Med. J. Cairo Univ., Vol. 92, No. 3, Accepted 31/3/2024
DOI: 10.22608/MJCU. 717-727, September 2024
www.medicaljournalofcairouniversity.net

The Effect of Intravitreal Injection of Anti-VEGF on Perfusion Indices in Eyes with Diabetic Macular Edema Measured by Optical Coherence Tomography Angiography

ABD EL RAHMAN G. SALMAN, M.D.; MOUAMEN M. MOSTAFA, M.D.; HATEM F. ABD ELFATAH, M.D. and MOSTAFA G. MANSOUR, M.Sc.

The Department of Ophthalmology, Faculty of Medicine, Ain Shams University

Abstract

Background: Anti-VEGF agents interfere with receptor binding, thus inhibiting VEGF's signal, which results in inhibition of abnormal blood vessel formation and decreased vascular permeability. Anti-VEGFs have significant roles in the treatment of many retinal diseases as age related macular degeneration, myopic choroidal neovascularization, proliferative diabetic retinopathy, diabetic macular edema and retinal vein occlusion.

Aim of Study: To evaluate changes in macular vessel density following first dose of intravitreal anti-VEGF injection of ranibizumab (Lucentis®) in patients with diabetic macular edema (DME).

Patients and Methods: This prospective study included 44 eyes of 44 DME patients indicated for IVI of Ranibizumab, with mean age 50.98±6.27 years, ranging from 41.0 years to 60.0 years. The majority of them were males (68.2%).

Results: Vessel density (central subfield) at baseline (20.29 ±1.89) didn't show statistically significant difference than that at one month (20.09±2.4) but showed a highly significant difference at two months (19.73±2.49) after IVI. Vessel density (average of the four parafoveal sub fields) at baseline (44.98±2.6) didn't show statistically significant difference than that at one month (44.8±2.21) but showed a highly significant difference at two months (44.14±2.2) after IVI.

Conclusion: A single IV injection of Ranibizumab in eyes with DME showed non significant vascular density changes after one month of injection in both central and paraoveal subfileds but a statistically significant decrease in vascular density 2 months after injection.

Key Words: Diabetic macular edema – Intra retinal microvascular abnormalities.

Correspondence to: Dr. Mostafa G. Mansour,
E-Mail: dr.mostafaghazaly@gmail.com

Introduction

DIABETIC macular edema (DME) is the main cause of visual disturbance in patients with diabetic retinopathy. The prevalence of DME among those with type 1 diabetes (T1D) and type 2 diabetes (T2D) varies by region. Prevalence rates range from 11% in Europe to 7.5% in some African countries. More than 21 million people are affected worldwide **[1].** Approximately one in 14 people with diabetes has some degree of DME. An estimated 20% of people living with T1D, and 25% of those with T2D, can expect to develop DME. Those diagnosed with proliferative diabetic retinopathy (PDR) are at particular risk for DME **[2].**

Diabetic retinopathy (DR) is classified into several stages based on the level of disease severity. Preretinopathy is characterized by hemodynamic changes and vascular permeability with no apparent retinopathy on clinical examination **[3].** Mild non-proliferative DR (NPDR) is characterized by the appearance of microaneurysms, intraretinal hemorrhages, and cotton-wool spots, which represent focal infarcts of the retinal nerve fiber layer. Increased permeability of the retinal vasculature can lead to retinal edema and the formation of protein and lipid-rich deposits, referred to as hard exudates **[4].**

In severe NPDR, the retinal vasculature gradually closes, which impairs perfusion and leads to retinal ischemia, characterized by venous caliber abnormalities, intra retinal microvascular abnormalities (IRMAs) (essentially, neovascularization within the retina), and widespread vascular leakage **[4].** Neovascularization on the surface of the retina, optic nerve, and other structures (such as the iris, in severe cases) characterizes the most advanced stage of DR, known as proliferative DR **[5].**

The abnormal new vessels are fragile and can bleed into the vitreous, causing sudden loss of vision. In some cases, spontaneous contraction of the retinal neovascular membranes detaches the retina from its support structures, a condition known as tractional retinal detachment [5].

In patients with diabetes, chronic hyperglycemia leads to the upregulation of vascular endothelial growth factor (VEGF), resulting in angiogenesis, increased vascular permeability, and the production of pro-inflammatory cytokines (e.g. intracellular adhesion molecule 1 and tumor necrosis factor α) [6]. Thickening of the basement membrane and pericyte loss, which are key hallmarks of DR, as well as sheer stress on endothelial cells, may further stimulate VEGF vascularized intraocular tissues, including the conjunctiva, iris, retina, and choroid-retinal pigment epithelium (RPE) complex [7]. In vitro and in situ studies have demonstrated that human RPE cells can synthesize and secrete VEGF, and VEGF is upregulated in human RPE cells in response to hypoxia. Furthermore, the vitreous concentrations of VEGF in patients with PDR were considered to be physiologically relevant and most likely produced by retinal ischemia [8].

In a comparative, cross-sectional study of undiluted aqueous humor samples taken from 54 eyes of 54 patients with DME undergoing cataract surgery, the aqueous levels of VEGF were significantly (p<0.001) associated with the severity of DME. These results demonstrate that VEGF is produced in the intraocular tissues of patients with diabetes and is involved in the pathogenesis of DME [9].

Fundus Fluorescein Angiography (FFA) remains invaluable in identifying leaking vessels in both DME and PDR. However, FFA is time-consuming, invasive and carries the risk of complications, including severe allergic reactions. Optical coherence tomography angiography (OCTA), an extension of optical coherence tomography (OCT), is a noninvasive, depth resolved imaging technique that allows visualization of the superficial and deep retinal capillary plexus, which is not possible on FFA [10].

Although the use of anti-VEGF treatment is now the standard treatment in cases of DME, its effect on retinal perfusion is still controversial. Some studies have shown slowing or even improvement in macular non-perfusion following anti-VEGF treatment, with a growing body of evidence for its use in PDR as well [11].

Fewer case report studies, however, considered increased VEGF as a compensatory mechanism in restoring macular perfusion; in addition, anti-VEGF treatment may increase the severity of non-perfusion with subsequent visual deterioration [12]. However, all the previous studies have relied on FFA to assess changes in macular perfusion, which has lower resolution and limited sensitivity. In this study, OCTA will be used to quantify vessel density (VD) for the evaluation of macular perfusion following anti-VEGF treatment [13].

Aim of the work:

Our study aims to evaluate changes in macular vessel density following first dose of intravitreal anti-VEGF injection of ranibizumab (Lucentis®) in patients with diabetic macular edema (DME).

Patients and Methods

This study was conducted on 44 patients admitted to the Ophthalmology Department at Ain Shams University Hospitals in a period of 12 months starting from March 2023 till February 2024.

Types of studies: A single arm clinical trial.

Study setting: This study was done at the Ophthalmology Department at Ain Shams University Hospitals.

Study population:

Inclusion criteria: Type 2 diabetic patients between (40-60) years of age who had been diagnosed with diabetes for more than 5 years with DME.

Exclusion criteria: Patients with myopia greater than 4 diopters. Confounding ocular conditions such as: Vitreomacular traction, panretinal photocoagulation (PRP) focal laser treatment within the last 3 months, intravitreal injection of corticosteroid any ocular surgery within the last 6 months. Eyes with media opacity degrading the quality of OCTA image was excluded.

Sample size: 44 eyes was enrolled in this prospective study.

Ethical considerations: Patients were informed about the study, its potential benefits and its objectives. Each patient was offered the proper management accordingly. None of the patients' data was published outside the field of medical research and every effort was done to preserve patient's privacy and dignity.

Study procedures:

All included patients were subjected to the following:

I- *Pre-injection assessment:*

Detailed history taking including: Demographic data. Medical history and comorbidities (hypertension, hyperlipidemia) of all participants were recorded. Detailed ocular history (Prior ocular surgeries, laser treatment, ocular surgery or other eye diseases or medications). Previous trauma.

Laboratory investigations were done for all the cases (Random blood glucose level, HBA1C).

Comprehensive ophthalmological assessment at the time of their visit, including: Visual acuity measurement: Using Landolt's VA chart and after

that transformed for statistical analysis to Decimal Notation. Slit lamp examination: To evaluate corneal transparency, anterior chamber, pupil, state of the lens, IOP and complications of DM which include accelerated senile cataract, rubeosis iridis. Fundus examination by indirect ophthalmoscopy. Spectral domain optical coherence tomography (SD-OCT) was performed, to confirm the diagnosis of DME and indication of injection. OCTA imaging of diabetic eyes was performed with the swept-source optical coherence tomograpy angiography instrument (Optovue AngioVue system technology for optical coherence tomography (OCT) angiography) to evaluate changes in macular vessel density before the injection.

Operative procedure:

Treatment with intravitreal Ranibizumab 0.5mg (0.05ml of 10mg/ml solution).

Technique of injection:

Conjunctival anesthesia was topically induced by instillation of 0.4% Benoxinate hydrochloride (Benox®). The eyelids and ocular surface were disinfected with povidone-iodine (10%) to the eyelashes and eyelid margins. The eyelids were retracted away by speculum from the intended injection site for the duration of the procedure. Povidone-iodine (5%) was applied to the conjunctival surface, including the intended injection site for 3-5mins. The needle was inserted perpendicular to the sclera, the injection site was the supero-temporal quadrant, 4 mm (phakic eyes), 3.5mm (pseudophakic eyes)posterior to the limbus, between the vertical and horizontal rectus muscles. A sterile cotton-tip applicator was applied over the injection site immediately following removal of the needle to reduce vitreous reflux.

II- *Postoperative evaluation 1-month and 2 months since the date of the first injection:*

Visual acuity measurement: Using Landolt's VA chart and after that transformed for statistical analysis to Decimal Notation. Slit lamp examination: to evaluate corneal transparency, anterior chamber, pupil, state of the lens, IOP and complications of DM which include accelerated senile cataract, rubeosis iridis. Fundus examination by indirect ophthalmoscopy. Spectral domain optical coherence tomography (SD-OCT) was performed, to follow-up the CFT of DME after injection. OCTA imaging of diabetic eyes was performed with the swept-source optical coherence tomograpy angiography instrument (Optovue AngioVue system technology for optical coherence tomography (OCT) angiography) to evaluate changes in macular vessel density before the injection. High-quality 3 x 3 mm images with strong signal–noise ratio and adequate centration on the fovea was selected. Vessel density analysis computes the percentage of area occupied by OCTA detected vasculature in a measured area. The vascular density in the whole ETDRS grid (composed of concentric rings at 1, 3, mm from the foveal center) and its subsets was automatically generated by the software as the proportion of the measured area occupied by blood vessels with flow.

Outcome:

To compare between macular vessel density before and after single dose of intravitreal ranibizumab injection.

Statistical package: Changes in vessel density pre and postoperative was be analyzed and correlated with the patient's data using the SPSS statistical package version 25 (SPSS, Inc., Chicago, IL, USA). Paired *t*-test and analysis of variance (ANOVA) was used for quantitative data analysis between parameters over successive observation points. A *p*-value of less than 0.05 was considered significant.

Statistical analysis:

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 25. The quantitative data were presented as mean, standard deviations and ranges. Also qualitative variables were presented as number and percentages. The comparison between two independent groups with quantitative data and parametric distribution was done by using Independent *t*-test while with non parametric distribution were done by using Mann-Whitney test. The comparison between more than two paired groups regarding quantitative data and parametric distribution was done by using Repeated Measures ANOVA test followed by post hoc analysis using Bonferoni test while with non parametric distribution was done by using Friedman test followed by post hoc analysis using Wilcoxon Rank test. Spearman correlation coefficients were used to assess the correlation between two quantitative parameters in the same group. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the *p*-value was considered significant as the following: *p*-value >0.05: Non-significant (NS). *p*-value <0.05: Significant (S). *p*-value <0.01: Highly significant (HS).

Results

Table (1): Demographic data and characteristics of the studied patients.

	Total No. = 44
Age (years):	
Mean ± SD	50.98±6.27
Range	41-60
Sex:	
Male	30 (68.2%)
Female	14 (31.8%)
Duration:	
Median (IQR)	15 (10-20)
Range	4-25
HBA1c:	
Mean ± SD	8.87±1.02
Range	7.4-11.1

Table (2): Visual acuity by Decimal Notation after transformation of Landolt's VA chart preoperative, 1 month and 2 months follow-up among the studied patients.

	Pre	1 Month	2 Month	Test value	*p*-value	Sig.
VA:						
Mean ± SD	0.14±0.09	0.28±0.14	0.38±0.16	124.482≠	0.000	HS
Range	0.05-0.3	0.1-0.5	0.1-0.6			
% of change:						
Mean ± SD	–	135.23±116.43	237.50±157.67			

Post hoc analysis

	Pre Vs 1 Month	Pre Vs 2 Month	1 Month Vs 2 Month
VA	0.000	0.000	0.000

p-value >0.05: Non significant.
p-value <0.05: Significant.
p-value <0.01: Highly significant.
≠: Friedman test.

Table (3): CMT level preoperative, 1 month and 2 months follow-up among the studied patients.

	Pre	1 Month	2 Month	Test value	*p*-value	Sig.
CMT:						
Mean ± SD	482.02±87.86	374.25±66.57	331.2±64.35	1853.847•	0.000	HS
Range	356-684	247-491	241-416			
% of change:						
Mean ± SD		–21.70±10.15	–29.99±13.21			

Post hoc analysis

	Pre Vs 1 Month	Pre Vs 2 Month	1 Month Vs 2 Month
CMT	0.000	0.000	0.000

p-value >0.05: Non significant.
p-value <0.05: Significant.
p-value <0.01: Highly significant.
•: Repeated Measures ANOVA test.

Table (4): OCTA of the vessel density in the central subfield (OCTA c) preoperative, 1 month and 2 months follow-up among the studied patients.

	Pre	1 Month	2 Month	Test value	*p*-value	Sig.
OCTA c:						
Mean ± SD	20.29±1.89	20.09±2.4	19.73±2.49	3629.057•	0.000	HS
Range	16.76-24.45	15.58-23.65	15.11-23.19			
% of change:						
Mean ± SD		–1.20±4.26	–3.00±6.14			

Post hoc analysis

	Pre Vs 1 Month	Pre Vs 2 Month	1 Month Vs 2 Month
OCTA c	0.354	0.009	0.006

p-value >0.05: Non significant.
p-value <0.05: Significant.
p-value <0.01: Highly significant.
•: Repeated Measures ANOVA test.

Table (5): OCTA of the vessel density average of the four parafoveal subfields (OCTA v) preoperative, 1 month and 2 months follow-up among the studied patients.

	Pre	1 Month	2 Month	Test value	*p*-value	Sig.
OCTA avg:						
Mean ± SD	44.98±2.6	44.8±2.21	44.14±2.2	16580.491•	0.000	HS
Range	41.04-51.16	41.89-50.01	41.28-49.04			
% of change:						
Mean ± SD		–0.36±1.83	–1.81±2.21			
Post hoc analysis						
	Pre Vs 1 Month		Pre Vs 2 Month	1 Month Vs 2 Month		
OCTA avg	0.410		0.000	0.000		

p-value >0.05: Non significant.
p-value <0.05: Significant.
p-value <0.01: Highly significant.
•: Repeated Measures ANOVA test.

Table (6): Correlation between age of the studied patients and VA, CMT, OCTA c and OCTA v at different times of measurements.

	Age (years)	
	r	*p*-value
VA:		
Pre	–0.247	0.106
Post 1 month	–0.166	0.282
Post 2 months	–0.116	0.452
% of change after 1 month	0.212	0.167
% of change after 2 months	0.284	0.061
CMT:		
Pre	0.127	0.410
Post 1 month	0.252	0.099
Post 2 months	–0.021	0.890
% of change after 1 month	0.141	0.362
% of change after 2 months	–0.078	0.615
OCTA c:		
Pre	–0.113	0.466
Post 1 month	–0.120	0.438
Post 2 months	–0.134	0.388
% of change after 1 month	–0.108	0.484
% of change after 2 months	–0.033	0.831
OCTA v:		
Pre	–0.169	0.272
Post 1 month	–0.160	0.301
Post 2 months	–0.154	0.317
% of change after 1 month	0.087	0.576
% of change after 2 months	0.088	0.569

p-value >0.05: Non significant.
p-value <0.05: Significant.
p-value <0.01: Highly significant.
Spearman correlation coefficient.

Table (7): Correlation between DM duration of the studied patients and VA, CMT, OCTA c and OCTA v at different times of measurements.

	Duration	
	r	*p*-value
VA:		
Pre	–0.310*	0.040
Post 1 month	–0.141	0.361
Post 2 months	–0.538**	0.000
% of change after 1 month	0.191	0.214
% of change after 2 months	–0.084	0.589
CMT:		
Pre	0.168	0.277
Post 1 month	0.249	0.104
Post 2 months	–0.038	0.805
% of change after 1 month	–0.293	0.054
% of change after 2 months	–0.149	0.334
OCTA c:		
Pre	–0.430**	0.004
Post 1 month	–0.450**	0.002
Post 2 months	–0.428**	0.004
% of change after 1 month	–0.222	0.147
% of change after 2 months	–0.444**	0.003
OCTA v:		
Pre	0.556**	0.000
Post 1 month	0.339*	0.024
Post 2 months	0.329*	0.029
% of change after 1 month	–0.836**	0.000
% of change after 2 months	–0.653**	0.000

p-value >0.05: Non significant.
p-value <0.05: Significant.
p-value <0.01: Highly significant.
Spearman correlation coefficient.

Table (8): Correlation of HbA1c with VA, CMT, OCTA c and OCTA v at different times among the studied patients.

	HbA1c	
	r	*p*-value
VA:		
Pre	–0.707**	0.000
Post 1 month	–0.607**	0.000
Post 2 months	–0.735**	0.000
% of change after 1 month	0.483**	0.001
% of change after 2 months	0.286	0.060
CMT:		
Pre	0.486**	0.001
Post 1 month	0.694**	0.000
Post 2 months	0.588**	0.000
% of change after 1 month	0.182	0.237
% of change after 2 months	0.139	0.369
OCTA c:		
Pre	–0.636**	0.000
Post 1 month	–0.683**	0.000
Post 2 months	–0.678**	0.000
% of change after 1 month	–0.513**	0.000
% of change after 2 months	–0.618**	0.000
OCTA v:		
Pre	–0.244	0.110
Post 1 month	–0.351*	0.020
Post 2 months	–0.335*	0.026
% of change after 1 month	–0.233	0.129
% of change after 2 months	–0.175	0.256

p-value >0.05: Non significant. *p*-value <0.01: Highly significant.
p-value <0.05: Significant. Spearman correlation coefficient.

Table (9): Relation of Gender with VA, CMT, OCTA c and OCTA v at different times among the studied patients.

	Male No. = 30	Female No. = 14	Test value	*p*-value	Sig.
Pre VA pre	0.14±0.09	0.14±0.10	–0.026#	0.979	NS
Post VA post 1	0.28±0.14	0.29±0.14	–0.237#	0.813	NS
Post VA post 2	0.38±0.17	0.38±0.15	0.000#	1.000	NS
% of change after 1 month	133.33±115.72	139.29±122.23	–0.083#	0.934	NS
% of change after 2 months	237.78±164.81	236.90±147.08	0.000#	1.000	NS
CMT pre	476.60±88.14	493.64±89.39	–0.595•	0.555	NS
CMT post 1	369.20±62.76	385.07±75.41	–0.733•	0.468	NS
CMT post 2	330.23±65.47	333.29±64.26	–0.145•	0.886	NS
% of change after 1 month	–21.79±9.86	–21.50±11.12	–0.114#	0.910	NS
% of change after 2 months	–29.42±13.44	–31.21±13.11	–0.518#	0.605	NS
OCTA c pre	20.28±1.89	20.32±1.96	–0.060•	0.953	NS
OCTA c post 1	20.08±2.41	20.12±2.47	–0.053•	0.958	NS
OCTA c post 2	19.66±2.56	19.87±2.41	–0.262•	0.795	NS
% of change after 1 month	–1.21±4.29	–1.18±4.37	–0.492#	0.622	NS
% of change after 2 months	–3.31±6.41	–2.35±5.68	–0.290#	0.772	NS
OCTA v pre	44.78±2.63	45.41±2.57	–0.746•	0.460	NS
OCTA v post 1	44.57±2.27	45.28±2.07	–0.994•	0.326	NS
OCTA v post 2	43.91±2.27	44.64±2.02	–1.023•	0.312	NS
% of change after 1 month	–0.42±1.83	–0.23±1.87	–0.063#	0.950	NS
% of change after 2 months	–1.89±2.19	–1.63±2.31	–0.366#	0.714	NS

p-value >0.05: Non-significant. • : Independent *t*-test.
p-value <0.05: Significant. #: Mann-Whitney test.
p-value <0.01: Highly significant.

Discussion

In 2019, 463 million adults aged between 20-79 years (8.8% of the adult population) were estimated globally to be suffering from DM **[14].**

The Global Burden of Disease Study found that in adults 50 years of age and older, diabetic retinopathy (DR) was the fifth leading cause of preventable blindness. In particular, the age-standardized global prevalence for blindness resulting from diabetic eye diseases has risen from 14.9% to 18.5% from 1990 to 2020 **[15].**

The treatment of DR with modern conservative methods in combination with the standard therapy improves the long-term prognosis of the disease. Today, tools that block vascular endothelial growth factor (VEGF), which is considered to be the main cause of the mechanism of neovascularization, as well as vascular hyperfiltration into the retina, have become widely available in practice **[16].**

Therefore, intravitreal anti-VEGF agents are today the gold standard in treatment of DME with large randomized clinical trials to show their efficacy and safety **[17].**

Several studies have since demonstrated a reduction in parafoveal vessel density in the superficial and deep retinal vascular layers in diabetic eyes compared to normal controls **[18,19].**

In light of the above, the purpose of this study was to evaluate any early vessel density changes in patients undergoing intravitreal antiVEGF injections (ranibizumab) for treatment of diabetic macular edema one month and two months after injection.

This prospective study included 44 eyes of 44 patients indicated for intravitreal injection (IVI) for treatment DME, with a mean age of 50.98±6.27 years, ranging from 41.0 to 60.0 years. The majority of them were males (68.2%).

Prevalence of either males or females showed great differences between the different studies. But females constituted nearly about two thirds (64%) of diabetic population, in previous epidemiological researches conducted in Egypt. This was attributed to the relatively higher hypercholesterolemia in females **[20,21].**

The difference in gender predominance might be attributed to the different study population, ethnic and racial characteristics.

In our study, the baseline visual acuity was 0.14 ±0.09, and at one month after injection it improved to 0.28±0.14 and two months after injection improved again to 0.38±0.16 with a highly significant difference.

The baseline central foveal thickness was 482.02 ±87.86 microns and at one month after injection it decreased to be 374.25±66.57 microns and two months after injection it reached 331.2±64.35 microns with a highly significant difference.

The baseline vessel density of the central subfield was 20.29±1.89 and at one month after injection it reached 20.09±2.4 with no significant difference, however at two months after injection it went down again to be 19.73±2.49 with a highly significant difference from the first month and the baseline.

The baseline average vessel density of the four para foveal subfields was 44.98±2.6 and at one month after injection it showed a little worsening to be 44.8±2.21 with no significant difference, however at two months after injection it decreased to 44.14 ±2.2 with a highly significant difference from the first month and the baseline.

Functional imaging studies also showed a reduction in choroidal blood flow in eyes with diabetic retinopathy **[22].**

Previous case series reported an increased risk of worsening of retinal nonperfusion in eyes with retinal vascular disease following the administration of VEGF inhibitors. These studies attributed the worsening of retinal nonperfusion to the blockage of VEGF, which is a survival factor for vascular endothelial cells **[23].**

Feucht N et al. **[24]** reported progressive enlargement of FAZ measured in FA images after anti-VEGF therapy in CME secondary to DR. However, the effect may be transient and vanishes within weeks and only noted if the retina is examined early after injection.

It was also reported that certain eyes may not respond to VEGF inhibitors and demonstrate a lower vessel density in the DCP but not the SCP **[25].**

Dastiridou A et al. **[26]** reported that vessel density in the central region decreased by 8% after 3 aflibercept injections but remained unchanged in the parafoveal region.

The underlying mechanism behind VD reduction is not so clear. The phenomenon of suspended scattering particles in motion (SSPiM) could be a plausible explanation for our results. This phenomenon is frequently observed in vascular cystic macular edema, in which some cysts have hyperreflective material as seen by OCT. This material is composed of particles with a Brownian movement that give a false-positive signal in OCTA **[27].**

The presence of SSPiM may lead to an overestimation of DCP vessel density in eyes with DME when 3-mm OCTA scans are used for analysis **[28].**

In our study we found a significant improvement of both the visual acuity and the central macular thickness with a highly significant difference after one month and two months from the injection.

It is interesting that the present study showed no statistically significant correlation of both the gender and the age of the studied patients and the levels of VA, CMT, OCTA c and OCTA v preoperative, at 1 month and at 2 months follow-up.

Also, we found that there was statistically significant negative correlation found between HbA1c level of the studied patients and both visual acuity level by Decimal Notation after transformation of Landolt's VA chart and CMT level at preoperative, 1 month and after 2 months.

Similarly, there was a statistically significant negative correlation found between HbA1c level of the studied patients and both OCTA c and OCTA v level at 1 month and at 2 months.

Our results showed a slight decrease of the vessel density in the central subfield one month after the injection with a percecntage change of –1.20± 4.26 but with no significant difference; however, there was more decrease in the vessel density in the same subfield from the preoperative density with a percentage change of –3.00±6.14 two months after the injection with a highly significant difference.

In addition, the vessel density in the four parafoveal subfields showed a slight decrease one month after the injection with a percentage change of –0.36±1.83 but it was of no significant difference while a highly significant difference with a percentage change of –1.81±2.21 was observed in the same fields two months after the injection.

Our study stands out from the previous studies in two aspects. The first is that all our patients had only diabetic macular edema and no other macular pathology or previous ocular surgeries within the last 6 months. The second is that only one anti-VEGF was used, namely Ranibizumab. The two factors may have helped to produce more reliable results.

Although we excluded images with severe distortion, the possibility of a measurement error due to other forms of artifacts including segmentation, motion, and projection artifact should be considered.

However, our limitations are also obvious, namely the small sample size, the short follow up period, and the fact that results were reported after only one IV injection and not after repeated injections. Also, despite OCTA providing an accurate method to measure the superficial retinal vessel density, the projection artifact embedded in the technology might lead to an overestimation of the deep retinal vessel density. We recommend further studies to rectify these limitations.

Conclusion:

A single IV injection of Ranibizumab in eyes with DME showed non significant vascular density changes after one month of injection in both central and paraoveal subfileds but a statistically significant decrease in vascular density 2 months after injection.

References

1- BOYER D.S., HOPKINS J.J., SOROF J. and EHRLICH J.S.: Anti-vascular endothelial growth factor therapy for diabetic macular edema. Therapeutic Advances in Endocrinology and Metabolism, 4 (6): 151-169, 2013.

2- International Diabetes Federation. Clinical Practice Recommendations for Managing Diabetic Macular Edema. Brussels, Belgium: International Diabetes Federation, 2019.

3- YAU J.W., ROGERS S.L., KAWASAKI R., LAMOUREUX E.L., KOWALSKI J.W., BEK T., CHEN S.J., DEKKER J.M., FLETCHER A., GRAUSLUND J. and HAFFNER S.: Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care, 35 (3): 556-64, 2012.

4- American Academy of Ophthalmology. Preferred Practice Pattern® Guidelines: Diabetic Retinopathy, 2016.

5- MORELLO CM.: Etiology and natural history of diabetic retinopathy: An overview. American Journal of Health-System Pharmacy, 64 (17): 3-7, 2007.

6- STEWART M.: Anti-vascular endothelial growth factor drug treatment of diabetic macular edema: The evolution continues. Current diabetes reviews, 8 (4): 237-46, 2012.

7- WITMER A.N., VRENSEN G.F., VAN NOORDEN C.J. and SCHLINGEMANN R.O.: Vascular endothelial growth factors and angiogenesis in eye disease. Progress in retinal and eye research, 22 (1): 1-29, 2003.

8- FERRARA N. and ADAMIS A.P.: Ten years of anti-vascular endothelial growth factor therapy. Nature reviews Drug discovery, 15 (6): 385-403, 2016.

9- FUNATSU H., YAMASHITA H., NOMA H., MIMURA T., YAMASHITA T. and HORI S.: Increased levels of vascular endothelial growth factor and interleukin-6 in the aqueous humor of diabetics with macular edema. American Journal of Ophthalmology, 133 (1): 70-7, 2002.

10- CHRIS O., SABROSA A.S., SOROUR O., ARYA M. and WAHEED N.: Use of OCTA, FA, and ultra-widefield imaging in quantifying retinal ischemia: A review. The Asia-Pacific Journal of Ophthalmology, 7 (1): 46-51, 2018.

11- CHANDRA S., SHETH J., ANANTHARAMAN G. and GOPALAKRISHNAN M.: Ranibizumab-induced retinal reperfusion and regression of neovascularization in diabetic retinopathy: an angiographic illustration. American Journal of Ophthalmology case reports, 9: 41-4, 2018.

12- SHIMURA M. and YASUDA K.: Macular ischaemia after intravitreal bevacizumab injection in patients with central retinal vein occlusion and a history of diabetes and vascular disease. British Journal of Ophthalmology, 94 (3): 381-3, 2010.

13- GROSS J.G., GLASSMAN A.R., JAMPOL L.M., et al.: Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. JAMA, 314 (20): 2137-46, 2015.

14- SAEEDI P., PETERSOHN I., SALPEA P., MALANDA B., KARURANGA S., UNWIN N., COLAGIURI S., GUARIGUATA L., MOTALA A.A., OGURTSOVA K., SHAW J.E., BRIGHT D. and WILLIAMS R.: IDF Diabetes Atlas Committee. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res. Clin. Pract., 2019.

15- COLLABORATORS G.B.D. and RAWAL L.: Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to VISION 2020: The Right to Sight: An analysis for the Global Burden of Disease Study, 2021.

16- MIRSHOVKATOVNA N.N., FARIDOVICH K.F. and TOLIBOVICH S.T.: Diabetik retinapatiyani davolashda anti vegf dorilarning ahamiyati (adabiyotlar sharhi). Journal of Biomedicine and Practice, 7 (6): 1, 2022.

17- STEWART S., YEONG J.L., VIRGILI G., AZUARA-BLANCO A. and LOIS N.: Pragmatism of randomized clinical trials on ranibizumab for the treatment of diabetic macular edema: impact on clinical outcomes. Retina (Philadelphia, Pa.), 40 (5): 919, 2020.

18- AGEMY S.A., SCRIPSEMA N.K., SHAH C.M., CHUI T., GARCIA P.M., LEE J.G., GENTILE R.C., HSIAO Y.S., ZHOU Q., KO T. and ROSEN R.B.: Retinal vascular perfusion density mapping using optical coherence tomography angiography in normals and diabetic retinopathy patients. Retina., 35 (11): 2353–2363, 2015.

19- DIMITROVA G., CHIHARA E., TAKAHASHI H., AMANO H. and OKAZAKI K.: Quantitative retinal optical coherence tomography angiography in patients with diabetes without diabetic retinopathy. Investigative ophthalmology & visual science, 58 (1): 190-6, 2017.

20- HERMAN W.H., AUBERT R.E., ENGELGAU M.M., THOMPSON T.J., ALI M.A., SOUS E.S., HEGAZY M., BADRAN A., KENNY S.J., GUNTER E.W. and MALARCHER A.M.: Diabetes mellitus in Egypt: glycaemic control and microvascular and neuropathic complications. Diabetic Medicine, 15 (12): 1045-51, 1998.

21- MACKY T.A., KHATER N, AL-ZAMIL M.A., EL FISHAWY H. and SOLIMAN M.M.: Epidemiology of diabetic retinopathy in Egypt: A hospital-based study. Ophthalmic Research, 45 (2): 73-8, 2011.

22- NAGAOKA T., KITAYA N., SUGAWARA R., et al.: Alteration of choroidal circulation in the foveal region in patients with type 2 diabetes. Br. J. Ophthalmol., 88 (8): 1060–3, 2004.

23- SABET-PEYMAN E.J., HEUSSEN F.M., THORNE J.E., CASPARIS H., PATEL S.J. and DO D.V.: Progression of macular ischemia following intravitreal bevacizumab. Ophthalmic Surg Lasers Imaging, 40: 316-318, 2009.

24- FEUCHT N., SCHÖNBACH E.M., LANZL I., KOTLIAR K., LOHMANN C.P. and MAIER M.: Changes in the foveal microstructure after intravitreal bevacizumab application in patients with retinal vascular disease. Clinical Ophthalmology, Jan. 18: 173-8, 2013.

25- MOON B.G., UM T., LEE J. and YOON Y.H.: Correlation between deep capillary plexus perfusion and long-term photoreceptor recovery after diabetic macular edema treatment. Ophthalmol Retina, 2: 235-243, 2018.

26- DASTIRIDOU A., KARATHANOU K., RIGA P., ANAGNOSTOPOULOU S., BALASUBRAMANIAN S., MATAFTSI A., BRAZITIKOS P., ZIAKAS N. and ANDROUDI S.: OCT angiography study of the macula in patients with diabetic macular edema treated with intravitreal aflibercept. Ocular Immunology and Inflammation, Jul 4; 29 (5): 926-31, 2021.

27- KASHANI A.H., GREEN K.M., KWON J., CHU Z., ZHANG Q., WANG R.K., GARRITY S., SARRAF D., REBHUN C.B., WAHEED N.K. and SCHAAL K.B.: Suspended scattering particles in motion: Anovel feature of OCT angiography in exudative maculopathies. Ophthalmology Retina, 2 (7): 694-702, 2018.

28- MALTSEV D.S., KULIKOV A.N., KAZAK A.A. and FREUND K.B.: suspended scattering particles in motion may influence optical coherence tomography angiography vessel density metrics in eyes with diabetic macular edema. Retina, 41 (6): 1259–1264, 2021.

تأثير الحقن داخل الجسم الزجاجى لمضاد عامل نمو بطانة الأوعية الدموية على مؤشرات التروية فى العيون المصابة بالوذمة البقعية السكرية المقاسة بالتصوير المقطعى للأوعية الدموية بالتصوير المقطعى البصرى

الوذمة البقعية السكرية هى السبب الرئيسي لاضطراب الرؤية لدى مرضى اعتلال الشبكية السكرى. يختلف انتشار الوذمة البقعية السكرية بين المصابين بداء السكرى من النوع ١ والنوع ٢ حسب المنطقة. تتراوح معدلات الانتشار من ١١٪ فى أوروبا إلى ٧,٥٪ فى بعض البلدان الأفريقية. يتأثر أكثر من ٢١ مليون شخص فى جميع أنحاء العالم. يعانى واحد من كل ١٤ شخصًا مصابًا بداء السكرى من درجة ما من الوذمة البقعية السكرية. يقدر أن ٢٠٪ من الأشخاص المصابين بداء السكرى من النوع ١، و ٢٥٪ من المصابين بداء السكرى من النوع ٢، يتوقعون أن يصابوا بالوذمة البقعية السكرية. أولئك الذين تم تشخيص إصابتهم باعتلال الشبكية السكرى التكاثرى معرضون بشكل خاص لخطر الإصابة بالوذمة البقعية السكرى.

يصنف اعتلال الشبكية السكرى إلى عدة مراحل بناءً على مستوى شدة المرض يتميز الاعتلال السابق للشبكية بالتغيرات الديناميكية الدموية ونفاذية الأوعية الدموية مع عدم وجود اعتلال الشبكية الظاهر فى الفحص السريرى. يتميز اعتلال الشبكية السكرى غير التكاثري الخفيف بظهور تمدد الأوعية الدموية الدقيقة، والتى يمكن أن تتطور فى المراحل المتوسطة إلى تشوهات الأوعية الدموية الدقيقة داخل الشبكية، ونزيف داخل الشبكية، وبقع من الصوف القطنى، والتى تمثل احتشاءات بؤرية لطبقة الألياف العصبية الشبكية. يمكن أن تؤدى زيادة نفاذية الأوعية الدموية فى الشبكية إلى وذمة الشبكية وتكوين رواسب غنية بالبروتينات والدهون، والتيشار إليها باسم الإفرازات الصلبة.

فى اعتلال الشبكية السكرى غير التكاثرى الحاد، تنغلق الأوعية الدموية فى الشبكية تدريجيًا، مما يضعف التروية ويؤدى إلى نقص تروية الشبكية، الذى يتميز بخلل فى العيار الوريدى، وتشوهات الأوعية الدموية الدقيقة داخل الشبكية (بشكل أساسى، توسع الأوعية الدموية داخل الشبكية)، وانتشار تسرب الأوعية الدموية. يميز اتساع الأوعية الدموية على سطح الشبكية والعصب البصرى والتركيبات الأخرى (مثل القزحية، فى الحالات الشديدة) المرحلة الأكثر تقدمًا من اعتلال الشبكية السكرى، والمعروف باسم اعتلال الشبكية السكرى التكاثرى.

تكون الأوعية الجديدة غير الطبيعية هشة ويمكن أن تنزف فى الجسم الزجاجى، مما يتسبب فى فقدان مفاجئ للرؤية. فى بعض الحالات، يؤدى الانكماش التلقائى لأغشية الأوعية الدموية فى شبكية العين إلى فصل الشبكية عن الهياكل الداعمة لها، وهى حالة تُعرف باسم انفصال الشبكية الجر.

على الرغم من أنه يمكن إجراء الجراحة لمحاولة إعادة ربط الشبكية، إلا أن فقدان البصر فى مثل هذه الحالات غالبًا ما يكون كبيرًا ولا رجعة فيه. قد تؤدى إصابة الأوعية الدموية الدقيقة التى تمت مناقشتها سابقًا إلى تسرب الأوعية الدموية فى شبكية العين مع تراكم السوائل الزائدة خارج الخلية والتى تتجلى على أنها وذمة البقعة الصفراء السكرية.

في مرضى السكرى، يؤدى ارتفاع السكر فى الدم المزمن إلى انتفاخ عامل نمو بطانة الأوعية الدموية، مما يؤدى إلى تكوين الأوعية وزيادة نفاذية الأوعية الدموية وإنتاج السيتوكينات المؤيدة للالتهابات (مثل جزيء الالتصاق داخل الخلايا ١ وعامل نخر الورم α). قد يؤدى زيادة سماكة الغشاء القاعدى وفقدان الحوائط، وهى السمات المميزة الرئيسية لاعتلال الشبكية السكرى، بالإضافة إلى الضغط الشديد على الخلايا البطانية، إلى تحفيز عامل نمو بطانة الأوعية الدموية فى أنسجة الأوعية الدموية داخل الأوعية، بما فى ذلك الملتحمة والقزحية والشبكية والصبغة المشيمية الشبكية مجمع ظهارة. أظهرت الدراسات فى المختبر وفى الموقع أن خلايا الظهارة الصباغية لشبكية العين يمكن أن تصنع وتفرز عامل نمو بطانة الأوعية الدموية، ويتم تنظيم عامل نمو بطانة الأوعية الدموية فى خلايا ظهارة الشبكية البشرية استجابة لنقص الأكسجة.

علاوة على ذلك، فإن التركيزات الزجاجية لعامل نمو بطانة الأوعية الدموية فى المرضى الذين يعانون من اعتلال الشبكية السكرى التكاثرى تعتبر ذات صلة من الناحية الفسيولوجية وعلى الأرجح تنتج عن نقص تروية الشبكية. فى دراسة مقطعية مقارنة لعينات الخلط المائى غير المخفف المأخوذة من ٥٤ عينًا لـ ٥٤ مريضًا يعانون من الوذمة البقعية السكرية الخاضعين لجراحة الساد، كانت المستويات المائية لعامل نمو البطانة الوعائية مرتبطة بشكل كبير ($p < ٠,٠٠١$) مع شدة البقعة الصفراء السكرية. الوذمة. توضح هذه النتائج أن عامل نمو بطانة الأوعية الدموية يتم إنتاجه فى أنسجة باطن العين لمرضى السكرى ويشارك فى التسبب فى الوذمة البقعية السكرى. لا يزال تصوير الأوعية بالفلوريسين لا يقدر بثمن فى تحديد الأوعية الدموية المتسربة فى كل من الوذمة البقعية السكرى واعتلال الشبكية السكرى التكاثرى. ومع ذلك، فإن تصوير الأوعية بالفلوريسين يستغرق وقتًا طويلاً، وهو غازى وينطوى على مخاطر حدوث مضاعفات، بما فى ذلك ردود الفعل التحسسية الشديدة. تصوير الأوعية بالتصوير المقطعى البصرى، وهو امتداد للتصوير المقطعى للتماسك البصرى، هو تقنية تصوير غير جراحية وحل عميق يسمح بتصور الضفيرة الشعرية السطحية والعميقة، وهو أمر غير ممكن فى تصوير الأوعية بالفلوريسين.

قد يساعد تطبيق تصوير الأوعية المقطعى بالتماس البصرى لدراسة تغيرات الأوعية الدموية الدقيقة لدى مرضى السكرى فى فهم الآلية المرضية لاعتلال الشبكية السكرى والتغيرات التى تحدث استجابة للعلاجات المختلفة. على الرغم من أن استخدام علاج عامل النمو البطانى المضاد للأوعية الدموية هو الآن العلاج القياسى فى حالات الوذمة البقعية السكرى، إلا أن تأثيره على التروية الشبكية لا يزال مثيرًا للجدل. أظهرت بعض الدراسات تباطؤًا أو حتى تحسنًا فى عدم التروية البقعى بعد علاج عامل النمو البطانى المضاد للأوعية الدموية، مع مجموعة متزايدة من الأدلة لاستخدامه فى اعتلال الشبكية السكرى التكاثرى أيضًا. ومع ذلك، فقد اعتبر عدد أقل من دراسات الحالة زيادة عامل نمو بطانة الأوعية الدموية كآلية تعويضية فى استعادة التروية البقعية؛ بالإضافة إلى ذلك، قد يؤدى علاج عامل النمو البطانى المضاد للأوعية الدموية إلى زيادة شدة عدم التروية مع التدهور البصرى اللاحق. ومع ذلك، فقد اعتمدت جميع الدراسات السابقة على تصوير الأوعية بالفلوريسين لتقييم التغيرات فى التروية البقعية، والتى تتميز بدقة أقل وحساسية محدودة. فى هذه الدراسة، سيتم استخدام التصوير الوعائى بالتصوير المقطعى البصرى لتحديد كثافة الأوعية لتقييم التروية البقعية بعد علاج عامل النمو البطانى المضاد للأوعية.