Ophthalmology

Study of the Changes in Choriodal Thickness Before and after Intravitreal Injection of Ranibizumab in Diabetic Macular Edema

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ABSTRACT

Background: Diabetic Macular Edema is a critical complication of diabetic eye disease, the effect of Anti-VEGF injection in diabetic eyes does not stop at the retina alone as it also influences the choroidal circulation.

Aim of the study: To compare subfoveal choroidal thickness (SFCT) before and after intravitreal injection of ranibizumab in DME with the use of Cirrus HD-OCT by enhanced depth spectral-domain imaging (EDI-OCT).

Patient and methods: A prospective study that was demonstrated on 50 eyes of 35 cases with DME. Fundus fluorescein angiography was done for all patients. All patients were received three intravitreal injection of (0.5 mg/0.05 ml ranibizumab) with one-month interval. EDI-OCT was done preoperative and one-month following the third injection.

Results: The mean CT (Choroidal Thickness) was 257.62 ±49.207 µm with a range from 154 µm to 361 µm preoperatively. While the mean CT was 239.78 ± 47.225 µm with a range from 150 µm to 346 µm postoperatively, There were obvious changes between the preoperative and the postoperative SFCT measured by EDI-OCT and there was a positive significant correlation among the baseline SFCT and the change of SFCT (p. value 0.03).

Conclusion: Intravitreal injection of 0.5 mg/0.05 ml ranibizumab in the treatment of DME resulting in significant reduction of SFCT with greater response in cases with higher baseline SFCT, but improvement of BCVA was related to retinal thickness not to CT which needs further evaluation.

Keywords: Choriodal thickness; Ranibizumab; Diabetic; macular edema

INTRODUCTION

Diabetic macular edema (DME) is a critical eye conditions resulted mainly from hyperglycemia. It is considered a common cause of loss of vision and blindness in diabetics. [1]

There is a complex pathological process with many contributing factors that are responsible for the pathogenesis of DME.[2]

The normal choroid has fundamental rule for retinal function. Until lately, the choroid can be assessed only via laser flowmetry, indocyanine green angiography and ultrasonography. However, these procedures can only show choroidal vessel abnormalities and variations in blood flow; they cannot display the 3D anatomy of choroid layers or the retinal pigment epithelium. [3]

OCT (Optical coherence tomography) is a non-invasive imaging technique, that was used to obtain a high definition segments of retina. Lately, EDI (enhanced depth imaging) spectral-domain OCT has been explained. (EDI) program routinely captures a cross sectional picture with the choroid near the zero delay line to enhance sensitivity on the external edge of the choroid.[3]

The pathogenesis of DME was referred to retinal vascular hyper permeability, which is accompanied by focal leak from micro aneurysms or spread leak from inefficient capillaries when displayed on fluorescein angiography. [4]

Functional imaging findings also presented a decrease in choroidal flow of the blood in eyes with diabetic retinopathy. Till now, the function of

choroidal perfusion in the path physiology of DME still not clear. [5]

The current purpose of (EDI-OCT), which employing the enhanced depth of field from the inverted picture by locating the OCT device near to the eye, has helped the researchers to study the anatomic variations in the choroid in diabetic eyes. [6]

In this study, we compare SFCT preoperative and postoperative intravitreal injection of ranibizumab in DME using the Cirrus HD-OCT by enhanced depth spectral-domain imaging (EDI-OCT).

PATIENT AND MATERIALS

The current work is a prospective study that was demonstrated on 50 eyes of 35cases suffering from DME. These patients were received three intravitreal injection of ranibizumab with one month interval. EDI-OCT was done preoperative and a month after the third injection.

Exclusion criteria: were patients who previously had laser photocoagulation , patients with repaired retinal detachment, patients with atrophic macular scars, high myopes , patients with posterior staphyloma, patients who underwent previous vitrectomy, patients with ischemic maculopathy,Patients with tractional DME and patients with previous intravitreal injection.

Preoperative workup: Detailed history taking, full ophthalmological examination with emphasis on best corrected visual acuity (BCVA), biomicroscopic check of for every patient with examination of the iris for neovascularization and examination of the lens for the presence of cataract or pseudophakia, refraction and detailed fundus examination.

Fluorescein Angiography (FA): was done with exclusion of patients with ischemic maculopathy.

OCT: was done excluding patients with tractional macular edema and included EDI-OCT .OCT image acquired then the SFCT(within 100M from the fovea) was measured manually using the manual measuring ruler.

The procedure: was performed using topical anesthesia as 0.5 mg/0.05 ml ranibizumab is injected 4 mm (3.5 mm in Pseudophakia) from the limbus intravitreally (in the lower temporal quadrant) by a needle (27gauge). Paracentesis was carried out in some patients.

Postoperative examination: Every patient was examined postoperatively to assess his condition and exclude any complications, the intra ocular pressure (IOP) was measured and the patient was assured.

Follow up: All the cases were followedup after 1 and 4 weaks and the postoperative examination was included full ophthalmological examination with special emphasis on BCVA, biomicroscopic assesment of the anterior segment to exclude any changes or complications, fundus examination to detect fundus changes after the injection and EDI-OCT (one month after the third injection). Variations in the CT were estimated by subtracting the preoperative from the postoperative CT for eachpatient.

Ethical consideration: A clear printed approval was taken from each patient before being included in the study.

Statistical analysis: Data were investigated and analyzed utelizing the SPSS V-19 (improved by IBM). Quantitative values were reportedin the form of mean±SD(standard deviation).Qualitative data were reportedin the form of numbers and percentage.

RESULTS

The current study was demonstrated on 50 eyes of 35 cases from both sexes, undergoing intravitreal injection of ranibizumab for DME.

As regard to the demographic data, the mean age of the studied cases was 63.3 ± 8.963 yrs. with a ranging from 42 – 85years.The studied cases included 15 patient (30 %) who were males and 35 cases (70 %) who were females.

This study included 25 patients with diseased right eyes (50 %) and 25 patients with diseased left eyes (50 %).

According to the time interval of the diabetes, this study reported that the mean duration of diabetes in the study population was19.05 ± 7.327 years with a range from 5 years to 30 years. This study contained 12 cases with diabetes duration from 5 to 10 years (24%), 22 cases from 11 to 20 years (44%) and 16 cases from 21 to 30 years (32%).

This study included 8 cases with normal lens (16%), 25 cases with Cataractous lens (50%) and 17 cases with Pseudophakia (34%) according to the lens status.

Regarding the pre-operative and postoperative BCVA: The mean pre-operative Snellen's BCVA $(0.4 \pm 0.2$ with a range from 0.03 to 0.9)and the mean post-operative Snellen's BCVA (0.5 ± 0.2 with a range from 0.05 to 1.0).table (1).

According to the change in BCVA there were 26 cases with improved postoperative BCVA (52%), 15 cases with the same BCVA postoperative (30%) and 9 cases with worse BCVA postoperative (18%).

As regard preoperative CT was measured using EDI-OCT and the mean subfoveal thickness was 257.62 ± 49.207µm with a range from154 µm to 361 µm and postoperative CT was measured using EDI-OCT and the mean subfoveal thickness was 239.78 ± 47.225 µm with a range from 150 µm to 346 µm figure (1) & table(2)

Regarding the correlation among baseline of SFCT and its change after Anti-VEGF treatment, there was a positive significant correlation among the baseline SFCT and the change of SFCT indicating that higher baseline SFCT is usually associated with greater response after Anti-VEGF therapy figure (2) & table (3)

As regard the retinal thickness: Preoperative retinal thickness was assessed, and the mean foveal thickness was 455.84 ± 127.29 µm and ranging from 267 µm to 773 µm. Three months postoperative retinal thickness was estimated, and the mean foveal thickness was 384.44 ± 111.887 µm with a range from 229 µm to 648 µm table (4).

Studying the effect of the change in the retinal thickness on the change of the CT established that there was a positive correlation, but it was statistically insignificant table (5).

The Correlation among the postoperative CT and the postoperative BCVA among the investigated patients proved that there was a negative insignificant correlation (p = 0.795) figure (3) & table (6)>

Studying the effect of the postoperative retinal thickness on the postoperative BCVA showed statistically significant negative correlation figure (4) & table (7).
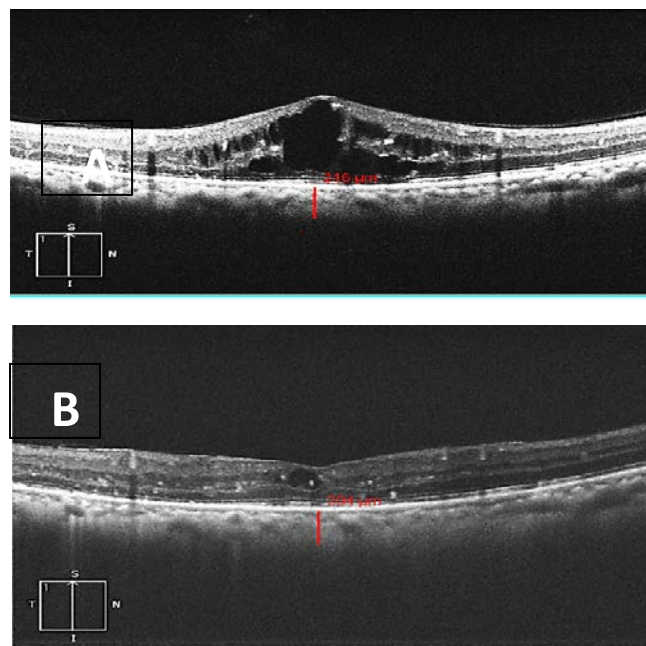

Figure (1): (A)preoperative (B)Postoperative Greyscale EDI-OCT images with CT measurement.
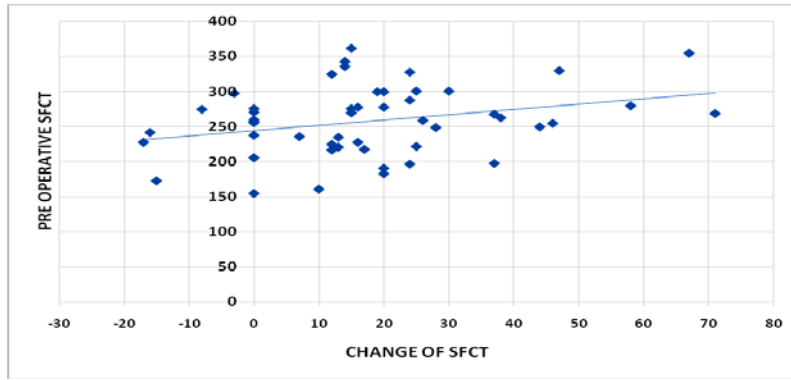
(measured by micrometer)

Fig.2: Correlation between the pre-operative CT and the change in CT among the investigated patients.

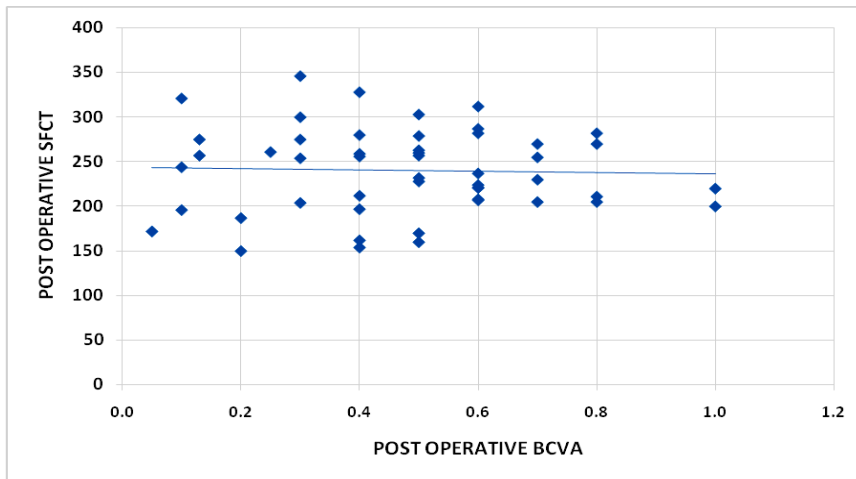Fig 3: Correlation between the post-operative CT and the post-operative BCVA among the investigated patients. (SFCT: sub foveal choriodal thickness (measured by micrometer) BCVA: best corrected visual acuity)
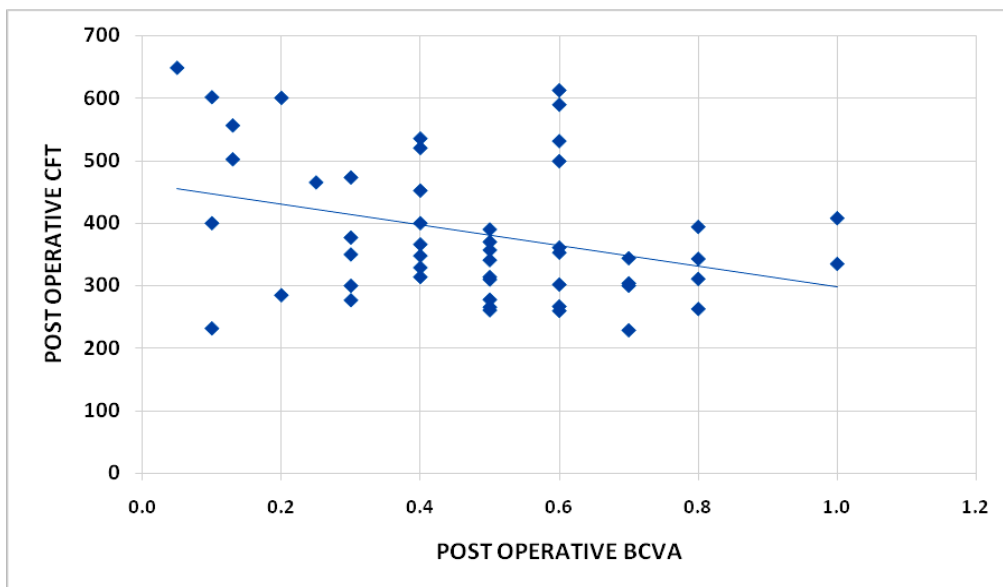

Fig 4: Correlation between the postoperative retinal thickness and the post operative BCVA among the investigated patients. (BCVA: best corrected visual acuity – CFT: central foveal thickness (measured by micrometer))

	Preoperative BCVA	3 months postoperative BCVA
Range	0.03 – 0.9	0.05 – 1.0
Mean ± SD	0.4 ± 0.2	0.5 ± 0.2
P	0.001	

Table 1: Mean and SD of the preoperative & 3 months postoperative BCVA.
(BCVA: Best corrected visual acuity – SD standard deviation)

Choroidal thickness	Preoperative	3 months postoperative	P
Range	154 – 361µm	150– 346µm	p< 0.001
Mean ± SD	257.62 ± 49.207µm	239.78 ± 47.225µm	

Table 2: The mean and SD of pre-operative & three months post-operative CT.
(µm: micrometer- SD standard deviation)

	Baseline SFCT	
	R	P
Change of SFCT	0.297	0.036

Table 3: shows positive statistically significant correlation among baseline SFCT and degree of change in it after Anti-VEGF treatment. (SFCT: sub foveal choroidal thickness)

Retinal foveal thickness	Preoperative	three months postoperative	P
Range	267 – 773µm	229 – 648µm	p< 0.001
Mean ± SD	455.84 ± 127.29µm	384.44 ± 111.887µm	

Table 4: The mean and standard deviation of preoperative and three months postoperative retinal foveal thickness.
(µm: micrometer)

		Difference in retinal thickness
Difference in choroidal thickness	R	0.223
	P	0.120

Table 5: Correlation among the difference in CT and the difference in retinal thickness between the investigated patients.

		BCVA
The postoperative CT	R	- 0.038
	P	0.795

Table 6: Correlation among the post-operative CT and the post-operative BCVA between the investigated patients. (CT: choriodal thickness - BCVA: Best corrected visual acuity)

		BCVA
The postoperative retinal thickness	R	--0.338
	p	0.016

Table 7: Correlation among the post-operative retinal thickness and the post-operative BCVA between the investigated patients. (BCVA: Best corrected visual acuity)

DISCUSSION

Several choroidal anomalies containing obstacle of the choriocapillaries, vascular collapse, choroidal aneurysms and choroidal neovascularization have been described in histopathological studies of diabetic eyes, these changes can be assessed indirectly using CT as an indicator. [7]

Intravitreal injection of Anti-VEGF is an effective and safe treatment to DME which is one of the biggest complications of diabetic eye diseases, the outcome of Anti-VEGF injection in diabetic eyes doesn't stop at the retina alone as it also has an effect on the choroidal circulation. [8]

The CT can be accessed via optical coherence tomography but acceptable visualization of the choroid using (OCT) wasn't available till lately, due to its location and the existence of pigmented cells which weaken the incident light, Spaide et al, developed an Enhanced depth imaging OCT that was a new method which allow a well imagining of the choroid permitting accurate evaluation of the CT. [9]

Latest studies exhibit an efficient evaluation of CT in healthy[10]and pathological states[11]utilizing the Cirrus HD-OCT (Carl Zeiss Meditec Inc. Dublin, CA) by Enhanced depth spectral-domain imaging using the Cirrus linear measurement tool, observers measured CT perpendicularly from the external edge of the hyper-reflective retinal pigment epithelium (RPE) to the internal sclera, the central subfoveal thickness was the measure used in almost all the studies to standardize the anatomical factor and avoid anatomical variations. [12]

Many researchers have been concerned about studying the choroidal changes in diabetic eye diseases using CT as a reference; though, the effect of Anti-VEGF injection as treatment for DME on the choroidal circulation is an additional issue that needs to be studied carefully, our study aims at studying the effect of ranibizumab on CT. [13]

Spaide et al. concluded that EDI is the finest technique to monitor all the choroid not only the external segments and so it is the best existing technique for examination and follow-up the CT. [14]

In our study the EDI- technique was employed to evaluate the CT. We stressed on the central SFCTto eliminate the anatomical variation and we measured the choroid using the same guidelines from previous studies i.e. vertically from the external edge of the hyper-reflective RPE(retinal pigment epithelium) to the internal sclera. [15,16,17]

We found significant changes between the preoperative and the postoperative measures and the results were as follow: The preoperative SFCTas assessed using EDI-OCT was 257.62 ± 49.207 μm and ranging from 154 μm to 361 μm. Studies done on the CT of healthy individuals found that it's true value is significantly changed among eyes especially in different age groups.

Erkul et al, in a recent work utilizing EDI-OCT to assay theSFCT reported that the estimated value range is 280.23 ± 81.15μm in normal adults. [18]

In our study at the postoperative period 4-weeksafterward the 3^{rd}injection, the mean subfoveal CT as evaluated using EDI-OCT 239.98 ± 47.225 μm and ranging from 150 μm to 346 μm. The post-operative CT was calculated to be significant with ($p< 0.001$) lesser than the pre-operative CT by a mean difference of 17.84 μm.

From the studies done in post Anti-VEGF injection in diabetic patients; Park YU et al. [19] compared CT

previously and afterwards injection of Anti-VEGF using EDI-OCT in 15 eyes and as a part of his consequences he found that: The postoperative CT was reduced after injection of Anti-VEGF with a mean difference of 19 μm.

The findings of our study compare favourably with this study and with Lee et al. [20] who reported after studying the effect of intravitreal injection of Anti-VEGF on 31 eyes that CT was reduced postoperatively. Another new study done by Lains et al. [21] on 50 eyes using EDI-OCT also supported the same finding that Diabetic eyes handled with anti-VEGF agents have decreased the CT.

Similarly, there was a positive significant correlation among the baseline SFCT and the change of SFCT indicating that higher baseline SFCT is usually associated with greater response after Anti-VEGF therapy (p. value 0.036).

In agreement with that, Nadim Rayess et al[22]reported that cases with a higher baseline subfoveal CT may suffer from a more intact choriocapillaries and thus a less ischemic external retina, preserving the role of the photoreceptor layer to a wider spread than in cases suffering from a thinner choroid and this may indicate the reason of having a better anatomical response after Anti-VEGF treatment.

Another clarification extracted from another investigation made by Kim et al [23]reporting that a more thick choroid in DME eyes may be a symptomatic of a more VEGF-driven procedure, that can describe the improved reaction noticed in the present work to anti-VEGF treatment, while eyes with thinner choroids may have DME due to (at least in part) a non-VEGF mediator and are consequently fewer receptive to anti-VEGF treatment.

In the current work the mean preoperative BCVA on snellen's was (0.4 ± 0.2) while the mean postoperative BVCA on snellen's chart was (0.5 ± 0.2) with (p =0.001).

There were 26 cases with improved postoperative BCVA (52%), 15 cases with the same BCVA postoperative (30%) and 9 cases with worse BCVA postoperative (18 percent) and this confirms the positive effect of ranibizumab injection on BCVA.

From the studies done in post intravitreal ranibizumab injection; Guesspie et al. [24] compared BCVA before and after ranibizumab injection on 18 eyes have reported a significant improvement in the postoperative BCVA.

The findings of our study compare favourably with this study and also with Park YU et al. [19] who reported that the mean preoperative BCVA on snellen's was (0.6 ± 0.3) while the mean postoperative BVCA on snellen's was 0.7 ± 0.3 implying a good visual outcome after intravitreal injection of ranibizumab.

In addition to comparing the BCVA preoperative and postoperative we studied also the effect of the postoperative choroidal and retinal thickness on the postoperative BCVA, a statistical significance was existing (p= 0.016) negative correlation among the postoperative retinal thickness and the postoperative BCVA among the investigated patients with (r = -0.338). Many previous papers supported this finding. [25,26]

Even though a negative correlation (r = - 0.038) was existing among the postoperative CT and the postoperative BCVA among the studied cases but it was statistically insignificant correlation (p = 0.795). This result also agreed with previous studies as Glenn et al[27] reported that central CT reduced after anti-VEGF treatment for DME but it cannot be accompanied by any functional or anatomical consequences in eyes with DME as there's no significant correlation among the variation in CT and the variation in visual acuity.

In the current work we studied the effect of the postoperative choroidal and retinal thickness on the postoperative visual acuity but our primary target was to compare the consequences of ranibizumab as Anti-VEGF on the CT by comparing the thickness before and after injection and our results as supported by many previously published papers confirmed that the subfoveal CT is significantly reduced after ranibizumab injection. These findings may be clarified as declared above by the outcome of ranibizumab on the choroidal vasculature. Along with the findings of this study, more experimental data on choroidal vasculature and more accurate means of choroidal measurement as well as a longer follow up period should be studied to provide better explanations for the CT variations in response to intravitreal injection of ranibizumab.

CONCLUSION

There was a significant change among the preoperative subfoveal CT and postoperative subfoveal CT. The higher baseline SFCT is usually associated with greater response after Anti-VEGF treatment and the reduction in CT following injection of ranibizumab reflect the effect of ranibizumab on the choroidal vasculature which needs additional investigation.

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