ORIGINAL RESEARCH PAPER
Volume - 10 | Issue - 04 | April - 2021 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

DIABETIC RETINOPATHY: PATHOPHYSIOLOGY AND TREATMENT

Ophthalmology

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ABSTRACT

Diabetic Retinopathy (DR) is the leading cause of blindness in the working aged population. Diabetic retinopathy (DR) is a micro vascular complication of diabetes mellitus (DM) that affects the blood vessels of the retina and leads to blindness. Patients with diabetes suffer many life-limiting and life-threatening complications, including macrovascular-related stroke, ischemic heart disease, and peripheral artery disease and/or microvascular-related retinopathy, neuropathy, and nephropathy. Diabetic retinopathy (DR) is the most common microvascular complication of diabetes.

Clinically, DR is divided into two stages: non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). NPDR represents the early stage of DR, wherein increased vascular permeability and capillary occlusion are two main observations in the retinal vasculature. During this stage, retinal pathologies including microaneurysms, hemorrhages and hard exudates can be detected by fundus photography although the patients may be asymptomatic. PDR, a more advanced stage of DR, is characterized by neovascularization.

KEYWORDS

INTRODUCTION

Diabetes is a global epidemic and already showing its devastating human, social and economic consequences. The disease claims as many lives per year as HIV/AIDS and a real cause for our health expenditure.[1] It has also been estimated by 2030, the number of people with diabetes in the world will increase by 552 million.[2]

According to the International Diabetes Federation, 61.3 million people in India had diabetes in 2011. That figure is projected to rise to 101.2 million by 2030.[3]In India, the expected growth in diabetes prevalence from 6.0 to 7.4% in 2025 is mainly due to increase in life expectancy and increasing urbanization(31 to 43%).Risk correlates diabetes are age ≥45 years, family history of diabetes, physical inactivity, obesity and body fat patterning, insulin-resistance and the metabolic syndrome, gestational diabetes, maternal under nutrition, low birth weight, and childhood catch-up obesity, genetic predisposition and race and ethnicity.

Diabetic retinopathy (DR) is a microvascular complication seen in type 1 and type 2 diabetes. The earliest signs are microaneurysms (10-100 µm sized saccular capillary extensions due to pericyte loss) in the retinal capillaries and retinal haemorrhages. The progression of retinopathy is gradual, advancing from mild abnormalities, characterized by increased vascular permeability to proliferative diabetic retinopathy, characterized by the growth of new blood vessels on the retina and posterior surface of the vitreous.

Retinopathy can be studied by direct ophthalmoscopy examination, indirect ophthalmoscopy examination, + 90 D lens on slit lamp, fundus photography and fluroscein fundus angiography (FFA). In developed nations, DR is the leading cause of blindness in the working population.[6] Given that proper management of patients with DR can prevent more than 90% of cases of visual loss, it is extremely important to categorize, classify and stage the severity of DR in order to establish adequate therapy.[7]The Optical coherence tomography (OCT) is a non-invasive, noncontact transpupillary imaging modality that has revolutionized ophthalmic clinical practice.

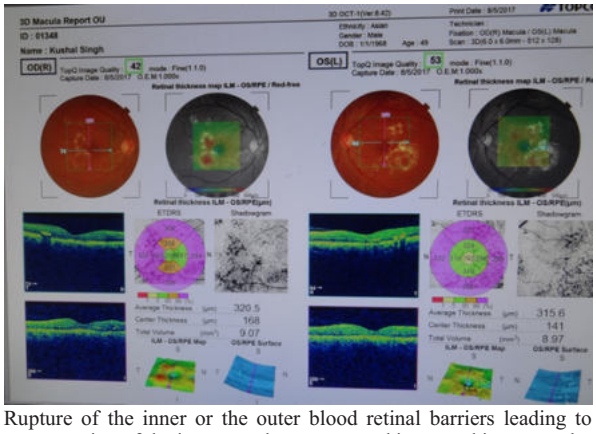
Pathophysiology

Diabetic retinopathy is a microangiopathy, the initial presenting sign of which is the appearance of retinal microaneurysms at the posterior pole. DR is the most frequent microvascular complication, the prevalence of which increases with the duration of diabetes, with an overall rate of up to 30% and a high risk of severe visual impairment in 10% of subjects [27]. Diabetic macular edema (DME) is more frequent in type 2 diabetes, occurs in approximately 7.5% of diabetic patients, and is the main cause of blindness in working-age adults in industrialized countries [28].

Elevated blood glucose levels per se and the metabolic pathways directly related to hyperglycemia, such as the polyol and hexosamine pathways, activation of the diacylglycerol-protein kinase C pathway, and accumulation of advanced glycation end products, are involved in the pathophysiology of DR [29]. Inflammation, alteration of retinal blood flow autoregulation, and hemorrheological factors also play an important role in the pathogenesis of DR [29]. Thickening of the basement membrane, pericyte loss, and disruption of interendothelial tight junctions are characteristic pathophysiological mechanisms in early stages of DR. Microaneurysm formation and fluid extravasation from the intravascular to the interstitial space can lead to retinal thickening and hard exudates [29]. This first stage is called nonproliferative diabetic retinopathy (NPDR).

Loss of the capillary endothelium, thrombus formation, retinal leukostasis, and complete occlusion of the capillary lumen appear at later stages of the disease. Cotton-wool spots or soft exudates, reflecting infarct zones and intraretinal microcirculatory alterations, are hallmark features of preproliferative DR [30].

Basement membrane digestion by proteolytic enzymes is essential for angiogenesis (neovascularization). Degradation products and hypoxia are potent activators of angiogenesis. Hypoxia promotes vessel growth by upregulating multiple proangiogenic pathways, particularly the vascular endothelial growth factor (VEGF), which plays a pivotal role in the development of pathologic angiogenesis [31]. This stage known as proliferative retinopathy (PDR) is characterized by growth of new vessels . The new vessels attached to the posterior hyaloid become fibrotic and may cause tractional retinal detachment. Vitreous hemorrhage may result from fragility and bleeding of neovascular vessels [30].



Rupture of the inner or the outer blood retinal barriers leading to extravasation of the intravascular content and increased intravascular colloid osmotic pressure are early events in the pathogenesis of diabetic macular edema (DME). Proinflammatory cytokines and VEGF are involved in the breakdown of blood-retinal barrier [32].

There is growing evidence suggesting that retinal neurodegeneration is an early event in the pathogenesis of DR, which participates in the development of microvascular abnormalities [33]. It is worth mentioning that electrophysiological abnormalities can appear even before that any impairment can be detected in the fundoscopic examination. Also, treatment based on neuroprotection opens up a new approach for preventing or arresting DR development [34].

TREATMENT

1. Anti-Angiogenic Therapy

Anti-VEGF Drugs

Currently, anti-VEGF drugs that have been tested in clinical trials for DR treatment include the U.S. Food and Drug Administration (FDA)-approved pegaptanib , ranibizumab, aflibercept and the off-label intravitreal bevacizumab. Among these agents, ranibizumab is the most comprehensively evaluated in clinical trials such as the Diabetic Retinopathy Clinical Research Network (DRCR.net). The results of the RESOLVE and RESTORE studies showed that greater gains in BCVA were obtained with intravitreal ranibizumab when compared with laser monotherapy in patients with clinically-significant DME [11,12]. In the VISTA and VIVID trials, intravitreal aflibercept was associated with better visual outcomes than standard laser therapy in patients with DME [13]. The DRCR.net Protocol S and CLARITY studies showed that anti-VEGF agents were also beneficial in the treatment of PDR [14,15].

Intravitreal Steroid

Intravitreal corticosteroids have become increasingly important in the treatment of DME, especially in refractory DME and cases lacking a response to anti-VEGF therapy [17]. Refractory cases of DME and nonresponders to anti-VEGF are presumed to be driven by multiple cytokines. As potent anti-inflammatory agents, corticosteroids target a broad array of mediators involved in the pathogenesis of DME including VEGF, TNF-α, chemokines, leukostasis and phosphorylation of tight-junction proteins. Currently, intravitreal corticosteroids used in the clinical trials for DME treatment include the off-label triamcinolone acetonide, the FDA-approved dexamethasone (DEX) intravitreal implant and the fluocinolone acetonide (FA) intravitreal implant .

Laser Treatment

2. Traditional Laser Treatments

Laser photocoagulation has been the gold standard for the treatment of both DME and PDR before the advent of anti-VEGF therapy. Focal/grid macular laser therapy was shown to effectively alleviate edema of the macula and reduced the risk of moderate visual loss by 50% in the three-year Early Treatment Diabetes Retinopathy Study (ETDRS) [18]. Panretinal photocoagulation (PRP) has also been used for the treatment of PDR and significantly reduced the risk of severe visual loss, especially in cases with high-risk complications such as vitreous hemorrhage [19]. It is hypothesized that direct closure of leaking microaneurysms, the decrease of retinal blood flow associated with reduced retinal tissues and improved oxygenation, as well as stimulation of retinal pigment epithelium (RPE) might be implicated [20,21]. Given its destructive nature, laser therapy may cause permanent damage to the retinal cells, leading to side effects such as mild central visual loss and reduced night vision [22]. The utility of focal laser as an adjuvant treatment dramatically reduced the frequency of anti-VEGF injections when compared with anti-VEGF treatment alone in DME patients [23].

3. New Laser Approaches

The pattern scanning laser (PASCAL) is a new laser method used for the treatment of DME and PDR. It reduces laser-induced retinal damage by providing a more precise control of the laser and a decrease in treatment time [24]. Micropulse techniques such as the subthreshold micropulse diode laser (D-MPL) have been employed to facilitate the delivery of subthreshold burns in order to minimize collateral damage [25]. More recently, the utilization of a navigated laser system (NAVILAS) further extended the accuracy of laser spots applied to the retina and resulted in favorable visual outcomes [26].

CONCLUSIONS

It is noticed that incidence of DR continues to increase, in the past decade but with the emergence of new treatment options, like VEGF, which have greatly improved the treatment of DME and PDR . However in clinical practice the use of anti-VEGF drugs is limited due to frequent injections, cost effect and poor compliance of patients. Laser photocoagulation still plays an important role in treatment of DR. Intravitreal corticosteroids have a clinical benefit in the treatment of refractory DME or patients failing to respond to anti – VGEF therapy . Current treatment options are to be optimized regarding the number of intravitreal injections dosage and duration. Further studies and investigations are required for better understanding the pathogenesis and management of DR.

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