Commentary: Hyperreflective foci on optical coherence tomography and their clinical implications in diabetic macular edema

Diabetic macular edema (DME) is the most common vision-threatening manifestation of diabetic retinopathy. It can be seen in approximately 30% of patients who are diabetic for more than 20 years.[1,2] Severity of DME can be assessed by various laboratory and imaging biomarkers. These biomarkers also help in monitoring the disease progression and the response to treatment. However, the evaluation of the laboratory biomarkers require invasive procedures. Laboratory biomarkers for DME include serum high sensitivity C reactive protein (hs-CRP) and intercellular adhesion molecule (ICAM)-1 levels; vitreous interleukin (IL)-6, IL-8, and vascular endothelial growth factor (VEGF), tumor necrosis factor (TNF) α levels, and aqueous IL-6, IL-8, and IL-12, and VEGF levels. In contrast, imaging biomarkers are noninvasive and provide *in vivo* and near-histological assessments of the retinal and choroidal layers. Currently, we have various imaging modalities, such as optical coherence tomography (OCT), OCT angiography,

fundus fluorescein angiography (FFA), that can assist in the treatment and prognosis of DME.[3-5]

OCT is an indispensable imaging tool in DME to determine the treatment guidelines. Spectral-domain OCT (SDOCT) with its advanced technology helps in detecting various prognostic biomarkers in eyes with DME, such as integrity of ellipsoid zone (EZ) and external limiting membrane (ELM), central subfield thickness (CST), subfoveal choroidal thickness (SFCT), hyperreflective retinal foci (HRF), and disorganization of inner retinal layers.[4,6]

Hyperreflective retinal foci (HRF) are intraretinal hyperreflective dots characterized by size <30 μm, absence of back-shadowing, and identical reflectivity to retinal nerve fiber layer on SDOCT.[4] HRF were first described by Coscas *et al*.[7] in 2009 in choroidal neovascular membrane (CNVM) cases. Subsequently, many investigators have described them in other retinal vascular diseases such as DME and retinal vein occlusions. There are various hypotheses regarding the origin and nature of HRF. One theory is that HRF are subclinical lipoproteins that extravasate after the breakdown of the inner blood–retinal barrier. Another theory is that they represent activated microglial cells as evident by the presence of raised levels of soluble CD14 in the aqueous humor of the eyes with HRF. Therefore, HRF serve as important biomarkers of retinal inflammation. HRF originate and are seen in the inner retinal layers in the early spectrum of diabetic retinopathy (DR). With progression of DR, they subsequently migrate to the outer retinal layers under the influence of various inflammatory mediators such as VEGF. Studies have shown that DME with HRF shows a better response to dexamethasone implants in comparison to anti-VEGF agents.[4,6,7]

HRF can migrate further from the retina into choroidal layers following disruption of the ELM and EZ; such lesions were termed as hyperreflective choroidal foci (HCF) by Roy *et al*.[6] ELM and EZ integrity are essential for maintenance of good visual acuity; therefore, eyes with HCF with compromised ELM/EZ integrity have poor visual prognosis. Therefore, HCF presence can serve as a surrogate biomarker for ELM/EZ disruption and poor prognosis in DME. Studies have also shown that HCF are present significantly more in eyes with proliferative diabetic retinopathy (PDR) than nonproliferative DR (NPDR).[4,6]

In the study[8] published in the current issue, the authors have gone one step further in trying to validate the role of HCF in patients of NPDR with treatment-naïve DME following treatment with anti-VEGFs. They have reported that presence of HCF was associated with worse initial VA compared to the eyes that had HRF alone, and the difference was statistically significant. This finding was in continuum with the existing knowledge on HRF and HCF. Mean VA difference between the groups following anti-VEGF treatment was maintained, although it did not reach statistical significance. CST at presentation and following treatment were also higher in eyes with HCF compared to eyes without HCF, although the differences were not significant statistically. Small sample size is a possible explanation for the observed statistical insignificance. Furthermore, the current study was a pilot study with a retrospective design. Therefore, future prospective studies with a larger sample size are recommended to further substantiate these findings.

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