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Original Research Article

Study of Imaging Biomarkers as a Prognostic Factor and Guide in the Management of Diabetic Macular Oedema at a Tertiary Care Center in Western Gujarat

Nayan R. Jethva[1], Lalu Vanrajsinh Badarubhai[2], Abhi Sureshbhai Khimani[3], Nihar Sanjaykumar Barot[4]

[1]Resident Doctor, GMERS Medical College, Porbandar, Gujarat, India
[2,3,4]MBBS, GMERS Medical College Junagadh, Gujarat, India

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Corresponding Author: Dr. Nihar Sanjaykumar Barot
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Abstract:

Introduction: Diabetic Macular Edema (DME) is a leading cause of visual impairment in diabetic patients and is closely linked to structural changes in the retina detectable via optical coherence tomography (OCT). Identifying imaging biomarkers can aid in predicting visual prognosis and guiding personalized treatment approaches.

Material and Methods: This prospective observational study was conducted over one year at a tertiary care center in Western Gujarat, including 123 patients diagnosed with center-involving DME. Comprehensive ophthalmic evaluation and SD-OCT imaging were performed to assess biomarkers such as intraretinal cysts, hyperreflective foci, disorganization of retinal inner layers (DRIL), and subretinal fluid. Systemic parameters including HbA1c and serum cholesterol levels were also recorded and analyzed.

Results: The most common biomarker observed was DRIL (27.64%), followed by intraretinal cysts (26.01%) and hyperreflective foci (22.76%). Patients with DRIL and disrupted ELM showed significantly worse BCVA (mean logMAR 1.30). Higher HbA1c levels were associated with intraretinal cysts (mean 8.56%, p=0.014) and VMI abnormalities (mean 8.91%, p=0.042). Hyper reflective foci correlated with higher cholesterol levels (mean 288.36 mg/dL, p=0.011), indicating systemic metabolic influence on retinal pathology.

Conclusion: OCT-based imaging biomarkers are predictive of visual outcomes in DME and reflect systemic disease severity. Integrating retinal imaging with metabolic control can optimize management strategies.

Keywords: Diabetic Macular Edema, OCT Biomarkers, Visual Acuity, Hyperreflective Foci, Intraretinal Cysts, HbA1c, Cholesterol, DRIL.

Introduction

Diabetic Macular Edema (DME) stands as one of the most prevalent and vision-threatening complications of diabetes mellitus, posing a significant challenge to patients and healthcare systems worldwide. With the increasing incidence of diabetes globally, the burden of DME is on the rise, emphasizing the critical need for effective prognostic tools and management strategies. [1]

The visual system is a remarkable and intricate part of human physiology, enabling us to perceive the world around us. However, this intricate system is not immune to the systemic effects of diabetes. [2] Diabetes exerts a multifaceted influence on ocular structures, and DME is a prime example of the sight-threatening consequences of the disease. Characterized by the accumulation of fluid within the macula, DME disrupts the critical processes of vision, causing blurred or distorted vision and, if left unmanaged, potentially leading to severe vision loss and legal blindness. [3] Historically, the management of DME has faced considerable challenges due to its complex pathophysiology and heterogeneity in clinical presentation. Traditional management strategies have relied heavily on interventions such as laser photocoagulation, which, while beneficial for some patients, may not be universally effective, particularly in cases of diffuse or center-involving DME. [4] The introduction of intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents and corticosteroid implants has marked a significant advancement in the treatment of DME, offering new hope for improved visual outcomes and disease control. [5]

Nonetheless, optimal DME management remains a multifaceted endeavor, and clinicians face a delicate balance between aggressive treatment to halt disease progression and avoiding over-

treatment, which can expose patients to unnecessary risks and healthcare costs. [6] Recent years have witnessed significant advancements in ocular imaging technologies, particularly optical coherence tomography (OCT). [7] OCT has revolutionized the assessment of macular morphology, offering high-resolution, non-invasive, and reproducible images of the retinal microstructure. These images not only provide clinicians with invaluable insights into the anatomical changes associated with DME but also hold the potential to serve as predictive biomarkers for disease progression and response to treatment. [8]

The promise of imaging biomarkers in DME management lies in their ability to bridge the gap between structural changes and functional outcomes. [9] While visual acuity remains the gold standard for assessing visual function, it may not capture the subtleties of DME progression and response to treatment. Imaging biomarkers, on the other hand, offer a more granular perspective by quantifying retinal thickness, volume, and other morphological characteristics that correlate with disease severity and prognosis. [10]

Material and Methods

The present study was a prospective, observational study conducted over a period of one year at the Department of Ophthalmology, a tertiary care center in Western Gujarat. The study was initiated after obtaining approval from the Institutional Ethics Committee. All patients included in the study were diagnosed with Diabetic Macular Edema (DME) based on clinical evaluation and imaging findings. Written informed consent was obtained from each participant before enrollment. Patients aged 18 years and above, presenting with center-involving DME confirmed through spectral-domain optical coherence tomography (SD-OCT), were included. Exclusion criteria involved patients with significant media opacities, history of vitreoretinal surgeries, concurrent retinal pathologies such as retinal vein occlusion, age-related macular degeneration, uveitis, or optic neuropathies that could confound macular edema assessment. Patients unwilling to consent or those lost to follow-up were also excluded.

Detailed clinical histories were recorded, including patient demographics (age, gender), type and duration of diabetes, systemic comorbidities (hypertension, nephropathy, dyslipidemia), and prior ocular interventions like laser photocoagulation, intravitreal injections, or vitrectomy.

Baseline ophthalmic evaluation comprised best-corrected visual acuity (BCVA) measurement using Snellen's chart, slit-lamp biomicroscopy, intraocular pressure (IOP) recording, and dilated fundus examination using indirect ophthalmoscopy and a +90D lens. All patients underwent SD-OCT imaging (specifically using the Heidelberg Spectralis device) to assess various imaging biomarkers such as central subfield thickness (CST), presence of intraretinal cysts, subretinal fluid, hyperreflective foci (HRF), disorganization of inner retinal layers (DRIL), and integrity of external limiting membrane (ELM) and ellipsoid zone (EZ).

Patients were managed as per standard treatment protocols tailored according to the severity and morphological patterns observed on OCT. Treatment strategies included intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections (bevacizumab, ranibizumab) and/or intravitreal corticosteroid injections where indicated. Laser photocoagulation was considered in select cases of non-center involving DME or as adjunct therapy. Patients were followed up monthly for six months post-intervention, and re-treatment decisions were based on OCT-guided evaluations of anatomical response and BCVA changes. Imaging biomarkers were reassessed at each visit to monitor the morphological changes and correlate them with functional outcomes. Data collection was meticulously recorded in structured case record forms, and imaging findings were evaluated independently by two experienced retinal specialists to minimize observer bias.

Statistical analysis was performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Quantitative variables like CST, BCVA, and number of hyperreflective foci were expressed as mean ± standard deviation, while qualitative variables such as the presence of SRF or DRIL were expressed as percentages. Pre- and post-treatment comparisons were done using paired t-tests or Wilcoxon signed-rank tests based on data normality. Association between baseline imaging biomarkers and final visual outcomes was analyzed using Chi-square tests for categorical variables and correlation analysis for continuous variables. A p-value of less than 0.05 was considered statistically significant.

Results

In the present study, we evaluated the demographic distribution of patients diagnosed with Diabetic Macular Edema (DME) attending a tertiary care center in Western Gujarat. Analysis of age groups revealed that the majority of patients were older than 60 years (45.5%), followed by those in the 51–60-year group (39%), highlighting that DME predominantly affects elderly individuals. Regarding gender distribution, there was a significant male predominance with 68.3% of the study population being males. These findings underscore that both aging and male gender may

contribute to the higher susceptibility of diabetic individuals to developing macular edema in this region.

In our study, we evaluated the association between Best Corrected Visual Acuity (BCVA) and various imaging biomarkers. Significant negative correlations were found, particularly with hyperreflective foci, disorganization of retinal inner layers (DRIL), and subretinal fluid, indicating that the presence of these biomarkers was linked to worse visual outcomes. (Table 1).

Table 1: Association between BCVA (logMar) and Different Imaging Biomarkers in DME Patients

S. No	Biomarkers	BCVA (LogMar)	Pearson Coefficient	P Value
1	Hyper reflective foci	0.7	-0.277	0.009
2	Disorganization of Retinal Inner Layers	1.3	-0.192	0.001
3	Intraretinal Cystic Spaces (Vertical diameter >100 µm)	1	-0.526	0.003
4	Intraretinal Cystic Spaces (Vertical diameter <100 µm)	0.5	-0.102	0.125
5	Subretinal Fluid with Serous Retinal Detachment	1.47	-0.492	0.002
6	Disrupted External Limiting Membrane	1.3	-0.501	0
7	Vitreomacular Interface Abnormalities	1.3	-0.666	0.088
8	Central Subfield Thickness >400 µm	1	-0.444	0.044
9	Central Subfield Thickness <400 µm	1.17	-0.468	0.051

In our study, the distribution of visual acuity groups was analyzed according to key biomarkers. Disorganization of retinal inner layers was the most frequent finding among patients with severe vision loss (less than 6/60), whereas intraretinal cysts and hyperreflective foci were seen across varying degrees of visual impairment. (Table 2)

Table 2: Distribution of Visual Acuity Groups Based on Presence of Imaging Biomarkers

Biomarker	6/12 to 6/24	6/60 to 6/24	Less than 6/60	Total (n=123)
Intra retinal cystic spaces	10	13	9	32
Hyper reflective foci	7	19	2	28
Disorganization of Retinal Inner Layers	1	10	23	34
Subretinal fluid with serous retinal detachment	0	6	8	14
Disrupted external limiting membrane	0	1	7	8
Vitreomacular interface abnormalities	0	3	4	7

In our study population, disorganization of retinal inner layers was the most frequently observed imaging biomarker, followed by intraretinal cystic spaces and hyperreflective foci. Biomarkers such as disrupted external limiting membrane and vitreomacular interface abnormalities were comparatively less common. (Fig 1).

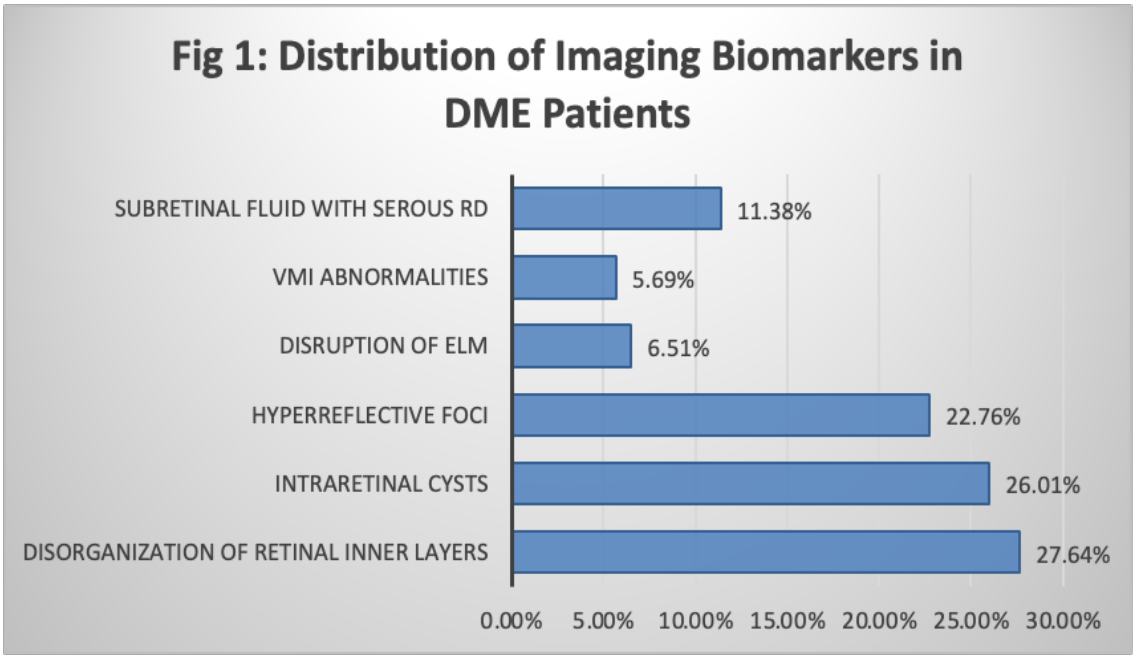

Figure 1: Distribution of imaging Biomarkers in DME Patients

In our study, patients exhibiting intraretinal cystic spaces and vitreomacular interface abnormalities had significantly higher mean HbA1c levels. This suggests a strong association between poor glycemic control and the severity of retinal changes in diabetic macular edema. (Table 3)

Table 3: Comparison of Mean HbA1c Levels in Relation to Presence of Imaging Biomarkers

Biomarker	Mean HbA1c (%) (Absent)	Mean HbA1c (%) (Present)	P Value
Disorganization of Retinal Inner Layers	8.14%	7.86%	0.071
Intra Retinal Cystic Spaces	8.02%	8.56%	0.014
Hyper Reflective Foci	8.12%	7.98%	0.308
ELM Disruption	8.04%	8.40%	0.072
Subretinal Fluid with Serous Retinal Detachment	8.08%	7.96%	0.767
VMI Abnormalities	7.01%	8.91%	0.042

Discussion

In our study, the majority of patients with diabetic macular edema (DME) were aged over 60 years (45.5%), which mirrors findings reported in other major studies. Borrelli et al. [11] found a slightly higher proportion (52%) of patients above 60 years, while Vujosevic et al. [12] and Zur et al. [13] similarly reported nearly half of their DME cohorts in the older age group. This trend is attributable to the cumulative vascular damage induced by chronic hyperglycemia over time, reinforcing the established understanding that DME is primarily a complication of long-standing diabetes. Studies by Mehta et al. and Apuzzo et al. also emphasized the same age-related vulnerability, highlighting the importance of early diabetes management to prevent retinal complications.

Regarding gender distribution, a male predominance was observed in our study, with 68.3% of the patients being males. This finding is in line with several other studies, including those by Borrelli et al. [11], Markan et al. [14], and Mehta et al. [15], all reporting higher male representation among DME patients. Possible explanations for this gender disparity include biological differences in retinal vasculature, differential exposure to risk factors such as smoking and hypertension, and gender-specific health-seeking behaviors. Borrelli et al. [11] further suggested that men might experience a more aggressive course of diabetic retinopathy, leading to higher rates of DME. Similarly, Vujosevic et al. [12] found comparable male predominance in their cohorts. These findings underline the necessity of tailored approaches that address gender-specific risk profiles in diabetes management and diabetic retinopathy screening programs.

When correlating imaging biomarkers with visual acuity, our study demonstrated a significant negative association between BCVA and the presence of hyperreflective foci, disorganization of retinal inner layers (DRIL), and subretinal fluid. These results parallel findings by Borrelli et al. [11], Zur et al. [13], and Gerendas et al. [16], all of whom reported similar correlations using SD-OCT analysis. Particularly, the strong association of DRIL and disrupted ellipsoid zones with poor visual outcomes has been emphasized by studies such as those by Esra Turkseven Kumral et al. [17] and Gayatri Dasari et al. [18]. Munk et al. [19] also demonstrated that the presence of hyperreflective foci predicted poorer responses to anti-VEGF therapy, advocating for early intervention or therapy modification. Collectively, our results and those of prior studies reinforce the pivotal role of OCT biomarkers not only in prognostication but also in guiding individualized treatment strategies for DME patients.

Our study further found that disorganization of retinal inner layers was the most common biomarker, significantly more prevalent among patients with severe visual impairment (less than 6/60). This observation is supported by findings from Costanzo et al. [20], Munk et al. [19], Kim et al. [21], and Gupta et al. [22], all of whom associated DRIL and ellipsoid zone disruption with worse visual acuity outcomes. In contrast, intraretinal cystic spaces were distributed more uniformly across visual acuity groups, consistent with the findings of Chou et al. [23] and Hui et al.[24], suggesting that while cystic changes indicate retinal edema, they are less directly predictive of severe vision loss. Overall, these studies corroborate the central role of structural retinal biomarkers, particularly DRIL and ellipsoid zone status, in assessing functional impairment in DME and guide the prioritization of patients needing aggressive treatment.

In analyzing systemic metabolic correlations, we observed that patients with intraretinal cystic spaces and vitreomacular interface abnormalities had significantly higher HbA1c levels, and patients with hyperreflective foci showed higher mean cholesterol levels. Similar associations have been detailed by Borrelli et al. [11], Liu et al. [25], and Gerendas et al. [16], confirming the adverse impact of poor glycemic and lipid control on retinal structure. Esra Turkseven Kumral et al. [17] also highlighted that elevated HbA1c correlated with increased macular thickness and worsening

biomarkers. Studies by Vujosevic et al. [12] and Zur et al. [13] suggested that dyslipidemia exacerbates retinal changes such as cystic spaces and hyperreflective foci.

These findings underline the necessity of tight systemic control (blood glucose and lipid levels) in DME patients. Integrating OCT biomarker evaluation with systemic health assessments could significantly enhance outcome prediction and therapeutic decision-making in real-world settings, as supported by converging evidence from multiple international studies.

The present study has certain limitations, including its single-center design and relatively modest sample size, which may limit the generalizability of the results to broader populations. Being an observational study, causal relationships between biomarkers and visual outcomes could not be firmly established. Variability in OCT interpretation and lack of long-term follow-up beyond six months may have also influenced the assessment of biomarker evolution over time.

Conclusion

In conclusion, our study highlights the significant role of imaging biomarkers in predicting visual outcomes and guiding management strategies for diabetic macular edema (DME) patients. Disorganization of retinal inner layers, intraretinal cystic spaces, and hyperreflective foci emerged as the most prevalent biomarkers associated with worse visual acuity. Systemic factors such as poor glycemic and lipid control were also closely linked to the severity of retinal changes. These findings emphasize the importance of early imaging assessment and comprehensive systemic management to optimize outcomes in DME patients, particularly among elderly males.

Bibliography

1. Atlas D. International diabetes federation. IDF Diabetes Atlas 7th Edn Bruss Belg Int Diabetes Fed. 2015; 33(2).
2. Sherwood L. Human physiology: from cells to systems. Cengage learning; 2015.
3. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy: IV. Diabetic macular edema. Ophthalmology. 1984; 91(12):1464–74.
4. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Arch Ophthalmol. 1985; 103:1796–806.
5. Wells JA, Glassman AR, Ayala AR, Jampol LM, Bressler NM, Bressler SB, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial. Ophthalmology. 2016; 123(6):1351–9.
6. Bressler S, Qin H, Beck R, Chalam K, Kim J, Melia M, et al. Diabetic Retinopathy clinical research network factors associated with changes in visual acuity and central subfield thickness at 1 year after treatment for diabetic macular edema with ranibizumab. Arch Ophthalmol. 2012; 130(9):1153–61.
7. Chen J, Lee L. Clinical applications and new developments of optical coherence tomography: an evidence-based review. Clin Exp Optom. 2007; 90(5):317–35.
8. Kashani AH, Chen CL, Gahm JK, Zheng F, Richter GM, Rosenfeld PJ, et al. Optical coherence tomography angiography: a comprehensive review of current methods and clinical applications. Prog Retin Eye Res. 2017; 60:66–100.
9. Kalra G, Kar SS, Sevgi DD, Madabhushi A, Srivastava SK, Ehlers JP. Quantitative imaging biomarkers in age-related macular degeneration and diabetic eye disease: a step closer to precision medicine. J Pers Med. 2021; 11(11):1161.
10. Richer S. Exam room, chair side evaluation of retinal edema: improving accuracy and precision for identification of subclinical diabetic macular edema. Optom-J Am Optom Assoc. 2007; 78(12):664–73.
11. Borrelli E, Barresi C, Feo A, Lari G, Grosso D, Querques L, et al. Imaging biomarkers and clinical factors associated with the rate of progressive inner and outer retinal thinning in patients with diabetic macular edema. Sci Rep. 2023; 13(1):3224.
12. Vujosevic S, Torresin T, Bini S, Convento E, Pilotto E, Parrozzani R, et al. Imaging retinal inflammatory biomarkers after intravitreal steroid and anti-VEGF treatment in diabetic macular oedema. Acta Ophthalmol (Copenh). 2017; 95(5):464–71.
13. Zur D, Iglicki M, Busch C, Invernizzi A, Mariussi M, Loewenstein A, et al. OCT biomarkers as functional outcome predictors in diabetic macular edema treated with dexamethasone implant. Ophthalmology. 2018; 125(2):267–75.
14. Markan A. Novel Imaging Biomarkers in Diabetic Retinopathy and Diabetic Macular Edema. Graefes Arch Clin Exp Ophthalmol. 2020; 258(5):935–45.
15. Mehta H, Tufail A, Daien V, Lee AY, Nguyen V, Ozturk M, et al. Real-world outcomes in patients with neovascular age-related macular degeneration treated with intravitreal vascular endothelial growth factor inhibitors. Prog Retin Eye Res. 2018; 65:127–46.
16. Gerendas BS, Prager S, Deak G, Simader C, Lammer J, Waldstein SM, et al. Predictive im-

aging biomarkers relevant for functional and anatomical outcomes during ranibizumab therapy of diabetic macular oedema. Br J Ophthalmol. 2018; 102(2):195–203.
17. Turkseven Kumral E, Ercalık NY, Alpogan O, Yenerel NM, Ozcelik Kose A, Ozturk Y, et al. Oct biomarkers of treatment-naive diabetic macular edema in patients with non-proliferative and proliferative diabetic retinopathy. Eur J Ophthalmol. 2023; 33(2):1061–7.
18. Gayatri D, Rao VN, Chavali SP. Assessing Diabetic Macular Edema through Spectral Domain Optical Coherence Tomography: An Analysis of Foveal Thickness, External Limiting Membrane, and Ellipsoid Zone Integrity. Arch Med Health Sci. 2023; 11(1):60–3.
19. Munk MR, Somfai GM, de Smet MD, Donati G, Menke MN, Garweg JG, et al. The role of intravitreal corticosteroids in the treatment of DME: predictive OCT biomarkers. Int J Mol Sci. 2022; 23(14):7585.
20. Costanzo E, Giannini D, De Geronimo D, Fragiotta S, Varano M, Parravano M. Prognostic Imaging Biomarkers in Diabetic Macular Edema Eyes Treated with Intravitreal Dexamethasone Implant. J Clin Med. 2023; 12(4):1303.
21. Kim KT, Kim DY, Chae JB. Association between hyperreflective foci on spectral-domain optical coherence tomography and early recurrence of diabetic macular edema after intravitreal dexamethasone implantation. J Ophthalmol. 2019; 2019.
22. Gupta C, Tan R, Mishra C, Khandelwal N, Raman R, Kim R, et al. Choroidal structural analysis in eyes with diabetic retinopathy and diabetic macular edema—A novel OCT based imaging biomarker. PLoS One. 2018; 13(12):e0207435.
23. Chou HD, Wu CH, Chiang WY, Chen NN, Hwang YS, Chen KJ, et al. Optical coherence tomography and imaging biomarkers as outcome predictors in diabetic macular edema treated with dexamethasone implant. Sci Rep. 2022; 12(1):3872.
24. Hui VW, Szeto SK, Tang F, Yang D, Chen H, Lai TY, et al. Optical Coherence Tomography Classification Systems for Diabetic Macular Edema and Their Associations with Visual Outcome and Treatment Responses–An Updated Review. Asia-Pac J Ophthalmol. 2022; 11(3):247–57.
25. Liu S, Wang D, Chen F, Zhang X. Hyperreflective foci in OCT image as a biomarker of poor prognosis in diabetic macular edema patients treating with Conbercept in China. BMC Ophthalmol. 2019; 19(1):1–6.