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Ehabeldin Mohamed Magahwry
Department of Ophthalmology, Faculty of Medicine, Ain Shams University, Cairo, Egypt

Corresponding Author:
Ehabeldin Mohamed Magahwry
Department of Ophthalmology, Faculty of Medicine, Ain Shams University, Cairo, Egypt

Visual outcomes and foveal avascular zone changes in diabetic macular edema patient's Post-ranibizumab treatment

Ehabeldin Mohamed Magahwry

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Abstract
Background: The permanent and disability-inducing vision loss is mostly caused by diabetic retinopathy (DR) and clinically severe macular edema. This study set intended to evaluate the effects of ranibizumab on diabetic macular edema (DME) patients' visual outcomes and any changes to their foveal avascular zone (FAZ).
Methods: This single-arm interventional study enrolled 30 eyes of 30 diabetic patients, aged ≥18 years, both sexes, and had DME requiring an intravitreal injection of ranibizumab (macular thickness >400 micron) as confirmed by optical coherence tomography angiography and fluorescein angiography. Three doses of Ranibizumab were administered intravitreally to each patient, with a one-month interval between each dosage.
Results: Best corrected visual acuity was significantly lower at (1, 2 and 3 months) than pretreatment (P<0.001). The contrast sensitivity test and normal color vision test were significantly higher at (1, 2 and 3 months) than pretreatment (P<0.05). Intraocular pressure (IOP) was insignificantly different between (1, 2 and 3 months) and pretreatment. FAZ area in superficial capillary plexus and FAZ area in deep capillary plexus was insignificantly different between (1, 2 and 3 months) and pretreatment. Fundus examination significantly improved at 3 months than 1 month (P=0.009) and was insignificantly different between 1 and 2 months.
Conclusions: Analyzing the form and size of FAZ is likely crucial for identifying pathological macular changes and forecasting visual outcomes in DR.

Keywords: Visual outcomes, diabetic macular edema, foveal avascular zone, ranibizumab

Introduction
Diabetic retinopathy (DR) is a major cause of blindness in people of working age in developed nations [1]. Although there are numerous ways in which diabetes mellitus (DM) can harm various parts of the eye and the visual pathway, DR remains the leading cause of blindness [2]. DR's potentially blinding side effects include tractional retinal detachment, vitreous hemorrhage, diabetic macular edema (DME), and macular ischemia [3].
The most prevalent of these is DME, which has a significant effect on the quality of life for patients. DME is a thickening of the retina that involves or approaches the macula centralis, the eye's central vision artery [4]. In the pathological process of DME production, one of the primary components is the collapse of the blood-retinal barrier [5].
There is evidence that an increase in vascular endothelial growth factor (VEGF) is one among the factors that leads to the blood-retinal barrier breaking down [6]. When treating center-involving DME that causes vision loss, intravitreal anti-VEFG medications have shown positive results [7, 8].
The first anti-VEFG medication authorized by the FDA for use in DME therapy was intravitreal ranibizumab (IVR) [9]. Its primary indication for approval was in the treatment of neovascular age-related macular degeneration (AMD) [10].
Different degrees of foveal affection and duration of oedema cause different visual symptoms in patients with DME. A unique area of the retina known as the foveal avascular zone (FAZ) contains the greatest concentration of cone photoreceptors and has a high oxygen consumption rate [11]. Since vascular diseases often manifest as irregularities in the normally round or elliptical shape of the fundus anterior zone (FAZ) [12], there is a correlation between visual acuity

(VA) and the degree to which the FAZ is circular; eyes with low VA tended to have a more asymmetrical FAZ [13].

The use of optical coherence tomography angiography (OCTA) has allowed for the detection of retinal microvascular abnormalities, including microaneurysms, increased FAZ, and capillary vasodilation, in diabetic eyes ranging from those without retinopathy to those with proliferative DR [14]. Prior research has shown that OCTA, in contrast to FA, can more precisely characterize areas of capillary dropout and scan the FAZ without dye leakage or macular xanthophyll pigment shadowing. Better yet, it paves the way for automatic and quantitative assessments of the VD in the retina [15].

This work aimed to evaluate the effects of ranibizumab on visual outcomes and changes in FAZ in patients with DME.

Patients and Methods

This single-arm interventional study enrolled 30 eyes of 30 diabetic patients, aged ≥18 years, both sexes, with DME and required an intravitreal injection (IVI) of ranibizumab (due to a macular thickness greater than 400 micron) as validated by OCTA and fluorescein angiography (FFA). The research took place from January to October of 2024 at the Ain Shams University Hospitals in Egypt. The patient's signed informed consent was acquired.

Exclusion criteria were vitreous surgery, intravitreal medication, substantial cataracts, and any other retinal pathology, glaucoma, macular degeneration, retinal vein blockage, or corneal opacity that could affect visual acuity.

In every case, a thorough history was taken, covering the patient's complaint, the length of their DM, and any previous surgeries or ocular traumas. In order to rule out systemic disorders, physical exams typically comprise a general examination.

The ophthalmological examination consisted of the following tests: a contrast sensitivity test using the Pelli-Robson chart, a best corrected visual acuity (BCVA) measured using Landolt's broken ring chart, and acuities given in logMAR units. A single big letter size is used to examine contrast sensitivity in the Pelli-Robson test, where the contrast varies across groups of letters. Patients would begin reading the letters at the highest contrast level and work their way down until they could no longer decipher more than two or three letters in a row.

A color vision test was administered using Ishihara pseudo isochromatic plates (Ishihara's 24 plates). Patients were asked to read the numerals shown on the plates within five seconds, and their score was determined based on the contrast of the last group in which two or three letters were correctly read. The results were evaluated by comparing the readings of plates 1 to 15, which determined whether the patients' color vision was normal or defective. Color vision is deemed normal if thirteen or more plates are read normally.

The following tests were performed: slit lamp examination to evaluate the clarity of the media, slit lamp bio microscopy to examine the fundus using a non-contact Volk lens +78D, applanation tonometry to measure the eye's tension, and OCTA to measure the foveal anterior zone (FAZ) using a Swept Source DRI OCT device (Triton, Topcon, Tokyo, Japan, version 2015). To conduct the OCTA examination, the patient's eyes were measured in a macular region centered at 3×3 mm^2.

A 3×3 mm^2 scan was conducted over the macular region to visualize the perifoveal capillary network and FAZ. The various retinal vascular planes were reduced to two main layers: the superficial and deep capillary plexuses. The size and shape of the FAZ were measured; the shape was manually delineated by selecting the area from the ruler and drawing a line along its boundaries, while the size was automatically displayed on the screen.

Intravitreal injections of ranibizumab

IVR ranibizumab were administered to patients with DME at 1-month intervals. Two applications of 5% betadine spaced five minutes apart were used to sterilize the injection site, and then two applications of 3% anesthetic eye drops were administered, spaced three minutes apart. A speculum with a lid was placed. Inject 0.05 ml of Ranibizumab IVI into each eye using a 27-gauge needle into the inferotemporal region 4mm posterior to the limbus in phakic eyes and 3.5mm posterior to the limbus in pseudophakic and aphakic eyes. The dosage is 0.23 ml/2.3 mg per vial. A gentle sponge was used to avoid flux.

Post-Injection Care and Follow Up

Following the injection, there was no need for paracentesis. Optic patching was used in conjunction with topical antibiotic eye drops, combined antibiotic and steroid eye drops, and antiglaucoma eye drops. For a week following injection, these drugs were to be taken by every patient.

The primary outcome was BCVA. The secondary outcomes were the contrast sensitivity test, color vision test, fundus examination, intraocular pressure (IOP), FAZ area in superficial capillary plexus (SCP) and deep capillary plexus (DCP).

Sample Size Calculation

G*Power 3.1.9.2 (Universitat Kiel, Germany) was employed to calculate the sample size. Based on a previous investigation [16], the mean±SD of BCVA was 1.03±0.13 LogMAR at baseline and 0.66±0.31 LogMAR at 6 months. The sample size was based on the following considerations: 95% confidence limit, 95% power, an effect size of 1.557, and six cases were incorporated to overcome dropout. Hence, we recruited a total of 30 patients.

Statistical analysis

SPSS v26 (IBM Inc., Chicago, IL, USA) was employed to conduct statistical analysis. Shapiro-A Wilks test and histograms were implemented to determine the normality of the data distribution. A paired T-test was employed to compare quantitative parametric data, which were presented as mean and standard deviation (SD). The Chi-square test was utilized to compare qualitative variables, which were expressed as frequency and percentage. Statistical significance was determined by a two-tailed P value that was lower than 0.05.

Results

The mean value (±SD) of age was 47.8 (±13.54) years. There were 13 (43.33%) male and 17 (56.67%) female. The right eye was affected in 18 (60%) patients and left eye was affected in 12 (40%) patients. The mean value (±SD) of duration of DM was 15.07±6.64) years. **Table 1.**

Table 1: Demographic data and duration of DM of the studied patients

		(n=30)
Age (years)		47.8±13.54
Sex	Male	13 (43.33%)
	Female	17 (56.67%)
Affected eye	Right	18 (60%)
	Left	12 (40%)
Duration of DM (years)		15.07±6.64

Data are presented as mean±SD or frequency (%). DM: Diabetes mellitus.

BCVA logMAR was significantly lower at (1, 2 and 3 months)

than pretreatment (P<0.001) which means better vision. The contrast sensitivity test and normal color vision test were significantly higher at (1, 2 and 3 months) than pretreatment (P<0.05). IOP was insignificantly different between (1, 2 and 3 months) and pretreatment. Table 2.

Table 2: BCVA, contrast sensitivity test, color vision test and IOP of the studied patients

		Pretreatment (n=30)	At 1 month (n=30)	At 2 months (n=30)	At 3 months (n=30)
BCVA (logMAR)		1.07±0.17	0.89±0.16	0.75±0.15	0.65±0.28
P value			<0.001*	<0.001*	<0.001*
Contrast sensitivity test		0.51±0.09	0.66±0.1	0.88±0.11	1.16±0.15
P value			<0.001*	<0.001*	<0.001*
Color vision test	Normal	8 (26.67%)	16 (53.33%)	21 (70%)	27 (90%)
	Defect	22 (73.33%)	14 (46.67%)	9 (30%)	3 (10%)
P value			0.035*	0.001*	<0.001*
IOP (mmHg)		12.1±2.53	12.6±3.17	12±3.1	11.6±3.27
P value			0.102	0.739	0.144

Data are presented as mean±SD or frequency (%). BCVA: Best corrected visual acuity. IOP: Intraocular pressure. *: Significant as P value ≤0.05. P: P value compared to pretreatment.

FAZ area in SCP and FAZ area in DCP was insignificantly different between (1, 2 and 3 months) and pretreatment. Table 3

Table 3: FAZ area in SCP and DCP of the studied patients

	Pretreatment (n=30)	At 1 month (n=30)	At 2 months (n=30)	At 3 months (n=30)
FAZ area in SCP (µm)	399.5±62.95	404.8±59.85	408.6±53.37	411.1±53.13
P value		0.202	0.131	0.054
FAZ area in DCP (µm)	426.9±46.05	431.5±51.02	433.8±50.98	437.4±47.8
P value		0.116	0.071	0.065

Data are presented as mean±SD. FAZ: Foveal avascular zone, SCP: Superficial capillary plexus. DCP: Deep capillary plexus. P: P value compared to pretreatment.

Fundus examination pretreatment showed hemorrhage (Hge) and exudate DME in 27 (90%) patients, cystoid macular edema (CME) in 2 (6.67%) patients and CME, Hge and exudate in 1 (3.33%) patient. Table 4.

Table 4: Fundus examination pretreatment of the studied patients

	(n=30)
Hge and exudate DME	27 (90%)
CME	2 (6.67%)
CME, Hge and exudate	1 (3.33%)

Data are presented as frequency (%). Hge: Hemorrhage. DME: Diabetic macular edema. CME: Cystoid macular edema.

Fundus examination significantly improved at 3 months than 1 month (P=0.009) and was insignificantly different between 2 and 1 months. Table 5.

Table 5: Fundus examination posttreatment of the studied patients

	At 1 month (n=30)	At 2 months (n=30)	At 3 months (n=30)
Improved	14 (46.67%)	22 (73.33%)	25 (83.33%)
Anatomically improved, functionally not	11 (36.67%)	4 (13.33%)	1 (3.33%)
Persistent DME	3 (10%)	2 (6.67%)	2 (6.67%)
Edema subsided but with remnant diabetic changes	2 (6.67%)	2 (6.67%)	2 (6.67%)
P value		0.154	0.009*

Data are presented as frequency (%). DME: Diabetic macular edema. *: Significant as P value ≤0.05. P: P value compared to 1 month.

Discussion

DR is believed to be a major microvascular complication of diabetes and a major cause of blindness worldwide [17]. There is evidence that alterations in blood flow, ischemia, increased VEFG expression, free radical production, endothelial dysfunction, inflammation, and chronic hyperglycemia lead to vision loss in DME [18]. Multiple factors contribute to the complex adverse event known as DME. The accumulation of macular fluid may have its origins in permeability anomalies of the blood retinal barrier [19].

The two primary factors that have been identified as increasing the risk of eye issues in diabetic individuals are the length of time that the disease has been present and the degree to which it is controlled [20].

Our result revealed that BCVA logMAR was significantly lower at (1, 2 and 3 months) than pretreatment.

El-Said *et al.* [21] confirmed our results by showing that BCVA significantly improved following IVR. The results of the ranibizumab therapy meta-analysis by Falcão [22] showed an improvement in BVCA, with the most notable change in BCVA happening in the initial year of treatment and persisting for a further three years. Also, Fu *et al.* [23] found that IVR

considerably enhanced BCVA compared to baseline, which was caused by a decrease in retinal edema. Following three and six months of therapy beginning, Nowacka *et al.* [24] found that IVR significantly improved VA, which was attributed to reduced retinal oedema and vascular leakage.

Our result revealed that the contrast sensitivity test and normal color vision test were significantly higher at (1, 2 and 3 months) than pretreatment. IOP was insignificantly different between (1, 2 and 3 months) and pretreatment.

Similarly, El-Said *et al.* [21] demonstrated that contrast sensitivity test and color vision test significantly improved after IVR. Additional research by Turkoglu *et al.* [25] shown that IVR patients' color vision and contrast sensitivity improved slightly. Preti *et al.* [26] observed substantial improvements in contrast sensitivity assessment following intravitreal injection of Bevacizumab.

De Vries *et al.* [27] found that IVI of anti-VEFG resulted in a considerably raised IOP on the day of administration. Following that, the IOP was marginally reduced the day after injection, and throughout the subsequent follow-up assessments, there was no significant variation from the basal value.

El-Said *et al.* [21] also discovered no statistically significant change in the proportion of FAZ area in SCP and DCP following injection compared to pre-injection values, which is consistent with our results. In eyes with DME, Bromeo *et al.* [28] observed no statistically significant change in the area, perimeter, and circularity of the FAZ within the first six months after intravitreal anti-VEFG treatment. Also, Busch *et al.* [29] revealed that inside the nine (3×3) mm^2 area, neither the retinal vascular area nor the FAZ altered significantly before nor after intravenous aflibercept treatment in instances involving DME. In cases of DME, it has been shown that maintaining retinal perfusion at the macula required many injections of intravenous aflibercept (2.6 injections on average over 8.5 months).

In contrast with our findings, Gill *et al.* [30] observed that that the FAZ area shrank with time in both DME-treated and untreated eyes.

Hence, although some research found a significant increase in the FAZ area after IVI of anti-VEFG, other investigations failed to substantiate this result. This could be because of the way DME affects the FAZ, how it interacts with anti-VEFG, and how analysis becomes more difficult in eyes with thick macular tissue. Due to structural edema in eyes affected by DME, the capillaries are forced to spin in a centrifugal fashion, causing the FAZ to enlarge [31].

Our finding showed that the Fundus examination pretreatment showed Hge and exudate DME in 27 (90%) patients, CME in 2 (6.67%) patients and CME, Hge and exudate in 1 (3.33%) patient. Fundus examination significantly improved at 3 months than 1 month and was insignificantly different between 1 and 2 months.

Consistent with this, El-Said *et al.* [21] demonstrated that 93.33% had diabetic complications, including Hge, exudate, and DME; 3.33% had CME; and 3.33% had CME, Hge, and exudate.

The study had some limitations, such as a small sample size, no control group, a single-center design, an observation period of only three months that might not have been long enough to detect changes in the FAZ, and the fact that we didn't find out how other factors like diabetic control, severity of DR, and pan retinal photocoagulation affected the FAZ parameters. To corroborate the current results, future studies should include a larger number of eyes, provide more injections, and have a longer follow-up time. To further evaluate the impact of any confounding factors, additional research may be necessary.

Conclusions

Analyzing the form and size of FAZ is likely crucial for identifying pathological macular changes and forecasting visual outcomes in DR.

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