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CLINICAL AND OPTICAL COHERENCE TOMOGRAPHY PREDICTORS OF VISUAL OUTCOME FOLLOWING INTRAVITREAL ANTI-VEGF THERAPY FOR DIABETIC MACULAR EDEMA

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ABSTRACT

Background: Diabetic macular edema is an important cause of visual impairment among patients with diabetes mellitus. **Objective:** To determine the clinical and optical coherence tomography predictors of visual outcome following intravitreal aflibercept therapy in patients with diabetic macular edema. **Methods:** This prospective observational study was conducted at Ophthalmology department, Services Hospital,Lahore from July 2022 to February 2023**,** ncluded 135 patients with diabetic macular edema treated with intravitreal aflibercept. Baseline demographic and clinical characteristics, best-corrected visual acuity, glycemic status, duration of diabetes and diabetic macular edema, and OCT findings were recorded. **Results:** Among 135 patients with diabetic macular edema, the mean age was 57.8 ± 9.6 years, 56.3% were male, the mean duration of diabetes was 11.9 ± 5.7 years, and the mean HbA1c was 8.4 ± 1.3%. Intraretinal fluid/cystoid spaces were the most common OCT finding, present in 90.4% of patients, followed by hyperreflective foci in 54.1%, DRIL in 37.8%, subretinal fluid in 35.6%, ellipsoid zone disruption in 34.1%, and external limiting membrane disruption in 28.9%. Following intravitreal aflibercept therapy, mean BCVA improved significantly from 0.68 ± 0.24 to 0.42 ± 0.21 logMAR, while central subfield thickness decreased from 438.6 ± 82.4 µm to 312.7 ± 61.5 µm (both $p < 0.001$). **Conclusion:** Intravitreal aflibercept therapy was associated with significant functional and anatomical improvement in diabetic macular edema. Clinical factors and retinal microstructural OCT biomarkers, particularly DRIL and integrity of the ellipsoid zone and external limiting membrane, may be useful for predicting visual prognosis and individualizing patient management.

KEYWORDS: Diabetic macular edema, aflibercept, anti-VEGF, optical coherence tomography, visual acuity

INTRODUCTION

Diabetic macular edema (DME) is a major vision-threatening complication of diabetic retinopathy, and an important cause of vision impairment in diabetic patients. It is caused by disruption of the blood-retinal barrier, hyperpermeability of the blood vessels and leakage of extra-cellular fluid into the macula [1]. There are multiple mechanisms that chronic hyperglycemia causes microvascular damage, such as oxidative stress, inflammation, endothelial dysfunction, and upregulation of vascular endothelial growth factor (VEGF) [2]. The changes cause the vessels in the retina to leak, which causes the macula to thicken. Uncontrolled macular edema can lead to permanent loss of central vision, structural changes in the retinal tissue and irreversible loss of photoreceptor function [3]. As the prevalence and duration of diabetes mellitus have increased so has the burden of DME. Macular edema can occur, or be more severe in patients with poor glycemic control, hypertension, nephropathy, dyslipidaemia and advanced diabetic retinopathy. Central vision is critical for reading, driving, facial recognition, and other tasks of daily living and DME can have a profound impact on functional independence and quality of life. Therefore, early identification and proper management is important to prevent permanent visual disability [4].

Intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy has revolutionized the treatment of DME. These agents have anti-VEGF activities, inhibiting the pathways that lead to retinal edema and decreased vascular permeability; they are now well established as first-line therapy in patients with DME and vision loss who have involvement of the central retina [5]. These are commonly used agents: bevacizumab, ranibizumab, aflibercept and newer anti-VEGF agents. Many patients have significant improvement in their best-corrected visual acuity and decrease in their central retinal thickness after repeated intravitreal injections. Treatments, however, are generally repeated and follow-up close, and could have a significant impact on patients and health systems [6]. Although anti-VEGF therapy has been shown to be effective, there is a wide range of visual recovery between patients. In some patients, improvement in visual acuity and retinal morphology is significant and others show only marginal or minimal functional gains despite decrease in macular thickness [7]. Improvement of the anatomical structure does not always directly reflect visual improvement, indicating that such improvement may

be influenced by baseline patient characteristics and/or structural retinal damage. This variability has made it necessary to determine reliable predictors of treatment response [8].
Variations in visual outcomes after anti-VEGF treatment may be related to clinical factors. Response may vary according to baseline visual acuity, age, duration of diabetes, glycemic control, duration of macular edema, severity of DR, systemic hypertension, renal disease, and prior ocular treatments [9]. There is a certain degree of retinal functional recovery that may be greater when the patients are seen with relatively preserved retinal structure, and less when they have had long-standing edema and chronic damage to the retina. Optical coherence tomography (OCT) is a vital imaging tool for the diagnosis, monitoring and management of DME [10]. It is a non-invasive method that allows for high-resolution cross-sectional images of the retina and gives a quantitative measurement of the thickness and shape of the macula. In addition to the CRT, OCT may allow for the detection of a number of microstructural characteristics that have prognostic significance [11]. These include the presence and size of intraretinal cystoid spaces, presence of subretinal fluid, disorganization of the retinal inner layers, hyperreflectivity of foci, integrity of the ellipsoid zone, disruption of the external limiting membrane, alterations in the retinal layer architecture, and abnormalities of the vitreomacular interface [12].

Objective

To determine the clinical and optical coherence tomography predictors of visual outcome following intravitreal aflibercept therapy in patients with diabetic macular edema.

METHODOLOGY

This prospective observational study was conducted at Ophthalmology department, Services Hospital,Lahore from July 2022 to February 2023. A total of 135 patients with diabetic macular edema (DME) who were planned for intravitreal anti-vascular endothelial growth factor therapy were included in the study. Patients included were 18 years or older with either type 1 or type 2 diabetes mellitus (DM) and had center involving diabetic macular edema (cDME) established by optical coherence tomography (OCT), and impaired vision due to DME. This final analysis included only patients who received intravitreal aflibercept and underwent the recommended follow-up. Patients were excluded who had other causes for macular edema besides diabetes, significant media opacity that prevented adequate OCT imaging, advanced glaucoma, retinal vascular occlusion, age-related macular degeneration, or other retinal or optic nerve disorders that could affect visual acuity, or had undergone vitreoretinal surgery or other prior retinal surgery. Patients who were recently treated with intravitreal anti-VEGF therapy, intravitreal corticosteroids, or laser therapy to their macula prior to enrollment were also excluded.

Data collection

Following informed consent, demographic and clinical data were obtained such as age, gender, diabetes mellitus duration, diabetes mellitus type, diabetes macular edema duration, glycemic control, hypertension, and other relevant systemic comorbidities. The best corrected visual acuity (BCVA) was measured using a standard visual acuity chart and converted to the logarithm of the minimum angle of resolution (logMAR) for analysis. All patients had intraocular pressure, anterior segment and dilated fundus examination. At baseline and at follow-up, spectral-domain OCT was conducted. Morphological features and central subfield thickness (CST) of DME was documented. Potential predictors for a good visual outcome evaluated via the OCT included central retinal thickness, intraretinal fluid or cystoid spaces, subretinal fluid, disorganization of the inner retinal layers, hyperreflective foci, integrity or disruption of the ellipsoid zone, external limiting membrane integrity, and vitreomacular interface abnormalities. The same set of criteria was used for the analysis of all OCT images. Intravitreal aflibercept was administered as anti-VEGF treatment under aseptic condition according to the treatment protocol of the institution, to all enrolled patients. Patients followed at regular visits, injection of aflibercept performed by qualified ophthalmologist. Each patient's number and timing of injections were recorded. The parameters of BCVA, clinical examination and OCT were re-evaluated at follow-up. The main result was an improvement in visual acuity after aflibercept intravitreal injection. Changes in the BCVA from baseline to the final follow-up visit were noted. Secondary outcomes included change in central retinal thickness and other OCT morphological features. Baseline clinical and OCT parameters were assessed in relation to clinical outcomes.

Data Analysis

The data were coded and analysed by using SPSS v26.0. For quantitative data, the result was presented as mean ± SD for normally distributed data and median (IQR) for non-normally distribution data. Categorical variables were described in terms of frequency and percentage. The Shapiro–Wilk test was used to determine normality. BCVA and CRT were compared before and after the treatment with the paired-samples t-test or Wilcoxon signed-rank test. Pearson or Spearman correlation was used to determine associations between continuous baseline variables and change in BCVA. A p-value of <0.05 was deemed as statistically significant.

Results

Data were collected from 135 patients and mean age of the 135 patients with diabetic macular edema was 57.8 ± 9.6 years. Males constituted 76 (56.3%) of the study population, while 59 (43.7%) were females. The mean duration of diabetes was 11.9 ± 5.7 years, mean HbA1c was 8.4 ± 1.3%, and hypertension was present in 79 (58.5%) patients. The mean duration of diabetic macular edema was 9.7 ± 6.2 months. At baseline, the mean best-corrected visual acuity was 0.68 ± 0.24 logMAR, while the mean central subfield thickness was 438.6 ± 82.4 µm.

Table 1. Baseline Clinical Characteristics of Patients with Diabetic Macular Edema (n = 135)

Variable	n (%) / Mean ± SD
Age, years	57.8 ± 9.6
Gender	
Male	76 (56.3%)
Female	59 (43.7%)
Duration of diabetes, years	11.9 ± 5.7
HbA1c, %	8.4 ± 1.3
Hypertension	79 (58.5%)
Duration of DME, months	9.7 ± 6.2
Baseline BCVA, logMAR	0.68 ± 0.24
Baseline central subfield thickness, µm	438.6 ± 82.4

Intraretinal fluid or cystoid spaces were the most frequent finding, observed in 122 (90.4%) patients, followed by hyperreflective foci in 73 (54.1%). Disorganization of the retinal inner layers was present in 51 (37.8%) patients, while subretinal fluid was observed in 48 (35.6%). Ellipsoid zone disruption and external limiting membrane disruption were identified in 46 (34.1%) and 39 (28.9%) patients, respectively.

Table 2. Baseline Optical Coherence Tomography Findings (n = 135)

OCT Finding	n (%)
Intraretinal fluid/cystoid spaces	122 (90.4%)
Subretinal fluid	48 (35.6%)
Disorganization of retinal inner layers (DRIL)	51 (37.8%)
Hyperreflective foci	73 (54.1%)
Ellipsoid zone disruption	46 (34.1%)
External limiting membrane disruption	39 (28.9%)
Vitreomacular interface abnormality	17 (12.6%)

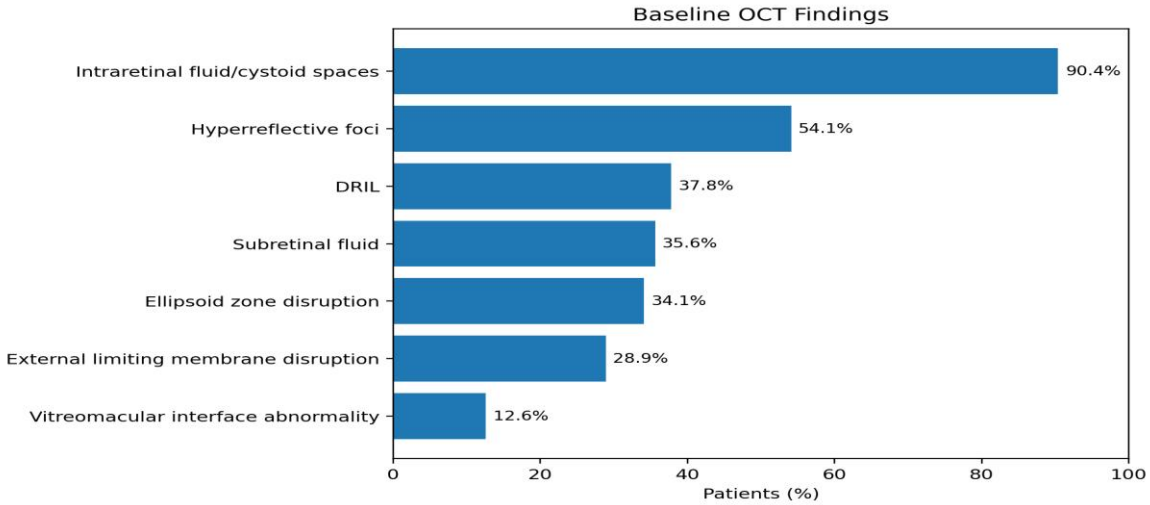


Figure 1. Baseline OCT findings in patients with diabetic macular edema.

Mean BCVA improved from 0.68 ± 0.24 logMAR at baseline to 0.42 ± 0.21 logMAR at final follow-up ($p < 0.001$). Similarly, mean central subfield thickness decreased significantly from 438.6 ± 82.4 µm to 312.7 ± 61.5 µm ($p < 0.001$), demonstrating a significant reduction in macular edema following treatment.

Table 3. Visual and Anatomical Outcomes Following Intravitreal Aflibercept Therapy

Outcome	Baseline Mean ± SD	Final Follow-up Mean ± SD	p-value
BCVA, logMAR	0.68 ± 0.24	0.42 ± 0.21	<0.001
Central subfield thickness, µm	438.6 ± 82.4	312.7 ± 61.5	<0.001

Baseline BCVA was positively associated with visual improvement ($\beta = 0.312$, $p < 0.001$), while increasing age ($\beta = -0.003$, $p = 0.031$), longer duration of DME ($\beta = -0.012$, $p = 0.018$), higher HbA1c ($\beta = -0.026$, $p = 0.041$), and presence of DRIL ($\beta = -0.142$, $p = 0.003$) were significantly associated with poorer visual improvement. An intact ellipsoid zone ($\beta = 0.176$, $p < 0.001$) and intact external limiting membrane ($\beta = 0.119$, $p = 0.009$) were significantly associated with better visual outcome.

Table 4. Multivariable Analysis of Clinical and OCT Predictors of Visual Improvement Following Aflibercept Therapy

Predictor	Regression coefficient (β)	p-value
Age	-0.003	0.031
Baseline BCVA	0.312	<0.001
Duration of DME	-0.012	0.018
HbA1c	-0.026	0.041
Baseline central subfield thickness	0.001	0.214
Presence of subretinal fluid	0.038	0.287
DRIL present	-0.142	0.003
Hyperreflective foci present	-0.057	0.164
Ellipsoid zone intact	0.176	<0.001
External limiting membrane intact	0.119	0.009

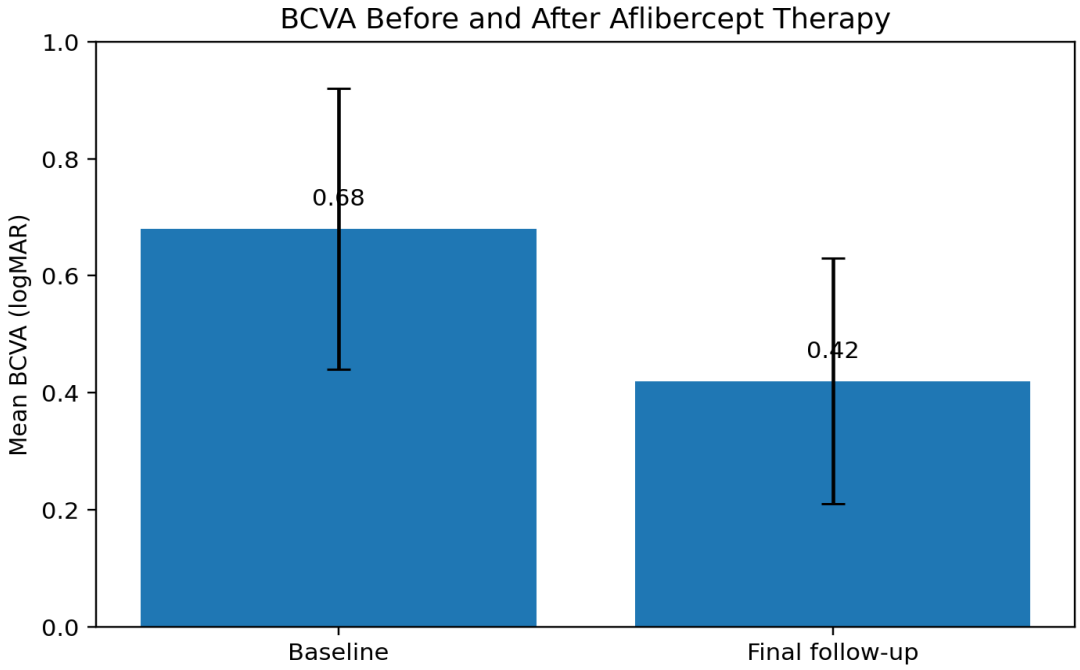


Figure 2. Change in best-corrected visual acuity following intravitreal aflibercept therapy (p < 0.001)

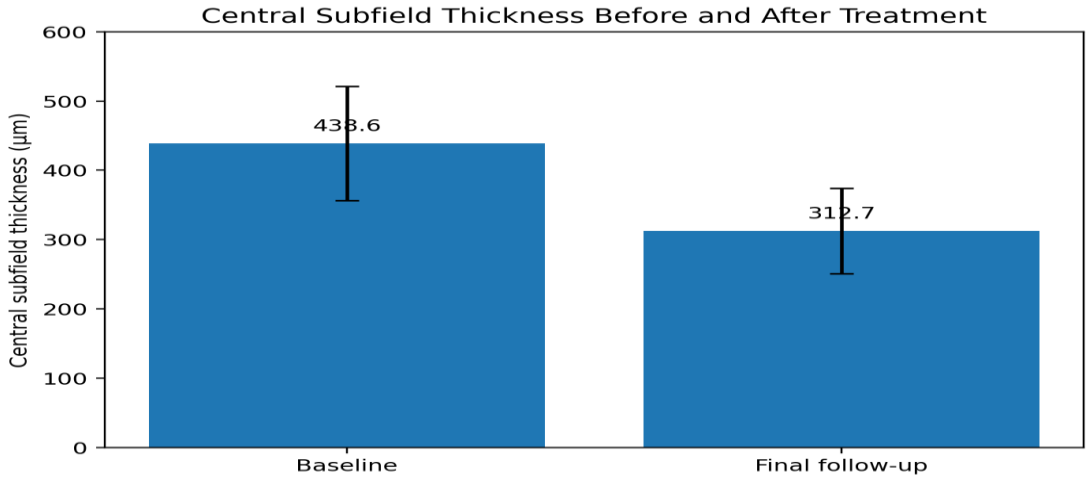


Figure 3. Change in central subfield thickness following intravitreal aflibercept therapy (p < 0.001).

DISCUSSION

In the current study, clinical parameters and OCT features to predict visual outcome after IVA in DME were assessed. The anatomical and functional results of the treatment were significantly improved. The mean best-corrected visual acuity at baseline was 0.68 ± 0.24 logMAR which improved to 0.42 ± 0.21 logMAR at final follow-up, while the mean central subfield thickness was 438.6 ± 82.4 µm at baseline, and 312.7 ± 61.5 µm at final follow-up. The results here support aflibercept's ability to diminish macular edema and enhance vision in

DME patients. In this study, 68.1% of the patients had a clinically relevant improvement in visual acuity. Even with the anatomical recovery, however, the amount of visual recovery was quite different among patients. This variation underscores the fact that recovery after a decrease of retinal thickness alone is not sufficient for functional recovery. The integrity of retinal microstructures, chronicity of edema, baseline visual function and systemic metabolic control influence the visual outcome of DME [13].

Of the clinical parameters, baseline BCVA was significantly correlated with subsequent visual improvement. Patients with less functional loss of visual function and visual structure tended to have more functional recovery potential. The time of DME was also a significant predictor, with longer duration of macular edema (MO) being correlated with worse visual improvement. Even with the decrease in retinal fluid after anti-VEGF treatment, chronic retinal edema can lead to irreversible damage to the photoreceptors and neural retina, which will not improve. Glycemic control also affected treatment outcome [14]. Long-term aflibercept treatment was associated with worse visual improvement with increased HbA1c levels. Chronic hyperglycemia leads to endothelial dysfunction, inflammation, vascular permeability and sequential microvascular lesions of the retina. So, systemic diabetes control is still the key along with intravitreal treatment. Again, the relatively small association of age with visual outcome is significant, but not as impactful as some of the structural OCT parameters [15].

The value of the OCT biomarkers was of great prognostic importance. Logical disruption of the inner layers of the retina was a strong predictor of poor visual outcome. DRIL is associated with disruption of normal retinal architecture and may be a sign of damage to pathways for the transmission of visual signals [16]. For patients without DRIL, however, it seemed that those who had better functional potential after macular edema resolved. This discovery is in line with what has been reported in other papers that DRIL can be an important OCT biomarker for prognosis in patients treated with anti-VEGF treatment. The results highlight the need for OCT diagnosis in DME to go beyond the measurement of central retinal thickness. Other more meaningful prognostic information can be gained from the evaluation of DRIL, ellipsoid zone integrity, external limiting membrane integrity, characteristics of fluid in the retina, and other microstructural features [17]. The use of these imaging biomarkers along with clinical parameters like baseline BCVA, the duration of DME, glycemic control and age might enhance the prediction of individual treatment response [18]. Overall, intravitreal aflibercept led to substantial improvement in visual acuity and decrease in central retinal thickness. Nevertheless, systemic and retinal structural factors had both an effect on visual outcome. The baseline visual status, duration of DME, HbA1c, and absence of DRIL were significantly associated with better visual outcomes. Anticipating these predictors prior to treatment could assist clinicians in giving more precise prognostic counseling and tailoring treatment and follow-up [19,20].

There are some limitations in the present study. The number of participants was relatively low and the study was conducted at a single center, which may affect the generalizability of the results. Follow-up period may also be too short to evaluate long-term modifications of retinal structure and visual function. Also, the response to treatment can be affected by treatment compliance, the number of injections, whether there is control of systemic disease, and other ocular features. More and larger multicenter studies with standardized treatment protocol and longer follow-up are recommended to validate the prognostic role of these clinical and OCT biomarkers.

CONCLUSION

Aflibercept intravitreal drug therapy led to substantial improvements in visual acuity and in central subfield thickness in DME patients. Good visual outcomes were correlated with better VA at baseline, shorter duration of DME, lower HbA1c level, lack of inner retinal layer disorganization, and maintenance of the Ellipsoid zone and External limiting membrane. Central thickness did not predict functional recovery on its own, suggesting that the integrity of the retinal microstructures is of key importance in predicting treatment response. Thus, analysis of these clinical and OCT biomarkers may be useful for predicting visual outcome, counseling, and tailoring treatment and follow-up in the patient with DME treated with intravitreal aflibercept.

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