDRS versus MMG trials. Unlike the absolute change in retinal thickness and the relative change in retinal

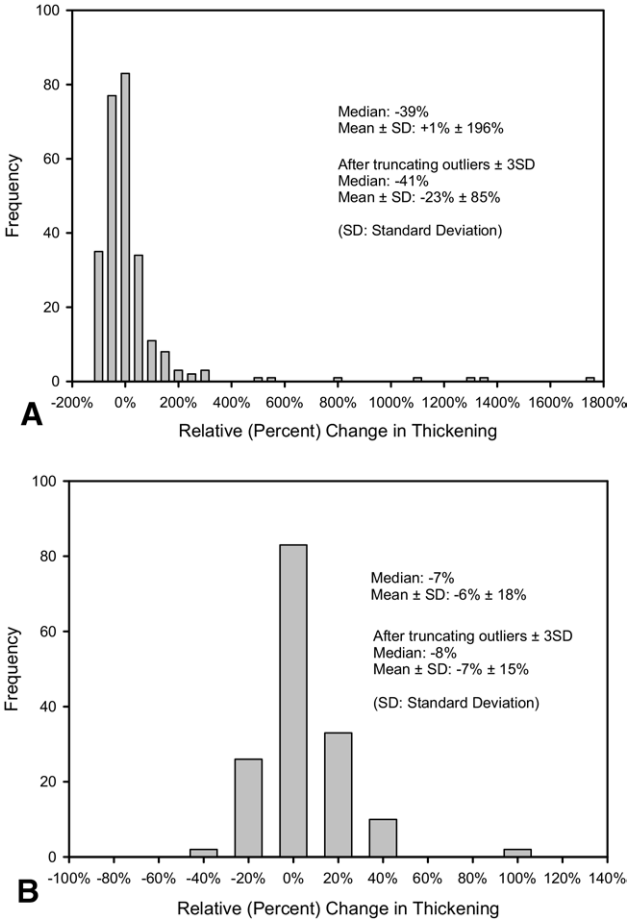

Figure 3. A, Distribution of relative change in thickening for the modified Early Treatment Diabetic Retinopathy Study versus Modified Macular Grid photocoagulation trial (n = 263). Excludes nine eyes where the baseline central subfield mean thickness (CSMT) was below the normal value of 202 microns. **B,** Distribution of relative change in thickening for the diurnal variation study (n = 156).

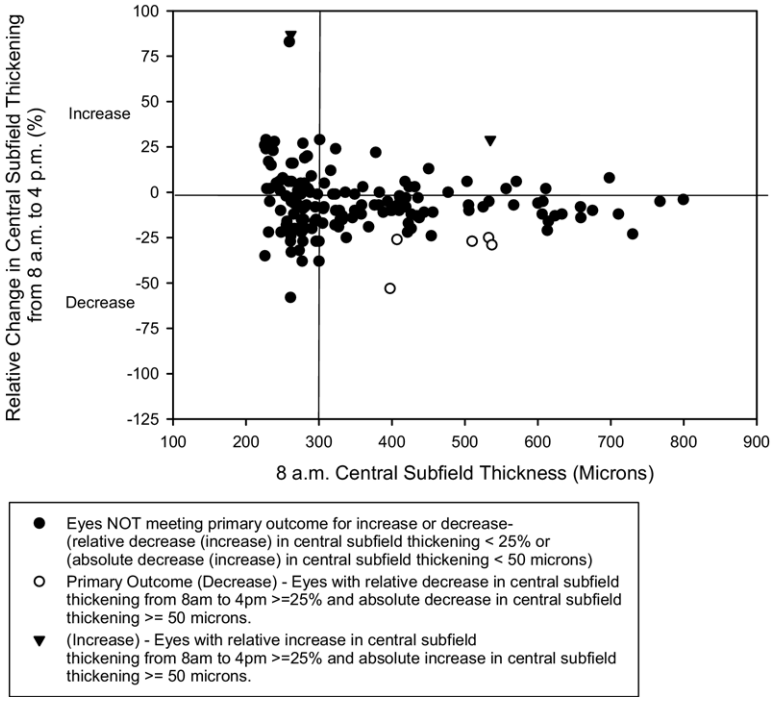

Figure 4. Relative change in central subfield thickening from 8 AM to 4 PM by 8 AM central subfield thickness in the diurnal variation study (n = 156).

thickening has a strong functional dependence on baseline retinal thickening. When the baseline thickening is small, the relative change in thickening is unstable; that is, small changes in baseline thickening are associated with large changes in relative change in thickening. Figure 4 shows this for the data set from the diurnal variation study. The scatter in the data points dramatically increases at small values of baseline retinal thickening. Figure 5 shows the same set of data in which absolute change in retinal thickness has been used as the measure of CSMT change. No instability is demonstrated.

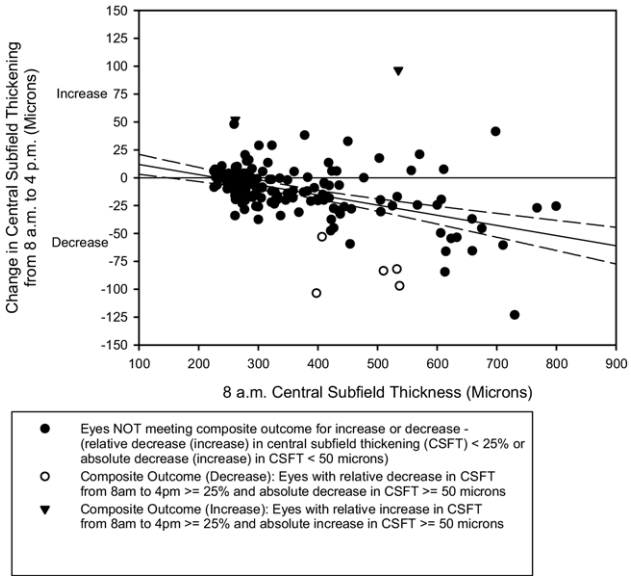

Figure 5. Absolute change in central subfield mean thickness from 8 AM to 4 PM by 8 AM central subfield mean thickness in the diurnal variation study (n = 156).

The predictive factors for change in CSMT at 12 months in the mETDRS versus MMG trial changed when relative change in retinal thickening was used as the variable for CSMT change. Sensory subretinal fluid on OCT was no longer significant (P = 0.24) and only baseline CSMT remained predictive. The results of a statistical comparison of outcomes for the 2 treatment groups changed (estimated difference, 9%; 95% confidence interval, −22% to 41%; P = 0.55). There was a significant difference between the 2 treatment groups in absolute change in thickness, but no significant difference in relative change in thickening.

Discussion

Preferred Optical Coherence Tomography Measurement for the Central Macula

Published studies on OCT measurements in DME have reported CPT and CSMT, often under synonymous names (Table 1 [available at http://aaojournal.org]). Chan and Duker were the first to identify the basis for preferring CSMT as a measurement of the central macular thickness, and we agree with their published rationale. They noted that CSMT should have a higher reproducibility because it is based on more scans than CPT. A DRCR.net reproducibility study in DME has confirmed this prediction.[16] The 14% figure for scans requiring manual grading is specific to DME, and should not be extrapolated to other conditions such as macular degeneration, in which the automated boundary algorithm produces a higher error rate, requiring more frequent manual grading.[6,9] For OCT scans with inaccurate automated central subfield values, an imputed

value can be derived from a regression equation using CPT. If manual grading of scans is not performed, decentration may be overlooked, which could influence CPT more than CSMT. This potential problem may be exaggerated for thicker maculas in which visual acuity may be more compromised, making fixation difficult.

Paracentral and Global Macular Optical Coherence Tomography Measurements

In DRCR.net studies to date, global macular measurements have consistently shown high correlations with CSMT, and have provided no additional information to that derived from analysis of CSMT. However, in particular eyes and interventions, there can be discordant responses[17]; thus, it is premature to emphasize the foveal measures to the exclusion of the parafoveal ones.[17] It is possible that certain interventions or subsets of eyes may show regional variation in macular thickening response.[14] Total macular volume, in particular, can be used when the macular edema is more diffuse or when it is anticipated that central subfield and paracentral subfield responses may be discordant.

Optical Coherence Tomography Analysis Methods

Chan and Duker[11] have stated that all studies involving treatment of macular edema should be analyzed using the relative change in thickening approach to CSMT change. The DRCR.net published the mETDRS versus MMG trial results using the absolute change in CSMT method of analysis despite knowledge of the recommendation of Chan and Duker.[12] There are rationales for the use of both approaches.

We agree that relative change in thickening is conceptually attractive. It provides a useful measure of the degree to which the thickening is reduced toward a normal level (zero thickening). One can eliminate thickening but not thickness; normal retinas have thickness. The practical disadvantages, however, seem to outweigh the theoretical advantage. The measure becomes unstable when there is little baseline thickening. Small variation in baseline thickening for these eyes translates into large variation in relative change in thickening. This measure of change in CSMT is more affected by measurement variability in the range of retinal thicknesses for DME most frequently observed in the United States.[12] An additional, relatively minor, disadvantage of relative change in thickening is that it is associated with nonnormal distributions of data (Fig 3).

These shortcomings are not demonstrated in the data that Chan and Duker[11] used to illustrate their proposal for using relative change in retinal thickening as the standard method for calculating OCT changes. They analyzed data sets of Martidis et al[18] (mean CSMT 540±96) and Massin et al[19] (mean CSMT 588±156), both of which had high values for baseline retinal thickness. For studies considering interventions for milder degrees of macular edema, the instability of relative change in thickening becomes apparent.[13,20]

In applying the formula for relative change in thickening, it is important to use the correct reference value in the denominator of the calculation. Chan and Duker have illustrated how easy it is to make such a mistake. For example, the data of Massin et al[19] were CSMTs, yet in the illustrative calculations of relative change in thickening, Chan and Duker[11] use 148 microns as the reference value, which applies to CPT (not CSMT). Instead of 148 microns, they should have used the normal reference value for the mean value of the central subfield in eyes measured by the model OCT used by Massin et al, a value not listed in Chan and Duker's paper. Normal values for OCT are model dependent and gender dependent, and both dependencies need to be incorporated in applying the formula for relative change in thickening.[21] The assumption that the normal value chosen for use in the formula is a good approximation of the sample normal for a given study could be erroneous. Use of a group normal value is an accommodation to our lack of information of each patient's true normal macular thickness.

Statistical comparisons of the treatment groups gave substantially different results depending on the method of analysis chosen. For the mETDRS versus MMG trial, the macular thinning response of the mETDRS group was greater than that of the MMG group when the absolute change in thickness method was used, but there was no difference between the groups when the relative change in thickness and relative change in thickening methods were employed. Moreover, the predictors for change in CSMT differed according to the method of analysis chosen. Caution is therefore warranted in claiming superiority of one method over another. In most studies, the choice of an analysis method can be made before data collection begins based on the expected characteristics of the study sample. For example, when macular thickness is mildly elevated, analysis of the absolute change in thickness may be the preferred method because of its stability. In studies of severely thickened maculas, relative change in thickening is preferred because it tends to control for the variable clinical importance of an observed absolute change in thickness depending on the baseline thickness. For example, a 150-micron decrease in macular thickness is striking in a macula with a baseline thickness of 350 microns, and of minor clinical significance in a macula with a baseline thickness of 750 microns. Because there are multiple possible outcomes, prespecification of the primary outcome is important. In this report, we have shown discrepant results by analysis method to rebut the claimed superiority of the relative change in thickening method, and do not think that it is practical to perform routine parallel analyses on all data sets.

A method of data analysis considered by DRCR.net was to convert retinal thickness values to a logarithmic scale with a base of 2. In considering data on this scale, a positive unit change in value equates to a doubling of retinal thickness, a convenient characteristic analogous to the doubling in visual angle of resolution for each 3-line change in visual acuity on the logarithm of the minimum angle of resolution (ETDRS) visual acuity charts. This method was not chosen because it was not thought to be intuitive to clinicians, just as logarithm of the minimum angle of resolution visual acuity data are unintuitive to many clinicians and are accompanied by parallel Snellen representations in publications.

In clinical trials for DME organized by the DRCR.net, most eyes have had mild degrees of macular thickening.

This subgroup of eyes is difficult to analyze with any method, but the difficulties vary among methods. For the relative change in thickening method, the problem is instability. For the absolute change in thickness method, the problem is the constrained range in which improvement can be manifest (floor effect). In studies with samples having a high percentage of eyes with a mildly thickened macula, we recommend that absolute change in thickness be the analysis method of choice. In randomized trials, treatment group comparisons can be made controlling for the baseline thickening because the degree of baseline thickening can be expected to be balanced between groups through randomization. For studies of sufficient sample size, analysis on the absolute change in microns should also be performed within baseline thickness subgroups to eliminate the primary disadvantage to this measure, namely, less room for improvement in eyes with little macular thickening.

Development of new analysis methods of OCT data will probably continue as additional experience is gained and new OCT technology introduced. Nevertheless, the concepts we have presented concerning methodology comparisons seem technology independent. The study of the OCT analysis methods warrants continued attention, as the importance of OCT imaging in management of DME increases.

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Table 1. Synonymous Terms in the Optical Coherence Tomography Literature

Term Used in This Study	Synonyms	References
Center point	Central fovea	Chan and Duker[11]
	Fovea	Brown et al,[22] Kang et al[23]
	Foveal center	Sadda et al[9]
	Foveal center point	Catier et al[24]
Central subfield	Fovea	Chan and Duker,[11] Browning et al[25]
	Area A1	Laursen et al[13]
	Zone 1	Frank et al[26]
	Foveal central subfield	Sadda etal[27]
Center point thickness	Central foveal thickness	Hussain etal,[28] Otani and Kishi[29]
	Foveal thickness	Hee et al[30]
	Foveal center thickness	Sadda et al[9]
Central subfield mean thickness	Central macular thickness	Catier et al,[24] Hee et al[30]
	Mean macular thickness	Frank et al,[26] Hussain et al[28]
Relative change in thickening	Standardized change in macular thickening	Chan and Duker[11]

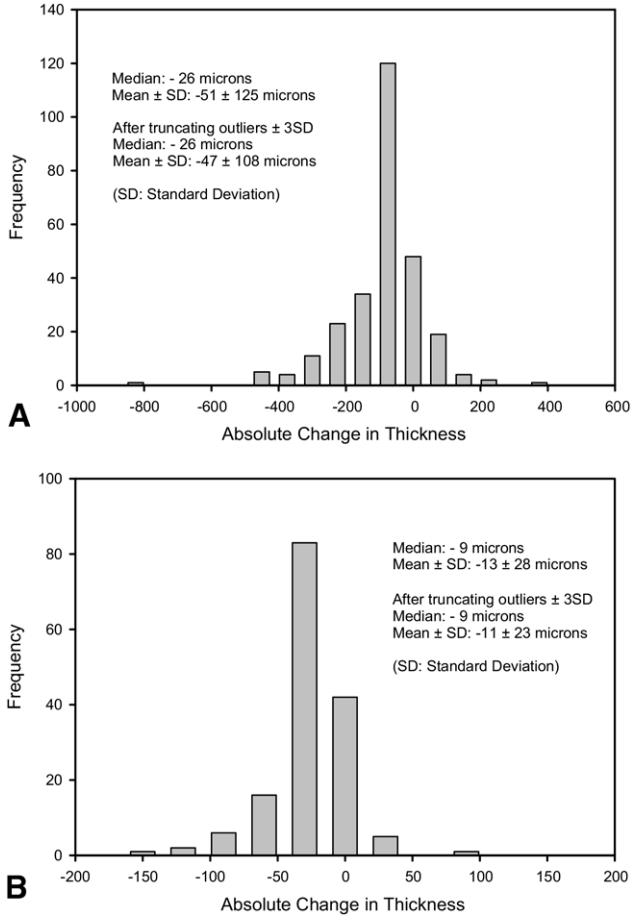

Figure 1. A, Distribution of absolute change in thickness for the modified Early Treatment Diabetic Retinopathy Study versus Modified Macular Grid photocoagulation trial (n = 272). **B,** Distribution of absolute change in thickness for the diurnal variation study (n = 156).

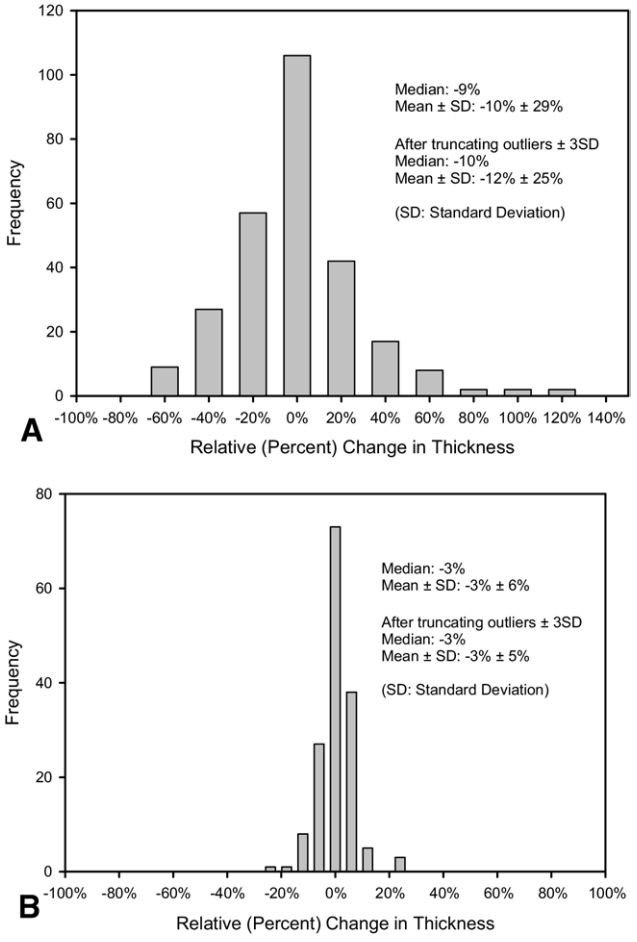

Figure 2. A, Distribution of relative change in thickness for the modified Early Treatment Diabetic Retinopathy Study versus Modified Macular Grid photocoagulation trial (n = 272). **B,** Distribution of relative change in thickness for the diurnal variation study (n = 156).