Hyper reflective foci on spectral domain optical coherence tomography as a biomarker for predicted recurrence rate and visual prognosis in diabetic macular edema

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Purpose: To investigate the correlation between hyperreflective retinal foci and recurrent rate in diabetes patients after treatment with anti-VEGF

Methods: We reviewed medical records of 82 patients, 101 eyes with diabetic macular edema between 2021 - 2023 at Thammasat Hospital with complete records of over 24 months. The study design compared recurrent and non-recurrent macular edema groups. Demographic data such as age, gender, details of the underlying disease (HbA_1c level) including biomarkers such as disorganization of retinal inner layer (DRIL), hyper-reflective retinal foci (HRF), subretinal fluid (SRF), intraretinal fluid (IRF) from OCT were collected at baseline.

Results: Hyper-reflective retinal foci was notably more abundant in the recurrent group, exhibiting statistically significant disparities (P value = 0.013). Furthermore, a substantial discrepancy emerged concerning HbA_1C levels, with values of 7.5 ± 1.4 in the non-recurrence group and 8.9 ± 2.3 in the recurrence group (P value = 0.044). Upon a 24-month evaluation, the visual acuity (log MAR) were measured at 0.363 ± 0.482 in the non-recurrence group and 0.527 ± 0.206 in the recurrence group, manifesting a notable difference (P value = 0.033). Hyperreflective retinal foci in the outer retina were markedly more prevalent in the recurrence group than the alternative group (P value: 0.026). Furthermore, the mean numbers of anti-VEGF injections were 10.54 ± 2.58 in the non-recurrence group and 17.82 ± 1.93 in the recurrence group, displaying a statistically significant divergence (P value = 0.041).

Conclusions : HRF in the outer retina displayed a favorable impact on visual prognosis and a tendency towards recurrence in cases of diabetic macular edema. Furthermore, Hemoglobin A_1C emerged as a noteworthy risk factor deserving attention to attain optimal treatment outcomes.

Keywords: recurrence macular edema, retinal biomarker, hyper reflective retinal foci, anti VEGF, diabetic macular edema

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Introduction

Diabetes mellitus[1-4] is an ailment characterized by abnormal sugar levels in the bloodstream, resulting in various complications within the body. These complications encompass conditions like coronary artery disease, diabetic retinopathy, diabetic nephropathy, and persistent diabetic foot ulcers. Presently, there is an escalating trend in the diagnosis of diabetes among individuals.

Reduced vision experienced by diabetic patients may stem from several factors, including macular ischemia (insufficient blood supply to the eye's macula), diabetic macular edema, abnormal growth of new retinal blood vessels

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(neovascularization, and vitreous hemorrhage). Among these causes, macular edema is the most frequently observed.[1,3,4,5] At the moment, the diagnosis and treatment planning for macular edema emphasize non-invasive investigative methods that are safe and minimally disruptive to patients. Some of these methods involve Optical Coherence Tomography (OCT) and Optical Coherence Tomography Angiography (OCTA).[5,9] OCT is a non-invasive imaging modality that employs light waves to capture cross-sectional retinal images. It aids in visualizing macular thickness and structural changes, facilitating macular edema diagnosis. Another non-invasive imaging technology is OCTA, which furnishes comprehensive images of retinal blood vessels, allowing for enhanced visualization of abnormal vessel growth and facilitating macular edema extent assessment.

Numerous studies are currently in progress to identify biomarkers that could aid in forecasting the visual prognosis for macular edema.[6,7,8] Certain biomarkers, such as Disorganization of Retinal Inner Layers (DRIL)[10,11], indicate the disruption of the retina's inner layers and have shown promise in predicting visual outcomes for patients with macular edema. Another potential biomarker is hyper reflective retinal foci (HRF)[12-14], which are highly reflective spots noticeable in OCT images and have been examined for their predictive potential regarding visual prognosis. Additionally, the concept of Central Retinal Bridging pertains to abnormal connections within the central retina and has been explored as a possible prognostic biomarker.[15,16] Utilizing these non-invasive investigative methods and biomarkers, clinicians can enhance the accuracy of macular edema diagnosis and customize treatment strategies for each patient. The ultimate goal is to enhance visual outcomes and effectively manage this condition.

Several hypotheses have been proposed to elucidate the genesis of hyper reflective retinal foci (HRF) in the ocular context.[17-19] One explanation by Bolz et al.[18] posits that HRF might stem from the extravasation of lipids from retinal blood vessels, migration of pigmented cells from the retinal pigment epithelium (RPE cells) into the outer retina, or potentially as an outcome of retinal inflammation. These factors collectively contribute to the manifestation of HRF within the eye. Recent investigations carried out by Akihito et al.[20] have ascertained the presence of HRF in patients experiencing early recurrent macular edema. Moreover, the study revealed that individuals with HRF demonstrated a comparatively subdued response to anti-VEGF treatment in contrast to those lacking HRF. This phenomenon might be attributed to a higher frequency of HRF indicative of heightened retinal inflammation, which could potentially exhibit greater responsiveness to intravitreous steroid treatment or steroid implantation, as opposed to the conventional anti-VEGF treatment.

Hence, the objective of this study is to explore the correlation between hyper-reflective retinal foci in individuals affected by recurring macular edema, employing Optical Coherence Tomography. The aim is to ascertain the potential of hyper-reflective retinal foci as predictive indicators for macular edema relapse, facilitating treatment planning, and forecasting disease advancement and levels of visual acuity.

Patients and Methods

We conducted a retrospective review study on eyes with diabetic macular edema (DME) and treated either with 1.25 mg of bevacizumab, 0.5 mg of ranibizumab, or 2 mg of Aflibercept, which had a follow-up period of interval at least 24 months at Thammasat Hospital between January 2021 and July 2023. This study was approved by the ethics committee for human research at Thammasat University. The inclusion criteria were as follows: age > 18 years old, visual acuity worse than 20/40, presence of center-involved DME at baseline (central subfield thickness (CST) > 300μm on OCT - Cirrus HD-OCT5000TM; Carl Zeiss, Dublin, California, USA), and a follow-up period of at least 2 years after treatment. Patients who experienced visual loss from other causes were excluded from this study, such as uncontrolled glaucoma, a history of uveitis, previous vitrectomy, laser panretinal photocoagulation (PRP), and those with a follow-up of less than 24 months. Recurrent macular edema was defined as macular edema that recurred after complete resolution for a period of at least 4 months. Demographic data, such as age, gender, details of the underlying disease (HbA1c), and stage of diabetic retinopathy, including biomarkers[6,7,10,18] such as Disorganization of retinal inner layer (DRIL), Hyper-reflective retinal foci (HRF), Subretinal

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fluid (SRF), Intraretinal fluid (IRF) from OCT were determined by experienced retinal specialist and collected at baseline.

Statistical Analysis

We had used descriptive statistics in general information of the sample Group such as Percentage number, Standard deviation (SD), Mean, Median, Interquartile Range (IQR), the range between the 25th percentile and the 75th percentile. Analysis Statistics using the significance level at P value < 0.05 to compare proportions of categorical data such as sex, underlying disease, macular thickness between the recurrent and non recurrent Groups by using Pair t-test. Comparing Means (Quantitative Data) of variables such as Age and Duration DME per eye between the Recurrent and No Recurrent Groups using Independent t-test and sample size was calculated by

$$n = \frac{\{Z_{\alpha/2}\sqrt{2\overline{P}(1-\overline{P})} + Z_{\beta}\sqrt{P_1(1-P_1)+P_2(1-P_2)}\}^2}{(P_1-P_2)^2}$$

Which had sample size 41 in each group. All data collection was performed by Statistical analysis SPSS v. 23.0.

Results

Baseline characteristics of 82 patients with diabetes macular edema were enrolled in the study, accounting for a total of 101 eyes. The mean age was 59.4 ± 12.7 in the non-recurrence group and 62.5 ± 11.3 in the recurrence group. A higher percentage of men were present in both groups, constituting 60.97% and 68.3% respectively. Notably, significant differences were observed in both hemoglobin A_1C (7.5 ± 1.4 in the non-recurrence group, 8.9 ± 2.3 in the recurrence group, (P value 0.044)) and optical coherence tomography (OCT) features which exhibited higher occurrences of hyper-reflective retinal foci and intraretinal fluid compared to the non-recurrence group (P value; 0.013 and 0.024 respectively). However, while subretinal fluid appeared more common in the non-recurrence group, this difference did not reach statistical significance (P value, 0.117). Regarding OCT features, the recurrence group had 5 eyes (8.47%) with disorganization of the retinal inner layer (DRIL), whereas the non-recurrence group had 1 eye (1.92%) with DRIL (P value, 0.559). Proliferative diabetic retinopathy (PDR) was more frequently observed in the recurrence group compared to the non-recurrence group (26 cases, 53.06% vs. 16 cases, 30.77%). Additionally, the mean central retinal thickness was 531.9 ± 141.2 in the non-recurrence group and 678.1 ± 153.5 in the recurrence group (Table 1).

We assessed the correlation of mean BCVA (logMAR) between the two groups. The study's results revealed that eyes in the non-recurrence group had a mean of 0.63 ± 0.24, while the recurrence group showed a mean of 0.51 ± 0.39, which demonstrated a significant improvement after treatment at 1 and 3 months (P value = 0.027 and 0.031, respectively). However, subsequent to this period, no significant correlation was observed, even though the recurrence group experienced instances of visual acuity decline due to recurrent macular edema, notably around the 9 month (P value = 0.158) (Figure 1). Regarding the disparity between HRF in the inner and outer retina post-treatment, it was noted that the recurrence group exhibited significantly higher HRF in the outer retina compared to the non-recurrence group (P value, 0.026). Conversely, while the recurrence group also showed a greater presence of HRF in the inner retina, this difference was not statistically significant (P value, 0.529) (Table 2).

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Table 1: Baseline Demographic and OCT feature between recurrence and non recurrence macular edema group

Characteristic	Non recurrence	Recurrence	P value
Number of patients (eyes)	41(52)	41(49)	-
Age, mean ± SD (year)	59.4 ± 12.7	62.5 ± 11.3	0.284
Gender n (%)			0.493
Male	25(60.97)	28(68.3)	
Female	16(39.03)	13(31.7)	
Hemoglobin A_1C, mean ± SD (%)	7.5 ± 1.4	8.9 ± 2.3	0.044
BCVA (log MAR), mean ± SD	0.71 ± 0.39	0.83 ± 0.24	0.414
Stage of DR, eyes(%)			0.372
NPDR	36(69.23)	23(46.94)	
PDR	16(30.77)	26(53.06)	
Central subfield thickness, mean ± SD (μm)	531.9 ± 141.2	678.1 ± 153.5	0.281
OCT feature, eyes(%)			
Subretinal fluid	19(36.53)	13(26.53)	0.117
Intraretinal fluid	5(9.61)	11(22.44)	0.024
Hyper- reflective retinal foci	8(15.38)	17(34.69)	0.013
DRIL	1(1.92)	5(8.47)	0.559

BCVA = Best corrected visual acuity, NPDR = Non proliferative diabetic retinopathy, PDR = Proliferative diabetic retinopathy, DRIL = Disorganization of retinal inner layer, OCT = Optical coherence tomography, P values for mean data were calculated with the use of independent t-test or Mann-Whitney U-test, for percentages with the use of Chi-square test or Fisher's exact test

Figure 1: Best corrected visual acuity (BCVA) change compare between non recurrence and recurrence macular edema group after follow up 24 month. Visual acuity (logMAR) in non recurrence group (0.363 ± 0.482) better than recurrence group (0.527 ± 0.206) after treatment with statistic significant (P value = 0.033).

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Table 2: Comparison between non recurrence and recurrence macular edema group in HRF and visual acuity during initial visit and after follow up 24 months

	Non recurrence	Recurrence	**P value**
Visual acuity (logMAR)	0.363 ± 0.482	0.527 ± 0.206	0.033
HRF in inner retina (eyes)	8	11	0.529
HRF in outer retina (eyes)	9	27	0.026

All analyses were performed by paired t-test

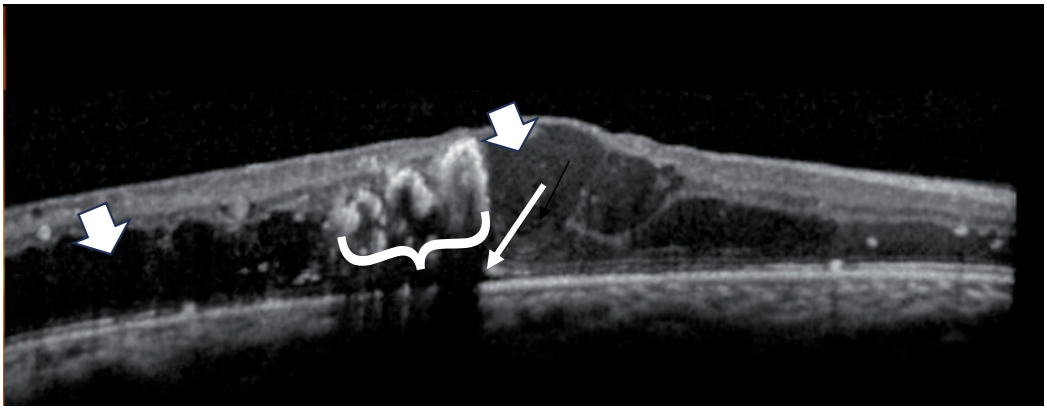

Figure 2: A 52-year-old male presented with blurred vision in his left eye. An optical coherence tomography (OCT) radial scan of the macular area revealed the presence of subretinal fluid (white arrow) and intra retinal fluid at the fovea (arrow head) and area of white bracket accompanied by irregularities in the ellipsoid layer. However, the layers of the retina were still distinguishable, indicating a negative result for the disorganization of the retinal inner layer (DRIL) in this case. Following treatment with anti-VEGF medication, his vision showed improvement, leading to a favorable prognosis.

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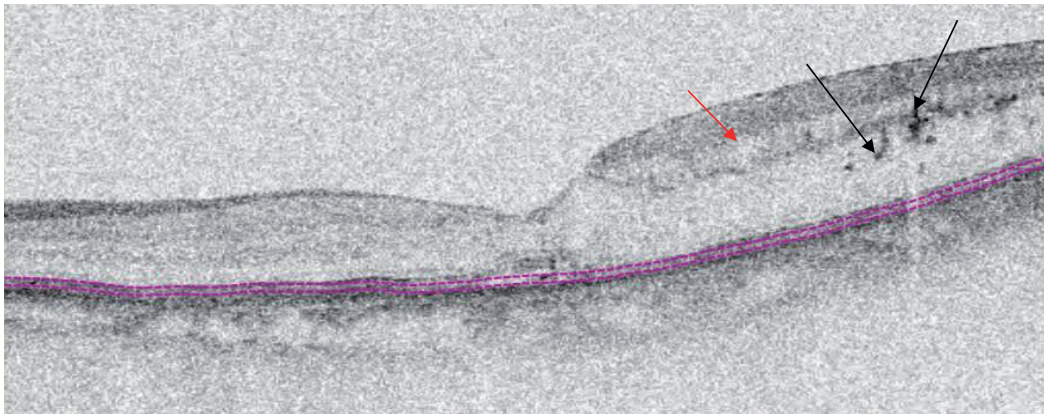

Figure 3: The optical coherence tomography scan of a 43-year-old female, who presented with chronic progressive painless visual loss in her left eye, revealed the presence of numerous dots in both the inner and outer retina (Black arrow). Additionally, inner retinal cystoid spaces were observed (Red arrow). The intact ellipsoid line is represented by the dashed purple line. Despite undergoing multiple anti-VEGF treatments, the final visual acuity in this case did not exhibit significant improvement.

Table 3: Compare factor between Non recurrence and Recurrence macular edema group in number of anti VEGF injection and central subfield thickness

Factor	Non recurrence (N = 52 eyes)	Recurrence (N = 49 eyes)	**P value**
Mean Total Anti-VEGF injection	10.54 ± 2.58	17.82 ± 1.93	0.041
Bevacizumab	8.84 ± 3.42	11.27 ± 2.26	0.137
Ranibizumab	6.13 ± 1.17	9.95 ± 1.21	0.056
Aflibercept	4.25 ± 2.37	3.51 ± 1.48	0.148
Mean CSF ± SD (μm)			
At month 3	336 ± 151.8	382 ± 173.5	0.073
At month 6	294 ± 114.6	323 ± 164.9	0.166
At month 9	251 ± 142.1	379 ± 135.8	0.042
At month 12	269 ± 167.4	352 ± 143.2	0.069
At month 24	264 ± 133.4	315 ± 123.2	0.195

All analyses were performed by paired t-test, *VEGF = Vascular endothelial growth factor,*
CSF = Central subfield thickness

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In the group experiencing recurrent macular edema, there was a notably greater count of Anti-VEGF injections in comparison to the alternate group (P value = 0.041), with an average of 17.82 ± 1.93 injections within the recurrence group and 10.54 ± 2.58 injections within the non-recurrence group. While both bevacizumab and ranibizumab demonstrated a higher injection frequency in the recurrence group compared to the non-recurrence group, these variations did not achieve statistical significance (11.27 ± 2.26 (P value = 0.137) and 9.95 ± 1.21 (P value = 0.056)). Conversely, aflibercept injections occurred more frequently in the non-recurrence group (3.51 ± 1.48) than in the recurrence group (4.25 ± 2.37), although this difference did not attain statistical significance (P value = 0.148). While the mean central subfield thickness exhibited a tendency to be higher in the recurrence group, statistically significant discrepancies were solely observable at 9-months (379 ± 135.8, P value = 0.042) (Table 3).

Discussion

In this study, we established a correlation between hyper reflective retinal foci (HRF) and visual outcomes, as well as recurrence rates, in diabetes patients with center-involved macular edema. Recent research[17-20] has highlighted the impact of HRF on visual outcomes after treatment due to various pathogenesis which suggest that HRF represent either of hard exudate and inflammatory cells so anti-VEGF treatment is rendered less responsive and becomes recurrent as a result of poor control of disease activity. For instance, Hyewon *et al*.[21] noted that the number and location of HRF can significantly affect the final visual outcome, particularly when located in the outer retina. Similarly, Uji *et al*.[20] demonstrated that the presence of HRF in the outer retina was associated with poor baseline vision and disrupted anatomical structure in diabetic macular edema prior to treatment. Moreover, another study[22-24] has reported a correlation between hyper reflective retinal foci (HRF) and visual acuity in patients with center involved macular edema, indicating that the number of HRF can serve as a predictive factor for prognosis. Similarly, our study demonstrated a notable association between HRF located at the outer retina and a higher recurrence rate, showing statistical significance (P value, 0.026). Therefore, when a patient exhibits HRF at the outer retina upon baseline evaluation, it's crucial to consider that this could lead to an elevated likelihood of recurrence compared to cases where HRF is not present post-treatment. Additionally, Vivian *et al*.[25] noted a correlation between HRF and the severity of diabetic retinopathy (DR). An increased number of HRF corresponded to a more advanced stage of DR diagnosis, and these findings were also linked to the morphology of the central retina.

Chu-Hsuan *et al*.[26] reported a positive association between Hemoglobin A_1C levels and hyper reflective retinal foci (HRF) both in the inner and outer retina (P value = 0.002 and 0.001, respectively), a correlation that was also observed in our investigation. Our results indicated that individuals within the recurrence group exhibited a notably elevated average HbA_1C level (8.9 ± 2.3) compared to the other group (P value = 0.044). Furthermore, intraretinal fluid (IRF) and hyper reflective retinal foci (HRF) were distinctly more frequent in the recurrence group, showing statistical significance (P value = 0.024 and 0.013, respectively). Recent studies[27] have emphasized that both IRF and HRF function as indicators predicting an unfavorable visual prognosis among patients with diabetic macular edema. Significantly, HRF not only exhibited a connection with HbA_1C levels but also emerged as a predictive marker for gauging disease severity. Additionally, Joon-Won *et al*.[21]'s findings reported a correlation between HRF and central retinal thickness; a higher count of HRF corresponded to an increase in central retinal thickness. This discovery aligns with our study, wherein the recurrence group displayed augmented central retinal thickness (678.1 ± 153.5) alongside a higher prevalence of HRF, even though multiple factors could contribute to the heightened thickness.

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Table 4: Subgroup analysis correlation between HRF and anti VEGF in recurrence macular edema group

	Number of HRF at baseline	Number of HRF after treatment	P value
Bevacizumab	19.28 ± 2.37	14.61 ± 1.19	0.573
Ranibizumab	12.66 ± 0.45	7.73 ± 0.51	0.041
Aflibercept	13.23 ± 1.54	5.92 ± 0.93	0.035

All analyses were performed by paired t-test

Presently, the accepted and established protocol for managing diabetic macular edema (DME) revolves around the utilization of anti-VEGF agents.[28-29] This subject has undergone thorough exploration and documentation in the academic literature.[30] The advantages of anti-VEGF therapy have been convincingly showcased, underscoring its multifaceted mechanisms to counteract vascular leakage. These mechanisms encompass the interaction with diverse factors like VEGF-A, VEGF-B, and PlGF, contingent on the specific anti-VEGF agent that is employed. In Thailand, a significant majority of patients diagnosed with diabetic macular edema and covered by the universal coverage scheme typically initiate their treatment with intravitreal bevacizumab as the primary therapeutic choice. If an insufficient clinical response is observed, medical practitioners possess the flexibility to transition to alternative anti-VEGF agents. In situations where the severity of diabetes-related retinopathy is notably high, healthcare professionals might for initiating treatment with ranibizumab or aflibercept as the initial step.

In the context of our investigation, the count of bevacizumab injections exceeded those of ranibizumab and aflibercept in both groups, although this discrepancy did not achieve statistical significance (P value = 0.137). Noteworthy is the fact that within the recurrence group, the count of hyperreflective retinal foci demonstrated a more favorable response to ranibizumab (P value = 0.041) and aflibercept (P value = 0.035) in comparison to bevacizumab (P value = 0.573), showing statistically meaningful differences (Table 4). This observation concurs with the findings of Neil *et al*.[31], who indicated that persistent diabetic macular edema was more commonly observed in the bevacizumab group compared to other anti-VEGF treatment categories. Furthermore, cases of persistent macular edema over an extended period were also more frequently linked with the bevacizumab group as opposed to the aflibercept group.

The retrospective nature of this study introduces certain limitations. The assessment of hyperreflective retinal foci was dependent on individual clinician discretion, possibly leading to variations in interpretation. Furthermore, the approach to switching anti-VEGF agents differed among clinicians, as did the intervals for follow-up and the treatment regimen[32] (pro re nata or treat and extend), resulting in varying injection frequencies. Despite our stringent adherence to the loading phase, meticulous maintenance of follow-up data, and consistent grading of diabetic retinopathy and treatment criteria, these discrepancies exerted an impact on our findings. Moreover, a limitation emerged within the subset of patients with proliferative diabetic retinopathy (PDR), as a considerable proportion in the recurrence group required supplementary panretinal photocoagulation (PRP) subsequent to treatment. This factor could potentially contribute to an elevation in the incidence of macular edema.[33]

To summarize, the existence of hyper reflective retinal foci (HRF) in the outer retina displayed an unfavorable impact on visual prognosis and a tendency towards recurrence in cases of diabetic macular edema. Both Aflibercept and Ranibizumab demonstrated greater efficacy in reducing the count of HRF in comparison to Bevacizumab. Importantly, the enhancement in visual acuity seen in the recurrence DME group after treatment did not parallel the level attained by the non-recurrence group. Furthermore, Hemoglobin A_1C emerged as a noteworthy risk factor deserving attention to attain optimal treatment outcomes.

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