

Evaluation of the Vitreomacular Interface Abnormalities in Diabetic Macular Oedema Treated with Intravitreal Injection of Ranibizumab by Spectral-Domain Optical Coherence Tomography

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ABSTRACT

Background: When treatment is postponed or administered incorrectly, diabetic macular edema (DME), the primary cause of visual impairment in the diabetic population, can lead to visual handicap. Inhibitors of vascular endothelial growth factor (VEGF) are a common treatment with a minimal risk of ocular and systemic effects, good tolerance and demonstrated effectiveness. **Objective:** This study aimed to assess vitreomacular interface abnormalities (VMIA) in DME cases who received ranibizumab intravitreal injections (IVI).

Patients and methods: In a prospective, cross-sectional interventional follow-up research with an analytical component, 25 eyes from 25 DME cases received three intravitreal ranibizumab (IVR) injections spaced one month apart at Menoufia University Hospital. **Results:** Our research demonstrated a moderately negative connection between baseline and final measurements of central retinal thickness (CRT) and best-corrected visual acuity (BCVA). Intraocular pressure (IOP) rose from 14.56 mmHg to 15.72 mmHg, CRT dramatically dropped from 391.48 μ m to 301.16 μ m, and BCVA improved from 0.42 to 0.64. Furthermore, a strong correlation between the final measurement and posterior vitreous detachment (PVD) was discovered. **Conclusion:** The studies emphasized how crucial it is to identify and treat VMIA in DME cases as soon as possible in order to maximize visual results. Notwithstanding these drawbacks, the research highlighted the need for all-encompassing treatment strategies by providing insightful information on the relationship between VMIA and other parameters in DME cases receiving IVI of ranibizumab. Also, highlighted the necessity of thorough approaches in subsequent research to improve case care and treatment plans.

Keywords: Diabetic macular oedema, Vitreomacular interface abnormalities, Intravitreal injection, Ranibizumab, Spectral-domain optical coherence tomography.

INTRODUCTION

When treatment is postponed or administered incorrectly, diabetic macular edema—the primary cause of visual impairment in the diabetic population—causes visual impairment ⁽¹⁾. The visual acuity of many DME cases treated with laser photocoagulation does not improve ⁽²⁾. VEGF inhibitors are a popular treatment with a minimal risk of ocular and systemic effects, good tolerance and demonstrated efficacy ⁽³⁾.

Stereophthalmoscopy and fluorescein angiography are two common diagnostic procedures used to evaluate macular edema. After a stereoscopic inspection of the fundus under a slit-lamp or on a stereoscopic color fundus image reveals a clinically significant level of macular edema, treatment can be started, according to the Early Treatment Diabetic Retinopathy Research ⁽⁴⁾.

The diagnosis of macular disease was completely transformed in 1991 with the advent of optical coherence tomography (OCT) ⁽⁵⁾. OCT morphological patterns in DME could help control DME by predicting how well intravitreal anti-VEGF injections work ⁽⁶⁾. Therefore, the purpose of this research was to assess VMIA in DME cases who received ranibizumab IVI.

PATIENTS AND METHODS

Sittings and duration: 25 eyes from 25 DME cases were studied at Menoufia University Hospital using three ranibizumab IVR injections spaced one month apart. **Inclusion criteria:** A diabetic macular edema case whose central macular thickness is greater than 300 μ m. **Exclusion criteria:** Eyes with any of the following conditions will not be accepted: Intravitreal injection within 6 months, prior intraocular surgery, before six-

month laser photocoagulation, Macular edema has a distinct etiology from glaucoma, inflammatory illnesses and other retinal disorders. Traction of vitreo-macular.

Research design: A cross-sectional, prospective interventional follow-up research that included analytical elements.

Methods: Three monthly intravitreal doses of 0.5 mg ranibizumab (Lucentis) were administered to each case. Prior to, during and six months after therapy, ophthalmological examinations were performed. The cases' full medical histories were taken, including their age, sex, history of systemic conditions like hypertension and hyperlipidemia, history of medications and history of any eye surgery or interventions. To measure intraocular pressure, a Volk 90 D lens and indirect ophthalmoscopy were utilized, a Landolt chart (converted to decimal) was utilized for assessing the BCVA. A slit lamp was employed for evaluating the anterior segment and a Goldmann applanation tonometer was employed for measuring intraocular pressure. OCT assessed changes in the posterior hyaloid face, quantified CMT, and looked for abnormalities of the VMIA both at baseline and throughout follow-up. The research evaluated how baseline VMIA, follow-up changes in the posterior hyaloid face and functional/anatomical results were related.

Surgical technique of intravitreal injection:

Aseptic procedures when preparing and administering drugs and anesthetics were maintained. Antimicrobial eye drops were used four times a day for

three days prior to therapy. Hands were washed and sterile gloves were used after the case comfortably lied down. Because the iodine solution is irritating, apply local anesthetic drops to both eyes. Draw 0.1 ml using a large bore needle in a sterile manner into a 1 ml syringe, remove the air, insert a 30G needle, and adjust the volume to 0.05 ml. Use a 5% aqueous povidone-iodine solution to cleanse and disinfect the eye, making sure the fluid reaches the conjunctival sac. After a minute or so, apply topical antibiotic drops. Hold the eye open by inserting a speculum. In the inferotemporal quadrant, measure a safe distance behind the limbus: 4 mm for phakic cases and 3.5 mm for pseudophakic cases. Before administering the injection, give the case a warning, insert the needle as soon as possible, inject the medication, take the needle out, and use a sterile cotton swab to stop reflux. Check the case's vision and administer additional topical antibiotic drops (Figure 1).

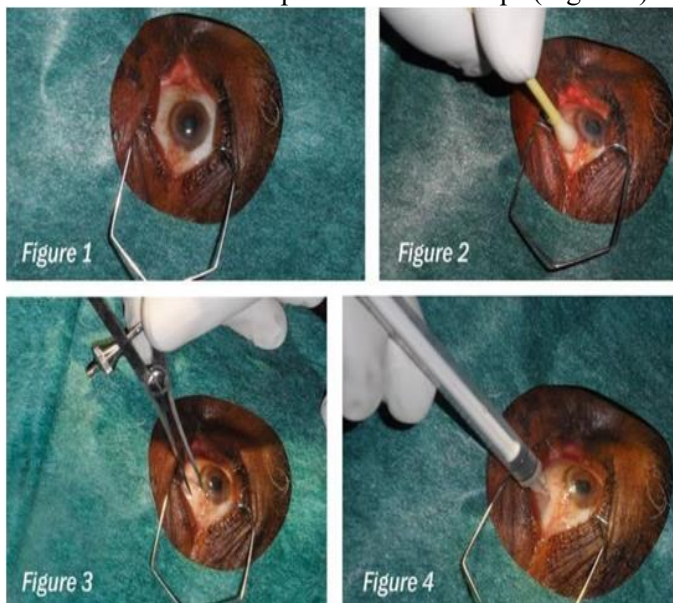


Figure (1): Illustration of intravitreal injection.

Ethical considerations: The Ethical Committee of Menoufia University Hospitals in Menoufia, Egypt, approved the study. The patients' written informed consents were acquired. All cases were fully told about the nature and goal of the research. To protect privacy and data confidentiality, the names of the participants were anonymised and substituted with code numbers. The research followed the guidelines laid out in the Declaration of Helsinki.

Statistical analysis

Data were entered and analyzed using the IBM Statistical Package for the Social Sciences, Version 20.0 (Armonk, NY: IBM Corp.). The qualitative data were reported using percentages and numbers. To ensure that distribution was normal, the Shapiro-Wilk test was used. Mean, standard deviation, median, and interquartile range (IQR) were the metrics used to depict the quantitative data. To evaluate the outcomes, we utilized a 5% significance level.

RESULTS

There were twenty-five eyes and twenty-five participants in the research. Analysis was done on the

distribution of different characteristics and how they related to the ERM. With ages ranged from 45 to 73, there were 10 (40%) men and 15 (60%) women. The cases' average age was 59.60 years. Females were the majority. Sixty percent of cases had hypertension and fifty-three percent had hyperlipidemia. HbA1c was 7.54 on average (range: 6.50-9.10) (Table 1).

Table (1): Distribution of the studied according to demographic data eyes

		N=25
Age (years)		59.08 ± 8.44
Sex	Male	10 (40.0%)
	Female	15 (60.0%)
Hypertension		13 (52.0%)
Hyperlipidaemia		12 (48.0%)
HbA1c		7.47 ± 0.83
Side	RT	11 (44.0%)
	LT	14 (56.0%)

Data are presented as mean ± SD or frequency (%). HbA1c: Glycated hemoglobin, RT: Right, LT: Left.

BCVA and CRT showed a moderately negative connection at baseline ($r = -0.528$, $p = 0.007$) and at the end ($r = -0.535$, $p = 0.006$) (Table 2).

Table (2): Correlation between Best corrected visual acuity and Central retinal thickness at baseline and during follow-up period

		r	P
BCVA vs CMT	Baseline	-0.528	0.007*
	Final	-0.535	0.006*

r: Pearson coefficient. *: Statistically significant at $p \leq 0.05$, BCVA: Best corrected visual acuity, CMT: Central retinal thickness.

Twenty-five eyes' baseline and end measures were compared. Of them, 17 had no ERM at the last measurement and 18 had none at baseline. The mean of the BCVA increased from 0.42 to 0.64 ($p < 0.001$) indicating a considerable improvement. From an average of 391.48 μm to 301.16 μm , the CRT dropped dramatically ($p < 0.001$). The mean IOP rose from 14.56 mmHg to 15.72 mmHg ($p < 0.001$). The final measurement and the existence of PVD were significantly correlated ($p = 0.046$) (Table 3).

Table (3): Comparison between baseline and final according to different parameters during follow-up period

		Baseline	Final	P
ERM	Absent	18(72.0%)	17(68.0%)	1.000
	Present	7(28.0%)	8(32.0%)	
BCVA (decimal)		0.42 ± 0.11	0.64 ± 0.16	<0.001*
CRT (μm)		391.48 ± 83.7	301.16 ± 50.9	<0.001*
IOP (mmHg)		14.56 ± 1.89	15.72 ± 1.70	<0.001*
PVD	Partial	8(32.0%)	10(40.0%)	0.046*
	Complete	2(8.0%)	3(12.0%)	

Data are presented as mean ± SD or frequency (%). *: Statistically significant at $p \leq 0.05$, t: Paired t-test, McN: McNemar test, MH: Marginal Homogeneity Test, BCVA: Best corrected visual acuity, ERM: Epiretinal Membrane, CRT: Central retinal thickness, IOP: Intra ocular pressure, PVD: Posterior vitreous detachment.

Eyes with and without epiretinal membranes had their baseline and ultimate visual acuities evaluated. When comparing eyes with and without epiretinal membrane, the mean and median visual acuity were considerably worse in the former (0.47 ± 0.10 vs 0.31 ± 0.07) and the latter (0.72 ± 0.12 vs 0.46 ± 0.05) ($p < 0.001$) respectively demonstrating a significant correlation between the highest corrected visual acuity and the epiretinal membrane (Table 4).

Table (4): Relation between epiretinal membrane and best corrected visual acuity (decimal) at baseline and during follow-up period

	Total (n=25)	ERM		P
		Absent (n=18)	Present (n=7)	
Baseline	0.42 ± 0.11	0.47 ± 0.10	0.31 ± 0.07	0.001*
Final	0.64 ± 0.16	0.72 ± 0.12	0.46 ± 0.05	<0.001*

Data are presented as mean $\pm$ SD or frequency (%). *: Statistically significant at $p \leq 0.05$, t: Student t-test, ERM: Epiretinal Membrane.

CASE

64-years-old woman who had diabetes for 20 years prior to and following an IVR injection. Prior to IVR injection, the initial OCT evaluation revealed a macular epiretinal membrane, a decimal BCVA of 0.3, a CMT of 469 μm and the resulting loss of the foveal depression and macular edema. An OCT evaluation one month following the injection showed a decrease in CMT to 361 μm and an improvement in BCVA to 0.4 (decimal). Three months after the injection, the BCVA was still at 0.4 and the CMT had dropped to 300 μm . Six months following the injection, CMT marginally rose to 325 μm , whereas BCVA remained at 0.4 (Figures 2).

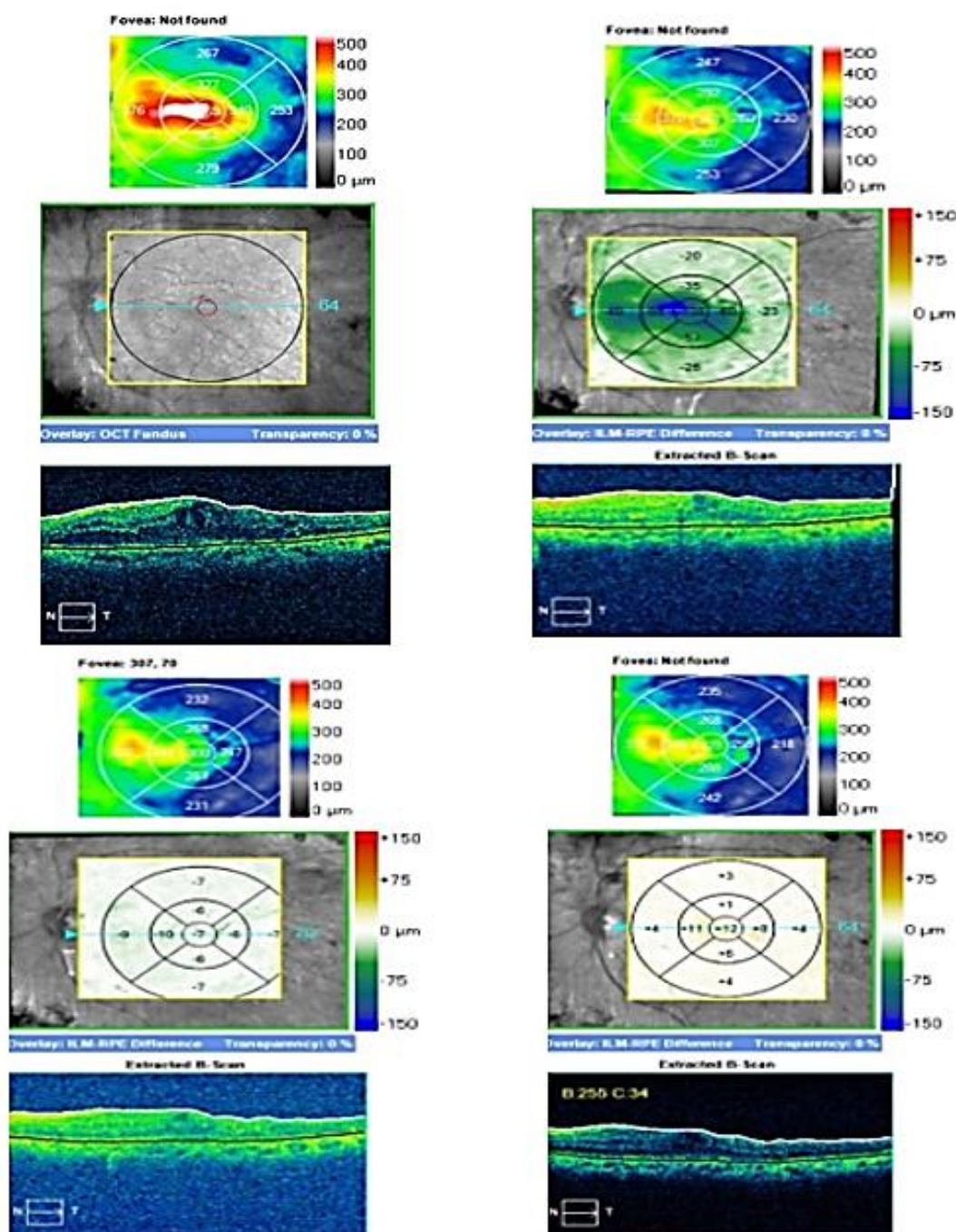


Figure (2): Case No 1. OCT evaluation before and after 1, 3 and 6 months of IVR injection.

DISCUSSION

VEGF-A is a desirable target for pharmacological therapies since it has been found to be a major contributor to neovascularization and blood-retinal barrier disruption. The purpose of our research was to assess VMIA in DME cases receiving ranibizumab intravitreal injection (IVI). In line with **Cui et al.** ⁽⁷⁾ findings that DME was more common in women than in men, the demographic analysis showed that women made up the majority of participants, accounting for 60% of cases. The average age of the cases in this research was 59.60 years (range: 45.0-73.0 years).

Mikhail et al. ⁽⁸⁾ research examined 146 eyes from 100 consecutive cases and discovered that the average age at presentation was 63.5 years old (range: 24–88 years).

Concerning HbA1c, the average HbA1c level was 7.54 (range: 6.50-9.10), which is comparable to the mean percentage of hemoglobin A1c of 8.2 reported by **Wong et al.** ⁽⁹⁾.

Sixty percent of the cases in the current research had hypertension, compared to ninety percent in the research by **Mikhail et al.** ⁽⁸⁾.

The baseline and final visual acuities in the current investigation were substantially lower in eyes with epiretinal membrane than in those without [(0.47 ± 0.10 vs 0.31 ± 0.07) and 0.72 ± 0.12 vs 0.46 ± 0.05] ($p < 0.001$) respectively]. Cases with clinically significant ERM at baseline had worse initial visual acuity than those without and their end visual acuity was considerably worse. According to research by **Wong et al.** ⁽⁹⁾ using mixed modeling removes the statistical significance of the difference in baseline visual acuity, but maintains a highly significant difference in end visual acuity ($p < 0.01$). These results are in line with earlier research showing that VMIA impairs visual acuity in a number of retinal disorders ⁽¹⁰⁾. Additionally, **Karaküçük and Okudan** ⁽¹¹⁾ discovered that there was no discernible difference in BCVA levels between the ERM (-) and ERM (+) cohorts at baseline, the first, second, or third months. In **Ercalik et al.** ⁽¹²⁾ They discovered that the baseline BCVA was considerably lower for cases in the ERM (+) cohorts (0.71 ± 0.27 vs. 0.46 ± 0.21 in the ERM (-) cohort; $p = 0.001$). Even while there was no discernible difference between the cohorts' BCVA improvement at the first-month follow up.

The mean baseline CRT in all of the cases examined in this investigation was 391.48 ± 83.70, which is close to the value reported in the research by **Wong et al.** ⁽⁹⁾, which came to 472. In our research, the mean baseline CRT was 377.06 µm in eyes without ERM and 428.57 µm in eyes with ERM. At the final measurement, the mean CRT was 291.83 µm in eyes without ERM and 325.14 µm in eyes with ERM. The differences in CRT between the two cohorts were not statistically significant ($p > 0.05$). **Wong et al.** ⁽⁹⁾ found that there was no difference in baseline CRT between the cohorts, but the final CRT was significantly worse

in the ERM cohort. In their research, **Cui et al.** ⁽⁷⁾ discovered no meaningful correlation between VMIA and CRT in DME. The mean baseline CRT was 458.1 ± 131.9 µm in eyes without ERM and 458.8 ± 112.2 µm in eyes with ERM, according to research by **Karaküçük and Okudan** ⁽¹¹⁾ with no discernible difference, the mean CRT at the end of the measurement was 308.6 ± 81.1 µm for eyes without ERM and 320.2 ± 87.4 µm for eyes with ERM. **Ercalik et al.** ⁽¹²⁾ discovered that between the ERM (+) and ERM (-) groups, the average baseline CMT values were 422.1 ± 82.8 µm and 439.5 ± 71.4 µm respectively with no statistically significant shift occurred (p -value of only 0.357). There was a significant decrease in CMT at the one-month postoperative follow-up in both groups ($p < 0.001$). According to CRT, the CRT significantly decreased from a mean of 391.48 µm to 301.16 µm ($P < 0.001$). This is in line with the findings of **Wong et al.** ⁽⁹⁾ who discovered that following treatment, the CRT significantly decreased from a mean of 472, 113 (270–856) µm to 345, 100 (203–758) ($p < 0.001$).

The BCVA in this research increased from a mean of 0.42 to 0.64 ($p < 0.001$) indicating a considerable improvement. From an average of 391.48 µm to 301.16 µm, the CRT dropped dramatically ($p < 0.001$). The mean IOP rose from 14.56 mmHg to 15.72 mmHg ($p < 0.001$). The final measurement and the existence of PVD were significantly correlated ($p = 0.046$). The impact of ERM on response to anti-VEGF drugs has only been examined in a small number of trials. In their research of 30 eyes given a single anti-VEGF injection, **Wu et al.** ⁽¹³⁾ discovered a negative impact on the Va and CRT response.

Following three intravitreal anti-VEGF injections (either 0.3 mg ranibizumab or 1.25 mg bevacizumab), **Yoon et al.** ⁽¹⁴⁾ investigated the effect of abnormalities at the vitreomacular interface in instances with DME. They found that neither the overall macular volume nor the decreased CRT differed significantly across the groups. The researchers also discovered that the greatest significant increase in BCVA was seen in diabetic individuals with a normal vitreomacular interface. This result demonstrated that a visual prognosis is negatively impacted by the presence of anomalies at the vitreomacular interface. Their research was severely hampered by the small number of cases (15 eyes out of 11 cases) and the fact that not every case received the identical anti-VEGF treatment. The low anti-VEGF response in diabetic cases with ERM may be caused by a number of factors. According to the first theory, increases in visual acuity may be limited by the extra structural harm that ERM does to the photoreceptors. Second, by blocking their penetration, ERM may lessen the effects of anti-VEGFs.

CONCLUSION

VMIA is linked to worse visual results in DME cases, which emphasized the importance of early

detection and treatment. The cross-sectional design, possible selection bias and small sample size are some of the research's drawbacks. To better understand VMIA's role in DME and enhance case care, future research should concentrate on longitudinal studies with bigger cohorts and objective measures. Notwithstanding these drawbacks, the research highlighted the need for all-encompassing treatment strategies by providing insightful information on the relationship between VMIA and other parameters in DME cases receiving IVI of ranibizumab.

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