Diabetic Retinopathy Requiring Vitrectomy: Epidemiology and Pathology

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Abstract:

Diabetic retinopathy (DR) is a chronic microvascular complication of diabetes mellitus and remains one of the leading causes of preventable blindness worldwide, particularly among individuals of working age. As global diabetes prevalence rises, the burden of DR is also increasing, with estimates indicating that over one-third of diabetic patients develop some form of retinopathy, and nearly 7% progress to the proliferative stage (PDR). Proliferative diabetic retinopathy is characterized by retinal ischemia-induced neovascularization, where fragile new blood vessels form on the retinal surface or optic disc. These vessels often extend along the posterior hyaloid, accompanied by fibrovascular tissue that may contract and exert traction on the retina, leading to tractional retinal detachment (TRD). Persistent or recurrent vitreous hemorrhage and macula-threatening TRD are the most common indications for pars plana vitrectomy (PPV) in diabetic patients. The pathological mechanisms leading to the need for surgical intervention involve a cascade of metabolic and vascular changes triggered by chronic hyperglycemia. These include capillary basement membrane thickening, pericyte loss, increased VEGF expression, and breakdown of the inner blood-retinal barrier, all of which contribute to neovascular complications and vision loss. Surgical management, particularly vitrectomy, plays a critical role in preventing irreversible blindness in advanced DR. However, surgical outcomes depend on multiple factors such as the extent of macular involvement, duration of detachment, systemic glycemic control, and presence of other ocular comorbidities.

Keywords: Diabetic Retinopathy, Vitrectomy, PDR.

Introduction:

Diabetic retinopathy (DR) is a major microvascular complication of diabetes mellitus and a leading cause of visual impairment globally, particularly among working-age adults. With the increasing prevalence of diabetes worldwide, the burden of DR is escalating, posing significant public health and socioeconomic challenges. Studies estimate that over one-third of people with diabetes will develop DR, and approximately 7% will progress to proliferative diabetic retinopathy (PDR)—the most severe form of the disease, which often necessitates surgical intervention **(1).**

PDR is characterized by the formation of abnormal, fragile blood vessels in response to chronic retinal ischemia. These neovessels proliferate along the retinal surface and posterior hyaloid face, accompanied by fibrovascular tissue that can contract and lead to tractional retinal

detachment (TRD). Additionally, persistent vitreous hemorrhage caused by ruptured neovessels can obscure vision and delay treatment, making pars plana vitrectomy (PPV) a critical therapeutic option in such cases **(2).**

The underlying pathology of advanced DR includes capillary nonperfusion, basement membrane thickening, pericyte loss, and increased vascular permeability. These changes disrupt the blood-retinal barrier and lead to chronic inflammation and neovascularization. VEGF (vascular endothelial growth factor) plays a central role in this process, promoting angiogenesis and vascular leakage, which further exacerbates the risk of retinal detachment and hemorrhage **(3).**

Timely vitrectomy in these patients serves to remove non-clearing vitreous hemorrhage, excise fibrovascular membranes, and reattach the retina. However, the visual prognosis is highly dependent on the duration of detachment, involvement of the macula, and systemic control of diabetes. Therefore, understanding the epidemiology and pathological mechanisms of DR requiring surgery is essential for optimizing outcomes and guiding management strategies **(4).**

Epidemiology:

Diabetic retinopathy (DR) is the leading cause of new blindness in patients aged 20–74 years in industrialized nations (4, 5). It has been estimated that 93 million people throughout the world have DR, with approximately one-third of them having diabetic macular edema (DME). DME is responsible for 75% of DR-related vision loss but advances in laser photocoagulation (6). And intravitreal pharmacotherapy, particularly corticosteroids (7). And drugs that inhibit the actions of vascular endothelial growth factor (VEGF) (8–10) have enabled physicians to stabilize retinopathy, decrease macular edema, and improve visual acuity (VA) in the majority of affected patients.

Vision loss in the other 25% of patients with DR stems from complications of proliferative diabetic retinopathy (PDR). Approximately 17 million patients throughout the world have PDR (11) and without treatment more than half of the patients with high-risk PDR – based on the classification system developed for the Diabetic Retinopathy Study – will be blind within 5 years (12). When panretinal photocoagulation (PRP) of the retina is performed prior to the development of severe PDR-related complications [vitreous hemorrhage and traction retinal detachment (TRD)], the incidence of severe vision loss decreases by about 50% (13).

The Early Treatment of Diabetic Retinopathy Study (ETDRS) showed that 5% of patients with PDR will require vitreous surgery despite having received what appeared to be adequate PRP (14) The prevalence of PDR in patients with DM varies depending on the type of DM and the population cohort. Prevalence of PDR is much higher (15 times) in type 1 DM as compared to type 2 DM (15).

The global prevalence of PDR was 7.24%, and when extrapolated to the World Diabetes population of 2010, 17.2 million people had PDR (15). Gange et al. Evaluated patients of type 2 DM at the end of 5 years and found that 1.74% developed PDR, 0.25% patients developed TRD, and 0.14% patients developed neovascular glaucoma (NVG) (16).

They concluded that important risk factors in these patients are insulin usage, hba1c >9%, kidney disease, neurological disease, older age at diagnosis, and peripheral vascular disease.

The Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) in patients with older onset DM (>30 years of age) reported the 4-year incidence of PDR at 7.4% in patients using insulin and 2.3% in patients not using insulin (17), while in the younger onset group, the 4-year incidence of PDR was 10.5% (18). The prevalence of PDR in the WESDR group was 22.7% for the younger onset group, 13.8% for the older onset group who were taking insulin, and 2.9% for the older onset group who were not taking insulin (18).

The WESDR XXII report demonstrated that the 25-year cumulative rate of progression to PDR was 42% in type 1 DM with increased risk associated with higher hba1c, higher systolic blood pressure, a greater body mass index, and proteinuria (19).

The United Kingdom National Ophthalmology Database study showed the prevalence of PDR to be 10.6%, while the Los Angeles Latino Eye Study (LALES) found 5.3% patients with NPDR progressed to PDR and 1.9% with NPDR progressed to PDR with high risk characteristics at 4 years of follow-up (20, 21). In a developing nation like India, the prevalence of any DR ranges from 10 to 30.4%, while the National Diabetic retinopathy study (2015–2019) revealed the prevalence of DR among patients with DM was 16.9% with 0.6% having PDR (Scottish classification) (22).

In early surgical series, TRD constituted 20% of diabetic vitrectomies (23) but this proportion has risen to 40% in more recent studies (24). Studies like the Early Treatment of Diabetic Retinopathy study (ETDRS) suggests 5.3% of patients required vitrectomy at the end of 5 years (14).

The CLARITY trial, which evaluated the clinical efficacy of intravitreal aflibercept versus PRP in PDR, determined that 6% of patients in the PRP group and 1% in the aflibercept group required vitrectomy at the end of 52 weeks (25).

In Protocol S, 15% patients required vitrectomy in the PRP group and 4% required vitrectomy in the intravitreal ranibizumab group at the end of 2 years (26). The 5-year outcomes of Protocol S showed that 41% of eyes in PRP group with VH underwent vitrectomy as compared to 22% in the ranibizumab group (27).

The first pars plana vitrectomy was performed in 1970 on an eye with a non-clearing vitreous hemorrhage and the VA improved from 2/200 to 20/50 (28).

A subsequent series of cases from 1977 described the following indications for diabetic vitrectomy: non-clearing vitreous hemorrhages (70%); TRD (20%); and combined traction/rhegmatogenous retinal detachment (TRD/RRD) (10%).[20] Between 1980 and 2004, VA improvements in eyes with TRD were limited because of what was believed to be excessively long durations of macular detachment prior to surgery (29).

Since then the benefits and safety of vitrectomy have steadily risen and the threshold for performing vitrectomy has decreased. Indications for vitrectomy have expanded during recent years to include severe fibrovascular proliferation, dense vitreous hemorrhage with rubeosis, ghost cell glaucoma, dense pre-macular hemorrhage, and a taut hyaloid with DME (30).

Pathophysiology

The mechanisms leading to the development of DR are complex and remain incompletely understood. Brownlee proposed the "unifying theory" for the development of DR, based on the observation that several biochemical pathways (activation of protein kinase C, increased flux through the hexosamine pathway, increased intracellular formation of advanced glycation end-products, and increased polyol pathway flux) are dysregulated in patients with DM and DR (31). He noted that each of these pathways interferes with electron transfer through the mitochondrial cytochrome chain resulting in the accumulation of superoxide ions.

Oxidative stress and retinal ischemia creates a pro-inflammatory state that upregulates the synthesis of various chemokines, cytokines, and angiogenic factors like VEGF. These molecules promote the development of DME by breaking down the blood-retinal barrier and the development of PDR by stimulating the growth of pre-retinal proliferative tissue (32).

Increased levels of nitric oxide (NO) pathway metabolites (citrulline and arginine) have been found in the vitreous of eyes with TRD (33) and excess NO creates toxic free radicals that may inhibit mitochondrial function and cause cell death by damaging DNA (34). Other pro-inflammatory and growth factor molecules found in eyes with PDR include the following: monocyte chemotaxis protein (MCP)-1, TGF-β1,2,3, interleukin (IL)-1β, IL-6, IL-8, erythropoietin, and adiponectin. (Fig.1)

The vitreomacular interface is key to the development of PDR as evidenced by the protective effect of posterior vitreous detachment. TRD represents an advanced form of PDR that results from neovascular growth from existing retinal vasculature into the vitreomacular interface with an accompanying vestment of fibrotic tissue and contractile elements (Fig.2).

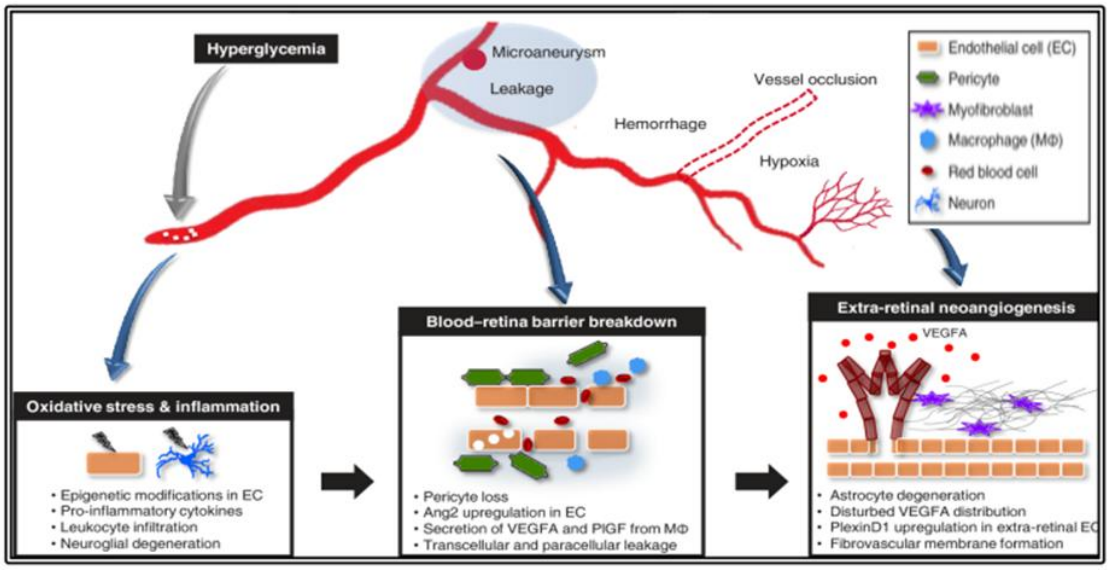

Figure (1): Pathophysiology of proliferative diabetic retinopathy (35).

Growth factors create a biochemical environment favorable for angiogenesis. Neovascular buds grow from the larger retinal blood vessels into the potential space between the internal limiting membrane and the posterior hyaloid. By using the hyaloid as a scaffold they eventually invade the cortical vitreous, thus creating firm adhesions between the hyaloid and the inner retina **(36, 37).** The co-development of contractile fibrous tissue results in anteroposterior and tangential traction on the fibro-vascular complex and thinned ischemic retina by the vitreous. Excessive traction frequently causes the fragile new vessels to bleed into the vitreous, pre-retinal space, or both, and causes the retina to deform and detach.

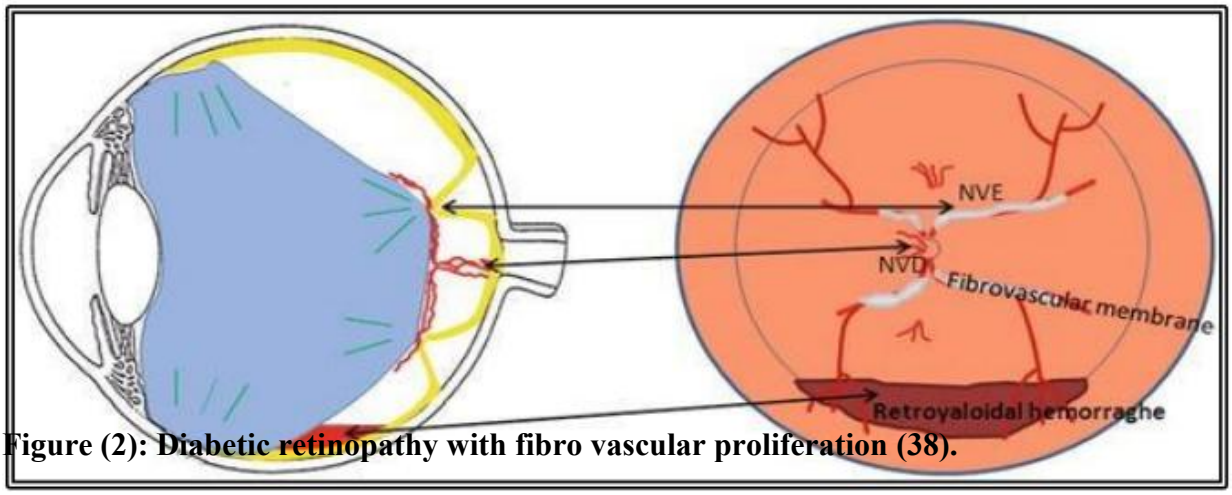

Figure (2): Diabetic retinopathy with fibro vascular proliferation (38).

The process of posterior vitreous detachment in eyes with PDR is altered by the presence of fibrovascular membranes, leading to the development of tractional forces at the sites of vitreoretinal attachment. These tractional forces can lead to various outcomes: vitreous haemorrhage, tractional retinal detachment, and combinedtractional–rhegmatogenous retinal detachment (retinal break formation usually occurs near fibrovascular epicentres) (Figure 1).

Alternatively, contraction of a fibrovascular membrane sheet across the posterior pole can lead to macular distortion or dragging. It should be recognised that some tractional elevations of the retina in PDR are tractional retinoschisis rather than tractional retinal detachment (39).

The retinal pigment epithelium (RPE) pump produces negative pressure in the subretinal space creating a concave retinal configuration between tractionally elevated areas with heavy pre-retinal fibrosis. Retinal elevation is highest at loci of anteroposterior vitreoretinal traction and beneath broader areas of tangential traction. A combined TRD/RRD has a convex or bullous configuration because liquefied vitreous moves through a full- thickness retinal break into the subretinal space (Fig.3)

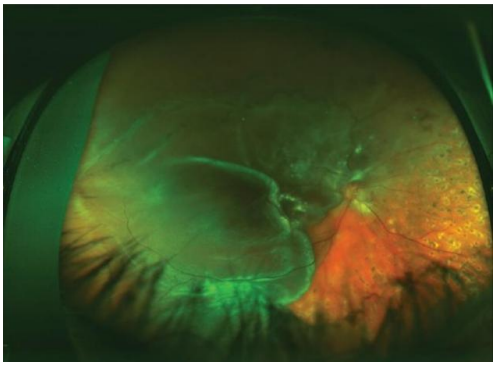

Figure (3): Traction/rhegmatogenous retinal detachment involves the entire temporal retina. Note the bullous or convex configuration of the retina and the extension of the detachment to the ora serrate (40).

Whereas trds are limited to areas of fibrosis and vitreoretinal traction, combined TRD/RRD is usually characterized by a detachment that extends to the ora serrata. Tangential traction from broad areas of fibrosis may create full-thickness retinal breaks that convert a pure traction detachment to one with a rhegmatogenous component (41).

Most cases of TRD/RRD have widespread and tightly adherent plaque-like pre-retinal proliferation, partial posterior vitreous detachment (pvds), and retinal folds. A few eyes develop flap tears but oval breaks near areas of extensive fibrosis are more commonly seen (42).

The presence of subretinal hemorrhage also indicate site of the break. Fibrosis sometimes increases following PRP, perhaps because of a decrease in VEGF levels and upregulation of connective tissue growth factor (CTGF). This sometimes leads to breaks near heavy laser photocoagulation. Older studies reported that TRD/rrds accounted for 17–35% of diabetic eyes

undergoing vitrectomy. However, earlier surgical intervention and new indications for surgery, these eyes now account for a smaller proportion of surgeries (43,44).

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