Original Article

Correlation of multicolor images and conventional color fundus photographs with foveal autofluorescence patterns in diabetic macular edema

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Purpose: The aim of this study is to assess the ability of multicolour imaging (MCI) to detect foveal cysts in diabetic macular edema (DME) and compare it with conventional color fundus photography (CFP) and foveal autofluorescence (FAF) pattern. **Methods:** It was a retrospective review of 112 eyes of 84 DME patients with central foveal thickness ≥250 μ who underwent MCI, CFP and shortwave autofluorescence imaging. MCI was performed with Sepctralis spectral domain optical coherence tomography (SDOCT) (Heidelberg Engineering, Germany). **Results:** 97 (86.6%) eyes had cystoid increased autofluorescence (cystoid iFAF), 9 (8%) had spot iFAF and 6 (5.35%) had irregular decreased FAF (dFAF). Among eyes with cystoid iFAF, OCT detected DME cysts in 93 (95.6%) eyes, MCI in 75 (77.3%) and CFP in 5 (5.15%) eyes. In all these eyes, the location of cysts on OCT and MCI corresponded with the location of cystoid iFAF, whereas none of the eyes with cyst seen on CFP correlated with the location of cystoid iFAF. **Conclusion:** MCI was superior to CFP in detecting DME cysts at fovea. It also correlated with hyperautofluorescence pattern in these eyes. MCI may have a potential role in diabetic retinopathy screening by segregating eyes with DME which would require treatment. Our findings need to be further validated in a larger and prospective study design.

Key words: Autofluorescence imaging, color fundus photo, diabetic macular edema, multicolour imaging, optical coherence tomography

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Diabetic retinopathy (DR) is essentially a microangiopathy which affects retinal vessels and lead to retinal hemorrhage, lipid exudation, macular edema and neovascularisation. Diabetic macular edema (DME) is the leading cause of reduction in vision in patients with DR.[1] Early detection and treatment of DME is the cornerstone of its management. The starting point in the treatment strategy of DR is the imaging of retina.[2] Color fundus photographs (CFP) are widely used in screening programs, clinical trials and treatment follow ups.[2] Though fluorescein angiography has shaped our understanding of DME, the advent of optical coherence tomography (OCT) as a non-invasive imaging modality has helped us in deciding appropriate management protocols.[3] Large clinical trials like RISE, RIDE, VIVID, VISTA and DRCR.net are based on OCT imaging characteristics of DME.

Fundus autofluorescence (FAF) is based on topographic analysis of lipofuscin molecule in the retina.[4] Lipofuscin is by-product of photoreceptor degradation and is a hallmark of ageing.[4,5] Being a peroxidation product of lipid and protein, lipofuscin is also considered a sign of oxidative damage to the retina.[6] The understanding of the changes in FAF pattern in eyes with DME is still evolving and unlike age related macular degeneration and other outer retinal diseases, FAF changes in DME are not attributed to photoreceptor degradation.[7] Vujosevic *et al*. have reported a decreased retinal sensitivity in areas of increased FAF in eyes with diabetes mellitus.[6] The increased FAF in DME is attributed partly to persistent activation of microglia. Activated microglia causes peroxidation of protein and lipid which results in accumulation of these peroxidation products called microglial lipofuscin in retina leading to increased FAF.[8] Another hypothesis to explain the increase in FAF signals in DME is based on mechanical displacement of xanthophyll pigments at the fovea. The cysts located in outer plexiform and inner nuclear layers are thought to mechanically displace the luteal pigments thereby unmasking the foveal autofluorescence.[9,10] These round or oval areas of increased FAF are surrounded by darker rim and their location corresponds to the location of the cysts noted on OCT.[11]

Based on these findings, DME has been classified into four types.[11] It can have normal FAF and increased or decreased FAF. Eyes with increased FAF are further of two types, namely cystoid increased FAF (cystoid iFAF) and spot increased FAF (spot iFAF). Cystoid iFAF is characterised by petaloid areas of hyperautofluorescence separated by darker rims and correspond to cysts on OCT. Spot iFAF is characterized by spoaradic areas of hyperautofluorescence. Correlation between areas of increased FAF and cysts on OCT is the defining criteria

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for cystoid iFAF and sustains the hypothesis of mechanical displacement of luteal pigments. Multicolour imaging (MCI) is a novel confocal scanning laser based imaging modality available on Spectralis spectral domain optical coherence tomography system.[12] It uses three colored laser lights to image the different layers of retina. The composite of these three images is rendered a pseudocolour coding and termed as multicolour image. MCI has been used in imaging of various retinal disorders affecting different levels of retina such as epiretinal membrane, age related macular degeneration and optic disc edema.[13-15] In eyes with optic disc pit maculopathy with large cystic macula, MCI shows the greenish hue due to retinal oedema and the cysts are shown as circumscribed orange pink lesions.[16] In this study, we assess the ability of MCI to detect cysts in DME in comparison to CFP. We further intend to correlate the location of cysts seen on MCI with same on OCT and cystoid iFAF.

Methods

The study was carried between June 2018 and December 2018 at a tertiary care center in Eastern India. It was a retrospective case series which included consecutive patients with clinically significant DME having central foveal thickness of 250 μ or more. The study was approved by institutional review board and adhered to the Tenets of Declaration of Helsinki. Approval from Institutional Review Board was obtained on 10th December 2017. Age and gender were captured from the electronic medical records. All patients underwent comprehensive ophthalmic examination which included visual acuity assessment, anterior segment examination with slit lamp and dilated fundus evaluation with indirect ophthalmoscope. Exclusion criteria were eyes with media opacity due to cataract, vitreous floaters or hemorrhage, pre- or coexisting macular pathology and inadequate image quality.

CFP was obtained with FF 450 Plus fundus camera (Carl Zeiss Meditec, Jena, Germany) after proper mydriasis and were viewed on the same machine with highest image setting. MCI, SDOCT and FAF were performed using Spectralis SDOCT system (HRA + OCT) with mydriasis on same day. These images were viewed using Heidelberg Eye Explorer software (version 1.7.1.0). Images were analysed by fellowship trained retina practitioner. FAF pattern at the fovea was noted and correlated with the OCT line scan through the fovea. Cysts at fovea were sought for on CFP and MC. Whenever noted, they were correlated with cyst seen on OCT and corresponding FAF pattern at fovea. Primary outcome measure was number of eyes

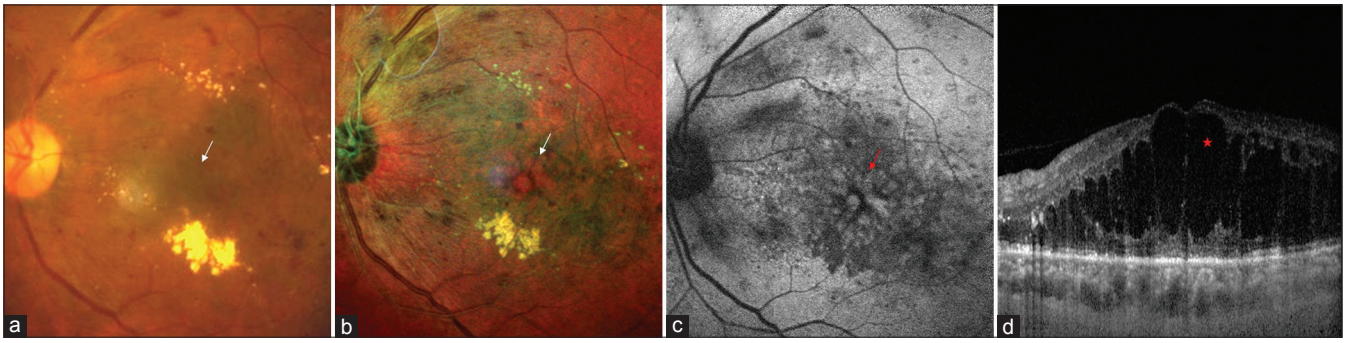

Figure 1: (a) Color fundus photo (CFP) of left eye shows hard exudates and retinal hemorrhage. Center of the fovea (white arrow) does not show any cystic change due to macular edema. (b) Multicolour image (MCI) shows greenish hue over macula due to macular edema. Orange – red foveal cysts (white arrow) are seen at the center of fovea suggestive of foveal cystic change. (c) Autofluorescence image of left eye shows cystoid increased autofluorescence (cystoid iFAF) (red arrow) corresponding to the orange – red cysts seen on MCI. (d) Optical coherence tomography (OCT) line scan through the fovea shows large cysts of diabetic macular edema corresponding to the cysts seen on MCI (b) and cystoid iFAF on autofluorescence (c)

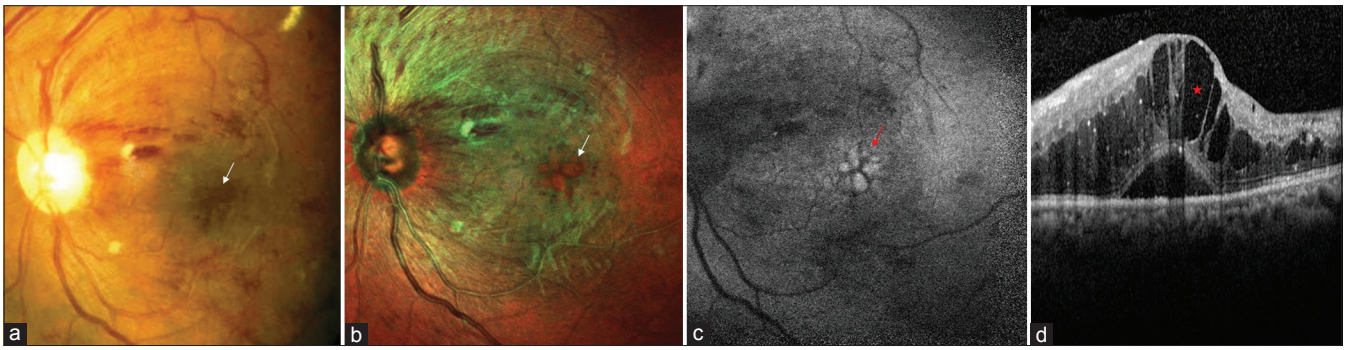

Figure 2: (a) CFP of the left eye shows retinal hemorrhage, cotton wool spots and macular edema. Note the darker appearance of fovea (white arrow) due to cystic changes. (b) MCI renders a greenish hue to the macula owing to macular edema. Cruciate pattern of orange – red foveal cysts (white arrow) is seen at the center of the macula. The extent of the foveal cysts is better demarcated on MCI than CFP. (c) Autofluorescence image of left eye shows cystoid iFAF having same cruciate pattern (red arrow) as seen on MCI and at the same location. Cruciate cystoid iFAF does not match in extent and location with the cystic changes seen on CFP (a). (d) OCT line scan through the fovea shows macular edema with intraretinal cysts (red star) at the fovea which corresponds to cruciate pattern seen on MCI (b) and cystoid iFAF (c)

with cystoid iFAF detected on MC and CFP. Data was analysed using SPSS software (version 20.0, SPSS, IBM, Chicago, IL).

Results

The study included 112 eyes of 84 consecutive patients of DME. 52 (62%) were male and 32 (38%) were female. Mean age of patients was 56.6 ± 8.9 years. A total of 97 (86.6%) eyes had cystoid iFAF, 9 (8%) had spot iFAF and six (5.35%) had irregular decreased FAF (dFAF).

Out of 97 eyes with cystoid iFAF, OCT could detect DME cysts in 93 (95.6%) eyes, MCI in 75 (77.3%) eyes and CFP in 5 (5.15%) eyes. The difference between ability of MCI and CFP to detect DME cysts in eyes with cystoid iFAF was statistically significant ($P = 0.0$). The location of the cyst on OCT correlated with location of cystoid iFAF in 93 (95.6%) out of total 97 eyes. Location of cyst on MCI and CFP correlated with location of cystoid iFAF in 75 (77.3%) and zero eyes, respectively ($P = 0.0$) Figs. 1 and 2 provide the representative images.

Discussion

The first step in the management of DR is retinal imaging. Since the time of seven standard fields of Early Treatment of Diabetic Retinopathy Study, imaging in DR has advanced significantly with the increased focus on non-invasive imaging modalities.[17] Fluorescein angiography has been modality of choice to detect leaking microaneurysms, retinal neovascularization and macular perfusion. OCT is the modality of choice to assess macular edema.[18] FAF is a non-invasive method to detect the autofluorescence emanating from lipofuscin in the human retina.[1,4] Since lipofuscin is predominantly a by-product of photoreceptor degradation, FAF has been mainly used to study outer retinal and retinal pigment epithelium disorders like choroiditis, drug toxicities and age related and hereditary macular degenerations.[19] However, with the understanding of autofluorescence due to lipid and protein peroxidation secondary to persistent microglial activation in DR, FAF has been used to study foveal changes in DME eyes as well.[6] Pece *et al*. have reported that DME eyes with higher FAF at fovea had worse visual prognosis.[20] Increased FAF at fovea persists even after resolution of macular edema pointing towards persistent microglial activation.[21] Further the correspondence between cystoid iFAF and cysts noted on OCT point in favour of an hypothesis which suggests that displacement of luteal pigments was responsible for unmasking of foveal hyperautofluorescence.[6,11] Moreover the persistent hyperautofluorescence after resolution of macular edema retains the shape of initial cystoid iFAF, suggesting a combination of both mechanisms of microglial activation and luteal pigment displacement as causes of foveal hyperautofluorescence in DME.[6,11,21] CFP has been a routine imaging modality to screen, document and follow-up of patients with DME.[2] MCI is a novel imaging modality which is similar to CFP, but by the virtue of using laser lights, provides topographic information from retina and is more comfortable to patients.[12] In a retrospective review of 130 eyes of DR, our group has reported that lesions like retinal hemorrhages, hard exudates and cotton wool spots were seen better on MCI compared to CFP.[22] In the current study, we have compared the ability of MCI vis a vis CFP to detect the cysts in DME. We have also correlated the cysts seen on MCI with areas of cystoid iFAF and cysts on OCT.

In the present series of DME, MCI was able to detect cysts at fovea in majority of eyes whereas CFP could detect cysts in significantly lesser number of eyes. This finding suggests that MCI was superior in isolating foveal changes in DME compared CFP. Further, there was a correspondence between location of cysts on MCI and area of cystoid iFAF in majority of eyes in our series. The correspondence between cysts on MCI and cystoid iFAF also correlated with the location of cysts on OCT. The floor of the cyst in these eyes lies at the deeper plane than the adjacent edematous retina and is predominantly imaged by infrared channel of MCI which has longest wavelength. Since the infrared channel of MCI is color coded as orange – red color the DME cysts stand out as orange – red lesions amidst greenish hue of adjacent swollen and elevated retina. On the other hand, white light based CFP does show macular thickness but due to lack of contrast fails to precisely show the cysts in the elevated retina or correspond to cystoid iFAF. The hypothesis that cystoid iFAF was caused by displacement of luteal pigments is based on correspondence between area of cystoid iFAF and cysts on OCT.[6,11] By virtue of showing correspondence between that DME cyst on MCI and cystoid iFAF, our study buttresses this hypothesis.

We understand that other hyperautofluorescence pattern seen in DME like spot iFAF is caused by increased photoreceptor death and not by the displacement of luteal pigments.[11] Similarly eyes with DME can have normal foveal autofluorescence as well as decreased autofluoroscence due to accumulation of hard exudtes.[11] Our findings are limited to those eyes with DME which have cystoid iFAF. Further present study has for the first time assessed the ability of MCI to detect the cystic changes in DME and compare it with current standards of CFP and OCT. The OCT is the gold standard to detect cysts in DME. However, the goal of the current study was to point out superiority of MCI imaging vis a vis CFP and second correlation with FAF to comment on cause of patterns of FAF seen, thus providing valuable insight into disease pathophysiology.

Conclusion

Our study may also provide impetus for combining FAF with MC for screening for DME in a larger, prospective study design to further buttress their combined superiority over CFP alone. As MCI fares better than CFP and comparable to OCT, it can be a potential tool for screening for DME. However larger study in a multicentric design will be needed to further substantiate the findings of this pilot study.

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Conflicts of interest

There are no conflicts of interest.

References

1. Cole ED, Novais EA, Louzada RN, Waheed NK. Contemporary retinal imaging techniques in diabetic retinopathy: A review. Clin Exp Ophthalmol 2016;44:289-99.
2. Williams GA, Scott IU, Haller JA, Maguire AM, Marcus D, McDonald HR. Single-field fundus photography for diabetic retinopathy screening: A report by the American academy of ophthalmology. Ophthalmology 2004;111:1055-62.

3. Sakata LM, Deleon-Ortega J, Sakata V, Girkin CA. Optical coherence tomography of the retina and optic nerve - A review. Clin Exp Ophthalmol 2009;37:90-9.
4. Spaide R. Autofluorescence from the outer retina and subretinal space: Hypothesis and review. Retina 2008;28:5-35.
5. Sepah YJ, Akhtar A, Sadiq MA, Hafeez Y, Nasir H, Perez B, *et al.* Fundus autofluorescence imaging: Fundamentals and clinical relevance. Saudi J Ophthalmol 2014;28:111-6.
6. Vujosevic S, Casciano M, Pilotto E, Boccassini B, Varano M, Midena E. Diabetic macular edema: Fundus autofluorescence and functional correlations. Invest Opthalmol Vis Sci 2011;52:442-8.
7. Calvo-Maroto AM, Perez-Cambrodi RJ, Garcia-Lazaro S, Ferrer-Blasco T, Cervino A. Ocular autofluorescence in diabetes mellitus. A review. J Diabetes 2016;8:619-28.
8. Midena E, Bini S. Multimodal retinal imaging of diabetic macular edema: Toward new paradigms of pathophysiology. Graefes Arch Clin Exp Ophthalmol 2016;254:1661-8.
9. McBain VA, Forrester JV, Lois N. Fundus autofluorescence in the diagnosis of cystoid macular oedema. Br J Ophthalmol 2008;92:946-9.
10. Smith RT, Koniarek JP, Chan J, Nagasaki T, Sparrow JR, Langton K. Autofluorescence characteristics of normal foveas and reconstruction of foveal autofluorescence from limited data subsets. Invest Ophthalmol Vis Sci 2005;46:2940-6.
11. Shen Y, Xu X, Liu K. Fundus autofluorescence characteristics in patients with diabetic macular edema. Chin Med J (Engl) 2014;127:1423-8.
12. Tan AC, Fleckenstein M, Schmitz-Valckenberg S, Holz FG. Clinical application of multicolor imaging technology. Ophthalmologica 2016;236:8-18.
13. Kilic Muftuoglu I, Bartsch DU, Barteselli G, Gaber R, Nezgoda J, Freeman WR. Visualization of macular pucker by multicolor scanning laser imaging. Retina 2018;38:352-8.
14. Graham KW, Chakravarthy U, Hogg RE, Muldrew KA, Young IS, Kee F. Identifying features of early and late age-related macular degeneration: A comparison of multicolor versus traditional color fundus photography. Retina 2018;38:1751-8.
15. Thomas NR, Ghosh PS, Chowdhury M, Saurabh K, Roy R. Multicolor imaging in optic disc swelling. Indian J Ophthalmol 2017;65:1251-5.
16. Saurabh K, Roy R, Shah D, Sinha Roy S. Multicolour imaging in a patient with optic disc pit maculopathy. Clin Exp Optom 2018;101:805-6.
17. Early Treatment Diabetic Retinopathy Study Research Group Grading diabetic retinopathy from stereoscopic color fundus photographs—An extension of the modified Airlie House classification. ETDRS report no. 10. Ophthalmology 1991;98(5 Suppl):786-806.
18. Diabetic Retinopathy Clinical Research Network, Elman MJ, Aiello LP, Beck RW, Bressler NM, Bressler SB, Edwards AR, *et al*. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 2010;117:1064-77.e35.
19. Calvo-Maroto AM, Cerviño A. Spotlight on fundus autofluorescence. Clin Optom (Auckl) 2018;10:25-32.
20. Pece A, Isola V, Holz F, Milani P, Brancato R. Autofluorescence imaging of cystoid macular edema in diabeticretinopathy. Ophthalmologica 2010;224:230-5.
21. Chung H, Park B, Shin HJ, Kim HC. Correlation of fundusautofluorescence with spectral-domain optical coherence tomographyand vision in diabetic macular edema. Ophthalmology 2012;119:1056-65.
22. Roy R, Saurabh K, Thomas NR, Chowdhury M, Shah DK. Validation of multicolor imaging of diabetic retinopathy lesions vis a vis conventional color fundus photographs. Ophthalmic Surg Lasers Imaging Retina 2019;50:8-15.