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Association of the Extent of Diabetic Macular Edema as Assessed by Optical Coherence Tomography with Visual Acuity and Retinal Outcome Variables

Diabetic Retinopathy Clinical Research Network

Abstract

Purpose—To determine whether the extensiveness of diabetic macular edema (DME) using a ten step scale based on optical coherence tomography (OCT) explains pretreatment variation in visual acuity and predicts change in macular thickness or visual acuity after laser photocoagulation.

Methods—323 eyes from a randomized clinical trial of two methods of laser photocoagulation for DME were studied. Baseline number of thickened OCT subfields was used to characterize DME on a ten step scale from 0 – 9. Associations were explored between baseline number of thickened subfields and baseline fundus photographic variables, visual acuity (VA), central subfield mean thickness (CSMT), and total macular volume (TMV). Associations were also examined between baseline number of thickened subfields and changes in VA, CSMT, and TMV at 3.5 and 12 months after laser photocoagulation.

Results—For baseline visual acuity, the number of thickened subfields explained no more variation than did CSMT, age and fluorescein leakage. A greater number of thickened subfields was associated with a greater baseline CSMT, TMV, area of retinal thickening, and degree of thickening at the center of the macula (r=0.64, 0.77, 0.61–0.63, and 0.45, respectively) and with a lower baseline visual acuity (r=0.38). Baseline number of thickened subfields showed no association with change in visual acuity (r≤0.01–0.08) and weak associations with change in CSMT and TMV (r from 0.11–0.35).

Conclusion—This OCT based assessment of the extensiveness of DME did not explain additional variation in baseline visual acuity above that explained by other known important variables nor predict changes in macular thickness or visual acuity after laser photocoagulation.

One characteristic of DME that has been hypothesized to be of clinical importance is described by the terms focal and diffuse. Although the terms have been in common use for thirty years, there are no generally accepted definitions of the terms[1]. Most are based, at least in part, on fluorescein angiography and involve some provision for extensiveness of macular thickening, although some also include other characteristics, such as amount and distribution of hard exudates and microaneurysms.[2, 3–16] Given the widespread availability of optical coherence

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tomography (OCT) and the lesser burden it places on the patient and the photography department relative to fluorescein angiography, we wondered whether an OCT based definition intended to capture the characteristic of DME described by the terms focal and diffuse might be useful in explaining variance in visual acuity and predicting outcome after focal laser photocoagulation. We investigated this topic using data from a randomized controlled clinical trial comparing two methods of laser photocoagulation for DME.

Methods

We analyzed data from the Diabetic Retinopathy Clinical Research Network (DRCR network) randomized trial comparing modified ETDRS style focal laser photocoagulation to mild macular grid laser photocoagulation for DME (mETDRS vs MMG trial).[17] The protocol has been described previously and is available on the DRCRnet website (www.drcr.net).[17] In brief, the study included eyes with previously untreated DME characterized by a central subfield mean thickness (CSMT) of at least 250 microns or an inner paracentral subfield mean thickness of at least 300 microns. Eyes were randomly assigned to receive either modified ETDRS focal photocoagulation or modified macular grid photocoagulation as defined previously. Follow-up visits occurred at 3.5, 8, and 12 months, and repeat treatment was administered by prespecified criteria.[17] Visual acuity (VA) was measured and OCT obtained at baseline and each visit. Fundus photographs and fluorescein angiography were obtained at baseline and graded by the Fundus Photograph Reading Center of the University of Wisconsin, Madison.

For the purpose of this work, we assigned to each eye at baseline the number of OCT subfields with mean thickness values ≥ 3 standard deviations above mean values for that subfield. The normal mean values for the subfields used in the definition come from a database of 97 eyes from patients with diabetes, no clinical DME, and no or minimal retinopathy.[18] Ten steps are defined by this grading system ranging from 0 to 9 subfields.

Associations between number of thickened subfields and other pre-specified baseline characteristics were explored. These characteristics included degree of retinal thickening at the macular center and area of retinal thickening on color stereo fundus photographs, baseline visual acuity, baseline CSMT, and baseline total macular volume (TMV). Associations between number of thickened subfields at baseline and pre-specified changes in outcome variables of interest were also explored. These outcome variables included change in visual acuity, CSMT, and TMV at 3.5 months and 12 months follow-up. The number of additional laser treatments after the initial treatment as a function of number of thickened subfields was also examined. For these analyses, the 10 subfield scale was collapsed to 4 steps: 0–2, 3–4, 5–7 and 8–9 with more eyes per step. Previously, a multiple regression model of patient and ocular characteristics from the mETDRS versus MMG trial data set was explored to determine which variables explained the variance of baseline visual acuity. The multiple regression model was re-tested incorporating the additional characteristic of number of thickened subfields to determine if additional variance was explained.

Mean subfield thickness was available for all 9 subfields in 270 (84%) of eyes. Table 1 shows the frequency distribution of eyes having subfields with missing mean thicknesses for the 16% of eyes with at least one missing value. Missing OCT data was imputed using Rubin's multiple imputation for the purpose of calculating number of thickened subfields.[19] Six eyes (2%) had all nine values missing and these were excluded from further analyses.

Correlations were calculated in repeated measures models to account for the correlation between eyes based on the likelihood ratio as defined by Magee[20]. Repeated measures least squares models were fit to explore if number of thickened subfields adds more predictive power

for baseline visual acuity variance. Statistical analyses were performed using SAS software version 9.1.

Results

Description of the Data Set

There were 323 eyes of 263 patients in the study. Demographic information of study subjects has been published previously.[17] The frequency distribution of eyes according to number of thickened subfields is shown in Table 2. The grading scale divided the study sample into approximately even partitions, each step containing from 8–13% of the eyes.

Contribution of Baseline Number of Thickened Subfields to a Multiple Regression Model Explaining Baseline Visual Acuity Variance

Table 3 presents a multiple regression model incorporating the previously published important predictor variables and the number of thickened subfields. The latter added no explanatory power to the model over that of CSMT, age, and fluorescein leakage in the central macula. However, number of thickened subfields was predictive of baseline visual acuity variance as a single variable.

Associations between Baseline Number of Thickened Subfields and Other Ocular Characteristics

Table 4 presents the associations between the number of thickened subfields and retinal thickening at the center or area of retinal thickening. Table 5 presents the associations with visual acuity, CSMT, and TMV. Retinal thickening at the center of the macula was associated with a greater number of thickened subfields (r=0.45). Greater area of retinal thickening was associated with a greater number of thickened subfields (r=0.61–0.63). Better baseline visual acuity was associated with fewer thickened subfields (r=0.38). Greater baseline CSMT and TMV were both associated with a greater number of thickened subfields (r=0.64 and 0.77, respectively).

Associations of Baseline Number of Thickened Subfields and Changes in Outcome Measures

Table 5 presents the associations between the number of thickened subfields at baseline and change in visual acuity, change in CSMT, and change in TMV at both 3.5 and 12 months. Change in visual acuity showed no association with baseline number of thickened subfields at either follow-up time (r=0.08 and r<0.01, respectively). Increasing reductions in CSMT and TMV at 3.5 and 12 months were weakly associated with a greater number of thickened subfields at the two follow-up times (r=0.26 and 0.35 for CSMT and r=0.11 and 0.34 for TMV, respectively).

Discussion

As a first step to determine whether a simple OCT measure could provide a clinically useful substitute for the concept of focal or diffuse DME, we examined the association of the number of thickened subfields at baseline with VA and other OCT measures (TMV and CSMT) at baseline, and with changes in these variables at follow-up. There was a modest correlation between number of thickened subfields at baseline and baseline VA but no correlation with change in VA during follow-up. In a regression analysis of baseline VA, number of thickened subfields did not explain additional variance over previously identified predictor variables (CSMT, age, and fluorescein leakage in the central macula). Number of thickened subfields

was strongly associated with baseline TMV and somewhat less strongly with baseline CSMT, but only weakly with change in these measures during follow-up.

The limitations of this study, including a data set comprised of milder cases of DME and its restriction to cases treated by laser photocoagulation, could be offset by analysis of more refined definitions applied to the DRCR network Intravitreal Triamcinolone Trial (available at www.drcr.net), which includes cases of greater DME severity and a different intervention. Newer versions of OCT should also enable more sophisticated definitions of focal or diffuse DME to be investigated. It is possible that information from clinical examination, color fundus photography, or fluorescein angiography will need to be added to OCT information to yield a definition of added explanatory and predictive power.

In conclusion, we have examined a simple definition of focal or diffuse DME based on OCT. It does not explain additional variance in pre-treatment visual acuity above that captured by previously identified variables, nor is it more predictive of vision outcomes after laser photocoagulation. Further studies of eyes with greater disease and treatment diversity, other definitions of focal or diffuse DME, and perhaps more advanced OCT machines may permit a better understanding of the value of the concept of focal and diffuse DME.

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Table 1

Distribution of Missing Subfields on OCT at Baseline (N =323 eyes)

# Missing Subfields	# Eyes (%)	Cumulative %
0	270 (84%)	84%
1	20 (6%)	90%
2	10 (3%)	93%
3	2 (<1%)	94%
4	1 (<1%)	94%
5	3 (<1%)	95%
6	2 (<1%)	95%
7	0	95%
8	9 (3%)	98%
9	6 (2%)	100%

Table 2

Distribution of Number of Thickened Subfields at Baseline (N = 317 eyes[†])

# Thickened SubFields[*]	# Eyes (%)	Cumulative %
None	26 (8%)	8%
1	26 (8%)	16%
2	39 (12%)	29%
3	35 (11%)	40%
4	33 (10%)	50%
5	39 (12%)	62%
6	25 (8%)	70%
7	27 (9%)	79%
8	25 (8%)	87%
9	42 (13%)	100%

[*] Thickened field defined as measurement is 3 SD over normal values

[†] Excludes 6 eyes with all OCT zones ungradable

Table 3

Factors with Significant Effect on Visual Acuity in a Multiple Regression Linear Model

Factor	Univariate Model of Baseline Visual Acuity and Predictive Factor			Multivariate Model of Baseline Visual Acuity†		
	r^2	Estimate [Decrease in letter score] (95% C.I.)	P-value*	Cumulative* r^2	Estimate [Decrease in letter score] (95% C.I.)	P-value* - Final Model (r^2 = 35%)
OCT Central Subfield Thickness (per 100 micron increase)	23%	5.1 (4.1, 6.1)	<.0001	23%	3.7 (2.5, 5.0)	<.0001
Age (per decade increase)	6%	2.9 (1.6, 4.1)	<.0001	29%	3.2 (2.1, 4.3)	<.0001
Fluorescein Leakage in the Center and Inner Subfields‡	14%	3.8 (2.7, 4.9)	<.0001	35%	2.8 (1.7, 3.9)	<.0001
# Thickened OCT Subfields	15%	1.7 (1.3, 2.2)	<.0001	35%	0.1 (−0.5, 0.7)	0.73

*Adjusted for the correlation within subjects with two study eyes.

†Additional factors explored not significantly associated with visual acuity in a multivariate model included: Inner zone thickness (within 1500 μ of the center or the macula), retinal volume, cystoid spaces on OCT or fluorescein angiography, subsensory retinal detachment on OCT, number of involved subfields, macular slope (the difference between center point mean thickness and the maximum inner paracentral zone thickness), race, gender, diabetes type, duration of diabetes, HbA1c, treatment for hypertension, hard exudates measured on fundus photos, lens status (phakic or pseudophakic), level of retinopathy measured on fundus photos, hemorrhage and microaneurysms within the grid measured on fundus photos.

‡Missing for 20 eyes.

Table 4

Baseline Fundus Photographic Measures by Baseline Number of Thickened Subfields (N = 317 eyes*)

		Baseline Number of Thickened Subfields				r
	N	0–2 N = 91	3–4 N = 68	5–6 N = 64	7–9 N = 94	
Retinal Thickening at Center[a]						0.45
None	69	36 (40%)	20 (30%)	7 (11%)	6 (7%)	
Questionable	34	17 (19%)	5 (7%)	8 (13%)	4 (4%)	
Definite, <1X	44	12 (13%)	9 (13%)	16 (25%)	7 (8%)	
Definite, <2X	150	24 (27%)	32 (48%)	30 (48%)	64 (71%)	
Definite, ≥2X	12	0	1 (1%)	2 (3%)	9 (10%)	
Retinal Thickening Area[a]		**Disc Area - median (25th, 75th percentiles)**				
Inner Zone[b]	309	0.72 (0.25, 1.34)	1.24 (0.44, 2.30)	1.93 (1.24, 2.72)	3.14 (1.87, 4.00)	0.61
Within the Grid[c]	309	1.34 (0.72, 3.11)	2.80 (1.54, 4.41)	5.30 (2.90, 6.56)	6.62 (4.56, 10.18)	0.63

*Excludes 6 eyes with all nine OCT zones ungradable at baseline.

[a]Missing for 8 eyes (photo lost for 1 eye, not graded for 2 eyes, and ungradable for 5 eyes).

[b]within 1800 μ of the center of the macula

[c]within 3600 μ of the center of the macula

Table 5

CSMT, TMV and VA at baseline, 3.5 and 12 months by Baseline Number of Thickened Subfields (N = 317 eyes*)

		Baseline Number of Thickened Subfields				r
	N	0–2 N (%)	3–4 N (%)	5–6 N (%)	7–9 N (%)	
CSMT Baseline						0.64
<300 microns	155	74 (81%)	42 (62%)	23 (36%)	16 (17%)	
300-<400 microns	82	17 (19%)	17 (25%)	26 (41%)	22 (23%)	
400-<500 microns	47	0	9 (13%)	14 (22%)	24 (26%)	
≥500 microns	33	0	0	1 (2%)	32 (34%)	
Total	317	91 (100%)	68 (100%)	64 (100%)	94 (100%)	
median (25th, 75th)	317	254 (228, 278)	284 (257, 335)	324 (278, 394)	438 (347, 524)	
CSMT 3.5 mo. Change						0.26
median (25th, 75th)	297	−3 (−24,+17)	−2 (−36,+22)	−4 (−68,+16)	−50 (−144,+14)	
CSMT 12 mo. Change						0.35
median (25th, 75th)	272	−15 (−39,+7)	−13 (−57,+18)	−45 (−94,+18)	−119 (−217, −11)	
TMV Baseline						0.77
<7 mm^3	16	16 (19%)	0	0	0	
7-<8 mm^3	94	62 (74%)	29 (59%)	3 (6%)	0	
8-<9 mm^3	74	6 (7%)	19 (39%)	40 (75%)	9 (13%)	
≥9 mm^3	73	0	1 (2%)	10 (19%)	62 (87%)	
Total	257	84 (100%)	49 (100%)	53 (100%)	71 (100%)	
median (25th, 75th)	257	7.4 (7.1, 7.8)	7.9 (7.6, 8.2)	8.6 (8.3, 8.8)	9.6 (9.2, 10.7)	
TMV 3.5 mo. Change						0.11
median (25th, 75th)	205	0 (−0.3,+0.1)	−0.2 (−0.7, −0.1)	−0.3 (−0.6,0.0)	−0.4 (−1.2,+0.2)	
TMV 12 mo. Change						0.34
median (25th, 75th)	198	−0.2 (−0.5,+0.1)	−0.4 (−1.1, −0.2)	−0.6 (−1.0, −0.1)	−1.1 (−2.4, −0.6)	
VA Baseline						0.38
>=84	74	35 (38%)	16 (24%)	15 (23%)	8 (9%)	
69–83 letters	164	49 (54%)	35 (51%)	33 (52%)	47 (50%)	
19–68 letters	79	7 (8%)	17 (25%)	16 (25%)	39 (41%)	
Total	317	91 (100%)	68 (100%)	64 (100%)	94 (100%)	
median (25th, 75th)	317	81 (75, 86)	78 (69, 83)	76 (69, 83)	71 (64, 76)	

		Baseline Number of Thickened Subfields				r
	N	0–2 N (%)	3–4 N (%)	5–6 N (%)	7–9 N (%)	
VA 3.5 Month Change						0.08
median (25th, 75th)	301	0 (−4,+4)	+1 (−4,+4)	+2 (−3,+6)	−2 (−8,+6)	
VA 12 Month Change						<0.01
median (25th, 75th)	278	−1 (−5,+3)	−1 (−4,+4)	+2 (−5,+6)	+1 (−6,+7)	
# Additional Laser Treatments Through12 Months[a]						
0	131	45 (49%)	32 (47%)	25 (39%)	29 (31%)	
1	110	33 (36%)	25 (37%)	20 (31%)	32 (34%)	
2	76	13 (14%)	11 (16%)	19 (30%)	33 (35%)	

*Excludes 6 eyes with all nine OCT zones ungradable at baseline.

[a]laser treatment performed after the initial treatment