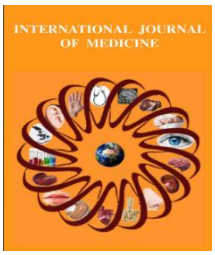

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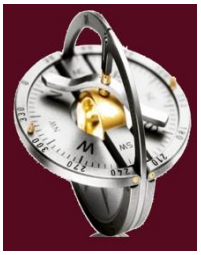

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Original Research

Correlation of Optical Coherence Tomography (OCT) Biomarkers with Visual Outcomes in Diabetic Macular Edema.

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Abstract

Background: Diabetic macular edema (DME) is a leading cause of vision loss in diabetes. Central subfield thickness (CST) correlates only modestly with visual acuity, prompting interest in microstructural OCT biomarkers. This study correlated baseline OCT biomarkers with visual outcomes in centre-involved DME treated with anti-VEGF therapy. *Methods:* In this prospective observational cohort, 96 eyes of 80 patients with treatment-naïve centre-involved DME underwent baseline spectral-domain OCT with grading of CST, disorganization of the retinal inner layers (DRIL), ellipsoid zone (EZ) and external limiting membrane (ELM) disruption, hyperreflective foci (HRF) and subretinal fluid (SRF). BCVA (logMAR) was recorded at baseline and at six months after three loading anti-VEGF injections followed by a pro re nata regimen. Correlation and multivariable regression analyses were performed. *Results:* DRIL and EZ disruption correlated most strongly with BCVA at baseline and six months (6-month ρ = +0.61 and +0.59, respectively), whereas CST correlated weakly (ρ = +0.22). Eyes with DRIL, EZ or ELM disruption and high HRF had significantly worse six-month BCVA, while SRF was associated with better outcomes. On multivariable regression, DRIL extent, EZ disruption and baseline BCVA independently predicted six-month BCVA ($R^2 = 0.52$); CST was not an independent predictor. *Conclusion:* Microstructural OCT biomarkers–particularly DRIL and photoreceptor/outer-retinal integrity–correlate with and predict visual outcomes in DME more reliably than central thickness, and may aid prognostication and individualised management.

Keywords: *diabetic macular edema; optical coherence tomography; biomarkers; disorganization of retinal inner layers; ellipsoid zone; visual acuity.*

Introduction

Diabetic macular edema (DME) is the principal cause of central vision loss in people with diabetes mellitus and can occur at any stage of diabetic retinopathy [1,15]. It arises from hyperglycaemia-induced breakdown of the blood-retinal barrier, with leakage of fluid and plasma constituents into the macula, producing retinal thickening, cystoid spaces and, in some eyes, subretinal fluid [2,15]. With the rising global prevalence of diabetes, DME represents a growing public-health and economic burden [1].

Spectral-domain optical coherence tomography (SD-OCT) has become indispensable for the diagnosis and management of DME, providing non-invasive, high-resolution cross-sectional imaging of the retina. Historically, central subfield thickness (CST) has served as the principal anatomical endpoint in trials and routine care. However, the correlation between CST and visual acuity is only modest: substantial reductions in thickness frequently fail to translate into proportionate visual gains, and eyes with similar CST may have markedly different acuities [3]. This discordance has driven a search for OCT-derived microstructural biomarkers that more faithfully reflect, and predict, visual function.

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Several such biomarkers have been characterised. Disorganization of the retinal inner layers (DRIL)–the loss of distinct boundaries between the ganglion cell-inner plexiform, inner nuclear and outer plexiform layers–has emerged as a robust correlate of visual acuity in both current and resolved DME [4,5]. Integrity of the outer retina, assessed through the ellipsoid zone (EZ) and external limiting membrane (ELM), is strongly associated with visual outcome, since photoreceptor disruption limits recovery despite anatomical resolution of oedema [6,7,11]. Hyperreflective foci (HRF), thought to represent lipid extravasation, activated microglia or inflammatory aggregates, have been linked to greater disease severity and poorer functional response [8,9,12]. Inner-retinal tissue measurements proposed by Pelosini and colleagues likewise predict acuity [10], whereas the presence of subretinal fluid has been associated with a relatively favourable treatment response in some series [12,13].

Anti-vascular endothelial growth factor (anti-VEGF) therapy is the current first-line treatment for centre-involved DME and produces substantial anatomical and visual improvement in many, though not all, eyes [16]. The heterogeneity of visual response underscores the clinical value of baseline structural predictors: identifying which OCT biomarkers most strongly correlate with, and forecast, visual outcome could refine prognosis, guide treatment expectations and inform individualised management.

Although individual biomarkers have been studied, comparative data on their relative strength in correlating with and predicting visual outcomes–within a single, uniformly treated cohort–remain valuable, particularly given variability in grading definitions and study populations [14]. The present prospective observational study was therefore designed to evaluate baseline SD-OCT biomarkers in eyes with centre-involved DME, to correlate them with visual acuity at baseline and at six months following anti-VEGF therapy, and to determine which biomarkers independently predict the six-month visual outcome.

Materials and Methods

Study design and ethics

This prospective, observational cohort study was carried out in the vitreoretina service of a tertiary referral centre. The study followed the principles of the Declaration of Helsinki and received institutional ethics committee approval; all participants provided written informed consent.

Participants

Adults aged ≥ 18 years with diabetes and treatment-naïve, centre-involved DME (central subfield thickness ≥ 300 µm on SD-OCT) were enrolled. Exclusion criteria included prior intravitreal anti-VEGF or steroid therapy, macular laser within six months, vitreoretinal surgery, coexisting maculopathy (e.g., age-related macular degeneration, retinal vein occlusion, epiretinal membrane with significant traction), advanced glaucoma, media opacity precluding quality imaging, and uncontrolled hypertension or renal failure. Where both eyes were eligible, both were included with adjustment for inter-eye correlation.

Clinical assessment

At baseline, all participants underwent best-corrected visual acuity (BCVA) testing using a standardised logMAR chart, slit-lamp biomicroscopy, intraocular-pressure measurement, dilated fundus examination and SD-OCT. Systemic variables (diabetes duration, HbA1c, blood pressure) were recorded.

OCT acquisition and biomarker grading

Macular SD-OCT was performed using a standard raster protocol centred on the fovea. Two masked graders independently assessed the following baseline biomarkers, with disagreements resolved by consensus: central subfield thickness (CST, automated with manual correction of segmentation errors); DRIL, defined as the inability to distinguish boundaries among the ganglion cell-inner plexiform, inner nuclear and outer plexiform layers and measured as horizontal extent within the central 1 mm; EZ and ELM disruption, graded as present/absent and measured as the length of foveal discontinuity; hyperreflective foci (HRF), counted as discrete, well-circumscribed reflective dots in the inner and outer retina and dichotomised as high (> 20) versus low; subretinal fluid (SRF) presence; largest intraretinal cyst dimension; and vitreomacular interface status.

Treatment, follow-up and statistics

All eyes received intravitreal anti-VEGF therapy comprising three monthly loading injections followed by a pro re nata regimen guided by OCT and BCVA, with reassessment at six months (primary time point). Continuous data were expressed as mean ± standard deviation. Correlations between baseline OCT biomarkers and BCVA (baseline and six-month) were assessed using Spearman rank correlation. Visual outcomes were compared between eyes with and without each dichotomous biomarker using the independent-samples t test. Multivariable linear regression, including biomarkers significant on univariate analysis and baseline BCVA, identified independent predictors of six-month BCVA, reported as standardised β coefficients with 95% confidence intervals. A two-sided p value < 0.05 was considered significant.

Results

Ninety-six eyes of 80 patients (mean age 61.4 ± 8.7 years; 55% male) completed six months of follow-up. Baseline characteristics are summarised in Table 1. Mean BCVA improved from 0.62 ± 0.28 logMAR at baseline to 0.41 ± 0.26 logMAR at six months, and mean CST decreased from 412 ± 98 µm to 298 ± 76 µm, after a mean of 4.6 ± 1.1 injections.

Table 1. Baseline demographic, clinical and anatomical characteristics.

Characteristic	Value
Eyes / patients, n	96 / 80
Age, years	61.4 ± 8.7
Male, n (%)	44 (55)
Diabetes duration, years	13.2 ± 6.1
HbA1c, %	8.2 ± 1.4
Baseline BCVA, logMAR	0.62 ± 0.28
6-month BCVA, logMAR	0.41 ± 0.26
Baseline CST, µm	412 ± 98
6-month CST, µm	298 ± 76
Anti-VEGF injections, n	4.6 ± 1.1

Data are mean ± SD unless stated. BCVA, best-corrected visual acuity; CST, central subfield thickness; VEGF, vascular endothelial growth factor.

Table 2. Prevalence of baseline OCT biomarkers (n = 96 eyes).

Baseline OCT biomarker	n (%)
Disorganization of retinal inner layers (DRIL)	52 (54)
Ellipsoid zone (EZ) disruption	47 (49)
External limiting membrane (ELM) disruption	39 (41)
Hyperreflective foci (> 20)	58 (60)
Subretinal fluid (SRF)	34 (35)
Large intraretinal cysts (> 200 µm)	61 (64)
Vitreomacular adhesion / traction	18 (19)

DRIL, disorganization of retinal inner layers; EZ, ellipsoid zone; ELM, external limiting membrane.
As shown in Table 2, DRIL was present in 54% of eyes and EZ disruption in 49%, while large intraretinal cysts (64%) and high hyperreflective foci counts (60%) were the most frequent findings. Subretinal fluid and vitreomacular traction were comparatively less common.

Table 3. Correlation of baseline OCT biomarkers with BCVA (logMAR).

OCT biomarker	Baseline ρ	p	6-month ρ	p
CST	+0.34	0.001	+0.22	0.03
DRIL extent	+0.58	<0.001	+0.61	<0.001
EZ disruption	+0.55	<0.001	+0.59	<0.001
ELM disruption	+0.49	<0.001	+0.52	<0.001
HRF count	+0.41	<0.001	+0.45	<0.001
SRF (present)	−0.18	0.08	−0.27	0.008

Spearman rank correlation (ρ). Positive ρ indicates association with worse acuity (higher logMAR). CST, central subfield thickness; HRF, hyperreflective foci; SRF, subretinal fluid.

DRIL extent and EZ disruption showed the strongest correlations with visual acuity, and these correlations were stronger at six months (ρ = +0.61 and +0.59) than at baseline, indicating particular value as predictors of treated outcome (Table 3). ELM disruption and HRF count showed moderate correlations. CST correlated only weakly, and this association weakened further after treatment. SRF presence correlated negatively with logMAR–i.e., with better acuity–reaching significance at six months.

Table 4. Six-month BCVA (logMAR) stratified by presence or absence of biomarkers.

Biomarker	Present	Absent	p-value
DRIL	0.54 ± 0.24	0.27 ± 0.18	<0.001
EZ disruption	0.55 ± 0.23	0.28 ± 0.19	<0.001
ELM disruption	0.53 ± 0.24	0.32 ± 0.20	<0.001
High hyperreflective foci	0.49 ± 0.23	0.31 ± 0.21	0.002
Subretinal fluid	0.33 ± 0.21	0.46 ± 0.27	0.02

Values are mean ± SD logMAR; p-values from independent-samples t test.
Eyes with DRIL, EZ disruption, ELM disruption or high HRF had significantly worse six-month visual acuity than those without (all $p < 0.005$; Table 4). In contrast, eyes with subretinal fluid achieved better acuity than those without (0.33 vs 0.46 logMAR; $p = 0.02$), consistent with the correlation analysis.

Table 5. Multivariable linear regression for six-month BCVA (logMAR).

Predictor	β	95% CI	p-value
DRIL extent	0.31	0.18 to 0.44	<0.001
EZ disruption	0.27	0.14 to 0.40	<0.001
Baseline BCVA	0.22	0.10 to 0.34	0.001
HRF count	0.12	0.02 to 0.22	0.02
CST	0.05	−0.06 to 0.16	0.36

Model $R^2 = 0.52$. β = standardised regression coefficient; CI, confidence interval.
On multivariable regression, DRIL extent, EZ disruption and baseline BCVA were independent predictors of six-month visual acuity, with HRF count contributing modestly; CST was not an independent predictor once these biomarkers were included (Table 5). The model explained 52% of the variance in six-month acuity.

Discussion

In this prospective cohort of eyes with centre-involved DME treated with anti-VEGF, baseline OCT biomarkers reflecting inner- and outer-retinal integrity correlated more strongly with visual acuity–both at presentation and after six months–than did central subfield thickness. DRIL and ellipsoid-zone disruption were the most powerful correlates and, alongside baseline acuity, the only structural biomarkers to independently predict the six-month outcome.

The weak correlation between CST and visual acuity confirms a long-recognised limitation of thickness as a functional surrogate, highlighted in large datasets by Browning and colleagues [3]. Anatomical resolution of oedema does not guarantee visual recovery, because the determinants of acuity lie in the integrity of the neurosensory retina rather than its thickness alone.

Our finding that DRIL is a robust correlate of acuity is concordant with the work of Sun and colleagues, who demonstrated that DRIL predicts current and future visual acuity in eyes with DME [4,5]. DRIL is thought to reflect disruption of the neuronal pathways connecting photoreceptors to ganglion cells, so its presence signals impaired visual signal transmission irrespective of fluid status. Similarly, the strong association between EZ and ELM disruption and poorer outcomes aligns with reports linking photoreceptor integrity to visual function [6,7,11]; intact outer-retinal bands indicate preserved photoreceptors capable of recovering function once oedema resolves.

Hyperreflective foci were associated with worse outcomes, supporting the view that these aggregates–representing lipid extravasation and inflammatory activity–mark a more refractory, inflammation-driven phenotype [8,9,12]. The relatively favourable outcomes in eyes with subretinal fluid are consistent with studies suggesting that SRF may identify a more treatment-responsive subgroup [12,13]. Together, these observations reinforce the concept that OCT biomarkers capture distinct pathophysiological processes that thickness measurement cannot.
The clinical implications are meaningful. Baseline assessment of DRIL and outer-retinal integrity could help clinicians counsel patients on realistic visual prognosis and distinguish eyes likely to respond well from those at risk of limited recovery despite anatomical improvement [14]. Such biomarkers may also serve as stratifying variables or surrogate endpoints in future trials.

Limitations include the single-centre design, modest sample size and six-month follow-up, which may not capture longer-term remodelling. Biomarker grading, although performed by masked graders, retains some subjectivity, and definitions vary across the literature [14]; the pro re nata regimen introduces variability in treatment intensity, and device-specific segmentation may affect quantification. Larger, multicentre, longitudinal studies with standardised, ideally automated grading are needed to validate these biomarkers and establish prognostic thresholds for routine practice.

Conclusion

In eyes with centre-involved diabetic macular edema, OCT microstructural biomarkers—particularly disorganization of the retinal inner layers and disruption of the ellipsoid zone and external limiting membrane—correlate with visual acuity and predict post-treatment visual outcomes more reliably than central subfield thickness. Hyperreflective foci portend poorer recovery, whereas subretinal fluid may signal a more favourable response. Incorporating these qualitative and quantitative OCT biomarkers into baseline evaluation can enhance prognostication and individualise management of DME, complementing thickness-based metrics. Validation in larger, longitudinal, multicentre cohorts with standardised grading will be essential before these biomarkers are adopted as routine prognostic tools or trial endpoints.

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