·Clinical Research·

Importance of 3-D image reconstruction of spectral-domain OCT on outcome of grid laser photocoagulation for diffuse diabetic macular edema

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Abstract

• AIM: To present the outcome of modified grid laser photocoagulation (GLP) in diffuse diabetic macular edema (DDME) in eyes without extrafoveal and/or vitreofoveal traction.

• METHODS: Inclusion criteria for the retrospective study were DDME eyes of patients with type II diabetes mellitus that had ≥4 months of follow-up following GLP. Only one eye per patient was analyzed. Using 3-D spectral-domain optical coherence tomography (3-D SD-OCT), eyes that had either extrafoveal or vitreofoveal traction, or had been previously treated by an intravitreal medication (s) were excluded. Treated DDME eyes were divided into 4 groups: A) "Classic" DDME that involved the central macula; B) edema did not involve the macular center; C) eyes associated with central epiretinal membrane (ERM); D) DDME that was associated with macular capillary dropout ≥2 disc-diameter (DD).

• RESULTS: GLP outcome in 35 DDME eyes after 4-24 (mean, 13.1±6.9) months was as follows: Group A) 18 eyes with "classic" DDME. Following one or 2 (mean, 1.2) GLP treatments, best-corrected visual acuity (BCVA) improved by 1-2 Snellen lines in 44.4% (8/18) of eyes, and worsened by 1 line in 11.1% (2/18). Central macular thickness (CMT) improved by 7%-49% (mean, 26.6%) in 77.8% (14/18) of eyes. Causes of CMT worsening (n=4) were commonly explainable, predominantly (n=3) associated with emergence of extrafoveal traction, 5-9 months post-GLP. Group B) GLP (s) in DDME that did not involve the macular center (n=6) resulted in improved BCVA by 1-2 lines in 2 eyes. However, the central macula became involved in the edema process after the GLP in 3 (50%) eyes, associated with an emergence of extrafoveal traction in one of these eyes 4 months following the GLP. Group C) GLP failed in all 5 eyes associated with central ERM. Group D) GLP was of partial benefit in 2 of 6 treated eyes with macular capillary dropout ≥2DD.

• CONCLUSION: Eyes with DDME that involved the macular center were found to achieve favourable outcomes after GLP (s) during mid-term follow-up, unless complicated pre-GLP or post-GLP by vitreoretinal interface abnormalities, often extrafoveal traction or ERM, or by capillary dropout ≥2DD. Prospective studies with larger cohorts are required.

• KEYWORDS: extrafoveal traction; vitreofoveal traction; grid laser; macular edema; non-center-involved macular edema; epiretinal membrane; Evi membrane; macular capillary dropout; 3-D spectral-domain optical coherence tomography

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INTRODUCTION

The therapy of diffuse diabetic macular edema (DDME) is still a major challenge. Relatively beneficial effects have been reported after focal laser photocoagulation for the treatment of clinically significant macular edema (CSME), whereas treatment by modified grid laser photocoagulation (GLP) for DDME has limited results [1-4]. Lee and Olk [2] reported, before the optical coherence tomography (OCT) era, on improved visual acuity (VA) by ≥3 Snellen lines following GLP in 13.7%-14.3% of 230 eyes, but of VA loss of ≥3 lines in 9.3%-16.5% at 2 years of follow-up. A recent publication using the Stratus time-domain (TD-) OCT reported that focal/GLP just for DDME (n=42) resulted in a higher loss (16.6%) than gain (11.9%) of ≥11 letters of best-corrected VA (BCVA) after 12 months of follow-up[3]. Evaluation of GLP for DDME by Cirrus spectral domain (SD-) OCT (n=30), revealed central macular thickness (CMT) worsening in 16.7% of eyes after a short follow-up of 4 months [4]. The efficacy of intravitreal administration of anti-vascular endothelial growth factor (anti-VEGF) agents or

steroids for diabetic macular edema (DME) was found, as a rule, to be temporary and partial[5-8].

The posterior vitreous cortex (=posterior hyaloid) is well accepted to play a role in the pathogenesis of DDME [9-12]. Lewis *et al* [13] hypothesized before the OCT era, that the clinically detected premacular thickened and glistening "taut" posterior hyaloid, could be associated with DDME. Pars plana vitrectomy (PPV) in these eyes, a study which was verified by others, resulted in VA improvement and resolution of macular edema for most patients [14]. Using TD-OCT in DDME eyes, premacular vitreous membranes with regular OCT reflectivity were more commonly evident than the clinically-detected "taut" ones, and were also believed to be associated with the pathogenesis of DDME[15]. Using OCT, we recently observed that part of such premacular vitreous membranes often had extrafoveal, vitreoretinal or vitreopapillary adherence or traction sites[10,16,17]. In other DDME eyes, where premacular membranes were not detected, we similarly looked by OCT at the area centralis and optic nerve head (ONH) area for extrafoveal vitreous traction (ext-f-t) membranes. Sole (without accompanying vitreofoveal traction) ext-f-t was directly associated with DDME in 10.8% (20/186) of eyes using TD-OCT-2, and in 34.5% (20/58) of eyes using a 3-D SD-OCT [16,17]. The superiority of the 3-D SD-OCT over the TD-OCT has been previously discussed[17].

Using a 3-D SD-OCT we present herein our GLP outcome in DDME eyes with neither vitreofoveal nor extrafoveal traction.

SUBJECTS AND METHODS

In a retrospective study we reviewed the charts of consecutive patients with DDME that underwent GLP, using 3-D SD-OCT 1000 (Topcon Corp., Tokyo, Japan) scanning. Ophthalmologic examinations included Snellen BCVA, slit-lamp and fundus examinations, and fluorescein angiography (FA). The FA enabled detection of leaking microaneurysms (MA's), areas of diffuse leakage, locations and sizes of capillary non-perfusion areas and sometimes leakage from neovascular tufts. Eyes were treated by focal/GLP [modified Early-Treatment Diabetic Retinopathy Study (ETDRS) protocol], as previously described [2]. The modified GLP was done by argon green laser, with burn size of 100μ, burn duration of 0.1s, burn separation that was 2 visible burn widths apart and burn intensity that was barely visible (light gray). Treatment was aimed to all areas of diffuse leakage, retinal thickening and nonperfusion as well as focally to leaking MA's, all within 500-3 000μ from the macular center.

All SD-OCT scans were performed through a dilated pupil by an experienced ophthalmologist, or by an ophthalmic technician under the direct instructions of an ophthalmologist. While performing the 3-D SD-OCT examination, 3-D data sets were centered on the fovea (6mm×6mm), followed by the ONH in association with the central macula, using a raster scan program of 8.2mm (horizontal) ×3mm (vertical) ×1.7mm (axial). Additional scans were taken at the area centralis and ONH area, either following a pre-foveal posterior hyaloid in order to look for its attachment at a retinal or ONH site, but also even if no pre-foveal posterior hyaloid was detected. Data, including the B- and 3-D modes, could also be re-evaluated by examining the recorded videos.

The study was limited only to eyes that had diffuse DME, as verified by the 3-D SD-OCT, with or without focal type of DME. DDME was identified as an ill-defined and widespread hyporeflective increased retinal thickness within one disk area of the center of the fovea and beyond, that often attains the appearance of sponge-like cavities, associated with or without cystoid macular edema [18]. Data on DDME eyes that involved the macular center are compared quantitatively by the 1-mm diameter of the CMT of the 3-D SD-OCT output. We defined DDME as "classic" if it involved the macular center and had neither vitreoretinal interface (VRI) abnormality, *i.e.* vitreofoveal traction, extrafoveal traction or central ERM, nor marked macular capillary dropout. A special group of DDME eyes without or with minimally central involvement (CI) was termed "non-CI DDME", as previously described [19]. The changes in macular thickness in these eyes were presented by the thicknesses of the edematous ETDRS inner-ring sub-field quadrant(s).

The diagnosis of ERM, which is presented in another group of eyes, was based on a difference in the brightness of the surface tissue, which is more easily noticeable by the SD-OCT than by the TD-OCT[20]. In a fourth group, included were eyes with enlarged foveal avascular zone (FAZ) ≥1 000μ, or a broken perifoveal capillary ring at the border of the FAZ, together with an adjacent distinct area of capillary nonperfusion in the transit phase on FA, that totally sized ≥2 disc-diameters (DD) in its larger diameter, *i.e.* "macular capillary dropout" group. All morphological diagnoses were graded by all the authors and disagreement was resolved by the majority. The various thicknesses were compared to our normative data-base on 80 eyes of 80 age-matched patients.

Evidence of traction required vitreous adherence to the retina or ONH associated with tissue elevation and deformity at the traction site, *i.e.* the shape of the inner retina at the site of traction changed its angle, and thus was typically thicker than that of the adjoining edematous retinal tissue [17]. Commonly, the posterior hyaloid also changed its angle of continuity at the traction site. Vitreous traction at one ("unifocal") or more ("multifocal") sites away from the edematous central macula was designated as "extrafoveal traction", either at the area centralis between the vascular arcades ("extrafoveal

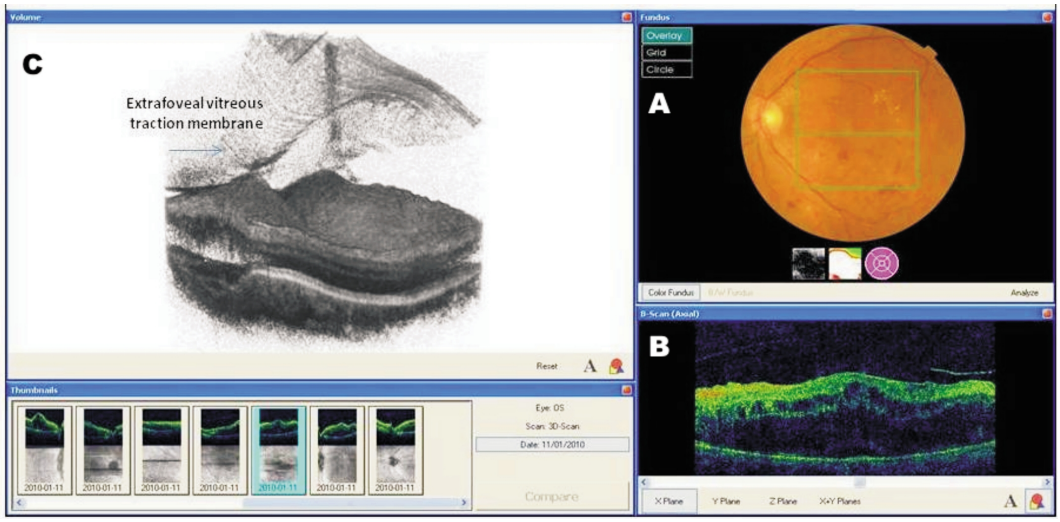

Figure 1 Diffuse diabetic macular edema associated with extrafoveal vitreous traction in a 61−year−old patient The clinical picture (A) and the B-scan (B) show diffuse macular edema. In (B), the central macula is void of vitreous traction, while a short pre-macular vitreous cortex membrane is detected temporal to the center, at an extrafoveal site. The 3-D image reconstruction (C) shows wide incompletely detached posterior vitreous cortex membrane (posterior hyaloid) with several extrafoveal traction sites, associated with the diffuse macular edema.

vitreoretinal" traction) or at the ONH ("vitreopapillary traction")[16,17]. "Vitreous adherence" (without traction) was relates to eyes in which the attachment of the vitreous was not associated with tissue deformity at that site[17].

Inclusion criteria were as follows: 1) DDME eyes of, 2) patients with type II diabetes mellitus that had, 3) ⩾4 months of follow-up following GLP; 4) only one eye per patient was analyzed. Priority for choosing one of two treated eyes of the same patient for analysis was the eye with "classic" DDME, and for the same Group-the eye with the longer follow-up.

Criteria for exclusion from the study were eyes that either had vitreofoveal or extrafoveal traction (Figure 1), had been treated anytime before the GLP by intravitreal medication(s) such as bevacizumab or ranibizumab, had undergone an earlier pars plana vitrectomy (PPV), had another vitreoretinal disease that could affect analysis, or if FA or the 3-D SD-OCT scans were not of sufficiently quality for a proper diagnosis. Data collection was terminated when an eye underwent any intravitreal intervention or sub-Tenon's injection of medication to treat macular edema during follow-up. Reproducibility level of the Topcon 1000 SD-OCT in eyes with DDME was found to be 2.7%[21]. Therefore, arbitrarily, thickness "improvement" or "worsening" was determined when it was changed by ＞5%. Otherwise, *i.e.* ≤5%, changes were termed "stable" if the thickness did not change during follow-up and termed "recurrence" if it temporarily improved.

Calculations of the mean BCVA were made after conversion to a logarithm of the minimum angle of resolution (Log-MAR). Comparison between the levels of CMT in the various Groups was analyzed statistically by using the Wilcoxon Signed Ranks Test. Research adhered to the tenets of the Declaration of Helsinki, and the approval of the Institutional Ethics Committee was obtained.

RESULTS

Out of 38 eyes that fulfilled the study criteria, analysis involved 35 eyes, one eye per patient. Patients' demographic data are presented in Table 1. For thickness comparison, mean CMT of our normal control eyes (80 eyes and patients) was 239±17μ (Table 1); and mean 4 EDTRS inner ring quadrants thicknesses were 296±14μ in the superior one, 298±20μ nasally, 296±14μ inferiorly, and 286±17μ in the temporal inner ring quadrant. (Mean normal CMT+2 SD=239+34=273μ).

Group A was comprised of 18 eyes with center-involved DDME that were neither associated with VRI abnormality nor with macular capillary dropout ⩾2DD, termed "classic" DDME (Table 2). Preoperative CMT levels in this Group ranged between 276 to 652μ(mean, 379±99μ), and subretinal fluid (SRF) was additionally detected preoperatively in 4 (22.2%) eyes. One or 2 (mean, 1.2) GLP treatments resulted in the reduction of CMT from 379±99μ at pre-GLP period to 342±132μ after 3-6 months post-GLP (n=18, P=0.02), 273±69μ after 9-15 months (n=14, P=0.001) and 269±55μ after 16-24 months following the first GLP (n=10, P=0.007). At the last examination of all 18 analyzed "classic" DDME eyes, 4 to 24 (mean, 15.9±7.4) months postoperatively, CMT was 313±142μ, or a 19.4% reduction from the pre-GLP level (P=0.002). Subretinal fluid absorbed completely in one eye (No.12) and partially in 2 others (No.14&16; non-significant). BCVA that ranged from 6/12 to 6/60 at base-line improved by 1-2 Snellen lines in 44.4% (8/18) of eyes, and worsened by one line in 11.1% (2 eyes). Of the 18 "classic" DDME eyes, CMT was reduced in each of 14 (77.8%) eyes (Nos.

Table 1 Baseline characteristics of 35 patients with diffuse diabetic macular edema

Characteristics	Group A: "Classic" DDME	Group B: Non-centre involved DDME	Group C: Epiretinal membrane	Group D: ≥2DD Capi. dropout	Normal controls
n	18	6	5	6	80
F/M	14/4	3/3	3/2	4/2	
Mean age±SD (a)	64±12	66±15	69±5	59±7	64± 10
Age, range (a)	42-90	48-85	65-75	48-70	41- 89
Mean CMT(μ)±SD	379±99	243±22	410±61	437±130	239±17
CMT, range (μ)	276-652	207-263	329-485	247-601	190-283
NPDR/PDR	15/3	5/1	4/1	4/2	---

DDME: Diffuse diabetic macular edema; DD: Disc-diameters; Capi.: Macular capillary; SD: Standard deviation; CMT: Central macular thickness; NPDR: Non proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy.

Table 2 Group A: outcome of modified grid laser photocoagulation in eyes with "classic" DDME

n/Age (a)	CMT (μ) baseline	Last CMT (μ) at 3-6 months	Last CMT (μ)	Follow-up (months)	Change CMT (%)	Last/BCVA change	Comments
1/75	276	244	200	15	-28	6/18, 1	S/P focal laser
2/90	305	250	236	24	-23	6/9, 1	
3/54	310	278	236	12	-24	6/12, 0	
4/71	350	306	280	20	-20	6/9, 2	
5/59	303	274	215	24	-29	6/18, 2	
6/60	340	231	285	24	-16	6/18, 1	Extrafoveal traction month 15
7/66	433	234	234	5	-46	6/24, 0	
8/62	309	276	286	18	-7	6/12, 0	Extrafoveal traction month 15
9/71	396	353	199	24	-49	6/12, 0	
10/50	335	377	258	24	-23	6/24, 2	
11/61	303	320	221	20	-27	6/60, 0	Second grid month 15; Pre-grid: 322μ; Central hard exudate
12/61	[1]372	361	267	12	-28	6/18; -1	[1]Subretinal fluid; reduced
13/42	309	238	238	4	-23	6/12; 1	Exudates resolved
14/73	[1]481	495	345	18	-28	6/60; 0	Extrafoveal epiretinal membrane month 12; [1]Subretinal fluid reduced
15/57	486	438	462	13	-5	6/36; 0	Second grid month 8; Pre-grid: 506μ; Extrafoveal traction month 9
16/51	[1]652	726	726	5	11	6/24,-1	Extrafoveal traction month 5; [1]Subretinal fluid reduced
17/82	349	227	364	20	4	6/36,1	Second grid month 15; Pre-grid: 304μ; Capillary dropout
18/60	[1]519	521	576	5	11	6/60; 0	Vitreopapillary traction month 5; [1]Subretinal fluid-stable; foveal cyst-month 4
Mean±SD	379±99	342±132	313±142	15.9±7.4	19.4±16.8	6/21	
Group A-second eye							
19/59	406	220	220	20	46	6/24; 3	Second grid month-14; Pre-grid: 450μ

DDME: Diffuse diabetic macular edema; BCVA: Best corrected visual acuity; CMT: Central macular thickness; [1]And additional SRF; SD: Standard deviation.

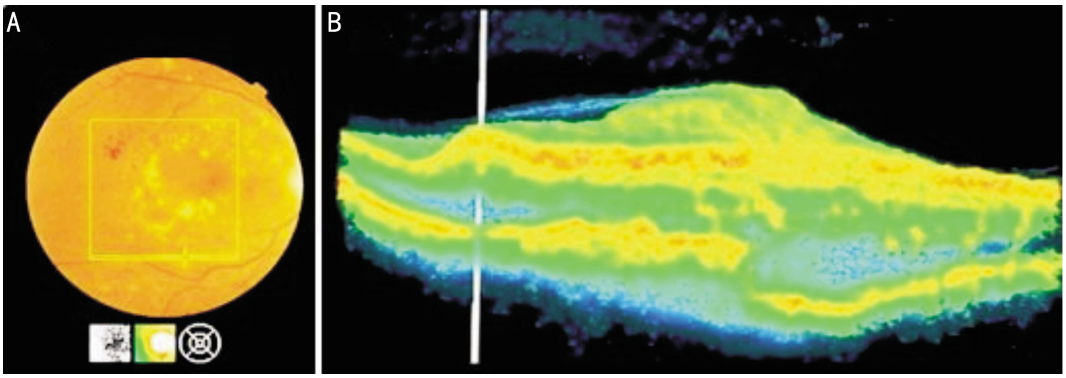

Figure 2 Diffuse diabetic macular edema associated with extrafoveal vitreous traction (case No. 16) A: Diffuse macular edema associated with multiple hard exudates; B: A 3-D image reconstruction shows diffuse macular edema associated with an extrafoveal vitreoretinal traction membrane (manually marked by a vertical line). This traction site is then automatically marked by a cross sign in (A), 3mm inferior to the fovea.

1-14) by 7%-49% (mean, 26.6%) at the last examination. The improvement was often (9/14 eyes) progressive during the first 12 post-GLP months, attaining CMT levels ＜290μ at the last examination in 13 of the 14 eyes.

Table 3 Group B: outcome of modified grid laser photocoagulation in eyes with non-centre involved DDME

n/Age	Follow-up (months)	CMT (μ) last/ base-line	Last change (%) of CMT	Last outcome of GLP (s)	Last BCVA/change from base-line	Events during follow-up
20/85	6	198/207	-3	N.I.R.-quad.: -13%		
21/48	4	670/251	167	worsened	3/60; -5	Extrafoveal traction-month 4
22/75	24	180/226	-20	N.I.R.-quad.: -17%	6/36; 0	New leak, temporally-month16
23/58	16	221/248	-11	T.I.R.-quad.: -20%	6/18; 0	second grid-month 12 Pre-second grid CMT: 323μ; exudates resolved
24/53	12	316/260	22	Worsened S.I.R.-quad.: -18%	6/9; 2	New leak-month 9; central exudates resolved
25/74	9	258/263	-2		6/12; 1	
Mean	11.8	307/242	25.5		6 /29	
SD	7.3	184.2/21.7	70.7			

DDME: Diffuse diabetic macular edema; BCVA: Best corrected visual acuity; CMT: Central macular thickness; GLP: Grid laser photocoagulation; SD: Standard deviation; N.I.R.-quad: Nasal inner-ring-quadrant; T.I.R.-quad.: Temporal inner-ring-quadrant; S.I.R.-quad.: Superior inner-ring-quadrant.

Table 4 Group C: outcome of modified grid laser photocoagulation in eyes with epiretinal membrane

n/Age(a)	Follow-up (months)	CMT (μ) last/base-line	Change (%) of CMT	Last BCVA/change from base-line
26/65	4	406/376	8	6/9, 0
27/65	7	532/485	10	6/60, -2
28/75	13	452/412	10	6/18, 0
29/72	12	327/329	-1	6/12, 0
30/66	18	504/447	13	6/36, -1
Mean	10.8	444/410	8	6/21
SD	5.4	81.4/61	5.3	

BCVA: Best corrected visual acuity; CMT: Central macular thickness; GLP: Grid laser photocoagulation; SD: Standard deviation.

Extrafoveal vitreous traction emerged in 2 of these 14 eyes (No. 6&8), each at month 15, and extrafoveal ERM emerged in one eye (No. 14) at month 12 following GLP. Each of these 3 eyes with new VRI abnormality resulted in partial worsening of the CMT after initial improvement, but last CMT remained lower than that at base-line throughout the follow-up period. Of the other 4 eyes (22.2%; Nos. 15-18), GLP failure already at an early stage (n=1, No.18) or CMT worsening above base-line level after initial improvement (n=3, No.15-17) were explainable, being associated with: 1) An enlargement of a base-line foveal cyst in one eye (No.17), which was detected at month 19, in association with increased capillary dropout to 2-DD in its larger diameter; 2) New emergence and persistence of ext-f-t membranes in 3 (16.7%) eyes (Nos. 15, 16, 18; Figure 2) that were initially detected at months 5-9 post GLP; one of them (No.15) emerged one month after a second GLP. A new large foveal cyst emerged in association with the ext-f-t in one eye (No. 18). The last CMT in each of these 3 eyes (15, 16, 18) was significant, exceeding 460μ in each (Table 2).

In the one fellow eye with "classic" DDME that was excluded from analysis, GLP was found efficacious (No.19, Table 2, Group A-fellow eye).

Group B was comprised of 6 eyes with DDME that did not involve the central macula, termed "non-CI DDME" (Table 3). The base-line CMT ranged between 207-263μ. At the last examination, after 4-24 (mean, 11.8±7.3) months' follow-up, the edema at the inner ring quadrant (s) reduced between 13%-20% in 4 (66.7%) eyes, and CMT reduced by 11% and 20% in 2 (33.3%) of them. BCVA improved by 2 Snellen lines in one eye associated with resolution of central hard exudates (No.24), and by 1 line in another eye (No.25). However, the central macula in this Group became involved in the edema process after the GLP in each of 3 (50%) eyes, one due to emergence of an ext-f-t (No.21) at month 4, associated with marked worsening of the BCVA; and in the other 2 eyes due to primary new leakage (No.23&24) at months 12 and 9, respectively. Primary new leakage without center involvement was found in another eye (No.22), 16 months after the first GLP. At the closure of the study, only one eye (No.23) was already treated for the second time by GLP.

Group C was comprised of 5 eyes having preoperative macular ERM (Table 4). After 3-6 months' follow up, the GLP was associated with worsening of the CMT in 2 eyes by 8% and 10%, and with stable CMT in the other eyes. At the last examinations, CMT was found worsened by 10% and 13% in 2 more eyes, 13 and 18 months post-GLP, respectively.

Group D was composed of 6 eyes with macular capillary

Table 5 Group D: Outcome of grid laser photocoagulation in eyes with macular capillary dropout ≥2DD

n/Age	Follow-up (month)	CMT (μ) last/ base-line	Change (%) of CMT	Last BCVA/change from base-line	Pre-grid findings
31/62	9	299/247	21	6/18; 0	
32/60	9	472/419	13	6/36; -2	Foveal cyst: 928×351μ; post GLP: 975×428μ
33/57	4	390/359	9	6/12; 0	SRF-200μ; stable
34/48	14	676/560	21	6/12; 0	Foveal cyst: 1190×553μ; post GLP: 1050×596
35/55	6	352/433	-19	6/60; +2	Foveal cyst: 802×307μ; post GLP: 948×603μ
36/70	6	485/601	-22	6/60, +2	Foveal cyst: 848×509μ; post GLP: 650×503μ
Mean	8	446/437	4	6/27	
SD	3.5	133/130	19.4		
Group D-second eyes					
37/50	24	373/372	0	6/24; 0	
38/42	4	485/520	-7	6/12; 0	s/p old GLP

DD: Disc diameters; BCVA: Best corrected visual acuity; CMT: Central macular thickness; GLP: Grid laser photocoagulation; SRF: Subretinal fluid.

dropout ≥2DD in its largest diameter (Table 5). The CMT worsened already at the early stages following GLP by 9%-21% in 4 (66.7%) eyes. On the other hand, CMT improved in the other 2 eyes (Nos. 35&36) by 19% and 22%, respectively, associated with improvement in BCVA in each by 2 Snellen lines. Yet, the CMT exceeded 350μ in these 2 eyes at last examination, after 6 months' follow-up. In the 2 excluded fellow eyes (Group D-fellow eyes), CMT improved in one eye (No.38) following a second GLP.

DISCUSSION

A group of eyes with DDME that involved the central macula had, as a rule, a favourable GLP outcome, unless complicated pre-GLP or post-GLP by VRI abnormalities, *i.e.* extrafoveal traction or ERM, or by macular capillary dropout ≥2DD. Revealing extrafoveal vitreous traction pre- or following GLP (s) that was directly associated with the DDME, enabled avoiding the first or repeat GLP. The GLP outcome gave us the ability to analyze the data from different categories, which were divided into groups. Proper grouping is expected to improve decision-making and patients' prognosis.

Four to 24 months (mean, 15.9±7.4) following one or two (1.2) times GLP (s) in 18 eyes with "classic" DDME (Group A), BCVA improved by 1 - 2 Snellen lines in 44.4% of eyes and worsened by 1 line in 11.1%. CMT reduced in 14 (77.8%) of the eyes by 7%-49% (mean, 26.6%), reaching CMT levels <290μ in 13 of the 14 eyes. Of the other 4 eyes, the failure in GLP was associated with an emergence of ext-f-t in 3 eyes, 5 to 9 months post-GLP. That outcome was substantially better than that previously reported following modified GLP either for focal/ diffuse DME, or for just DDME, which ranged between mild improvement, stabilization or even worsening after 1 to 5 years of follow-up [2-4,7,22]. In contrast to our study, in these aforementioned studies, a) eyes with ext-f-t were not excluded; b) all treated DDME eyes, including ERM, were considered and analyzed as one group (with some differences among the studies); c) the more recent studies used only a TD-OCT. Yet, using Cirrus SD-OCT, improvement in mean CMT was found in 8.2% of 30 eyes, while its worsening was observed in 16.7% of eyes already after 4 months follow-up[4]. Again, however, ext-f-t was not mentioned or ruled out preoperatively in that study. Furthermore, in none of the above studies the causes of edema recurrences were described.

In the current study, ext-f-t or extrafoveal ERM were initially detected in Groups A and B, in 5 eyes and one eye, respectively, 4-15 months after the first GLP. The CMT thereafter increased in each. An ext-f-t emerged in another eye after the second GLP (No.15), and CMT partially improved one month after that treatment. The detection of ext-f-t was mainly attributed to the 3-D characteristics of the SD-OCT [17]. In contrast to the 2-D B-mode output, the 3-D image reconstruction presents the whole scanned vitreoretinal field, which is then much more clearly perceived [17]. Additional data may be achieved by manual rotation of the 3-D scanned image for 360°, enabling the evaluation of the sides and back of the field of interest.The ext-f-t sites are thus often plainly detected, allowing also the judgment whether they are directly associated (or not) with the DDME.

The superiority of 3-D SD-OCT over the TD-OCT in other aspects has been previously discussed [17]. It refers to the fact that detection is perceived by TD-OCT only at the scanned lines. Each scan line has a beam width of several microns, hence only <0.5% of the entire ETDRS circle is represented in the images[16,23]. Furthermore, according to the equation of a circumference of a circle, 2×π (3.14)×R (=radius), the arc between 2 radial lines of the Automatic 6-radial lines program of the TD-OCT is >1500μ at a 3-mm distance from the center: 2×3.14×3mm/12, and >500μ if the traction site is just 1mm from the central macula (Figure 3). Therefore, vitreoretinal traction site at 1 or 2mm from the center of the spoke-like Stratus 6 radial lines, but between 2

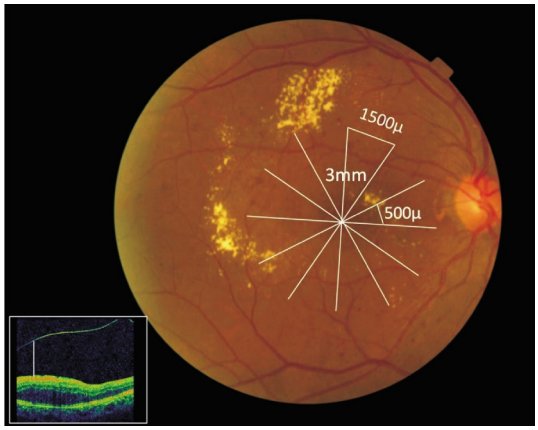

Figure 3 Wide skipped areas while using the 6-radial lines program for detection of vitreomacular traction The ETDRS 6-mm macular map presents the 6-radial lines of a time-domain OCT. The distance between 2 adjacent radial lines is about 1 500μ (1.5mm) at a site 3-mm away from the central macula, and 500μ if it is just 1-mm from the fovea. The areas between 2 neighboring radial lines are not scanned while using that program. The small B-scan figure (left bottom) shows posterior vitreous cortex membrane at a distance about 400μ away from the macula. However, the next radial scan line, 30 degrees away, might miss its possible adherent site to the retina or the ONH.

radial lines, would be often seen as a premacular vitreous membrane (and if detected clinically-often as a taut posterior hyaloid) rather than vitreoretinal adherence, or not centrally detected at all. There is time-consuming, progressive patient fatigue and corneal drying, in trying to "seize" and unambiguously verifying a point of ext-f vitreoretinal adherence / traction while using TD-OCT, as previously discussed [16,17]. This may inevitably result in omission of adhesion and ext-f-t sites. In contrast, the SD-OCT does scan each point at the studied area, and vitreoretinal traction would commonly be plainly detected. Furthermore, the SD-OCT completes one scanned area such as 6mm× 6mm in 3.7 seconds; and has a higher resolution than the TD-OCT (6μ *vs* 12μ).

Six eyes with CSME had non-CI DDME (Group B), with CMT that ranged between 207-263μ. The thickness of the edematous inner ring quadrant (s) was reduced between 13%-20% in 4 eyes (66.7%) following GLP (s) and BCVA improved by 2 lines in one eye (No.24). However, the fovea itself became also edematous in 3 eyes (50%) following the GLP. In one of these (No.21), the pre-GLP normal CMT worsened markedly due to emergence of an ext-f-t at Month 4, associated with parallel worsening of the BCVA. Of note, of the rare reports on non-CI DDME, Scott *et al* [19] (for the DRCR. net) using Stratus OCT, reported on 22 eyes, mostly having BCVA of 6/12-1 that underwent 1.4 times (mean) GLP(s). Whereas 18% (4/22) of eyes had VA improvement of ≥5 letters (one line) and a mild decrease in CMT (≥25 microns), yet as many as 32% (7/22) had VA decrease of ≥5 letters, associated with worsening of 2 levels of DDME severity. Although VRI abnormalities such as ext-f-t were not excluded in Scott study [19], however, their outcome and our findings seem to suggest that further studies may be required in order to indicate when it is justified to consider GLP in diabetic CSME without central involvement that seems to threaten the fovea.

In DDME eyes associated with ERM (Group C), the data show (for the first time; search by PubMed) that GLP is of no benefit and may be harmful: CMT worsened in 2/5 eyes at the early postoperative stages, bearing also a potential injury due to the GLP per se in each. Few authors reported improvement in BCVA and/or level of the macular edema following PPV and peeling of the ERM [9,24]. They theorized the DDME as having been developed by the ERM mechanical traction. This assumption may be in accordance with recent 3-D SD-OCT observations at the incomplete posterior vitreous detachment stage, disclosing that the ERM in DDME is regularly in continuation with the posterior vitreous cortex, thus termed "Evi membrane" (or ERM-posterior vitreous cortex membrane)[12].

Of the DDME eyes associated with macular capillary dropout ≥2DD (Group D), GLP resulted in partial improved BCVA and CMT in 2 of the 6 analyzed eyes (No.35&36) and in the CMT in one fellow eye, No.38). Of note, a previous study reported on favorable changes in BCVA and CMT throughout 1-year of follow-up after repeated intravitreal bevacizumab injections in DME eyes with severe capillary loss [25]. Although the latter outcome was challenged by a study of Chung *et al* [26] yet the improvement in the 2 analyzed eyes in our study and in the first aforementioned study following grid laser treatment raises the possibility that factors other than angiographically-detected marked macular capillary dropout might play a role in the issue related to efficacy or failure of treating such maculae[25].

In 4 (66.7%) of the 6 analyzed eyes with macular capillary dropout ≥2DD, large foveal cystoid cavities between 800μ to 1 190μ in their larger diameter were detected preoperatively (Table 5). Histopathologic studies by Yanoff and associates suggest that death of Muller cells may result in the formation of large cystoid cavities or CME [27]. However, improvement or worsening following the GLP in that small group of eyes was not associated with the absence or presence of these cystoid spaces.

Limitations of the study are related to its retrospective design, which was associated with available data of HA1C levels in less than 50% of the patients, and the relatively small groups, mainly groups B-D. However, the current series using 3D SD-OCT presents objectively, for the first time (search *via* PubMed), that: A) GLP (s) for a designated group termed "classic" DDME, was found efficacious (>77%) during mid-term of follow-up. That outcome was found better than

the outcome achieved either for DDME or for focal/ diffuse DME in previous studies, which had not excluded eyes with extrafoveal traction and ERM from treatment or analysis; b) causes of edema recurrence following GLP in these classic DDME eyes during mid-term follow-up period were commonly explainable and potentially treatable, since they were frequently related to an emergence of new extrafoveal traction or ERM in each. Other eyes with recurrent DDME that remained at the "classic" type were efficaciously retreated by GLP. Prospective studies with larger cohorts are required to verify our observations.

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