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Case Report

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A Review on Diabetic Retinopathy

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ABSTRACT

Diabetes mellitus is a major cause of avoidable blindness in both the developing and the developed countries. Significant technological advances have taken place to improve the diagnostic accuracy of diabetic retinopathy. In the last three decades, the treatment strategies have been revised to include, besides laser photocoagulation, early surgical interventions and pharmacotherapies.

Introductio:

Diabetes mellitus(DM)is a major cause of avoidable blindness among the working age groups. Patients with diabetic retinopathy(DR) are 25 times more likely to become blind than non-diabetics.[1] Good glycemic control arrests the development and progression of DR and decreases the visual loss. Technological advances have improved the diagnostic accuracy of screening methods and access of the diabetic patients to the specialist care

Epidemiology :

India will become one of the majorhubs of diabetic population during the next 2 decades, according to the World health organization. The prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030,the total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030.[2] A global estimate of the prevalence of DR and the severe stages of DR,[3]from population-based studies worldwide estimated that among individuals with diabetes, the overall prevalence of any DR was 34.6%, proliferative diabetic retinopathy was 7.0%, diabetic macular edema was 6.8%, and vision threatning diabetic retinopathy was 10.2%. In two studies from South India, the prevalence rates of DR in type 2 diabetic patients were 34.1% and 37%.[4] In the Chennai Urban Rural Epidemiology Study, they evaluated urban sample of diabetic patients and estimated the overall prevalence of DR as 17.6%.[5]

Pathophysiology:

There is a complicate interplay of various factors in the pathogenesis of diabetic retinopathy,such as bio-chemical mechanisms,rheological changes and structural changes. Bio-chemical mechanism includes prolonged hyperglycemia,excess sorbitol formation[6], proteinkinase C activation[7] and vascular endothelial growth factor release. Prolonged hyperglycemia[8] is the major etiologic agent in the micro vascular complications of diabetes mellitus. Chronic hyperglycemia causes accelerated oxidative stress in cells resulting in toxic end products.[9] Rheological changes[10] includes increased platelet adhesion and aggregation, and increased rouleax formation and reduced deformability of red blood cells. Structural changes include capillary basement[11]membrane thickening,loss of microvascular intramural pericytes and breakdown of blood retinal barrier. However the final metabolic pathway causing DR is still unknown.

Risk Factors of Diabetic Retinopathy:

Level of glycemia:

Hyperglycemia is a strong factor in the development and progression of diabetic retinopathy. Benefits of better control continue to manifest even after non

proliferative and proliferative diabetic retinopathy has developed. Elevated glycosylated hemoglobin(HbA1c) is a strong factor for the progression to high risk proliferative diabetic retinopathy.[12]Serum lipids Elevated levels of serum cholesterol is associated with increased severity of hard exudates[13]. Elevated serum triglyceride levels are associated with an increased risk of developing high risk and decreased visual acuity.

Blood Pressure:

Intensive control of blood pressure slows down the progression of retinopathy and reduces the risk of other microvascular and macrovascular complications of diabetes mellitus.[14] Abnormal systolic and diastolic blood pressures are associated with the severity of retinopathy in both type I and type II disease.

Duration of diabetes:

Duration of diabetes is a significant risk factor for the development of diabetic retinopathy[15]. After 20 years of diabetes, all the type I and > 60% of type II patients have some degree of retinopathy.

Pregnancy:

Retinopathy is accelerated during pregnancy because of pregnancy itself or the changes in the metabolic control.[16]

Genetic Factors:

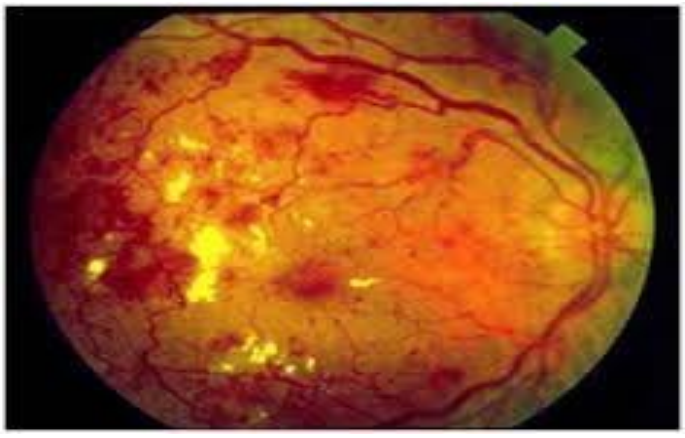
Relationship between HLA antigens expressed on the cell surface and the presence of retinopathy has already been documented. HLA – DR phenotypes 4/0, 3/0, and XX expression is associated with increased proliferative retinopathy.[17]

Ocular Factors:

Myopia reduces the prevalence and severity of diabetic retinopathy,Retinochoroidal scarring from trauma or inflammatory disease, reduces the prevalence of retinopathy by decreasing the retinal metabolism and thereby decreasing the need for oxygen and the release of vasoproliferative factors.

Clinical Features of Diabetic Retinopathy:

Non-proliferative and proliferative diabetic retinopathyNon-proliferative diabetic retinopathy (NPDR) is characterized by the presence of: (i) microaneurysms, which are the first clinically detectable lesions of DR located in the inner nuclear layer of the retina, (ii) dot and blot hemorrhages, which are located in the middle retinal layers, (iii) hard exudates, which are located between the inner plexiform and inner nuclear layer of the retina, (iv) vascular changes such as beading, looping and sausage like segmentation of the veins, (v) cotton wool spots, also called soft exudates or nerve fiber infarcts, result from capillary occlusion of the retinal nerve fiber layer, (vi) intraretinalmicrovascular abnormalities (IRMA), which are dilated capillaries that seem to function as collateral channels, frequently seen adjacent to the areas of capillary closure, (vii) retinal edema characterized by accumulation of fluid between the outer plexiform layer and inner nuclear layer, which may later involve the entire layers of the retina.



NPDR with CSME PDR:

In the natural course, approximately 50% of patients with very severe NPDR progress to proliferative diabetic retinopathy(PDR) within 1 year.[18] PDR is characterized by the presence of neovascularization. New vessels may proliferate on the optic nerve head (new vessels at disc - NVD) and along the course of the major vascular arcades (new vessels elsewhere - NVE). The new vessels mostly grow along the posterior hyaloid and sudden vitreous contraction may result

in rupture of these fragile vessels. When the vitreous detachment occurs, the new vessels are pulled anteriorly along with the underlying retina, resulting in tractional retinal detachment. On the other hand, vitreous might detach completely without any pull on the retina and new vessels regress, thus resulting in the development of an end-stage disease.The Early Treatment Diabetic Retinopathy Study(ETDRS)[19] has classified NPDR into mild, moderate, severe and very severe and PDR into early PDR and high-risk PDR. This is as follows:

A. Moderate NPDR: Hemorrhages and/or microaneurysms, presence of soft exudates, venous beading, IRMA definitely present, definition not met for C, D, E, or F.

B. Mild NPDR: Presence of at least one microaneurysm, definition not met for B, C, D, E, or F.

C. Severe NPDR: Hemorrhages and/or microaneurysms in all four quadrants, or venous beading in two or more quadrants, or IRMA in at least one quadrant, definition not met for D, E, or F.

D. Very severe NPDR: Any two or more of the changes seen in severe NPDR, definition not met for E, or F.

E. Early PDR: Presence of new vessels, definition not met for F.

F. High-risk PDR: Includes any of the following characteristics - neovascularization of disc (NVD) > $1/3^{rd}$ to $1/4^{th}$ disc diameter, NVD < $1/3^{rd}$ to $1/4^{th}$ disc diameter with vitreous/ pre-retinal hemorrhage, NVE with vitreous/pre-retinal hemorrhage. High-risk characteristics (HRC) were defined by Diabetic Retinopathy Study, as the patient, if not treated urgently, is at a high risk of severe visual loss.

Diabetic macular edema:

Macular edema or retinal thickening is an important manifestation of DR and the most common cause of moderate visual loss. Diabetic macular edema patients were categorized into clinically significant macular edema(CSME)[20] or non-CSME by ETDRS. CSME includes any one of the following lesions:

1. Retinal thickening at or within 500 microns from the center of macula.
2. Hard exudates at or within 500 microns from the center of macula associated with thickening of the adjacent retina.
3. An area or areas of retinal thickening at least one disc area in size, at least a part of which is within one disc diameter of the center of macula.

The intraretinal fluid comes from leaking microaneurysms or diffuses from capillary incompetence areas. Diabetic macular edema is retinal thickening within two disc diameters of the center of macula.

ManagementInvestigations:

Diabetic retinopathy is essentially a clinical diagnosis. Slit lamp biomicroscopy, dilated fundus evaluation with a direct ophthalmoscope and indirect ophthalmoscope or contact/non- contact slit lamp biomicroscopic examination are essential in the diagnosis of DR. However, several ancillary investigations are required to aid the diagnosis, plan and execute the treatment and to document the lesions for research purposes. Stereoscopic fundus photographs may be required for research purposes and are especially useful for the assessment of macular edema.

Laser photocoagulation:

The treatment depends on the type and severity of retinopathy,

Non proliferative Retinopathy:

For mild and moderate NPDR, strict adherence to normal levels of glycemia, blood pressure and lipid status is the mainstay of effective treatment. Scatter laser photocoagulation is generally not recommended. The Early Treatment Diabetic Retinopathy Study[21] and the Diabetic Retinopathy Study recommend photocoagulation as the treatment of choice for severe and progressive form of retinopathy and clinically significant macular edema.Severe Nonproliferative diabetic retinopathyFor severe NPDR, scatter laser treatment is appropriate when, the disease process is progressing rapidly and when close follow-up of patients are unlikely.Macular edema ETDRS demonstrated that retinal laser therapy applied to macula reduces the risk of substantial worsening of vision by 50%.[22] Parameters for focal treatment should be the Spot size about 50-100µm of ≤0.1s duration and power sufficient to cause blanching of microaneurysm and retinal pigment epithelium.

Pars plana vitreous surgery:

Diabetic retinopathy vitrectomy study[23]randomized 370 eyes with extensive neovascularization and visual acuity of 20/400 or better into two groups of early vitrectomy or observation alone The results indicate that such patients probably do not benefit from early vitrectomy. They should be observed closely so that vitrectomy, when needed, can be undertaken promptly. This group also studied diabetic eyes with vitreous hemorrhage and visual acuity less than 5/200 for 6 months and randomized these into two groups of those who received immediate surgery and those whose surgery was deferred for another 6 months. The study recommended early surgery in type 1 diabetic patients, more so in bilateral cases and one-eyed patients. Other strategies in diabetic retinopathy management Diabetes Control and Clinical Trial(DCCT)[24] showed that in intensively treated group, the risk of onset of retinopathy was reduced by 76%, risk of progression of retinopathy by 63%, risk of development of CSME by 23% and the need for laser treatment by 56% compared to the conventional group. This benefit persisted even 4 years after initiation of intensive therapy.United Kingdom Prospective Diabetes Study(UKPDS) showed that in intensive blood pressure control group, there was a 34% and 47% reduction in risk of DR progression and moderate visual acuity loss, respectively, compared to the control group after a median follow-up of 8.4 years.[25]ETDRS[26] identified elevated levels of serum cholesterol and low-density lipoproteins as independent risk factors for the development of hard exudates, which a major risk factor is leading to subfoveal fibrosis.In patients with refractory CSME, intravitrealadministration of corticosteroids showed to be useful. Many trials have been done reporting the efficiency of intravitrealantiVEGF agents.[27]Currently, several drug delivery modalities are in clinical trials to investigate their efficacy.

Screening for Diabetic Retinopathy:

Ophthalmoscopy is the most commonly used technique to screen for DR. When performed by an ophthalmologist, specificity of direct and indirect ophthalmoscopy was high, but the sensitivity was low.The Digital imaging makes fundus photography easier and more widely accessible. Single-field fundus photography with interpretation by trained readers could serve as a screening tool to identify patients with DR. The automated retinal image screening[28] for diabetic retinopathy had a high sensitivity in high and medium quality images and this software hold promise in future screening programs.

Conclusion:

There were 31.7 million diabetics in India in year 2000 with a projection to reach 79.4 million by year 2030. Developing strategies for screening of population for early detection of DR is engaging attention of several groups in India. The present review outlines the magnitude of the problem in India, conventional and current strategies to manage the potentially blinding complications of DM. While laser photocoagulation and pars plana vitreous surgery remain the standards of care, recent successful use of several molecules is bringing about a paradigm shift in favor of pharmacotherapy. The ophthalmologists should encourage a good comprehensive systemic control for better outcomes.

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