Original Article

Validation of choroidal hyperreflective foci in diabetic macular edema through a retrospective pilot study

Kumar Saurabh, Rupak Roy, Sujay Herekar, Suraj Mistry, Shruti Choudhari

Purpose: Choroidal hyperreflective foci (HCF) are novel spectral-domain optical coherence tomography (SDOCT) biomarkers in diabetic macular edema (DME). The present study intended to validate HCF and assess their role in the treatment outcome. **Methods:** It was a retrospective, longitudinal, records-based pilot study recruiting consecutive patients of nonproliferative diabetic retinopathy with treatment naïve DME. Patients were treated with three intravitreal anti-vascular endothelial growth factor injections and followed by a pro re nata regimen. **Results:** A total of 43 eyes of 28 patients were included in the study. Eyes were divided into two groups. Group A (n = 19) comprised eyes with retinal hyperreflective foci (HRF) and group B (n = 24) had eyes with both HRF and HCF. The mean age of patients in group A and B was 58.5 ± 2.1 years and 55.2 ± 8.8 years, respectively. Mean best-corrected visual acuity at presentation was 0.38 ± 0.25 in group A and 0.59 ± 0.29 in group B (P = 0.01). Final BCVA was 0.35 ± 0.39 in group A and 0.47 ± 0.34 in group B (P = 0.3). External limiting membrane was intact in 19 out of 19 eyes in group A and two (8.3%) eyes in group B (P = 0). **Conclusion:** Presence of HCF meant significantly worse initial BCVA compared to the eye that had HRF alone. The final BCVA was also worse in eyes with HCF compared to those with HRF and without HCF; however, the difference did not reach a significance level, probably pointing toward the fact that HCF and HRF are pathophysiologically identical. Further studies with a larger sample size and prospective design are needed to take these findings forward.

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Diabetic macular edema (DME) is a vision-threatening complication of diabetic retinopathy. The pathogenesis of DME is multifactorial and involves breakdown of the inner and outer blood-retinal barriers due to release of growth factors, including vascular endothelial growth factor (VEGF) and inflammatory cytokines.[1]

Retinal hyperreflective foci (HRF) have been hypothesized as clinical biomarkers of inflammation in various retinal diseases including DME.[2-4] Bolz *et al*.[5] described HRF in DME as focal deposits in the retinal layers due to the breakdown of the inner blood-retinal barrier. These HRF are considered as activated resident microglia that migrate from the inner to the outer retinal layers along with the progression of diabetic retinopathy under the influence of inflammatory mediators.[4] Uji *et al*.[6] demonstrated a significant association between HRF in the outer retinal layers and disrupted external limiting membrane (ELM) and ellipsoid zone. While migrating from the inner to the outer retina, these hyperreflective foci have been imaged in the inner choroid as well, where they are termed as choroidal hyperreflective foci (HCF).[7,8] Cross-sectional study design has shown that HCF were associated with greater severity of diabetic retinopathy, higher central foveal thickness, and worse visual acuity.[7] However, there has been no longitudinal study to examine the significance of HCF in the management of DME. Present retrospective pilot study was aimed to assess the effect of HCF on the treatment outcomes in eyes with DME.

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Methods

It was a retrospective, record-based comparative study conducted between January 2020 and January 2021. The study was approved by the institutional review board and adhered to the tenets of the Declaration of Helsinki. Medical records of consecutive patients with nonproliferative diabetic retinopathy and treatment-naive DME having central foveal thickness of 250 μ or more and minimum follow up of six months were analyzed. Eyes with media opacity precluding fundus visualization such as corneal opacity, cataract, and vitreous hemorrhage were excluded from the study. Similarly, eyes with other vision-threatening disorders such as glaucoma, high myopia (more than 6 diopters), age-related macular degeneration, and history of uveitis were excluded. Patients with diabetic nephropathy were excluded. Inability to follow up at the advised time, poor SDOCT image quality, and lack of patient consent were other exclusion criteria. Ethics committee approval obtained on 6th June 2019.

Best-corrected visual acuity was measured with Snellen's distant vision chart and converted to logMAR reading. Intraocular pressure was measured with an applanation tonometer. Fundus

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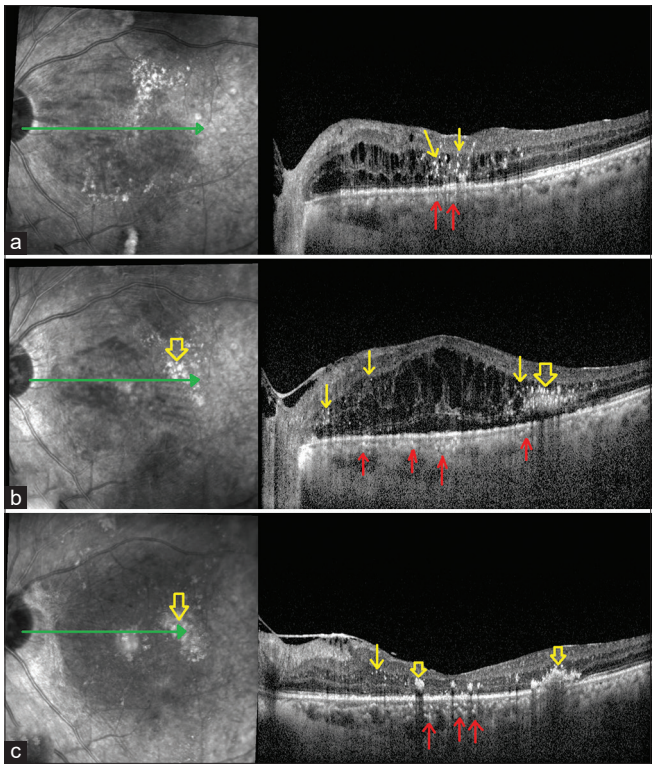

Figure 1: a: Spectral-domain optical coherence tomography (SDOCT) line scan and corresponding infrared reflectance (IR) image of the left eye shows cystoid macular edema (CME) with numerous retinal hyperreflective foci (HRF) (yellow arrow). Tiny punctate hyperreflective dots in the inner choroid are the hyperreflective choroidal foci (HCF) (red arrow). Disruption of the external limiting membrane (ELM) and ellipsoid zone (EZ) is evident near the location of HCF. **b:** IR image in the left panel and SDOCT line scan at seven months show increased CME with hard exudates as a hyperreflective patch (blank yellow arrow). Few of the HRF are marked by yellow arrows in the entire length of the scan. The hard exudate clump is bigger (not punctate) and tends to cast a posterior shadow. HCF (red arrow) are more in number than in the previous scan. **c:** At the most recent visit, the left eye shows hard exudate clump (blank yellow arrow) nasal and temporal to fovea with posterior shadowing. HRF (yellow arrow) are seen. HCF (red arrow) are numerous.

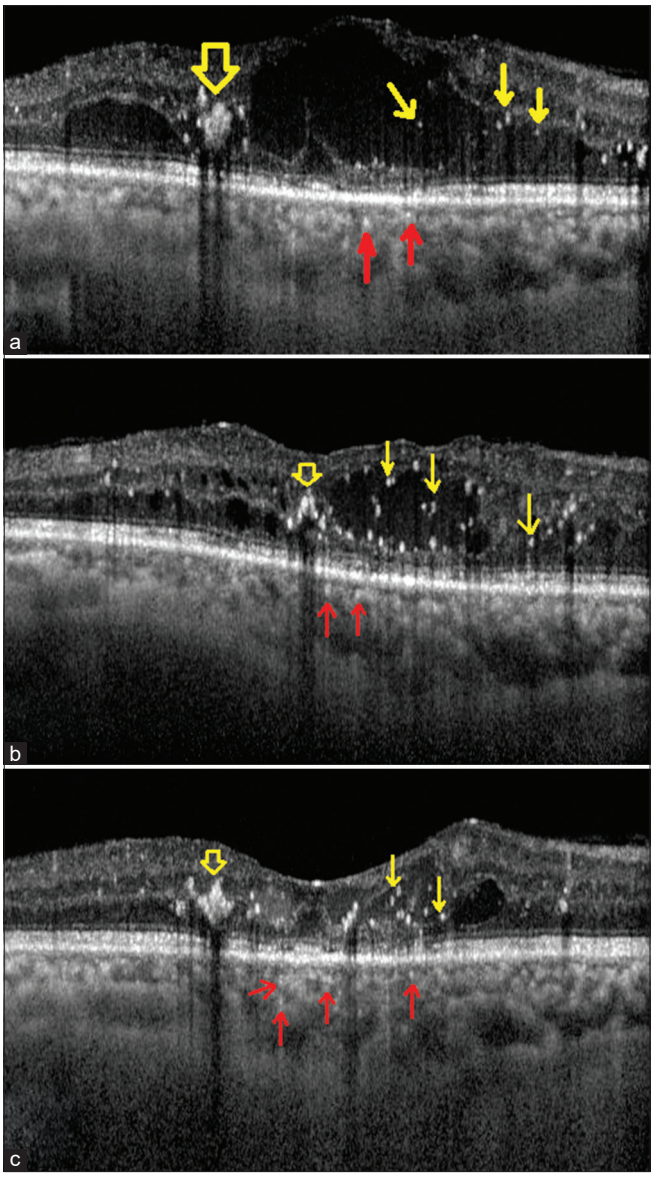

Figure 2: a: SDOCT line scan shows cystoid macular edema with a large cyst at fovea. Hard exudate clump is marked with a blank yellow arrow. Few of the HRF are marked by yellow arrows. Scattered HCF (red arrow) are seen in the inner choroid. **b:** After three monthly intravitreal anti-vascular endothelial growth factor injections the foveal thickness has reduced. The hard exudate clump (blank yellow arrow) is seen with posterior shadow. HRF (yellow arrow) are noted. HCF (red arrow) are seen in the inner choroid. **c:** At final follow-up, the foveal thickness has reduced further with persistent hard exudate clump (blank yellow arrow) and HRF (yellow arrow) on the sides of the fovea. HCF (red arrow) are numerous and present in the inner choroid.

was examined with an indirect ophthalmoscope and slit-lamp biomicroscopy. Fluorescein angiogram and spectral-domain optical coherence tomography (SDOCT) were performed with Spectralis system (Heidelberg Retina Angiograph, HRA2; Heidelberg Engineering, Germany). Hyperreflective foci were defined on SDOCT line scan as well-circumscribed dots having equal or higher reflectivity than retinal pigment epithelium (RPE) band. Hyperreflective foci present between ILM and RPE bands were defined as HRF and those present beyond the RPE band were defined as HCF. The identification of HRF and HCF were independently performed by two retina specialists who were blinded to the rest of the patient data. The integrity of ELM and EZ overlying the HCF was recorded. The central foveal thickness (CFT) was defined as the distance between the ILM and RPE at the fovea. Based on the hyperreflective foci, eyes were divided into two groups: Group A (having HRF) and Group B (having both HRF and HCF) [Figs. 1-3].

The eyes were treated with three monthly intravitreal anti-vascular endothelial growth factor (Anti-VEGF) (ranibizumab, Accentrix 0.5 mg/0.05 ml, Novartis Pharmaceutical) injections followed by pro re nata protocol. Intravitreal steroid in the form of dexamethasone implant (Ozurdex 0.7 mg, Allergan Inc.) was considered in patients with recent cardiovascular thromboembolic events. It was also considered in non-responders who did not have a reduction in central foveal thickness to below 300 μ after the first three intravitreal anti-VEGF injections. Focal laser photocoagulation was considered beyond the first three intravitreal anti-VEGF injections to treat leaking microaneurysms, alone or in

Table 1: Comparison of group A and B

Parameters	Group A (*n*=19)	Group B (*n*=24)	*P*
Initial BCVA (logMAR)	0.38±0.25	0.59±0.29	0.01
Phakic	19 (100%)	22 (91.7%)	0.17
Initial CFT (μ)	387.6±112.2	467.2±152.7	0.06
Intact ELM	19 (100%)	2 (8.3%)	0.0
Intact EZ	18 (94.7%)	1 (4.2%)	0.0
Mean number of intravitreal Anti-VEGF	1.52±0.7	1.7±1.3	0.1
Mean number of intravitreal steroid	0.21±0.5	0.2±0.5	0.6
Final BCVA (logMAR)	0.35±0.39	0.47±0.34	0.3
Final CFT (μ)	287.42±92	340.8±95	0.7

BCVA: Best corrected visual acuity, CFT: Central foveal thickness, ELM: External limiting membrane, EZ: Ellipsoid zone, Anti-VEGF: Anti-vascular endothelial growth factor

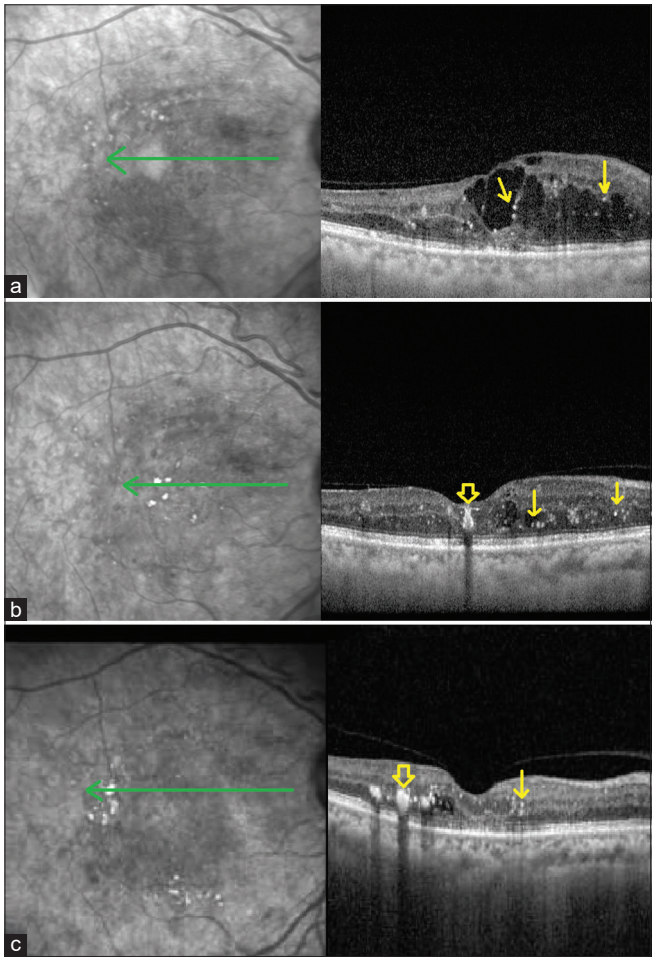

Figure 3: a: SDOCT line scan of the right eye shows cystoid macular edema. HRF are marked by a yellow arrow. There is no HCF. **b:** After intravitreal anti-vascular endothelial growth factor injections the cystoid macular edema has reduced. Hard exudate (blank yellow arrow) with back shadowing is seen adjacent to the fovea. HRF (yellow arrow) are seen nasal to the fovea. No HCF are noted. **c:** At final follow-up, the right eye has restored foveal contour with hard exudate clumps (blank yellow arrow) temporal to fovea and HRF (yellow arrow) nasal to fovea without any HCF. This eye had HRF without HCF.

combination with intravitreal pharmacotherapy. BCVA, CFT, mean number of anti-VEGF, and steroid injections were noted and compared between the two groups. Data were entered to Microsoft Excel version 14.0 (Microsoft Corporation, Redmond, WA), and SPSS version 20.0 statistical software (SPSS; IBM, Chicago, IL) was used for analysis.

Results

A total of 43 eyes of 28 patients were included in the study. There were 12 (63.1%) males and seven (36.9%) females in group A (HRF only) while group B (HRF and HCF) had 17 (70.8%) males and seven (29.2%) females. There were 19 (44.2%) eyes in group A, whereas group B had 24 (55.8%) eyes. The mean age of patients in group A and B was 58.5 ± 2.1 years and 55.2 ± 8.8 years, respectively.

The initial mean BCVA at presentation was 0.38 ± 0.25 in group A and 0.59 ± 0.29 in group B. The difference was statistically significant with P = 0.01. Mean CFT at presentation was 387.6 ± 112.2 μ in group A and 467.2 ± 152.7 μ (P = 0.06) [Table 1]. ELM was intact in 19 out of 19 eyes in group A and two (8.3%) eyes in group B (P = 0). Intact EZ was noted in 18 (94.7%) eyes in group A and one (4.2%) eyes in group B (P = 0). Final BCVA was 0.35 ± 0.39 in group A and 0.47 ± 0.34 in group B (P = 0.3). Final CFT in group A was 287.42 ± 92 μ, whereas it was 340.8 ± 95 μ in group B (P = 0.7). Mean follow up was 19.3 ± 9.2 months.

Discussion

HCF are novel SDOCT biomarkers recognized in various retinal diseases of diverse pathophysiology. They have been reported as discrete hyperreflective dots consisting of lipofuscin deposits in Stargardt's disease.[9] In the case of retinitis pigmentosa, HCF have been considered as accumulations of migrated RPE cells and photoreceptors.[10] HCF have been reported in central serous chorioretinopathy as well wherein they were hypothesized as cellular extravasation from choroidal circulation.[11] In cases of DME, HCF have been reported as outward migration of HRF into choroid suggesting an inflammatory origin to HCF similar to HRF.[7] HCF have been reported to be associated with high CFT and are considered an SDOCT biomarker of worse presenting visual acuity in eyes with DME. The present pilot study intended to assess the role of HCF in management and the outcome of DME retrospectively.

The presenting BCVA was significantly lower in eyes which had both HRF and HCF (group B) compared to eyes which had HRF but did not have HCF (group A). This is in keeping with the previous report describing HCF in DME.[7,12] Eyes

in group B had thicker macula and higher CFT compared to group A at presentation. However, this difference could not reach statistically significant levels. Further, a large majority of eyes in group B had disrupted ELM and EZ. These findings support the existing knowledge about the HCF which says that they are activated microglia who migrate to choroid due to the breakdown of the barrier effect of ELM along with the severity of DME.

Additionally, the present study found that though final BCVA was worse and final CFT higher in group B compared to group A; the difference was not statistically significant. In other words, it appears that though the presence of HCF meant worse presenting BCVA and thicker macula in eyes with DME, it did not appear to actually foretell that when compared with eyes that had only HRF, the eyes with HCF will continue to have significantly worse BCVA and thicker macula at final follow up. As HCF are pathophysiologically indistinct from HRF, or both are activated microglia at different locations of retinochoroid, the presence of HRF and HCF should be seen as a continuum. Another plausible explanation of the nonsignificant difference between final visual acuity in group B compared to that in Group A may be the fact that while predicting the visual outcome, the continuum of HRF to HCF merely takes into account the status of ELM and EZ, whereas the final visual outcome in DME is a multifactorial phenomenon that is influenced and decided by macular perfusion, retinopathy status, and systemic glycemic control. However, the findings of this pilot study do reiterate the hypothesis about HCF presented in the preceding studies.[7,12]

Being a retrospective study with a small sample size can be considered as a drawback of this study. HCF has been studied in DME in a cross-sectional study where it was associated with worse visual acuity. Present retrospective pilot does take the initial knowledge about HCF a step forward; supporting the hypothesis and suggesting a possible continuum from HRF to HCF. A prospective study design with a larger sample size is needed to further analyze the role of HCF in DME. Such a study should also assess HCF against SDOCT biomarkers other than HRF.

Conclusion

HCF are HRF migrated to choroid. They point towards worse initial visual acuity and may potentially point to worse final visual acuity as well; which needs to be further substantiated in a prospective study design.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Bahrami B, Zhu M, Hong T, Chang A. Diabetic macular oedema: Pathophysiology, management challenges and treatment resistance. Diabetologia 2016;59:1594-608.
2. Framme C, Schweizer P, Imesch M, Wolf S, Wolf-Schnurrbusch U. Behavior of SD-OCT-detected hyperreflective foci in the retina of anti-VEGF-treated patients with diabetic macular edema. Invest Ophthalmol Vis Sci 2012;24:5814-8.
3. Coscas G, de Benedetto U, Coscas F, Li Calzi CI, Vismara S, Roudot-Thoraval F, *et al*. Hyperreflective dots: A new spectral-domain opticalcoherence tomography entity for follow-up and prognosis in exudative age-related maculardegeneration. Ophthalmologica 2013;229:32-7.
4. Vujosevic S, Bini S, Midena G, Berton M, Pilotto E, Midena E. Hyperreflective intraretinal spots in diabetics without and with nonproliferative diabetic retinopathy: An *in vivo* study using spectraldomain OCT. J Diabetes Res 2013;2013:491835.
5. Bolz M, Schmidt-Erfurth U, Deak G, Mylonas G, Kriechbaum K, Scholda C, *et al*. Optical coherence tomographic Hyperreflective foci: A morphologic sign of lipid extravasation in diabetic macular edema. Ophthalmology 2009;116:914-20.
6. Uji A, Murakami T, Nishijima K, Akagi T, Horii T, Arakawa N, *et al*. Association between hyperreflective foci in the outer retina, status of photoreceptor layer, and visual acuity in diabetic macular edema. Am J Ophthalmol 2012;153:710-7, 717.e1.
7. Roy R, Saurabh K, Shah D, Chowdhury M, Goel S. Choroidal hyperreflective foci: A novel spectral domain optical coherence tomography biomarker in eyes with diabetic macular edema. Asia Pac J Ophthalmol (Phila) 2019;8:314-8.
8. Chung Y, Lee SY, Kim YH, Byeon H, Kim JH, Lee K. Hyperreflective foci in diabetic macular edema with serous retinal detachment: Association with dyslipidemia. Acta Diabetol 2020;57:861-6.
9. Piri N, Nesmith BL, Schaal S. Choroidal hyperreflective foci in Stargardt disease shown by spectral-domain optical coherence tomography imaging: Correlation with disease severity. JAMA Ophthalmol 2015;133:398-405.
10. Kawaguchi Y, Takahashi A, Nagaoka T, Ishibazawa A, Ishiko S, Yoshida A. Retinal and choroidal hyperreflective foci on spectral-domain optical coherence tomographic images in a patient with retinitis pigmentosa accompanied by diabetic retinopathy. Am J Ophthalmol Case Rep 2016;3:25-30.
11. Hanumunthadu D, Matet A, Rasheed MA, Goud A, Vuppurabina KK, Chhablani J. Evaluation of choroidal hyperreflective dots in acute and chronic central serous chorioretinopathy. Indian J Ophthalmol 2019;67:1850-4.
12. Markan A, Agarwal A, Arora A, Bazgain K, Rana V, Gupta V. Novel imaging biomarkers in diabetic retinopathy and diabetic macular edema. Ther Adv Ophthalmol 2020;12:2515841420950513.