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Study of Structural Changes in Diabetic Macular Edema by Spectral Domain Optical Coherent Tomography after Intravitreal Injection of Triamcinolone Acetonide

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ABSTRACT

Purpose: is to study the morphological changes in Diabetic Macular Edema (DME) before and after intravitreal injection of triamcinolone acetonide using the spectral domain–optical coherence tomography (SD-OCT) parameters.

Patient and methods: The study was held at Al-Zahraa University Hospital. It included 49 eyes of 40 patients with clinically significant diabetic macular edema (CSDME). A single intravitreal injection of triamcinolone acetonide (IVTA) at the dose of 4 mg in 0.1 ml was administered. Best corrected visual acuity (BCVA), intraocular pressure (IOP) and OCT scanning of the macula were done before and 3 months after IVTA. The OCT study parameters included central foveal thickness (CFT), OCT pattern of DME, vitreomacular interface (VMI), presence or absence of serous macular detachment (SMD), hard exudates (HEs), hyper-reflective spots (HRS) and IS/OS junction (Foveal ellipsoid zone) & ELM integrity.

Results: Mean BCVA ± SD were (0.23 ± 0.13) and (0.39 ± 0.22) pre and 3 months after IVTA respectively. The initial mean CFT ± SD was (424 ± 127.1 um) while 3 months after IVTAit was (283.1 ± 70.2 um). Eighteen eyes showed SMD which was completely absent 3 months after a single IVTA. There was insignificant statistical difference of the VMI state before and 3 months after IVTA. Out of thirty-four eyes that showed the presence of HEs in this study, twenty-seven eyes showed diminution of these HEs size 3 months after injection. Forty-one eyes and forty-three eyes showed the presence of HRS before and after IVTA respectively. There was insignificant statistical difference in foveal ellipsoid zone and ELM integrity before and 3 months after IVTA. Complications were reported in 16 eyes (32.6%). Cataract progression was noted in 6 eyes (12.2 %). Steroid induced IOP elevation was reported in 10 eyes (20.4%).

Conclusions: The data collected from OCT macular B scan are effective in the prognosis and follow up of diabetic macular edema. IVTA remains a promising primary therapy for DME at least in short terms. It seems relatively safe, but not without complications.

Keywords: Spectral Domain Optical Coherence Tomography, Diabetic Macular Edema, Intravitreal triamcinolone, Central foveal thickness, Hard Exudates, Hyper-reflective spots.

INTRODUCTION

Diabetic macular edema (DME) remains a major cause of vision loss in developed countries despite continued improvements in the care of both diabetes mellitus and diabetic retinopathy.Intravitreal pharmacotherapies have largely replaced photocoagulation or used as adjuvant therapy for patients with center-involving DME. Most patients with DME improve with anti-VEGF treatment and many will also benefit from treatment with corticosteroids [(1)].

The visual acuity is not always improved after treatments of the macular edema, which suggests that macular thickness is only one of the factors that worsen the visual function. Therefore, quantitative measurements may not explain all variations in visual acuity, and other factors including macular ischemia and retinal cell function might be important as well [(2)].

The advancement in optical coherence tomography (OCT) technologies including the increase in speed of scanning and higher axial resolution (up to 3 microns for certain OCT machines) has made visualization of the retinal microstructures possible and provided retinal sectional images as in a histology study[(3)].

PATIENTS AND METHODS

The study is a single group, randomized, prospective and interventional. It was performed on 49 eyes of 40 patients with clinically significant diabetic macular edema (CSDME) according to the ETDRS classification. It was held at Al Zahraa University Hospital between March, 2015 and May, 2016. **The study was approved by the Ethics Board of Al-Azhar University.**

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Inclusion criteria included eyes with nonprolifeative diabetic retinopathy (NPDR) and (CSME) that had central subfield macular thickness more than 250 µm on OCT examination and intraocular pressure (IOP) less than 15 mmHg.

Exclusion criteria included macular edema of etiologies other than DM, previous retinal laser treatment, surgery, trauma or intravitreal injection, media opacity interfering with posterior segment visualization, proliferative diabetic retinopathy and ischemic DME.

All included patients were subjected to full history taking, complete ophthalmic examination including: best corrected visual acuity(BCVA), applanation tonometry, slit lamp examination, lens status evaluation, dilated fundus examination, and biomicroscopy of the posterior pole, colored photography and fundus fluorescein angiography (FFA).

All patients had baseline OCT macula scanning that was done using NIDEK RS-3000L Spectral Domain OCT (software version NAVIS EX 1.1.0.0; Nidek Co. Ltd., Gamagori, Japan). At each visit the desired scanning type is located, we used three scan types for each eye: 1) Macula line:(scan angle changeable by 15°), we considered horizontal scan at 0°, vertical at 90°and oblique at 45°. 2) Macula Multi: (X-Y scans: 5 x 5). 3) Macula Map: that imaged a 6 × 6 mm area with 64 raster B-scans, each composed of 1024 A-scans. Multiple scans were taken throughout the whole macular area. Scans with the strongest signal strength were selected (signal strength of more than 6/10). According to these scans, we were able to measure certain dimensions and evaluate certain morphological changes and findings within the scans. For each eye, the study OCT parameters included were: CFT, OCT pattern of DME, presence or absence of serous macular detachment (SMD), vitreomacular interface (VMI) state, presence or absence of hard exudates (HEs), presence or absence of hyper-reflective spots (HRS) and Foveal ellipsoid zone & ELM integrity. Colour fundus photographs and FFA were obtained at baseline visit for all patients. FFA assessed the dye leakage in the macula in late phases (3-4 minutes after dye injection). The macular capillary perfusion was also assessed. Cases of ischemic maculopathy were excluded.

A single intravitreal injection of triamcinolone acetonide (IVTA) was administered. An informed consent was signed by the patient. An IVTA injection was performed as described below for all patients.

Topical anaesthesia was applied using (benoxinate) eye drops in the eye 5 minutes prior to injection, followed by 5% povidone-iodine solution for few minutes. Triamcinolone acetonide (Kenakort-A 40 mg/ml; Smith Kline Beecham Company, Egypt) was then injected into the vitreous inferotemporally using a 30 gauge needle at a dose of 4 mg in 0.1 ml. Anterior chamber paracentesis was immediately done after injection.

Patients were instructed to attend for follow up after 1 day, 1 week, 1 month, and 3 monthsafter injection. OCT examination was performed at baseline and at 1 and 3 months after IVTA for all patients. Potential corticosteroid induced and injection related complications were also observed.

RESULTS

Forty-nine eyes of forty patients were enrolled in this study including 10 males (25%)and 30 females (75%). The mean age ± SD was (56.7 ± 7.3years) (Range 39 – 70 years). Demographic data of patients were taken according to patient's history, and it was shown in (**table 1)**.

Table (1). General characteristics of the studied cases (SD=standard deviation)

	General characteristics	**Cases, no.= 40**
Age / years	Mean ± SD	56.7 ± 7.3
Sex	Male	10 25.0 %
	female	30 75.0 %
Type of DM	Type 1	2 5.0%
	Type 2	38 95.0 %
Duration of DM / years	Mean ± SD	9.7 ± 4.5
Laterality	Unilateral	31 77.5 %
	Bilateral	9 22.5 %

The mean BCVA ± SD were (0.23 ± 0.13) and (0.39 ± 0.22) pre and 3 months after IVTA respectively **(table 2)** and **(Figure 1)** with an improvement of 2 Snellen lines in mean BCVA (*P* value was 0.000).

Table (2). Comparison between pre and post injection BCVA (* Significant p-value)

BCVA	Mean±SD	Paired *t-test*	p-value
Pre BCVA	0.23±0.13	7.4	0.000*
Post BCVA	0.39±0.22		

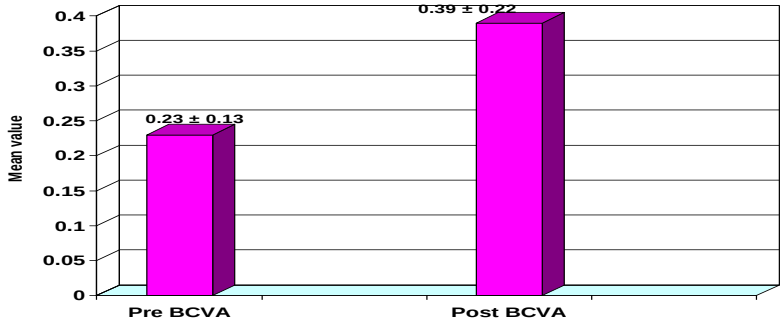


Figure (1). Mean value ± SD of the best corrected visual acuity of the studied eyes

The initial mean CFT ± SD was (424 ± 127.1 um).Three months after IVTA, it was (283.1 ± 70.2 um) **(table 3)** and **(Figure 2)** with a reduction of the mean CFT by 140.9 um (33.23%) (*P* value was 0.000).

Table (3). Comparison between pre and post injection CFT (* Significant p-value)

CFT	Mean± SD	Paired *t-test*	p-value
Pre-injection CFT (um)	424.0±127.1	9.1	0.000*
Post-injection CFT (um)	283.1±70.2		

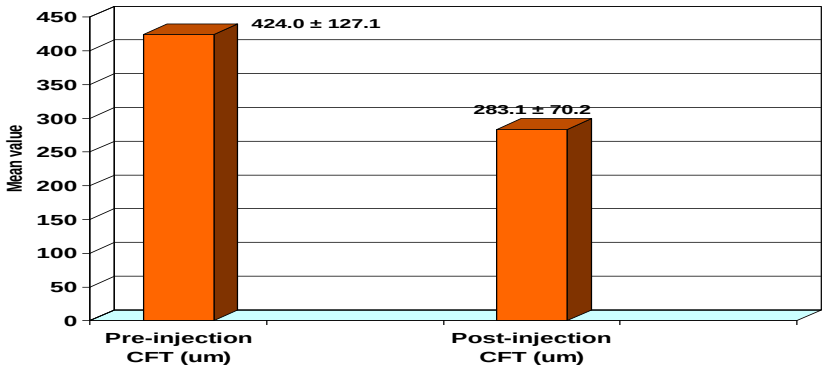


Figure (2). Mean values ± SD of CFT pre and post injection

There was **a significant negative correlation** between pre BCVA &Pre-injection CFT and **a significant negative correlation** between the post BCVA & post-injection CFT **(table 4)**.

Table (4). Pearson Correlation among BCVA & CFT (* Significant p-value)

Correlated variables		Correlation coefficient(r)	P-value
Pre BCVA	Pre-injection CFT	- 0.46	0.001**
Post BCVA	Post-injection CFT	- 0.299	0.03*

* Correlation is significant at the 0.05 level.
** Correlation is significant at the 0.01 level.

There were associations between different OCT patterns of DME in some eyes enrolled in this study and distinct patterns in others as following **(table 5)**:

Table (5). OCT pattern of DME according to the number of eyes

Pattern	no. = 49	%
Focal macular thickening	15	30.6
Diffuse retinal thickening (DRT)	8	16.3
Cystoid macular edema (CME)	3	6.1
Posterior hyaloid traction (PHT)	1	2.0
Focal macular thickening + Serous retinal detachment (SRD)	3	6.1
Diffuse retinal thickening (DRT)+ Serous retinal detachment (SRD)	3	6.1
Diffuse retinal thickening (DME) + Posterior hyaloid traction (PHT)	3	6.1
Cystoid macular edema (CME) + Posterior hyaloid traction (PHT)	1	2.0
Cystoid macular edema +Serous retinal detachment (SRD)	10	20.4
Cystoid macular edema +Serous retinal detachment (SRD) + Posterior hyaloid traction (PHT)	2	4.1

Out of 49 eyes enrolled in this study, 18 eyes showed SMD that had been absent 3 months after a single IVTA (*p*-value = 0.000) **(table 6)** and **(figure 3)**.

Table (6). Comparison between pre and post injection presence of SMD (* Significant p-value)

SMD	Pre injection no. %	Post injection no. %	Chi-square test (X^2) & p-value
Absent	31 (63.3%)	49 (100 %)	X^2 test = 22.0
Present	18 (36.7%)	0 (0.0%)	p-value = 0.000*

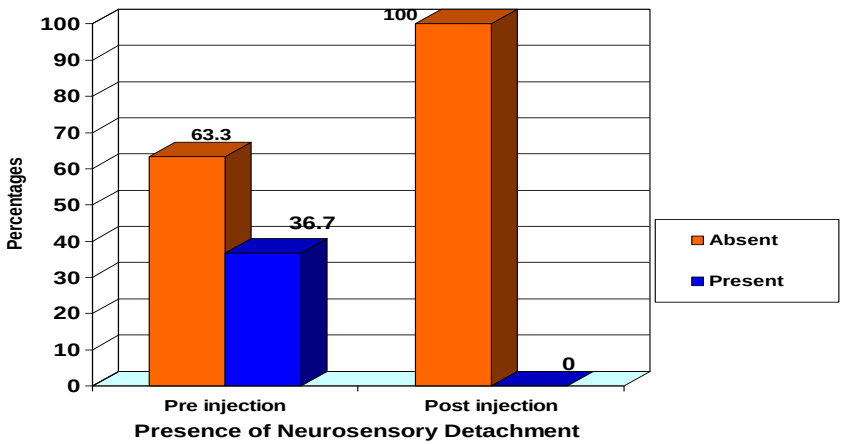


Figure (3). Presence of neurosensory detachment pre and post injection

As for vitreomacular interface state, there were **insignificant statistical difference** of the VMI state before and 3 months after IVTA (p-value = 0.232). These results were summarized in **table (7)**and**(Figure 4).**

Table (7). Comparison between pre and post injection of VMI

VMI	**Pre injection**		**Post injection**		**Chi-square test (X^2) & p-value**
	no.	**%**	**no.**	**%**	
NormalVMIstate	19	38.8 %	19	38.8 %	X^2 test = 4.285 p-value = 0.232
Partial PVD with no traction	20	40.8%	15	30.6%	
Partial PVD with traction	9	18.4%	9	18.4%	
Total (PVD)	1	2.0%	6	12.24%	
Total	49	100.0	49	100.0	

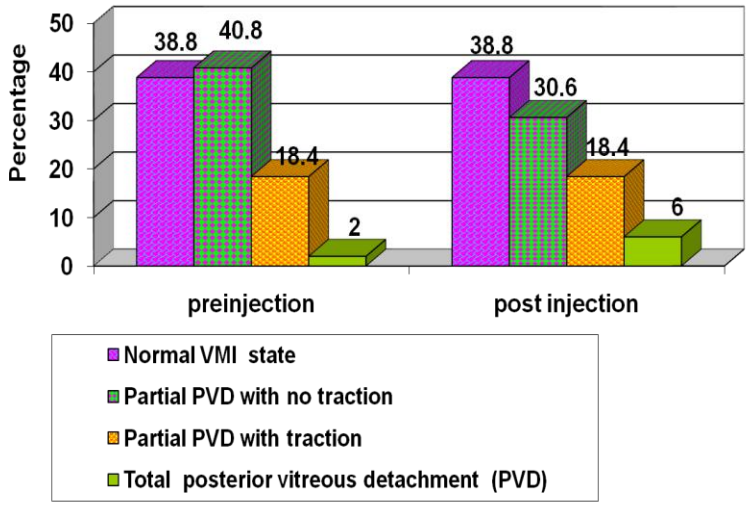


Figure (4). VMI state in the OCT findings before and 3 months after IVTA

Out of 34 eyes that showed the presence of HEs in this study, 27 eyes had showed diminution of these HEs size 3 months after a single IVTA (*p*-value = 0.00). These results were shown in **table (8)** and **(Figure 5)**

Table (8). Comparison between pre and post injection presence of HEs (* Significant p-value)

Hard exudates (HE)	Pre injection no. %	Post injection no. %	Chi-square test (X^2) & p-value
Absent HE	15 (30.6%)	15 (30.6%)	
Presence of HE	34 (69.4%)	7 (14.3%)	X^2 test = 44.8
HE diminished in size	0 0%	27(55.1%)	p-value = 0.00*
Total	49 (100%)	49 (100%)	

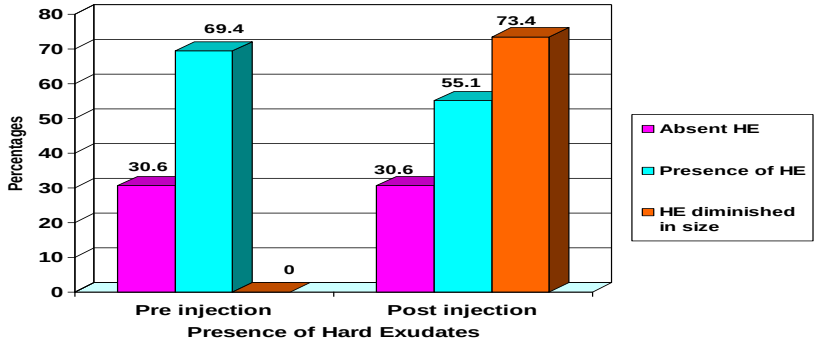


Figure (5). Hard exudates pre and post injection

Forty-one eyes and forty-three eyes showed presence of HRS before and after IVTArespectively with insignificant statistical difference (p-value = 0.563). These results were summarized in **table (9)** and **(Figure 6)**.

Table (9). Comparison between the presence of HRS pre and post injection

Presence of HRS	Pre injection no. %	Post injection no. %	Chi-square test (X^2) & p-value
Absent HRS	8 (16.3%)	6 (12.2%)	
Presence of HRS	41 (83.7%)	43 (87.8%)	X^2 test = 0.333
Total	49 100.0	49 100.0	p-value = 0.563

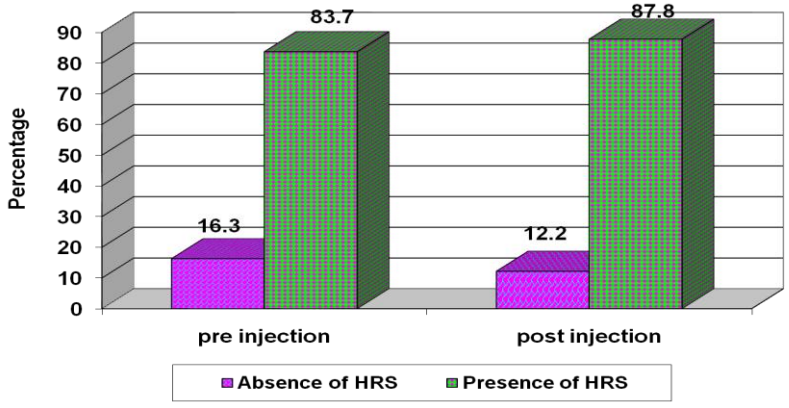


Figure (6). Presence of HRS pre and post injection

There was insignificant statistical difference in foveal ellipsoid zone integrity (*p*-value = 0.296) and ELM integrity (*p*-value = 0.424) before and 3 months after IVTA **(figure 7)**.

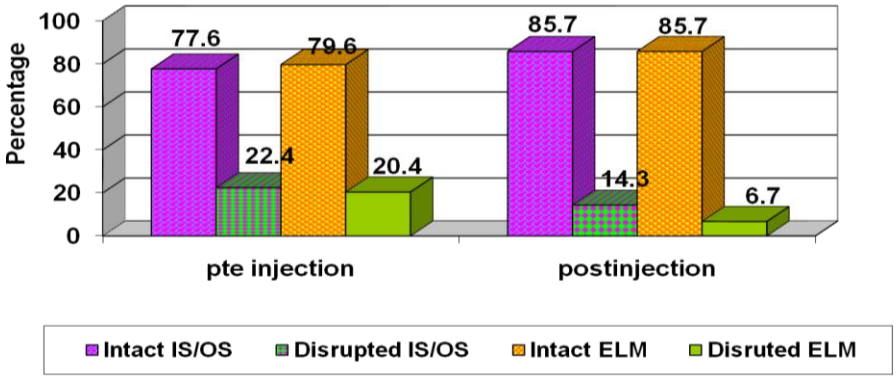


Figure (7). The status of IS/OS & ELM integrity pre and post injection

Intravitreal complications were reported in 16 eyes (32.6%) enrolled in the study, while 33 eyes (67.4%) showed no complications. Cataract progression was reportedin 6 eyes (12.2 %), but there was no one needed a cataract surgery during the follow up period. Steroid induced IOP rise was reported in 10 eyes (20.4%). The mean ± SD value of IOP before injection was (11.837 ± 1.625 mmHg) and first day post injection it was (17.959 ± 3.937mmHg). IOP was controlled using beta blockers eye drops for one month during the follow up period. No other intravitreal complications were reported in this study as shown in **table (10)** and **(Figure 8)**:

Table (10). Incidence of complications

Complications	**no.**	**%**
No complication	33	67.4
IOP rise	10	20.4
Cataract	6	12.2
Total	49	100

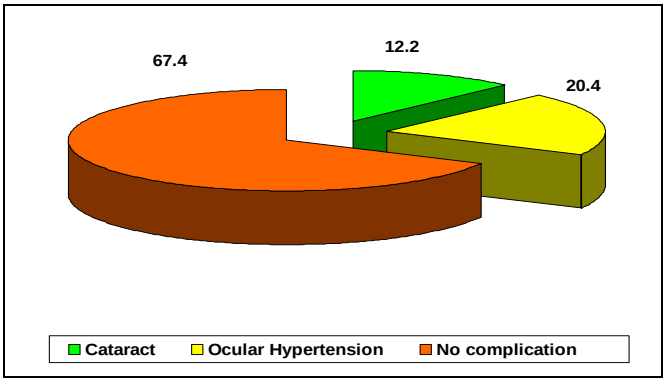
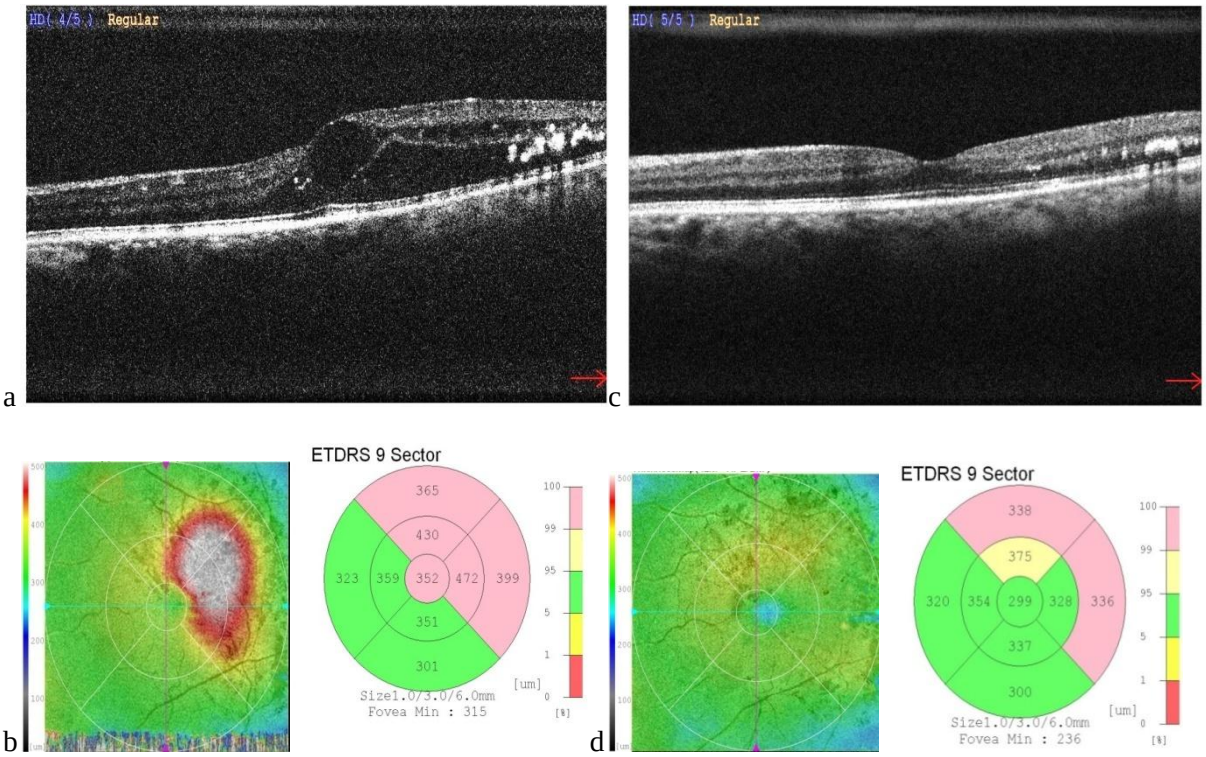


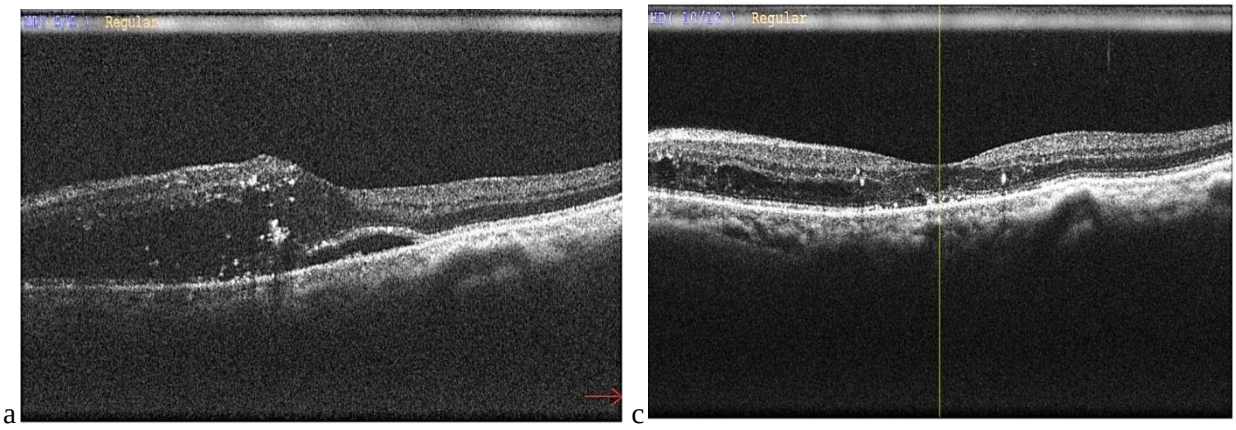
Figure (8): Incidence of complications

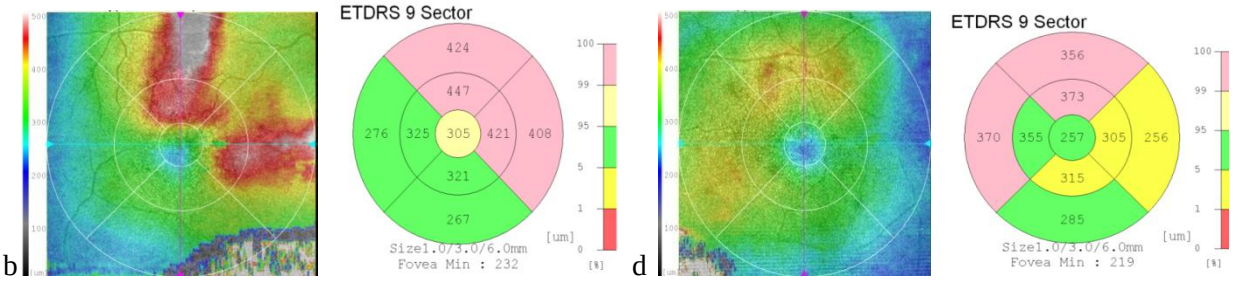
CASE 1



(Fig. 9). OCT scans of (case no. 1) before IVTA showing: (a) *a horizontal OCT scan obtained through the fovea revealed centrally involved cystoid macular edema (CME) with large subfoveal cyst and hard exudates (HEs) at temporal macula (**Pre BCVA was 0.25**). **(b)** ETDRS map of the case before IVTI with initial central subfield thickness (CFT) =352 µm. **After IVTA: c)** the retinal layers reflectivity retained to the normal with preservation of foveal contour. The cyst turned into diffuse spongy edema. HEs begin to coalesce and decrease in size. **d)** (CFT) the central subfield thickness had become 299 µm (**Post BCVA was 0.7).***

CASE 2





(Fig.10). OCT scans of (case no. 3) before IVTA showing:

(a) a horizontal OCT scan obtained through the fovea revealed centrally involved spongy like focal thickening with large cystic spaces and HEs. Serous retinal detachment (SRD) is observed with disrupted IS/OS line (**Pre BCVA was 0.07)**.
b) ETDRS map of the case before IVTI with initial central subfield thickness (CFT) = 305 µm. **After IVTA:**
c) the retinal layers hypo-reflectivity had decreased and the cystic spaces were turned into diffuse spongy edema with preserved foveal contour and no more SRD. Foveal ellipsoid zone (IS/OS line) and ELM are disrupted.
d) (CFT) the central subfield thickness had decreased and become 257 µm (**Post BCVA was 0.1).**

DISCUSSION

In the present study, we assessed the morphological changes that occurred in DME pre and 3 months post a single IVTA in a dose of (4 mg/0.1ml) as a primary treatment, using analysis of spectral domain–optical coherence tomography (SD-OCT) macular parameters.

The results of this study demonstrated that **the mean BCVA** showed a statistically significant change after the 3 months follow up period following IVTA with an improvement in mean BCVA that equal to 2 Snellen lines. This agrees with ***Martidis et al. study*** [(4)]in which all eyes demonstrated a functional response at 1 and 3 months, with an average improvement in visual acuity of 2.4 and 2.4Snellen lines at 1 and 3 months follow up periods respectively.

In the current study, **the mean CFT** showed a statistically significant reduction at the 3 months follow up period by (140.9 um) (33.23 %). The initial mean CFT was 424 microns (SD was ±127.1) and the mean CFT was 283.1 microns (SD was ±70.2) at 3 months. This agree with ***Sutter et al.*** [(5)] and ***Ciardella et al.*** [(6)]who reported that IVTA was effective in improving VA and reducing DME.

We found that eyes with **SMD** gained the greater structural improvement after a single IVTA, where there were 18 eyes out of 49 eyes enrolled in the study (36.7%) that showed SMD pre intravitreal TA injection and no SMD after IVTA.

The results of the present study showed insignificant statistical difference of the **VMI** state before and 3 months after IVTA. These results differed from that of ***Sivaprasad and associates*** [(7)]who reported that after 12 months following intravitreal injection of TA, the prevalence of PVD was significantly higher than at the base line. This difference may be due to the long follow up period of the latter study, or because the latter study was concerned with DME that fails to respond to at least two previous sessions of laser photocoagulation, while the present study was concerned with TA as a primary treatment for DME.

As for **hard exudates**, 34 eyes (69.4%) that were evident to have hard exudates in the OCT scans before the treatment, 27 eyes (55.1%) have been showed reduction of hard exudates size after the treatment. These results were in agreement with that of ***Ciardella and associates*** [(6)]who first reported progressive reabsorption of hard exudates present in the macula over the follow up period. Also agree with ***Larsson et al. study*** [(8)]who reported that a single injection of 4 mg triamcinolone acetonide rapidly reduces hard exudate deposition and improves VA, compared with placebo.

In the last years, **the hyper reflective spots (HRS)** have been described by some authors, who hypothesized different pathogenetic origin, and who also used different terms to name these lesions.

They named HRS as hyperreflective foci or hyperreflective dots [9]. We suggest that the term spots better encompasses the aspect of these lesions. In the present study, 41 eyes (83.6%) showed the presence of these hyper reflective spots across all retinal layers. After the follow up period following intravitreal TA injection, the presence of HRS appeared in OCT scans of two eyes in which they weren't seen before IVTA.

The presence of similar HRS on SD-OCT, across all retinal layers, has also been reported in DME in the studies of ***Bolz et al.*** [10].***Framme et al.*** [11] observed reduction of hyper reflective spots after anti-VEGF treatment in DME, but there was lack of literature observation about the behavior of HRS following TA intravitreal injection in patients with DME.

Regarding the intravitreal TA intervention in the present study, **complications** were noted in 16 eyes (32.6%), while 33 eyes (67.4%) showed no complications. Cataract progression was reported in 6 eyes (12.2 %), but no one needed a cataract surgery during the follow up period. Steroid induced IOP rise was reported in 10 eyes (20.4%). IOP was controlled under medical treatment during the follow up period.

These results were in agreement with ***Martidis et al. study*** [4] who reported in their study an average rise of IOP by 45%, 20%, and 13% at 1, 3, and 6month follow-up intervals. One eye progressed to cataract. ***Sutter et al.*** [5]had elevation of IOP in 30% of their treated cases, with 24% of patients requiring topical anti-glaucoma medication. They had one case of cataract and one case of infectious endophthalmitis. The follow-up period was 3 months.

CONCLUSION

Data collected from OCT macular B scan such as (ELM integrity, foveal ellipsoid zone integrity, presence or absence of hard exudates & HRS) other than macular map and central macular thickness are effective in the prognosis and follow up of diabetic macular edema.

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