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Optical Coherence Tomography Angiography After Macular Laser Treatment for Diabetic Macular Edema

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Abstract:

Background: Diabetic macular edema (DME) affect vision greatly in diabetic populations. Optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA) are non-invasive technology to have a cross-sectional image of the retina.

Purpose: to assess changes and to assess ischemia that may occur post. Macular laser treatment for DME using OCT and OCTA and its relation with BCVA.

Methods: prospective, observational, cohort study with a total 40 eyes were evaluated with OCT and OCTA before and after macular grid laser used in patients with non-central involving diabetic macular edema.

Results: There was highly significant improvement in BCVA ($p < 0.0001$). There was significant reduction of macular thickness ($p<0.0001$). There is high relation between IS-OS integrity, DRIL and BCVA. There was significant enlargement of foveal avascular zone (FAZ) post. Laser ($p = 0.001$). Vascular density in superficial capillary plexus decreased (statistically highly significant) when we compare before and after laser and during period of follow-up but it is non-significant reduction at period of follow -up 3&6 months except in whole density. Vascular density in deep capillary plexus was statistically significant (reduction) ($p<0.0001$) before and after laser treatment and at all periods of follow-up except at period of follow- up between 3 and 6 months which is statistically non-significant.

Conclusion: macular grid laser is an influential treatment for diabetic macular edema with relative ischemia and mild effect on macular perfusion. Anatomical and functional factors other than central macular thickness are also related to best corrected visual acuity. OCT and OCTA are very helpful during follow -up cases with DME to assess macular thickness, inner and outer retinal integrity, degree of macular ischemia and any complication as ERM that may result from laser.

keywords: macular laser, OCT, OCTA, CMT, BCVA.

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Introduction:

About half of patients with DME within two years will lose nearly two lines of visual acuity or more. Nearly 1-3% of diabetic population all over the world have DME with some impairment of vision.(1) Diabetic macular edema treatm-

ent include focal/grid macular laser photocoagulation and anti-VEGF, macular laser was the main treatment for DME since1985, as recommended by the Early Treatment Diabetic Retinopathy Study (ETDRS) to decrease 50% of the risk of vision loss, while complete stop of loss of vision and improvement of visual acuity are rarely occurred.(2)

Fluorescein angiography (FA) is the main investigative tool now(.3)

But FA is a relatively invasive investigation which require injection of fluorescein dye intravenously and this carries many risks as vomiting, itching and even rarely anaphylaxis(.3)

Also, non-perfusion assessment by FA may be limited by masking effect of hemorrhage and leakage and it cannot assess the deep retinal capillary plexus accurately(.4)

Recently Optical coherence tomography angiography (OCTA) enables us to visualize the microvasculature of the retina and it is a non-invasive investigative tool and it enable us to segment retinal vasculature and to is possible to visualize individual retinal vascular layers separately as superficial capillary plexus (SCP) and the deep capillary plexus (DCP)(.5)

The aim of our study:

to assess anatomical changes and assess ischemia that may occur post. Macular laser treatment for DME using OCT and OCTA and its relation with BCVA.

Patients and methods

Study design

Prospective observational cohort study.

Subjects

The study included 40 eyes. At first the study enrolled 50 eyes with non-center involving diabetic macular edema (diffuse), they were defined according to early treatment diabetic retinopathy study group (ETDRS) who were treated with macular laser (grid laser). but 8 of them missed their follow-up schedule. And 2 were excluded as they have non-measured FAZ or macular density at any time during their follow-up. All eyes had undergone grid macular laser photocoagulation using argon laser (Zeiss-Humphrey systems, Carl Zeiss, Jena, Germany) which was adapted from the modified ETDRS. The Grid treatment utilizes spot size of 50 um for a duration of 0.05 to 0.5 seconds, not placed within 500 um of the center of the macula or within 500 um of the disc margin, with treatment goal of mild retinal pigment epithelium grayness. The laser burns are placed approximately two visible burn widths apart in the areas of the macular edema (retinal thickening) that are thought to be related to diffuse leakage

Data was collected between august 2020 and December 2022 at Sohag Ophalmology Investigation Center and Sohag University Hospital.

All participants were informed about the investigations that will be done to them. Approval from ethical committee of Sohag Faculty of Medicine was obtained.

Inclusion criteria: patients with non – center involving macular edema (diffuse). On OCT, the retinal thickening involves 1 or more of the non-central fields on the ETDRS grid. Retinal thickening is defined as (>320 μm) and central subfield thickness (CST) of less than normal +2 SD (machine-specific) with BCVA < 6/9 were treated with grid macular laser. We take in consideration that all participants had good quality scans obtained by OCT and OCT angiography

Exclusion criteria:1 - Patients with uveitis, glaucoma not controlled medically. **2-** Patients with vitreous opacities or hemorrhages .**3-** tractional RD threaten

the macula.**4-** Eyes with media opacity significant enough to affect the images quality.**5-** Eyes with marked image distortion or significant artifact prevent measurement of the FAZ and vessel density accurately.

Ethical consideration and written informed consent

An approval of the study was obtained from Sohag University Academic and Ethical Committee. And a consent for acceptance of the procedure was obtainned from all patients.

Methods

Patient evaluation: Each participant was subjected to full history, Comprehensive ophthalmological examination, including refraction, best-corrected visulal acuity (measured by Snellen`s or Decimal notation scale then all converted to decimal), IOP measurement using Goldman applanation tonometer, ant. Segment examination by slit lamp bio-microscopy and examination of fundus by auxiliary lens and \or indirect ophthalmoscope.

Examination of the macula was done by Swept source OCT (SS- OCT) and by Optical coherence tomography angiography.

Methods of study

OCT was performed using swept source OCT (SS-OCT).

1) OCT parameters:

-According to ETDRS:

1- 1-central macular thickness
2- 2-parafoveal in 4 quadrants
3- Perifoveal in 4 quadrants.
4- 4-Integrity of outer retinal layers (IS-OS ellipsoid layer, ELM integrity and interdigitation zone): if it disrupted or intact or absent. It is important to be evaluated in cases of DME.
5- RPE integrity.
6- Organization of inner retinal layers and detection of disorganization (DRIL).
7- Post maneuvers we look for development of complications as ERM and scaring.

2) OCT angiography:

Was performed using an RTVue XR Avanti with Angio Vue software (Optovue, Inc., Fremont, California, USA). For each eye, a 6 X 6 -mm scan centered on the fovea. Automated OCT segmentation will be Performed using the Angio-Vue module.

OCTA parameters:

1-Vessel density (superficial and deep capillary plexus).
2- FAZ area.

FAZ the area of the central fovea in which there is no vessels. FAZ size was calculated automatically using the software of the machine.

Vessel densities: Vessel density is defined as the proportion of the measured area occupied by blood vessels in both deep vascular plexus (DVP) and superficial vascular plexus (SVP).

Follow –up with:

1) BCVA (best corrected Visual acuity).
2) OCT parameters.
3) OCT angiography parameters.

Follow-up was scheduled to be at one month, three months and 6 months.

Statistical analysis

Using SPSS version 18 we analyzed the data. Comparison was made between pre and post treatment follow up data at 1, 3 and 6 months (repeated measure ANOVA) RMANOVA test. Sphericity were examined using Mauchly's Test of Sphericity. Bonferroni post hoc test to examine the difference at each time point. The different time points used as within subject factors. Student t test was used to compare injection and laser gro-

up. Chi square test used for categorical data. P value was considered significant if it was < 0.05.

Criteria of studied group:1) Age & gender: include 40 eyes with 17 eyes of 17 females and 23 eyes of 20 males with mean age 54.18±10.09 years old.

Table (1): demographic criteria of studied group

Variable	Laser group N=40
Age/years Mean ± SD Median (range)	54.18±10.09 54 (36:70)
Gender Female Male	17 (42.50%) 23 (57.50%)
Eye OD OS	15(37.50%) 25 (62.50%)

1) **IS-OS ellipsoid layer and external limiting membrane integrity:** ELM was disrupted in 5 eyes (12.5%), and IS/OS was disrupted in 7 eyes (17.5%).
2) **DRIL:** no eye has drill

Table (2): OCT criteria of group (2):

Variable	Frequency	Percentage
Disturbed IS-OS	7	17.5
Disturbed ELM	5	12.5%

Parameters which were studied: in all following parameters:
P value for repeated measures**.**
Pairwise comparison P1 compared before & 1m, P2 compared before &3ms, P3 compared before & 6ms, P4 compared 1m &3ms, P5 compared 1m & 6ms, P6 compared 3ms & 6ms.

1)Visual acuity at different time in laser group

Table (3): Visual acuity at different time in laser group:

Variable	Before laser	Post laser (1 month)	Post laser (3 month)	Post laser (6month)	P value
VA Mean±SD Median (range)	0.33±0.06 0.32 (0.25:0.5)	0.35±0.06 0.32 (0.25:0.5)	0.35±0.06 0.32 (0.25:0.5)	0.35±0.06 0.32 (0.25:0.5)	<0.0001
P1=0.01, P2=0.001, P3=0.001, P4=0.50, P5=0.50, P6=1.00					

It was statistically significant improvement of visual acuity before and after macular laser treatment but it was statistically non-significant during period of follow-up (1,3 & 6m). with 62.5% (25 eyes) have improvement of visual acuity, 35% (14 eyes) has stabilized visual acuity and only 2.5% (2 eyes) have deteriorated visual acuity.

2) IS -OS ellipsoid layer and ELM integrity: we found slight increase in number of cases with IS-OS disruption but no effect on ELM integrity. With 8 eyes with disturbed IS-OS at 6m. follow-**up** while it was 7 eyes at baseline. And still 5 eyes with disturbed ELM at 6m. follow-up. We correlate that with visual acuity a significant difference was found between those with intact IS-OS (+) and disrupted group in BCVA at baseline it was 0.32 and 0.27 and after 6 months it was 0.41 and 0.31. Results were similar for ELM groups. Significant difference was found after 6 months and it was 0.39 and0.32

Table (4): Outer retnal integrity and its relation with BCVA:

	Mean BCVA at baseline	Mean BCVA at 6m.
Intact IS-OS	0.32	0.41
Disrupted IS-OS	0.27	0.31
Intact ELM	0.33	0.39
Disrupted ELM	0.29	0.32

3) DRIL: 1 eye develop DRIL.
4) 1 eye develop ERM Post macular laser, but no eyes develop foveal scarring.
5) Macular thickness at different time in laser group

Table (5): Macular thickness before and after laser treatment:

Variable	Before laser	Post laser (1 month)	Post laser (3 month)	Post laser (6 month)	P value
Fovea Mean ± SD Median (range)	255.7±24.82 257 (208:294)	235.78±26.14 236 (177:294)	227.4±26.21 224.5 (177:275)	225.43±24.86 224.5 (177:271)	<0.0001
P1<0.0001, P2<0.0001, P3<0.0001, P4<0.0001, P5<0.0001, P6=0.009					
Parafovea temporal Mean ± SD Median (range)	309.4±30.88 316 (204:378)	300.73±28.86 305.5 (204:365)	292.55±25.58 298 (199:357)	291.4±24.93 296 (197:346)	<0.0001
P1=0.03, P2<0.0001, P3<0.0001, P4<0.0001, P5<0.0001, P6=0.03					
Parafovea superior Mean ± SD Median (range)	340.5±30.33 345 (267:396)	311.03±25.28 311 (240:377)	299.53±23.33 302 (240:366)	297.73±21.97 300 (240:361)	<0.0001
P1<0.0001, P2<0.0001, P3<0.0001, P4<0.0001, P5<0.0001, P6=0.11					
Parafovea nasal Mean ± SD Median (range)	340.5±45.38 340 (275:494)	322.65±41.79 321.5 (265:494)	308±24.91 305.5 (265:366)	306.38±23.82 303 (265:361)	<0.0001
P1<0.0001, P2<0.0001, P3<0.0001, P4=0.002, P5=0.001, P6=0.005					
Parafovea inferior Mean ± SD Median (range)	327.63±46.76 324 (267:442)	309.58±38.23 301 (260:411)	294.83±27.07 290 (261:380)	293.53±25.11 290 (261:365)	<0.0001
P1<0.0001, P2<0.0001, P3<0.0001, P4=0.006, P5=0.003, P6=0.13					
Perifovea temporal Mean ± SD Median (range)	289.08±32.80 279 (218:356)	276.08±26.60 267 (218:342)	268.6±25.41 264 (202:335)	267.6±24.66 264 (202:326)	<0.0001
P1<0.0001, P2<0.0001, P3<0.0001, P4<0.0001, P5<0.0001, P6=0.14					
Perifovea superior Mean ± SD Median (range)	340.95±39.37 335.5 (271:420)	312.95±33.10 306 (255:389)	302.08±27.81 297 (245:366)	299.95±26.44 297 (245:365)	<0.0001
P1<0.0001, P2<0.0001, P3<0.0001, P4<0.0001, P5<0.0001, P6=0.44					
Perifovea nasal Mean ± SD Median (range)	323.35±37.08 320 (270:400)	303.4±30.88 300 (255:382)	293.35±29.05 290.5 (254:367)	291.83±27.37 290.5 (254:356)	<0.0001
P1<0.0001, P2<0.0001, P3<0.0001, P4<0.0001, P5<0.0001, P6=0.047					
Perifovea inferior Mean ± SD Median (range)	297.83±44.11 280 (249:408)	283.53±36.44 273.5 (235:392)	275.88±30.65 268 (233:371)	275.33±30.62 268 (231:371)	<0.0001
P1<0.0001, P2<0.0001, P3<0.0001, P4<0.0001, P5<0.0001, P6=0.60					

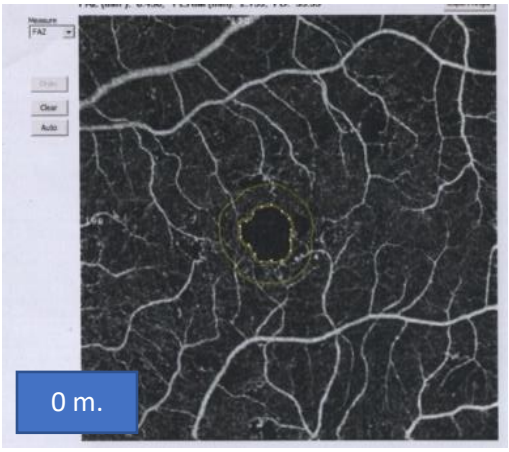
It was statistically significant changes of macular thickness before and after laser treatment and during period of follow up (1 ,3 &6) except during follow-up between 3 and 6 months which is statistically non-significant except in fovea, parafoveal nasal and parafoveal temporal areas.

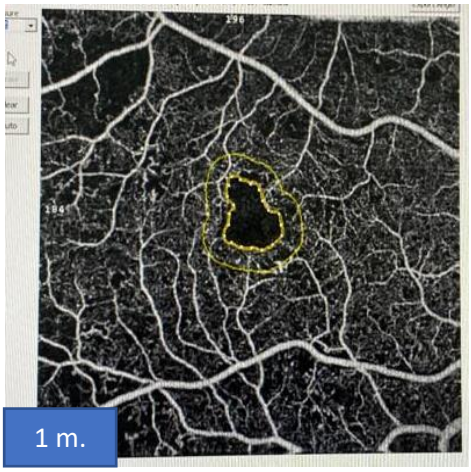
6) FAZ

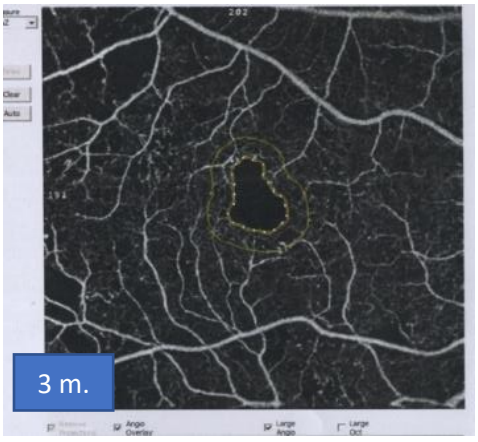
Table (6): FAZ before and after macular laser treatment

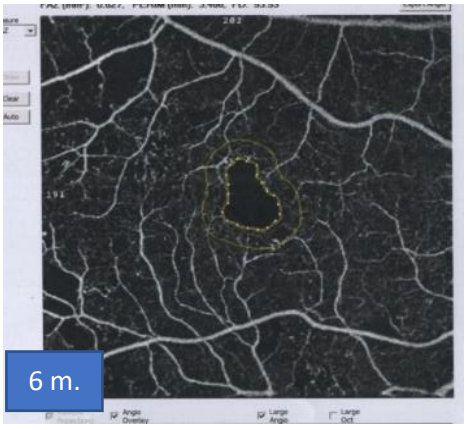
FAZ Mean ± SD Median (range)	0.28±0.08 0.31 (0.09:0.39)	0.33±0.11 0.32 (0.10:0.66)	0.34±0.11 0.35 (0.11:0.69)	0.34±0.11 0.35 (0.11:0.69)	0.001
P1=0.02, P2=0.004, P3=0.003, P4=0.004, P5=0.001, P6=0.02					

it was statistically significant (enlarged FAZ) before and after macular laser treatment and during periods of follow -up (1,3 &6m)









7) Superficial vascular density at different time in laser group:

Table (7): Superficial vascular density at different time in laser group:

Variable	Before laser	Post laser (1 month)	Post laser (3 month)	Post laser (6 month)	P value
Whole density Mean ± SD Median (range)	43.15±7.23 43.85 (27.5:54.9)	42.67±7.12 43.5 (26.1:53.9)	42.34±7.08 43.05 (26.1:53.1)	42.26±7.03 43.05 (26.1:53.1)	<0.0001
P1=0.001, P2<0.0001, P3<0.0001, P4<0.0001, P5<0.0001, P6=0.06					
Fovea Mean ± SD Median (range)	21.39±11.36 18.7 (3.4:40.9)	20.86±11.28 18 (3.1:40.2)	20.63±11.27 17.9 (3.1:40.1)	20.6±11.27 17.9 (3.1:40.1)	<0.0001
P1<0.0001, P2<0.0001, P3<0.0001, P4<0.0001, P5<0.0001, P6=0.31					
Parafovea Mean ± SD Median (range)	44.13±6.99 46.2 (28.3:52.4)	43.60±6.95 45.5 (28:52)	43.15±6.91 44.85 (27.5:51.4)	43.08±6.88 44.7 (27.5:51.4)	<0.0001
P1<0.0001, P2<0.0001, P3<0.0001, P4<0.0001, P5<0.0001, P6=0.10					
Perifovea Mean ± SD Median (range)	44.95±7.74 44.9 (28.6:57.5)	44.32±7.85 44.45 (26.4:56.5)	44.02±7.89 43.9 (26:56.5)	44.00±7.87 43.9 (26:56.1)	<0.0001
P1<0.0001, P2<0.0001, P3<0.0001, P4<0.0001, P5<0.0001, P6=0.96					

It was statistically significant reduction in vascular density of superficial capillary plexus before and after laser treatment and during period of follow-up but it is non-significant reduction at period of follow -up 3&6 months except in whole density, parafoveal nasal, perifoveal nasal and parafoveal superior.

8)Deep vascular density at different time in laser group

Table (8): Deep vascular density at different time in laser group

Variable	Before laser	Post laser (1 month)	Post laser (3 month)	Post laser (6 month)	P value
Whole density Mean ± SD Median (range)	43.69±8.38 42.5 (29.1:59.1)	43.07±8.16 41.8 (28.7:58.1)	42.69±8.11 41.5 (28.6:57.8)	42.67±8.08 41.4 (28.6:57.1)	<0.0001
P1<0.0001, P2<0.0001, P3<0.0001, P4<0.0001, P5<0.0001, P6=0.88					
Fovea Mean ± SD Median (range)	34.94±11.13 31 (22.3:64.8)	34.33±10.53 30.65 (22.1:62.2)	34.03±10.45 30.15 (22:62.2)	33.99±10.38 30.15 (22:62.2)	<0.0001
P1<0.0001, P2<0.0001, P3<0.0001, P4<0.0001, P5<0.0001, P6=0.46					
Parafovea Mean ± SD Median (range)	50.20±6.29 51.15 (31.6:61.2)	49.51±6.03 50.5 (31.5:60)	49.21±6.08 50.25 (31.5:59.2)	49.10±6.18 50.05(31.5:59.2)	<0.0001
P1<0.0001, P2<0.0001, P3<0.0001, P4=0.001, P5<0.0001, P6=0.03					
Perifovea Mean ± SD Median (range)	44.31±8.42 43.5 (29.9:58.3)	43.69±8.46 43.2 (29.1:58.1)	43.47±8.46 43.1 (28.8:58.1)	43.42±8.43 43.1 (28.8:58.1)	<0.0001
P1<0.0001, P2<0.0001, P3<0.0001, P4<0.0001, P5<0.0001, P6=0.23					

There was statistically significant reduction of vascular density of deep capillary plexus before and after laser treatment and at all periods of follow-up but at period of follow- up between 3 and 6 months which is statistically non-significant changes in vascular density except at parafovea and parafoveal temporal which is statistically significant.

Discussion:

we found that visual acuity has statistically significant improvement before and after macular laser treatment (1&3 m.) but it was statistically non-significant during period of follow-up (between 3 and 6m). with 62.5% (25 eyes) have improvement of visual acuity, 35% (14 eyes) has stabilized visual acuity and only 2.5% (2 eyes) have deteriorated visual acuity.

While in Keshav B.R., et al. study found that more than 50% of eyes of patients who underwent laser had stabilization of VA and >25% of eyes had improvement in VA and 14.54% showed worsening of VA. This difference from our study may be due to larger study group (their study includes 165 eyes), their follow-up was only 3 months and their study include any case of CSME not only those with non-central involved macular edema[.6]

Alvi, et al. study also found that laser therapy is an effective treatment in stabilizing/improving the vision in diabetic macular edema but the best corrected visual acuity had declined in 2.4% eyes, stabilized in 67% eyes and improved in 30.7% eyes. This difference from our study might be due to their larger study group, longer follow-up and also, they include all eyes with CSME not only those with non-central involvement macular edema[.7]

Our study evaluate laser therapy and macular thickness and we found that macular thickness had statistically significant changes before and after laser treatment and during period of follow up (1 ,3 &6) except during follow-up between 3 and 6 months which is statistically non-significant except in fovea, parafoveal nasal and parafoveal temporal areas where more effect still occur (more reduction in macular thickness still obtained).

This is in agreement with Shahidi, et al. study who demonstrated that focal laser treatment seem to be effective in preventing the progression of macular oedema by reducing or maintain the degree of thickening[.8]

Perente, et al. study, disagree with our study as they report that the mean baseline VA letter score decreased by 0.2 at 3 months, 0.1 at 6 months, and 0.4 at 12 months. While the average CMT decreased (improved) by 15.9 microns at 3 months, 18.7 microns at 6 months, and 22.6 microns at 12 months. Which is in agreement with our study that laser treatment was associated with reduction of CMT and its effect continue more than 3 m. and improvement still occur at 6months[.9]

We assessed macular perfusion before and after laser and during whole period of follow-up (1,3&6), we found that FAZ was statistically significant changed (enlarged FAZ), also, it was statistically significant reduction in vascular density of superficial capillary plexus before and after laser treatment and during period of follow-up but it is non-significant reduction at period of follow -up 3&6 months except in whole density, parafoveal nasal, perifoveal nasal and parafoveal superior. But there was statistically significant reduction of vascular density of deep capillary plexus before and after laser treatment and at all periods of follow-up but at period of follow- up between 3 and 6 months which is statistically non-significant changes in vascular density except at parafovea and parafoveal temporal which is statistically significant. From that we can say that laser treatment for macular edema was associated with relative macular ischemia.

Li , et al study found that superficial parafoveal vascular density decreased post

laser, deep parafoveal vascular density also decreased ,central macular thickness decreased and this reduction continue to 6 month of follow-up after laser(.10)

Although laser was associated with improvement of vision and reduction of macular thickness but there was relative ischemia (affect macular perfusion) and was associated with development of complication as ERM in one case so long follow -up after laser is recommended.

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