A Review on Pathophysiology, Diagnosis and Management of Diabetic Retinopathy

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Abstract - Prolonged hyperglycemia and other conditions linked to diabetes mellitus such as hypertension leads to a chronic, progressive, potentially sight threatening disease of the retinal microvasculature that is globally recognized with the nomenclature of diabetic retinopathy. It is caused due to growth of new vessels in the eye leading to intraocular hemorrhage and retinal detachment with localized damage to the macula/fovea part of the eye resulting into loss of central visual acuity. Prevalence of Diabetic retinopathy is dependent on factors like longevity of diabetes mellitus in diabetic patients, blood pressure, lipid concentration, vascular endothelial growth factors and hereditary factors. Various ophthalmological techniques such as visual acuity test, pupil dilation technique, ophthalmoscopy, fundus photography, fundus fluorescein angiography and optical coherence tomography can be employed for the detection of diabetic retinopathy. There are three major treatments available for it namely laser surgery, injection of corticosteroids such as triamcinolone or anti-vascular endothelial growth factor agents (anti-VEGF) into the eye and vitrectomy, which are very effective in reducing vision loss from this disease.

Keywords: Retinopathy, Hyperglycemia, Macular edema, Anti-VEGF, Microvascular injury.

1. INTRODUCTION

Diabetes Mellitus which is globally recognized as silent killer disease may cause damage to the retina part of the eye and affects vision physiology in addition to its damaging effects on nerves, muscles and blood vessels. This deleterious effect of diabetes on the eye is referred as diabetic retinopathy [1]. It is reported in nearly all patients with type 1 diabetes and in more than 60% of patients with type 2 diabetes within a decade of diabetic attack [2, 3]. The risk of development and progression of diabetic retinopathy is closely associated with the type and duration of diabetes, blood pressure and possibly lipids [4]. Approximately 12% of new cases of diabetic retinopathy are reported every year in USA. It is also the leading cause of blindness for people aged 20 to 64 years [5].

2. SIGNS AND SYMPTOMS

Diabetic retinopathy develops in two different stages namely non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). In the first stage which is called non-proliferative diabetic retinopathy, there are no symptoms, the signs are not visible to the eye and patients will have normal vision. The fundus photography is capable to detect it in which microscopic blood-filled bulges in the artery walls can be seen. The fluorescein angiography technique can show narrowing or blocked retinal blood vessels clinically refereed as retinal ischemia. This may result into macular edema due to leakage of blood vessels in the macular region of eye ball. Macular edema is characterized by blurred vision and darkened or distorted images that are not the same in both eyes and responsible for vision loss in 10% of diabetic patients. Macular edema can be diagnosed by Optical Coherence Tomography [6]. Proliferative diabetic retinopathy, the second stage of development of diabetic retinopathy is associated with the formation of new blood vessels at the back of the eye, which can show hemorrhage in the vitreous area of the eye. Initially small and temporary blood spots are formed that floats in the visual field, but it is followed within a few days or weeks by a much greater leakage of blood, which blurs the vision. These blood spots appear like cotton wool spots or flame.

3. RISK FACTORS

Prevalence of Diabetic retinopathy is dependent on factors like longevity of diabetes mellitus in diabetic patients, blood pressure, lipid concentration, vascular endothelial growth factors and hereditary factors. All categories of diabetic patients such as type 1 diabetics, type 2 diabetics and those with gestational diabetes are susceptible to the development of diabetic retinopathy. It is evident from a study conducted on Americans that indicates 40-45% prevalence of diabetic retinopathy among diabetics [7]. Further investigations carried out in this regard in the year 2002 show that some degree of retinopathy is shown by the patients having type 1 diabetes for more than 20 years and more than 60% type 2 diabetics are affected with retinopathy. A genetical resistance mechanism has been reported among individuals suffering from Down's syndrome due to trisomy of chromosome 21.This chromosome bears collagen XVIII gene which generates elevated levels of endostatin an anti-angiogenic protein, derived from collagen [8].Increased level of endostatin prevents leakage and bursting of the walls of blood vessels of eye region.

4. PATHOGENESIS

The clinical trials conducted such as diabetes control and complications trial as well as United Kingdom prospective diabetes study highlighted the strong relationship between chronic hyperglycemia and the development and progression of diabetic retinopathy[9, 10].The development of diabetic retinopathy involves narrowing of the retinal arteries associated with reduced retinal blood flow leading to dysfunction of the neurons of the inner retina and followed in later stages by changes in the function of the outer retina associated with subtle changes in its visual function. It also results into dysfunction of the blood-retinal barrier that protects the retina from toxins and immune cells leading to the leaking of blood constituents into the retinal neuropile. It is followed by thickening of basement membrane of the retinal blood vessels, degeneration of capillaries and inflammation [11, 12].Small blood vessels of retina are more susceptible to hyperglycemia. Another complication of diabetic retinopathy is

macular edema characterized by leakage of fluid containing lipids from damaged blood vessels of macula region of the eye, resulting into swelling of macula that interferes with normal vision physiology and causes blurring of vision. Cotton wool spots or microvascular abnormalities or as superficial retinal hemorrhages characterize nonproliferative diabetic retinopathy. If the non-proliferative diabetic retinopathy is severe, it enters into an advanced stage referred as proliferative diabetic retinopathy characterized by proliferation of new fragile blood vessels along the retina, into the angle of the anterior chamber of the eye (Neovascular glaucoma) and in the vitreous humor. Any delay in the treatment can lead to lysis of these blood vessels resulting into cloudy vision. Tractional retinal detachment may occur due to fibrovascular proliferation. The advanced proliferative diabetic retinopathy can remain asymptomatic for a very long time, and so should be monitored closely with regular checkups. The biochemical pathways which act as key contributors in the development of diabetic retinopathy are increased polyol pathway, activation of protein kinase C (PKC), increased expression of growth factors such as vascular endothelial growth factor (VEGF) and insulin-like growth factor-1 (IGF-1), haemodynamic changes, accelerated formation of advanced glycation endproducts (AGEs), oxidative stress, activation of the renin-angiotensin-aldosterone system (RAAS), and subclinical inflammation and capillary occlusion. The polyol pathway within retinal cells produces sorbitol, 3-deoxyglucosone and reduced glutathione. Sorbitol causes multiple damaging effects in retinal cells including osmotic damage [13], and 3-deoxyglucosone that act as strong glycating agent that can result in the production of advanced glycation endproducts (AGEs) [14]. The reduced glutathione availability resulting into oxidative stress in retinal cells due to the production of reactive oxygen species [15, 16]. Another mechanism involved in the development of retinopathy is leukocyte adhesion to endothelial cells or leukostasis [17] .The formation and accumulation of advanced glycation end products in diabetics due to increased availability of glucose in their blood promotes diabetic retinopathy[18-21].This heterogeneous group of molecules is formed by nonenzymatic reaction of reducing sugars with free amino groups of proteins, lipids, and nucleic acids leading to deformation of their natural functional structure, thus affecting cellular matrix, basement membranes, and vessel-wall components. The development of diabetic retinopathy is induced by the interaction of advanced glycation end products with specific cell surface receptors [22]. Hyperglycemic condition in diabetics promotes an increase in glucose flux through the glycolysis pathway, which in turn increases de novo synthesis of diacylglycerol (DAG), the key activator of Protein kinase C [23].The activation of this enzyme has a cascade-like effect on several other pathways which in turn influence changes in endothelial permeability, retinal haemodynamics, and expression of vascular endothelial growth factor (VEGF) in the retinal tissue as well as increased activation and adhesion of leukocytes (leukostasis) [24-26]. This mechanism contributes to the pathogenesis and progression of diabetic retinopathy. Renin-Angiotensin-Aldosterone System (RAAS) that plays significant role in the maintenance of blood pressure as well as fluid balance gets disturbed in diabetics [27-29]. During proliferative diabetic retinopathy stage, there is an increase in the concentration of renin, angiotensin converting enzymes I and II that elevates blood pressure. High blood pressure produces mechanical stretch and stress on endothelial cells of retinal capillaries resulting into diabetic retinopathy [30,31] .There are a number of growth factors which have been associated with the development of diabetic retinopathy such as basic fibroblast growth factor (bFGF) insulin-like growth factor-1 (IGF-1), angiopoietin-1 and 2, epidermal growth factor (EGF), transforming growth factor-beta 2 (TGF-β2), platelet-derived growth factors (PDGFs), and erythropoietin [32] .The most significant role is played by vascular endothelial growth factor that promotes angiogenesis; causes breakdown of the blood-retinal barrier, stimulation of endothelial cell growth, and neovascularisation; and increases vascular permeability in the ischemic retina [33,34].

5. DIAGNOSIS

Diabetic retinopathy is detected by various ophthalmological techniques such as Visual acuity test, Pupil dilation technique, Ophthalmoscopy, Fundus photography, Fundus fluorescein angiography and Optical coherence tomography [35, 36].Visual acuity test uses an eye chart to measure how well a person sees at various distances. In Pupil dilation technique, the eye care professional put drops into the eye to dilate the pupil for broad field visualization of retina and look for signs of diabetic retinopathy. Ophthalmoscopy is an examination of the retina in which the eye care professional looks through a slit lamp biomicroscope with a special magnifying lens that provides a narrow view of the retina or wearing a headset (indirect ophthalmoscope) with a bright light looks through a special magnifying glass and gains a wide view of the retina. Fundus photography generally captures considerably larger areas of the fundus, and has the advantage of photo documentation for future reference. An advanced method of fundus photography is fundus fluorescein angiography that is an imaging technique which relies on the circulation of fluorescein dye to show staining, leakage, or non-perfusion of the retinal and choroidal vasculature. Optical coherence tomography is an optical imaging modality based upon interference, and analogous to ultrasound. It is one of the best techniques to diagnose retinal damage. It produces cross-sectional images of the retina (B-scans) which can be used to measure the thickness of the retina and to resolve its major layers, allowing the observation of swelling. The ophthalmologist looks up for early signs of disease such as leaking blood vessels, retinal swelling, such as macular edema, pale, fatty deposits on the retina (exudates) – signs of leaking blood vessels, damaged nerve tissue (neuropathy), and any changes in the blood vessels by using any of the above mentioned suitable appropriate technique for example, If macular edema is suspected, fundus fluorescein angiography and optical coherence tomography may be performed.

6. MANAGEMENT

There are three major treatments available for diabetic retinopathy namely laser surgery, injection of corticosteroids such as triamcinolone or anti-vascular endothelial growth factor agents (anti-VEGF) into the eye and vitrectomy, which are very effective in reducing vision loss from this disease. Laser photocoagulation can be used to treat macular edema and neovascularization. There is a risk of damage to retinal tissue with laser surgery treatment and may also slightly reduce color and night vision. Instead of laser surgery, some people require a vitrectomy to restore vision. A surgical procedure called vitrectomy is performed when there is a lot of blood in the vitreous. It involves removing the cloudy vitreous and replacing it with a saline solution. The common medication used to treat diabetic retinopathy is a long acting steroid preparation triamcinolone and anti-VEGF drugs. However, there is growing evidence that intravitreal VEGF inhibitors with or without combination with laser photocoagulation provide better visual outcome with a potential to improve visual acuity. Hence, anti-VEGF injections are considered the new gold standard of therapy for eyes with centre-involving macular edema and reduced vision. Triamcinolone reduces the macular edema and results in an increase in visual acuity [37]. Its effect is temporary lasting up to three months which necessitates its repeated injections for maintenance of effective vision. Furthermore, a number of complications like cataract, steroid-induced glaucoma and endophthalmitis are associated with intravitreal injection of triamcinolone. Research and development for the treatment of diabetic retinopathy is going on especially

in the field of light treatment device and stem cell therapy. Light treatment device is a mask that delivers green light through the eyelids while a person sleeps. The light from the mask stops rod cells in the retina from dark adapting, which is thought to reduce their oxygen requirement, which in turn diminishes new blood vessel formation and thus prevents diabetic retinopathy [38]. Stem cell therapy for the treatment of diabetic retinopathy involves isolation of patients own stem cells from bone marrow and their infusion into the degenerated areas of eye in an effort to regenerate the vascular system[39].The onset and delaying the progression of diabetic retinopathy can be achieved by glycemic control [40]. Proper treatment and monitoring of the eyes may reduce the incidence of diabetic retinopathy by 90%. Avoiding tobacco use and correction of associated hypertension are important therapeutic measures in the management of diabetic retinopathy.

7. CONCLUSION

The prevalence of diabetic retinopathy can be minimized by reduced by control of blood glucose level, blood pressure and lipids. There is an urgent need of research and development in the field of its pathogenesis and treatment which must be targeted to development of novel therapeutic agents for the effective treatment of diabetic retinopathy. All people with diabetes should have a dilated eye examination at least once every year to check for diabetic retinopathy.

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