INTERPRETING THICKNESS CHANGES IN THE DIABETIC MACULA: THE PROBLEM OF SHORT-TERM VARIATION IN OPTICAL COHERENCE TOMOGRAPHY–MEASURED MACULAR THICKENING (AN AMERICAN OPHTHALMOLOGICAL SOCIETY THESIS)

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ABSTRACT

Purpose: To estimate the short-term variability of macular thickness in eyes with refractory and regressed diabetic macular edema (DME).

Methods: In this retrospective review of consecutive cases from a retina practice, optical coherence tomography (OCT) measurements of macular thickness were extracted from the clinical charts of patients with refractory DME and regressed DME. Variation in macular thickness was defined as maximal central subfield mean thickness (CSMT) minus minimal CSMT during a period of observation in which clinical macular status did not change.

Results: There were 36 eyes of 29 patients in the refractory DME group and 93 eyes of 93 patients in the regressed DME group. Median intervals during which macular status was unchanged and OCTs were collected were 7 months for the refractory DME group and 22 months for the regressed DME group. Baseline CSMTs were 321 μm for the refractory DME group and 217 μm for the regressed DME group. The median variation in CSMT was 89 μm for the refractory DME group and 19 μm for the regressed DME group. Results for total macular volume paralleled those for CSMT.

Conclusions: In consonance with eyes having treatment-naïve DME, eyes with refractory DME have short-term fluctuation in macular thickness larger than OCT measurement variability. In eyes with regressed DME, short-term fluctuation is less than in eyes with refractory DME, yet can also exceed measurement variability. This information is clinically important in deciding whether subsequent treatment is indicated.

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INTRODUCTION

Reduction in visual acuity in association with diabetic retinopathy most commonly occurs from diabetic macular edema (DME).[1,2] Intraretinal hemorrhage, preretinal and vitreous hemorrhage, macular ischemia, optic nerve ischemia, and traction retinal detachment can also reduce visual acuity, but they do so less commonly than DME. Although the correlations between macular thickness and visual acuity and between changes in macular thickness and changes in visual acuity are both modest, with correlation coefficients of 0.52 and 0.44, respectively, macular edema remains the most common reason for intervention by ophthalmologists in patients with diabetes confronting visual loss.[3] Measuring macular edema is therefore of major importance in managing patients with DME.

Until 1995, assessment of macular thickness was subjective, relying on slit-lamp stereoscopic biomicroscopy of the fundus with a contact or noncontact lens.[4] When optical coherence tomography (OCT) and retinal thickness analysis machines were invented, assessment became objective and more reliable.[5-7] Over the past decade, OCT has superseded retinal thickness analysis to become the predominant technology for measurement of macular thickness. The current generation of OCT machines is characterized by capture and analysis of spectral domain rather than time domain data, resulting in improved image resolution and improved reproducibility characteristics compared to previous machines.[8]

In this thesis, the objective is to measure the short-term variability of DME in patients with refractory and regressed DME. Short-term variability can be defined as the variation in OCT-measured macular thickness or volume over a series of visits during which there is no trend of increasing or decreasing thickness or volume. The author's hypothesis is that short-term variability related to changes in cardiac status, renal status, and systemic fluid balance is greater than measurement variability and should be accounted for in clinical decision making. Specifically, an intervention need not be implemented if an OCT measurement change is less than short-term variation even if the change is greater than measurement variability. It has been recognized that systemic fluid balance can influence DME,[9] but the theoretical knowledge has not been reflected in the literature on interpreting OCT measurements, an omission this work is intended to redress.

Previous work has established the range of reproducibility of OCT measurements in normal eyes and eyes with DME, that is, the measurement variability of OCT.[10-16] For eyes with DME, this measurement variability expressed as the coefficient of repeatability is 11% of the OCT-measured average central subfield thickness.[12] The magnitude of diurnal variation of OCT-measured macular thickness in DME has also been established.[17] Recently, short-term variability of macular thickness for the subset of eyes of diabetics with varying levels of retinopathy but no clinical edema has been investigated.[18] It was reported that short-term variability in macular thickness is little different than OCT measurement variability in these eyes. Toda and colleagues[19] have reported on short-term variability of 8 eyes with DME before they received treatment. Short-term variability in these eyes was much greater than measurement variability. The limited published data on 12 eyes with refractory DME despite previous treatment suggest that short-term variability in these eyes is also larger than measurement variability.[20] A larger group of patients with refractory DME is reported

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herein. Based on a Pubmed search of the terms *diabetic macular edema* and *optical coherence tomography*, no similar data are available for eyes with regressed DME. Patients with regressed DME are addressed herein. In the eyes with refractory DME, estimated bounds on short-term fluctuation of macular thickness should be helpful in indicating when an eye is worsening and possibly in need of renewed treatment attempts. Knowledge of short-term variability in macular thickness should be useful in clinical management of eyes with regressed DME by providing bounds above which a change in macular thickness is likely to represent a recurrence of DME and not simply short-term variation in macular thickness.

Many cases of DME are refractory to focal laser photocoagulation, the only therapy with proven efficacy in a large, multicenter, randomized controlled clinical trial.[4] In the Early Treatment Diabetic Retinopathy Study (ETDRS),[4] 35% of the eyes randomized to immediate focal laser treatment continued to have clinically significant DME at the end of 1 year despite multiple treatments. Ten years later, in the British National Diabetic Retinopathy Laser Treatment Audit,[21] 35% of eyes treated with focal or grid laser treatment had not improved at 9 months follow-up. Twenty years after the ETDRS, with OCT now available for objective macular thickening measurement, the Diabetic Retinopathy Clinical Research (DRCR) Network randomized trial of modified ETDRS focal laser treatment vs modified macular grid laser treatment showed that 70% of the focal/grid laser group continued to have OCT-measured macular thickening at the end of 1 year despite one or more treatments.[22]

In brief, refractory DME remains an important clinical problem despite refinements in focal/grid photocoagulation technique in the past 20 years, including smaller spot size, allowance of laser wavelengths between green and yellow, no requirement that microaneurysms be darkened as long as a faint subjacent retinal pigment epithelial blanching is achieved, and no requirement that fluorescein angiography be used to guide treatment.[23] Other treatments of nonproven efficacy for DME, such as intravitreal triamcinolone or anti–vascular endothelial growth factor (VEGF) drugs and vitrectomy surgery, are also associated with persistence or recurrence of DME despite treatment.[24-27] Thus, the macular thickness variability of eyes with refractory DME has clinical importance.[20] Moreover, the natural history of visual acuity and macular thickness in eyes considered refractory to intervention for DME has been little investigated in the OCT era. It is unknown whether refractory DME tends to worsen once treatment attempts are halted, or whether spontaneous improvement in edema eventually occurs in some eyes. A secondary goal of this thesis, therefore, is to estimate the effect of refractory DME on visual acuity and macular thickness over time.

Although many cases of DME are refractory to treatment, the various available treatments for DME are effective in causing regression of DME in an important proportion of cases. In three DRCR network clinical trials with focal/grid photocoagulation treatment arms, 25% of 169 eyes had regression of DME at 4 months follow-up.[28] Because DME is a chronic disease subject to recurrences, however, monitoring of macular thickness must continue, usually aided by OCT measurements. The interpretation of these measurements depends on knowing the sources of variation, which include measurement error and short-term fluctuation. Thus, the study of macular thickness variability in eyes with regressed DME is clinically relevant. Besides the short-term variability of macular thickness, the natural history of visual acuity and macular thickness has not been studied in eyes with regressed DME. It is unknown whether such eyes progressively thin from neuronal atrophy over time or whether macular thickness remains stable. Another secondary goal of this thesis, therefore, is to determine whether macular thickness and visual acuity change over time in eyes with regressed DME.

To make concrete the clinical significance of the issues addressed in this work, two illustrative case reports are presented.

CASE 1

A 67-year-old woman who had type 2 diabetes for 28 years had a history of DME in both eyes. She had had argon laser focal/grid photocoagulation of the right eye three times previously as well as vitrectomy and internal limiting membrane peeling when the DME did not resolve after laser treatment. Panretinal photocoagulation of the right eye had been administered for proliferative diabetic retinopathy with regression of the neovascularization. Despite multiple treatments, refractory DME of the right eye persisted (Figure 1), yet her visual acuity was sufficient that she was able to read a newspaper and pass a driver's test. Treatment had been suspended as futile over the past 2 years, but she was monitored at 3- to 6-month intervals. The corrected visual acuity in March 2008 was 20/50 OD and 20/200 OS. The central subfield mean thickness (CSMT) of the right eye was 273 μm. The left eye had chronic, more severe, refractory DME. She returned 6 months later and reported worse blurring of vision. At that time visual acuity was 20/80 OD and 20/200 OS. The OCT-measured DME of the right eye had worsened, with CSMT of 371 μm (Figure 1). The fundus appearance and the fluorescein angiography for the right eye are shown in Figure 1. Loss of the ability to drive was feared, and reconsideration was therefore given to further intervention for the refractory DME. In attempting to decide the wisest recommendation for this patient, the question arose whether the 98-μm thickening of the CSMT witnessed between the last two visits was within the expected range of short-term OCT variability for eyes with refractory DME. In other words, was she truly worsening—showing increasing macular thickening—or was this compatible with short-term variability of macular thickening in an eye with refractory DME?

The patient returned 1 month later, and the CSMT and visual acuity of the right eye had improved spontaneously to 178 μm and 20/60, respectively (Figure 1). This macular thinning did not represent irreversible atrophy of the macula resulting from ischemic and edema-induced neuronal cell death, because at the next visit 6 weeks later, CSMT had increased again, to 336 μm (Figure 1). That is, as this case exemplifies and the data below will show, short-term fluctuation in CSMT in refractory DME can be larger than OCT measurement variability, which for an eye with macular thickness of 273 μm would be approximately 30 μm. The clinician may need to include this factor of short-term variability of macular thickness in refractory DME in clinical decision making to avoid restarting previously futile styles of treatment and possibly inducing further side effects, such as laser-induced paracentral scotomata or corticosteroid-induced pressure elevation, without benefiting visual acuity.[29,30] The currently available ophthalmic literature does not address this issue.

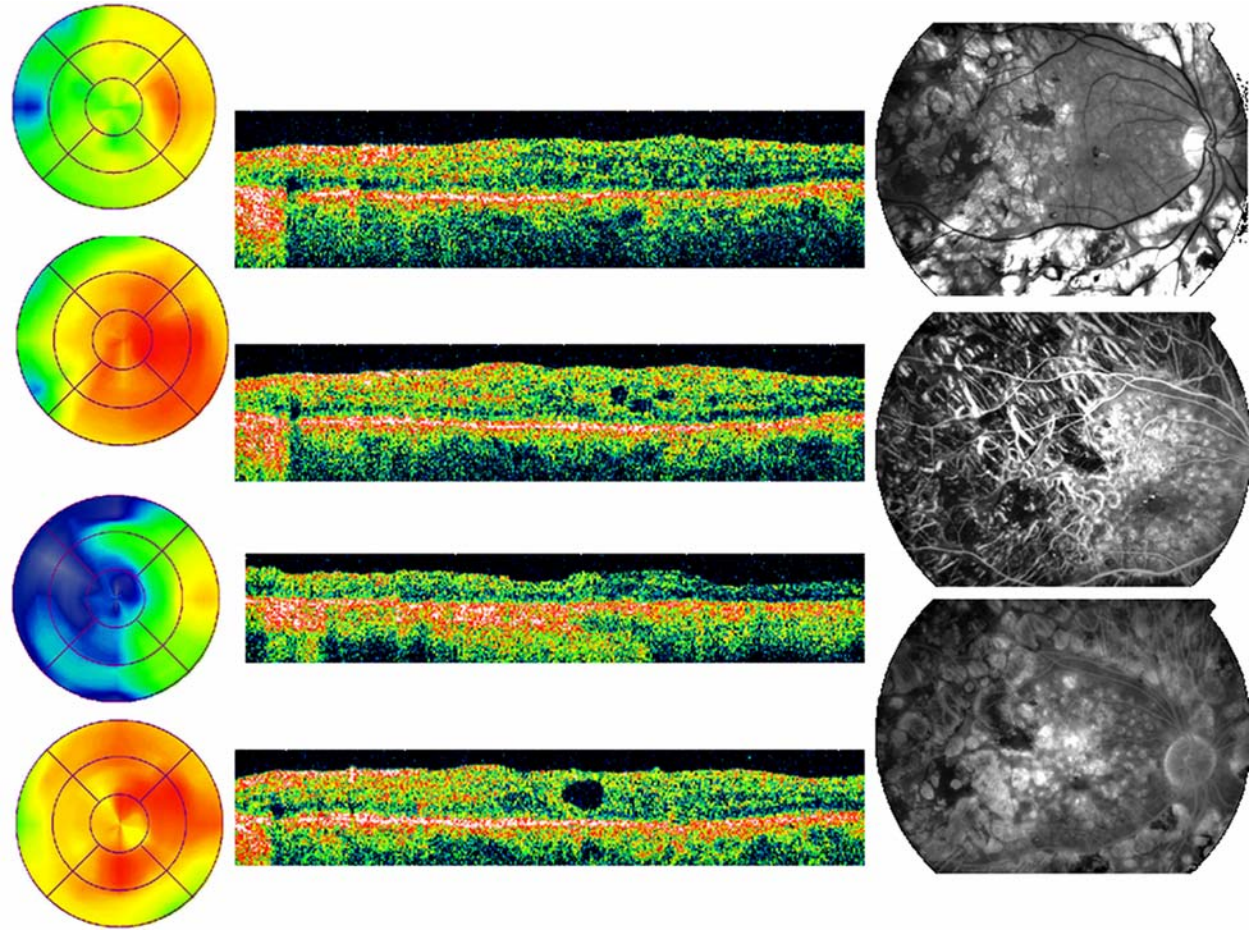

FIGURE 1

Case 1, right eye. Top row left and top middle, optical coherence tomography (OCT) images in March 2008, when the patient could see sufficiently to pass a driver's license examination. Second row left and middle, OCT images in September 2008, when the patient had experienced deterioration of visual acuity, had more difficulty driving, and was found to have increased diabetic macular edema (DME). Third row left and middle, OCT images in October 2008, when the patient had spontaneous regression of the exacerbated macular thickening. Fourth row left and middle, OCT images in December 2008, when the patient had spontaneous recurrent DME. All of the radial line scans are oriented vertically. Top right, Red-free photograph in September 2008, when exacerbation of DME was observed. Two large microaneurysms on the foveal avascular zone border and several others more remote from the border are noted. Middle right, Midphase fluorescein angiogram in September 2008. The location of two large microaneurysms on the border of the foveal avascular zone is documented. Bottom right, Late-phase fluorescein angiogram in September 2008. There is petalloid hyperfluorescence most prominent superior and temporal to the fovea, although the epicenter of the thickening on the OCT false color map is inferonasal to the fovea.

CASE 2

A 77-year-old man with diabetes mellitus of 10 years duration and hypertension of 1 year duration was examined in 2000 and found to have DME, reducing visual acuity in the left eye to 20/50. No OCT was available in our clinic in 2000, but clinically significant macular edema was found on stereoscopic slit-lamp biomicroscopy with a noncontact fundus lens, and two sessions of argon laser focal/grid photocoagulation were given on March 16, 2000, and January 28, 2002. The DME resolved both on clinical examination and by OCT measurements once that instrument became available to the practice. During follow-up, four consecutive normal CSMTs were recorded between January 25, 2005, and August 21, 2007, in consonance with the clinical examination that showed no macular thickening on stereoscopic slit-lamp biomicroscopy. The appearance of the fundus at this time is shown in Figure 2. At follow-up on May 9, 2008, the CSMT increased to 283 μm compared to the value of 205 μm on August 21, 2007 (Figure 2). Clinically the center of the macula was judged to be not thickened. The question arose whether the 78-μm increase in macular thickness represented a change in the macula in excess of the short-term fluctuation in macular thickness in an eye with regressed DME. In other words, was this recurrent DME, and did it need to be treated?

The patient was observed without treatment, and at follow-up on November 11, 2008, he was noted to have spontaneous resolution of the macular thickening present at the previous examination (Figure 2). That is, as this case exemplifies and the data below will show, short-term fluctuation in CSMT in regressed DME is potentially larger than OCT measurement variability. For an eye with macular thickness of 205 μm, measurement variability would be approximately 21 μm. The clinician may be advised to include the larger short-term fluctuation factor for eyes with regressed DME in clinical decision making. The currently available ophthalmic literature does not address this issue.

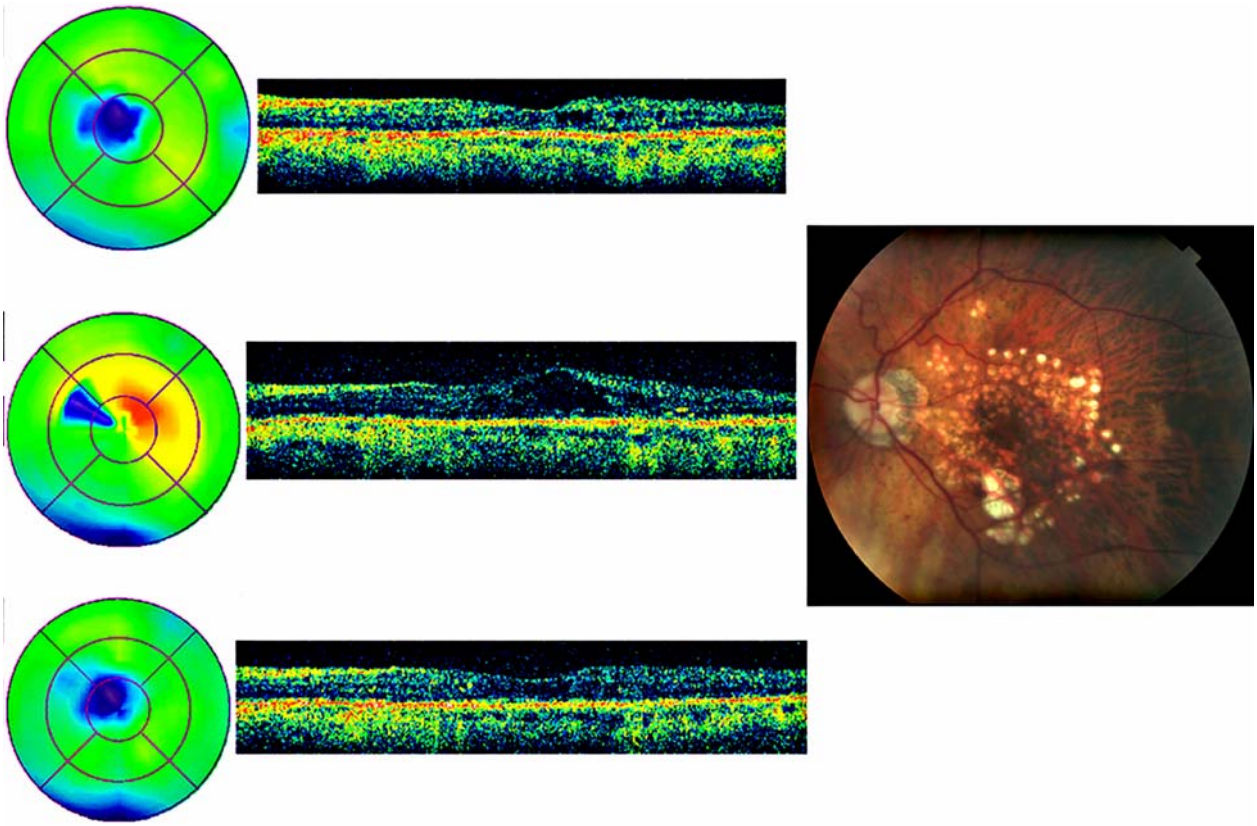

FIGURE 2

Case 2, left eye. Left panels, Three optical coherence tomography (OCT) false color maps documenting the regional pattern of macular thickness in a patient with regressed diabetic macular edema (DME) after two sessions of focal/grid photocoagulation given 7 years earlier. On 5/9/2008 (middle left panel) there is OCT thickening that was not present at the 8/21/2007 visit (top left panel). Without any therapy, there is spontaneous regression of this thickening as shown in the map from 11/11/2008 (bottom left panel). Middle panels, Three OCT horizontal radial line scans documenting the macular morphology on the same three dates shown in the left panels. On 5/9/2008 (middle panel, second row) there is intraretinal cystoid change and thickening that was not present on 8/21/2007 (middle panel, top row). The thickening has spontaneously resolved by the scan of 11/11/2008 (middle panel, bottom row), although there is still some lesser degree of intraretinal cystoid change. Right panel, Color fundus photograph documenting the appearance with regressed DME and a pattern of focal/grid laser scars.

METHODS

This report is a retrospective study of data extracted from the clinical charts and OCT records of two groups of eyes of patients with diabetic retinopathy—refractory DME and regressed DME. The Presbyterian Hospital (Charlotte, North Carolina) Institutional Review Board approved this retrospective chart review. Both series of cases derive from a single retina referral practice.

In the refractory DME group, 36 eyes of 29 consecutive patients were studied. All patients had DME that had been treated with argon laser focal/grid photocoagulation, and most had undergone other types of treatment, yet clinically significant DME persisted (refractory DME). In each patient, treatment efforts for DME had been suspended by the ophthalmologist because of apparent futility

after repeated treatments or by the patient's refusal to undergo recommended further treatment. *Apparent futility* is a concept recognized in the ETDRS and DRCR Network studies. Patients cannot be indefinitely re-treated with focal/grid laser photocoagulation. Eventually there is no further room for treatment, and the risk of scotoma formation from laser scarring outweighs the potential benefit of further laser treatment. Apparent futility for treatment modalities other than focal laser has been explicitly defined in DRCR Network protocols.[31] We refer to these definitions to establish that futility is a recognized concept in DME management.

For inclusion in the study, clinically significant DME or OCT-measured macular edema was necessarily present at the first and last visit of the study interval. Diabetic macular edema was classified as clinically significant based on slit-lamp biomicroscopy with a noncontact fundus lens. The definition of clinically significant macular edema used in this study is thickening on clinical examination at or within 500 μm of the center of the macula or retinal thickening greater than a disc area in size, any part of which is within 1 disc diameter of the center of the macula.[4] No patient had vitreomacular adhesion with a glistening, taut posterior hyaloid as seen on fundus biomicroscopy, nor did any patient have OCT evidence of vitreomacular adhesion including a thickened posterior hyaloid.[32-34] OCT-measured macular edema is defined as a CSMT ≥250 μm. At least two OCT studies had to be performed during the follow-up period for inclusion, and all available OCT studies obtained during follow-up were included in the data analysis. In an effort to remove confounding effects of treatments for DME and isolate the posttreatment course of refractory DME, no treatment known to affect DME could have been administered for 3 months before the baseline examination for this study or during the follow-up period, including focal/grid laser treatment, intravitreal injections of triamcinolone or anti-VEGF drugs, vitrectomy surgery, panretinal photocoagulation, cataract surgery, or other intraocular surgery. Visual acuity (logarithm of the minimum angle of resolution [logMAR]) was obtained using ETDRS charts, but protocol refractions were not performed. Visual acuity was obtained with the patient's spectacles, if spectacles were worn, with and without a superimposed pinhole. The visual acuity used was the better of the corrected vision or corrected vision through a pinhole. Patients were accrued by a review of the practice records and constitute a consecutive series of patients with refractory DME encountered in one retina practice between May 20, 2003, and July 9, 2009. Visual acuity analyses were performed only for the subset of patients who were pseudophakic before the interval of data collection, because of the confounding influence of progressing cataract in those patients who were phakic, an approach taken before in studies of DME.[35] To help in orienting the reader to the figures in which visual acuity is the ordinate, an increasing logMAR and normalized logMAR visual acuity equate to a decreasing Snellen visual acuity (worsening visual acuity).

In the regressed DME group, 93 eyes of 93 consecutive patients from a single retina practice were studied. All patients had DME that had been treated with focal argon laser, and many had other types of treatment with successful clinical resolution of DME. For inclusion in the study, macular thickening had to be clinically absent during each follow-up visit throughout the study. At least two OCT studies had to be performed during the follow-up period for inclusion, and all available OCT studies obtained during follow-up were included in the data analysis. No treatment known to affect DME could have been administered for 4 months before the baseline examination for this study or during the follow-up period, including focal laser treatment, intravitreal injections of triamcinolone or anti-VEGF drugs, vitrectomy surgery, panretinal photocoagulation, cataract surgery, or other intraocular surgery. Visual acuity (logMAR) was obtained using ETDRS charts, but protocol refractions were not performed. Visual acuity was obtained with the patient's spectacles, if spectacles were worn, with and without a superimposed pinhole. The visual acuity used was the better of the corrected vision or corrected vision through a pinhole. Patients were accrued by a review of the practice records and constitute a consecutive series of patients with regressed DME between October 13, 2003, and November 8, 2007. Visual acuity analyses were performed only for the subset of patients who were pseudophakic before the interval of data collection, because of the confounding influence of progressing cataract in those patients who were phakic, an approach taken before in studies of DME.[35]

For both groups, OCT studies were performed on a Zeiss Meditec Stratus OCT3 machine (Dublin, California). The 3.45-mm display was used for all OCTs in the study. The numerical OCT data were extracted from the machine printout. No manual measurements were done. Only OCT studies with signal strength ≥4 and standard deviation of the centerpoint thickness determination ≤20 μm were included in the study. No OCT study had analysis confidence low. For both groups, the clinical classification of diabetic retinopathy severity was based on the International Clinical Diabetic Retinopathy Severity Scale.[36]

Descriptive statistics and analysis of variance were performed with JMP software, version 4.0 (2001, SAS Institute, Inc, Cary, North Carolina). Variation in CSMT and total macular volume (TMV) for each eye were calculated as the maximal value minus the minimal value for the respective variables during the follow-up period.[21,37] Normalized CSMT, TMV, and logMAR visual acuity were calculated by dividing CSMT, TMV, and logMAR visual acuity by their respective baseline values. For the comparison of variation in CSMT and TMV between refractory DME and regressed DME groups, the Mann-Whitney test was used. For the analyses of influence of binary or ordinal baseline factors on variation in CSMT and TMV, a nonparametric method was used (Kruskal-Wallis test) as the distributions were nonnormally distributed by Shapiro-Wilk testing.

RESULTS

REFRACTORY DME GROUP

Of the 29 patients in the refractory DME group, 16 (55%) were male (Table 1). Twenty-two (76%) of the patients were white, and 7 (24%) were black. Median age was 67 years (interquartile range [IQR], 63-72 years). Median duration of diabetes was 15 years (IQR, 10-26 years). Sixteen (55%) were taking insulin. Twenty-four (83%) were taking antihypertensive medications. Median baseline

diastolic blood pressure was 75 mm Hg (IQR, 70-82 mm Hg). Median baseline systolic blood pressure was 135 mm Hg (IQR, 121-151 mm Hg). Baseline hemoglobin A_{1C} was available in 19 patients, with a median value of 6.5 (IQR, 6.2-7.1).

TABLE 1. CHARACTERISTICS OF EYES WITH REFRACTORY DME AND REGRESSED DME

CHARACTERISTIC	REFRACTORY DME GROUP	REGRESSED DME GROUP
Patients	29	93
Eyes	36	93
Gender, F (%)	13 (45%)	45 (48%)
Race, W (%)	22 (76%)	63 (68%)
Age, median, IQR	67 (63, 72)	66 (60, 72)
Duration of DM, median, IQR	15 (10, 26)	19 (13, 25)
Taking insulin (%)	16 (55%)	60 (65%)
Taking BP medication (%)	24 (83%)	83 (89%)
Baseline DBP, median, IQR	75(70, 82)	75 (69, 81)
Baseline SBP, median, IQR	135 (121, 151)	140 (129, 154)
Baseline HbA_{1c}, median, IQR	6.5 (6.2, 7.1)	7.0 (6.4, 8.0)
Retinopathy level		
NPDR	16 (44%)	52 (56%)
PDR	1 (3%)	4 (4%)
Regressed PDR	19 (53%)	37 (40%)
Previous treatments potentially influencing DME		
Focal photocoagulation	36 (100%)	93 (100%)
IVTA	18 (50%)	20 (22%)
IVB	6 (17%)	2 (2%)
VTX/ILM peel	12 (33%)	21 (23%)
PRP	18 (50%)	50 (54%)
CE/IOL	16 (44%)	32 (34%)
Time from last treatment (months), median, IQR	7 (5, 17)	18 (10, 39)
Interval of OCTs (months), median, IQR	7 (4, 21)	22 (13, 22)
Baseline CSMT (μm), median, IQR	321 (262, 387)	217 (184, 249)
Baseline TMV (mm^3), median, IQR	2.86 (2.50, 3.04)	2.44 (2.18, 2.63)
Baseline Snellen VA (logMAR VA), median, IQR	20/50 (0.40) (0.301, 0.602)	20/30 (0.17) (0.097, 0.349)
Dependence of variation of CSMT on factors, Y/N, *P* value*		
Baseline CSMT	N (.5852)	Y (<.0001)
Age	N (.8855)	Y (.0383)
Gender	N (.3236)	N (.8960)
Race	N (.2233)	N (.0587)
Duration of diabetes	N (.2886)	N (.1042)
HbA_{1c}	N (.3556)	N (.2929)
Use of BP medication	N (.3841)	N (.4871)
Use of insulin	N (.2720)	N (.4194)
Retinopathy level	N (.3063)	N (.1598)
Interval of OCTs	Y (.0248)	Y (.0125)
Variation of CSMT, median, IQR	89 (46, 158)	19 (10, 52)
Variation of TMV, median, IQR	0.38 (0.18, 0.68)	0.13 (0.066, 0.0254)
Rate of decline of VA (days per ETDRS letter lost)	72	81

BP, blood pressure; CE/IOL, cataract extraction with intraocular lens implantation; CSMT (μm), central subfield mean thickness; DBP, diastolic blood pressure; DM, diabetes mellitus; DME, diabetic macular edema; ETDRS; Early Treatment Diabetic Retinopathy Study; HbA_{1c}, hemoglobin A_{1c}; IQR, interquartile range; IVB, intravitreal bevacizumab; IVTA, intravitreal triamcinolone; logMAR, logarithm of the minimum angle of resolution; NPDR, nonproliferative diabetic retinopathy; OCT, optical coherence tomography; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation; SBP, systolic blood pressure; TMV (mm^3), total macular volume; VA, visual acuity; VTX/ILM peel, vitrectomy and internal limiting membrane peeling.

*Kruskal-Wallis testing.

The distribution of the 36 eyes in the refractory DME group by levels of retinopathy was as follows: mild nonproliferative retinopathy, 8 (22%); moderate nonproliferative retinopathy, 8 (22%); proliferative retinopathy, 1 (3%); and regressed proliferative retinopathy following previous panretinal laser photocoagulation, 19 (53%).

Median baseline CSMT was 321 μm (IQR, 262-387 μm). Median baseline TMV was 2.86 mm^3 (IQR, 2.50-3.04 mm^3). Median baseline logMAR visual acuity was 0.40 (20/50) (IQR, 0.301-0.602 [20/40-20/80]).

All eyes had been treated previously with focal laser. The total number of treatments ranged from 1 to 6 (median 2, IQR 1-3). The total number of focal laser spots given ranged from 119 to 1760 (median 542, IQR 332-889, n=32 [four operative notes lacked number of focal spots]). Eighteen eyes (50%) had previous intravitreous injection(s) of triamcinolone. Six eyes (17%) had a previous intravitreous injection of bevacizumab. Twelve eyes (33%) had previous vitrectomy with internal limiting membrane peeling. Eighteen eyes (50%) had previous panretinal laser photocoagulation. Sixteen eyes (44%) had uncomplicated cataract surgery with posterior chamber intraocular lens implants before the interval of data collection. The duration of time from the last treatment for DME or potentially influencing DME ranged from 3 months to 58 months (median 7 months, IQR 5-17 months).

The follow-up intervals of eyes with refractory DME ranged from 1 to 43 months (median 7 months, IQR 4-21 months). The number of OCTs obtained during follow-up observation ranged from 2 to 12 (median 3, IQR 2-5).

For the 36 eyes in the study, there were 142 OCTs obtained during the follow-up period. The CSMTs and TMVs for each eye were normalized by the baseline values in order to pool the data and look for any time-dependent behavior. Figure 3 shows normalized CSMT plotted vs follow-up time. The slope of the best fit line (0.001 per month of follow-up) did not differ from zero (*P*=.5482). Because of the lack of time dependence, for each eye the replicate CSMT values during the follow-up period were treated as a single sample to determine variation in CSMT. The median variation was 89 μm (IQR 46-158 μm, range 9-310 μm). A plot of variation in CSMT vs baseline CSMT showed no dependence of variation in CSMT on baseline CSMT (slope of best fit line 0.08, *P*=.5852). The variation in CSMT did not depend on age, sex, race, duration of diabetes, hemoglobin A_{1C}, use of antihypertensive medications, use of insulin, or clinically determined retinopathy level (*P*=.8855, .3236, .2233, .2886, .3556, .3841, .2720, and .3063, respectively). A plot of variation in CSMT vs follow-up time showed dependence of variation in CSMT on length of follow-up (slope of best fit line 3 μm/month, *P*=.0248).

Figure 3 also shows normalized TMV plotted vs follow-up time. The slope of the best fit line (-0.0001 per month of follow-up) did not differ from zero (*P*=.8895). Because of the lack of time dependence, for each eye the replicate TMV values during the follow-up period were treated as a single sample to determine variation in TMV. The median variation was 0.38 mm^3 (IQR 0.18-0.68 mm^3, range 0.05-2.64 mm^3). A plot of variation in TMV vs baseline TMV showed a statistically significant dependence (slope of best fit line 0.41 mm^3/month, *P*=.023). A plot of variation in TMV vs follow-up time showed dependence of variation in TMV on length of follow-up (slope of best fit line .02 mm^3/month, *P*=.0065).

Figure 4 shows normalized logMAR visual acuity vs time for the 16 eyes that were pseudophakic before the interval of data collection. The best fit line to the data shows a deterioration of visual acuity with time amounting to a loss of 1 ETDRS letter per 72 days (*P*=.0393).

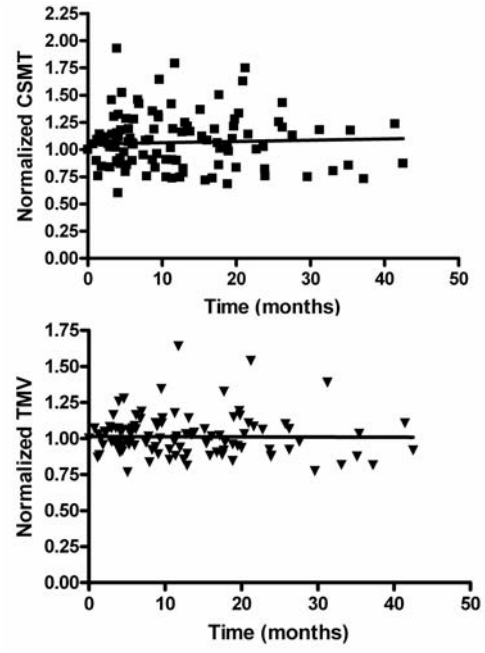

FIGURE 3

Top, Plot of normalized central subfield mean thickness (CSMT) vs time for eyes with refractory diabetic macular edema (DME). The slope of the best fit line does not differ from zero (*P*=.5482). Bottom, Plot of normalized total macular volume (TMV) vs time for eyes with refractory DME. The slope of the best fit line does not differ from zero (*P*=.8895).

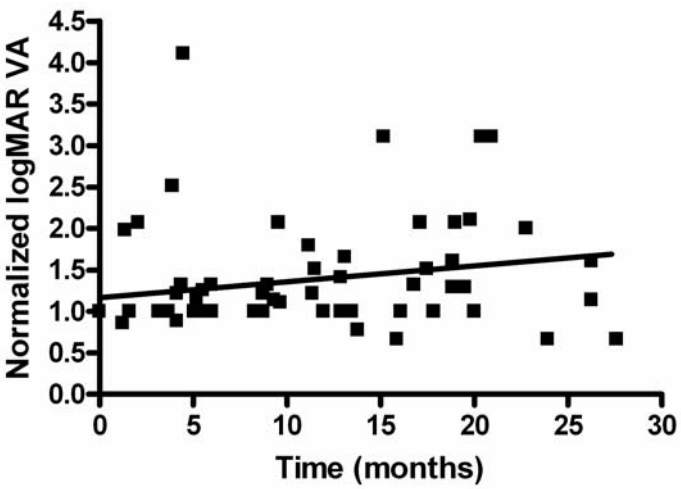

FIGURE 4

Plot of the normalized logarithm of the minimal angle of resolution (logMAR) visual acuity (VA) vs time for pseudophakic eyes with refractory diabetic macular edema. The slope of the best fit line differs significantly from zero (*P*=.0393) and indicates a decrease in visual acuity over time. Based on the average baseline logMAR VA, this decrease averages approximately 1 ETDRS letter lost per 72 days.

REGRESSED DME GROUP

Of the 93 patients in the regressed DME group, 45 (48%) were female (Table 1). Sixty-three (68%) of the patients were white, 29 (31%) were black, and 1 (1%) was Asian. Median age was 66 years (IQR, 60-72 years). Median duration of diabetes was 19 years (IQR, 13-25 years). Sixty (65%) were taking insulin, and 83 (89%) were taking antihypertensive medications. Median baseline diastolic blood pressure was 75 mm Hg (IQR, 69-81 mm Hg). Median baseline systolic blood pressure was 140 mm Hg (IQR, 129-154 mm Hg). Baseline hemoglobin A_{1C} was available in 66 of 93 patients with median value 7.0 (IQR, 6.4-8.0).

The distribution of 93 eyes in the regressed DME group by levels of retinopathy was as follows: mild nonproliferative retinopathy, 42 (45%); moderate nonproliferative retinopathy, 6 (6%); severe nonproliferative retinopathy, 4 (4%); proliferative retinopathy, 4 (4%); and regressed proliferative retinopathy following previous panretinal laser photocoagulation, 37 (40%).

Median baseline CSMT was 217 µm (IQR, 184-249 µm). Median baseline TMV was 2.44 mm^3 (IQR, 2.18-2.63 mm^3). Median baseline logMAR visual acuity was 0.174 (20/30) (IQR, 0.097-0.349 [20/25-20/45]).

All eyes had been treated previously with focal laser. The total number of treatments ranged from 1 to 4 (median 2, IQR 1-2). Twenty eyes (22%) had previous intravitreous injection(s) of triamcinolone. Two eyes (2%) had a previous intravitreous injection of bevacizumab. Twenty-one eyes (23%) had previous vitrectomy with internal limiting membrane peeling. Fifty eyes (54%) had previous panretinal laser photocoagulation. The duration of time from the last treatment for DME or potentially influencing DME ranged from 6 months to 150 months (median 18 months, IQR 10-39 months).

The follow-up intervals of eyes with regressed DME ranged from 1 to 51 months (median 22 months, IQR 13-32 months). The number of OCTs obtained during follow-up observation ranged from 2 to 10 (median 4, IQR 2-5).

For the 93 eyes in the study, there were 378 OCTs obtained during the follow-up period. The CSMTs and TMVs for each eye were normalized by the baseline values in order to pool the data and look for any time-dependent behavior. Figure 5 shows normalized CSMT plotted vs follow-up time. There was evidence of slight progressive macular thinning over the follow-up period (*P*<.0001).

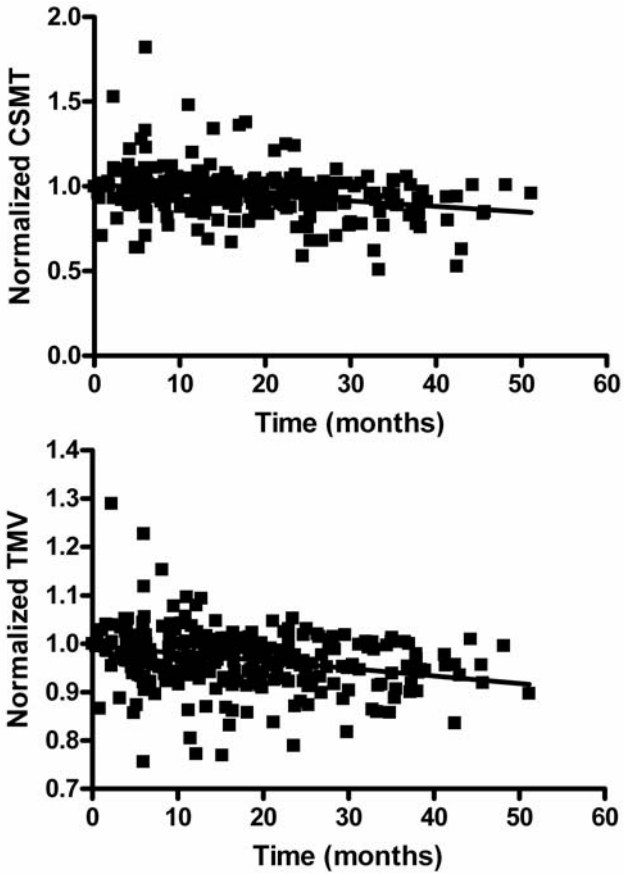

FIGURE 5

Top, Plot of normalized central subfield mean thickness (CSMT) vs time for eyes with regressed diabetic macular edema (DME). The slope of the best fit line was -0.003 per month of follow-up (*P*<.0001). Bottom, Plot of normalized total macular volume (TMV) vs time for eyes with regressed DME. The slope of the best fit line was -0.0016 per month of follow-up (*P*<.0001).

Because the slope of the best fit line (-0.003 per month of follow-up) was small, the replicate CSMT values during the follow-up period were treated as single samples to determine variation in CSMT for each eye. The median variation was 19 µm (IQR 10-52 µm, range 1-170 µm). A plot of variation in CSMT vs baseline CSMT showed that variation in CSMT increases with baseline CSMT (slope of best fit line 0.38, *P*<.0001). The variation in CSMT did not depend on gender, race, duration of diabetes, hemoglobin A_{1C}, use of antihypertensive medications, use of insulin, or clinically determined retinopathy level (*P*=.8960, .0587, .1042, .2929, .4871, .4194, and .1598, respectively). The data suggest that variation in CSMT increases with increasing age (*P*=.0383). A plot of variation in CSMT vs follow-up time showed no clinically important dependence of variation in CSMT on length of follow-up (slope of best fit line 0.8 µm/month, *P*=.0125).

Figure 5 shows normalized TMV plotted vs follow-up time. There was evidence of slight progressive macular volume decrease over the follow-up period (*P*<.0001).Because the slope of the best fit line was small (-0.0016 per month of follow-up), the replicate TMV values during the follow-up period were treated as single samples for each eye to determine variation in TMV. The median variation was 0.13 mm^3 (IQR 0.066-0.254 mm^3, range 0.003-0.817 mm^3). A plot of variation in TMV vs baseline TMV suggested that variation of TMV increases with the value of baseline TMV (slope of best fit line 0.15 mm^3/month, *P*=.0038).

Figure 6 shows normalized logMAR visual acuity vs time for the 32 eyes that were pseudophakic before the interval of data collection. The best fit line to the data shows a deterioration of visual acuity with time amounting to a loss of 1 ETDRS letter per 81 days (*P*=.0024).

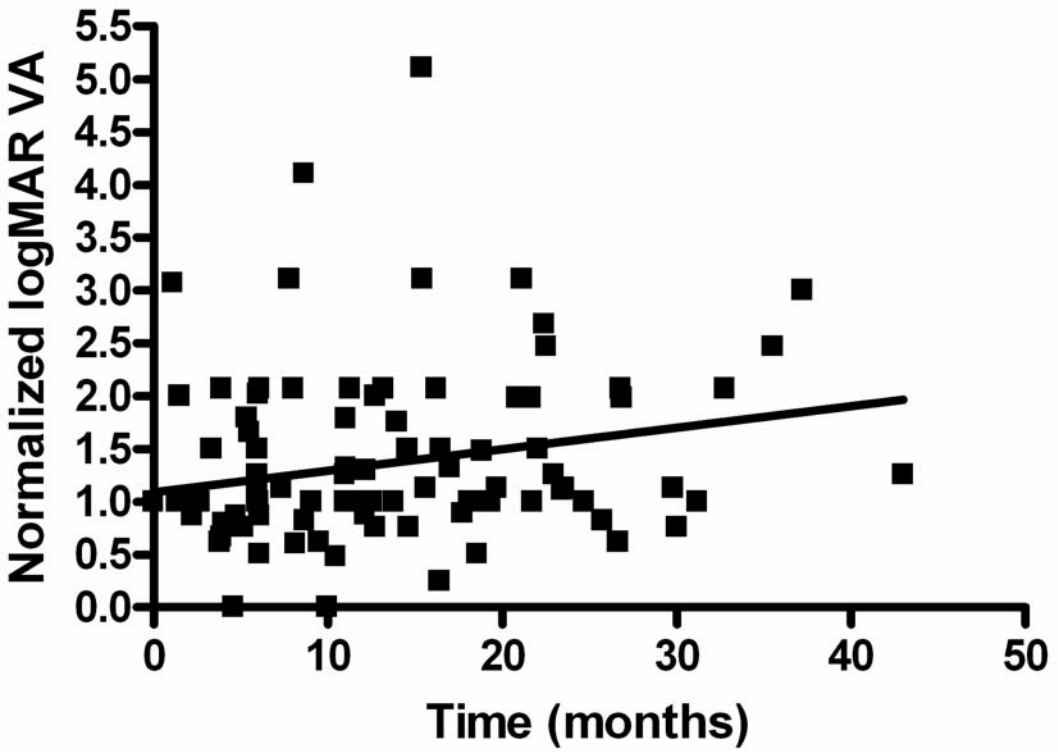

FIGURE 6

Plot of the normalized logarithm of the minimal angle of resolution (logMAR) visual acuity (VA) vs time for eyes with regressed diabetic macular edema. The slope of the best fit line differs significantly from zero (*P*=.0024) and indicates a decrease in VA over time. Based on the average baseline logMAR VA, this decrease averages approximately 1 ETDRS letter lost per 81 days.

COMPARISON OF REFRACTORY DME AND REGRESSED DME GROUPS

The variation of CSMT differed between the refractory DME and regressed DME groups. The median variation for CSMT was 89 µm and 19 µm for the refractory DME and regressed DME groups, respectively (*P*<.0001). The median variation for TMV was 0.38 mm^3 and 0.13 mm^3 for the refractory DME and regressed DME groups, respectively (*P*<.0001).

DISCUSSION

Primary goals of physicians are to help patients preserve and regain health and to avoid treatments that might cause harm.[38] Toward these goals, physicians use measurements of biologic variables to determine if disease is present and, if present, is abating or worsening in response to treatment. The range of variability is large among the types of measurements physicians make, and types of measurements characterized by low variability are prized by physicians. For example, in internal medicine, the presence or absence of hepatomegaly to abdominal palpation is highly variable from examiner to examiner and has relatively low clinical value as a result, especially when negative, whereas body mass measurements have low variability and are prized clinical data in part for this reason.

In ophthalmology, OCT measurement of macular thickness is a prized measurement in part because it has low variability as compared to assessment of macular thickness by other techniques, such as slit-lamp biomicroscopy or grader assessment of stereoscopic color fundus photographs.[39,40] Despite the recognition of the clinical value added by OCT, our understanding of the characteristics of this ancillary test is incomplete. Sources of variation in OCT measurements include measurement variability, diurnal variation in macular thickness, and short-term variation in macular thickness. Measurement variability refers to the variation in macular thickness that arises from imprecision in the instrument and its use. This component assesses variability that occurs when a measurement is made several times within a short time span. It can be further decomposed into intraobserver variability, when the measurements are repeatedly made by the same observer over a short time span, and interobserver variability, when the measurements are made by different observers over a short time span. Theoretically, one can also speak of intermachine variability; however, it is generally assumed that this variability is small relative to other sources of variability, and in the typical clinical setting, measurements are generally made on the same machine over time.

Intraobserver variation in normal eyes is expressed as the coefficient of repeatability, which is the change in measurement above which one can be 95% confident that a real change in the macular thickness has occurred.[41,42] This value has been reported to be 37 µm in normal eyes.[10] In eyes with DME, which can vary in thickness, the absolute value of the coefficient of repeatability depends on the macular thickness such that the coefficient of repeatability increases with macular thickness, but the relative value of the coefficient of repeatability does not so vary.[12] The relative value of the coefficient of repeatability is 11% in DME over a wide range of macular thicknesses.[12] That is, one can be 95% confident that a change in thickness of more than 11% represents a real change in macular thickness and not measurement variation. Interobserver variation in macular thickness has been less studied than intraobserver variation but appears to be no greater than intraobserver variation.[11] Diurnal variability in DME is small relative to measurement variability in DME, and accommodation for it need not be made in clinical care.[17]

Whereas it is widely recognized that OCT measurement variability exists, and that diurnal variability of macular thickness is present for certain diseases, the effects of day-to-day variability in cardiorenal function and systemic fluid balance on OCT variability have been unstudied. In this thesis, work is reported attempting to redress this lack of information. The work represents continuation of a multistage project. The first stage concerned patients with diabetes with retinopathy but without clinical DME. Short-term variation in macular thickness for these eyes was insignificantly greater than OCT measurement variability (Table 2).[18] In the present work, the cohorts of interest were eyes with refractory and regressed DME, respectively. Toda and colleagues[19] have reported on short-term variability of macular thickness in eyes with treatment-naïve DME. The last group to consider, patients with DME in the midst of treatment, would be difficult to study. One cannot separate the effects of the treatment from the variability of the macular thickness that results from the disease alone.

TABLE 2. SHORT-TERM VARIATION IN CENTRAL SUBFIELD MEAN THICKNESS IN SUBGROUPS OF EYES WITH DIABETIC RETINOPATHY

DIABETIC RETINOPATHY GROUP	STUDY	n	BASELINE CSMT, MEDIAN, IQR, µm	SHORT-TERM VARIATION IN CSMT, MEDIAN, (IQR), [RANGE], µm
Diabetic retinopathy without DME	Browning et al[18]	56	219 (195-235)	18 (11-31) [2-172]
Treatment-naïve DME	Toda et al[19]	8	374 (274-761)	137 (54-237) [27-299]
Refractory DME	Present work	36	321 (262-387)	89 (46-158) [9-310]
	Massin[20]	12	463 (407-541)	153 (80-296) [40-368]
Regressed DME	Present work	93	217 (184-249)	19 (10-52) [1-170]

CSMT, central subfield mean thickness; DME, diabetic macular edema; IQR, interquartile range.

Diabetic macular edema is a chronic disease that can wax and wane over the course of many years and require multiple treatments over time.[43] Decisions regarding when to apply treatment for DME depend critically on OCT, which provides objective measurements of macular thickness that have superseded the subjective clinical assessments of macular thickness by contact and noncontact lens slit-

lamp biomicroscopy popularized in the ETDRS era.[44] It is established that OCT more accurately detects presence and absence of DME, particularly in eyes with mild degrees of thickening.[6,7] In eyes with macular thickness less than 300 μm, clinical examination with a fundus contact lens has been estimated to miss DME 77% of the time.[7] In the DRCR clinical trial comparing modified macular grid photocoagulation and modified ETDRS photocoagulation, such eyes having center point thickness less than 300 μm accounted for 55% of all eyes enrolled.[22] Given the importance of OCT in the longitudinal follow-up of patients with DME, understanding the characteristics of the measurement method is important in properly interpreting OCT data. In particular, the clinician needs to know the sources of variation of OCT measurements and their respective sizes.

REFRACTORY DME

There has been no previous formal study of short-term variation of macular thickness in refractory DME, although one can deduce insights from published data gathered for other purposes. Two separate cases of marked variation in OCT-measured macular thickness in refractory DME have been reported, as has one case series studying the variability of persistent DME despite previous focal photocoagulation.[15-17] Massin and colleagues[20] reported on 12 patients with persistent DME despite focal photocoagulation who had three or four macular thickness measurements over a 6-month period. These eyes with mean baseline thickness of 474 μm did not show a change in mean macular thickness over the period of follow-up, but they experienced significant variation in macular thickness from visit to visit. The median variation was 153 μm (IQR 76-296 μm, range 40-296 μm). Our results were similar to those of Massin and colleagues, although our sample had eyes generally less edematous than that of Massin and colleagues, with median baseline thickness of 324 μm. There was no trend for change in macular thickness over a median follow-up of 7 months. The median range of variation was 89 μm (IQR 46-158 μm, range 9-310 μm). The absolute coefficient of repeatability for OCT measurements has been reported to be 37 μm in eyes without DME, and the relative coefficient of repeatability to be 11% of the macular thickness in eyes with DME not characterized as refractory; thus, this study and that of Massin and colleagues suggest that day-to-day variation in macular thickness of eyes with refractory DME can be greater than OCT measurement error.[10,12] This should be taken into account in making treatment decisions in DME. Increase in CSMT at a single visit may represent a transient fluctuation in the course of macular thickness and may not imply a need for additional intervention. In Case 1 reported herein, the patient returned 1 month after the exacerbation in macular thickening with spontaneous resolution of her increase in macular thickness and decrease in visual acuity.

Massin and colleagues[20] did not examine the possible effect of patient or eye factors on variation in CSMT in eyes with refractory DME. We found no evidence to suggest that the commonly assessed patient and eye factors in patients with DME influence variation in CSMT in refractory DME, but caution is required in interpreting these negative findings because our sample size was only 36, making it difficult to detect potentially small effects. Moreover, in general, our patients had relatively good blood pressure and glycemic control, such that potential effects of more elevated blood pressures and blood glucose cannot be ruled out from results derived from our sample. In addition, duration of DME could conceivably influence the course of refractory DME, but duration of DME is difficult to determine and could not be assessed in this retrospective study. Patients with poor glycemic control, more elevated blood pressure, and renal insufficiency might show different variation in macular thickness than that observed in our sample. Further studies in samples more diverse with respect to these factors are needed to test these possibilities.

In a related type of study, Toda and colleagues[19] reported on the spontaneous variability of central subfield mean thickness in eight eyes with treatment-naïve clinically significant macular edema over a 3-month period of observation. These eyes, with mean baseline thickness of 478 μm, did not show a change in mean macular thickness over the period of follow-up, but they experienced significant variation in macular thickness from visit to visit. The median variation was 137 μm (IQR 54-237 μm, range 27-299 μm).[19] It therefore appears, based on the literature, that the spontaneous variability in macular thickness in treatment-naïve eyes with DME and eyes with refractory DME is similar in magnitude and larger in both cases than measurement variability in eyes with or without DME.

The data presented tend to support the clinical impression that refractory DME exerts injurious effects on the macula with adverse consequences to visual acuity. A statistically significant decrease in the slope of visual acuity over time was documented in the eyes with refractory DME. The ETDRS showed that eyes with untreated DME lose visual acuity over time.[4] Eyes with DME refractory to treatment similarly lose visual acuity over time. For the eyes in the studied sample, the estimated rate of visual acuity loss was 1 ETDRS letter per 72 days. Thus, although available treatments for DME have expanded beyond focal/grid laser photocoagulation, there remain eyes unresponsive to available interventions, and additional effective salvage therapies are needed.

Because short-term variation in refractory DME has a larger size than measurement variability, it may be necessary to obtain more measurements to develop confidence of a suspected trend in the true value of macular thickness. This is a general principle in attempts to extract a signal from measurements that are noisy.[45] Longitudinal display of OCT data can aid the clinician in detecting a signal in the midst of noise in OCT data.[43]

REGRESSED DME

Treatments for DME are designed to induce regression of the edema, but eyes with regressed DME have not been closely studied. Although it is known that DME can recur in eyes with successfully treated DME, the short-term variability of OCT-measured macular thickness in such eyes is unknown. Our data suggest that the short-term variability is smaller than in eyes with refractory DME, but larger than measurement error. Additionally, our data showed slight progressive macular thinning and volume decrease in eyes after successfully treated DME and slow and slight progressive deterioration of visual acuity over a median follow-up of 22 months in the absence of macular thickening. A slow decrease in visual acuity may result from the effects of ischemia. Further studies looking for evidence of late macular atrophy in eyes with regressed DME and possible functional consequences may be worthwhile.

To apply our results to the patient described in Case 2, the 78-μm increase in macular thickening that was documented is not only within the range of macular thickness variation seen in eyes with regressed DME, but is within the 90th percentile of short-term variation. On the basis of this information, there should be no rush to consider the eye to have recurrent DME and apply further treatment. In fact, as Figure 2 shows, without further treatment the macular thickening regressed spontaneously and fell into the normal range again. As with eyes having refractory DME, when in doubt, a longer period of observation and further OCT measurements can help to establish whether OCT changes represent signal or noise.

OTHER CLINICAL AIDS

In recognizing thickness changes in the diabetic macula, it helps to know the short-term variability in different categories of eyes. On a more practical plane, however, there are additional ways to assist in recognition. One method is data organization and presentation. The current analysis of OCT data in the management of DME resembles the analysis of Goldmann visual fields in management of glaucoma in the past. A series of visual fields was obtained and laid out on a tabletop for review. This is analogous to the OCT presentations in published papers documenting the response of DME to laser photocoagulation, vitrectomy, or intravitreal triamcinolone and to the format of Figures 1 and 2 in this thesis.[20,24] Automated perimetry software now provides useful longitudinal plots of key indices such as mean deviation of the visual field. We are witnessing the start of a similar process for efficiently combining OCT data over time and various interventions.[43] For example, CSMT can be presented longitudinally over time and tied to interventions applied for DME (Figure 7). The clinician's eye can discern trends from noise in the data, but explicit use of regression trend lines can guide the eye. The choice of variables to display and the manner in which to display them will need to be chosen based on experience and consensus of the retina community. This methodology is already incorporated in some electronic medical records software.[43]

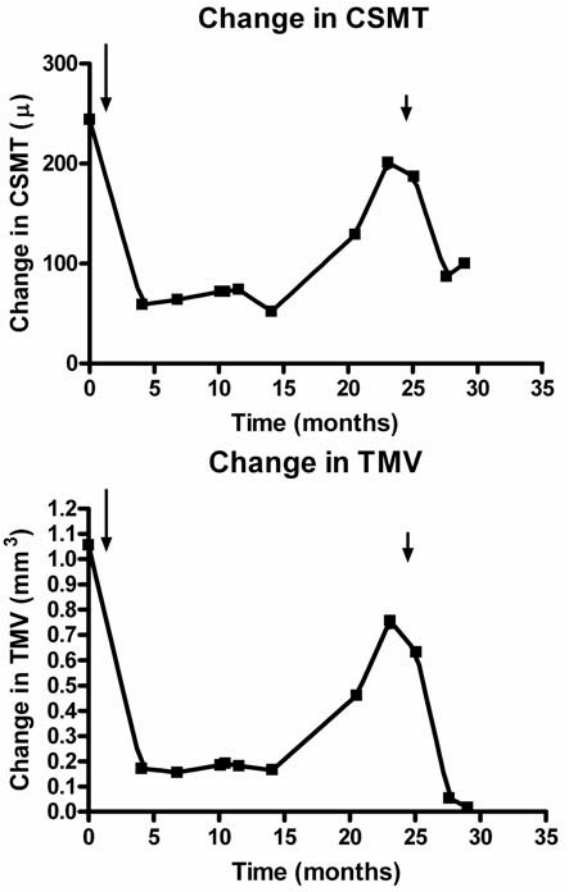

FIGURE 7

Longitudinal plot of change in central subfield macular thickness (CSMT) and total macular volume (TMV) of a patient with diabetic macular edema followed over 29 months. The longer arrows indicate argon laser focal/grid laser treatment. The shorter arrows indicate vitrectomy and internal limiting membrane peeling. The longitudinal display allows easier recognition of signal (true changes in macular thickness) from noise (measurement variability, diurnal variation in macular thickness, and short-term variation in macular thickness).

LIMITATIONS AND CONCLUSIONS

Limitations of this study include its retrospective design, lack of protocol refractions, single physician source, relatively small size for the refractory DME group, and relatively short follow-up. The statistical power to analyze the influence of baseline factors on variation of CSMT and TMV in the refractory DME group is limited with a sample size of 36. The use of visual acuities obtained from a retrospective chart review implies greater variability in the data, but there is no reason to suppose that a systematic bias over time would exist in this noisier data. Despite the limitations, the study is the only one, to my knowledge, to address questions of clinical importance; is the largest study regarding other, previously addressed questions; and may stimulate larger prospective studies with more rigorous design that provide more definitive information.

In conclusion, the results suggest that eyes with refractory DME exhibit greater variability in macular thickness than the measurement variability in eyes without DME or eyes with DME not characterized as refractory. Because of this greater variability, it becomes more difficult to determine if such eyes are experiencing longitudinal worsening of edema. Relatively large increases in macular thickness can spontaneously reverse. Nevertheless, refractory DME continues to exert slow deleterious effects on visual acuity as shown in the subset of eyes with pseudophakia throughout the period of observation, and other effective therapies are needed to improve visual prognosis in patients not responding to focal laser treatment, intravitreal injection therapy, and vitrectomy surgery. Although lesser in degree than in eyes with refractory DME, eyes with regressed DME also exhibit greater short-term variability in macular thickness than the measurement variability in eyes without DME or eyes with DME not characterized as refractory. Evidence exists for a slight progressive decrease in macular thickness and volume over median follow-up of 22 months in eyes with regressed DME. A slow and slight visual acuity decline associated with this slight progressive macular thinning was detected in eyes with pseudophakia throughout the period of observation.

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