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Original Article

THE CHANGE OF SUBFOVEALCHOROIDAL THICKNESS AFTER INTRAVITREAL INJECTION OF RANIBIZUMAB AND ITS CORRELATION WITH VISUAL ACUITY IN DIABETIC RETINOPATHY

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Abstract

Background: *Optical coherence tomography (OCT) is a non-invasive imaging technique that is used to obtain high-resolution cross-sectional images of the retina. Diabetic choroidopathy refers to the presence of choroidal abnormalities in individuals with diabetes, which may contribute to the deterioration of visual acuity.* ***Aim:*** *To assess the subfoveal choroidal thickness (SFCT) and its relation with visual acuity in patients with diabetic macular edema (DME) after and before receiving intravitreal injections of ranibizumab. This assessment will be conducted using improved depth spectral-domain imaging (EDI-OCT) with a focus on controlling for confounding variables.* ***Patients and Methods:*** *The study included a total of 50 participants, composeding of 27 females and 23 men, all between the ages of 70 and 50. These individuals were diagnosed with DME, type 2 diabetes mellitus (DM) and had central foveal thickness not exceeding 450 microns as determined using OCT. The SFCT was assessed using the manual caliper function inside the Heidelberg Spectralis OCT program after and before the administration of intravitreal ranibizumab injections at three and one months.* ***Results:*** *The differences in best-corrected visual acuity (BCVA) between the postoperative and preoperative three-month measurements were found to be statistically important (p = 0.001). Similarly, the variances in SFCT between the postoperative and preoperative three-month measurements were also found to be statistically important (p = 0.001).* ***Conclusions:*** *A reduction in the average SFCT has been observed after Anti-VEGF therapy, additionally, there is evidence of improved BCVA.*

Keywords: *Choroid, DME, Anti-VEGF, BCVA*

1. Introduction

The choroid is characterized by a rich circulatory network, which facilitates the delivery of essential nutrients to the outer region of the retina. This includes the retinal pigment epithelium and photoreceptors, both of which play crucial roles in visual perception. The blood flow in this system is characterized by a high velocity, facilitated by the choriocapillaris, layer of inner and outer vascular [1]. The maintenance of a healthy choroid is essential for the optimal functioning of the retina. Optical coherence tomography (OCT) is a non-invasive imaging technique that is used for the acquisition of high-resolution cross-sectional images of the retina. In

recent literature, the use of improved depth imaging (EDI) spectral-domain OCT has been documented. The EDI program is designed to acquire a cross-sectional picture of the choroid in close proximity to the zero delay line in order to optimize sensitivity at the outer boundary of the choroid [2]. The etiology of diabetic macular edema (DME) has traditionally been linked to retinal vascular hyperpermeability, characterized by localized leakage from microaneurysms or generalized leaking from compromised capillaries as shown during fluorescein angiography. Nevertheless, histopathological investigations have also shown the involvement of choroidal dysfunction in individuals with diabetes. The observed alterations include the deprivation of the choriocapillaris, constriction and expansion of blood vessels, increased tortuosity and the emergence of sinusoidal-like structures amongst choroidal lobules [3]. Furthermore, it has been shown via functional imaging investigations that eyes afflicted with diabetic retinopathy have a decline in choroidal blood flow. However, the precise contribution of choroidalperfusion to the underlying mechanisms of DME has not been definitively established [4] However, investigations on choroidal thickness in diabetes have shown conflicting findings, with some reports indicating choroidal thickening, thinning, and no change in eyes with diabetic retinopathy [5] diabeteschoroidopathy refers to choroidal abnormalities that occur in diabetes individuals and may have a role in processes that lead to a reduction in visual acuity [6]. The objective of this research was to compare and evaluate the subfovealchoroidal thickness (SFCT) and visual acuity after and before intravitreal injection of ranibizumab in patients with DME. This assessment was conducted using improved depth spectral-domain imaging EDI-OCT, while controlling for other confounding variables.

2. Methods and Subjects

This study is a prospective, interventional, uncontrolled, longitudinal investigation conducted on a cohort of fifty people with DME who were receiving treatment at the outpatient clinic of the Ophthalmology Department at Elmabra Hospital - Assiut. The study was carried out over a period spanning from November 2021 to February 2023.

2.1. *Inclusion criteria*

Patients with controlled DM (Hba1c range seven-eight throughout study period), DME from three hundred to forty hundred and fifty mm and not neglected for log time, Mild to moderate Non-PDR.

2.2. *Exclusion criteria*

Patient with high myopia of more than six diopters, previous argon laser retina, history of previous injection before testing and history of previous retinal surgeries before test. All participants underwent a series of assessments, including uncorrected visual acuity (UCVA), best corrected visual acuity (BCVA),fundus fluorescein angiography (FFA), slit lamp examination, fundus examination, and OCT using both enhanced depth imaging (EDI) and conventional technology. These assessments were used to measure the baseline SFCT of the macula and baseline central foveal thickness (CFT)

2.3. *Treatment*

Three doses of intravitreal anti VEGF (Ranibizumab) injections with four weeks interval. The procedure was conducted using topical anesthetic, namely Benoxinate HCL drops at a concentration of 0.4%. These drops were administered twice, with a 2-minute interval between each administration, prior to the trea-

tment. The procedure was carried out under sterile settings in accordance with established standards. Povidone iodine solution with a concentration of ten percent is often used for the purpose of disinfecting the skin. The patient was completely draped. An eye lid speculum was used to stabilize the eye lids then eye wash with five % povidone-iodine for three minutes, 1.25 mg (0.05 ml) ranizumab will be injected into the vitreous through pars plana four mm posterior to the limbus using a sharp thirty-G needle, pressure for one minute with microsponge was done at the site of the injection toreflux of the injected material and prevent vitreous prolapse. The further interventions administered after a surgical procedure are as follows: The patient's eye was treated with a topical antibiotic, namely Gatifloxacin ophthalmic solution. Following this treatment, the eye was covered with a patch for duration of several hours. Additionally, the patient was advised to use topical antibiotic eye drops four times daily for a period of three days. To prevent an increase in intraocular pressure (IOP), the patient was also told to use a topical antiglaucoma drug, specifically Betoptic (Betaxolol 0.5%, Alcon).

2.4. *Follow up*

On the first day, all patients had check-in procedures, followed by further evaluations at one month and three months after the surgical intervention. During each visit, the following aspects were evaluated: visual acuity using the metrics of UCVA, BCVA, and manifest refraction (MR). Additionally, SFCT was quantified using the manual caliper tool inside the Heidelberg Spectralis OCT program**.**

2.5. *Ethical consent*

An approval of the study was obtained from Al-Azhar University academic and Al-Azhar faculty of medicine in Assiut; code number MD/AZ.AST./OPH026/2/ 199/9/2021. The clinical Trial registration number NCT06173245. Each patient provided their informed written agreement for the acceptance of the surgical procedure.

2.6. *Statistical analysis*

The present study included 50 eyes of 50 patients fulfilled inclusion criteria all patients (Male and Females) came to Elmabra hospital -Assiut during the period from November 2021 to February 2023. The mean and standard deviation values were computed. The normality of the data was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Categorical variables were represented using numerical values and percentages (N, %), whereas continuous variables were characterized using measures of central tendency and dispersion (Mean, SD, Median). The chosen significance level was established at a threshold of $P < 0.05$. The statistical analysis was conducted using IBM® SPSS® Statistics Version 16 for Windows.

3. Results

Fifty eyes examination in fifty patients revealed the following: **1)** *Demographic findings*; the study population composed of, twenty three males and twenty seven females. The age of the patients was ranging from fifty to seventy years, tab. (1) & fig. (1). **2)** *History of systemic diseases associated with DM*; 21 cases are diabetic only, 16 cases are diabetic and hypertensive, 5 cases are diabetic and hepatic, 2 cases are diabetic, hypertensive and hepatic and 6 cases are diabetic, hypertensive and cardiac , tab. (2) & fig. (2). **3)** *BCVA*; the average preoperative BCVA was 0.19±0.11, and in six months postoperative was 0.32±0.11. It showed statistically important improvement of BCVA (p. value is <0.001), tab. (3) & fig. (3). **4)** *SFCT*; before injection, the mean baseline SFCT in the studied eyes was 211.22±20.71 microns. Twelve weeks after injection, the

average post-injection (After twelve weeks) SFCT in the studied eyes was 197.92±18.27 microns and it demonstrated statistically impotant decline (p. value 0.001), tab. (4) & fig. (4). **5)** *Central Foveal Thickness (CFT)*; before injection, the mean baseline central foveal thickness (CFT) in the studied eyes was 368.42±28.8 microns. Twelve weeks after injection, the mean post-injection central foveal thickness (CFT) in the studied eyes was 336.8±18.1 microns and it showed statistically significant decrease of the mean CFT (p. value <0.001), tab. (5) & fig. (5). 37 eyes were functional responders (eyes with BCVA gains of 1 line or more from baseline). 13 eyes were functional non-responders (eyes with stable or deteriorated BCVA), tab. (6) & fig. (6).

Table 1: Distribution of the studied cases according to their gender.

Sex	No	%
Male	23	46
Female	27	54

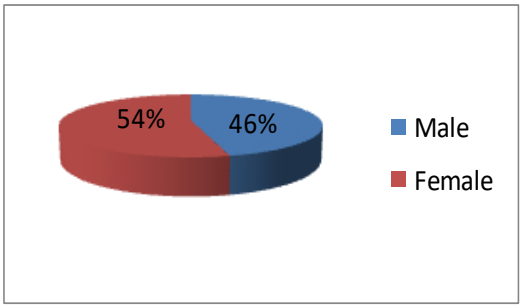

Figure 1: Distribution of the studied cases according to their sex.

Table 2: Distribution of the studied cases according to presence or absence of associated systemic co-morbidities.

Associated Co-morbidities	No	%
Diabetic only	21	42%
Diabetic and Hypertensive	16	32%
Diabetic and hepatic	5	10%
Diabetic, Hypertensive and hepatic	2	4%
Diabetic, hepatic and cardiac	6	12%

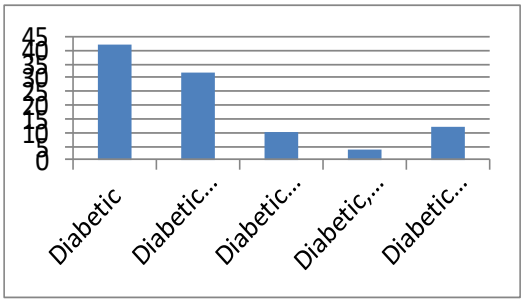

Figure 2: Distribution of the studied cases according to presence or absence of associated systemic co-morbidities.

Table 3: Shows statistically important improvement of BCVA at twelve weeks after injection**.**

	BCVA(n=50)	P. value
	Average ±SD	
Pre	0.19±0.11	**<0.001****
Post3	0.32±0.11	

*Abbreviations:BCVA,Best corrected visual acuity; Paired samples T Test; * Statistically important variance (p<0.05),* ********Highly statistically important difference (p<0.01).*

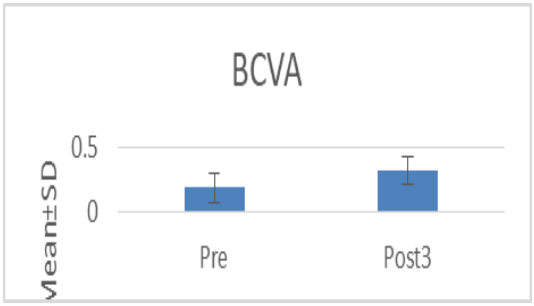

Figure 3: show pre and post 3 months BCVA

Table 4: demonstrates statistically significant decline of the average SFCT at twelve weeks after injection

	SFCT(n=50)	P. value
	Average ±SD	
Pre	211.22±20.71	**0.016***
Post1	201.72±17.86	
Pre	211.22±20.71	**0.001****
Post3	197.92±18.27	
Post1	201.72±17.86	0.295
Post3	197.92±18.27	

*Abbreviations SFCT subfoveal choroidal thickness; Paired samples T Test; * Statistically essential variance (p<0.05)**, ****Highly statistically important variance (p<0.01).*

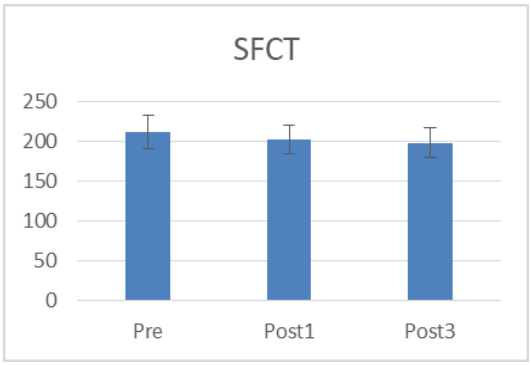

Figure 4: show pre, post 1and post 3 months SFCT

Table 5: shows statistically significant decrease of the mean CFT at 12 weeks after injection.

	CFT (n=50)	P. value
	Mean±SD	
Pre	368.42±28.8	**<0.001****
Post	336.8±18.1	

*Paired samples T Test; * Statistically significant difference (p<0.05)**; **** Highly statistically significant difference (p<0.01).*

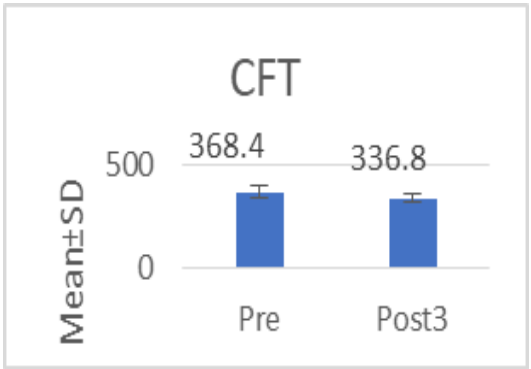

Figure 5: The mean central foveal thickness (baseline and 12 weeks after injection.

Table 6: Distribution of the studied eyes according to their functional response into responders and non-responders.

Functional response (Log MAR BCVA)	
Responder	**Non responder**
37	**13**

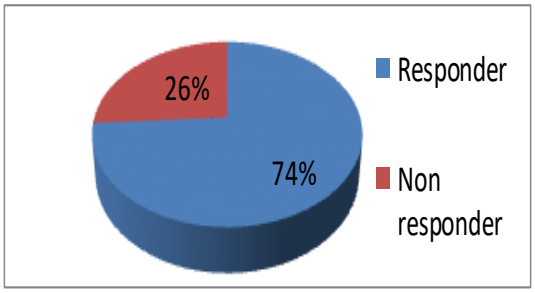

Figure 6: Distribution of the studied eyes according to their functional response into responders and non-responders.

4. Discussion

The current research demonstrated that the average baseline SFCT in the studied eyes was 211.22±20.71microns and at twelve weeks after injection, the average SFCT was 197.92±18.27 microns showing statistically important decline in the average SFCT. This agree with Lains, et al [7] and Yiu, et al [8] who demonstrated important decline of choroidal thickness in DME patients following treatment with Anti-VEGF therapy. In disagree with that, Hyo Kyung Lee, et al. [9] reported that the retinopathy progression from mild to proliferative changes did not induce important additional choroidal thinning. In contrast, Shiragami, et al [10] documented a noteworthy decline in choroidal thickness among individuals with DME, suggesting a general decline in choroidal blood flow in this patient population. This ischemic condition afterwards triggers an augmented release of vascular endothelial growth factor (VEGF), hence contributing to the development of retinal edema. In accordance with this observation, Rayess, et al. [11] found that individuals with a higher initial SFCT may exhibit a more preserved choriocapillaris, resulting in a lesser degree of ischemia in the outer retina. Consequently, the photoreceptor layer's functionality is better maintained compared to individuals with a thinner choroid. This finding may elucidate the superior anatomical response and potentially improved visual outcomes observed in these patients subsequent to the aforementioned intervention. The use of anti-VEGF treatment. In their research, Kang, et al. [12] examined the relationship between initial choroidal thickness and treatment outcomes in patients with neovascular age-related macular degeneration (AMD). The researchers found that a greater baseline SFCT was associated with improved visual and anatomical outcomes after three and six months of Ranibizumab therapy. According to Rayess, et al. [11], it has been proposed that a more favorable anatomical response for SFCT may be linked to a more favorable functional response. In agreement with that, Byeon, et al [13] and Małgorzata, et al [14] reported in their study done in 2007 and 2013 respectively; a significant improvement of visual acuity associated with significant reduction of central retinal thickness after multiple intravitreal bevacizumab therapy for diabetic macular edema. Eyes that showed anatomical response for CFT and/or SFCT but did not experience functional response (stable or deteriorated BCVA) may be due to progression of cataract, presence of neurosensory detachment, disruption of ELM and IS/OS layers, presence of subfoveal hard exudate, ext-

ensive disruption of Muller'sfibers causing severe cystoid edema and center involving large cyst. In agreement with that, Manoj Soman, et al [15] suggested that presence of systemic co-morbidity associated with DM may cause decreased response to Anti-VEGF and subsequently suboptimal anatomical response in this group in their research done in 2013 and reported that in diabetic patients, other than glycemic control, control of blood pressure(BP), anemia, anephropathy and dyslipidemia may affect macular thickness and therefore macular edema and the presence of systemic comorbidity should be investigated in all cases of DME especially those associated with submacular detachment (SMD) and that association may be responsible for suboptimal response to any management for DME. However, the short duration of their and our research may not allow us to evaluate the effectiveness of control of systemic co-morbidities on improving the response to any management for DME. Regarding the best corrected visual acuity (BCVA), the average baseline BCVA was 0.19±0.11Log MAR, while at twelve weeks after injection, the average BCVA was 0.32±0.11 Log MAR denoting statistically important improvement of BCVA. In agree with that, both Byeon, et al [13] and Malgorzata, et al [14] in their research done in 2007 and 2013 respectively reported significant improvement of visual acuity after multiple intravitreal bevacizumab therapy for diabetic macular edema.

5. Conclusion

A reduction in the average SFCT has been observed after Anti-VEGF therapy, additionally, there is evidence of improved BCVA.

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