Pathophysiological Changes of Retinal Inner Layers in Diabetic Macular Edema

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Abstract :

Diabetic macular edema (DME) remains the major cause of vision loss in the highly prevalent type 2 diabetes. Retinal inner layers comprise of 4 layers, namely; ganglion cell layer -inner plexiform layer complex, inner nuclear layer and outer plexiform layer. Spectral domain optical coherence tomography (SD-OCT) is a non-invasive imaging tool for in vivo cross-sectional retinal histology. SD-OCT is an important tool in diagnosing and managing a patient with DME. Disorganization of retinal inner layers (DRIL) is defined as the failure to ascertain any of the inner retinal layers' boundaries. DRIL has been found to be a predictor of visual acuity (VA) in DME.Serial OCT scans demonstrating changes in DRIL correlate with the severity of diabetic retinopathy (DR). Many artificial intelligence softwares can read SD-OCT and identify DRIL to screen patients of DR.

Keywords : Diabetic Macular Edema, Disorganization of Retinal Inner Layers, Spectral Domain Optical Coherence Tomography

INTRODUCTION :

The 2015 International Diabetes Federation Atlas reported that DM affects 415 million people worldwide.[1] The global burden due to diabetes is mostly contributed by type 2 diabetes (80-95% of the total diabetic population).The prevalence rate of DR in the Indian subcontinent is reported from 12% to 37% in patients with type 2 DM. DR is the leading cause of vision loss in adults aged 20–74 years.[2]Diabetic macular edema (DME) is responsible for most of the visual loss experienced by patients with diabetes as it remains the major cause of vision loss in the highly prevalent type 2 diabetes.[3]

RETINAL INNER LAYERS :

Spectral domain optical coherence tomography (SD-OCT) is a non-invasive reliable imaging tool for in vivo cross-sectional retinal histology.

Retinal inner layers comprise of 4 layers, namely; ganglion cell layer -inner plexiform layer (GCL-IPL) complex, inner nuclear layer (INL) and outer plexiform layer (OPL). These are visualized on SD-OCT.

Figure 1 : SD-OCT image showing intact inner retinal layers

Increased severity of DR has been found to be associated with disorganization of retinal inner layers(DRIL). DRIL has been found to be a predictor of visual acuity (VA) in center-involved DME.[4] DRIL was defined as the failure to ascertain any of the inner retinal layers boundaries.[4-6] DRIL was graded as Grade 0: absence of DRIL, and Grade 1: presence of DRIL .

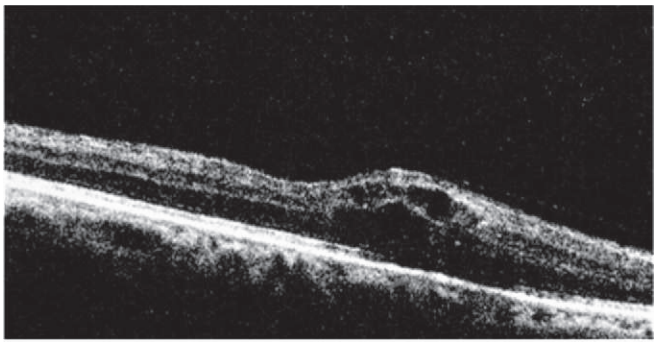

Figure 2 : SD-OCT showing DRIL with disruption of ELM and EZ.

S. No.	RETINAL LAYER	BLOOD SUPPLY
1.	Ganglion cell layer	Central retinal artery
2.	Inner plexiform layer	Central retinal artery
3.	Inner nuclear layer	Central retinal artery
4.	Outer plexiform layer	Central retinal artery, ophthalmic artery via choriocapillaris

PATHOPHYSIOLOGICAL CHANGES TAKING PLACE IN RETINAL VESSELS IN DME :

In DME, basement membrane thickening, pericyte loss,[7,8]increased expression of ICAM-1[9], oxidative and nitrosative stress[10], rheological changes[11]and decreased capillary perfusion lead to capillary endothelium damage. This results in fluid leakageout of the capillaries resulting in DME, capillary closure and decreased capillary blood flow. These changes lead to decreased blood flow to retina with consequential retina lischemia and increased vascular endothelial growth factor (VEGF) release[12]. Retinal oximetry studies have shown that increase in retinal venous oxygen saturation is associated with increasing levels of DR. Several studies also found increased retinal arterial oxygen saturation in patients with DR.[13]

Retinal blood flow in adjacent capillaries increases due to retinal is chemia thereby increasing shear stress in the vesselwall. Increased viscosity and capillary closure also contribute to increasing shear stress on the vessel wall.[14] Tooke hypothesized that increased glycation and thickening of the basement membrane results in "locking" of the vessel.[15] This tends to increases hear stress as the vessel diameter is unable to change, leading to mechanical injury to the vascular endothelium.

Capillary pressure is increased in diabetes mellitus due to the presence of dilated vasculature; the systemic blood pressure is more easily transmitted to the micro circulation.

Vessel wall of larger vessels of the retinal circulation suffer more circumferential stress damage. This occurs as the circumferential stress that is responsible for mechanical damage to the endothelium of the vessel wall is direct lyproportional to the perfusion pressure and radius and inversely proportional to the thickness of the vessel wall.[16] As a result, the vessel has a tendency to dilate. As stated by Laplace law, vesselwall tension resisting distension pressure is inversely proportional to the radius of the vessel. Vessel has a tendency towards dilatation as the vessel wall tension required to counteract distending pressure is not achieved in a dilated vessel, resulting in subsequent hyperperfusion.

Blood flow to adjacent retinal capillaries is increased due to retinal is chemia, resulting in increase in vessel wall shear stress.[14] Resistive index has been characterised as a marker of vascular resistance which increases with increasing resistance, with vascular compliance taken into account.[17]

DISRUPTION OF RETINAL INNER LAYERS IN DME :

Role of SD-OCT :

DRIL has been highlighted as a predictive biomarker for VA in DME. This biomarker may be useful not only as a predictor of VA but also for stratification of eyes with regard to a high likelihood of future VA improvement or decline.[6]

DRIL as visualized on SD-OCT represents an anatomic interruption in the visual transmission pathway. Disruption has been hypothesized to result when bipolar axons snap after their elasticity limit has been exceeded due to edema.[6,18]

Our recent study found that presence of DRIL correlated with severity of DR. A significant positive correlation was found between DRIL and central subfoveal thickness (CST) and cube average thickness (CAT) and ellipsoid zone disruption on SD-OCT. [5]

Role of doppler ultrasonography :

CRA supplies the retinal inner layers.[19]Our other colour doppler study also highlighted an increase in RI of CRA in DME. This was found to correlate significantly with an increase in CST and CAT.[20]Hence it can be concluded that increased RI of CRA also plays a significant role in pathogenesis of DRIL.

Another microvascular complication of diabetes is diabetic nephropathy. Resistive index of intrarenal artery has been used to detect renal dysfunction in patients of diabetic nephropathy. Shirin et al concluded that resistive index has value in identifying diabetic patients who are developing nephropathy and can be used as an additional diagnostic tool as RI of renal artery well correlates with serum creatinine and albuminuria which are the biochemical parameters to diagnose diabetic nephropathy.[21]

Role of serum VEGF :

In our earlier study, we have found that significantly elevated levels of serum VEGF come into play even before the evidence of DR. Increase in VEGF has been found to correlate with increase in CST and CAT. Estimation of serum VEGF is a useful laboratory test for predicting the onset of DR.[22]

Role of Artificial Intelligence :

Artificial intelligence systems are being developed to screen patients of diabetic retinopathy, read OCTs and identify lesions in retinal layers. The current AI screening systems for DR have been developed using two-dimensional images and lack stereoscopic qualities. Additionally, the medicolegal aspects and the regulatory approvals vary in different countries and settings. However, it can be an effective way to screen patients of diabetic retinopathy in a physicians' or endocrinologists' OPD.[23]

TAKE HOME MESSAGE :

1. SD-OCT is an important tool in diagnosing and managing a patient with DME. Serial OCT scans demonstrating improvement or decline in DRIL correlates with the severity of diabetic retinopathy.

2. Serum VEGF levels serve as a simple and reliable biomolecular biomarker for severity of DR.
3. Administration of intra-vitreal anti-VEGF causes reduction in DME and may show improvement in DRIL.
4. Doppler ultrasonography of CRA can be an additional easy modality of screening patients with DR.
5. Artificial intelligence is an upcoming tool for the screening of patients for DRIL in DME

References:

1. International Diabetes Federation. IDF Diabetes Atlas, 7th edition. Brussels, Belgium: International Diabetes Federation; 2015.
2. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. Lancet. 2010;376(9735):124–36.
3. Tong L, Vernon SA, Kiel W, Sung V, Orr GM. Association of macular involvement with proliferative retinopathy in type 2 diabetes. Diabet Med. 2001;18:388–94.
4. Maheshwary AS, Oster SF, Yuson RM, et al. The association between percent disruption of the photoreceptor inner segment-outer segment junction and visual acuity in diabetic macular edema. Am J Ophthalmol2010;150:63-7.
5. Nadri G, Saxena S, Stefanickova J, et al. Disorganization of retinal inner layers correlates with ellipsoid zone disruption and retinal nerve fiber layer thinning in diabetic retinopathy. J Diab and Compl2019;33:550-3.
6. Sun JK, Lin MM, Lammer J, et al. Disorganization of the retinal inner layers as a predictor of visual acuity in eyes with center-involved diabetic macular edema. JAMA Ophthalmol2014;132:1309–16.
7. Kuwabara T, Cogan DG. Retinal vascular patterns VI: mural cells of the retinal capillaries. Arch Ophthalmol. 1963;69:492–502.
8. Takahashi K, Brooks RA, Kanse SM, Ghatei MA, Kohner EM. Endothelin I is produced by cultured bovine retinal endothelial cells and endothelin receptors are present on associated pericytes. Diabetes. 1989;38:1200–1202.
9. Jain A, Saxena S, Khanna VK, Shukla RK, Meyer CH. Status of serum VEGF and ICAM-1 and its association with external limiting membrane and inner segment-outer segment junction disruption in type 2 diabetes mellitus. Mol Vis. 2013;19:1760–1768.
10. Sharma S, Saxena S, Srivastav K, Shukla R, Mishra N, Meyer CH, Kruzliak P, Khanna VK. Nitric oxide levels in diabetic retinopathy and its association with disruption of photoreceptor IS-OS junction and topographic alterations in retinal pigment epithelium. Clin Exp Ophthalmol. 2015;43:429–436.
11. DE McMillan.The effect of diabetes on blood flow properties. Diabetes. 1983;32(suppl 2):56–63.
12. Crawford TN, Alfaro DV, Kerrison JB, Jablon EP. Diabetic retinopathy and angiogenesis. Curr Diabetes Rev. 2009;5:8–13.
13. Rilvén S, Torp TL, Grauslund J. Retinal oximetry in patients with ischaemic retinal diseases. Acta Ophthalmol. 2017;95:119–127.
14. Fry DL. Certain histological and chemical responses of the vascular interface to acutely induced mechanical stress in the aorta of the dog. Circ Res. 1968;159(24):93–108.
15. Tooke JE. Microvascular haemodynamics in diabetes mellitus. Clin Sci. 1986;70:119–125.
16. Burton AC. Relation of structure to function of the tissues of the walls of blood vessels. Physiol Rev. 1954;34:619–642.
17. Bude RO, Rubin JM. Relationship between the resistive index and vascular compliance and resistance. Radiology. 1999;211:411–7.
18. 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(5):2741-2748.
19. Blodi FC. Eugene Wolff's anatomy of the eye and orbit. Arch Ophthalmol. 1977;95:1284.
20. Khatri M, Saxena S, Kumar M, et al. Resistive index of central retinal artery is a bioimaging biomarker for severity of diabetic retinopathy. Int J Retina Vitreous. 2019;5:38.
21. Shirin M, Sharif MM, Gurung A, Datta A. Resistive Index of Intrarenal Artery in Evaluation of Diabetic Nephropathy. Bangladesh Med Res Counc Bull. 2015;41(3):125-130.
22. Ahuja, S., Saxena, S., Akduman, L. et al. Serum vascular endothelial growth factor is a biomolecular biomarker of severity of diabetic retinopathy. Int J Retin Vitr5, 29 (2019).
23. Ting DSW, Pasquale LR, Peng L, et al Artificial intelligence and deep learning in ophthalmology British Journal of Ophthalmology2019;103:167-175.