The Baseline Ocular Coherence Tomography Morphology of Diabetic Macular Edema as a Prognostic Factor for Response to Anti-Vascular Endothelial Growth Factor

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Purpose: Diabetic retinopathy is a major complications of diabetes mellitus and remains a leading cause for visual loss in working-age populations. This work aims to evaluate the difference in response to anti-vascular endothelial growth factor agents based on the baseline ocular coherence tomography in patients with diabetic macular edema.

Methods: In this retrospective case-control study, the study population was evaluated and divided based on their baseline ocular coherence tomography(OCT) morphological features into cystoid, diffuse and mixed groups. Furthermore, changes in ganglionic cell- inner plexiform layer thickness, nerve fiber layer thickness, and central macular thickness and visual acuity in patients who received intravitreal injections of anti- vascular endothelial growth factor (anti-VEGF) agents for diabetic macular edema were measured. The difference in these outcome measures were studied before and after commencement of treatment for an average follow-up period of 1-year.

Results: Fifty-six eyes were included in this study. The mean age was 60.55±10.47years (Range (25-81) years); there were 35 males (62.5%) and 21 females (37.5%). The mean duration of follow up was 13.8 months (Range 12.0- 22.0 months) with a mean number of 4.38±2.15 injections throughout follow up. The ocular coherence tomographic morphology of diabetic macular edema was cystoid (42.9%), diffuse (48.2%), and mixed (8.9%). Post hoc comparisons using the Tukey HSD test showed that the mean changes in central macular thickness in the cystoid group (93.21±145.82 µm) was significantly different from the mean differences in thickness in either diffuse group (15.26±140.36 µm) or mixed group (34.4±89.71) (p=0.02).

Conclusion: Eyes with baseline cystoid diabetic macular edema treated with intravitreal injections of anti-VEGFs were associated with significantly more reduction in central macular thickness after treatment when compared to diffuse or mixed morphology. This finding may indicate that patients who present with cystoid macular edema have a favorable response to anti- VEGFs.

INTRODUCTION

Diabetes mellitus is a major global health epidemic, and diabetic macular edema is the most common cause of vision loss in the working-age population[1,2]. Vascular endothelial growth factor (VEGF) plays a vital role in the development of diabetic macular edema (DME) as well as the development of microangiopathy, angiogenesis and neovascularization[2-5]. The pathogenesis of diabetic macular edema is multifactorial and includes oxidative stress, sorbitol accumulation intracellularly, endothelial cell damage, breakdown of the retinal blood barrier, dilated capillaries, microaneurysm formation, and loss of pericytes. Subsequently, vascular leakage of lipids and serum proteins into the intraretinal space leads to increased macular thickness and DME[2,3]. Nowadays, intravitreal anti-VEGF agents are the preferred first-line treatment for DME[6]. Spectral domain optical coherence tomography (SD-OCT) was documented to be a practical approach in measuring retinal thickness and detecting morphological changes in vivo accurately; thus, making the longitudinal study of disease-related retinal alteration easy and precise[7]. A wide range of morphology patterns of DME are clinically present even though all patients have the same underlying disease[8-10]. DME was classified based on OCT scans into sponge-like diffuse retinal thickness (SLDRT), cystoids macular edema (CME), and sub-retinal fluid (SRF) and mixed type[11]. OCT characteristics are predictive for the treatment response in patients with age-related macular degeneration[12].

The aim of this study was to evaluate the differences in OCT measurements and visual acuity before and after treatment with Anti-VEGFs between subtypes of OCT morphology in DME patients.

MATERIALS AND METHODS

Study Design: This retrospective case-control study was approved by the Institutional Review Board (IRB) of Jordan University Hospital. The study evaluated the relationship between treatment outcomes in eyes with diabetic macular edema (DME) receiving intravitreal anti-vascular endothelial growth factor (VEGF) injections and baseline ocular coherence tomography (OCT) morphological features.

Patients were divided into three groups according to their baseline OCT morphological features: cystoid, diffuse, and mixed. Furthermore, changes in GCL-IPL thickness, nerve fiber layer thickness, central macular thickness, and visual acuity in patients who received intravitreal injections of anti-VEGF agents' (bevacizumab, ranibizumab, or aflibercept) for diabetic macular edema were measured. Data obtained was compared at baseline and after receiving multiple anti-VEGFs

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injections. Findings were compared in intragroup and intergroup. All patients were treated at Jordan University Hospital. They were followed clinically for at least one year with a pretreatment OCT imaging and follow up OCT imaging at 12 months.

Participants: Patients who received anti-VEGF agents for DME from March 2017 to September 2019 were retrieved from the hospital archives. Only those with a baseline OCT showing centrally involving macular edema were included in the study. The centrally involving DME was defined clinically as macular thickening and exudation involving the fovea confirmed by OCT. Subsequently, all patients received monthly anti-VEGF injections for the first three months followed by a PRN protocol. All patients had OCT imaging of the macula and NFL at 1-year follow up.

Patients with the following conditions were excluded from the study: 1) any ocular condition that could affect the retinal thickness, including retinal detachment, vitrectomy, glaucoma, abnormal peripapillary nerve fiber layer, or central laser; 2) Myopia more than three diopters; 3) other vitreoretinal conditions such as age-related macular degeneration, uveitis, epiretinal membrane, or vireo-macular traction; 4) systemic diseases like collagen vascular disease, neurological, or thyroid problems; or 5) cataract surgery during the investigated period. Eyes with unsatisfactory OCT image quality initially or at follow up were also excluded.

Variables: All study participants had a detailed clinical examination at baseline, including ETDRS letters visual acuity examination to determine best-corrected visual acuity (BCVA), intraocular pressure measurement, and dilated fundus exam. All cases received at least three injections of anti-VEGFs during the 12-month follow up period.

Using the same equipment, OCT imaging was obtained of the central and paracentral macular area, as well as, thickness measurements of the ganglion cell-inner plexiform layer (GC-IPL) and the nerve fiber layer (NFL) before the initiation of treatment and at 12-month follow up.

Regarding macular thickness, an 8x8 mm macular area focused around the fovea thickness was recorded using the OPTOPOL SD-OCT machine, Nevonx (SD-OCT version 7.2.0, OPTOPOL Technology Sp. z.o.o., Poland). The central foveal and the average macular thicknesses were recorded, with foveal thickness segmented by a single retinal specialist. The OCT machine differentiated retinal tissue interfaces and detected the GC-IPL thickness. The RNFL thickness measurements (diameter 3.5 mm, 768 A-scans) were also obtained. The device's eye-tracking system compensated for eye movements. The automatic re-scan function using a reference point was activated to minimize variation in allocating the acquisition protocols to the follow up sessions. RNFL thickness from the internal limiting membrane's inner margin to the outer margin of the RNFL layer was automatically segmented using OCT. Evaluating and grading morphological changes were carried by a retinal specialist using the OCT's cross-sectional scans before initiating treatment and at 12-months follow-up. The morphological patterns were divided into cystoid macular edema (based on the presence of cystic changes in the inner nuclear layer), diffuse macular edema (non-cystic swelling in the outer nuclear layer), or mixed type (a combination of both) based on the pattern of macular edema seen on OCT.

Statistical analysis: SPSS version 21.0 (Chicago, USA) was used for analysis. The mean (± standard deviation) to describe continuous variables (i.e., age and measurements), and count (frequency) to show other nominal variables (i.e., gender).

A paired sample t-test was used to analyze the mean difference in OCT measurements at baseline and follow up. The data was presented in mean (95% confidence interval (CI)). An independent sample t-test was performed to analyze the mean difference between OCT measurements and visual acuity in treated patients and OCT morphology subtypes. The one-way analysis of variance (ANOVA) test was used to analyze the mean difference in changes in OCT measurements and visual acuity between different OCT morphology subtypes. The Tukey's honestly significant difference test (Tukey's HSD) was used to compare mean differences of OCT measurements, visual acuity, and OCT morphology subtypes. All underlying assumptions were met unless otherwise indicated. We adopted a p-value of 0.05 as a significant threshold.

RESULTS

Fifty-six eyes of a random sample met the inclusion criteria. Patients' demographics and comorbidities were analyzed and tabulated. A total of 35 males (62.5%) and 21 females (37.5%) were included in the study giving a male: female ratio of 1.67:1. The mean age was 60.55 years with a standard deviation of 10.47years (range 25-81 years). Most patients had received anti-VEGF treatment (76.8%) when recruited, while the remaining were treatment-naïve (23.2%). The follow up duration ranged between 12-22 months with a mean of 13.8 months. The mean number (Standard Deviation) of injections were 4.38(2.15) injections over the investigated period. The baseline DME morphology incidence was 42.9%, 48.2%, and 8.9% for cystoid, diffuse, and mixed, respectively. The average HbA1c was 7.71. The patients' characteristics are summarized in table1.

Table 1: Demographic and clinical characteristics of study subjects

Mean±SD	%	N	
60.55±10.47			Age (years)
			Gender
	62.5	35	Male
	37.5	21	Female
			HTN
	85.7	48	Yes
	14.3	8	No
			IHD
	19.6	11	Yes
	80.4	45	No
			History of anti-VEGF
	76.8	43	Not Naïve
	23.2	13	Naïve
			Morphology of DME
	42.9	24	Cystoid
	48.2	27	Diffuse
	8.9	5	Mixed
7.71±1.74			HbA1c (%)
4.38±2.15			Number of injections
13.77±2.23			Duration of follow up (months)

SD: Standard deviation; HTN: Hypertension; IHD: Ischemic heart disease; VEGF: Vascular endothelial Growth factor

There was no statistically significant difference between the mean OCT central macular thickness measurements, visual acuity and OCT morphology subtypes between naïve patients and previously treated patients.

Table 2 shows a comparison between OCT measurements and visual acuity at baseline and follow up. The mean baseline visual acuity (EDTRS) of the treated eye was 80±12.5 ETDRS letters and improved to 89±10.5 at 12 months ($p < 0.05$). An overall significant difference in central macula thickness at baseline 392.39±118.64 µm and follow up 347.80±125.77 µm with mean reduction 44.59±149.38 µm ($p < 0.05$)

was found. Furthermore, an overall statistically significant reduction in macular retinal nerve fiber layer at baseline 40.34±7.53 µm and at follow up 38.04±7.02 µm with mean reduction 2.304±6.97 µm ($p<0.05$) was detected. Moreover, a statistically significant difference between macular ganglion cell-inner plexiform layer at baseline and at follow up was observed. Values of cases for GL-IPL (p=0.029.) from 89±13 µm to 84±14.7 µm.

Table 2: Comparison between OCT measurements and visual acuity at baseline and at follow up

	follow up > 12 months	Baseline	
P*	Mean±SD	Mean±SD	
0.030	347.80±125.77	392.39±118.64	CMT (µm)
0.057	354.59±69.26	375.96±74.96	AMT (µm)
0.017	38.04±7.02	40.34±7.53	Macular NFL (µm)
0.029	84.04±14.73	89.13±13	Macular GC-IPL (µm)
0.050	89+/10.5	80+/- 12.5	Visual acuity (LogMAR)

SD: Standard deviation; *paired sample t-test; CMT: Central macular thickness; AMT: Average macular thickness; NFL: Nerve fiber layer; GC-IPL: Ganglion cell-inner plexiform layer.

Table 3 shows changes in central macular thickness, average macular thickness, nerve fiber layer thickness, ganglion cell-inner plexiform layer thickness, and gains in visual acuity in cystoid, spongiform and mixed type baseline OCT morphology of DME.

Table 3: Comparison between OCT morphology of DME with changing OCT

	Mixed	Diffuse	Cystoid	
P*	Mean±SD	Mean±SD	Mean±SD	
0.01	34.4±89.71	-15.26±140.36	93.21±145.82	changing in CMT (µm)
0.14	19.6±32.85	0.07±90.98	45.71±73.91	changing in AMT (µm)
0.014	8.80±11.30	-0.04±6.75	3.58±5.02	changing in Macular NFL (µm)
0.016	0.60±14.59	-1.44±15.27	5.58±9.69	changing in Macular GC-IPL (µm)
0.001	-0.5±0.1	-0.2±0.2	-2.5±1	changing in Visual acuity (ETDRS letters)

Post hoc comparisons using the Tukey HSD test indicated that average changes in central macular thickness in the cystoid group (93.21±145.82 µm) was significantly different from the mean changes in thickness in either diffuse group (15.26±140.36 µm) or mixed group (34.4±89.71) (p=0.02).

A significant reduction in the mean macular nerve fiber layer thickness in mixed group 8.80±11.30 µm was detected compared to the diffuse group -0.04±6.75 µm (p=0.02) as shown in Figure 1.

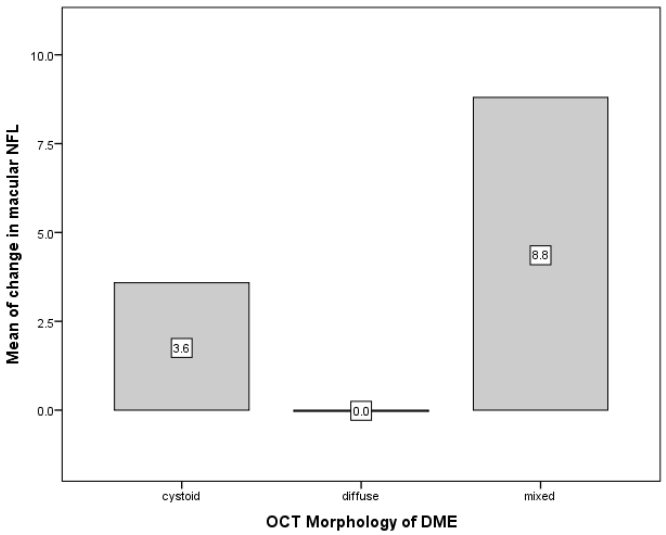

Figure 1: Changes in macular NFL in cystoid, diffuse and mixed morphology; a significant reduction in the mean macular nerve fiber layer thickness in mixed group 8.80±11.30 µm was detected compared to the diffuse group -0.04±6.75 µm (p=0.02) and cystoid group(3.58±5.02um) p=0.014

There was a statistically significant relationship between changes in central macular thickness and macular nerve fiber layer between groups ($p<0.05$). Regarding measurements and visual acuity; the difference in visual acuity was only significant with the difference in average macular thickness (Pearson coefficient = 0.481, p= 0.0001) and the difference in central macular thickness, Pearson coefficient =0.433, p=0.001) as shown in table 4.

Table 4: Pearson correlation between changes in average macular thickness, central macular thickness, macular NFL, and GL-IPL thickness.

		Difference in Visual acuity
Average macular thickness	Pearson Correlation	.481**
	Sig. (2-tailed)	.000
Central macular thickness	Pearson Correlation	.433**
	Sig. (2-tailed)	.001
Macular NFL	Pearson Correlation	.194
	Sig. (2-tailed)	.152
(GL-IPL)	Pearson Correlation	.260
	Sig. (2-tailed)	.053

Furthermore, the Anova test shows a significant difference in the average macular thickness, macular GC-IPL, and visual acuity gain between the groups ($P<0.05$). In which the cystoid group was significantly associated with more reduction in central macular thickness (p=0.01), macular RNFL (p=.014), GC-IPL thickness (p=0.016), and it was associated with a more significant gain of ETDRS letters (p=0.001).

DISCUSSION

In this set of data, the overall treatment response, assessed as a change in BCVA and central retinal thickness (CRT), was in accordance with previous studies, which have shown the clinical efficacy of anti-VEGFs for DME therapy[11].

Additionally, the study demonstrated that baseline cystoid morphology in eyes with diabetic macular edema treated with intravitreal injections of anti-VEGFs were associated with significantly more reduction in central macular thickness after treatment with anti-VEGFs. This finding may indicate that patients who present with cystoid macular edema have a favorable response to treatment with anti- VEGFs. OCT features were predictive of response to therapy in age-related macular degenerations[12]. In general, morphologic features in DME have been described in detail, and some characteristics graded at baseline were found to be associated with better treatment response to DME therapy. However, the long-term response was not reported and the follow up period was less than 12 months[13-16]. One study evaluated the short-term efficacy of intravitreal bevacizumab and posterior sub-tenon triamcinolone injections (PSTI) on the basis of spectral-domain optical coherence tomography (SD-OCT) patterns in diabetic macular edema. It was concluded that, in DME patients' eyes with serous retinal detachment, intravitreal bevacizumab (IVB) achieved a more significant reduction of serous retinal detachment compared to posterior sub-tenon injection of triamcinolone. Additionally, it was suggested that the classification of DME based on OCT findings might be useful to predict responses to IVB or PSTI treatments. However, this study only had a follow up of one month[16]. It was also found that patients with DME, a good BCVA, sub-macular fluid, no cardiovascular disease, no scatter photocoagulation, and male gender were good responders to ranibizumab treatment to the sham group. On the other hand, intraretinal cysts, severe thickening, or renal disease responded to sham treatment poorly when left untreated[17]. In diabetic macular edema, serous retinal detachment and large outer nuclear cysts are the two morphologic changes with the greatest negative impact on retinal function because protein-rich subretinal fluid affects both oxygenation and elimination of metabolites from the photoreceptor layer, thus decreasing retinal sensitivity. Additionally, in DME, subretinal fluid accumulation and large outer nuclear cyst are seen as one of the latest steps in the development of diabetic macular disease since; it highlights the final step in retinal layer changes secondary to intraretinal vascular leakage. Subretinal fluid and inner nuclear layer cystoid spaces resolved early in the treatment course, while fluid accumulation in the outer nuclear layer seemed to be more persistent when treated with both ranibizumab and triamcinolone[18].Enadi et al. found mixed DME eyes treated with dexamethasone implant relapsed later and frequently without subretinal fluid compared to eyes with intraretinal cysts[19].

CONCLUSION

The study's primary limitation is its retrospective nature and the single center design, including a relatively small number of study patients; therefore, a prospective study with a more extensive patient series is required to confirm the study's findings. The study population is larger than most previously published research data, and the hospital is a tertiary referral hospital.

In conclusion, this descriptive data of morphologic characteristics in DME indicate the vast diversity of diabetic macular edema patterns that cannot be expressed in central retinal thickness alone. In addition, it gives a detailed insight into the treatment response to anti-VEGFs for over one year. Predicting morphological features and detailed retinal image analyses might add to individualized treatment strategies by detecting reliable and predictive morphological factors allowing physicians to counsel their patients more accurately about the possibility of improvements after treatment with anti- VEGFs.

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Competing Interest: None.

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Ethical Approval: Ethical Committee Approval was needed and approved.

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