# Commentary: Diabetic retinopathy and its correlation with other diabetic complications

Diabetes mellitus (DM) of long duration is known to be associated with chronic microvascular complications (MVC), namely, retinopathy (DR), nephropathy (DN), peripheral neuropathy (PDN), and cardiac autonomic neuropathy. In spite of being MVC, they differ in their prevalence and severity.[1] These complications are risk factors for mortality. Presence/absence of MVC in a DM patient predicts cardiovascular diseases related morbidity and mortality better than lipid profile and hypertension.[1] In a large population-based study of patients with type 2 DM, the presence of 0, 1, 2, and 3 MVC was 25.26%, 38%, 28.32%, and 8.41%, respectively.[1] Mortality increases with an increase in cumulative burden of MVC. In a study by Garofolo *et al*.,[2] the risk of death increased 7.2% to 14.7% and 66.7% in patients with one, two, or three MVC. This underscores the importance of identifying the co-existence of all MVC in diabetics as is done by authors in the study published in the current volume of Indian Journal of Ophthalmology.[3]

Common established risk factors for their incidence of MVC that are modifiable include glycemic control, abnormal blood pressure, lipid profile, smoking, and obesity. Nonmodifiable risk factors include genetic predisposition, gender, and age. Beyond the management of above mentioned modifiable risk factors, management of each MVC is different.

Advances in our understanding of three MVC suggest them to be heterogeneous and multifactorial. Multimodal imaging tools such as optical coherence tomography (OCT), fundus autofluorescence, and ultra-widefield fluorescein angiography have defined changes in patients with DR better. Some of these changes also have a prognostic value. Similarly, there have been advances in the evaluation of DN and PDN. Evaluation of microvascular changes using currently available methods and their correlation might be helpful in improving our knowledge and provide better methods of managing DM patients rather than treating each of MVC in isolation as it is done now.

Authors in aforementioned study showed that the association of severity of DR with the severity of DN was found to be statistically significant. This unidirectional correlation is well known in patients of both type 1 and 2 DM.[4] Moreover, DR has been observed to precede DN in type 1 DM while in type 2 DM, DN precedes DR.[4] The similarity between retinal and kidney vascular architecture may be the reason for a better correlation between DR and DN.[5] In spite of this, variation in the chronology of appearance of DR and DN in type 1 and 2 DM can be due to differential effect of risk factors, difference

in pathogenic pathways involved, and/or bundling of various manifestations as a single entity.

In aforementioned Indian study, correlation of clinically significant macular edema/diabetic macular edema (CSME/DME), which is a major cause of blindness among diabetics with DN and PDN, was not attempted. Morphology of DME is better evaluated with the help of OCT and it may provide a better correlation with DN as capillary leakage is a common underlying pathophysiologic change in both MVC. Based on OCT classification of DME, Koo *et al*.[6] observed serous type of DME occurring more frequently in patients with microalbuminuria.[6]

Authors also observed that the correlation between DR and PDN in their study was inconclusive. Clinical evaluation and fundus photography inadequately document early neuroretinal degeneration seen in DR affecting retinal ganglion cells and amacrine cells, which is known to precede microangiopathy.[7] Evaluation of retinal nerve fiber layer (RNFL) thickness and inner retinal layers on OCT may be helpful in such scenarios and can also help to correlate DR and PDN better. This may suggest that the pathophysiology of DR may be similar to PDN, but involving retinal parenchyma.

In the early stages of both DR and DN, there is an increase in vascular endothelial growth factor (VEGF-A) expression along with tight junction loss in endothelium of capillaries leading to hyperpermeability. This manifests as incipient nephropathy (microalbuminuria) and DME. The role of angiotensin-converting enzyme inhibitors (ACEI) and sodium-glucose cotransporter 2 inhibitors (SGLT2i) is known in the management of DN.[8] However, their impact in managing DME, proliferative DR, and PDN is less explored. Evaluation of two conditions using current methods may be of help to identify patients 1) with DME who are likely to benefit from ACEI drugs and 2) for delaying the development of nonproliferative DR and progression to proliferative DR using ACEI drugs. SGLT2i drugs have shown to reduce cardiovascular morbidity and mortality. They are known to reduce oxidative stress, improve vascular endothelial function, and prevent arteriole wall thickening.

Utilizing currently available methods for evaluation of MVC and correlation among themselves might help us in better management of a subset of patients with DME and PDR using systemic therapies already found useful in the management of other MVC. These may also include glucagon-like peptide1 receptor agonists, lipid-lowering agents in addition to ACEI and SGLT2i.

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