## Commentary: Systemic versus imaging biomarkers for diabetic macular oedema – Where do we stand?

Diabetic macular edema (DME) is the leading cause of moderate visual loss in patients with diabetes. The National Diabetic Retinopathy Survey 2015–2019 among the Indian population aged ≥50 years showed the prevalence of diabetes to be 11.8%. Among these 16.9% had some form of diabetic retinopathy (DR) and almost 7% had DME.[1] This translates into a large number of the population requiring screening and treatment for DME. Biomarkers are surrogate tools that help us detect referrable patients who need to be prioritized for treatment as well as determine those who may not benefit from extensive treatment. Type of treatment may also vary depending on presence or absence of certain biomarkers. Both systemic and ocular imaging biomarkers have been described for DME.

Systemic biomarkers include blood pressure, lipid profile, glycaemic control, obstructive sleep apnoea, albuminuria, body weight, smoking, and pregnancy status. The UK Prospective Diabetes Study Group showed that high BP constitutes a significant risk factor for diabetic retinopathy.[2] Diabetic patients with BP > 140/90 mm Hg or anti-hypertensive drugs are more likely to develop DME than those with normal BP. Lipid-lowering therapy with statins protects against the development of DME and progression of diabetic retinopathy in patients with type 2 diabetes, and hypertriglyceridemia could be considered as a surrogate marker for DME.[3] Severe obstructive sleep apnoea (apnoea-hypopnea index > 30) and nocturnal hypoxemia (cumulative time of SPO2 below 90%) are associated with DME.[4] Sharma *et al*.[5] demonstrated that baseline glycaemic control could affect the treatment outcome of intravitreal bevacizumab in the management of DME and the response was better in patients with good glycaemic control (low HbA1c). Microalbuminuria and macroalbuminuria are also strong risk factors for DME, with macroalbuminuria

carrying a higher risk.[6] Vascular endothelial growth factor (VEGF) A (serum/plasma, aqueous and vitreous) is the most commonly studied molecule apart from angiopoietin 2, endothelial growth factor, human growth factor, fibroblast growth factor, placental growth factor that cause increased vascular permeability, leading to development of DME.[7]

Various imaging biomarkers are considered the key identifiers in individualized treatment regimens as these can predict future course and vision in patients with DME. On spectral domain-optical coherence tomography (SD-OCT), these include retinal thickness, choroidal thickness, disorganization of inner retinal layers (DRIL), hyperreflective foci (HRF), hyperreflective choroidal foci (HCF), subretinal neurosensory retinal detachment (SSRD), cystoid spaces, and disruption of ellipsoid zone (EZ).[8] When central subfield thickness (CST) increases beyond the retina's stretching capability limit, it can damage bipolar axons leading to decreased visual signal transmission; thus, despite the resolution of DME, vision may not improve.[9] Baseline subfoveal choroidal thickness is a predictor of response to anti-VEGF therapy. Patients with greater choroidal thickness are presumed to have an intact choriocapillaris and thus a less ischemic outer retina, thus better response to anti-VEGF therapy.[8] DRIL is defined as an inability to distinguish between ganglion cell layer inner plexiform layer complex, inner nuclear layer, outer plexiform layer and can be present with or without center involving DME. Its presence is a poor prognosticator of visual acuity.[8] HRF are now thought to be activated microglial cells. They are indicative of inflammation and respond poorly to anti-VEGF therapy. The presence of HCF is a poor prognostic marker in terms of visual acuity, and it is believed that HCF has migrated from the retina into choroidal layers with disruption of the EZ.[8] Hard exudates are an indicator of deranged lipid profile and intravitreal steroids may be a better alternative in such cases than anti-VEGF agents.[10] Hyperreflectivity within the cyst of DME is associated with severe disruption of the blood-retinal barrier. Treatment with intravitreal anti-vascular endothelial growth factor agents did not seem to change their natural course directly.[8]

Systemic and imaging biomarkers have each been studied in isolation and there is lack of literature correlating the two. This study from southern India attempts to address this issue partially. They found increased HRF to be associated with higher BP and lower serum triglycerides.[11] However, till the time we have a better level of evidence in the form of prospective longitudinal studies, both systemic and imaging biomarkers will have to be taken into consideration while making an informed choice about the type of treatment to be offered in cases with DME.

*Vipin Rana, Mohit Dogra, Simar R Singh*

Advanced Eye Centre, Department of Ophthalmology, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India.

Correspondence to: Dr. Simar Rajan Singh, Advanced Eye Centre, Department of Ophthalmology, Post Graduate Institute of Medical Education and Research, Chandigarh - 160012, India.
E-mail: simarrajansingh@gmail.com

## References

1. Kumar A, Vashist P. Indian community eye care in 2020: Achievements and challenges. Indian J Ophthalmol 2020;68:291-3.
2. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. BMJ 1998;317:703-13.
3. Gupta A, Gupta V, Thapar S, Bhansali A. Lipid-lowering drug atorvastatin as an adjunct in the management of diabetic macular edema. Am J Ophthalmol 2004;137:675-82.
4. Vié A-L, Kodjikian L, Agard E, Voirin N, El Chehab H, Denis P, *et al*. Evaluation of obstructive sleep apnea syndrome as a risk factor for diabetic macular edema in patients with type II diabetes. Retina 2019;39:274-80.
5. Sharma S, Joshi SN, Karki P. HbA1c as a predictor for response of bevacizumab in diabetic macular oedema. BMJ Open Ophthalmol 2020;5:e000449.
6. Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, *et al*. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care 2012;35:556-64.
7. Malik TG, Ahmed SS, Gul R, Khalil M, Malik AA, Khan M. Effect of intravitreal bevacizumab on macular thickness: Exploring serum and vitreous proangiogenic biomarkers in patients with diabetic macular edema. Turk J Med Sci 2018;48:833-9.
8. 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.
9. Pelosini L, Hull CC, Boyce JF, McHugh D, Stanford MR, Marshall J. Optical coherence tomography may be used to predict visual acuity in patients with macular edema. Invest Ophthalmol Vis Sci 2011;52:2741-8.
10. Shin YU, Hong EH, Lim HW, Kang MH, Seong M, Cho H. Quantitative evaluation of hard exudates in diabetic macular edema after short-term intravitreal triamcinolone, dexamethasone implant or bevacizumab injections. BMC Ophthalmol 2017;17:182.
11. Arthi M, Sindal MD, Rashmita R. Hyperreflective foci as biomarkers for inflammation in diabetic macular edema: Retrospective analysis of treatment naïve eyes from south India. Indian J Ophthalmol 2021;69:1197-202.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

**Access this article online**

Quick Response Code:

**Website:** www.ijo.in

**DOI:** 10.4103/ijo.IJO_304_21

**Cite this article as:** Rana V, Dogra M, Singh SR. Commentary: Systemic versus imaging biomarkers for diabetic macular oedema – Where do we stand? Indian J Ophthalmol 2021;69:1202-3.