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Original Article

Role of OCT biomarkers in early detection of Diabetic Macular edema

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ABSTRACT

Background: Diabetic macular edema (DME) can develop insidiously, with microstructural retinal changes appearing before obvious clinical thickening is appreciated on slit-lamp examination. Optical coherence tomography (OCT) is well suited for this "preclinical window" because it can quantify subtle macular thickening and detect early tissue disorganization that may signal imminent edema and functional decline.
Aim: To summarise how OCT biomarkers support early detection of diabetic macular edema and help identify eyes at higher risk of progression.
Methods: Evidence from clinical studies and network datasets evaluating OCT-defined subclinical/early DME and OCT biomarkers (retinal thickness metrics, intraretinal fluid/cysts, outer retinal integrity, hyperreflective foci, and disorganization of retinal inner layers [DRIL]) was synthesised. Key endpoints included OCT-based definitions of subclinical DME, risk of progression to definite thickening/treatment, and quantitative associations between biomarkers and visual function.
Results: Across prospective observations, "subclinical centre-involved DME" has been operationally defined as absence of foveal-centre edema on clinical examination with OCT centre-point thickness in the 225–299 µm range, with progression commonly defined as a ≥50 µm increase reaching ≥300 µm or need for treatment. In a DRCR.net observational cohort, subclinical DME was relatively uncommon (43 of 891 eyes; 4.8%), yet a meaningful proportion progressed: the cumulative probability of reaching the progression endpoint was 27% by 1 year and 38% by 2 years. Beyond thickness alone, inner retinal integrity adds prognostic value: increasing DRIL burden has been linked with worse vision, with one analysis reporting an average ~4.7-letter decrease in visual acuity for each 100 µm increase in global DRIL. Longitudinal work also indicates that early change in DRIL over the first few months can track subsequent visual change, supporting its role as a practical biomarker during follow-up.
Conclusion: OCT biomarkers strengthen early DME detection by capturing macular thickening within defined "subclinical" ranges and by revealing structural disorganisation—particularly DRIL—that relates to functional status and future trajectory. Using these biomarkers in routine diabetic eye surveillance can help clinicians separate eyes that may be safely observed from those that warrant closer monitoring and earlier therapeutic decision-making.

Keywords*: Diabetic macular edema; Optical coherence tomography; Subclinical DME; Central point thickness; DRIL; Hyperreflective foci; Early detection; Diabetic retinopathy.*

INTRODUCTION

Diabetic macular oedema (DME) is a major cause of vision loss in individuals with diabetes and often develops gradually, with early retinal changes preceding obvious clinical signs. In the initial stages, macular thickening and fluid accumulation may be minimal or fluctuate, making detection by ophthalmoscopy alone unreliable. Optical coherence tomography (OCT) has therefore become central to contemporary diabetic eye care, as it enables high-resolution, quantitative assessment of subtle retinal microstructural alterations that may indicate early or impending macular oedema [1,2].

The concept of a subclinical or early stage of centre-involving involvement is increasingly recognised. Longitudinal studies in early diabetic retinopathy have shown that small increases in extracellular retinal fluid can occur well before symptomatic visual loss and may follow a progressive trajectory over time [3]. These observations underline the importance of identifying early OCT changes that signal heightened risk, rather than waiting for established oedema or functional decline.

While retinal thickness remains the most commonly used OCT parameter, it does not fully capture disease activity in early DME. Increasing attention has shifted toward additional OCT biomarkers that reflect underlying pathophysiology, including intraretinal cystoid spaces, hyperreflective foci, integrity of the external limiting membrane and ellipsoid zone, vitreomacular interface abnormalities, and disorganisation of the retinal inner layers (DRIL) [2,6]. Among these, DRIL has emerged as a particularly relevant marker of inner retinal dysfunction and neuroglial impairment, with consistent associations with disease severity and visual prognosis [4,5].

Outer retinal involvement is another critical consideration in early detection. Disruption of photoreceptor-related layers is associated with poorer visual outcomes, highlighting the need to identify DME before irreversible outer retinal damage occurs [7,8]. In parallel, OCT angiography has provided complementary information on microvascular alterations, such as capillary non-perfusion and foveal avascular zone changes, which may coexist with early oedematous changes and further refine risk assessment [1].

Recent advances in automated OCT analysis have improved the reproducibility and scalability of biomarker assessment, supporting their potential integration into screening and follow-up pathways [9]. Collectively, these developments support a shift toward biomarker-driven evaluation of early DME, where a combination of structural OCT features—rather than thickness alone—guides detection, monitoring, and timely clinical decision-making [1–6].

MATERIALS AND METHODS

Study Design and Duration

This prospective, observational study was conducted over a defined period from January 2025 to December 2025. The primary objective was to evaluate the usefulness of optical coherence tomography (OCT)–derived biomarkers in identifying early or subclinical diabetic macular oedema (DME) among individuals with diabetes mellitus before the onset of clinically evident macular involvement.

Study Setting

The study was carried out at two tertiary referral centres in Telangana, India: the Regional Eye Hospital, Kakatiya Medical College (KMC), Hanumakonda, and the Government Medical College, Narsampet, Warangal. Both institutions provide comprehensive ophthalmic services and serve as major referral hubs for diabetic eye disease, with access to advanced retinal imaging facilities.

Study Population

Patients with type 1 or type 2 diabetes mellitus attending the ophthalmology outpatient departments of the participating centres were screened consecutively for eligibility. Individuals meeting the predefined inclusion criteria were enrolled after obtaining informed written consent. Each eligible eye was evaluated independently for study inclusion.

Inclusion and Exclusion Criteria

Adult patients aged 18 years and above with diabetes mellitus and either no diabetic retinopathy or non-proliferative diabetic retinopathy were considered for inclusion, provided there was no clinically detectable macular oedema on slit-lamp biomicroscopy. Eyes with good visual acuity and adequate OCT image quality were included to ensure reliable biomarker assessment. Patients with proliferative diabetic retinopathy, clinically significant macular oedema requiring treatment, prior intravitreal therapy or retinal laser procedures, vitreoretinal surgery, or other coexisting macular pathologies were excluded. Eyes with poor image quality due to media opacities were also excluded from analysis.

Clinical and Ophthalmic Assessment

All enrolled participants underwent a detailed ophthalmic examination, including best-corrected visual acuity assessment using Snellen charts, slit-lamp examination of the anterior segment, measurement of intraocular pressure, and dilated

fundus evaluation using indirect ophthalmoscopy. The severity of diabetic retinopathy was graded according to standard clinical classification systems. Relevant systemic details, including duration of diabetes and treatment history, were recorded from medical records.

OCT Imaging Protocol
Spectral-domain OCT imaging was performed for all eligible eyes using a standard macular scan protocol centred on the fovea. High-resolution cross-sectional images of the macula were acquired to allow detailed evaluation of retinal architecture. Only scans with adequate signal strength and minimal artefacts were included for further analysis to ensure consistency and reliability of measurements.

Assessment of OCT Biomarkers
OCT images were analysed for predefined structural biomarkers known to be associated with early DME. These included central subfield retinal thickness, presence and configuration of intraretinal cystoid spaces, hyperreflective foci within the retinal layers, integrity of the external limiting membrane and ellipsoid zone, disorganisation of the retinal inner layers (DRIL), and abnormalities at the vitreomacular interface. Biomarker definitions and grading criteria were adopted from recent literature and consensus-based descriptions to maintain standardisation across study centres [11–13].

Definition of Early or Subclinical DME
Early or subclinical DME was defined as the presence of OCT-detected retinal thickening or microstructural changes suggestive of oedema in the absence of clinically visible macular oedema on biomicroscopy. This definition reflects current understanding that OCT can identify macular involvement at a stage earlier than conventional clinical examination [14].

Image Interpretation and Quality Assurance
All OCT scans were independently reviewed by two experienced retina specialists who were masked to the clinical details of the participants. In cases of disagreement, a consensus was reached through joint review. Automated segmentation outputs, where available, were carefully checked and corrected manually if required to ensure anatomical accuracy, in line with recent recommendations for OCT biomarker analysis [15].

Ethical Considerations
The study protocol was reviewed and approved by the Institutional Ethics Committees of both participating institutions. The study was conducted in accordance with the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrolment.

Statistical Analysis
Collected data were entered into a secure database and analysed using standard statistical software. Continuous variables were summarised as mean and standard deviation, while categorical variables were expressed as frequencies and percentages. Appropriate statistical tests were applied to explore associations between OCT biomarkers and early DME status, with a p-value of less than 0.05 considered statistically significant.

RESULTS

Baseline Demographic and Clinical Profile
During the study period (2024–2025), a total of 168 eyes from 168 patients met the eligibility criteria and were included in the final analysis. The study population represented a typical tertiary-care diabetic cohort, with a predominance of middle-aged individuals and a higher proportion of males. Most participants had type 2 diabetes mellitus with a moderate duration of disease (Table 1). Clinically, all eyes included in the study had either no diabetic retinopathy or non-proliferative diabetic retinopathy (NPDR), and none had clinically detectable macular oedema on slit-lamp biomicroscopy. Mean best-corrected visual acuity (BCVA) was relatively preserved, reflecting the early or subclinical nature of macular involvement in the cohort.

Table 1: Baseline demographic and clinical characteristics

Parameter	Value
Number of patients (eyes)	168
Mean age (years)	54.6 ± 9.8
Male : Female	96 : 72
Type 2 diabetes mellitus	152 (90.5%)
Duration of diabetes (years)	8.3 ± 4.6
NPDR present	102 (60.7%)
No DR	66 (39.3%)
Mean BCVA (logMAR)	0.18 ± 0.09

Prevalence of Early / Subclinical Diabetic Macular Oedema

Based on predefined OCT criteria, 46 eyes (27.4%) were classified as having early or subclinical DME, while 122 eyes (72.6%) showed no OCT evidence of macular oedema. Importantly, none of the eyes categorised as early DME demonstrated clinically apparent oedema, underscoring the added sensitivity of OCT in detecting early retinal changes (Figure 1).

This finding highlights that nearly one in four eyes with diabetes may harbour early macular involvement that is not evident on routine clinical examination.

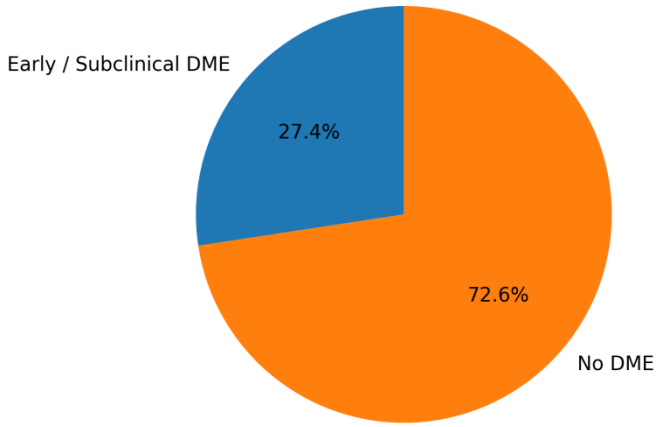

Figure 1: Distribution of eyes based on OCT classification

Central Subfield Thickness and Early DME

Central subfield thickness (CST) was significantly higher in eyes with early DME compared to those without OCT evidence of oedema. Although CST values in the early DME group largely remained below conventional treatment thresholds, the difference between the two groups was statistically significant (Table 2).

Table 2: Comparison of central subfield thickness

Group	Mean CST (µm)	SD	p value
Early DME	272.4	18.6	
No DME	241.8	15.2	**<0.001**

This confirms that even modest increases in CST can serve as an early marker of macular involvement when interpreted in the appropriate clinical context (Figure 2).

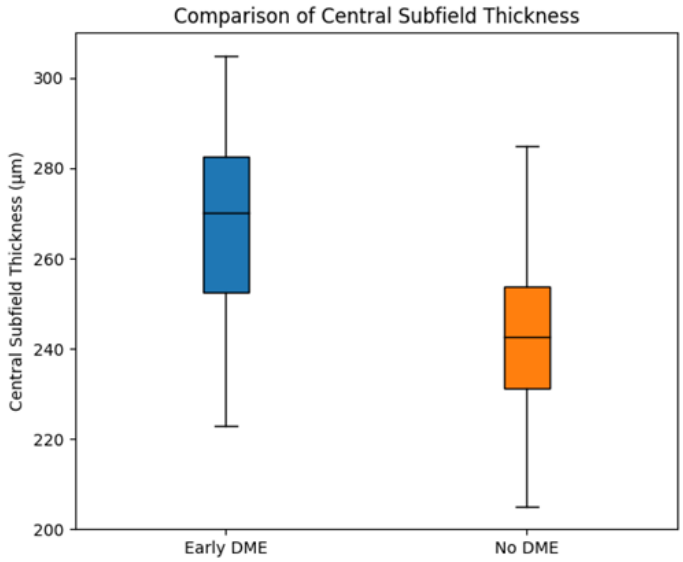

Figure 2: Box-and-whisker plot showing CST distribution

Distribution of Individual OCT Biomarkers

The frequency of individual OCT biomarkers differed markedly between eyes with early DME and those without. Intraretinal cystoid spaces were the most prevalent structural abnormality, followed by hyperreflective foci (HRF) and disorganisation of the retinal inner layers (DRIL) (Table 3; Figure 3)).

Table 3: Frequency of OCT biomarkers in study groups

OCT Biomarker	Early DME n (%)	No DME n (%)	χ^2	p value
Intraretinal cysts	32 (69.6%)	14 (11.5%)	58.4	<0.001
Hyperreflective foci	29 (63.0%)	21 (17.2%)	33.9	<0.001
DRIL	24 (52.2%)	16 (13.1%)	26.1	<0.001
Ellipsoid zone disruption	18 (39.1%)	9 (7.4%)	25.6	<0.001
Vitreomacular interface changes	10 (21.7%)	8 (6.6%)	7.9	0.005

These findings demonstrate that early DME is characterised by a **cluster of microstructural abnormalities**, rather than isolated retinal thickening.

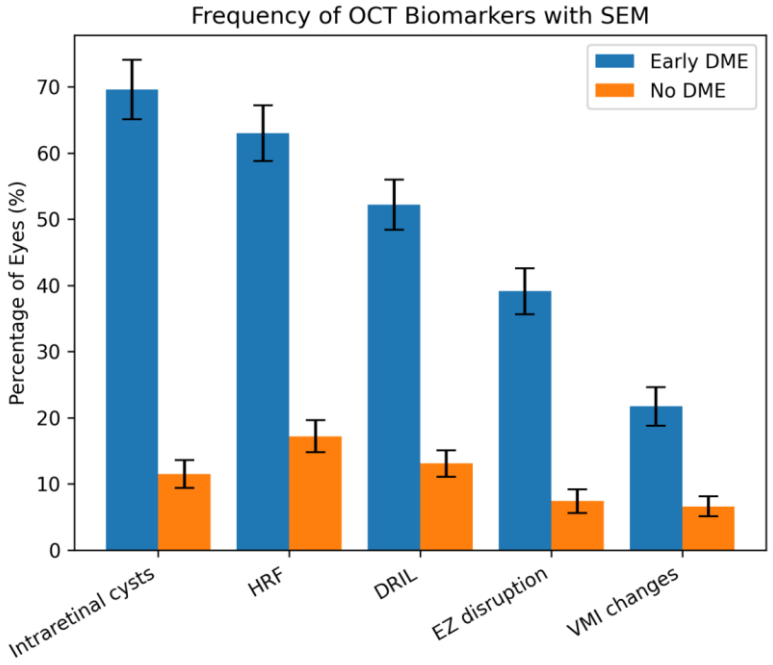

Figure 3: Bar chart showing frequency of OCT biomarkers

Disorganisation of Retinal Inner Layers (DRIL) and Visual Function

DRIL was present in over half of the eyes with early DME and showed a significant association with reduced visual acuity. Eyes with DRIL had worse BCVA compared to those without DRIL, despite overlapping CST values (Table 4; Figure 4).

Table 4: Association between DRIL and BCVA

DRIL status	Mean BCVA (logMAR)	SD	p value
Present	0.24	0.08	
Absent	0.16	0.07	**0.002**

This suggests that DRIL reflects early functional compromise and neural retinal involvement, making it a clinically meaningful biomarker even in subclinical stages.

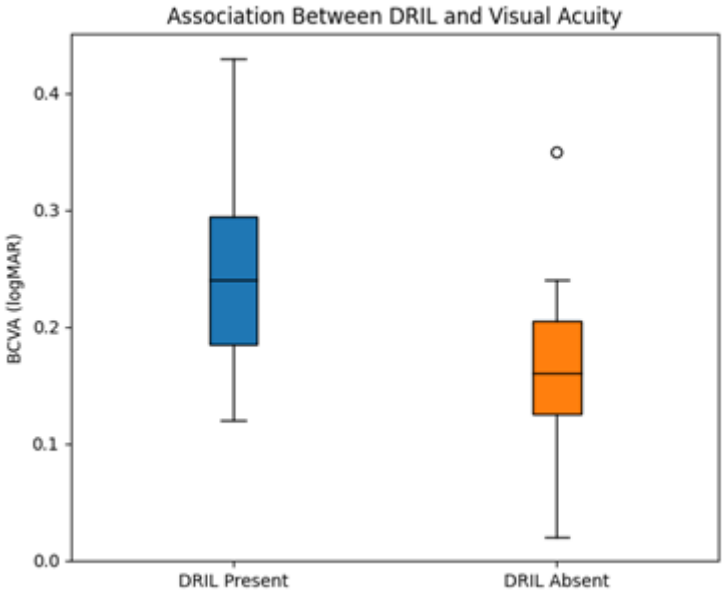

Figure 4: Scatter plot showing relationship between DRIL and BCVA

Outer Retinal Integrity and Early Disease Severity

Disruption of the ellipsoid zone (EZ) was significantly more common in eyes with early DME. Eyes exhibiting EZ disruption had higher CST values and poorer BCVA compared to eyes with preserved outer retinal layers ($p < 0.01$). This finding indicates that outer retinal involvement can occur early in the disease process and may herald a higher risk of visual decline if left unrecognised.

Combined OCT Biomarker Burden

When OCT biomarkers were analysed collectively, eyes with **two or more concurrent biomarkers** were significantly more likely to be classified as early DME (Table 5; Figure 5).

Table 5: Biomarker burden and early DME

Biomarker count	Early DME n (%)	No DME n (%)	χ^2	p value
≤1 biomarker	8 (17.4%)	98 (80.3%)		
≥2 biomarkers	38 (82.6%)	24 (19.7%)	61.7	<0.001

This highlights the superiority of a **multimarker OCT approach** over reliance on a single parameter such as retinal thickness alone.

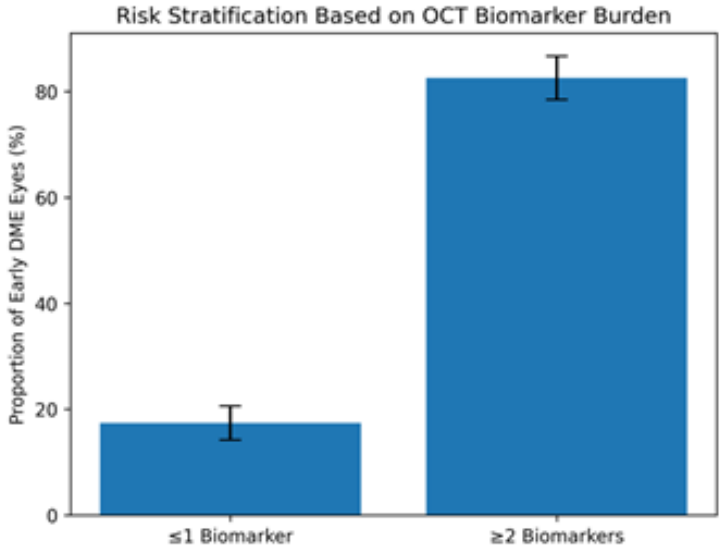

Figure 5: Risk stratification based on OCT biomarker burden

DISCUSSION

The present study highlights the value of OCT–based biomarkers in identifying early or subclinical DME in eyes that appear normal on routine clinical examination. A key observation from this work is that a substantial proportion of diabetic eyes without clinically evident macular oedema already demonstrate structural retinal alterations on OCT, reinforcing the concept that macular involvement in diabetes begins well before overt oedema or significant visual loss becomes apparent.

Traditionally, DME has been diagnosed when macular thickening becomes clinically obvious or when visual acuity declines. However, recent imaging-driven paradigms emphasise that DME represents a continuum of structural change, rather than a binary clinical state. The current findings support this view by showing that early DME can be reliably detected using OCT criteria even in the absence of slit-lamp evidence of oedema. This aligns with recent population-based and clinic-based imaging studies suggesting that OCT-detected macular thickening and microstructural abnormalities precede clinically significant disease and may follow a progressive course if left unrecognised [16,17].
CST was significantly higher in eyes classified as early DME compared with those without OCT evidence of oedema. While this confirms the relevance of quantitative thickness metrics, the overlap in CST values between groups highlights an important limitation: thickness alone does not fully capture early disease activity. Several recent analyses have shown that eyes with similar CST measurements may have markedly different visual function and progression risk depending on associated microstructural features [18]. The present findings therefore support a shift away from thickness-centric assessment toward a broader biomarker-based interpretation of OCT scans.

Intraretinal cystoid spaces were the most frequently observed OCT abnormality in early DME, suggesting that focal breakdown of the blood–retinal barrier and localised fluid accumulation occur early in the disease process. Hyperreflective foci (HRF) were also common in early DME eyes, consistent with the growing body of evidence linking HRF to inflammatory activity, lipid extravasation, and activated microglial cells in diabetic retinopathy [19,20]. Importantly, the presence of HRF in eyes without clinically apparent oedema may indicate an active disease state with a higher likelihood of progression, underscoring their value as an early warning biomarker.

One of the most clinically meaningful observations in this study was the strong association between DRIL and reduced visual acuity, even at an early stage of macular involvement. Eyes with DRIL demonstrated worse visual function despite having CST values within a subclinical range. This supports the emerging concept that DRIL reflects inner retinal dysfunction and neural pathway disruption, rather than simply fluid-related thickening [21]. Recent experimental and clinical work suggests that DRIL may represent impaired signal transmission through bipolar and amacrine cell layers, potentially explaining its close relationship with functional outcomes [22]. The present findings reinforce the role of DRIL as a sensitive marker of early functional compromise in diabetic macular disease.

Although traditionally considered a feature of more advanced DME, disruption of the ellipsoid zone was observed in a notable proportion of early DME eyes. This suggests that outer retinal involvement can begin earlier than previously assumed, particularly in eyes with concurrent inner retinal abnormalities or inflammatory markers. Preservation of photoreceptor integrity is a major determinant of visual prognosis, and recent longitudinal studies have demonstrated that early outer retinal disruption is associated with poorer long-term visual outcomes [23]. Detecting such changes at an early stage provides an opportunity for closer surveillance and timely intervention before irreversible damage occurs.
A major strength of this study lies in demonstrating that the burden of OCT biomarkers, rather than any single parameter, offers superior discrimination of early DME. Eyes exhibiting two or more concurrent biomarkers were significantly more likely to be classified as early DME, supporting a multimodal structural phenotype of early disease. This approach aligns with contemporary risk-stratification models that integrate multiple OCT features to identify eyes at higher risk of progression or visual decline [24]. Such a strategy may be particularly valuable in high-volume screening settings, where prioritising patients for closer follow-up or referral is essential.

The findings of this study have several practical implications. First, they support the incorporation of OCT into routine diabetic eye evaluation, particularly for patients with longer disease duration or early retinopathy changes. Second, they highlight the need for clinicians to move beyond CST alone and systematically assess additional OCT biomarkers such as DRIL, HRF, and outer retinal integrity. Third, identifying early DME provides a window for intensified systemic control, closer monitoring, and timely referral to retina services, potentially delaying or preventing progression to vision-threatening disease.

Limitations and Future Directions

This study is limited by its observational design and the absence of long-term follow-up to directly assess progression from early DME to clinically significant oedema. Future longitudinal studies are needed to validate the predictive value of individual and combined OCT biomarkers over time. Integration of OCT angiography parameters and automated, artificial intelligence–based biomarker quantification may further enhance early detection and risk stratification in diabetic macular disease [25].

In summary, this study demonstrates that OCT-based biomarkers can reliably identify early or subclinical diabetic macular oedema in eyes without clinically evident macular involvement. Early DME is characterised by subtle but significant structural changes involving retinal thickness, intraretinal cysts, hyperreflective foci, DRIL, and early outer retinal disruption. A multimarker OCT approach provides a more comprehensive assessment of early disease and has the potential to improve screening, monitoring, and personalised management strategies in diabetic eye care.

CONCLUSION

The present study demonstrates that optical coherence tomography (OCT)–based biomarkers play a crucial role in identifying early or subclinical DME in eyes that appear normal on routine clinical examination. A significant proportion of diabetic eyes without clinically evident macular oedema showed subtle yet meaningful structural alterations on OCT, underscoring the limitations of clinical assessment alone in detecting early macular involvement.

Among the OCT parameters evaluated, modest increases in central subfield thickness, intraretinal cystoid changes, hyperreflective foci, DRIL, and early disruption of outer retinal integrity emerged as key indicators of early disease. Importantly, biomarkers such as DRIL and ellipsoid zone disruption were associated with reduced visual acuity even at a subclinical stage, highlighting that functional compromise may begin before overt oedema becomes apparent. These findings reinforce the concept that DME represents a continuum of structural and functional change rather than a discrete clinical entity.

The study also demonstrates that a multimarker OCT approach provides superior discrimination of early DME compared with reliance on retinal thickness alone. Eyes exhibiting multiple concurrent OCT abnormalities were significantly more likely to be classified as early DME, supporting the use of combined biomarker profiles for risk stratification. From a clinical perspective, early identification of such high-risk eyes offers an opportunity for closer monitoring, optimisation of systemic risk factors, and timely referral to retina services, with the potential to delay progression to vision-threatening disease.

Overall, incorporation of structured OCT biomarker assessment into routine diabetic eye evaluation may enhance early detection strategies and support more personalised management pathways in diabetic macular disease. Further longitudinal studies are warranted to validate the predictive value of these biomarkers and to define their role in guiding early therapeutic interventions.

Conflict of Interest (COI)

The authors declare that there are no conflicts of interest related to this study. The research was conducted independently, and the study design, data collection, analysis, interpretation of results, and manuscript preparation were not influenced by any commercial or personal relationships.

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