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Inflammatory Biomarkers by Swept Source Optical Coherence Tomography in Diabetic Maculopathy

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Abstract: ***Aims: To assess the prevalence of inflammatory markers in diabetic patients with macular edema and to assess some factors related to it. Patients and methods: This is a cross - section study enrolled patients with diabetic maculopathy, the study was carried out at Jenna Ophthalmic Center in Baghdad between February 2023 and April 2023 including diabetic patients type 2 with diabetic macular edema with no history of previous intravitreal injections or laser therapy. All patients were examined by swept - source optical coherence tomography (OCT) to examine for inflammatory and other biomarkers. Results: This study enrolled 81 diabetic patients, with a mean age of 56.53± 8.18 years, 42 (51.9%) signs of inflammation on OCT. The inflammatory biomarkers that were identified included 12/42 (28.6%) with hyper - reflective foci (HRF), 36/42 (85.7%) with subretinal fluid (SRF). There was a statistically significant difference in central macular thickness between cases with positive HRF±SRF and negative HRF±SRF, as the CMT was 427.1±100.67 µm in negative cases while it was 510.26±123.66 µm in positive cases (P - value =0.001). Conclusion: Inflammatory biomarkers on OCT should not be ignored anymore, and central macular thickness should not be the sole factor that is depended on during follow - up.***

Keywords: inflammatory markers, diabetic macular edema, diabetic maculopathy, diabetic patients, optical coherence tomography, central macular thickness

1. Introduction

Diabetes macular edema (DME) remains a major complication of diabetic retinopathy (DR) and is one of the most frequent causes of visual impairment among productive age individuals. [(1)]

The pathogenesis of DME is complex and only partially related to hyperglycemia. [(2)] Long - term exposition to hyperglycemia, inflammation, and oxidative stress all play a role in the disruption of the blood - retinal barrier (BRB), vascular endothelial growth factor (VEGF), inflammatory chemokines (e. g., CCL2, CCL5, CXCL8), and cytokines (e. g, IL - 6, IL - 8, IL - 1β, and TNF - α), as well as adhesion molecules are all involved in the development of DME, [(3)] it is recognized that inflammation may have a central role in the development and subsequent progression of DR and that differences in how the inflammatory process is initiated and expressed may be responsible for the different rates of disease progression that are observed. [(4)]

In the early stages of the disease, the edema is responsible for the reduced visual acuity through the alteration of the retinal thickness and refractive index, in the later stages of the disease, ischemia and disorganization of the inner retinal layers, caused by glial reaction and neuro - retinal damages are the causes of irreversible vision. [(5)]

Optical coherence tomography (OCT) is one of the most accurate methods to evaluate the macular layers and changes in DME. [(5)] Numerous OCT biomarkers have been suggested to predict the functional and anatomical outcomes of different treatments, Saxena et al. demonstrated that mean central subfield thickness (CST), cube average thickness (CAT), and cube volume (CV) are all independent markers of DME severity and prognostic factors for visual acuity. [(6)] The inflammatory markers include subretinal fluid (SRF), hyper - reflective foci (HRF), and turbid fluid in cystoid macular edema are best diagnosed with swept or high - resolution OCT. [(7)]

The accumulation of subretinal fluid (SRF) suggests alteration of the outer BRB, probably due to fluid movement from the retina through a weakened and permeable external limiting membrane or from the increased permeability of the choriocapillaris through the dysfunctional retinal pigmented epithelium (RPE), [(8)] analysis of the intravitreal concentrations of cytokines in the eyes with the SRF type of DME indicated elevated intravitreal concentrations of VEGF, IL - 6, and IL - 8. [(9)] An elevated level of IL - 6 had a strong association with the presence of the SRF type of DME, suggesting that inflammation has an important role in the development of this phenotype. [(10)] Disruption of the external limiting membrane in the SRF type of DME is accompanied by cellular damage, and this attracts scavenger cells to the retina, which in turn produces IL - 6. [(9)] Another possibility might be due to migration towards and accumulation of the activated microglia in the outer segments of the retinal layer, which could produce an excess amount of IL - 6 and lead to the collection of fluid in the subretinal space. [(7)] Greater choroidal thickness is also present in the SRF type of DME, which suggests increased choriocapillaris permeability caused by excessive production of VEGF from dysfunctional RPE. [(7)]

Hyper - reflective foci (HRF) in OCT can be detected with high - resolution OCT, which appears as discrete intraretinal spots but differs from hard exudates with no shadow. [(11)] Some reports hypothesized that these HRF were extravasated lipoproteins that precede the formation of hard exudates, [(12)]

and one study hypothesized that HRF represents microglial activation and migration. [13] Moreover, the number of HRF is greater in patients with diabetes than in those without diabetes and greater in diabetic patients with diabetic retinopathy (DR) than diabetic patients without DR. [10] This suggests that HRF indicates the presence of microglial activation in the diabetic retina and are associated with the progression of DR. [10] A recent study investigating soluble CD14, a cytokine released by microglia and macrophage, reported that DME patients with diffuse edema showed higher levels of soluble CD14 in the aqueous humor as well as more HRF in the inner retina than those with focal edema, this suggests that HRF observed on OCT might be due to activated microglia, associated with severe inflammatory reaction. [9]

Turbid fluid in macular edema occurs more in inflammatory macular edema and is also reported in diabetic macular edema [14] and patients with turbid macular edema show more response to intravitreal steroids than to anti VEGF, [15] turbid cysts or reflectivity within the cysts have been observed in DME and retinal vein occlusion (RVO), Horii et al suggested that reflective grey signal within cysts could represent high molecular weight proteins, fibrin, hyaline material, macrophages or erythrocytes that occur with inflammation. [16] Spaide et al observed that as RBCs have Brownian movement, these intracystic structures may be picked up even on OCTA. [17]

Rationale of the study: The significance of this research goes beyond diagnostic advancements. It offers a precursor to precision medicine in the diabetic retinopathy realm, where tailored therapies based on individual biomarker profiles could potentially improve outcomes for patients with DME. However, further longitudinal studies are necessary to elucidate the causal relationships and the full clinical implications of these biomarkers in DME pathophysiology.

Aim of the Study

The primary aim is to assess the prevalence of inflammatory markers in diabetic patients with macular edema and the secondary aim is to assess some factors that might affect the prevalence of inflammatory markers.

Patients and Method

Study design and setting: This is a cross - section study done at Jenna Ophthalmic Center in Baghdad between February 2023 and April 2023 including diabetic patients type 2 with diabetic macular edema with no history of previous intravitreal injections or laser therapy.

Participants: The study includes diabetic patients (type 2) with macular edema.

Examination: Macular edema was diagnosed clinically and by Triton™ Swept source OCT (Topcon Corporation, Tokyo, Japan), as retinal thickening within one disc area at the center of the fovea on clinical biomicroscopic examination with central retinal thickness in OCT is more than 300 µm. The OCT was done with two experienced retinal specialists (who have more than ten years of experience) to identify the inflammatory markers in oct.

Exclusion criteria: Any patients with a previous history of intravitreal injection or laser therapy or vitreous surgery or other ocular surgery less than six months and excludes any other retinal or ocular disease that might affect maculopathy or OCT results as:

1) Significant media opacities that affect OCT signal as cataract or vitreous haziness, therefore eyes with poor quality with less than 40 Image Quality Value following the device manual instruction.
2) Other retinal diseases that might affect the macula such as age - related maculopathy, epiretinal membrane, retinal vein occlusion, uveitis, and idiopathic macular telangiectasia.
3) Moderate and advanced glaucoma.

Ethical considerations: This study was approved by the institutional review board of the Jena Ophthalmic Center Clinical Research Ethics Committee before performing this study. In addition, patients gave informed consent for the use of their data.

Statistical analysis: Ch - square test was used to study the association between two categorical variables. Data normality was examined by Anderson Darling Test, if variables followed normal distribution; independent samples - T - test was used, while if the variables did not follow normal distribution Mann Whitney U Test was used. P - value less than 0.05

2. Results

This study enrolled 81 diabetic patients, 39 (48.1%) had no evidence for inflammatory biomarkers (IB) on OCT, while 42 (51.9%) showed signs of inflammation on OCT. The mean age of the study participants was 56.53± 8.18 years, and there was no statistically significant difference in mean age between cases negative and positive cases. Males showed significantly more inflammatory evidence in comparison to females, with 31 (73.8%) in comparison to 11 (26.2%), respectively. Visual acuity whether it was 6/9 and better or not did not show a significant association with positivity for IB. As shown in Table - 1.

Table - 1: Distribution of basic characteristics of patients according to inflammatory biomarkers.

Variables		HRF±SRF		Total	P - value
		Negative	Positive		
		No. (%)	No. (%)	No. (%)	
Age in years (mean± SD)		57.31± 8.8	55.81±7.6	-	0.413
Laterality	OD	23 (59)	21 (50)	44 (54.3)	0.418
	OS	16 (41)	21 (50)	37 (45.7)	
Gender	Male	16 (41)	31 (73.8)	47 (58)	0.003
	Female	23 (59)	11 (26.2)	34 (42)	
Visual acuity	6/9 and better	6 (15.4)	10 (23.8)	16 (19.8)	0.341
	Worse than 6/9	33 (84.6)	32 (76.2)	65 (80.2)	

Chi - square test

The inflammatory biomarkers that were identified included 12/42 (28.6%) with hyper - reflective foci, 36/42 (85.7%) with subretinal fluid, 4/42 (9.5%) with turbid CMO, and 13/42 (31.0%) with Disorganization of inner retinal layers (DRIL) as shown in Figure - 1.

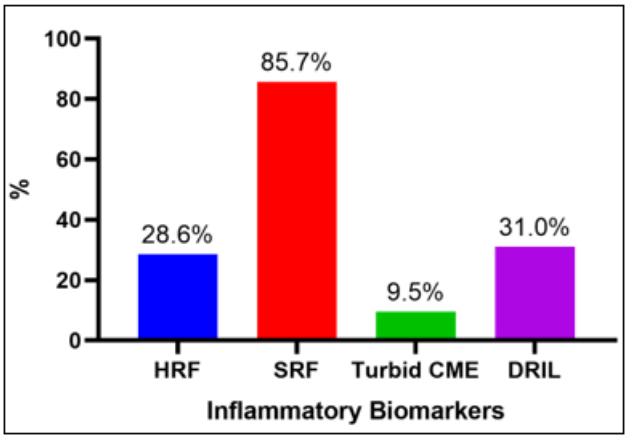

Figure 1: Inflammatory biomarkers types (classes are not mutually exclusive)

There was a statistically significant difference in CMT between cases with positive HRF±SRF and negative HRF±SRF, as the CMT was 427.1±100.67 µm in negative cases while it was 510.26±123.66 µm in positive cases (P - value =0.001), as shown in Table - 2. However, after examining each biomarker separately, there were no statistically significant differences in CMT between the presence or absence of each biomarker, as shown in Table - 3.

Table 2: Distribution of central retinal thickness according to inflammatory biomarkers

Variables	HRF±SRF		Mean difference	P - value*
	Negative	Positive		
	Mean± SD	Mean± SD		
Central retinal thickness	427.1±100.67	510.26±123.66	83.16	0.001

HRF: Hyper - reflective foci, SRF: Sub - retinal fluid, *: significant difference at P<0.05 using independent samples T - test

Table 3: Distribution of central retinal thickness according to inflammatory biomarkers

Variables		Central macular thickness		Mean difference	P - value*
		Mean	SD		
Hyper reflective foci	No	511.69	122.6	9.52	0.810
	Yes	502.17	135.6		
Subretinal fluid	No	499.50	136.4	14.67	0.778
	Yes	514.17	126.7		
Turbid central macular edema	No	501.09	124.4	43.7	0.460
	Yes	544.75	104.7		
Disorganization of inner retinal layers (DRIL)	No	499.14	124.8	35.9	0.390
	Yes	535.08	122.1		

DRIL (Disorganization of inner retinal layers), *: Mann Whitney U Test

3. Discussion

Inflammatory biomarkers play an integral role in the pathogenesis of diabetic macular edema, a leading cause of vision loss in patients with diabetic retinopathy. The discovery of specific biomarkers associated with inflammation provides insight into the molecular mechanisms driving DME and aids in the stratification of disease severity. The current study's results indicate a relationship between the presence of HRF or SRF with the extent of macular edema as measured by OCT.

In the current study, hyper - reflective foci were observed in 12/42 (28.6%), while 36/42 (85.7%) had subretinal fluid, and 4/42 (9.5%) had turbid CMO. These were higher in comparison to results of Zhou et al., (2022) who reported that 37.8% of their study sample had SRF, while they reported that all there study sample had HRF with a mean of 34.52 foci, in addition their results showed that HRF were correlated with higher systemic inflammation markers. [18] Notably, OCT's ability to detect subclinical changes in the macular region allows for the early identification of patients at risk of disease progression. In conjunction with biomarker profiling, OCT contributes to a more comprehensive understanding of disease dynamics. These criteria led to the development of the yet to expand OCT - based classification of diabetic maculopathy named: TCED - HFV, which was proposed by Panozzo et al., (2020) in Switzerland. [19] In related topic, this classification was reported by Yanxia et al., (2024) to be correlated with systemic inflammation, especially with combination of SRF and more than or equal to 20 HRF on OCT, and identifying OCR - based biomarkers could streamline the risk assessment process, enabling clinicians to personalize treatment strategies. [20]

Additionally, the observed associations point to possible therapeutic targets; modulating these biomarkers' expression

or activity may offer new avenues to mitigate the inflammatory response and, consequently, the progression of DME, like Dazdotuftide, which is a novel anti - inflammatory agent that is comprised of Tuftsin and phosphorylcholine, the latter is a naturally occurring immunomodulator produced by the spleen, dazdotuftide has mechanism of action includes anti - VEGF, anti - Toll - like receptor 4, and macrophage polarization. [21]

4. Conclusions

Inflammatory biomarkers on OCT should not be ignored anymore, and central macular thickness should not be the sole factor that is depended on during follow - up.

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