Commentary: Recent concepts of pathophysiology and advancements in treatment strategies of diabetic retinopathy

Diabetic retinopathy (DR) is a major complication of diabetes and a leading cause of visual impairment among the middle age group.[1] According to a recent survey conducted, the prevalence of DR for all diabetic adults in India was estimated to be 16.9%.[2] This upsurge of diabetes mellitus (DM) and consequent diabetic retinopathy cases in the last decade is a serious concern and requires a new understanding of the pathophysiology of DR and a refined approach to its prevention and treatment.

Diabetes retinopathy is a neurovascular manifestation of systemic metabolic stress affecting all retinal cell types mediated by the interplay of various mediators of inflammations and angio-proliferation. Currently, the management of DR is based on the categorical classification based on its microvascular signs and there is a dearth of options to prevent the progression at the time of diagnosis itself. With recent years of research, the concept of neurodegeneration and neuronal apoptosis affecting retinal ganglion cells as well as photoreceptors has emerged.[3] Neurodegenerative changes are even seen to precede the vascular manifestations of DR.[4] Retinal glial cells, including astrocytes, Muller cells, and microglia, are not only responsible for providing structural support but are also involved in maintaining the complex homeostasis in the retina.[5] Hyperglycemia is associated with activation of these microglial cells and their dysfunction is involved in the early retinal inflammatory response seen in DR. These perturbations in neurons and glial cells are believed to drive a variety of structural and functional changes that often precede clinically visible vascular lesions in DR.[6] The structural alterations are seen on optical coherence tomography (OCT) as ganglion cell/nerve fiber layer thinning, disorganization of the retinal inner layers, and photoreceptors.[7-9] Whereas the functional alterations are seen as altered micro-perimetric and perimetric testing, increased implicit times, and reduction in oscillatory potentials in the multifocal ERG (mfERG).[6] These newer insights have led to the emergence of the concept that retinal dysfunction associated with diabetes is not just limited to microvascular components (endothelial cells and pericytes) but also affects retinal neurons (photoreceptors, horizontal and bipolar cells, amacrine and ganglion cells) and their supporting cells (astrocytes and Müller glial cells).

Retinal glial cells when activated under chronic metabolic stress acts as a source for cytokines, cytotoxic molecules, and growth factors (VEGF), which have a key role in perpetuating vascular dysfunction and neurodegeneration. Various interconnected biochemical pathways are involved in the pathogenesis of diabetic retinopathy, with the inflammatory pathway having a critical contribution.[10-12] Ocular sample proteomics have proved that raised quantity of cytokines, chemokines, and various growth factors in ocular samples of early as well advanced diabetic retinopathy patients contributes to its various clinical manifestation.[6] Raised levels of inflammatory cytokines—IL-1β, IL-6, IL-8, TNF-α, and MCP-1—have been attributed to early neuronal cell death seen in the retina in DM. Animal models have suggested that cytokines such as MIP-1, IL-1, and IL-3 are seen to contributes and precedes the development of neovascularization in PDR.[13,14] Angiopoietin-2 (Ang-2), VEGF, and ICAM-1 are raised in patients with DME.[15] Various studies have also reported that intravitreal concentrations of VEGF, HGF, IL-6, and MCP-1 have been shown to positively correlate with the progression of DR from the nonproliferative to active proliferative diabetic retinopathy (PDR).[16,17] Furthermore, IL6 has also been shown to have a positive correlation with retinal macular thickness.[18]

Present-day therapeutic approaches in the early stages of diabetic retinal disease are limited to strict control of modifiable DR risk factors, particularly hyperglycemia, lipid profile, and blood pressure. Specific therapeutic options such as laser coagulation, surgery, intravitreal injection of anti-VEGF agents, and intravitreal steroids are mainly effective in advance stages of DR to treat the aftermath of inflammatory and angiogenic insult. Though intravitreal steroids is an impressive therapeutic option, as it reins inflammatory cascade, inhibits leukostasis, inhibits VEGF gene transcription and translation, reduces vascular permeability and breakdown of the blood retinal barrier.[19] In real-world scenarios, its utility is limited as a second-line treatment option due to its potential side effects of inducing cataract and glaucoma. This has led to alternative corticosteroid delivery strategies and other safer anti-inflammatory therapeutic agents. One of the recent corticosteroid delivery strategies includes suprachoroidal drug delivery, which can achieve up to 10 times greater chorioretinal concentration compared to the intravitreous route.[20] Recent evidence has suggested that suprachoroidal triamcinolone acetonide is well tolerated and may improve functional and anatomical outcomes among treatment-resistant DME patients.[21] Leukocyte adhesion to the vascular endothelium and infiltration is an early step of inflammation. Blockade of alpha 4 integrin/CD49d can prevent endothelial injury and blood–retina barrier breakdown. A recent trial of intravitreal ALG-1001 (Luminate, Allegro Ophthalmics), an integrin inhibitor, has suggested its potentiality to be an alternative for DME treatment with fewer intravitreal injections.[22] Furthermore, it could provide hope for patients unresponsive to anti-VEGF therapy.

Search for newer strategies to amend the course of DR at an earlier stage is the need of the hour. Increasing evidence has suggested that anti-VEGF in patients with NPDR can lead to substantial regression in DR severity.[23] With availability for newer long-acting anti-VEGFs such as brolucizumab and undergoing research molecules such as Abicipar pegol, the potential number of intravitreal injections to achieve therapeutic outcome could also be reduced. Prolonged hyperglycemia and oxidative stress along with other molecular mediators drive chronic inflammation. Inhibition or modulation of pro-inflammatory mediators such as TNF-α and IL-1β could act as an important target to prevent early neuronal damage in DR. Although animal studies have revealed promising results with anti-TNF-α therapy, clinical trials have failed to show any functional or anatomical benefit.[24] Muller glial cells (MGCs) play an important role in the initiation and amplification of inflammatory response secondary to metabolic insult in DM. Restoring the normal functioning of MGC as well as receptor modulation can pave a path for developing effective

therapies in the treatment of DR. Lutein is a naturally occurring carotenoid and a potent antioxidant that has been shown to reduce gliosis and production of pro-inflammatory factors from Müller cells.[25] Lutein has been shown to improve contrast sensitivity but has failed to show any significant improvement in visual acuity in treated DR patients.[23]

The discovery of the role of inflammation and neurodegeneration in DR pathogenesis has revealed several molecules that can act as potential therapeutic targets. Novel targeted therapeutic strategies of blocking these crucial mediators may look promising but may fail to achieve therapeutic effect as DR is a continuum of various parallel inflammatory processes, unlike its clinical classification. As of now identification of these inflammatory mediators in aqueous or vitreous samples may act as prognosticating biomarkers. Further studies are needed to better understand the exact molecular mechanisms in DR and search for novel therapeutic agents targeting multiple rate-limiting steps so that DR can be prevented in the early stages.

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